AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–08079–MAS–LHG	12/30/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI–AVENTIS U.S. LLC	ACCORD HEALTHCARE, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,847,170	12/8/1998	AVENTIS PHARMA S.A.
2		
3		
4		
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	12/30/2014

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

AO 120 (Rev. 08/10)

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____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–08082–MAS–LHG	12/29/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI–AVENTIS U.S. LLC	FRESENIUS KABI USA, LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,847,170	12/8/1998	Aventis Pharma S.A.
2 7,241,907	7/10/2007	Aventis Pharma S.A.
3		
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Melissa M. Haneke	12/29/2014

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AO 120 (Rev. 08/10)

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X Trademarks or ____ Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15–cv–00287–MAS–LHG	1/15/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI–AVENTIS U.S. LLC	APOTEX CORP.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,847,170	12/8/99	Aventis Pharma S.A.
2 7,241,907	7/10/2007	Aventis Pharma S.A.
3		
4		
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ BETH JONIAK	1/15/2015

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AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

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____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15–cv–00290–PGS–LHG	1/15/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI–AVENTIS U.S. LLC	ONCO THERAPIES LIMITED

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,847,170	12/8/1998	AVENTIS PHARMA S.A.
2 7,241,907	7/10/2007	AVENTIS PHARMA S.A.
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	1/15/2015

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AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15–cv–00776–MAS–LHG	2/2/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI–AVENTIS U.S. LLC	ACTAVIS LLC

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,847,170	12/8/1998	AVENTIS PHARMA S.A.
2 7,241,907	7/10/2007	AVENTIS PHARMA S.A.
3		
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	2/2/2015

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of New Jersey on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
16-5678	9/16/2016	for the District of New Jersey

PLAINTIFF	DEFENDANT
SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI	SANDOZ INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	5,847,170	12/8/1998	Aventis Pharma S.A.
2	8,927,592	1/6/2015	Aventis Pharma S.A.
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED

INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
WILLIAM T. WALSH		9/19/16

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Trials@uspto.gov
Tel: 571-272-7822

Paper 10
Entered: August 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN LABORATORIES LIMITED,
Petitioner,

v.

AVENTIS PHARMA S.A.,
Patent Owner.

Case IPR2016-00627
Patent 5,847,170

Before: BRIAN P. MURPHY, TINA E. HULSE, and CHRISTOPHER M. KAISER, *Administrative Patent Judges.*

MURPHY, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Mylan Laboratories Limited ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1 and 2 of U.S. Patent No. 5,847,170 (Ex. 1001, "the '170 patent"). Paper 3 ("Pet."). Aventis Pharma S.A. ("Patent Owner"), filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). We have statutory authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Petitioner challenges claims 1 and 2 of the '170 patent as unpatentable under 35 U.S.C. § 103(a). Pet. 13–14. Based on the arguments and evidence presented in the Petition and Preliminary Response, we are not persuaded there is a reasonable likelihood Petitioner would prevail with respect to at least one of the claims challenged in the Petition. Therefore, we decline to institute *inter partes* review.

A. Related Proceedings

Petitioner identifies the following as related district court proceedings in the District of New Jersey regarding the '170 patent: *Sanofi-Aventis U.S. LLC, Aventis Pharma S.A. and Sanofi v. Mylan Laboratories Ltd.*, C. A. No. 3:15-cv-00290 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-07869 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 14-08079 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-08081 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-08082 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Apotex Corp. et al.*, C. A. No. 15-0287 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et*

al. v. Breckenridge Pharmaceutical, Inc., C. A. No. 15-0289 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Mylan Laboratories Limited*, C. A. No. 15-0290 (MAS)(LHG); and *Sanofi-Aventis U.S. LLC et al. v. Actavis LLC et al.*, C. A. No. 15-0776 (MAS)(LHG). Pet. 12–13.

B. Proposed Grounds of Unpatentability

Petitioner advances two grounds of unpatentability under 35 U.S.C. § 103(a) in relation to the challenged claims in the '170 patent:

Reference[s]	**Statutory Basis**	**Challenged Claims**
Kant (Ex. 1005)[1] in view of Klein (Ex. 1006)[2]	§ 103	1 and 2
Colin (Ex. 1007)[3] in view of Klein and Kant	§ 103	1 and 2

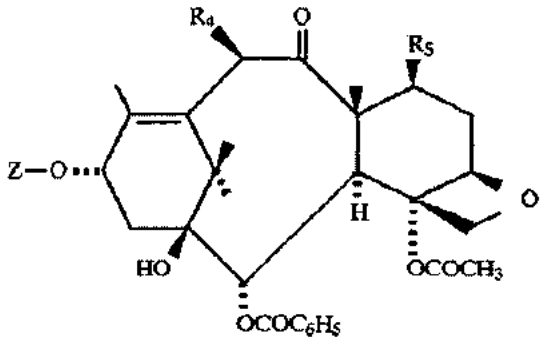
Pet. 13–14. Petitioner supports its challenge with a Declaration by Eric N. Jacobsen, Ph.D. ("Jacobsen Decl."). Ex. 1002.

C. The '170 Patent

The '170 patent, titled "Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them," issued December 8, 1998,

[1] Kant et al., *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III Synthesis and Biological Properties of Novel C-10 Taxol® Analogues*, Tetrahedron Letters, 35 (31), 5543–46 (1994) ("Kant"). Ex. 1005.
[2] Klein et al., Ch. 20 *Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes in Taxane Cancer Agents*, ACS Symposium Series Vol. 58, 276–287 (Georg et al., eds., 1994). Ex. 1006.
[3] U.S. Patent No. 4,814,470 issued March 21, 1989 to Colin et al. ("Colin"). Ex. 1007.

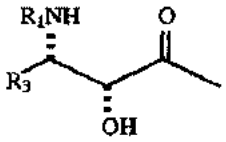
from an application filed March 26, 1996. Ex. 1001.[4] The '170 patent is directed to new taxoids of general formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):



(II)

Ex. 1001, 1:7–28. The '170 patent discloses and claims, in particular, a compound known as cabazitaxel, pharmaceutical compositions containing cabazitaxel, and processes to prepare cabazitaxel. *Id.* at 12:52–13:33. The compounds of the '170 patent, including cabazitaxel, inhibit abnormal cell proliferation and have "antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®."[5] *Id.* at 11:59–61, 26:32–37. Cabazitaxel is indicated for treatment of certain types of prostate cancer. Ex. 2002.

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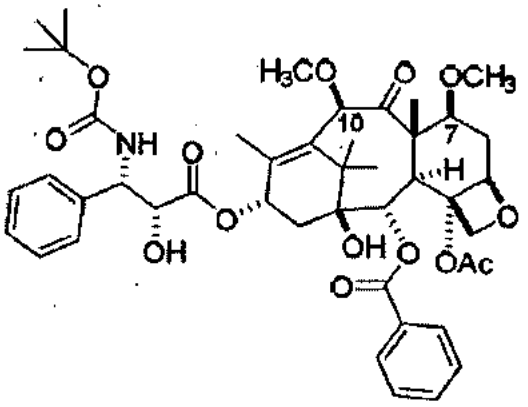
[4] The '170 patent claims priority to a provisional application dated January 17, 1996 and to French applications 95 03545 and 95 15381, dated March 27, 1995 and December 22, 1995, respectively. Ex. 1001, [60], [30].

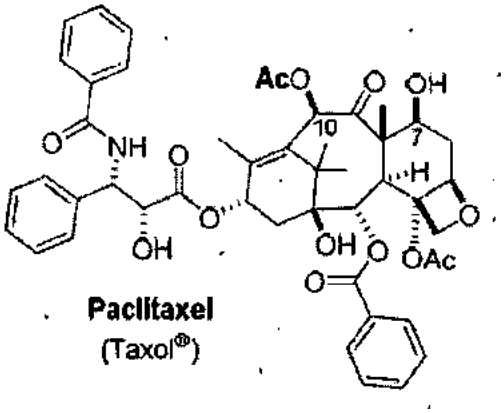
[5] Taxol® is the brand name for paclitaxel. Taxotere® is the brand name for docetaxel. We also refer to "Taxol" and "Taxotere" in this Decision.

The chemical name for cabazitaxel is 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. *Id.* at 13:9–12, 28:57–60. The chemical structure of cabazitaxel is:

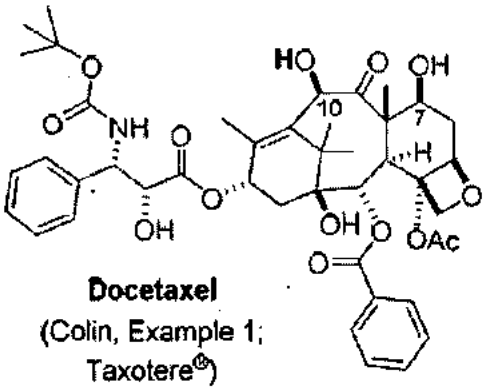


Pet. 3. Of particular interest in cabazitaxel are the presence of a methoxy group (OCH_3) at both the C-7 position (R_5 in formula I) and C-10 position (R_4 in formula I), and a carbonyl (C=O) at the C-9 position. Ex. 1001, 2:40–42, 3:1–3.

The prior art paclitaxel and docetaxel compound structures are shown below.



Paclitaxel
(Taxol®)



Docetaxel
(Colin, Example 1; Taxotere®)

Pet. 9; Ex. 1002 ¶¶ 36–38. Paclitaxel and docetaxel are synthesized from a key "advanced precursor" known as 10-deacetyl baccatin III ("10-DAB").

Ex. 1002 ¶¶ 37–38. Paclitaxel has a different synthetic side chain (left side of molecule) than docetaxel, attached to the C-13 position of the core taxoid structure, and an acetyl (CH_3CO or "Ac") group rather than a hydroxyl (OH) group at C-10. In contrast to cabazitaxel, neither paclitaxel nor docetaxel has a methoxy group at C-7 or C-10, although both have a carbonyl at C-9. *Id.* Cabazitaxel has a docetaxel side chain (i.e., 3'-NHBOC or (3-tert-butoxycaronylamino)). *Id.* ¶¶ 11, 38.

D. Challenged Claims

Petitioner challenges claims 1 and 2 of the '170 patent, which are reproduced below:

> 1. 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.
>
> 2. A pharmaceutical composition comprising at least the product according to claim **1** in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

II. ANALYSIS

A. Claim Construction

We determine that no claim terms require express construction for purposes of this Decision. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quotation omitted).

B. Asserted Obviousness of Claims 1 and 2 over Kant and Klein

Petitioner asserts that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a person of ordinary skill in the art

("POSA") based on the combined teachings of Kant and Klein. Pet. 29–38. Patent Owner opposes. Prelim. Resp. 18–38. We address the parties' arguments below.

1. Kant

Kant discloses a "chemoselective approach to functionalize the C-10 position of 10-deacetyl baccatin III [10-DAB], a key intermediate for the semi-synthesis of paclitaxel." Ex. 1005, 5543 (Abstract). Kant selects 10-DAB as "the ideal starting material" for synthesizing analogues of paclitaxel with the "aim of obtaining drugs having more desirable properties." *Id.* ¶¶ 2–3. Kant's reasoning is that "with the more reactive C-7 hydroxyl protected, an opportunity was available to *selectively deprotonate* the C-10 hydroxyl." *Id.* at 5544. Thus, Kant selectively introduced a variety of substituents at the C-10 position of 10-DAB to synthesize "a variety of C-10 paclitaxel analogues" shown in our annotated Table II, below.

Scheme 1

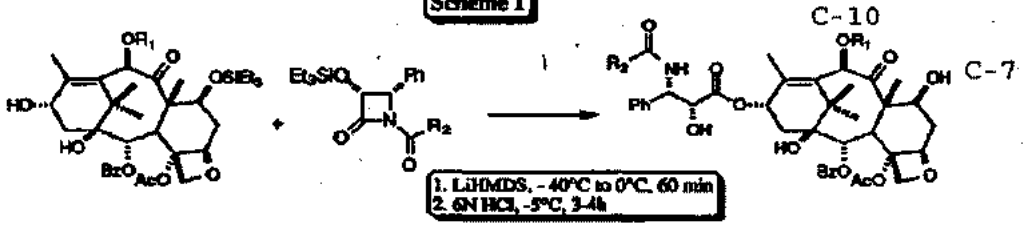
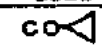


Table II

Paclitaxel Analogue	R_1	R_2	% Yield	Tubulin Ratio[a]	IC_{50} (nM)[b] HCT 116
Taxol®	Ph	Ph	-	1.0	2.0
15	COMe	OBu^t	80	0.7	2.0
16	COBu	Ph	78	1.5	3.4
17		Ph	85	1.1	2.3
18	$CON(Me)_2$	Ph	88	1.0	1.1
19	Me	Ph	73	1.0	12.0
20	Me	OBu^t	83	0.3	1.3
21	CO_2Me	Ph	76	1.1	3.0
22	CO_2Me	OBu^t	83	0.8	1.5
23	COPh	Ph	82	19	2.2
24	COPh	OBu^t	74	2.1	2.0

a=Ratio of analogue relative to paclitaxel ($EC_{0.01}$ @ 5 μM).

b=Drug concentration required to inhibit cell proliferation to 50% vs. untreated cells (incubated at 37°C for 72 h).

Id. at 5545. Kant Compound 20 contains a methoxy group at C-10 (R_1 is "Me" (methyl)), a hydroxyl group at C-7, a carbonyl at C-9, and a docetaxel side chain (R_2 is "OBu^t" (tert-butoxy)). *Id.* Kant concludes "it is reasonable to suggest that the functional group present at the C-10 position does modulate the antitumor activity, which is quite contrary to some of the earlier predictions." *Id.* at 5546.

2. Klein

Klein discloses 9(R)-dihydrotaxanes, a new family of compounds having "increased water solubility and stability as compared to taxol [paclitaxel] and also exhibit[ing] excellent activity in tumor models." Ex. 1006, 276 (Abstract). Klein highlights several advantages of replacing the C-9 carbonyl with a hydroxyl in both Taxol (paclitaxel) and Taxotere

(docetaxel): 1) the C-9 hydroxyl "serves as an additional site for modifications," 2) the C-9 hydroxyl "increase[s] the water solubility of these analogs," and 3) the absence of a C-9 carbonyl "stabilize[s] the system." *Id.* at 277. Klein discloses the synthesis of 9(R)-dihydrotaxol and 9(R)-dihydrotaxotere, which exhibit enhanced stability and aqueous solubility compared to paclitaxel and docetaxel due to the C-9 hydroxyl replacing the C-9 carbonyl, while maintaining "good efficacy." *Id.* at 279–280 (Table I).

Klein also experiments with substituting the C-7 and/or the C-9 hydroxyl groups with various alkylating substituents. *Id.* at 281. The experimental compounds include a methoxy group at C-9 (entry 7) or at C-7 (entries 8 and 10, with a hydroxyl at C-9), and all have an acetyl at C-10, as shown in our annotated Table III, below.

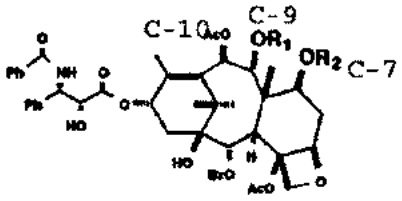
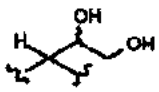
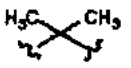


Table III. Tumor Cell Cytotoxicity of C-7,9 Analogs

Entry	Compound R_1 C-9	R_2 C-7	Tumor cell lines, IC_{50} (ng/mL) *A549*	*HT-29*	*B16F10*	*P388*
1.	H	H	16-22	6.4-9.6	25	49-57
	9-Dihydrotaxol 12					
2.	H	$CH_2CH(OH)CH_2OH$	>100	>100	>100	>100
3.	H	$CH_2CH_2NEt_2$	>100	>100	>100	>100
4.			>100	79	90	>100
5.			25	26	34	42
6.			19	11	20	35
7.	CH_3	H	4.7	3.1	4.8	7.8
8.	H	CH_3	1.2	1.4	1.5	3.9
9.	H	$CH_2CH{=}CH_2$	1	1.2	2.7	5.3
10.	H	CH_3 (3'-NBoc)	0.27	0.15	0.2	0.6

Id. at 281. Klein observes that the methylated C-7 analog in entry 10 exhibits "extremely potent cytotoxicity." *Id.* at 282.

3. Analysis

Petitioner acknowledges that "Kant does not describe the C-7 methoxy substitution needed to form" cabazitaxel.[6] Pet. 28. Petitioner further acknowledges that "Klein does not disclose the C-10 methoxy substitution" in cabazitaxel. *Id.* Petitioner argues, however, that a POSA would have selected Kant's Compound 20 "for further modification" (a so-

[6] Petitioner refers to cabazitaxel as 7,10-dimethoxy docetaxel. Pet. 28.

called "lead compound") because of its superior binding ability and cytotoxicity among the chemical analogues having the docetaxel side chain. Pet. 31 (citing Ex. 1002 ¶¶ 79–81). Petitioner reasons that a POSA would have modified Kant Compound 20 in view of Klein's Table III (compounds 8 and 10), teaching increased anti-tumor potency by substituting a methoxy group for a hydroxyl group at C-7, which would have led to the synthesis of cabazitaxel. *Id.* at 32–33.

We agree with Patent Owner that Petitioner's evidence is insufficient to establish a sufficient motivation for a POSA to have selected Kant's Compound 20 as a lead compound for further modification in view of Klein's Table III (compounds 8 and 10), to synthesize cabazitaxel with a reasonable expectation of success. Prelim. Resp. 20–37. For compositions containing new chemical compounds, there must have been a reason for a POSA to: (1) select the prior art "most promising to modify" (referred to as the "lead compound"), and (2) make all of the necessary modifications to arrive at the claimed invention. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012); *see also Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) ("[T]he attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art at the time the invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed invention."). There also must have been a "reasonable expectation" both of making the new compound, and of its advantageous properties. *Otsuka Pharm.*, 678 F.3d at 1292 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

a. Kant Compound 20 as a lead compound

We begin by observing that Kant uses 10-DAB as "the ideal starting material" to synthesize paclitaxel analogues by selective substitution at only the C-10 position. Ex. 1005, 5543 ¶ 3. Kant does not teach or suggest additional structural modifications to Compound 20 or docetaxel, which cuts against the notion of selecting Kant Compound 20 as a lead compound for further modification of this docetaxel analogue. Kant itself indicates the authors chose to use 10-DAB as the starting material for making selective C-10 substitutions in order to synthesize "novel paclitaxel analogues." *Id.*

We agree with Patent Owner that Petitioner also errs by starting with a hindsight-biased structural comparison of docetaxel, Kant Compound 20, and cabazitaxel in side-by-side fashion. Prelim. Resp. 31–34 (citing Pet. 31). As noted by Patent Owner, without a docetaxel control, Kant does not provide any information as to whether a particular compound performs better or worse than docetaxel. *Id.* at 33. Kant makes clear that the authors were synthesizing paclitaxel analogues and using paclitaxel, not docetaxel, as a control. Ex. 1005, 5545 Table II n.a (IC_{50} cytotoxicity measured as a "[r]atio of analogue relative to paclitaxel"). In addition to Compound 20, Kant also identifies Compound 22, which has a methyl carbonate group rather than a methoxy group at C-10, as more cytotoxic than paclitaxel or C-10 acetyl taxotere (docetaxel). Ex. 1005, 5546. Kant does not otherwise analyze the significance of the structural differences between Compounds 20 and 22 or the other synthesized compounds, apart from generally recognizing that the functional group at C-10 modulates antitumor activity. *Id.*

Kant also does not teach or suggest the possibility of simultaneous substitution of both the C-7 and C-10 positions, whether to increase potency and lipophilicity (cell membrane permeability) as argued by Petitioner (Pet. 21–22, 33), or for some other reason. Prelim. Resp. 20–26. Rather, Kant focuses on the possibility of improving anti-tumor cytotoxicity of paclitaxel analogues by *selective* substitution and functionalization of *only* the C-10 position, a point aptly made in the title, abstract, and text of Kant's article. Ex. 1005, 5543 ("a chemoselective approach to functionalize the C-10 position of 10-deacetyl baccatin III"), 5544 ("with the more reactive C-7 hydroxyl protected, an opportunity was available to *selectively deprotonate* the C-10 hydroxyl"), 5545 ("a variety of C-10 paclitaxel analogues were synthesized").

Patent Owner persuasively argues that Petitioner does not address why a POSA would have simultaneously modified the C-7 and C-10 positions in Kant Compound 20 to optimize lipophilicity, thereby minimizing aqueous solubility, when a POSA would have known docetaxel and paclitaxel were highly lipophilic and insoluble in water, which made their commercial formulation challenging. Prelim. Resp. 21–24 (citing Ex. 1006; Ex. 1011, 495 ("[Paclitaxel] is highly lipophilic and insoluble in water, but soluble in Cremophor EL, polyethylene glycols 300 and 400, chloroform, acetone, ethanol and methanol. For clinical use paclitaxel is formulated in 50% Cremophor EL and 50% dehydrated alcohol . . . . [Docetaxel] is insoluble in water . . . . The formulation used in the most recent clinical studies consists of 100% polysorbate 80."); Ex. 1015; Ex. 1019, 1:64–67; Ex. 1020, 206 ("Taxol is a promising antitumor agent with poor water solubility. Intravenous administration of a current taxol

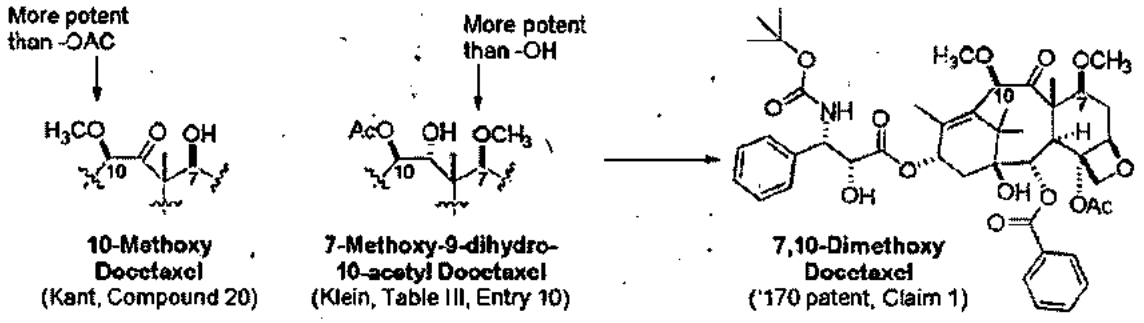
formulation in a non-aqueous vehicle containing Cremophor EL may cause allergic reaction and precipitation upon aqueous dilution. . . . The purpose of this study was to develop an aqueous based i.v. formulation of taxol that did not cause precipitation of the drug upon dilution and did not contain Cremophor EL."); Ex. 2004, 2:42–44; Ex. 2015, 648 ("Because of its limited aqueous solubility, it was necessary to formulate taxol in a vehicle consisting of 50% ethanol and 50% Cremophor EL (polyoxyethlated castor oil), a vehicle with known toxicity in dogs."); Ex. 2024, 45 ("Docetaxel . . . is practically insoluble in water but freely soluble in alcohol, and is currently formulated in polysorbate 80"); Ex. 2025, 91 ("[Paclitaxel's] poor water solubility poses delivery problems that have not been adequately resolved."); Ex. 2026, 996. Petitioner recognizes that alkylating the C-7 and C-10 functional groups would optimize lipophilicity (Pet. 22) but does not address the well-known problems with lipophilicity and limited aqueous solubility of intravenously administered paclitaxel and docetaxel. Therefore, we are not persuaded by Petitioner's argument that a POSA would have been motivated to optimize lipophilicity in a paclitaxel or docetaxel analogue via simultaneous substitution of the C-7 and C-10 positions.

For the reasons given above, there is insufficient evidence for us to conclude that a POSA would have selected Kant Compound 20 as a lead compound for further modification of both the C-7 and C-10 positions.

b. Rationale for further modifying Kant Compound 20 based on the teachings of Klein

We also are not persuaded by Petitioner's rationale and supporting evidence that a POSA would have modified Kant Compound 20 in view of Klein to make the required substitutions at C-7 and C-10 to synthesize

cabazitaxel. According to Petitioner, after selecting Kant Compound 20 for further modification, a POSA would have needed to make at least three more significant decisions to achieve the cabazitaxel structure from the teachings of Klein: 1) substitute Kant Compound 20's protected C-7 hydroxyl group with Klein's methoxy group, 2) retain Kant Compound 20's methoxy group at C-10 instead of Klein's C-10 acetyl group, and 3) retain Kant's carbonyl at C-9 instead of using Klein's C-9 hydroxyl to improve chemical stability and aqueous solubility of the compound. Pet. 32–34. Petitioner represents the proffered structural teachings below.



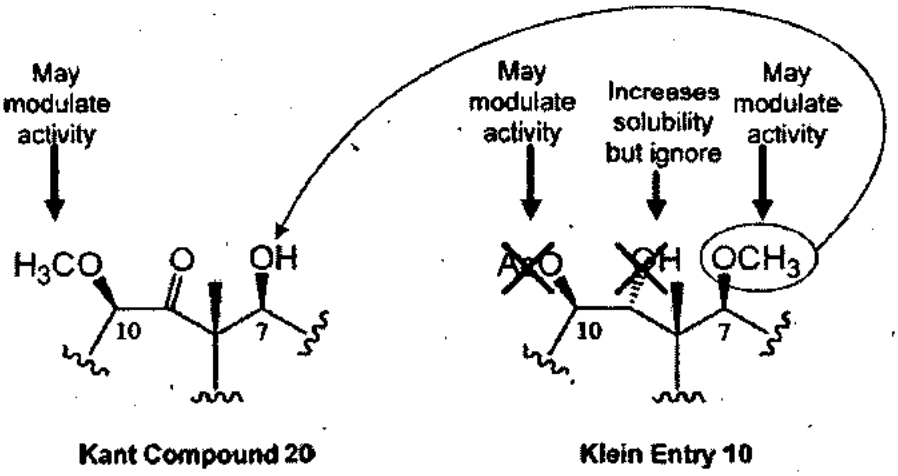
Id. at 32–33. The Petition, however, does not explain persuasively why a POSA would have disregarded two key teachings of Klein – i) increase aqueous solubility and chemical stability by reducing the C-9 carbonyl to a hydroxyl, and ii) maintain the C-10 acetyl (9-dihydrotaxol) to modulate activity while retaining good efficacy – in order to synthesize cabazitaxel from Kant Compound 20. Prelim. Resp. 27–30, 34–38 (citing Ex. 1006, 276–77); Ex. 1006, 279–280.

Klein expressly teaches the reduction of the C-9 carbonyl to a C-9 hydroxyl to increase aqueous solubility and chemical stability of the compounds, while maintaining "excellent in vivo activity in several solid

tumor models." Ex. 1006, 276; Prelim. Resp. 28 (citing Ex. 1006, 276–77). Petitioner argues that Klein teaches a "reduction at C-9 results in reduced potency" when compared to docetaxel (Pet. 34, 42-43), but the cytotocity data in Klein Table I shows that 9-Dihydrotaxotere (docetaxel with a C-9 hydroxyl) has comparable activity to docetaxel (Table I) and compound 10 (Table III) in at least 3 out of 4 cell lines. Ex. 1006, 280 (Table I), 281 (Table III). Klein, moreover, clearly teaches that "[t]hese products [*i.e.*, those with a C-9 hydroxyl] were shown to have excellent tubulin assembly activity and *similar in vitro activity* as compared to taxol and taxotere; therefore, these preliminary results establish that the *C-9 carbonyl is not required for activity*." *Id.* at 279 (emphasis added). Contrary to Petitioner's argument, Klein teaches that a C-9 carbonyl was not required to maintain anti-tumor activity and that reducing the C-9 carbonyl to a hydroxyl improves aqueous solubility and chemical stability of these notoriously insoluble compounds. *Id.* at 277, 279. Thus, we are not persuaded a POSA would have disregarded the improved aqueous solubility and stability provided by a C-9 hydroxyl, a key teaching in Klein, when considering possible modifications to Kant Compound 20.

We reach the same conclusion with respect to Klein's C-10 acetyl. Petitioner argues that a POSA would have retained Kant Compound 20's C-10 methoxy group over Klein's C-10 acetyl, because Kant teaches increased cytotoxicity of Compound 20 having a methoxy group at C-10 when compared to the C-10 acetyl of docetaxel (compound 15). Pet. 32–33 (citing Ex. 1005, 5546; Ex. 1002 ¶ 89). Klein, however, states that "facile deacetylation of the C-10 acetate is not trivial in the C-9 carbonyl series and reflects the greater stability of the 9(R)-dihydro series." Ex. 1006, 279.

Klein, therefore, does not necessarily teach or suggest replacing the C-10 acetyl unless the C-9 carbonyl is reduced to a hydroxyl group, such as in 9(R)-dihydrotaxotere. *Id.* We also are persuaded by Patent Owner's argument that Petitioner's analysis reflects improper hindsight by having a POSA select the C-7 methyl from compound 10 in Klein's Table III but reject the other teachings of Klein, as reflected in Patent Owner's diagram, reproduced below.



Prelim. Resp. 29.

Therefore, for the reasons given above, we are not persuaded Petitioner has established a reasonable likelihood of prevailing in its assertion that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a POSA over Kant and Klein.

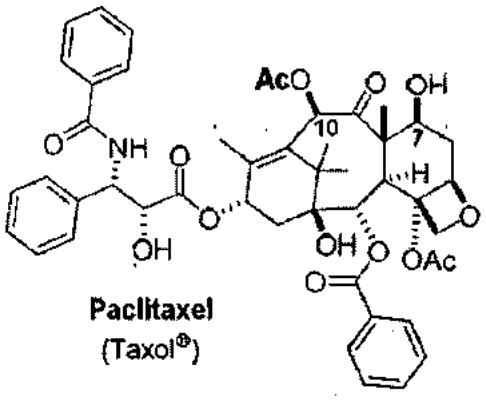
C. Asserted Obviousness of Claims 1 and 2 over Colin, Klein, and Kant

Petitioner asserts that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a POSA based on the combined teachings of Colin, Klein, and Kant. Pet. 38–49. Patent Owner opposes.

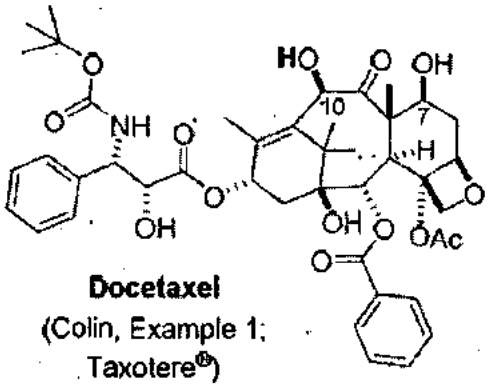
Prelim. Resp. 38–43. We incorporate our findings with respect to Klein and Kant and address the parties' arguments below.

1. Colin

Colin discloses four taxane compounds that are "useful anti-tumor agents." Ex. 1007, Abstract. Colin specifically describes docetaxel as having "valuable biological activities" and the four taxane compounds as being "approximately twice as active as taxol." *Id.* at 3:19-23, 3:29-30. The structure of docetaxel is shown below, to the right of paclitaxel.



Paclitaxel
(Taxol®)



Docetaxel
(Colin, Example 1;
Taxotere®)

Pet. 9; Ex. 1002 ¶ 71. As can be seen, docetaxel has a different side chain (3-tertbutoxycarbonylamino) from paclitaxel. Docetaxel has a hydroxyl group at C-7 and at C-10, and paclitaxel has a hydroxyl group at C-7 and an acetyl at C-10. Both have a carbonyl group at C-9. Colin discloses formulating docetaxel (the product of Example 1) for intravenous administration by dissolving it in Emulphor EL 620 (an emulsifier) and ethanol. *Id.* at 10:5–11.

2. Analysis

Petitioner argues that Colin discloses docetaxel and a reason for a POSA to select docetaxel as a lead compound for "further optimization,"

because docetaxel was known to have greater activity against various tumor cell lines and a longer elimination half-life when compared to paclitaxel. Pet. 8–9 (citing Ex. 1002 ¶¶ 70–71), 38–40 (citing Ex. 1011, 496 [497]; Ex. 1002 ¶¶ 98-103). Petitioner further argues that Klein and Kant provide sufficient reasons for a POSA to substitute the C-7 and C-10 hydroxyl groups in the docetaxel structure with methoxy groups, to achieve cabazitaxel with a reasonable expectation of success. Pet. 40–45 (citing Ex. 1002 ¶¶ 66, 84, 87–89, 102–117). Regardless of whether Colin's docetaxel would have been selected as a lead compound for further optimization, Petitioner's argument is insufficient for the same reasons articulated above. For example, Petitioner repeats the argument that a POSA would have sought to optimize docetaxel's cell membrane permeability by replacing the C-7 and C-10 hydroxyl groups with more lipophilic groups, without addressing the well-known difficulties of formulating highly lipophilic, water-insoluble paclitaxel and docetaxel into a useful intravenous dosage form. Pet. 40.

Petitioner further argues that Klein teaches methylation of the C-7 hydroxyl and acetylation of the C-10 hydroxyl to improve potency over a hydroxylated docetaxel analogue, but acknowledges that Klein compound 10 in Table III still contains "two minor" structural differences from cabazitaxel. *Id.* at 41–42. As explained above in section II.B.3.b. of this Decision, Petitioner does not address persuasively the question of why a POSA would have disregarded Klein's teachings to reduce the C-9 carbonyl to a hydroxyl group to improve aqueous solubility and chemical stability of the modified docetaxel compound, and to maintain a C-10 acetyl group with a hydroxylated C-9 to modulate biological activity of the compound. *Id.* at

42–43. Nor does Petitioner persuasively rationalize Kant's teaching of selective substitution at only the C-10 position to increase cytotoxicity, with Klein's teaching to functionalize the C-7 and/or C-9 positions, particularly given the absence in Kant of a docetaxel control. *Id.* at 44–45 (citing Ex. 1002 ¶¶ 91, 97, 107–108, 113–115, 117).

Weighing the evidence as a whole, Petitioner's argument that a POSA would have selectively methylated both the C-7 and C-10 positions of docetaxel to create a more potent analogue (cabazitaxel) based on the teachings of Klein and Kant, is not persuasive.[7]

III. CONCLUSION

Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to its assertions of obviousness of claims 1 and 2 of the '170 patent.

IV. ORDER

Accordingly, it is

ORDERED that the Petition is denied.

[7] In view of our Decision, we need not consider the parties' arguments and evidence regarding secondary considerations of nonobviousness. Pet. 49–50; Prelim. Resp. 44–53; *see Transocean Offshore Deepwater Drilling, Inc., v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) ("objective evidence of nonobviousness . . . may be sufficient to disprove or rebut a prima facie case of obviousness").

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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

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DOCKET NO. 14-1496	DATE FILED 12/18/2014	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF SANOFI-AVENTIS U.S. LLC, et al.		DEFENDANT FRESENIUS KABI USA, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	5,847,170	12/8/1998	Aventis Pharma S.A.
2	7,241,907 B2	7/10/2007	Aventis Pharma S.A.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI	)	
Plaintiffs,	)	
v.	)	C.A. No. 14-1496-LPS
FRESENIUS KABI USA, LLC	)	
Defendant.	)	

NOTICE OF VOLUNTARY DISMISSAL PURSUANT TO RULE 41(a)(1)(A)(i)

PLEASE TAKE NOTICE that pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), Plaintiffs Sanofi-Aventis U.S., Aventis Pharma S.A., and Sanofi hereby dismiss the above-captioned action, without prejudice, against defendant Fresenius Kabi USA, LLC.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Derek J. Fahnestock

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March 24, 2015
8998149.1

AO 120 (Rev. 08/10)

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DOCKET NO. 14-1533	DATE FILED 12/30/2014	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF SANOFI-AVENTIS U.S. LLC, et al.		DEFENDANT FRESENIUS KABI USA, LLC

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DOCKET NO. 15-44	DATE FILED 1/15/2015	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF SANOFI-AVENTIS U.S. LLC, et al.		DEFENDANT APOTEX CORP., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	5,847,170	12/8/1998	Aventis Pharma S.A.
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3:15-cv-00776-MAS-LHG	2/2/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
SANOFI-AVENTIS U.S. LLC	ACTAVIS LLC

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1 5,847,170	12/8/1998	AVENTIS PHARMA S.A.
2 7,241,907	7/10/2007	AVENTIS PHARMA S.A.
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PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/18/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
SANOFI-AVENTIS U.S. LLC, et al.	FRESENIUS KABI USA, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206/P.O. Box 6800
MAILCODE: BWD-303A
Bridgewater, NJ 08807-0800

In Re: Patent Term Extension
Application for
U.S. Patent No. 5,847,170

FEB -4 2014

Dear Mr. Conway:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 5,847,170 for a period of 5 years. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6284
Silver Spring, MD 20993-0002

RE: JEVTANA® (cabazitaxel)
Docket No.: FDA-E-2010-0661

Attention: Beverly Friedman

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	5,847,170
(45)	ISSUED	:	December 8, 1998
(75)	INVENTOR	:	Hervé Bouchard et al.
(73)	PATENT OWNER	:	Aventis Pharma S.A.
(95)	PRODUCT	:	JEVTANA® (cabazitaxel)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 5,847,170 based upon the regulatory review of the product JEVTANA® (cabazitaxel) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 5 years

from March 26, 2016, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 30th day of January 2014.

Michelle K. Lee

Michelle K. Lee
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: **U.S. Patent No. 5,847,170** Issue Date: **December 8, 1998**

Application No. **08/622,011**

Patentees: **Hervé Bouchard, Jean-Dominique Bourzat, Alain Commerçon**

Title: **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

CERTIFICATE OF EFS-WEB TRANSMISSION
I hereby certify that the correspondence below is being transmitted via the USPTO's electronic filing system in accordance with 1.6(a)(4), on the date indicated below.

Date of November 20. 2013
Printed Name of Person Signing Marijke W. Abbes
Certificate

Signature /Marijke W. Abbes/

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO REQUIREMENT FOR ELECTION OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 AND PURSUANT TO 37 C.F.R. § 1.785(b)

This is in response to the Notice of Final Determination and Requirement for Election mailed on October 30, 2013, by the United States Patent and Trademark Office, setting a one month period for response set to expire on November 30, 2013. This response is timely filed.

Pursuant to 37 C.F.R. § 1.785(b), Applicant elects U.S. Patent No. 5,847,170 for patent term extension based upon the regulatory review of JEVTANA® (cabazitaxel). For clarity, Applicant does not elect U.S. Patent No. 6,331,635.

It is believed that no fees are due in connection with this submission. However, should it be determined that fees are due, the Commissioner is authorized to charge any necessary fees to Deposit Account No. 18-1982, upon which the undersigned is authorized to draw.

Respectfully submitted,

November 20, 2013
Date

/ Brian R. Morrill /
Brian R. Morrill, Reg. No. 42,908
Attorney for Applicants

sanofi-aventis U.S. Inc.
U.S. Patent Operations
55 Corporate Drive
Mail Stop – 55A-505A
Bridgewater, New Jersey 08807
Telephone (617) 768-1879
Telefax (908) 981-7832

Electronic Acknowledgement Receipt

EFS ID:	17452204
Application Number:	08622011
International Application Number:	
Confirmation Number:	1663
Title of Invention:	NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM
First Named Inventor/Applicant Name:	HERVE BOUCHARD
Customer Number:	5487
Filer:	Brian Raymond Morrill/marijke abbes
Filer Authorized By:	Brian Raymond Morrill
Attorney Docket Number:	3806.0367-00
Receipt Date:	20-NOV-2013
Filing Date:	26-MAR-1996
Time Stamp:	13:29:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	ST95019G1US_20131120_COT.pdf	95299 6c73cb6b763d1a06de919ab2589be022f37d5ae7	no	1

Warnings:	
Information:	

2	Miscellaneous Incoming Letter	ST95019G1US_20131120_ResponseToElectionOfPatent.pdf	93432 28879058fcf8c67174853 46bce80c0ba6d6f7cf4a	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	188731

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patentees: **Hervé Bouchard, Jean-Dominique Bourzat, Alain Commerçon**

U.S. Patent No. 5,847,170

Application No.:
08/622,011

Issue Date:
December 8, 1998

Title: **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

CERTIFICATE OF EFS-WEB TRANSMISSION

I hereby certify that the correspondence below is being transmitted via the USPTO's electronic filing system in accordance with 1.6(a)(4), on

November 20, 2013
Date of Deposit

/Marijke W. Abbes/
Signature

TO: Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Attached are the following documents:

			Number of Pages
☐	Application Data Sheet		
☐	Declaration		
☐	Drawings		
☐	Extension of Time		
☐	Information Disclosure Statement and Form 1449		
☐	Response to		
☐	Specification, Claims and Abstract	Specification	
		Claims	
		Abstract	
☐	Transmittal Letter:		
☒	Other *(specify)*: **RESPONSE TO NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION**		2
☐	Other *(specify)*:		
☐	Other *(specify)*:		

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206/P.O. Box 6800
MAILCODE: BWD-303A
Bridgewater, NJ 08807-0800

In Re: Patent Term Extension
Application for
U.S. Patent No. 5,847,170

OCT 30 2013

NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION

A determination has been made that U.S. Patent No. 5,847,170, which claims the xxx human drug product JEVTANA® (cabazitaxel), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 5 years.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period.

Applicant also has applied for patent term extension of U.S. Patent No. 6,331,635 based on the regulatory review period for the human drug product, JEVTANA® (cabazitaxel).

When patent term extension applications are filed for extension of the terms of different patents based upon the same regulatory review period for a product, the certificate of extension is issued to the patent having the earliest date of issuance unless applicant elects a different patent. In the absence of an election by applicant within one month of the date of this notice, and in accordance with 37 CFR 1.785(b), the application for patent term extension in U.S. Patent No. 6,331,635 will be denied. Accordingly, the application for patent term extension of the patent having the earlier date of issuance will be granted. A certificate of extension will be issued to U.S. Patent No. 5,847,170. In the absence of such request for reconsideration and if U.S. Patent No. 5,847,170 is elected, the Director will issue to the applicant a certificate of extension, under seal, for a period of 5 years in U.S. Patent No. 5,847,170.

The period of extension, if calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of May 4, 2012 (77 Fed. Reg. 26558), would be 2,145 days. Under 35 U.S.C. § 156(c):

$$\text{Period of Extension} = \text{RRP} - \text{PGRRP} - \text{DD} - \tfrac{1}{2}(\text{TP} - \text{PGTP})^{1}$$

[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act

= 4,250 - 40 - 0 - ½ (4171 days - 40)
= 2145 days (5.9 years)

Since the regulatory review period began October 30, 1998, before the patent issued (December 8, 1998), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From October 30, 1998, to and including December 8, 1998, is 40 days; this period is subtracted for the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

However, the five year limitation of 35 U.S.C. § 156(g)(6)(A) applies in the present situation, because the patent was issued after the date of enactment of 35 U.S.C. § 156. Since the period of extension calculated under 35 U.S.C. § 156(c) for the patent cannot exceed five years under 35 U.S.C. § 156(g)(6)(A), the period of extension will be for five years.

The 14 year limitation of 35 U.S.C. § 156(c)(3) does not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	5,847,170
Granted:	December 8, 1998
Original Expiration Date[2]:	March 26, 2016
Applicant:	Hervé Bouchard et al.
Owner of Record:	Aventis Pharma S.A.
Title:	New Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them
Product Trade Name:	JEVTANA® (cabazitaxel)

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with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Term Extended: 5 years

Expiration Date of Extension: March 26, 2021

Any correspondence with respect to this matter should be submitted via the USPTO's EFS-Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: JEVTANA® (cabazitaxel)
Docket No.: FDA-E-2010-0661

Department of Health and Human Services | Public Health Service

Food and Drug Administration
Rockville, MD 20857

DEC 18 2012

Re: JEVTANA
U.S. Patent Nos. 5,847,170 and 6,331,635
Docket Nos. FDA-2010-E-0661
FDA-2010-E-0662

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the patent term extension applications for U.S. Patent Nos. 5,847,170 and 6,331,635 filed by Aventis Pharma S.A. under 35 U.S.C. § 156. The patents claim JEVTANA, which was assigned new drug application 201023.

In the May 4, 2012, issue of the Federal Register (77 Fed. Reg. 26558), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before October 31, 2012, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John D. Conway
Sanofi-Aventis U.S. Inc.
US Patent Operations
Route #202-206/ P.O. Box 6800
Bridgewater, NJ 08807-0800

review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product FERAHEME (ferumoxytol). FERAHEME is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for FERAHEME (U.S. Patent No. 6,599,498) from AMAG Pharmaceuticals, Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated May 2, 2011, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of FERAHEME represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for FERAHEME is 3,680 days. Of this time, 3,120 days occurred during the testing phase of the regulatory review period, while 560 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* June 5, 1999. The applicant claims June 4, 1999, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 5, 1999, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* December 19, 2007. The applicant claims December 18, 2007, as the date the new drug application (NDA) for FERAHEME (NDA 22–180) was initially submitted. However, FDA records indicate that NDA 22–180 was submitted on December 19, 2007.

3. *The date the application was approved:* June 30, 2009. FDA has verified the applicant's claim that NDA 22–180 was approved on June 30, 2009.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,209 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by July 3, 2012. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 31, 2012. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written petitions. It is only necessary to send one set of comments. However, if you submit a written petition, you must submit three copies of the petition. Identify comments with the docket number found in brackets in the heading of this document.

Comments and petitions that have not been made publicly available on *http://www.regulations.gov* may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 16, 2012.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2012–10849 Filed 5–3–12; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2010–E–0661 and FDA–2010–E–0662]

Determination of Regulatory Review Period for Purposes of Patent Extension; JEVTANA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for JEVTANA and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov*. Submit written petitions along with three copies and written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6284, Silver Spring, MD 20993–0002, 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when

the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product JEVTANA (cabazitaxel). JEVTANA, in combination with prednisone, is indicated for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. Subsequent to this approval, the Patent and Trademark Office received patent term restoration applications for JEVTANA (U.S. Patent Nos. 5,847,170 and 6,331,635) from Aventis Pharma S.A., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated February 11, 2011, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of JEVTANA represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for JEVTANA is 4,250 days. Of this time, 4,171 days occurred during the testing phase of the regulatory review period, while 79 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* October 30, 1998. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on October 30, 1998.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* March 31, 2010. FDA has verified the applicant's claim that the new drug application (NDA) for JEVTANA (NDA 201023) was submitted on March 31, 2010.

3. *The date the application was approved:* June 17, 2010. FDA has verified the applicant's claim that NDA 201023 was approved on June 17, 2010.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 1,591 days and 5 years of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments and ask for a redetermination by July 3, 2012. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by October 31, 2012. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) electronic or written comments and written petitions. It is only necessary to send one set of comments. However, if you submit a written petition, you must submit three copies of the petition. Identify comments with the docket number found in brackets in the heading of this document.

Comments and petitions that have not been made publicly available on *http://www.regulations.gov* may be viewed in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 16, 2012.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2012–10828 Filed 5–3–12; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Agency Information Collection Activities: Submission for OMB Review; Comment Request

Periodically, the Substance Abuse and Mental Health Services Administration (SAMHSA) will publish a summary of information collection requests under OMB review, in compliance with the Paperwork Reduction Act (44 U.S.C. Chapter 35). To request a copy of these documents, call the SAMHSA Reports Clearance Officer on (240) 276–1243.

Project: 2012 National Mental Health Services Survey (N–MHSS) (OMB No. 0930–0119)—Revision

The Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality (CBHSQ), is requesting approval for a revision to the National Mental Health Services Survey (N–MHSS) (OMB No. 0930–0119), which expires on February 28, 2013. The N–MHSS provides national and state-level data on the number and characteristics of mental health treatment facilities in the United States.

An immediate need under N–MHSS in 2012 is to update the information about facilities on SAMHSA's online Mental Health Facility Locator (see: *http://store.samhsa.gov/mhlocator*), which was last updated with information from the 2010 N–MHSS. A full N–MHSS is anticipated within about two years, and a separate request for OMB approval will be submitted for that collection. However, until then, an abbreviated version of the N–MHSS will be conducted to collect only the information needed to update the Locator, such as the facility name and address, specific services offered, and special client groups served. The data on the Locator are becoming outdated and need an update method. Other fields in the full N–MHSS not needed for updating the Locator, such as client counts and client demographics, will not be collected in the Locator survey. In addition to the data collection for updating facilities on the Locator, a data collection in conjunction with adding new facilities to the Locator is being requested. Both activities will use the same abbreviated N–MHSS–Locator instrument.

This requested revision seeks to change the content of the currently approved full-scale N–MHSS survey instrument into an abbreviated survey

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 18 2012

Re: JEVTANA
Patent Nos. 5,847,170 and 6,331,635
Docket Nos.: FDA-2010-E-0661
and FDA-2010-E-0662

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,847,170 and 6,331,635, filed by Aventis Pharma S.A., under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the application and have determined the regulatory review period for JEVTANA (cabazitaxel), the human drug product claimed by the patents.

The total length of the regulatory review period for JEVTANA (cabazitaxel) is 4,250 days. Of this time, 4,171 days occurred during the testing phase and 79 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: October 30, 1998.

   FDA has verified the applicant's claim that the date the investigational new drug application became effective was on October 30, 1998.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: March 31, 2010.

   FDA has verified the applicant's claim that the new drug application (NDA) for JEVTANA (NDA 201023) was submitted on March 31, 2010.

3. The date the application was approved: June 17, 2010.

   FDA has verified the applicant's claim that NDA 201023 was approved on June 17, 2010.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John D. Conway
Sanofi-Aventis U.S. Inc.
US Patent Operations
Route #202-206/ P.O. Box 6800
Bridgewater, NJ 08807-0800

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

AUG 1 2011

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,847,170. The application was filed on August 10, 2010, under 35 U.S.C. § 156. Please note that a patent term extension application for U.S. Patent No. 6,331,635 for NDA 201023 for the human drug product JEVTANA® (cabazitaxel) was filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206/P.O. Box 6800
MAILCODE: BWD-303A

RE: JEVTANA® (cabazitaxel)
Docket No. FDA-2010-E-0662

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 11 2011

Re: JEVTANA
Patent Nos. 5,847,170 and 6,331,635
Docket Nos. FDA-2010-E-0662
FDA-2010-E-0661

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,847,170 and 6,331,635 filed by Aventis Pharma S.A., under 35 U.S.C. § 156. The human drug product claimed by the patents is JEVTANA (cabazitaxel), which was assigned new drug application (NDA) No. 201023.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on June 17, 2010, which makes the submission of the patent term extension applications on August 10, 2010, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patents are eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John D. Conway
Sanofi-Aventis U.S. Inc.
US Patent Operations
Route #202-206/ P.O. Box 6800
Bridgewater, NJ 08807-0800

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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www.uspto.gov

OCT 13 2010

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,847,170 was filed on August 10, 2010, under 35 U.S.C. § 156. Please note that Applicant has also applied for patent term extension for U.S. Patent No. 6,331,635, pursuant to 37 C.F.R. § 1.785, for NDA No. 20-1023 approved on June 17, 2010.

The assistance of your Office is requested in confirming that the product identified in the application, JEVTANA® (cabazitaxel), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206/P.O. Box 6800
MAILCODE: BWD-303A
Bridgewater, NJ 08807-0800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,847,170 Attorney Docket No. ST95019G1 US NP

Application No. 08/622,011 Issue Date: December 8, 1998

Patentees: Hervé Bouchard, Jean-Dominique Bourzat, and Alain Commerçon

Title: TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Mail Stop Hatch-Waxman PTE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, Aventis Pharma S.A., the address of which is 20 Avenue Raymond Aron, Antony FRANCE 92160 (hereinafter referred to as "Applicant,") represents that it is the owner and assignee of the entire interest in and to United States Patent No. 5,847,170 (Exhibit 1, "the '170 patent"), granted to Hervé Bouchard, Jean-Dominique Bourzat, and Alain Commerçon (hereinafter referred to as the "Inventors") for "TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM" on December 8, 1998, by virtue of a name change from Rhone-Poulenc Rorer S.A. to Applicant, recorded June 7, 2001 at Reel 011641, Frame 0962. Rhone-Poulenc Rorer S.A. became assignee of record by virtue of assignment from all of the inventors recorded May 24, 1996 at Reel 007959, Frame 0343 (See Exhibit 2).

The '170 patent matured from Application No. 08/622,011, filed March 26, 1996.

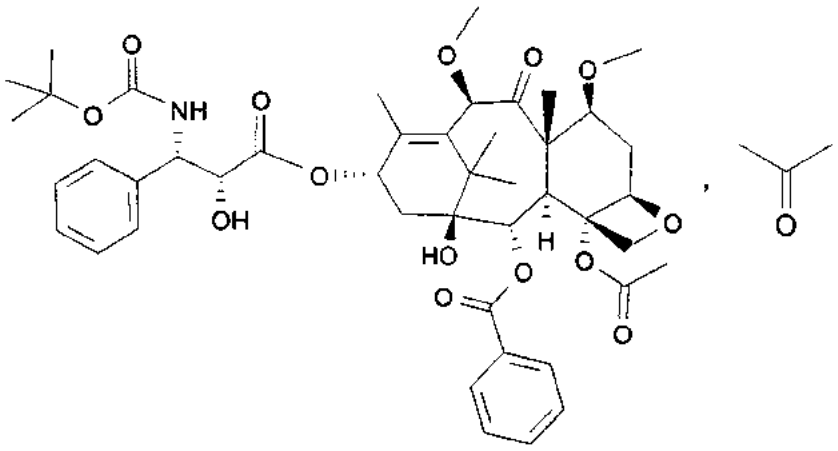
The approved product that is relevant to this application is JEVTANA® (cabazitaxel) Injection, 60 mg/1.5 mL, referred to herein as "JEVTANA®" or "Approved Product".

The Marketing Applicant for JEVTANA® is sanofi-aventis U.S. LLC of 55 Corporate Drive, Bridgewater, New Jersey 08807, USA. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 3.

The following information is submitted by Applicant, through its duly authorized attorney, in accordance with 35 U.S.C. §156 and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791, and follows the numerical format set forth in 37 C.F.R. §1.740. The undersigned is authorized to act on behalf of Applicant and proper Power of Attorney has been submitted to and accepted by the USPTO (see Exhibit 4).

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is JEVTANA® (cabazitaxel) Injection. Cabazitaxel has the chemical name (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one(1:1). The chemical structure of cabazitaxel is:



Cabazitaxel alternatively has the chemical name 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate – propan-2-one(1:1).

The approved product, JEVTANA® (cabazitaxel), is a concentrate for solution for injection. The approved dosage form is a single-use vial containing 60 mg cabazitaxel (anhydrous and solvent free) in 1.56 g polysorbate 80 and is supplied with a separate diluent vial containing approximately 5.7 ml of 13% (w/w) ethanol in water for injection.

JEVTANA® is currently indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen (A copy of the approved labeling is attached to the FDA's letter of approval, Exhibit 5).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review period occurred:

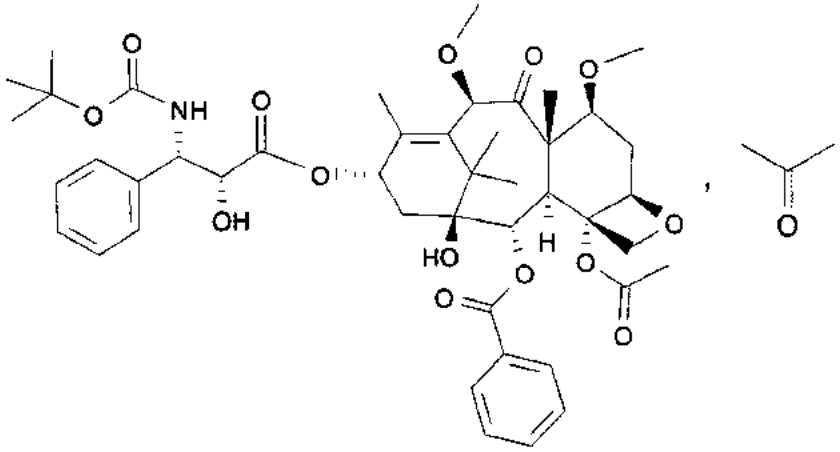
The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Regulatory approval for JEVTANA® (cabazitaxel) Injection, based on NDA No. 201023, was received on June 17, 2010. A copy of the letter from FDA setting forth such approval is attached hereto as Exhibit 5.

(4) An identification of each active ingredient in the product and as to each active ingredient a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act:

The sole active ingredient in the Approved Product is cabazitaxel, having the chemical structure:



Neither cabazitaxel nor any salt or any ester thereof has previously been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 CFR 1.720(f) and an identification of the date of the last day on which the application could be submitted:

This application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on June 17, 2010 when the product received permission under 21 U.S.C. § 355(b) and that will expire on August 16, 2010. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on August 15, 2010.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

1. **United States Patent Number**: 5,847,170
2. **Inventors**: Hervé Bouchard, Jean-Dominique Bourzat, and Alain Commerçon
3. **Issued**: December 8, 1998
4. **Expiration Date**: March 26, 2016

The expiration date of United States Patent No. 5,847,170 is March 26, 2016 based on the following: The '170 patent matured from Application No. 08/622,011, filed March 26, 1996, and claims the benefit of U.S. Provisional Application No. 60/010,144, filed January 17, 1996, and claims foreign priority to French Patent Application No. 9503545, filed March 27, 1995 and French Patent Application No. 9515381, filed December 22, 1995. Thus, the earliest filing date under 35 U.S.C. §§ 120, 121 or 365(c) for the '170 patent is March 26, 1996. The '170 patent term is 20 years from the earliest filing date under 35 U.S.C. §§ 120, 121 or 365(c) (i.e., March 26, 2016)). Therefore, the '170 patent will expire on March 26, 2016, in the absence of an extended term.

(7) A copy of the patent for which an extension is being sought:

A copy of the patent for which extension is sought, including the entire specification and claims, is attached hereto as Exhibit 1.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

United States Patent No. 5,847,170 is not subject to a terminal or statutory disclaimer.

United States Patent No. 5,847,170 has not been reexamined, and, thus, no reexamination certificate has been issued.

A copy of a Request for Certificate of Correction under 37 C.F.R. § 1.322, filed May 12, 1999, and a copy of a Certificate of Correction issued by the U.S. Patent and Trademark Office on September 7, 1999 are attached hereto as Exhibit 6.

The first (four year) maintenance fee for the '170 patent was paid April 22, 2002. The second (eight year) maintenance fee was paid February 14, 2006. The third (twelve year) maintenance fee was paid May 12, 2010.

Attached as Exhibit 7 are maintenance fee records for the payment of all maintenance fees, a copy of a USPTO record showing that the 4th, 8th, and 12th year maintenance fees have all been paid for the '170 patent, and a copy of a USPTO record confirming that no further fees are due. All records were downloaded from the USPTO website.

(9) A statement that the patent claims the approved product, a method of using the approved product, or a method of manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which at least

one such patent claim reads on the approved product, method of using the approved product, or method of manufacturing the approved product:

The patent claims the approved product and a method of manufacturing the approved product. Specifically, claims 1 and 2 claim the approved product, and at least claims 6 to 8, 10, 11 to 15, 18, 19, 21 and 22 claim a method of manufacturing the approved product.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which one product claim and one method of manufacturing claim read on the approved product is set forth herein below.

Claim 1 claims 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Claim 1 covers the approved product, JEVTANA® (cabazitaxel) Injection, as the active ingredient of JEVTANA®, cabazitaxel, is a propan-2-one solvate of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Claim 6 claims a process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising: converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Claim 6 claims a method of manufacturing the approved product JEVTANA® (cabazitaxel) Injection as the active ingredient of JEVTANA®, cabazitaxel, is a propan-2-one solvate of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, which can be made by converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

[CONTINUED ON NEW PAGE]

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g)

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the Investigational New Drug application (IND) and the IND number, the date on which a New Drug Application (NDA) or a Product License Application (PLA) was initially submitted, and the NDA or PLA number; and the date on which the NDA was approved or the Product License Issued

An investigational new drug application ("IND") was submitted on September 30, 1998, and assigned IND No. 56,999. A copy of the letter acknowledging receipt of the IND on September 30, 1998 is attached as Exhibit 8. Accordingly, IND No. 56,999 became effective 30 days from September 30, 1998, which is October 30, 1998.

A new drug application ("NDA") was submitted on March 31, 2010 and acknowledged as received on March 31, 2010, in a letter from FDA dated June 9, 2010. (Exhibit 9). The NDA number assigned to the application for cabazitaxel was NDA 201023. Accordingly, NDA 201023 was submitted on March 31, 2010. The NDA was approved on June 17, 2010. (Exhibit 5).

[CONTINUED ON NEW PAGE]

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of communications between the FDA and the Marketing Applicant, its predecessor, and affiliates, in IND No. 56,999 and NDA No. 201023 during the applicable regulatory review period with respect to the approved product is provided at Exhibits 10 and 11.

The original sponsor of IND No. 56,999 was Rhône-Poulenc Rorer Pharmaceuticals, Inc. Following a series of name changes and mergers, Rhône-Poulenc Rorer Pharmaceuticals, Inc. has become sanofi-aventis U.S. LLC.

The IND was filed on September 30, 1998, and became effective on October 30, 1998. A clinical hold was imposed on December 23, 1998, and Rhône-Poulenc Rorer Pharmaceuticals, Inc. worked diligently to address the clinical hold, which was lifted on April 14, 1999.

Clinical trials were begun shortly thereafter. An End of Phase II meeting with the FDA was held on or about June 28, 2006. The first Phase III protocols were submitted to the FDA on or about July 27, 2006.

The NDA was filed on March 31, 2010 and was assigned Application No. NDA 201023. From March 31, 2010 through approval on June 17, 2010, sanofi-aventis U.S. LLC replied to multiple queries from the FDA.

[CONTINUED ON NEW PAGE]

(12) A statement that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed including how the length of extension was determined:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154 and 35 U.S.C. §251, and for reasons discussed above, the term of United States Patent No. 5,847,170 is currently set to expire on March 26, 2016. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 5,847,170.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Applicant, Aventis Pharma S.A., the owner of record of United States Patent No. 5,847,170. (See Exhibit 2).

Aventis Pharma S.A. is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on June 17, 2010, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on August 16, 2010. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the June 17, 2010 letter from the FDA to sanofi-aventis U.S. LLC submitted as Exhibit 5, the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the JEVTANA® (cabazitaxel) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See Section 4, above).

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 5,847,170, now expiring March 26, 2016, should be extended to March 26, 2021, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 56,999 of October 30, 1998 and the submission of the NDA 201023 on March 31, 2010 (i.e., the "testing phase"), a period of 4,170 days, plus the length of time between the submission of the NDA 201023 on March 31, 2010 to NDA approval on June 17, 2010 (i.e., the "approval phase"), a period of 78 days. These two periods added together equal 4,248 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 4,248 day regulatory review period the following:

(i) 39 days, which is the number of days in the IND and NDA periods on or before the issuance of original United States Patent No. 5,847,170 on December 8, 1998; and

(ii) 2,065 days, which is one-half the number of days remaining in the IND period after the subtraction of 39 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 2,144 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (2,066 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (78 days). This length of an extension would provide a new expiration date for U.S. Patent No. 5,847,170 of February 7, 2022. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. 5,847,170 is March 26, 2016, no patent term extension could extend the term of the patent beyond March 26, 2021. Consequently, this provision limits the possible extension available to U.S. Patent 5,847,170 to March 26, 2021.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that is, a patent term expiring after June 17, 2024, the period of extension would be limited so that this period does not exceed 14 years. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. 5,847,170.

Accordingly, United States Patent No. 5,847,170 is eligible for the maximum five year extension allowable under 35 U.S.C. §156(g)(6)(A), namely an extension to March 26, 2021.

(13) A statement that Applicant acknowledges a duty to disclose to the Director of the United States Patents and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (See 37 C.F.R. §1.765)

Applicant acknowledges a duty to disclose to the Director of the United States Patents and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In accordance with the duty of disclosure described in 37 C.F.R. § 1.765 and acknowledged under 37 C.F.R. § 1.740(13), the Applicant wishes to formally inform the Office that two patent term extension applications are being filed concurrently with respect to the regulatory review period for JEVTANA® (cabazitaxel). Such patent term extension applications pertain to U.S. Patent Nos. 5,847,170 (i.e., the present application) and 6,331,635. It is requested that the Office examine these applications concurrently so that a meaningful election can be made upon the receipt of a Notice of Final Determination and Requirement of Election as to which patent to ultimately extend in accordance with 37 C.F.R. § 1.785.

(14) The prescribed fee for receiving and acting upon the application for extension (See 37 C.F.R. §1.20(j))

The Director is hereby authorized to charge any fees due to this submission to our Deposit Account No. **18-1982**, under Docket No. ST95019G1 US NP, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by or on behalf of Applicant), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1 to 11) is attached.

[CONTINUED ON NEW PAGE]

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

John D. Conway
sanofi-aventis U.S. Inc.
US Patent Operations
Route #202-206 / P.O. Box 6800
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Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits **1-11**, is accompanied by two additional copies, for a total submission of three copies.

Dated: August 9, 2010

Respectfully submitted,

By _____
Kelly L. Bender
Registration No. 52,610
Attorney for Applicant

List of Exhibits Attached:

Exhibit 1	A copy of the U.S. Patent No. 5,847,170 for which extension is sought
Exhibit 2	A copy of the Patent Assignment Abstract
Exhibit 3	A letter of authorization from the NDA Holder, sanofi-aventis U.S. LLC
Exhibit 4	A copy of the Power of Attorney and Notice of Acceptance thereof
Exhibit 5	A copy of the NDA Approval Letter from the FDA
Exhibit 6	A copy of the Certificate of Correction and corresponding request
Exhibit 7	A copy of Patent Maintenance Fees Statement
Exhibit 8	A letter of acknowledgment of IND Submission
Exhibit 9	A letter of acknowledgement of NDA Submission
Exhibit 10	IND 65,999 History Log
Exhibit 11	NDA 201023 History Log

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US Patent Operations
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Exhibit 1

US005847170A

United States Patent [19]

Bouchard et al.

[11] **Patent Number: 5,847,170**

[45] **Date of Patent: Dec. 8, 1998**

[54] **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Hervé Bouchard**, Ivry-sur-Seine; **Jean-Dominique Bourzat**, Vincennes; **Alain Commerçon**, Vitry-sur-Seine, all of France

[73] Assignee: **Rhône-Poulenc Rorer, S.A.**, Antony Cedex, France

[21] Appl. No.: **622,011**

[22] Filed: **Mar. 26, 1996**

Related U.S. Application Data

[60] Provisional application No. 60/010,144, Jan. 17, 1996.

[30] **Foreign Application Priority Data**

Mar. 27, 1995 [FR] France 95 03545
Dec. 22, 1995 [FR] France 95 15381

[51] **Int. Cl.**[6] **C07D 305/14**
[52] **U.S. Cl.** **549/510**; 549/511
[58] **Field of Search** 549/510, 511

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,229,526	7/1993	Holton et al.	549/213
5,319,112	6/1994	Kingston et al.	549/510
5,486,601	1/1996	Holton et al.	514/337
5,739,362	4/1998	Holton et al.	549/510

FOREIGN PATENT DOCUMENTS

0 336 841	10/1989	European Pat. Off. .
604910	7/1994	European Pat. Off. .
0 639 577	2/1995	European Pat. Off. .
694539	1/1996	European Pat. Off. .
WO 92/09589	6/1992	WIPO .
WO 94/07878	4/1994	WIPO .
WO 94/18164	8/1994	WIPO .
WO96/00724	1/1996	WIPO .

OTHER PUBLICATIONS

Greene et al, "Protective Groups in Organic Synthesis", pp. 10–14, 2nd edition, 1991.

M.L. Shelanski et al., "Microtubule Assembly in the Absence of Added Nucleotides", Proc. Natl. Acad. Sci. vol. 70, No. 3,pp. 765–768 (1973).

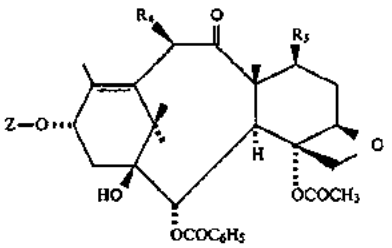
G. Chauvière et al., "Analyse structurable et etude biochimique de produits isoles de l'if: Taxus baccata L. (Taxaces)", C.R. Acad. Sc. Paris, t.293, pp. 501–503 (1981).

J. Kant et al., "A Chemoselective Approach to Functionalize the C–10 Position of 10–Deacetylbaccatin III. Synthesis and Biological Properties of Novel C–10 Taxol Analogues", Tetrahedron Letters, vol. 35, No. 31, pp. 5543–5546, 1994.

Primary Examiner—Ba K. Trinh
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

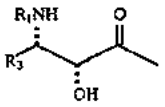
[57] **ABSTRACT**

New taxoids of general formula (I):



(I)

their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):



(II)

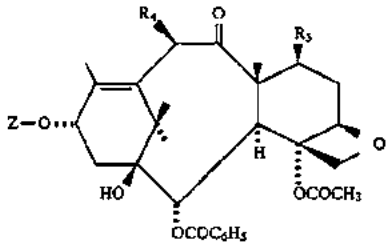
display noteworthy antitumour and antileukaemic properties.

22 Claims, No Drawings

TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the priority of U.S. provisional application 60/010,144 filed Jan. 17, 1996.

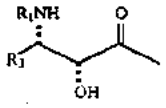
The present invention relates to new taxoids of general formula (I)



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):



(II)

in which:

R_1 represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical preferably selected from furyl and thienyl radicals,

or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 4 to 6 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

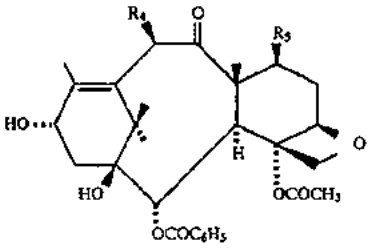
Preferably, the radicals R_4 and R_5, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

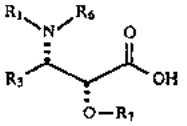
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):



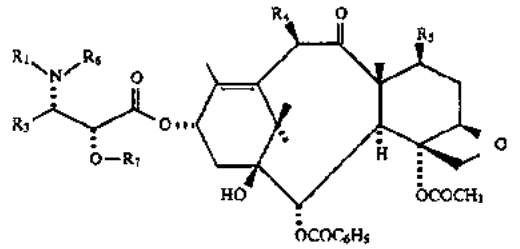
(III)

in which R_4 and R_5 are defined as above, by means of an acid of general formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, followed by replacement of the protective groups represented by R_7 and/or R_6 and R_7 by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from −10° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitrites, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 80° C.

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

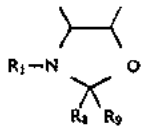
When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the following manner:

1) when R_8 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from −10° to 60° C., or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

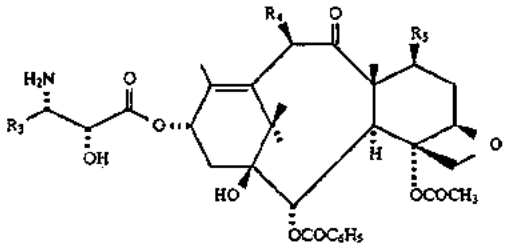
2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and R_9 represents a hydrogen atom, or alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms may be performed, depending on the meanings of R_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or alternatively R_8 and R_9 together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):



(VII)

in which R_3, R_4 and R_5 are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2—O—CO—X \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

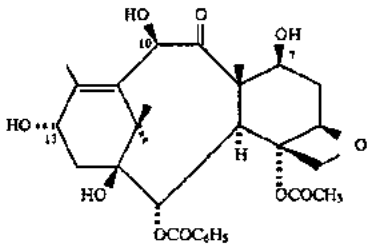
Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20° C. to yield the product of general formula (VII).

Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent

chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0° to 50° C., and preferably at about 20° C.

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C., and preferably from 15° to 30° C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and R_4 and R_5 are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):

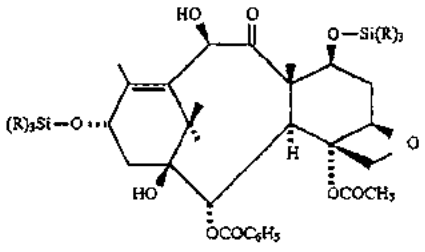


(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:

$$(R)_3—Si—Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):

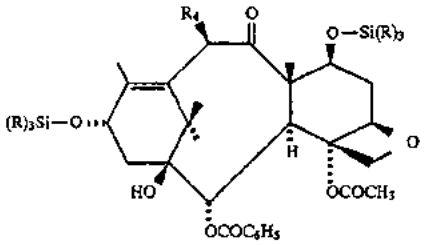


(XI)

in which R is defined as above, followed by the action of a product of general formula:

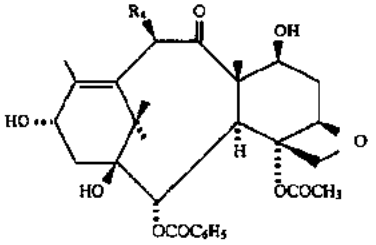
$$R'_4—X_1 \qquad (XII)$$

in which R'_4 represents a radical such that $R'_4—O$ is identical to R_4 defined as above and X_1 represents a reactive ester residue such as a sulphuric or sulphonic ester residue or a halogen atom, to obtain a product of general formula (XIII):



(XIII)

in which R and R_4 are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):



(XIV)

in which R_4 is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

$$R'_5—X_2 \qquad (XV)$$

in which R'_5 represents a radical such that $R'_5—O$ is identical to R_5 defined as above and X_2 represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonic ester residue, to give the product of general formula (III).

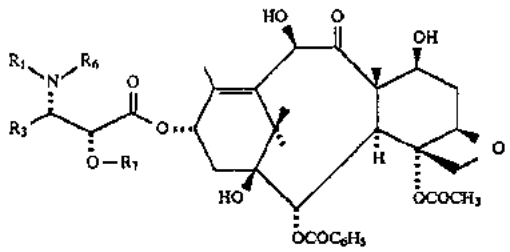
Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0° C. and the refluxing temperature of the reaction mixture.

Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0° to 50° C.

Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0° to 80° C.

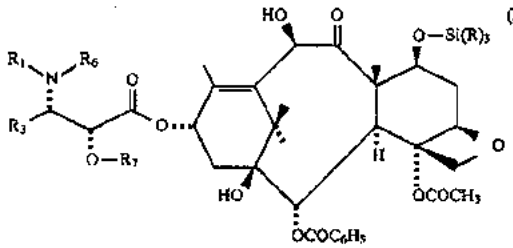
Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4 is defined as above and R_5 is defined as above may be obtained from a product of general formula (XVI):



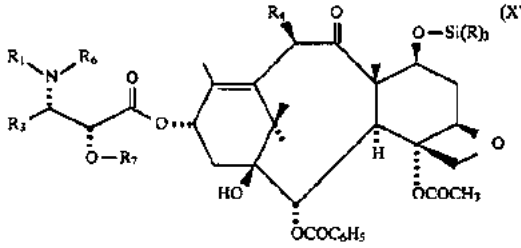
(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):



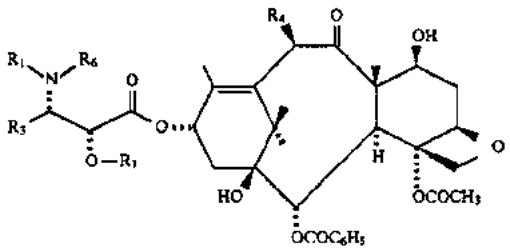
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):

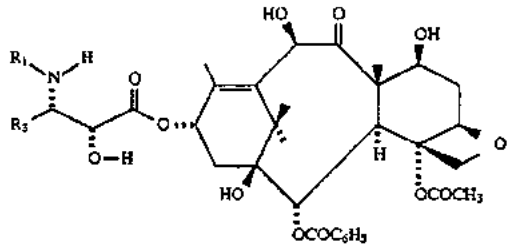


(XIX)

which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

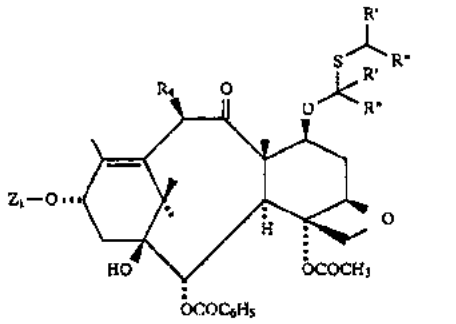
The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336,841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):



(XX)

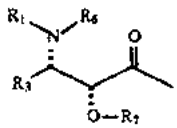
in which R_1 and R_3 are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):



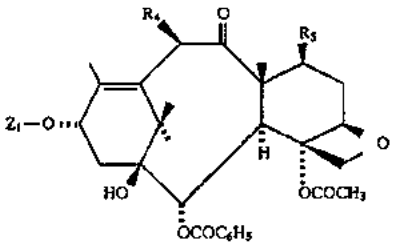
(XXI)

in which R_4 is defined as above and R' and R", which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of general formula (XXII):



(XXII)

in which R_1, R_3, R_6 and R_7 are defined as above, and, to obtain a product of general formula (XXIII):

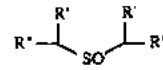


(XXIII)

followed, when Z_1 represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by R_6 and/or R_6 and R_7 by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from −10° to 60° C.

According to the invention, the product of general formula (XXI) in which Z_1 and R_4 are defined as above may be obtained by the action of a sulphoxide of general formula (XXIV):



(XXIV)

in which R' and R" are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50° C., and preferably at about 25° C.

The new products of general formula (I) obtained by carrying out the processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M. L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765–768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501–503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 2 cm^3 of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 10:90 to 40:60 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$ with a few drops of CD_3OD-d_4; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.63 (s, 3H: CH_3); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; CH_2 at position 6); 1.78 (unres. comp., 3H: CH_3); 2.02 and 2.15 (2 dd, J=14 and 9, 1H each: CH_2 at position 14); 2.14 (s, 3H: CH_3); 3.22 and 3.35 (2 s, 3H each: OCH_3); 3.64 (d, J=7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: $ArOCH_3$); 4.06 and 4.16 (2 d, J=8.5, 1H each; CH_2 at position 20); 4.53 (d, J=5, 1H: H at position 2'); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J=10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J=7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J=8, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to OCH_3); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.58 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 7.96 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 cm^3 of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0° C. for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 cm^3 of dichloromethane and 5 cm^3 of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 cm^3 of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatog-

raphy [12 Merck preparative silica gel $60F_{254}$ plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40° C., 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

optical rotation $[\alpha]_{20}^{D}$=−32.9 (c=0.5; methanol)

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.39 (s, 9H: $C(CH_3)_3$); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: CH_3); 1.82 and 2.72 (2 mts, 1H each: CH_2 at position 6); 1.91 (s, 3H: CH_3); 2.31 (limiting AB, 2H: CH_2 at position 14); 2.39 (s, 3H: $COCH_3$); 3.33 and 3.48 (2 s, 3H each: OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: H 3); 3.88 (dd, J=11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J=10, 1H: H at position 5); 5.30 (broad d, J=10, 11H: H at position 3'); 5.47 (d, J=10, 1H: CONH); 5.66 (d, J=7, 1H: H at position 2); 6.24 (broad t, J=9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene in 5 cm^3 of iodomethane and 0.5 cm^3 of dimethylformamide. After 45 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 50 cm^3 of ethyl acetate and 8 cm^3 of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene were thereby obtained in the form of a pale yellow solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; with a few drops of CD_3OD-d_4, chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: CH_3); 1.11 (s, 3H: CH_3); 1.65 (s, 3H: CH_3); 1.72 and 2.67 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.21 (limiting AB, J=14 and 9, 2H: CH_2 at position 14); 2.25 (s, 3H: $COCH_3$); 3.26 and 3.40 (2 s, 3H each: OCH_3); 3.85 (d, J=7, 1H: H at position 3); 3.89 (dd, J=11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.78 (broad t, J=9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.53 (d, J=7, 1H: H at position 2); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.56 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.05 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyoxy)-11-taxene in 30 cm^3 of dichloromethane. After 48 hours at a temperature in the region of 20° C., the reaction mixture was poured into a suspension of 100 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 cm^3 of dichloromethane and then twice 80 cm^3 of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm: coupling constants J in Hz): 1.10 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.48 (d, J=8.5, 1H: OH at position 13); 1.70 (s, 3H: CH_3); 1.81 and 2.61 (2 mts, 1H each: CH_2 at position 6); 2.09 (d, J=5, 1H: OH at position 7); 2.11 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J=9, 2H: CH_2 at position 14); 3.48 (s, 3H: OCH_3); 3.97 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J=10, 1H: H at position 5); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl) baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-

bis(triethylsilyloxy)-11-taxene in 25 cm^3 of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0° C., and then for 5 hours 30 minutes at a temperature in the region of 20° C. The reaction mixture was cooled again to a temperature in the region of 0° C., and 125 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise. After 1 hour at 20° C. and then 18 hours at 5° C., the reaction mixture was diluted by adding 50 cm^3 of dichloromethane and poured into 50 cm^3 of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 cm^3 of dichloroemethane, and the organic phases were then combined, washed with 10 cm^3 of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 5.15 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063–0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^1H NMR spectrum (600 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl CH_2); 0.97 and 1.04 (2 t, J=7.5, 9H each: ethyl CH_3); 1.15 (s, 3H: CH_3); 1.18 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: CH_3); 1.89 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.04 (s, 3H: CH_3); 2.15 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.29 (s, 3H: $COCH_3$); 3.40 (s, 3H: OCH_3); 3.83 (d, J=7, 1H: H: H at position 13); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 7, 1H: H at position 7); 4.91 (s 1H: H at position 10); 4.96 (broad d, J=10, 1H at position 5); 5.01 (broad t, J=9, 1H: H at position 13); 5.62 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 cm^3 of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetylbaccatin III) in 50 cm^3 of anhydrous pyridine. After 17 hours at a temperature in the region of 20° C., the reaction mixture was brought to a temperature in the region of 115° C. and 10.8 cm^3 of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115° C., the reaction mixture was brought back to a temperature in the region of 20° C. and diluted with 30 cm^3 of ethyl acetate and 100 cm^3 of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 cm^3 of ethyl acetate. The organic phases were combined, washed with 50 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063–0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.08 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.91 and 2.57 (2 mts, 1H each: CH_2 at position 2); 2.04 (s, 3H: CH_3); 2.12 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.88 (d, J=7, 1H: H at position 3); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.27 (d, J=1, 1H: OH at position 10); 4.40 (dd, J=11 and 7, 1H: H at position 7); 4.95 (broad d, J=10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13): 5.16 (d, J=1, 1H: H at position 10); 5.60 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 2

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 cm^3 of a 0.1N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20° C. and then for 80 hours at 4° C., and 20 cm^3 of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 cm^3 of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates is 20×20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 cm^3 of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. A white foam was obtained, which was repurified according to the same technique [3 plates; 20×20×1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)]. 205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

optical rotation: $[\alpha]_{20}^{D}$=−33 (c=0.5; methanol).

^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: —CH_3); 1.25 (s, 3H: —CH_3); 1.39 [s, 9H: —$C(CH_3)_3$]; 1.70 (s, 1H: —OH at position 1); 1.75 (s, 3H: —CH_3); 1.82 and 2.72 (2 mts, 1H each: —CH_2 at position 6); 1.91 (s, 3H: —CH_3);

2.31 (limiting AB, 2H: —CH_2 at position 14); 2.39 (s, 3H: —$COCH_3$); 3.33 and 3.48 (2 s, 3H each: —OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: —H at position 3); 3.88 (dd, J=11 and 7, 1H: —H at position 7); 4.20 and 4.33 (2d, J=8.5, 1H each: —CH_2 at position 20); 4.65 (mt, 1H: —H at position 2'); 4.83 (s, 1H: —H at position 10); 5.00 (broad d, J=10, 1H: —H at position 5); 5.30 (broad d, J=10, 1H: —H at position 3'); 5.47 (d, J=10, 1H: —CONH—); 5.66 (d, J=7, 1H: —H at position 2); 6.24 (broad t, J=9, 1H: —H at position 13); from 7.30 to 7.50 (mt, 5H: —C_6H_5 at position 3'); 7.52 [t, J=7.5, 2H: —$OCOC_6H_5$ (—H at position 3 and H at position 5)]; 7.63 [t, J=7.5, 1H: —$OCOC_6H_5$ (—H at position 4)]; 8.12 [d, J=7.5, 2H: —$OCOC_6H_5$ (—H at position 2 and H at position 6)].

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 cm³ of an ethanolic suspension of activated nickel according to Raney (obtained from 80 cm³ of the approximately 50% commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 cm³ of distilled water and with 5 times 100 cm³ of ethanol) were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm³ of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20° C. and then filtered through sintered glass. The sintered glass was washed with 4 times 80 cm³ of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-cm³ fractions. Fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 350 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxy-phenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 cm³ of acetic acid and 7.55 cm³ of acetic anhydride were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 cm³ of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20° C., and then poured into a mixture of 500 cm³ of distilled water and 250 cm³ of dichloromethane. 30 cm³ of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with twice 250 cm³ of dichloromethane. The organic phases were combined, washed with 250 cm³ of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063–0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-cm³ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 1.25 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 cm³ of methanol and 100 cm³ of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60° C., and 10 g of powdered zinc were then added. The reaction mixture was then stirred for 15 minutes at 60° C., thereafter cooled to a temperature in the region of 20° C. and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 cm³ of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 50 cm³ of ethyl acetate and 25 cm³ of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 cm³ of saturated aqueous sodium hydrogen carbonate solution and with 25 cm³ of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy-carbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

EXAMPLE 3

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 135 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 1 cm³ of anhydrous toluene. The suspension obtained was stirred at

a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: Merck preparative silica gel 60F_{254} plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

^{1}H NMR spectrum (600 MHz; $CDCl_3$; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: $C(CH_3)_3$); 1.19 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.27 (t, J=7, 3H: ethyl CH_3); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: CH_3); 1.68 (s, 3H: CH_2); 1.77 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.86 (s, 3H: $COCH_3$); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.27 (s, 3H: OCH_3); 3.45 and 3.68 (2 mts, 1H each: ethyl CH_2); 3.76 (d, J=7, 1H: H3); 3.81 (s, 3H: $ArOCH_3$); 3.85 (dd, J=11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.58 (d, J=4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.46 (d, J=4.5, 1H: H at position 3'); 5.60 (d, J=7 Hz, 1H: H2); 6.13 (broad t, J=9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.50 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ H at the meta position); 7.59 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm^3 of ethyl acetate and 0.004 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel 60F_{254} plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.32 (t, J=7, 3H: ethyl CH_3); 1.38 (s, 9H: $C(CH_3)_3$); 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H; CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each ethyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 cm^3 of iodomethane and 1 cm^3 of dimethylformamide After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 6 cm^3 of distilled water and 8 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$ with the addition of a few drops of CD_3OD-d_4; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: CH_3); 1.09 (s, 3H: CH_3); 1.22 (t, J=7, 3H: ethyl CH_3); 1.62 (s, 3H: CH_3); 1.68 and 2.66 (2 mts, 1H each: CH_26); 2.03 (s, 3H, CH_3); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.23 (s, 3H: $COCH_3$); 3.23 (s, 3H: OCH_3); from 3.40 to 3.65 (mt, 2H: ethyl CH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.88 (dd, J=10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J=8.5, 1H each: CH_2 20); 4.75 (broad t, J=9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J=10, 1H: H at position 5); 5.51 (d, J=7.5, 1H: H at position 2); 7.42 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position);

7.53 (t, J=7.5, 1H: $OCOC_6H_5$ at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 21 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 40 cm^3 of dichloromethane and poured into a suspension of 40 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$: chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: ethyl CH_3); 1.38 (d, J=9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: CH_3); 1.82 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.02 (d, J=5, 1H: OH at position 13); 2.08 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$),; 2.32 (d, J=9, 2H: CH_2 at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl OCH_2); 3.98 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5 Hz, 1H each: $CH_2$20); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J=10 and 1.5, 1H: H at position 5); 5.05 (s, 1H: H at position 10); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.2 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

^1H NMR spectrum (400 MHz, $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl CH_2); 0.97 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.13 (s, 3H: CH_3); 1.20 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: CH_3 of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: CH_3); 1.89 and 2.58 (2 mts, 1H each: CH_2 at position 2); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.53 (mt, 2H: CH_2 of ethoxy at position 10); 3.84 (d, J=7, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5), 5.01 (s, 1H: H at position 10); 5.61 (d, J=7, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20° C. to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through

cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 84.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.97 (t, J=7, 3H: propyl CH_3); 1.07 (s, 9H: $C(CH_3)_3$); 1.19 (s, 6H: CH_3); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central CH_2 of propyl); 1.60 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.78 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.82 (unres. comp. 3H: $COCH_3$); 2.07 and 2.19 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.26 (s, 3H: OCH_3); 3.30 and 3.58 (2 mts, 1H each: propyl OCH_2); 3.73 (d, J=7.5, 1H: H at position 3); 3.81 (s, 3H: $ArOCH_3$); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.57 (d, J=4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J=7.5, 1H: H at position 2); 6.13 (broad t, J=9, 1H: H at position 13); 6.40 (spread unres. comp 1H: H at position 5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ meta H); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm^3 of ethyl acetate and 0.0071 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 27 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R ,3S)-3tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate were obtained in the form of a white foam, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.99 (t, J=7, 3H: propyl CH_3); 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central CH_2 of propyl); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H: CH_2 at position 14): 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.36 and 3.64 (2 mts, 1H each: propyl OCH_2); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J=7.5, Hz, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-7β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 165 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene in 1.7 cm^3 of iodomethane and 1 cm^3 of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 5 cm^3 of distilled water and 7 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 cm^3 of distilled water and then 7 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 117.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl) oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.98 (t, J=7, 3H: propyl CH_3); 1.05 (s, 3H: CH_3), 1.19 (s, 3H: CH_3); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: CH_2 at position 6); 1.72 (s, 3H: CH_3); 2.10 (s, 3H: CH_3); from 2.05 to 2.35 (mt, 2H: CH_2 at position 14); 2.28 (s, 3H: $COCH_3$); 3.32 (s, 3H: OCH_3); 3.45 and 3.65 (2 mts, 1H each: propyl OCH_2); 3.92 (d, J=7.5, 1H: H3); 3.93 (dd, J=11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J=10, 1H: H at position 5); 5.60 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.11 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 585 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis

(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 24 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 30 cm^3 of dichloromethane and poured into a suspension of 30 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J=7, 3H: propyl CH_3); 1.06 (s, 3H: CH_3); 1.22 (s, 3H: CH_3); 1.45 (d, J=7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); 1.67 (s, 3H: CH_3); 1.83 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: CH_2 at position 4); 2.28 (s, 3H: $COCH_3$); 3.40 and 3.57 (2 mts, 1H each: propyl OCH_2); 3.97 (d, J=7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J=10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J=7.5, 1H: H at position 2); 7.50 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.00 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethyl-silyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis (triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz); 0.57 and 0.70 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 0.94 (t, J=7.5, 3H: propyl CH_3); 1.14 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.67 (s, 3H: CH_3); 1.69 (mt, 2H: central CH_2 of propyl); 1.88 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.40 (mt, 2H: propyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.44 (dd, J=11 and 6.5, 1H: H at position 7); 4.96 (broad d, J=10 Hz, 1H: H5); 4.97 (s, 1H: H 10), 4.99 (broad t, J=9 Hz, 1H: H at position 13); 5.62 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared

according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained.

For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to 100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

The example which follows illustrates a composition according to the invention.

EXAMPLE

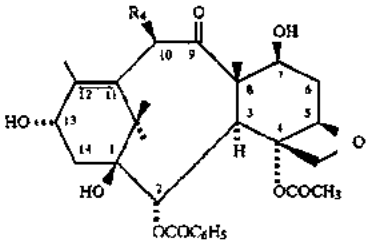
40 mg of the product obtained in Example 1 are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

We claim:

1. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

3. A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):



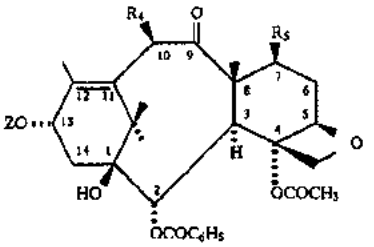
(XIV)

wherein R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

with a compound of the formula (XV):

$$R'_5—X_2 \quad (XV)$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and X_2 represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

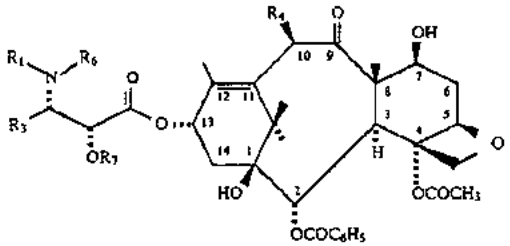
wherein Z is hydrogen, R_4 is as defined above, and R_5 is identical to R'_5 as defined above.

4. A method comprising the step of reacting a product of the formula (XV):

$$R'_5—X_2 \quad (XV)$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, and X_2 represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

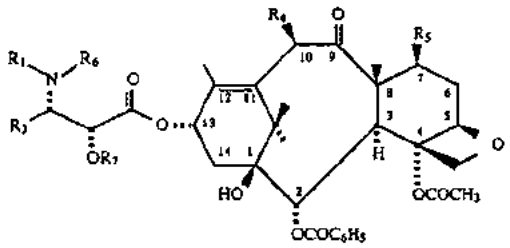
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

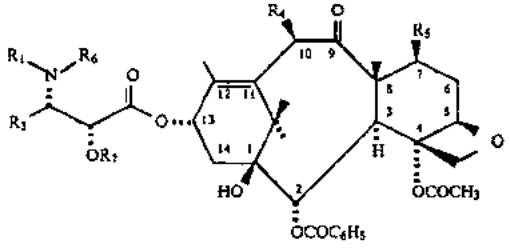
either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to form a compound of the formula (V):



wherein R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and R_1, R_2, R_4, R_6, and R_7 are as defined above.

5. A method comprising the step of replacing with hydrogen atom(s) group(s) R_6 and R_7 in a compound of the formula (V):



wherein:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

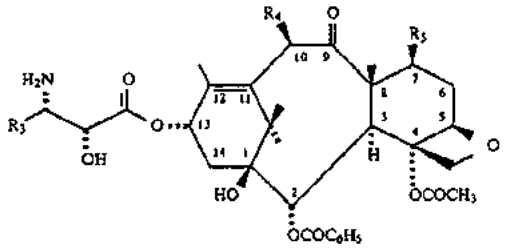
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, optionally in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein R_3, R_4, and R_5 are as defined above.

6. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-

taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

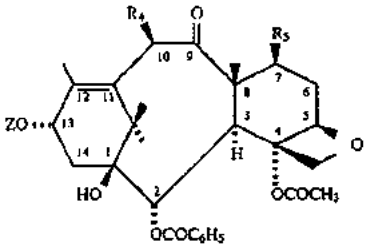
7. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tertbutoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

(c) reacting the product obtained in (b) with an acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

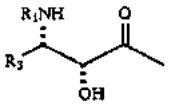
8. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

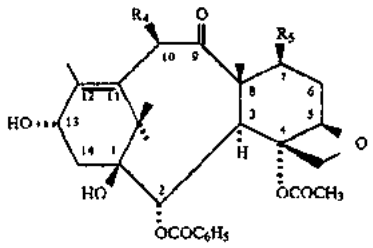
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

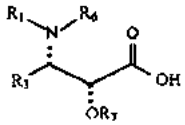
esterifying a product of formula (III):



(III)

in which R_4 and R_5 are defined as above

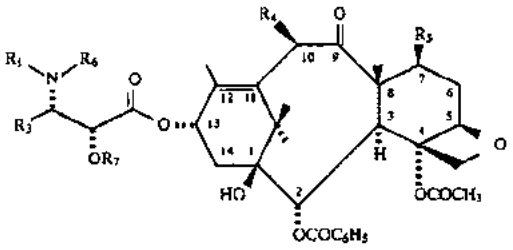
with an acid of formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or

with a derivative of said acid, to obtain an ester of formula (V):

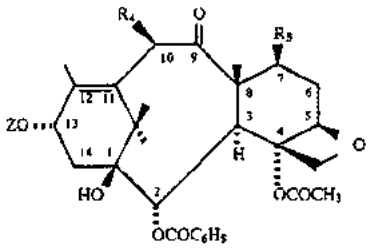


(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, and

replacing the protective group(s) of said ester of formula (V), represented by R_7 or R_6 and R_7 together, by hydrogen atoms.

9. A process for preparing a new taxoid of the following formula (I):



(I)

in which:

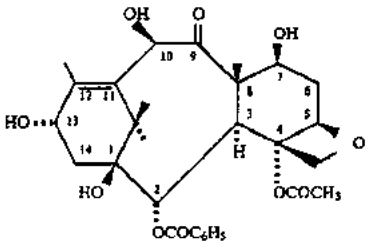
Z represents a hydrogen atom,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating 10-deacetylbaccatin III of formula (IX):

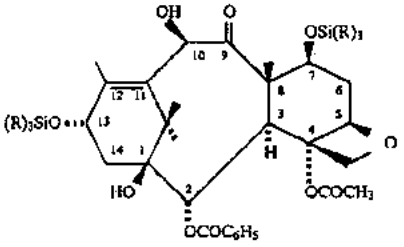


(IX)

with a silyl halide of formula:

$$(R)_3—Si—Hal \quad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



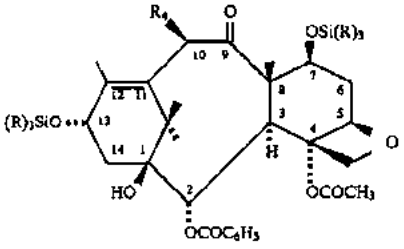
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4—X_1 \quad (XII)$$

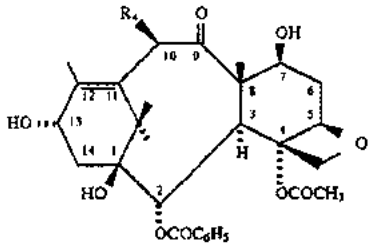
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined above and X_1 represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):



(XIII)

in which R and R_4 are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):



(XIV)

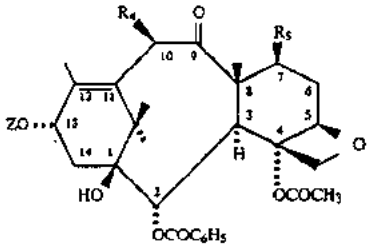
in which R_4 is defined as above, and

etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

in which R'_5 represents a radical such that R'_5—O is identical to R_5 defined as above and X_2 represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

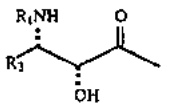
10. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

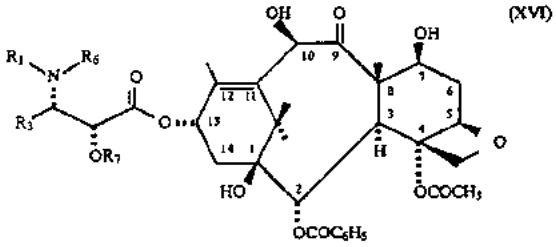
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating a product of formula (XVI):

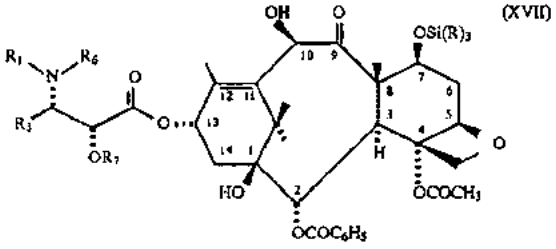


(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, with a product of formula (X):

(X)

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



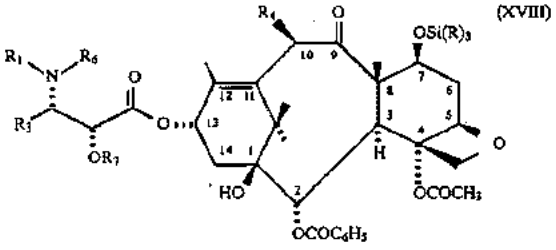
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:

(XII)

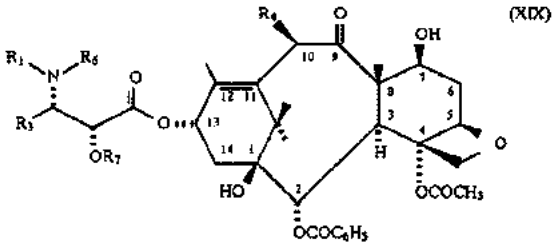
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined as above and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

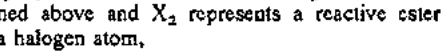
in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



(XIX)

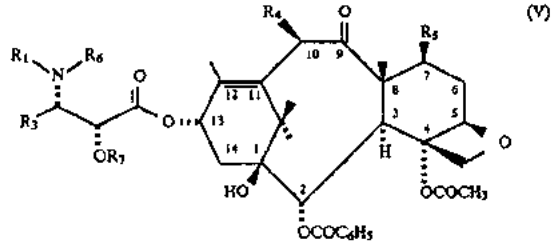
in which R_1, R_3, R_4, R_6 and R_7 are defined as above which, when reacted with a product of formula (XV):



(XV)

in which R'_5 represents a radical such that R'_5O is identical to R_5 defined above and X_2 represents a reactive ester residue or a halogen atom,

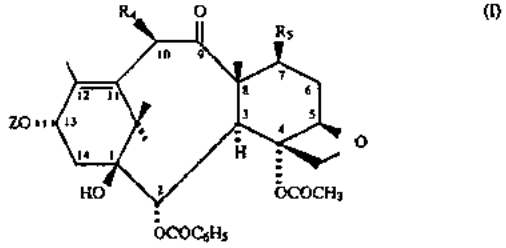
yields the product of formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

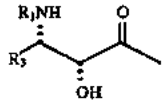
11. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an

alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

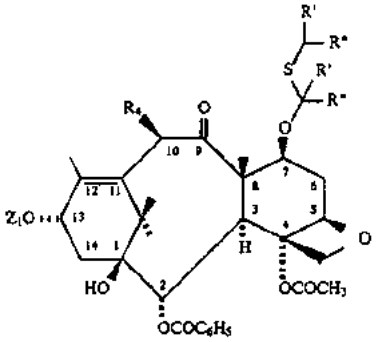
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

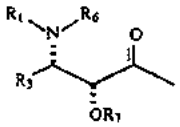
said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):



(XXI)

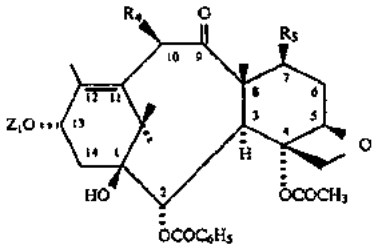
in which R_4 is defined as above, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of formula (XXII):



(XXII)

in which R_1 and R_3 are defined as above and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, to obtain a product of formula (XXIII):



(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 together by hydrogen atoms under the following conditions:

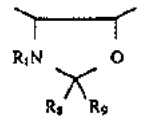
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation, or

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

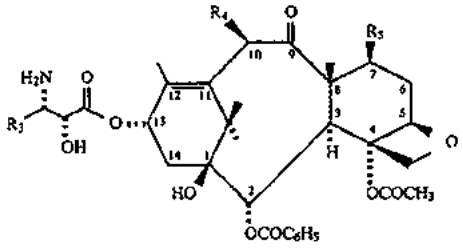
alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

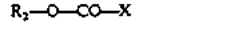
alternatively R_8 and R_9 together form a 4- to 7-membered ring, said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



(VII)

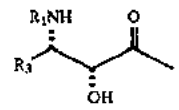
in which R_3, R_4 and R_5 are defined as in claim 1, and acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):



(VII)

in which R_2 is defined as above and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

or

b) R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O—CO— in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

said replacing of the protective group formed by R_6 and R_7 together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from −10° to 60° C.

12. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from −10° to 90° C.

13. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0° to 90° C.

14. A process according to claim 8, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0° to 80° C.

15. A process according to claim 8, further comprising replacing the protective group(s) R_7 or R_6 and R_7 together by hydrogen atoms, wherein:

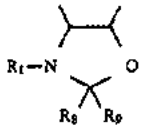
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI).



(VI)

in which R^1 is defined as in claim 8 and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

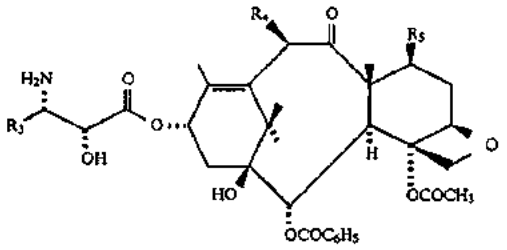
alternatively R_8 and R_9 together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9 which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_6 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, and optionally, in an organic solvent, to obtain the product of formula (VII):



(VII)

in which

R_3, R_4 and R_5 are defined in claim 8, and

said product of formula (VII) is acylated with benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):

$$R_2—O—CO—X \quad \text{(VIII)}$$

in which R_2 is defined in claim 8 and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O—CO— in which R_2 is defined as above, R_6 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

the protective group formed by R_6 and R_7 is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C.

16. A process according to claim 15, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9 which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

17. A process according to claim 15, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

18. A process according to claim 15, wherein said temperature ranges from 15° to 30° C.

19. A process according to claim 15, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

20. A process according to claim 15, wherein said trihalomethyl radical is trichloromethyl.

21. A process according to claim 15, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

22. A process according to claim 7, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170
DATED : Dec. 8, 1998
INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete " , ";

Claim 4, Column 30, Line 63, after "chain", insert –and–;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert –(V)--;

Claim 8, Column 33, Line 34, "(1)" should read –(I);

Claim 11, Column 42, Line 66, "nitrites" should read –nitriles–;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles–;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R_9", insert –,–;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 2 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 45, Line 34, "R6" should read --R_6--.

Signed and Sealed this

Seventh Day of September, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

exhibit 2

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 3

Patent #: 5847170 **Issue Dt:** 12/08/1998 **Application #:** 08622011 **Filing Dt:** 03/26/1996

Inventors: HERVE BOUCHARD, JEAN-DOMINIQUE BOURZAT, ALAIN COMMERCON

Title: NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM

Assignment: 1

Reel/Frame: 007959/0343 **Recorded:** 05/24/1996 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: BOUCHARD, HERVE **Exec Dt:** 04/24/1996

BOURZAT, JEAN-DOMINIQUE **Exec Dt:** 05/02/1996

COMMERCON, ALAIN **Exec Dt:** 05/02/1996

Assignee: RHONE-POULENC RORER, S.A.
20, AVENUE RAYMOND ARON
ANTONY CEDEX, FRANCE 92165

Correspondent: FINNEGAN, HENDERSON, FARABOW ET AL.
THALIA V. WARNEMENT
1300 I STREET, N.W.
WASHINGTON, D.C. 20005

Assignment: 2

Reel/Frame: 011641/0962 **Recorded:** 06/07/2001 **Pages:** 17

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: RHONE-POULENC RORER S.A. **Exec Dt:** 12/20/1999

Assignee: AVENTIS PHARMA S.A.
20 AVENUE RAYMOND ARON
ANTONY, FRANCE 92160

Correspondent: AVENTIS PHARMACEUTICALS INC.
GERALD V. DAHLING
ROUTE 202-206/ P.O. BOX 6800
BRIDGEWATER, NJ 08807-0800

Assignment: 3

Reel/Frame: 011566/0692 **Recorded:** 02/28/2001 **Pages:** 11

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: RHONE-POULENC RORER S.A. **Exec Dt:** 01/31/2001

Assignee: AVENTIS PHARMA S.A.
20 AVENUE RAYMOND ARON
ANTONY CEDEX, FRANCE F-921

Correspondent: FINNEGAN, HENDERSON, FARABOW ET AL
CAROL P. EINAUDI
1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

exhibit 3

sanofi aventis

Because health matters

John D. CONWAY, Esq.
Vice President and Global Head
Innovative Healthcare Patent Support

Aventis Pharma S.A.
20 Avenue Raymond Aron
Antony, FRANCE 92160

Re : Application for Extension of U.S. Patent No. 5,847,170

To Whom It May Concern:

On behalf of sanofi-aventis U.S. LLC, Marketing Applicant for New Drug Application No. 201023 for JEVTANA® (cabazitaxel) Injection, I hereby authorize the patent owner of record, Aventis Pharma S.A., in connection with its application for extension of U.S. Patent No. 5,847,170, to rely upon the activities of sanofi-aventis U.S. LLC, and its predecessors and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No.201023. Sanofi-aventis U.S. LLC is an affiliate of Aventis Pharma S.A. and henceforth the activities of the marketing applicant are permitted under the patent.

Sincerely yours,

Aug 4 2010
Date

John D. Conway
Vice President and Global Head
Innovative Healthcare Patent Support
sanofi-aventis U.S. LLC
1041 Route 202-206
Bridgewater, NJ 08807

exhibit 4

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/622,011	03/26/1996	HERVE BOUCHARD	3806.0367-00

CONFIRMATION NO. 1663

POA ACCEPTANCE LETTER

5487
ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

Date Mailed: 07/13/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/02/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/stlam/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/82 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REVOCATION OF POWER OF ATTORNEY WITH NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	08/622011
Filing Date	March 26, 1996
First Named Inventor	Hervé BOUCHARD et al.
Art Unit	1612
Examiner Name	TRINH, Bak
Attorney Docket Number	ST95019G1 US NP

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☑ I hereby appoint the practitioners associated with the Customer Number: **005487**

☑ Please change the correspondence address for the above-identified application to:

☑ The address associated with Customer Number: **005487**

OR

☐ Firm *or* Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature			
Name	Joslane Mesller		
Date	2nd July 2010	Telephone	+ 33 1 55 71 12559

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PTO/SB/96 (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owners: **BOUCHARD, Hervé, et al.**

Application No./Patent No.: **08/622011** Filed/Issue Date: **March 26, 1996**

Titled: **NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

Aventis Pharma S.A. (Name of Assignee), a **corporation** (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel , Frame , or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: **Inventors** To: **Rhone-Poulenc Rorer S.A.**
The document was recorded in the United States Patent and Trademark Office at
Reel **007959** Frame **0343** or for which a copy thereof is attached

2. From: **Rhone-Poulenc Rorer S.A.** To: **Aventis Pharma S.A.**
The document was recorded in the United States Patent and Trademark Office at
Reel **011641** Frame **0962** or for which a copy thereof is attached

3. From: To:
The document was recorded in the United States Patent and Trademark Office at
Reel Frame or for which a copy thereof is attached

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — 2nd July 2010 (Date)

Josiane Merlier (Printed or Typed Name) — **Director, Patent Administration** (Title)

Exhibit 5

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023 **NDA APPROVAL**

sanofi-aventis U.S., LLC
c/o sanofi-aventis U.S., Inc.
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, NJ 08807

Attention: Linda M. Gustavson
Director, U.S., Associate Therapeutics Head, Oncology

Dear Ms. Gustavson:

Please refer to your New Drug Application (NDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL.

We acknowledge receipt of your submissions dated April 16 (2), May 5, 7, 10, 18, 21, 24, 25 (2), 28, June 1, 4 (2), 8, 14, 16, and 17, 2010.

This new drug application provides for the use of Jevtana® (cabazitaxel) Injection in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 201023.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Jevtana® (cabazitaxel) Injection was not referred to an FDA advisory committee because taking this NDA to an advisory committee would result in a several month delay in making this advance in prostate cancer therapy available to patients for whom there is currently no available therapy.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since prostate cancer does not occur in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of intravenous infusion of particulate matter into the blood stream.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risk(s).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1649-1:
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated pre-mix. Conduct a study to provide data which address particulate nucleation and kinetic factors of precipitation in the pre-mix. Conduct this study using multiple samples drawn from multiple batches so as to more fully support an in-use life of the pre-mix.

Study considerations include (but are not necessarily limited to); interior surface properties of the container closure (e.g., treatments, roughness, scratches, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, syringe use, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the pre-mix solution (e.g., 1 to 4 hours).

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible, in the final report.

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content, in the final report.

The timetable you submitted on June 16, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2010
Study Completion Date:	March 2011
Final Report Submission:	June 2011

PMR 1649-2:
To evaluate the potential for a serious risk of intravenous infusion of particulate matter into the blood stream, it is necessary to better understand and characterize the supersaturated infusion solution. Conduct a study which addresses particulate nucleation and kinetic factors of precipitation from the infusion solution. Conduct this study using multiple samples drawn for at least three additional batches in the containers (bags and sets) which you propose to label for this use so as to more fully support an in-use life of the infusion solution.

Study factors include (but are not necessarily limited to); interior surface properties of the container (e.g., treatments, roughness, plasticizers, etc.), initial mixing agitation force (vigorous shaking), physical shock on standing (e.g., vigorous shaking during in-use storage), needle sticks, temperature (and temperature changes during in-use storage), and additional time point sampling beyond the proposed duration of in-use storage of the infusion solution.

Collect and provide photographs of the precipitate as it appears in the container and isolated photomicrographs of the particles, as feasible, for each observed precipitation or evidence of precipitation (e.g., clogged filters, impeded infusion flow, etc.), in the final report.

Provide by mass balance, the mass of precipitated drug as precipitated mass and as mass percent of the total cabazitaxel content in the final report.

The timetable you submitted on June 16, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2010
Study Completion Date:	March 2011
Final Report Submission:	June 2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks of the unusually high incidence and severity of the entire toxicity spectrum observed in your Phase 3 Jevtana® (cabazitaxel) Injection trial in metastatic hormone refractory prostate cancer, with special concern for neutropenia, febrile neutropenia, infection, diarrhea, renal and cardiac toxicities and the increased incidence of drug-related death. A lower Jevtana® (cabazitaxel) Injection dose may be equally effective with less toxicity. We have also determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signals of the serious risks of hepatic impairment, Q-T prolongation and drug-drug interaction with Jevtana® (cabazitaxel) Injection.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1649-3:
Conduct a Phase 3 randomized controlled trial in patients with hormone-refractory metastatic prostate cancer comparing 75 mg/m^2 docetaxel with prednisone with cabazitaxel 25 mg/m^2 with prednisone and cabazitaxel 20 mg/m^2 with prednisone as first-line therapy. The primary endpoint should be overall survival to evaluate the incidence of drug-related death as well as efficacy. The trial should be powered to detect a 25% difference in overall survival. The trial will include interim analyses for evaluation of efficacy based on overall survival and safety of the 25 mg/m^2 with prednisone arm versus the 20 mg/m^2 with prednisone arm to potentially drop one of the cabazitaxel arms. Submit the protocol for agency review prior to commencing the trial.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2010
Trial Completion Date:	December 2017
Final Report Submission:	June 2018

PMR 1649-4:
Conduct a Phase 3 randomized controlled trial in 1222 patients with hormone-refractory metastatic prostate cancer **previously treated** with docetaxel comparing cabazitaxel 20 mg/m^2 with prednisone versus cabazitaxel 25 mg/m^2 with prednisone and powered to preserve 50% of the treatment effect of cabazitaxel 25 mg/m^2. The study will include interim analyses for evaluation of drug-related deaths and safety as well as overall survival of the cabazitaxel 25 mg/m^2 with prednisone arm versus the cabazitaxel 20 mg/m^2 with prednisone arm to potentially discontinue the trial. Submit the protocol for agency review prior to commencing the trial.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2010
Trial Completion Date:	September 2017
Final Report Submission:	June 2018

PMR 1649-5:
Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel to cause QTc interval prolongation in patients.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2010
Trial Completion Date:	December 2011
Final Report Submission:	June 2012

PMR 1649-6:
Conduct the trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2010
Trial Completion Date:	May 2012
Final Report Submission:	November 2012

PMR 1649-7:
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in cancer patients.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2010
Trial Completion Date:	April 2012
Final Report Submission:	December 2012

PMR 1649-8:
Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in cancer patients.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2010
Trial Completion Date:	April 2012
Final Report Submission:	December 2012

PMR 1649-9:
Organize a group of renal experts to review and analyze renal toxicity from all currently available cabazitaxel clinical trials to identify etiologies and to provide recommendations for toxicity mitigation by patient selection or other measures and for trials needed to delineate the mechanism of toxicity. This group's findings and recommendations should be submitted within 9 months of the cabazitaxel approval date.

Final Report Submission Date: March 2011

PMR 1649-10:
Submit integrated analyses of renal toxicity from two randomized trials in patients with metastatic hormone refractory prostate cancer every 6 months for 3 years from the initiation of the clinical trial. These trials have been described in PMR 1649-3 and PMR 1649-4.

The timetable you submitted on June 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2010
Interim Report Submission:	May 2011
	November 2011
	May 2012
	November 2012
	May 2013
Final Report Submission:	November 2013

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Based on the available primary and supportive drug substance stability data, an 18-month retest date for the drug substance is granted when stored under the long term storage conditions of 5° C.

Based on the provided stability data, an 18-month expiration dating period for the drug product is granted when stored under the following long term storage conditions:

- Store at 25° C (77° F); excursion permitted between 15° C – 30° C (59° F – 86° F)
- Do not refrigerate

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JEVTANA safely and effectively. See full prescribing information for JEVTANA.

JEVTANA (cabazitaxel) Injection, 60 mg/1.5 mL, for intravenous infusion only
Initial U.S. Approval: 2010

WARNING

See full prescribing information for complete boxed warning.

- **Neutropenic deaths have been reported. Obtain frequent blood counts to monitor for neutropenia. Do not give JEVTANA if neutrophil counts are ≤1,500 cells/mm³. (2.2)(4)**
- **Severe hypersensitivity can occur and may include generalized rash/erythema, hypotension and bronchospasm. Discontinue JEVTANA immediately if severe reactions occur and administer appropriate therapy. (2.3)(5.2)**
- **Contraindicated if history of severe hypersensitivity reactions to JEVTANA or to drugs formulated with polysorbate 80. (4)**

----------INDICATIONS AND USAGE----------

JEVTANA is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. (1)

----------DOSAGE AND ADMINISTRATION----------

Recommended dose: JEVTANA 25 mg/m² administered every three weeks as a one-hour intravenous infusion in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment. (2.1)

- JEVTANA requires two dilutions prior to administration (2.5)
- Use the **entire** contents of the accompanying diluent to achieve a concentration of 10 mg/mL JEVTANA. (2.5)
- PVC equipment should not be used (2.5)
- **Premedication Regimen**: Administer intravenously 30 minutes before each dose of JEVTANA:
  - Antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent antihistamine)
  - Corticosteroid (dexamethasone 8 mg or equivalent steroid)
  - H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist) (2.3)

  Antiemetic prophylaxis (oral or intravenous) is recommended as needed. (2.3)
- **Dosage Modifications**: See full prescribing information (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Single use vial 60 mg/1.5 mL, supplied with diluent (5.7 mL) for JEVTANA (3)

----------CONTRAINDICATIONS----------

- Neutrophil counts of ≤1,500/mm³ (2.2)(4)
- History of severe hypersensitivity to JEVTANA or polysorbate 80 (4)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia, febrile neutropenia: Neutropenic deaths have been reported. Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features. (2.2)(4)(5.1)
- Hypersensitivity: Severe hypersensitivity reactions can occur. Premedicate with corticosteroids and H2 antagonists. Discontinue infusion immediately if hypersensitivity is observed and treat as indicated. (4)(5.2)
- Gastrointestinal symptoms (nausea, vomiting, diarrhea): Mortality related to diarrhea has been reported. Rehydrate and treat with anti-emetics and anti-diarrheals as needed. If experiencing Grade ≥ 3 diarrhea, dosage should be modified. (2.2)(5.3)
- Renal failure, including cases with fatal outcomes, has been reported. Identify cause and manage aggressively. (5.4)
- Elderly patients: Patients ≥ 65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely (5.5)(6)(8.5).
- Hepatic impairment: Patients with impaired hepatic function were excluded from the randomized clinical trial. Hepatic impairment is likely to increase the cabazitaxel concentrations. JEVTANA should not be given to patients with hepatic impairment. (5.6)(8.7)
- JEVTANA can cause fetal harm when administered to a pregnant woman. (5.7)(8.1)

----------ADVERSE REACTIONS----------

Most common all grades adverse reactions (≥10%) are neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Use with caution in patients taking concomitant medicines that induce or inhibit CYP3A. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2010

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FULL PRESCRIBING INFORMATION

WARNING

Neutropenic deaths have been reported. In order to monitor the occurrence of neutropenia, frequent blood cell counts should be performed on all patients receiving JEVTANA. JEVTANA should not be given to patients with neutrophil counts of ≤1,500 cells/mm^3.

Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy *[see Warnings and Precautions (5.2)]*. Patients should receive premedication *[see Dosage and Administrations (2.3)]*. JEVTANA must not be given to patients who have a history of severe hypersensitivity reactions to JEVTANA or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

JEVTANA® is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

- The individual dosage of JEVTANA is based on calculation of the Body Surface Area (BSA) and is 25 mg/m^2 administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment.
- Premedication is recommended prior to treatment *[see Dosage and Administration (2.3)]*.
- JEVTANA should be administered under the supervision of a qualified physician experienced in the use of antineoplastic medicinal products. Appropriate management of complications is possible only when the adequate diagnostic and treatment facilities are readily available.
- JEVTANA Injection single-use vial requires two dilutions prior to administration *[see Dosage and Administration (2.5)]*.
- Do not use PVC infusion containers and polyurethane infusions sets for preparation and administration of JEVTANA infusion solution *[see Dosage and Administration (2.5)]*.
- Both the JEVTANA Injection and the diluent vials contain an overfill to compensate for liquid loss during preparation.

2.2 Dose Modifications

The JEVTANA dose should be reduced to 20 mg/m^2 if patients experience the following adverse reactions.

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA

Toxicity	Dosage Modification
Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF	Delay treatment until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Febrile neutropenia	Delay treatment until improvement or resolution, and until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA to 20 mg/m^2.

Discontinue JEVTANA treatment if a patient continues to experience any of these reactions at 20 mg/m^2.

2.3 Premedication

Premedicate at least 30 minutes prior to each dose of JEVTANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed.

2.4 Administration Precautions

JEVTANA is a cytotoxic anticancer drug and caution should be exercised when handling and preparing JEVTANA solutions, taking into account the use of containment devices, personal protective equipment (e.g., gloves), and preparation procedures. Please refer to *Handling and Disposal (16.3)*.

If JEVTANA Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

If JEVTANA Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water.

2.5 Instructions for Preparation

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of JEVTANA infusion solution.

Read this entire section carefully before mixing and diluting. JEVTANA requires **two** dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the JEVTANA Injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL JEVTANA.

The following two-step dilution process must be carried out under aseptic conditions to prepare the second (final) infusion solution.

Set aside the JEVTANA Injection and supplied diluent vials. The JEVTANA Injection is a clear yellow to brownish-yellow viscous solution, if appropriately stored.

Step 1 – First Dilution

Each vial of JEVTANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the **entire contents** of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEVTANA.

When transferring the diluent, direct the needle onto the inside wall of JEVTANA vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted JEVTANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

Step 2 – Second (Final) Dilution

Withdraw the recommended dose from the JEVTANA solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of JEVTANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

JEVTANA should not be mixed with any other drugs.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

JEVTANA final infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion) or within a total of 24 hours if refrigerated (including the one-hour infusion).

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the JEVTANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

Discard any unused portion.

2.6 Administration

The final JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

Use an in-line filter of 0.22 micrometer nominal pore size during administration.

The final JEVTANA infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions, i.e., 8 hours under ambient conditions (including the one-hour infusion) or for a total of 24 hours if refrigerated (including the one-hour infusion) *[see Dosage and Administration (2.5)]*.

3 DOSAGE FORMS AND STRENGTHS

JEVTANA (cabazitaxel) Injection 60 mg/1.5 mL is supplied as a kit consisting of the following:

- JEVTANA Injection 60 mg/1.5 mL: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80,
- Diluent for JEVTANA Injection 60 mg/1.5 mL: contains approximately 5.7 mL of 13% (w/w) ethanol in water for injection.

4 CONTRAINDICATIONS

JEVTANA should not be used in patients with neutrophil counts of $\leq 1,500/mm^3$.

JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection.

G-CSF may be administered to reduce the risks of neutropenia complications associated with JEVTANA use. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications.

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed *[see Dosage and Administration (2.2)]*.

JEVTANA should not be administered to patients with neutrophils $\leq 1,500/mm^3$ *[see Contraindications (4)]*.

If a patient experiences febrile neutropenia or prolonged neutropenia (greater than one week) despite appropriate medication (e.g., G-CSF), the dose of JEVTANA should be reduced *[see Dosage and Administration (2.2)]*. Patients can restart treatment with JEVTANA only when neutrophil counts recover to a level $> 1,500/mm^3$ *[see Contraindications (4)]*.

5.2 Hypersensitivity Reactions

All patients should be premedicated prior to the initiation of the infusion of JEVTANA *[see Dosage and Administration (2.3)]*. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. Patients with a history of severe hypersensitivity reactions should not be re-challenged with JEVTANA *[see Contraindications (4)]*.

5.3 Gastrointestinal Symptoms

Nausea, vomiting and severe diarrhea, at times, may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trial. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Patients should be treated with

rehydration, anti-diarrheal or anti-emetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥ 3 diarrhea *[see Dosage and Administration (2.2)]*.

5.4 Renal Failure

Renal failure, including four cases with fatal outcome, was reported in the randomized clinical trial. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy *[see Adverse Reactions (6.1)]*. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.5 Elderly Patients

In the randomized clinical trial, 3 of 131 (2%) patients < 65 years of age and 15 of 240 (6%) ≥ 65 years of age died of causes other than disease progression within 30 days of the last cabazitaxel dose. Patients ≥ 65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia *[see Adverse Reactions (6) and Use in Specific Populations (8.5)]*.

5.6 Hepatic Impairment

No dedicated hepatic impairment trial for JEVTANA has been conducted. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 × ULN) were excluded from the randomized clinical trial.

Cabazitaxel is extensively metabolized in the liver, and hepatic impairment is likely to increase cabazitaxel concentrations.

Hepatic impairment increases the risk of severe and life-threatening complications in patients receiving other drugs belonging to the same class as JEVTANA. JEVTANA should not be given to patients with hepatic impairment (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 × ULN).

5.7 Pregnancy

Pregnancy category D.

JEVTANA can cause fetal harm when administered to a pregnant woman. In non-clinical studies in rats and rabbits, cabazitaxel was embryotoxic, fetotoxic, and abortifacient at exposures significantly lower than those expected at the recommended human dose level.

There are no adequate and well-controlled studies in pregnant women using JEVTANA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with JEVTANA *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Neutropenia *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.
- Gastrointestinal Symptoms *[see Warnings and Precautions (5.3)]*.
- Renal Failure *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with hormone-refractory metastatic prostate cancer treated in a single randomized trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥ 10%) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysguesia, cough, arthralgia, and alopecia.

The most common (≥ 5%) grade 3-4 adverse reactions in patients who received JEVTANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received JEVTANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEVTANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVTANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2 – Incidence of Reported Adverse Reactions[1] and Hematologic Abnormalities in ≥ 5% of Patients Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone

	JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Any Adverse Reaction				
Blood and Lymphatic System Disorders				
Neutropenia[2]	347 (94%)	303 (82%)	325 (87%)	215 (58%)
Febrile Neutropenia	27 (7%)	27 (7%)	5 (1%)	5 (1%)
Anemia[2]	361 (98%)	39 (11%)	302 (82%)	18 (5%)
Leukopenia[2]	355 (96%)	253 (69%)	343 (93%)	157 (42%)
Thrombocytopenia[2]	176 (48%)	15 (4%)	160 (43%)	6 (2%)
Cardiac Disorders				
Arrhythmia[3]	18 (5%)	4 (1%)	6 (2%)	1 (< 1%)
Gastrointestinal Disorders				
Diarrhea	173 (47%)	23 (6%)	39 (11%)	1 (< 1%)
Nausea	127 (34%)	7 (2%)	85 (23%)	1 (< 1%)
Vomiting	83 (22%)	6 (2%)	38 (10%)	0
Constipation	76 (20%)	4 (1%)	57 (15%)	2 (< 1%)
Abdominal Pain[4]	64 (17%)	7 (2%)	23 (6%)	0
Dyspepsia[5]	36 (10%)	0	9 (2%)	0
General Disorders and Administration Site Conditions				
Fatigue	136 (37%)	18 (5%)	102 (27%)	11 (3%)
Asthenia	76 (20%)	17 (5%)	46 (12%)	9 (2%)
Pyrexia	45 (12%)	4 (1%)	23 (6%)	1 (< 1%)
Peripheral Edema	34 (9%)	2 (< 1%)	34 (9%)	2 (< 1%)
Mucosal Inflammation	22 (6%)	1 (< 1%)	10 (3%)	1 (< 1%)
Pain	20 (5%)	4 (1%)	18 (5%)	7 (2%)
Infections and Infestations				
Urinary Tract Infection[6]	29 (8%)	6 (2%)	12 (3%)	4 (1%)
Investigations				
Weight Decreased	32 (9%)	0	28 (8%)	1 (< 1%)
Metabolism and Nutrition Disorders				
Anorexia	59 (16%)	3 (< 1%)	39 (11%)	3 (< 1%)
Dehydration	18 (5%)	8 (2%)	10 (3%)	3 (< 1%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	60 (16%)	14 (4%)	45 (12%)	11 (3%)
Arthralgia	39 (11%)	4 (1%)	31 (8%)	4 (1%)
Muscle Spasms	27 (7%)	0	10 (3%)	0
Nervous System Disorders				
Peripheral Neuropathy[7]	50 (13%)	3 (< 1%)	12 (3.2%)	3 (< 1%)
Dysgeusia	41 (11%)	0	15 (4%)	0
Dizziness	30 (8%)	0	21 (6%)	2 (< 1%)
Headache	28 (8%)	0	19 (5%)	0
Renal and Urinary Tract Disorders				
Hematuria	62 (17%)	7 (2%)	13 (4%)	1 (< 1%)

Dysuria	25 (7%)	0	5 (1%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	43 (12%)	4 (1%)	16 (4%)	2 (< 1%)
Cough	40 (11%)	0	22 (6%)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	37 (10%)	0	18 (5%)	0
Vascular Disorders				
Hypotension	20 (5%)	2 (<1 %)	9 (2%)	1 (< 1%)
Median Duration of Treatment	6 cycles		4 cycles	

[1]Graded using NCI CTCAE version 3
[2]Based on laboratory values, cabazitaxel: n =369, mitoxantrone: n = 370.
[3]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
[4]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
[5]Includes gastroesophageal reflux disease and reflux gastritis.
[6]Includes urinary tract infection enterococcal and urinary tract infection fungal.
[7]Includes peripheral motor neuropathy and peripheral sensory neuropathy.

Neutropenia and Associated Clinical Events:

Five patients experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%).

Hematuria:

Adverse events of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥ 2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.

Hepatic Laboratory Abnormalities:

The incidences of grade 3-4 increased AST, increased ALT, and increased bilirubin were each ≤ 1%.

Elderly Population:

The following grade 1-4 adverse reactions were reported at rates ≥ 5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40% vs. 30%), neutropenia (97% vs. 89%), asthenia (24% vs. 15%), pyrexia (15% vs. 8%), dizziness (10% vs. 5%), urinary tract infection (10% vs. 3%) and dehydration (7% vs. 2%), respectively.

The incidence of the following grade 3-4 adverse reactions were higher in patients ≥ 65 years of age compared to younger patients; neutropenia (87% vs. 74%), and febrile neutropenia (8% vs. 6%) *[see Use in Specific Populations (8.5)]*.

7 DRUG INTERACTIONS

No formal clinical drug-drug interaction trials have been conducted with JEVTANA.

Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.

7.1 Drugs That May Increase Cabazitaxel Plasma Concentrations

CYP3A4 Inhibitors: Cabazitaxel is primarily metabolized through CYP3A *[see Clinical Pharmacology (12.3)]*. Though no formal drug interaction trials have been conducted for JEVTANA, concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) is expected to increase concentrations of cabazitaxel. Therefore, co-administration with strong CYP3A inhibitors should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

7.2 Drugs That May Decrease Cabazitaxel Plasma Concentrations

CYP3A4 Inducers: Though no formal drug interaction trials have been conducted for JEVTANA, the concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) is expected to decrease cabazitaxel concentrations. Therefore, co-administration with strong CYP3A inducers should be avoided. In addition, patients should also refrain from taking St. John's Wort.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category D. See 'Warnings and Precautions' section.

JEVTANA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of JEVTANA in pregnant women.

Non-clinical studies in rats and rabbits have shown that cabazitaxel is embryotoxic, fetotoxic, and abortifacient. Cabazitaxel was shown to cross the placenta barrier within 24 hours of a single intravenous administration of a 0.08 mg/kg dose (approximately 0.02 times the maximum recommended human dose-MRHD) to pregnant rats at gestational day 17.

Cabazitaxel administered once daily to female rats during organogenesis at a dose of 0.16 mg/kg/day (approximately 0.02-0.06 times the Cmax in patients with cancer at the recommended human dose) caused maternal and embryofetal toxicity consisting of increased post-implantation loss, embryolethality, and fetal deaths. Decreased mean fetal birth weight associated with delays in skeletal ossification were observed at doses $\geq$ 0.08 mg/kg (approximately 0.02 times the Cmax at the MRHD). *In utero* exposure to cabazitaxel did not

result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking JEVTANA.

8.3 Nursing Mothers

Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats. It is not known whether this drug is excreted in human milk. Within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the maximum recommended human dose), radioactivity related to cabazitaxel was detected in the stomachs of nursing pups. This was detectable for up to 24 hours post-dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from JEVTANA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of JEVTANA in pediatric patients have not been established.

8.5 Geriatric Use

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients < 65 years (n=100) and older (n=70).

Of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of neutropenia, fatigue, asthenia, pyrexia, dizziness, urinary tract infection and dehydration occurred at rates ≥ 5% higher in patients who were 65 years of age or greater compared to younger patients *[see Adverse Reactions (6.1)]*.

8.6 Renal Impairment

No dedicated renal impairment trial for JEVTANA has been conducted. Based on the population pharmacokinetic analysis, no significant difference in clearance was observed in patients with mild (50 mL/min ≤ creatinine clearance (CLcr) < 80 mL/min) and moderate renal impairment (30 mL/min ≤ CLcr < 50 mL/min). No data are available for patients with severe renal impairment or end-stage renal disease *[see Clinical Pharmacology (12.3)]*. Caution should be used in patients with severe renal impairment (CLcr < 30 mL/min) and patients with end-stage renal diseases.

8.7 Hepatic Impairment

No dedicated hepatic impairment trial for JEVTANA has been conducted. The safety of JEVTANA has not been evaluated in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.

As cabazitaxel is extensively metabolized in the liver, hepatic impairment is likely to increase the cabazitaxel concentrations. Patients with impaired hepatic function (total bilirubin ≥ ULN, or AST and/or ALT ≥ 1.5 × ULN) were excluded from the randomized clinical trial.

10 OVERDOSAGE

There is no known antidote for JEVTANA overdose. Anticipated complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders.

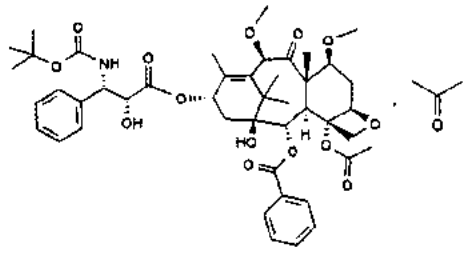
In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

11 DESCRIPTION

JEVTANA (cabazitaxel) is an antineoplastic agent belonging to the taxane class. It is prepared by semi-synthesis with a precursor extracted from yew needles.

The chemical name of cabazitaxel is (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one(1:1).

Cabazitaxel has the following structural formula:



Cabazitaxel is a white to off-white powder with a molecular formula of $C_{45}H_{57}NO_{14}\cdot C_3H_6O$ and a molecular weight of 894.01 (for the acetone solvate) / 835.93 (for the solvent free). It is lipophilic, practically insoluble in water and soluble in alcohol.

JEVTANA (cabazitaxel) Injection 60 mg/1.5 mL is a sterile, non-pyrogenic, clear yellow to brownish-yellow viscous solution and is available in single-use vials containing 60 mg cabazitaxel (anhydrous and solvent free) and 1.56 g polysorbate 80. Each mL contains 40 mg cabazitaxel (anhydrous) and 1.04 g polysorbate 80.

DILUENT for JEVTANA is a clear, colorless, sterile, and non-pyrogenic solution containing 13% (w/w) ethanol in water for injection, approximately 5.7 mL.

JEVTANA requires two dilutions prior to intravenous infusion. JEVTANA injection should be diluted only with the supplied DILUENT for JEVTANA, followed by dilution in either 0.9% sodium chloride solution or 5% dextrose solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cabazitaxel is a microtubule inhibitor. Cabazitaxel binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

12.2 Pharmacodynamics

Cabazitaxel demonstrated antitumor activity against advanced human tumors xenografted in mice. Cabazitaxel is active in docetaxel-sensitive tumors. In addition, cabazitaxel demonstrated activity in tumor models insensitive to chemotherapy including docetaxel.

12.3 Pharmacokinetics

A population pharmacokinetic analysis was conducted in 170 patients with solid tumors at doses ranging from 10 to 30 mg/m^2 weekly or every three weeks.

Absorption

Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m^2 every three weeks, the mean C_{max} in patients with metastatic prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the one-hour infusion (T_{max}). The mean AUC in patients with metastatic prostate cancer was 991 ng•h/mL (CV 34%).

No major deviation from the dose proportionality was observed from 10 to 30 mg/m^2 in patients with advanced solid tumors.

Distribution

The volume of distribution (V_{ss}) was 4,864 L (2,643 L/m^2 for a patient with a median BSA of 1.84 m^2) at steady state.

In vitro, the binding of cabazitaxel to human serum proteins was 89 to 92% and was not saturable up to 50,000 ng/mL, which covers the maximum concentration observed in clinical trials. Cabazitaxel is mainly bound to human serum albumin (82%) and lipoproteins (88% for HDL, 70% for LDL, and 56% for VLDL). The *in vitro* blood-to-plasma concentration ratio in human blood ranged from 0.90 to 0.99, indicating that cabazitaxel was equally distributed between blood and plasma.

Metabolism

Cabazitaxel is extensively metabolized in the liver (> 95%), mainly by the CYP3A4/5 isoenzyme (80% to 90%), and to a lesser extent by CYP2C8. Cabazitaxel is the main circulating moiety in human plasma. Seven metabolites were detected in plasma (including the 3 active metabolites issued from O-demethylation), with the main one accounting for 5% of cabazitaxel exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and feces.

Based on *in vitro* studies, the potential for cabazitaxel to inhibit drugs that are substrates of other CYP isoenzymes (1A2,-2B6,-2C9, -2C8, -2C19, -2E1, -2D6, and 3A4/5) is low. In addition, cabazitaxel did not induce CYP isozymes *in vitro*.

Elimination

After a one-hour intravenous infusion [^{14}C]-cabazitaxel 25 mg/m^2, approximately 80% of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the feces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel and metabolites account for 3.7% of the dose (2.3% as unchanged drug in urine).

Based on the population pharmacokinetic analysis, cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%; 26.4 L/h/m^2 for a patient with a median BSA of 1.84 m^2) in patients with metastatic prostate cancer. Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic model with α-, β-, and γ-half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Renal Impairment

Cabazitaxel is minimally excreted via the kidney. No formal pharmacokinetic trials have been conducted with cabazitaxel in patients with renal impairment. The population pharmacokinetic analysis carried out in 170 patients including 14 patients with moderate renal impairment (30 mL/min $\leq$ CLcr < 50 mL/min) and 59 patients with mild renal impairment (50 mL/min $\leq$ CLcr < 80 mL/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. No data are available for patients with severe renal impairment or end-stage renal disease *[see Use in Special Populations (8.6)]*.

Hepatic Impairment

No formal trials in patients with hepatic impairment have been conducted. As cabazitaxel is extensively metabolized in the liver, hepatic impairment is likely to increase the cabazitaxel concentrations *[see Warnings and Precautions (5.6), and Use in Special Populations (8.7)]*.

Drug interactions

As cabazitaxel is mainly metabolized by CYP3A *in vitro*, strong CYP3A inducers or inhibitors are expected to affect the pharmacokinetics of cabazitaxel.

Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.

In vitro, cabazitaxel did not inhibit the multidrug-resistance protein 1 (MRP1) or 2 (MRP2). *In vitro* cabazitaxel inhibited the transport of P-gp and BRCP, at concentrations at least 38 fold what is observed in clinical settings. Therefore, the *in vivo* risk of cabazitaxel to inhibit MRPs, P-gp, or BCRP is unlikely at the dose of 25 mg/m^2.

In vitro, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, or BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of cabazitaxel.

Cabazitaxel was positive for clastogenesis in the *in vivo* micronucleus test, inducing an increase of micronuclei in rats at doses ≥ 0.5 mg/kg. Cabazitaxel increased numerical aberrations with or without metabolic activation in an *in vitro* test in human lymphocytes though no induction of structural aberrations was observed. Cabazitaxel did not induce mutations in the bacterial reverse mutation (Ames) test. The positive *in vivo* genotoxicity findings are consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization).

Cabazitaxel may impair fertility in humans. In a fertility study performed in female rats at cabazitaxel doses of 0.05, 0.1, or 0.2 mg/kg/day there was no effect of administration of the drug on mating behavior or the ability to become pregnant. There was an increase in pre-implantation loss at the 0.2 mg/kg/day dose and an increase in early resorptions at doses ≥ 0.1 mg/kg/day (approximately 0.02-0.06 times the human clinical exposure based on Cmax). In multi-cycle studies following the clinically recommended dosing schedule, atrophy of the uterus was observed at the 5 mg/kg dose level (approximately the AUC in patients with cancer at the recommended human dose) along with necrosis of the corpora lutea at doses ≥ 1 mg/kg (approximately 0.2 times the AUC at the clinically recommended human dose).

Cabazitaxel did not affect mating performances or fertility of treated male rats at doses of 0.05, 0.1, or 0.2 mg/kg/day. In multiple-cycle studies following the clinically recommended dosing schedule, however, degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats treated intravenously with cabazitaxel at a dose of 1 mg/kg (approximately 0.2-0.35 times the AUC in patients with cancer at the recommended human dose), and minimal testicular degeneration (minimal epithelial single cell necrosis in epididymis) was observed in

dogs treated with a dose of 0.5 mg/kg (approximately one-tenth of the AUC in patients with cancer at the recommended human dose).

14 CLINICAL STUDIES

The efficacy and safety of JEVTANA in combination with prednisone were evaluated in a randomized, open-label, international, multi-center study in patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

A total of 755 patients were randomized to receive either JEVTANA 25 mg/m^2 intravenously every 3 weeks for a maximum of 10 cycles with prednisone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m^2 intravenously every 3 weeks for 10 cycles with prednisone 10 mg orally daily (n=377) for a maximum of 10 cycles.

This study included patients over 18 years of age with hormone-refractory metastatic prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. Patients had to have neutrophils >1,500 cells/mm^3, platelets > 100,000 cells/mm^3, hemoglobin > 10 g/dL, creatinine < 1.5 x upper limit of normal (ULN), total bilirubin < 1xULN, AST < 1.5 x ULN, and ALT < 1.5 x ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

Demographics, including age, race, and ECOG performance status (0-2) were balanced between the treatment arms. The median age was 68 years (range 46-92) and the racial distribution for all groups was 83.9% Caucasian, 6.9% Asian, 5.3% Black, and 4% Others in the JEVTANA group.

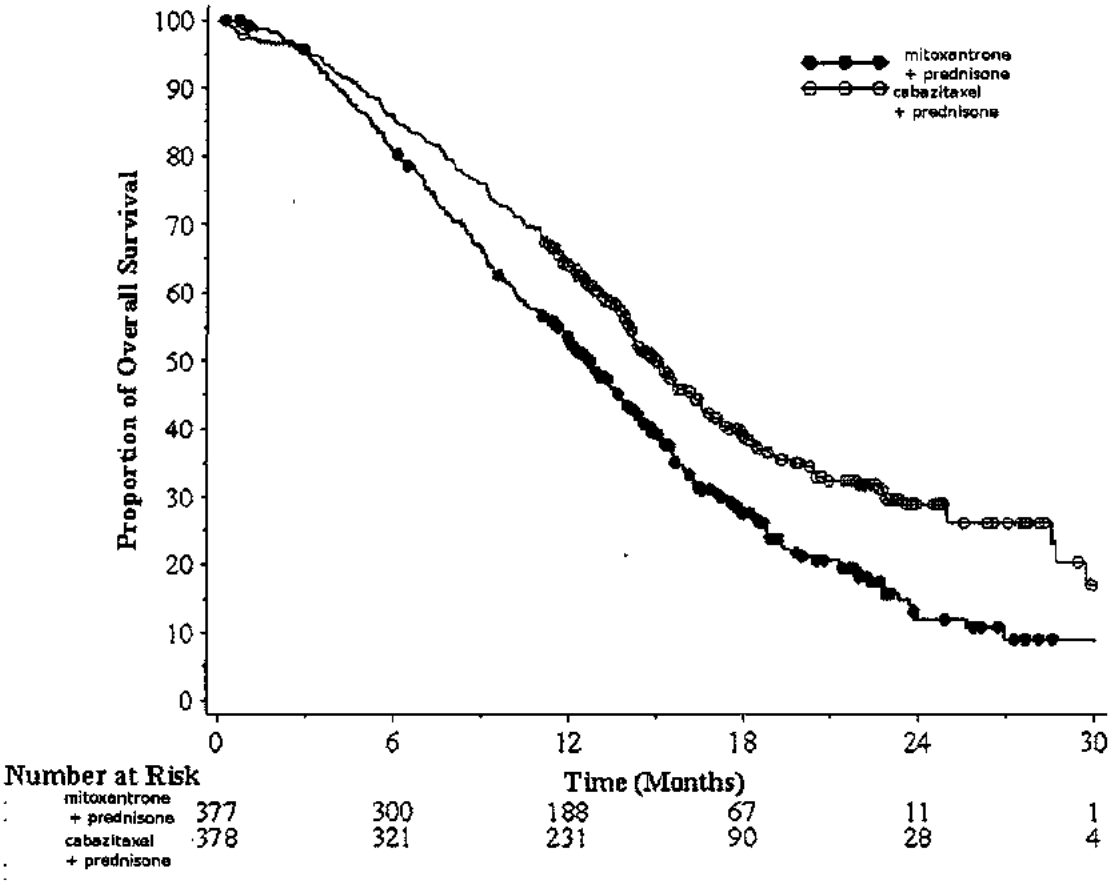
Efficacy results for the JEVTANA arm versus the control arm are summarized in Table 3 and Figure 1.

Table 3 - Efficacy of JEVTANA in the Treatment of Patients with Hormone Refractory Metastatic Prostate Cancer (Intent-to-Treat Analysis)

	JEVTANA + Prednisone n=378	Mitoxantrone + Prednisone n=377
Overall Survival		
Number of deaths (%)	234 (61.9 %)	279 (74%)
Median survival (month) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard Ratio[1] (95% CI)	0.70 (0.59-0.83)	
p-value	<0.0001	

[1]Hazard ratio estimated using Cox model; a hazard ratio of less than 1 favors JEVTANA

Figure 1 - Kaplan-Meier Overall Survival Curves



Investigator-assessed tumor response of 14.4% (95%CI: 9.6-19.3) was higher for patients in the JEVTANA arm compared to 4.4% (95%CI: 1.6-7.2) for patients in the mitoxantrone arm, p=0.0005.

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm 2006; 63:1172-1193.*

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

JEVTANA is supplied as a kit containing one single-use vial of JEVTANA (cabazitaxel) Injection (clear glass vial with a grey rubber closure, aluminum cap and light green plastic flip-off cap) and one vial of Diluent for JEVTANA (13% (w/w) ethanol in water for injection) in a clear glass vial with a grey rubber closure, gold-color aluminum cap and colorless plastic flip-off cap. Both items are in a blister pack in one carton.
NDC 0024-5824-11

16.2 Storage

JEVTANA Injection and Diluent for JEVTANA:
Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).
Do not refrigerate.

Stability of the First Diluted Solution in the Vial:
First diluted solution of JEVTANA should be used immediately (within 30 minutes). Discard any unused portion *[see Dosage and Administration (2.5)]*.

Stability of the Second (Final) Dilution Solution in the Infusion Bag:
Fully prepared JEVTANA infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

In addition, chemical and physical stability of the infusion solution has been demonstrated for 24 hours under refrigerated conditions. As both the first diluted solution and the second (final) infusion solution are supersaturated, the solutions may crystallize over time. If crystals and/or particulates appear, the solutions must not be used and should be discarded *[see Dosage and Administration (2.5)]*.

16.3 Handling and Disposal

Procedures for proper handling and disposal of antineoplastic drugs should be followed. Several guidelines on this subject have been published *[see References (15)]*. Any unused product or waste material should be disposed of in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Educate patients about the risk of potential hypersensitivity associated with JEVTANA. Confirm patients do not have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80. Instruct patients to immediately report signs of a hypersensitivity reaction.
- Explain the importance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever to the treating oncologist.
- Explain that it is important to take the oral prednisone as prescribed. Instruct patients to report if they were not compliant with oral corticosteroid regimen.
- Explain to patients that severe and fatal infections, dehydration, and renal failure have been associated with cabazitaxel exposure. Patients should immediately report fever, significant vomiting or diarrhea, decreased urinary output, and hematuria to the treating oncologist.
- Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to the treating oncologist *[see Drug Interactions (7)]*.
- Inform elderly patients that certain side effects may be more frequent or severe.

Patient Information
JEVTANA® (JEV-TA-NA)
(cabazitaxel)
Injection

Read this Patient Information before you start receiving JEVTANA and each time before you receive your infusion. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about JEVTANA?
JEVTANA may cause serious side effects including:

1. **Low white blood cells**. Low white blood cells can cause you to get serious infections, and may lead to death. People who are 65 years or older may be more likely to have these problems. Your doctor:
    - will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.

- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your doctor decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

Tell your doctor right away if you have any of these symptoms of infection while receiving JEVTANA:

- fever. Take your temperature often during treatment with JEVTANA.
- cough
- burning on urination
- muscle aches

Also, tell your doctor if you have any diarrhea during the time that your white blood cell count is low. Your doctor may prescribe treatment for you as needed.

2. **Severe allergic reactions**. Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your doctor should prescribe medicines before each infusion to help prevent severe allergic reactions.

   Tell your doctor or nurse right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA:

   - rash or itching
   - skin redness
   - feeling dizzy or faint
   - breathing problems
   - chest or throat tightness
   - swelling of face

3. **Gastrointestinal symptoms.** Vomiting and diarrhea can happen when you take JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Tell your doctor if you have vomiting or diarrhea. Your doctor will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA. Tell your doctor if your symptoms get worse or do not get better. You may need to go to the hospital for treatment.

4. **Kidney failure**. Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your doctor will check you for this problem and treat you if needed. Tell your doctor if you develop:

   - swelling of your face or body
   - decrease in the amount of urine that your body makes each day.

What is JEVTANA?
JEVTANA is a prescription anti-cancer medicine used with the steroid medicine prednisone. JEVTANA is used to treat people with prostate cancer that has worsened (progressed) after treatment with other anti-cancer medicines, including docetaxel.

It is not known if JEVTANA is safe and works in children.

Who should not receive JEVTANA?
Do not receive JEVTANA if:

- your white blood cell (neutrophil count) is too low
- you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80. Ask your doctor if you are not sure.

What should I tell my doctor before receiving JEVTANA?
Before receiving JEVTANA, tell your doctor if you:

- had allergic reactions in the past
- have kidney or liver problems
- are over the age of 65
- have any other medical conditions
- if you are a female and:
  - are pregnant or plan to become pregnant. JEVTANA can harm your unborn baby. Talk to your doctor about the best way for you to prevent pregnancy while you are receiving JEVTANA.
  - are breastfeeding or plan to breastfeed. It is not known if JEVTANA passes into your breast milk. You and your doctor should decide if you will take JEVTANA or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your doctor first. Your doctor will tell you if it is safe to take the new medicine with JEVTANA.

How will I receive JEVTANA?

- JEVTANA will be given to you by an intravenous (IV) infusion into your vein.
- Your treatment will take about 1 hour.
- JEVTANA is usually given every 3 weeks. Your doctor will decide how often you will receive JEVTANA.
- Your doctor will also prescribe another medicine called prednisone, for you to take by mouth every day during treatment with JEVTANA. Your doctor will tell you how and when to take your prednisone.

It is important that you take prednisone exactly as prescribed by your doctor. If you forget to take your prednisone, or do not take it on schedule, make sure to tell

your doctor or nurse. Before each infusion of JEVTANA, you may receive other medicines to prevent or treat side effects.

What are the possible side effects of JEVTANA?

JEVTANA may cause serious side effects including:

- **See "What is the most important information I should know about JEVTANA?"**

Common side effects of JEVTANA include:

- **Low red blood cell count** (anemia). Your doctor will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- **Low blood platelet count**. Tell your doctor if you have any unusual bruising or bleeding.

- **tiredness**
- **nausea**
- **constipation**
- **weakness**
- **blood in the urine.** Tell your doctor or nurse if you see blood in your urine.
- **back pain**
- **decreased appetite**
- **fever**
- **shortness of breath**
- **stomach (abdominal) pain**
- **change in your sense of taste**
- **cough**
- **joint pain**
- **hair loss**
- **numbness, tingling, burning or decreased sensation in your hands or feet**

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of JEVTANA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about JEVTANA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

This leaflet summarizes the most important information about JEVTANA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JEVTANA that is written for health professionals.

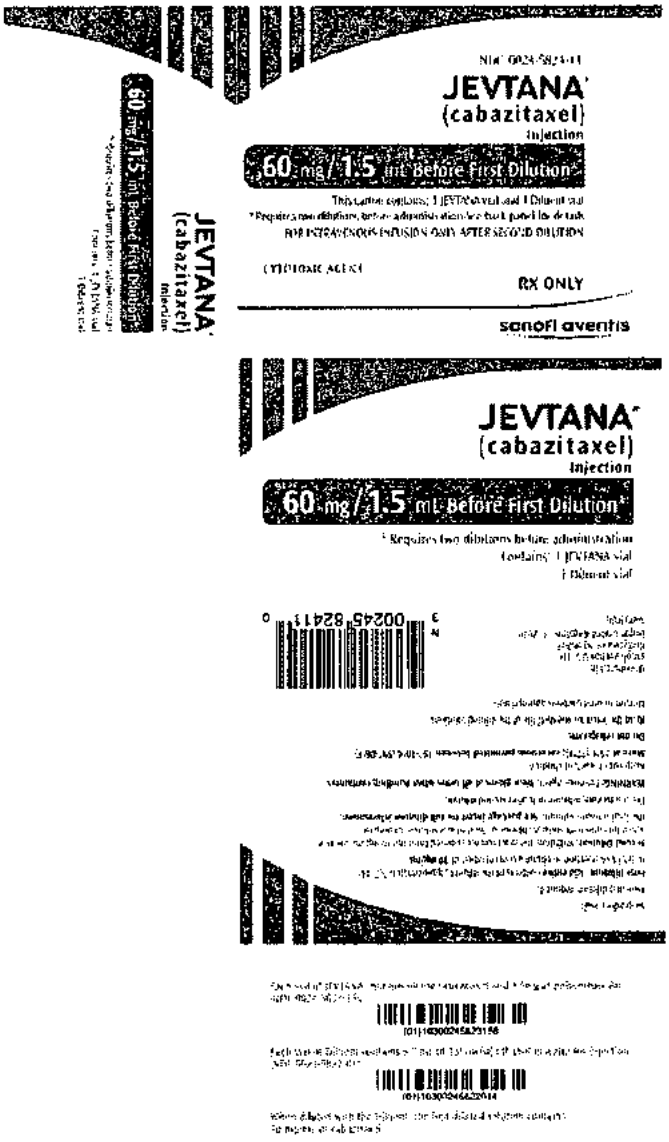
For more information, go to **www.sanofi-aventis.us** or call 1-800-633-1610.

What are the ingredients in JEVTANA?
Active ingredient: cabazitaxel
Inactive ingredient: polysorbate 80

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Issued June 2010

JEVTANA® is a registered trademark of sanofi-aventis



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Artwork created in: Adobe Illustrator CS2, Mac format
Minimum point size of text: 7 pt
Barcode: UPC-A - 300245824110, Pharma - 777
RSS Limited (01)10300245823158, (01)10300245822014
Colors Used: PMS 285 PMS Reflex Blue
sanofi aventis

Batch :
EXP :

File name: Jevtana-60mg/1.5mL-1ct-vial-label-5009366ZD
Revision: D
Date: 6.16.10
Operator: TW
Site/Supplier: Dagenham
Dimensions: 62 mm x 33 mm
Product Desc.: 60mg/1.5mL label, Jevtana
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Minimum point size of text: 6 pt
Barcode: RSS Limited (01)10300245823158
Colors Used: PMS Reflex Blue PMS 116 PMS 186 black
PMS 360

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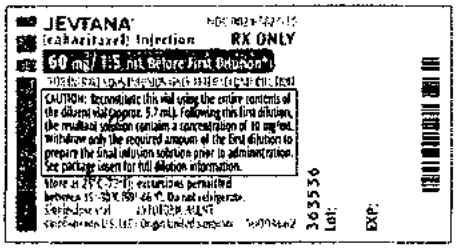

File name: Jevtana-5.7mL-Diluent-1 vial-label-50093661C

Revision: C

Date: 6.16.10

Operator: TW

sanofi aventis

Site/Supplier: Dagenham

Dimensions: 62 mm x 33 mm

Product Desc.: 5.7mL Vial of 13% (w/w) label, Jevtana Diluent

Artwork created in: Adobe Illustrator CS2, Mac format

Minimum point size of text: 6 pt

Barcode: RSS Limited (01)10300245822014

Colors Used: PMS Reflex Blue PMS 145

PMS 369 [illegible]

DILUENT NDC 0024-5822-01

5.7 mL of 13% (w/w) ethanol in water for injection.

Use ONLY for dilution of JEVTANA.

See package insert for full preparation instructions.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). Do not refrigerate.

Single-dose vial.

RX ONLY

sanofi-aventis U.S. LLC / Origin United Kingdom

50093661

363537

Lot:

EXP:

NEPTUNE GENERICS EX. 00136

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
06/17/2010

exhibit 6

COPY

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TOKYO
011 • 813 • 3431 • 6943
BRUSSELS
011 • 322 • 646 • 0353

CERTIFICATE Attorney Docket No. 03806.0367

MAY 24 1999

OF CORRECTION

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

U.S. Patent for Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them

#23 Jones

Inventors: Hervé Bouchard, Jean-Bominique Bourzat, Alain Commerçon

Patent No: 5,847,170 Issued: December 08, 1998

APPROVED
AUG 12 1999
THE COMMISSIONER OF PAT. & T.M.

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. 254 and 37 C.F.R. 1.322, this is a request for the issuance of a Certificate of Correction in the above-identified patent. Two (2) copies of Form PTO 1050 are attached. The complete Certificate of Correction involves ONE (1) page.

The mistakes identified in the attached form occurred through the fault of the Office, as clearly disclosed by the records of the application which matured into this patent. Issuance of the Certificate of Correction containing the correction is earnestly requested.

If it should be determined that any of the mistakes resulted from an error made in good faith by the applicants, then, pursuant to 35 U.S.C. 255 and 37 C.F.R. 1.323, it is requested that a Certificate of Correction be issued correcting such mistakes. Under

such circumstances, it is requested that the fee set forth in 37 C.F.R. 1.20(a) and any additional fees needed, be charge to our Deposit Account No. 06-0916, for which authorization is hereby given.

Respectfully submitted

FINNEGAN, HENDERSON, FARABOW
GARRETT & DUNNER, L.L.P

By: _____
Carol P. Einaudi
Reg. No. 32,220

Dated: **MAY 12, 1999**

Staple Here Only !

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170
DATED : December 08, 1998
INVENTOR(S) : Hervé Bouchard et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete " , "; (Amdt B) Amdt C/CK

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read --(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R_9", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

Claim 15, Column 45, Line 34, "R6" should read --R_6--.

Note

MAILING ADDRESS OF SENDER:

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005

PATENT NO. 5,847,170

No. of addt'l copies @ 60¢ per page

FORM PTO 1050 (Rev. 2-93)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 1 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete " , ";

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read --(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R_9", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 2 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 45, Line 34, "R6" should read --R_8--.

Signed and Sealed this

Seventh Day of September, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer *Acting Commissioner of Patents and Trademarks*

exhibit 7

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1300 I STREET NW
WASHINGTON DC 20005-3315

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,847,170	**$880.00**	**$0.00**	**04/22/02**	**08/622,011**	**12/08/98**	**03/26/96**	**04**	**NO**	**3806.0367-00**

PTOL-439 (Rev. 09/2006)

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,847,170	**$2,300.00**	**$0.00**	**02/14/06**	**08/622,011**	**12/08/98**	**03/26/96**	**08**	**NO**	**3806.0367-00**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,847,170	**$4,110.00**	**$0.00**	**05/12/10**	**08/622,011**	**12/08/98**	**03/26/96**	**12**	**NO**	**AVENTIS PHARMA SA**

PTOL-439 (Rev. 09/2006)

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Patent Bibliographic Data				06/17/2010 06:25 PM	
Patent Number:	5847170		**Application Number:**	08622011	
Issue Date:	12/08/1998		**Filing Date:**	03/26/1996	
Title:	NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINI				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	05/12/2010 02/14/2006 04/22/2002	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	FINNEGAN HENDERSON FARABOW GARRETT AND DUNNER 1300 I STREET NW WASHINGTON, DC 200053315				

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Patent Maintenance Fees			06/17/2010 06:24 PM EDT
Patent Number:	5847170	Application Number:	08622011
Issue Date:	12/08/1998	Filing Date:	03/26/1996
Window Opens:		Surcharge Date:	
Window Closes:		Payment Year:	
Entity Status:	LARGE		
Customer Number:	000000		
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exhibit 8

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 56,999

OCT 6 1998

Rhone Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road, H14- P.O. Box 1200
Collegeville, PA 19426-0107

ATTN: Anne-Margaret Martin
Associate Director, Regulatory Affairs

Dear Ms. Martin:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 56,999

Sponsor: Rhone Poulenc Rorer Pharmaceuticals, Inc.

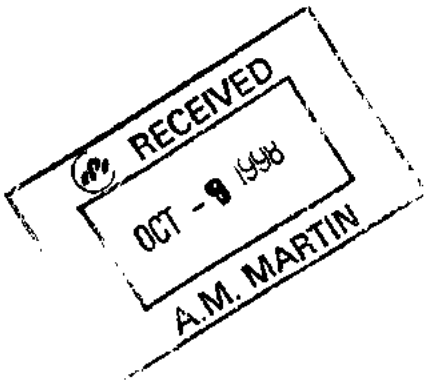
Name of Drug: RPR 116258A

Date of Submission: September 30,1998

Date of Receipt: September 30, 1998

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.


RECEIVED
OCT - 9 1996
A.M. MARTIN

As sponsor of this IND, your are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days of initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

(If via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug Products
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(If via courier)

FDA/CDER
Division of Oncology Drug Products
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Should you have any questions concerning this submission, please contact: Ann Staten
301-594-5770

Sincerely yours,

Ann Staten

Dottie Pease
for Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center of Drug Evaluation and Research

exhibit 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201023

NDA ACKNOWLEDGMENT

sanofi-aventis U.S., LLC
c/o sanofi-aventis U.S., Inc.
200 Crossing Boulevard, Mailstop: BX2-712B
Bridgewater, NJ 08807

RECEIVED
JUN 15 2010
Linda Gustavson, Ph.D., RAC

Attention: Linda M. Gustavson
Director, U.S., Associate Therapeutics Head, Oncology

Dear Ms. Gustavson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL

Date of Application: March 31, 2010

Date of Receipt: March 31, 2010

Our Reference Number: NDA 201023

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY L COTTRELL
06/09/2010

exhibit 10

IND 65,999 History Log

Contact Date	Contact Type	Contact SubType	Suppl./ Serial #	Contact Description
05-DEC-1997	Telephone	Chemistry, Manufacturing and Controls / Other		Contact Report
18-FEB-1998	Fax	Pre-Clinical / Chemistry, Manufacturing and Controls		Contact Report
23-FEB-1998	Fax	Chemistry, Manufacturing and Controls		Presubmission Activity
05-MAY-1998	Fax	Pre-Clinical		Presubmission Activity
13-MAY-1998	Fax	Pre-Clinical		Presubmission Activity
30-JUN-1998	Fax	Pre-Clinical		Presubmission Activity
07-JUL-1998	Fax	Pre-Clinical		Presubmission Activity
07-JUL-1998	Fax	Pre-Clinical		Presubmission Activity
08-JUL-1998	Fax	Pre-Clinical		Presubmission Activity
27-JUL-1998	Submission	Other		Presubmission Activity
28-JUL-1998	Fax	Pre-Clinical		Presubmission Activity
28-JUL-1998	Telephone	Other		Contact Report
30-JUL-1998	Telephone	Other		Contact Report
18-AUG-1998	Submission	Clinical		Presubmission Activity
09-SEP-1998	Fax	Clinical		Presubmission Activity
11-SEP-1998	Telephone	Other		Contact Report
15-SEP-1998	Fax	Clinical		Presubmission Activity
17-SEP-1998	Fax	Pre-Clinical		Presubmission Activity
18-SEP-1998	Fax	Other		Presubmission Activity
25-SEP-1998	Fax	Pre-Clinical		Presubmission Activity
30-SEP-1998	Submission	New Protocol / New Investigator / Chemistry, Manufacturing and Controls	S-000	IND original submission
01-OCT-1998	Telephone	Pre-Clinical		Contact Report
02-OCT-1998	Fax	Pre-Clinical		General Correspondence
06-OCT-1998	Letter	Other		General Correspondence
06-OCT-1998	Letter	Other		General Correspondence
09-OCT-1998	Fax	Other		General

				Correspondence
09-OCT-1998	Submission	Pre-Clinical	S-001	Provide Information
23-OCT-1998	Fax	Chemistry, Manufacturing and Controls / Clinical		General Correspondence
28-OCT-1998	Telephone	Other		Contact Report
29-OCT-1998	Submission	Clinical	S-002	Request information
29-OCT-1998	Submission	Pre-Clinical	S-003	Information amendment
30-OCT-1998	Fax	Pre-Clinical		General Correspondence
04-NOV-1998	Fax	Pre-Clinical		General Correspondence
09-NOV-1998	Fax	Pre-Clinical		General Correspondence
23-NOV-1998	Fax	Clinical		General Correspondence
30-NOV-1998	Submission	Clinical	S-004	IND protocol amendment
01-DEC-1998	Fax	Pre-Clinical		General Correspondence
02-DEC-1998	Fax	Clinical		General Correspondence
02-DEC-1998	Submission	Clinical	S-005	IND protocol amendment
03-DEC-1998	Fax	Clinical		General Correspondence
03-DEC-1998	Submission	Clinical	S-006	IND protocol amendment
09-DEC-1998	Letter	Pre-Clinical		General Correspondence
10-DEC-1998	Letter	Clinical		General Correspondence
10-DEC-1998	Submission	Pre-Clinical	S-007	Information amendment
11-DEC-1998	Submission	Pre-Clinical	S-008	Information amendment
18-DEC-1998	Submission	Clinical / Pre-Clinical	S-009	Provide Information
23-DEC-1998	Letter	Pre-Clinical		General Correspondence
23-DEC-1998	Telephone	Pre-Clinical		Contact Report
29-DEC-1998	Letter	Pre-Clinical		General Correspondence
30-DEC-1998	Letter	Chemistry, Manufacturing and Controls / Pre-Clinical		General Correspondence
07-JAN-1999	Submission	Pre-Clinical	S-010	Response to FDA request
19-JAN-1999	Telephone	Other		Contact Report
20-JAN-1999	Fax	Pre-Clinical		General Correspondence

12-MAR-1999	Submission	Other	S-011	IND Amendment
12-MAR-1999	Telephone	Clinical		Contact Report
07-APR-1999	Submission	Pre-Clinical	S-012	Information amendment
12-APR-1999	Fax	Clinical		General Correspondence
13-APR-1999	Fax	Clinical	S-013	Response to FDA request
13-APR-1999	Submission	Clinical	S-013	Response to FDA request
14-APR-1999	Fax	Clinical		General Correspondence
14-APR-1999	Letter	Clinical		General Correspondence
22-APR-1999	Fax	Pre-Clinical		General Correspondence
28-APR-1999	Fax	Pre-Clinical		General Correspondence
29-APR-1999	Submission	Other / Clinical	S-014	IND protocol amendment
30-APR-1999	Fax	Other		General Correspondence
05-MAY-1999	Fax	Pre-Clinical		General Correspondence
06-MAY-1999	Fax	Pre-Clinical		General Correspondence
14-MAY-1999	Fax	Clinical		General Correspondence
01-JUL-1999	Submission	Pre-Clinical	S-015	Provide Information
02-JUL-1999	Submission	Pharm/Tox	S-016	Information amendment
23-AUG-1999	Submission	Pre-Clinical	S-017	Information amendment
08-SEP-1999	Fax	Pre-Clinical		General Correspondence
09-SEP-1999	Telephone	Pre-Clinical		Contact Report
27-SEP-1999	Submission	Pre-Clinical	S-018	Information amendment
14-DEC-1999	Submission	Other / Pre-Clinical	S-019	Information amendment
22-DEC-1999	Submission	Clinical	S-020	IND protocol amendment
30-DEC-1999	Submission	Annual	S-021	Annual report
30-DEC-1999	Submission	Other	S-023	Provide Information
04-APR-2000	Submission	Adverse Drug Report	S-0026	IND safety report(s)
05-JUN-2000	Submission	Clinical	S-027	IND protocol amendment
23-JUN-2000	Submission	Other	S-028	IND protocol amendment

19-JUL-2000	Submission	Adverse Drug Report / Follow-up	S-0029	IND safety report(s)
07-SEP-2000	Submission	Adverse Drug Report / Follow-up	S-030	IND safety report(s)
29-DEC-2000	Submission	Annual	S-029	Annual report
04-JAN-2001	Submission	Clinical	S-030	IND protocol amendment
08-MAR-2001	Submission	Clinical	s-034	General Correspondence
26-APR-2001	Submission	Clinical	S-035	IND protocol amendment
11-MAY-2001	Submission	Clinical	S-036	IND protocol amendment
11-JUL-2001	Submission	Clinical	S-037	IND protocol amendment
21-DEC-2001	Submission	Annual	S-038	Annual report
05-FEB-2002	Submission	Chemistry, Manufacturing and Controls	S-039	Information amendment
08-FEB-2002	Submission	Clinical	S-040	Information amendment
06-MAR-2002	Submission	Other	S-041	Response to FDA request
12-MAR-2002	Fax	Other	S-041	Contact Report
02-APR-2002	Submission	Chemistry, Manufacturing and Controls	S-042	Response to FDA request
08-APR-2002	Submission	Adverse Drug Report	S-0043	IND safety report(s)
15-APR-2002	Submission	Adverse Drug Report / Follow-up	S-0044	IND safety report(s)
25-APR-2002	Submission	Adverse Drug Report / Follow-up	S-0045	IND safety report(s)
18-JUL-2002	Submission	Clinical	S-047	IND protocol amendment
26-NOV-2002	Submission	Clinical	S-048	IND protocol amendment
26-DEC-2002	Submission	Annual	S-049	Annual report
30-JAN-2003	Submission	Adverse Drug Report	S-0050	IND safety report(s)
19-FEB-2003	Submission	Clinical	S-051	IND protocol amendment
24-FEB-2003	Fax	Adverse Drug Report		IND safety report(s)
05-MAR-2003	Submission	Adverse Drug Report / Follow-up	S-0053	IND safety report(s)
05-MAR-2003	Submission	Adverse Drug Report	S-0052	IND safety report(s)
18-MAR-2003	Submission	Clinical	S-054	IND protocol amendment
09-APR-2003	Submission	Adverse Drug Report / Follow-up	S-0055	IND safety report(s)

30-APR-2003	Submission	Clinical	S-056	IND protocol amendment
15-JUL-2003	Submission	Adverse Drug Report	S-0058	IND safety report(s)
15-JUL-2003	Submission	Clinical	S-057	IND Amendment
04-AUG-2003	Submission	Adverse Drug Report	S-0059	IND safety report(s)
08-AUG-2003	Submission	Other	S-060	IND Amendment
18-AUG-2003	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0061	IND safety report(s)
27-AUG-2003	Fax	Adverse Drug Report		IND safety report(s)
03-SEP-2003	Submission	Adverse Drug Report / Follow-up	S-0062	IND safety report(s)
10-SEP-2003	Submission	Adverse Drug Report	S-0063	IND safety report(s)
29-SEP-2003	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0064	IND safety report(s)
01-OCT-2003	Submission	Clinical	S-065	IND protocol amendment
16-OCT-2003	Fax	Adverse Drug Report / Follow-up		IND safety report(s)
16-OCT-2003	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0066	IND safety report(s)
12-NOV-2003	Submission	Adverse Drug Report	S-0067	IND safety report(s)
20-NOV-2003	Submission	Adverse Drug Report	S-0068	IND safety report(s)
23-DEC-2003	Submission	Annual	S-069	Annual report
21-JAN-2004	Submission	Clinical	S-070	IND protocol amendment
06-MAY-2004	Submission	Clinical	S-071	IND protocol amendment
19-MAY-2004	Submission	Adverse Drug Report	S-0072	IND safety report(s)
01-JUN-2004	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0073	IND safety report(s)
10-JUN-2004	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0074	IND safety report(s)
21-JUN-2004	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0075	IND safety report(s)
27-AUG-2004	Submission	Clinical	S-076	IND protocol amendment
17-DEC-2004	Submission	Annual	S-077	Annual report
21-DEC-2004	Submission	Annual	S-078	Annual report
21-DEC-2004	Telephone			Contact Report

28-JAN-2005	Submission	Clinical	S-079	IND Amendment
26-MAY-2005	Submission	Adverse Drug Report / Follow-up	S-0080	IND safety report(s)
03-JUN-2005	Submission	Adverse Drug Report / Follow-up / Follow-up	S-0081	IND safety report(s)
21-DEC-2005	Submission	Annual	S-082	Annual report
30-JAN-2006	Submission	Other	S-0083	General Correspondence
30-JAN-2006	Submission	Other	S-0084	General Correspondence
05-MAY-2006	Submission	Other	S-0085	General Correspondence
08-MAY-2006	E-mail	Other		General Correspondence
08-MAY-2006	E-mail	Other		General Correspondence
09-MAY-2006	E-mail	Other		General Correspondence
10-MAY-2006	E-mail	Other		General Correspondence
10-MAY-2006	E-mail	Other		General Correspondence
17-MAY-2006	E-mail	Other		General Correspondence
25-MAY-2006	Submission	Other	S-0086	General Correspondence
02-JUN-2006	Submission	Other	S-0087	Investigator Brochure
15-JUN-2006	E-mail	Other		General Correspondence
23-JUN-2006	Telephone	Follow-up		Contact Report
26-JUN-2006	E-mail	Other		General Correspondence
27-JUN-2006	Fax	Other		General Correspondence
28-JUN-2006	E-mail	Other		General Correspondence
29-JUN-2006	E-mail	Other		EOP II meeting
18-JUL-2006	E-mail	Other		General Correspondence
27-JUL-2006	E-mail	Other		General Correspondence
27-JUL-2006	Submission	Other	S-0088	Special Protocol Assessment
09-AUG-2006	Telephone	Other		Contact Report
25-AUG-2006	E-mail	Other		General Correspondence
25-AUG-2006	Submission		S-0089	General Correspondence

11-SEP-2006	E-mail	Clinical		General Correspondence
11-SEP-2006	Letter	Other		General Correspondence
11-SEP-2006	E-mail	Clinical		General Correspondence
14-SEP-2006	Submission	Chemistry, Manufacturing and Controls	S-0090	Information amendment
15-NOV-2006	Submission	Clinical	s-0091	Information amendment
16-NOV-2006	Submission	Change in Protocol	S-092	IND protocol amendment
12-DEC-2006	E-mail	Other		General Correspondence
21-DEC-2006	Submission	Annual	S-0093	Annual report
22-DEC-2006	Submission	Change in Protocol	S-0094	IND protocol amendment
09-FEB-2007	Submission	New Investigator / Other	S-0095	IND protocol amendment
21-MAR-2007	Submission	New Investigator / Other	S-0096	IND protocol amendment
25-APR-2007	Submission	New Investigator / Other	S-0097	IND protocol amendment
29-MAY-2007	Submission	New Investigator	S-098	IND protocol amendment
14-JUN-2007	Submission	Clinical	S-0099	Information amendment
15-JUN-2007	Fax	Adverse Drug Report		IND safety report(s)
25-JUN-2007	Submission	Adverse Drug Report	0101	IND safety report(s)
25-JUN-2007	Submission	New Investigator	S-0100	IND protocol amendment
11-JUL-2007	Submission	Change in Protocol	S-0102	IND protocol amendment
12-JUL-2007	Submission	Clinical	S-0103	Investigator Brochure
30-JUL-2007	Submission	New Investigator	S-0104	IND protocol amendment
07-AUG-2007	E-mail	Other		General Correspondence
07-AUG-2007	E-mail	Other		General Correspondence
28-AUG-2007	Submission	New Investigator	S-0105	IND protocol amendment
21-SEP-2007	Submission	Change in Protocol	S-0106	IND protocol amendment
02-OCT-2007	Submission	New Investigator / Other	S-0107	IND protocol amendment
03-OCT-2007	Submission	Other	S-0108	Response to FDA request
04-OCT-2007	Submission	Other	S-0109	General Correspondence

02-NOV-2007	Submission	New Investigator / Other	S-0110	IND protocol amendment
14-NOV-2007	Letter	Active Comparator / Adverse Drug Report / Other		General Correspondence
19-NOV-2007	Fax	Adverse Drug Report		IND safety report(s)
19-NOV-2007	Submission	Adverse Drug Report	S-0111	IND safety report(s)
20-NOV-2007	Letter	Active Comparator / Adverse Drug Report / Follow-up		General Correspondence
14-DEC-2007	Submission	Annual	S-0112	Annual report
14-DEC-2007	Submission	New Investigator	S-0113	IND protocol amendment
26-DEC-2007	Fax	Adverse Drug Report		IND safety report(s)
26-DEC-2007	Submission	Adverse Drug Report / Follow-up	S-0114	IND safety report(s)
31-DEC-2007	Submission	Adverse Drug Report / Follow-up	S-0115	IND safety report(s)
14-JAN-2008	Submission	New Investigator	S-0116	IND protocol amendment
01-FEB-2008	Submission	Adverse Drug Report	S-0117	IND safety report(s)
19-FEB-2008	Submission	New Investigator / Other	S-0118	IND protocol amendment
28-FEB-2008	Submission	Adverse Drug Report	S-0119	IND safety report(s)
03-MAR-2008	Fax	Adverse Drug Report		IND safety report(s)
03-MAR-2008	Submission	Adverse Drug Report / Follow-up	S-0120	IND safety report(s)
04-MAR-2008	Fax	Adverse Drug Report		IND safety report(s)
04-MAR-2008	Submission	Adverse Drug Report	S-0121	IND safety report(s)
05-MAR-2008	Submission	Adverse Drug Report / Follow-up	S-0122	IND safety report(s)
13-MAR-2008	Submission	Adverse Drug Report	S-0123	IND safety report(s)
24-MAR-2008	Submission	New Investigator	S-0124	IND protocol amendment
01-APR-2008	Submission	Adverse Drug Report / Follow-up	S-0125	IND safety report(s)
18-APR-2008	Submission	Adverse Drug Report / Follow-up	S-0126	IND safety report(s)
21-APR-2008	Submission	Adverse Drug Report	S-0128	IND safety report(s)
21-APR-2008	Submission	Adverse Drug Report	S-0129	IND safety report(s)
21-APR-2008	Submission	New Investigator / Other	S-0127	IND protocol amendment
22-APR-2008	Letter	Active Comparator / Adverse Drug Report		General Correspondence

29-APR-2008	Submission	Adverse Drug Report	S-0130	IND safety report(s)
06-MAY-2008	E-mail	Other		General Correspondence
06-MAY-2008	Letter	Active Comparator / Adverse Drug Report		General Correspondence
09-MAY-2008	Telephone	Follow-up		Contact Report
13-MAY-2008	Fax	Adverse Drug Report		IND safety report(s)
13-MAY-2008	Submission	Adverse Drug Report / Follow-up	S-0132	IND safety report(s)
13-MAY-2008	Submission	Adverse Drug Report	S-0131	IND safety report(s)
15-MAY-2008	Telephone	Follow-up / Other		Contact Report
16-MAY-2008	Fax	Adverse Drug Report		IND safety report(s)
16-MAY-2008	Submission	Adverse Drug Report	S-0133	IND safety report(s)
23-MAY-2008	Submission	Adverse Drug Report / Follow-up	S-0134	IND safety report(s)
23-MAY-2008	Submission	Adverse Drug Report	S-0135	IND safety report(s)
28-MAY-2008	Submission	Adverse Drug Report / Follow-up		IND safety report(s)
03-JUN-2008	Submission	New Investigator	S-0136	IND protocol amendment
05-JUN-2008	Fax	Adverse Drug Report		IND safety report(s)
05-JUN-2008	Submission	Adverse Drug Report	s-0137	IND safety report(s)
11-JUN-2008	Submission	Adverse Drug Report	S-0138	IND safety report(s)
12-JUN-2008	E-mail	Other		General Correspondence
17-JUN-2008	Submission	Adverse Drug Report / Follow-up	S-0139	IND safety report(s)
19-JUN-2008	E-mail	Follow-up / Other		General Correspondence
19-JUN-2008	E-mail	Other		General Correspondence
19-JUN-2008	Submission	Adverse Drug Report / Follow-up	S-0140	IND safety report(s)
19-JUN-2008	Telephone	Other		Contact Report
02-JUL-2008	Submission	Adverse Drug Report / Follow-up	S-0142	IND safety report(s)
02-JUL-2008	Submission	Other	S-0141	General Correspondence
03-JUL-2008	E-mail	Follow-up / Other		General Correspondence
07-JUL-2008	Submission	Adverse Drug Report / Follow-up	S-0143	IND safety report(s)
09-JUL-2008	Submission	New Investigator / Other	S-0144	IND protocol amendment
10-JUL-2008	Submission	Adverse Drug Report	s-0145	IND safety report(s)

23-JUL-2008	Letter	Active Comparator / Adverse Drug Report		General Correspondence
30-JUL-2008	E-mail	Other		General Correspondence
30-JUL-2008	E-mail	Other / Follow-up		General Correspondence
30-JUL-2008	Telephone	Change in Protocol		Contact Report
15-AUG-2008	Fax	Adverse Drug Report		IND safety report(s)
15-AUG-2008	Submission	Adverse Drug Report	S-0146	IND safety report(s)
18-AUG-2008	Submission	Adverse Drug Report / Follow-up	S-0149	IND safety report(s)
18-AUG-2008	Submission	Adverse Drug Report	S-0148	IND safety report(s)
18-AUG-2008	Submission	Clinical	S-0147	Information amendment
21-AUG-2008	E-mail	Other		General Correspondence
22-AUG-2008	E-mail	Other		General Correspondence
22-AUG-2008	Telephone	Other		Contact Report
25-AUG-2008	E-mail	Other	s-0150	General Correspondence
25-AUG-2008	Submission	Other	S-0150	General Correspondence
11-SEP-2008	E-mail	Other		General Correspondence
19-SEP-2008	Submission	New Investigator / Other	S-0151	IND protocol amendment
26-SEP-2008	Submission	Other	S-0152	Waiver request
01-OCT-2008	Submission	Change in Protocol	S-0153	IND protocol amendment
03-OCT-2008	E-mail	Other		General Correspondence
10-OCT-2008	E-mail	Chemistry, Manufacturing and Controls / Other		General Correspondence
10-OCT-2008	E-mail	Chemistry, Manufacturing and Controls / Other		General Correspondence
20-OCT-2008	Fax	Adverse Drug Report		IND safety report(s)
20-OCT-2008	Submission	Adverse Drug Report	S-0154	IND safety report(s)
22-OCT-2008	Submission	Adverse Drug Report / Follow-up	S-0155	IND safety report(s)
27-OCT-2008	Submission	Pharm/Tox	S-0156	Information amendment
03-NOV-2008	Submission	Adverse Drug Report / Follow-up	S-0157	IND safety report(s)
12-NOV-2008	Fax	Adverse Drug Report		IND safety report(s)
12-NOV-2008	Submission	Adverse Drug Report	S-0158	IND safety report(s)
01-DEC-2008	Letter	Active Comparator / Adverse Drug		General Correspondence

		Report / Follow-up		
09-DEC-2008	Submission	Adverse Drug Report / Follow-up	S-0160	IND safety report(s)
09-DEC-2008	Submission	New Investigator / Other	S-0159	IND protocol amendment
11-DEC-2008	Submission	Adverse Drug Report / Follow-up	S-0161	IND safety report(s)
16-DEC-2008	Submission	Other	S-0162	General Correspondence
17-DEC-2008	E-mail	Chemistry, Manufacturing and Controls	S-0162	General Correspondence
22-DEC-2008	Submission	Annual	S-0163	Annual report
29-DEC-2008	E-mail	Follow-up / Chemistry, Manufacturing and Controls		General Correspondence
08-JAN-2009	E-mail	Chemistry, Manufacturing and Controls		General Correspondence
08-JAN-2009	Telephone	Chemistry, Manufacturing and Controls / Follow-up		Contact Report
15-JAN-2009	E-mail	Chemistry, Manufacturing and Controls / Follow-up		General Correspondence
15-JAN-2009	Letter	Chemistry, Manufacturing and Controls / Follow-up		General Correspondence
20-JAN-2009	Submission	Chemistry, Manufacturing and Controls	S-0164	Information amendment
21-JAN-2009	Submission	Chemistry, Manufacturing and Controls	S-0165	Provide Information
22-JAN-2009	Telephone	Chemistry, Manufacturing and Controls		General Correspondence
23-JAN-2009	E-mail	Chemistry, Manufacturing and Controls / Provide Desk Copy / Follow-up		General Correspondence
24-JAN-2009	E-mail	Chemistry, Manufacturing and Controls / Provide Desk Copy / Follow-up		General Correspondence
27-JAN-2009	E-mail	Chemistry, Manufacturing and Controls / Provide Desk Copy / Follow-up		General Correspondence
29-JAN-2009	Submission	New Investigator	S-0166	IND protocol amendment
02-FEB-2009	Submission	Adverse Drug Report	S-0167	IND safety report(s)
05-FEB-2009	Submission	New Protocol / Clinical	S-0168	IND protocol amendment
11-FEB-2009	E-mail	Chemistry, Manufacturing and Controls		General Correspondence
11-FEB-2009	Telephone	Chemistry, Manufacturing and Controls		Contact Report
12-FEB-2009	E-mail	Chemistry, Manufacturing and Controls		General Correspondence
17-FEB-2009	E-mail	Chemistry, Manufacturing and Controls		General Correspondence
18-FEB-2009	E-mail	Chemistry, Manufacturing and Controls		General Correspondence

23-FEB-2009	E-mail	Pre-Clinical		General Correspondence
03-APR-2009	Submission	Adverse Drug Report / Follow-up	S-0169	IND safety report(s)
06-APR-2009	Submission	New Investigator / Clinical	S-0170	IND protocol amendment
01-MAY-2009	Letter	Active Comparator / Adverse Drug Report		General Correspondence
01-MAY-2009	Submission	Adverse Drug Report / Follow-up	S-0172	IND safety report(s)
01-MAY-2009	Submission	Adverse Drug Report / Original	S-0171	IND safety report(s)
05-MAY-2009	Submission	New Investigator / Clinical	S-0173	IND protocol amendment
07-MAY-2009	Submission	Adverse Drug Report / Follow-up	S-0174	IND safety report(s)
27-MAY-2009	Submission	Pre-Clinical	S-0175	IND safety report(s)
05-JUN-2009	Submission	New Investigator / Clinical	S-0176	IND protocol amendment
08-JUN-2009	Submission	New Protocol / Clinical	S-0177	IND protocol amendment
10-JUL-2009	Submission	New Investigator / Clinical	S-0178	IND protocol amendment
30-JUL-2009	Submission	Clinical	S-0179	Waiver request
13-AUG-2009	Submission	New Investigator / Clinical	S-0180	IND protocol amendment
27-AUG-2009	Submission	Chemistry, Manufacturing and Controls / Labeling	S-0181	Information amendment
14-SEP-2009	Submission	Other / Clinical	S-0182	General Correspondence
17-SEP-2009	Submission	New Investigator / Clinical	S-0183	IND protocol amendment
19-OCT-2009	Submission	Change in Protocol / Clinical	S-0184	IND protocol amendment
21-OCT-2009	Submission	Clinical	S-0185	Information amendment
23-OCT-2009	Submission	Clinical / New Investigator	S-0186	IND protocol amendment
30-OCT-2009	E-mail	Other		Contact Report
30-OCT-2009	Submission	Pharm/Tox	S-0187	Information amendment
02-NOV-2009	E-mail	Clinical / Other	S-0182	Request information
02-NOV-2009	Telephone	Clinical / Other		Contact Report
02-NOV-2009	E-mail	Other		Contact Report
03-NOV-2009	Submission	Clinical	S-0188	General Correspondence
09-NOV-2009	Letter	Clinical / Other		General Correspondence
09-NOV-2009	E-mail	Clinical / Other	S-	Contact Report

			0182	
09-NOV-2009	Submission	Other	S-0190	Briefing Document
09-NOV-2009	Submission	Pharm/Tox	S-0189	Information amendment
20-NOV-2009	E-mail	Other		Contact Report
20-NOV-2009	Submission	Pharm/Tox	S-0191	Information amendment
01-DEC-2009	E-mail	Other		General Correspondence
02-DEC-2009	Submission	Clinical / New Investigator	S-0192	IND protocol amendment
17-DEC-2009	E-mail	Other		Contact Report
17-DEC-2009	E-mail	Other		Contact Report
17-DEC-2009	Submission	Other		General Correspondence
18-DEC-2009	Submission	Annual	S-0193	Annual report
22-DEC-2009	Letter	Other		FDA acknowledgement of submission
05-JAN-2010	Submission	Other		General Correspondence
06-JAN-2010	Submission	Clinical	s-0194	IND protocol amendment
07-JAN-2010	Submission	New Protocol	S-0195	IND protocol amendment
26-JAN-2010	E-mail	Other		Contact Report
27-JAN-2010	E-mail	Other		General Correspondence
29-JAN-2010	Submission	Other	S-0196	Briefing Document
21-FEB-2010	E-mail	Other		General Correspondence
17-MAR-2010	E-mail	Other		General Correspondence
23-MAR-2010	Submission	New Investigator	S-0197	IND protocol amendment
29-MAR-2010	Submission	New Protocol	S-0198	IND protocol amendment
02-APR-2010	Submission	New Protocol	S-0199	IND protocol amendment
13-APR-2010	Submission	Other		General Correspondence
14-APR-2010	Submission	Chemistry, Manufacturing and Controls	S-0200	Information amendment
23-APR-2010	Submission	Change in Protocol	s-0202	IND protocol amendment
26-APR-2010	Submission	Other	S-0203	General Correspondence
27-APR-2010	E-mail	Chemistry, Manufacturing and Controls		IND Amendment
27-APR-2010	E-mail			General Correspondence

29-APR-2010	Submission	Clinical	S-0204	Information amendment
29-APR-2010	Submission	New Protocol	S-0205	IND protocol amendment
11-MAY-2010	Letter			General Correspondence
12-MAY-2010	Telephone	Chemistry, Manufacturing and Controls		Contact Report
13-MAY-2010	Submission	Chemistry, Manufacturing and Controls	S-0206	Information amendment
27-MAY-2010	Letter			IND protocol amendment
27-MAY-2010	Submission	New Investigator	S-0207	IND protocol amendment
03-JUN-2010	Submission	Change in Protocol	S-0208	IND protocol amendment

exhibit 11

NDA 201023 History Log

Date	Contact Type	Initial contact	Contact Description
3/18/2010	Email	s-a	General Correspondence
3/19/2010	Telephone	FDA	Contact Report
3/19/2010	Email	FDA	General Correspondence
3/19/2010	Email	s-a	General Correspondence
3/23/2010	Email	FDA	General Correspondence
3/29/2010	Email	s-a	General Correspondence
3/30/2010	Email	FDA	General Correspondence
3/30/2010	Email	s-a	General Correspondence
3/31/2010	Telephone	FDA	Contact Report
3/31/2010	Email	s-a	General Correspondence
3/31/2010	Email	s-a	General Correspondence
4/1/2010	Email	FDA	General Correspondence
4/1/2010	Email	s-a	General Correspondence
4/1/2010	Telephone	s-a	Contact Report
4/1/2010	Email	s-a	General Correspondence
4/1/2010	Email	FDA	General Correspondence
4/1/2020	Email	s-a	General Correspondence
4/7/2010	Telephone	s-a	Contact Report
4/7/2010	Email	FDA	General Correspondence
4/8/2010	Email	s-a	General Correspondence
4/9/2010	Email	s-a	General Correspondence
4/19/2010	Email	s-a	General Correspondence
4/22/2010	Email	s-a	General Correspondence
4/23/2010	Email	FDA	General Correspondence
4/27/2010	Email	s-a	General Correspondence
4/27/2010	Email	s-a	General Correspondence
4/27/2010	Email	FDA	General Correspondence
5/3/2010	Email	s-a	General Correspondence
5/3/2010	Email	FDA	General Correspondence
5/12/2010	Letter	FDA	General Correspondence
5/19/2010	Email	FDA	General Correspondence
5/25/2010	Email	FDA	General Correspondence
5/26/2010	Email	FDA	General Correspondence
5/26/2010	Letter	FDA	General Correspondence
5/26/2010	Letter	FDA	General Correspondence
6/1/2010	Telephone	s-a	Contact Report
6/2/2010	Email	FDA	General Correspondence
6/8/2010	Telephone	s-a	Contact Report

6/9/2010	Letter	FDA	General Correspondence
6/9/2010	Letter	FDA	General Correspondence
6/10/2010	Email	FDA	General Correspondence
6/14/2010	Email	FDA	General Correspondence

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/622,011	03/26/1996	HERVE BOUCHARD	3806.0367-00

CONFIRMATION NO. 1663

FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON, DC 200053315

POWER OF ATTORNEY NOTICE

OC000000042528960

Date Mailed: 07/13/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/02/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/stlam/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/622,011	03/26/1996	HERVE BOUCHARD	3806.0367-00

CONFIRMATION NO. 1663

POA ACCEPTANCE LETTER

5487
ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

OC000000042528980

Date Mailed: 07/13/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/02/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/stlam/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/82 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REVOCATION OF POWER OF ATTORNEY WITH NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	08/822011
Filing Date	March 26, 1996
First Named Inventor	Herve BOUCHARD et al.
Art Unit	1612
Examiner Name	TRINH, Bak
Attorney Docket Number	ST95019G1 US NP

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☑ I hereby appoint the practitioners associated with the Customer Number: **005487**

☑ Please change the correspondence address for the above-identified application to:

☑ The address associated with Customer Number: **005487**

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

I am the:

☐ Applicant/inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature			
Name	Josiane Mellier		
Date	2nd July 2010	Telephone	+ 33 1 55 71 12559

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 2 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PTO/SB/96 (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owners: **BOUCHARD, Hervé, et al.**

Application No./Patent No.: **08/622011** Filed/Issue Date: **March 26, 1996**

Titled: **NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

Aventis Pharma S.A. (Name of Assignee) , a **corporation** (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title , and interest in
(The extent (by percentage) of its ownership interest is %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel , Frame , or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: **Inventors** To: **Rhone-Poulenc Rorer S.A.**
The document was recorded in the United States Patent and Trademark Office at
Reel **007959** Frame **0343** or for which a copy thereof is attached

2. From: **Rhone-Poulenc Rorer S.A.** To: **Aventis Pharma S.A.**
The document was recorded in the United States Patent and Trademark Office at
Reel **011641** Frame **0962** or for which a copy thereof is attached

3. From: To:
The document was recorded in the United States Patent and Trademark Office at
Reel Frame or for which a copy thereof is attached

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document (s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — 2nd July 2010 Date

Josiane Mertier Printed or Typed Name — **Director, Patent Administration** Title

Sanofi-aventis U.S. template

If you need assistance in completing the form, call 1-800-PTO-9199 and selection option 2.

Electronic Acknowledgement Receipt

EFS ID:	7944901
Application Number:	08622011
International Application Number:	
Confirmation Number:	1663
Title of Invention:	NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM
First Named Inventor/Applicant Name:	HERVE BOUCHARD
Correspondence Address:	FINNEGAN HENDERSON FARABOW GARRETT AND DUNNER 1300 I STREET NW - WASHINGTON DC 200053315 US - -
Filer:	Kelly L. Bender/Linda Remer
Filer Authorized By:	Kelly L. Bender
Attorney Docket Number:	3806.0367-00
Receipt Date:	02-JUL-2010
Filing Date:	26-MAR-1996
Time Stamp:	13:10:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	ST95019G1_USNP_REV_POA.pdf	332299 2dd6876dedb6557ab02b6b9b58676559f2f2a9f2	no	1
Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73(b).	ST95019G1_USNP_Executed_373B.pdf	423454 402ec736bd77902d41151490c2c74a76cac542bc	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	755753		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Attorney Docket No. 03806.0367

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

U.S. Patent for Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them

Inventors: Hervé Bouchard, Jean-Bominique Bourzat, Alain Commerçon

Patent No: 5,847,170 Issued: December 08, 1998

#23 Jms

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. 254 and 37 C.F.R. 1.322, this is a request for the issuance of a Certificate of Correction in the above-identified patent. Two (2) copies of Form PTO 1050 are attached. The complete Certificate of Correction involves ONE (1) page.

The mistakes identified in the attached form occurred through the fault of the Office, as clearly disclosed by the records of the application which matured into this patent. Issuance of the Certificate of Correction containing the correction is earnestly requested.

If it should be determined that any of the mistakes resulted from an error made in good faith by the applicants, then, pursuant to 35 U.S.C. 255 and 37 C.F.R. 1.323, it is requested that a Certificate of Correction be issued correcting such mistakes. Under

such circumstances, it is requested that the fee set forth in 37 C.F.R. 1.20(a) and any additional fees needed, be charge to our Deposit Account No. 06-0916, for which authorization is hereby given.

Respectfully submitted

FINNEGAN, HENDERSON, FARABOW
GARRETT & DUNNER, L.L.P

By: _____
Carol P. Einaudi
Reg. No. 32,220

Dated: **MAY 12, 1999**

Staple Here Only t

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170
DATED : December 08, 1998
INVENTOR(S) : Hervé Bouchard et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(Amdt B) Amdt C/CK

Claim 4, Column 29, Line 42, after "chain", delete " , ";

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read --(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "R_9", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

Claim 15, Column 45, Line 34, "R6" should read --R_8--.

Note

MAILING ADDRESS OF SENDER:

FINNEGAN, HENDERSON, FARABOW,
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PATENT NO. 5,847,170

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

EXHIBIT 1

Alain Commerçon
Rhône-Poulenc Rorer
CRVA
Oncology Chemistry
13 Quai Jules Guesde
94403 Vitry-sur-Seine Cedex

Education:

1973

Degree of "Ingénieur Chimiste" from ENSCT (Ecole Nationale Supérieure de Chimie de Toulouse).

1973-1976

Laboratory of Professor Jean François Normant (University Paris VI).
1976: Docteur-ès-Sciences (PhD), from "Université Pierre et Marie Curie" (Paris VI). Thesis: "Substitution reactions of 1-halo-alkenes and -alkynes, ethylenic ethers and ketals using organocopper derivatives in stoechiometric or catalytic amount".

1977-1978

Research Scientist in the French institute called IRCHA (Institut National de Recherche Chimique Appliquée). Asymmetric synthesis, fluorine chemistry, drug substance synthesis.

1979-present

At Rhône-Poulenc (and then Rhône-Poulenc Rorer) since 1979
1979-1988: Senior Research Scientist
1988-1991: Senior Research Fellow
1990-1991: Visiting Scientist at the University of Rochester in the laboratory of Prof. R.K. Boeckman (total synthesis of natural products)
1991: Department Manager (Oncology Chemistry)
1992-present: Rhône-Poulenc Group Senior Research Advisor
1995: Director (Oncology Chemistry)
1996-present : Director New Lead Generation

Research Interests (1986-1996):

Our research programs dealt with medicinal chemistry in oncology. I was involved with my colleagues for nearly 10 years in the total synthesis and semisynthesis of new antitumor agents of natural origin such as taxoids. We also looked for new types of anticancer agents able to interfere with novel targets linked to intracellular signalling pathways. Our main topics were the inhibition of specific enzymes activity as well as protein-protein interactions.

Research Interests (1996-present):

My new activities deal with new technologies, natural products chemistry, combinatorial chemistry, robotic equipments and drug designed approaches. I am in charge of the New Lead Generation Chemistry group at RPR-France. Our main goals are the design and synthesis of the new molecules for the RPR new biological targets in most of our therapeutic areas. Many of these new targets are going to be produced by genomics and bioinformatics. I have also the responsibility of managing and coordinating an international collaboration network (TeknoMed - 24 Postdocs) and a number of research programs involving PhDs and Postdocs in different Universities.

Publications:

Author or co-author of nearly 120 papers and patents. Lecturer in many symposia and meetings in the USA, Japan and Europe.

In re RUSCHIG, AUMULLER, KORGER, WAGNER, SCHOLZ, AND BANDER

Court of Customs and Patent Appeals

Appl. No. 7254

Decided Apr. 22, 1965

United States Patents Quarterly Headnotes

PATENTS
[1] Patent grant--Intent of patent laws (§ 50.15)
Patentability--Composition of matter (§ 51.30)
35 U.S.C. 103 is applicable to claimed chemical compounds; it is court's duty to so apply section 103 as to carry out fundamental congressional intent, expressed in Constitutional mandate to Congress, to make patent laws adapted to promote progress in the useful arts; Congress points out the general direction and leaves detailed application to specific problems to court; court's solution should be in terms that Patent Office, the bar, and other courts can understand and which also appear to make practical as well as legal and logical sense.

PATENTS
[2] Interference--In general (§ 41.01)
Interferences are set up only on allowable applications.

PATENTS
[3] Patentability -- Anticipation -- In general (§ 51.201)
To say that prior art compounds are "within the scope of" rejected claims is to say that claims are "anticipated."

PATENTS
[4] Claims--In general (§ 20.01)
Inclusion in compound claim of statement of inherent property adds nothing to claim definition of named compound where balance of claim fully identifies compound and the property is inherent.

PATENTS
[5] Patentability--Composition of matter (§ 51.30)
Court did not intend In re Petering, 133 USPQ 275, to become a precedent for mechanistic dissection and recombination of components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of applicant's disclosures, on the theory that such reconstructed disclosures describe specific compounds within meaning of 35 U.S.C. 102; In re Petering does not apply where a small recognizable class with common properties is not obtained after dissection and recombination of components of prior compounds.

PATENTS
[6] Patentability--Composition of matter (§ 51.30)
Claims to compounds are not rejected as obvious over the next lower homologue thereof since claimed compounds have unexpected advantageous properties not possessed by homologue.

PATENTS
[7] Patentability--Composition of matter (§ 51.30)
Patentability -- Invention -- In general (§ 51.501)
Use of "obvious" in 35 U.S.C. 103, a section intended to ameliorate effect of certain harsh court decision on patentability, does not make unpatentable chemical compounds which would have been patentable under decisions antedating enactment of that section.

PATENTS
[8] Patentability--Composition of matter (§ 51.30)
On issue of obviousness of claimed compounds, vague "basket" disclosure of possible uses in prior patents is unimportant; what is important is fact that utility discovered by applicants is not disclosed in prior art; claims are allowed.

PATENTS
[9] Claims--In general (§ 20.01)

Claims--Process (§ 20.80)

Recognizing the practical advantages which product claims have over process claims from standpoint of protection, court allow product claims covering new compounds in which unobvious inherent properties have been found; balancing alternatives of providing adequate protection to applicants' limited group of anti-diabetic agents against the mere possibility that someone might wish to use some of them for some such purpose as making a textile size, court favors the former.

PATENTS

[10] Patent grant--Intent of patent laws (§ 50.15)

Basic principle of patent system is to protect inventions which meet statutory requirements; valuable inventions should be given protection of value in the real world of business and the courts.

PATENTS

Particular patents--Ureas

Ruschig, Aumuller, Korger, Wagner, Scholz, and Bander, New Benzene Sulfonyl Ureas and Process for Their Preparation, claims 1 to 6 and 8 to 13 of application allowed.

***275** Appeal from Board of Appeals of the Patent Office.

Application for patent of Heinrich Ruschig, Walter Aumuller, Gerhard Korger, Hans Wagner, Josef Scholz, and Alfred Bander, Serial No. 601,107, filed July 31, 1956; Patent Office Group 120. From decision rejecting claims 1 to 6 and 8 to 13, applicants appeal. Reversed; Martin, Judge, concurring with opinion.

GEORGE E. FROST, Chicago, Ill., HENRY W. KOSTER, New York, N.Y., and EUGENE REITTER and JOHN KEKICH, both of Kalamazoo, Mich., for appellants.

CLARENCE W. MOORE (JOSEPH SCHIMMEL of counsel) for Commissioner of Patents.

Before WORLEY, Chief Judge, and RICH, MARTIN, SMITH, and ALMOND, Associate Judges.

RICH, Judge.

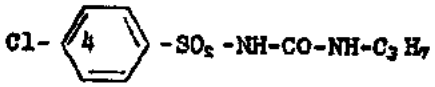
This appeal is from the decision of the Patent Board of Appeals affirming the examiner's rejection of claims 1-6 and 8-13 of application serial No. 601,107, filed July 31, 1956, for a patent on "New Benzene Sulfonyl Ureas and Process for their Preparation." All appealed claims are directed to compounds. The appeal from the examiner to the board was on claims 1-13 but in his answer before the board the examiner said, "upon reconsideration claim 7 is deemed allowable."

The board's opinion recites the fact that there were other claims, 17 and 19- 25, referred to as the "non-elected" claims herein, "directed to the process of lowering blood sugar in the treatment of diabetes by the oral administration of, and to pharmaceutical tablets containing, compounds recited in substantially the same manner as in compound claims 1, 2, 3 and 13" (our emphasis) but that the examiner required restriction as between those claims and the claims here on appeal, as a result of which "A divisional application containing claims 17 and 19 to 25 as claims 1 to 8 thereof has been filed and is pending." [FN1] We see no relevancy of these facts to the issue of the patentability of the claims to the compounds before us but recite them because the board, possibly the examiner, and certainly the solicitor for the Patent Office seem to have had them in mind in stating their reasons for rejection, as will appear.

The Invention

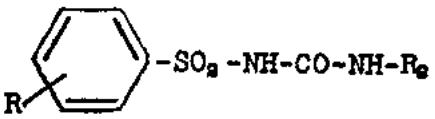
The invention here is more than the making of new compounds in the abstract. The field of endeavor in which the claimed invention is found is the production of an oral medication for the control of diabetes mellitus, the common type of diabetes long treated by daily injections of insulin. As is well known, a characteristic of the disease is an abnormal amount of sugar in the blood due to insulin deficiency.

The obvious practical disadvantages of the hypodermically injected insulin *276 gave rise to research to discover and develop an oral medication to take its place and as a result of this research of recent years a few such oral pharmaceuticals have become available. One of them is sold under the trademark "Orinase," which has the descriptive name tolbutamide [FN2] and is N-(4-methylbenzenesulfonyl)-N'-n-butyl urea. Another one developed later and approved for marketing by the Federal Food and Drug Administration in November 1958, is sold under the trademark "Diabinese," which has the descriptive name chlorpropamide and is N-(4-chloro-benzenesulfonyl)-N'-n-propyl urea. This compound is the subject matter of claim 13 on appeal of the application at bar where it is designated "N-(P-chlorobenzenesulfonyl) - N' - propylurea," the graphic formula of which is



We have marked the "4" position of the chlorine, which is also the para or "p" position. It is interesting to compare this with allowed claim 7, which reads:

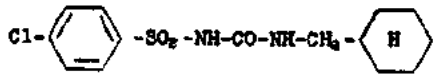
7. The compound of the formula



It will be useful in this discussion to bear in mind the basic nomenclature of such compounds as the above. They are of the general class of sulfonyl ureas. The sulfonyl group is the -SO sub2 -. Urea is NH sub2 -CO-NH sub2 and these compounds are substituted urea. It will be noted that urea has two N (nitrogen) atoms and to distinguish them in substitution products they are conventionally referred to as N and N'. We will hereafter refer to the nitrogen atom bearing the sulfonyl group as N. In the above claims it will be seen that one of the H (hydrogen) atoms attached to N has been replaced or substituted by the chlorobenzene-sulfonyl group. In claim 13, above, one of the hydrogens attached to N' has been substituted by the propyl group -C sub3 H sub7 , an alkyl group having 3 carbon atoms. In claim 7 the same H has been substituted by a cycloalkylalkyl radical, cyclohexymethyl, -CH sub2 - or methylene attached to the hexagon containing "H" representing a cyclohexyl or -C sub6 H sub11 ring, not to be confused with the benzene ring. Thus there is always the urea group -NH-CO-NH-, preceded by the benzene-sulfonyl group, on the ring of which there may be one or more additional substituents like Cl-, and followed by an N'-substituent.

Claims 7 and 13, above, are two of ten species claims in the application, the other claims being generic (claims 1 and 2) or subgeneric (claims 8 and 9). Of the broad claims the board selected claim 2 for purposes of its analysis of the patentability issue. It reads:

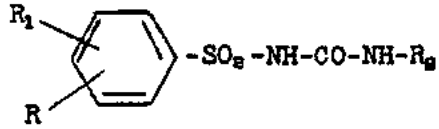
2. Benzenesulphonylureas of the formula



wherein R is chorine and R super2 is alkyl of 2 to 7 carbon atoms.

Claim 1 is the broadest, generic to all species claimed but still defining a limited class, and it reads:

1. Compounds selected from the group consisting of (1) benzenesulphonyl ureas of the formula



wherein R is selected from the group consisting of hydrogen, chlorine, bromine, methyl and methoxy, R sub1 is selected from the group consisting of chlorine and bromine and R sub2 is of 2 to 7 carbon atoms selected from the group consisting of alkyl-, alkenyl-,

cycloalkyl- and cycloalkyl-alkyl atoms [sic] and (2) non-toxic basic addition salts thereof. [FN3]

The board put some emphasis on the fact that the claims on appeal define compounds "without limitation," which we presume adverts to the lack of any reference in these compound claims to a use for them, though it would not seem that reference to a use in a compound claim would in law be a "limitation," on the question of patentability, a point we need not go into. See In re Thuau, 30 CCPA 979, 135 F.2d 344, 57 USPQ 324, and In re Jones, 32 CCPA 1020, 149 F.2d 501, 65 USPQ 480. Perhaps the board's observation was stimulated by the following statement in *277 the concluding paragraph of the examiner's answer before the board:

> The claims are directed to compounds and not to the use of these compounds in any particular manner. Appellants do not, however, recognize the necessity for this conjunction of utility and product in the claims presented but seek a patent on the compounds per se. [Emphasis ours.]

We confess a failure to grasp what the examiner intended by that observation, made as part of his insistence that the compounds are unpatentable because they would be obvious from the prior art, under 35 U.S.C. 103, unless it be that in his view applicants are entitled only to claims for a process of treating diabetes. Would a statement in the claims of what the compounds are useful for convert them into claims to compounds which are any less obvious? It is the compounds the examiner says are obvious, not the claims, and it is compounds which the claims define.

To return to our consideration of the place of this invention in the useful arts, these compounds, as here defined in generic and specific claims, have been discovered to have a particular utility which is extensively described in the specification and further expounded in five of the nine affidavits of record.

The claimed compounds fall into the general class of sulfonylureas, which the Patent Office admits may number in the millions. Those singled out here for patenting have been discovered by appellants, as a result of their systematic, extensive, and presumably expensive research, to possess the ability to lower the level of blood sugar (known as hypoglycemic activity), for which reason they are useful in treating diabetes, but particularly because of other desirable properties they possess in connection with such use. We quote relevant passages from the specification:

> As has been demonstrated by experiments on animals and in clinical tests, the products of the invention produce a substantial lowering of the blood sugar level. They may be used as such or in the form of their salts, or in the presence of substances that cause salt formation. * * * These salts have the same blood sugar lowering properties. * * * The compounds can be made up, inter alia, into preparations suitable for oral administration and lowering the blood sugar in the treatment of diabetes.
>
> In animal tests the action on the blood sugar level has been demonstrated, for example, on mice, rats, guinea pigs, rabbits, cats and dogs. * * *
>
> The testing of the compounds on dogs has the advantage that the resorption conditions in the alimentary canal are similar to those of human beings, and that the blood sugar level exhibits smaller individual variations than in rabbits. * * *
>
> As compared with compounds of similar constitution of the sulphanilyl series the compounds of the present invention are distinguished, on one hand, in that they are more resistant to external oxidising influences, such as atmospheric oxygen, which is of importance to their shelf-life and handling, and, on the other, in that they have no bacteriostatic action.
>
> Furthermore, the new compounds do not produce the secondary effects of sulphonamides on the blood (Heinz bodies) or

on the thyroid gland, nor the digestive disturbances caused by action on the bacterial flora of the alimentary tract. * * *

Together with these general statements there are included two tables, the first giving the specific blood sugar level reduction produced in rabbits by ten specific compounds here claimed, the second showing the lowering of blood sugar in the dog at various periods after administration, the showing being that the hypoglycemic activity of the compounds of species claims 3 and 5, at least, is long lasting. To illustrate, the figures for N-(4-chlorobenzenesulfonyl) - N' - n - butyl - urea, the claim 3 compound, are:

% sugar level lowering....	27	40	40	32	15	0
after stated hours.....	1	3	24	48	72	96

An affidavit of record by Dr. Dumas, Director of Clinical Research for Chas. Pfizer & Co., Inc., which sells the "Diabinese" (chlorpropamide) product of claim 13, which is the same as the claim 3 compound except that instead of the butyl (4 carbon) radical it has a propyl (3 carbon) radical, indicates by reference to published clinical studies [FN4] that the here claimed chlorpropamide sometimes has advantages over tolbutamide ("Orinase") in that *278 human patients who lost responsiveness to tolbutamide were satisfactorily managed with chlorpropamide in 62% of 84 cases studied and that of another group of 118 cases treated for from 2 to 14 months with chlorpropamide it was successful in 79% of the cases, in a number of which the disease was either poorly controlled by tolbutamide or in which secondary failure occurred, that is the patient had originally been treated with tolbutamide and subsequently become unresponsive to the drug.

It should be explained why it is significant that, as the specification states, supra, the claimed compounds do not have bacteriostatic action, the inhibition of the growth of bacteria, also herein termed "sulfa-drug action." Such action is present in a closely related anti-diabetic drug "BZ-55," [N-(4-aminobenzenesulfonyl) - N' - n - butl urea, also named N subl -sulfanilyl-N sub2 -n-butyl carbamide], its disadvantage being that it produces in a diabetic, who must have drug therapy continuously, bacteria strains which are resistant to sulfa-drug therapy. This is medically recognized as disadvantageous, as is suppression of intestinal flora which interferes with the digestive process.

To summarize as to the invention, appellants Ruschig, Aumuller, Korger, Wagner, Scholz and Bander, assignors to the firm of Farbwerke Hoechst AG, vormals Meister Lucius & Bruning at Frankfurt/Main, Federal Republic of Germany, which conducts pharmaceutical research laboratories, working in the vast field of sulfonylurea compounds for the purpose of finding or developing improved oral diabetic control medications, have succeeded in preparing and delimiting a restricted group of sulfonylureas, prepared by reactions of a type known to the art, between known materials, which have the desirable properties, necessary to the purpose, of (1) lowering the level of blood sugar, (2) non-toxicity, (3) no bacteriostatic or "sulfa-drug" action, (4) prolonged action, (5) the ability to control some diabetics who have shown inadequate response to other quite similar oral drugs.

Claims Tabulated

The sulfonylureas claimed are relatively few in number. First we will list those of the specific claims.

Claim	N-benzene Substituent		N' Substituent	
3	4-chloro	-benzenesulfonyl	-n-butyl	urea
4	3-chloro	"	-n-butyl	"
5	4-bromo	"	-n-butyl	"
6	4-chloro	"	-cyclohexyl	"
(7) all'd.	4-chloro	"	-cyclohexylmethyl	"
10	3-chloro-4-methyl	"	-isobutyl	"
11	3-chloro-4-methyl	"	-n-butyl	"
12	6-chloro-2-meythl	"	-n-butyl	"
13	4-chloro	"	-propyl	"

The generic and subgeneric claims may be summarized thus:

1	a chloro or a bromo with which there may be a methyl or a methoxy or another chloro or bromo	"	alkyl, alkenyl, cycloalkyl, or cycloalkylalkyl; with 2-7 carbon atoms	"
2	a chloro in any position on the ring	"	alkyl, 2-7 carbon atoms	"
8	both chloro and methyl in any positions on the ring	"	alkyl, 2-7 carbon atoms	"

9	[same as claim 8]	"	-butyl	"

For the reason appearing in the first column, we treat claim 9 as subgeneric though it appears to have been treated by the parties as specific; it includes more than one compound.

Claim, 2, it will be seen, is even narrower than the specific claims taken collectively except for the position of the -chloro. Appellants state that, neglecting insomers it covers only six compounds. Claim 8, and certainly claim 9, are likewise of quite limited scope. Claim 1 is of not much greater scope than the specific claims taken collectively, is in accord with the broad statement of the invention in the specification *279 and appears to us to be only such a generic claim as would be drafted to include all of the disclosed species and obvious variants thereof to meet the Patent Office requirement for a generic claim. See Rule 141. In any event, this is the group of compounds disclosed as having the properties above referred to so as to be useful as an oral anti-diabetic medication.

Before leaving our discussion of the invention, we make the observation that in a case of this character, chemists do not merely puddle about in their laboratories making new compounds which any competent chemist possibly could make, given some purpose for making them. They proceed according to some plan and having made new compounds they still have laboriously to test out their biological properties on mice, rats, rabbits, dogs, and humans, in order to locate those compounds of therapeutic use to mankind and to determine the principle, if there is one, or the group classification, if there is one, related to that utility. We are quite aware that in such situations there is always the philosophical question, susceptible of various theoretical answers, of just who invented what? Is the "invention"in the new compounds, in the determination of their utility, or in some pill made according to known pill- making techniques? Or is it in the administering or the swallowing of the pill? Is it not self-evident that the "invention" in such cases is in the nature of a legal abstraction? And is it not also evident that a patent system must be related to the world of commerce rather than to the realm of philosophy?

The most recent thinking on these problems to come to our attention--which has not a little to say about our recent decisions--is entitled, "Is 35 U.S.C. 103 Applicable to Chemical Compounds?," by Marion Wayne Western, IDEA, Vol. 8, No. 3, Fall 1964, published by the Patent, Trademark and Copyright Institute of the George Washington University, pages 443-454.

[1] We do not have the freedom of the author to speculate as to whether section 103 is applicable to claimed chemical compounds, as Congress has told us that it is; and it is our duty to so apply it as to carry out the fundamental congressional intent, expressed in the Constitutional mandate to Congress, to make patent laws adapted to promote progress in the useful arts. This is often a difficult task; Congress points the general direction and leaves the detailed application to specific problems to us. Our solution should be in terms that the Patent Office, the bar, and other courts can understand and which also appear to make practical as well as legal and logical sense. To that task we now specifically apply ourselves. Hopefully, it will also make sense to chemists, biologists, and pharmacologists.

The Rejection

The examiner and the board rely on three references, all patents issued to the firm of J. R. Geigy A. G., Basel, Switzerland:

Martin et al. U.S., 2,371,178, Mar. 13, 1945.

Swedish Patent, 120,428, Dec. 16, 1947.

French Patent, 919,464, Nov. 25, 1946. [FN5]

However, the examiner explained that "The Geigy (French Patent) teaches essentially the same subject matter as the Swedish Patent," the board agreed that the two are "substantial

duplicates except that the Swedish patent has two examples not in the French patent" and said "Only the French patent will be discussed as our study of this reference has been with the French text." (We have only its English translation of record.) The solicitor, after naming the references, said "no need is seen to make any further reference here to the Swedish patent." The two added examples of the Swedish patent are not relied on. In effect, therefore, we are concerned with the disclosures of but two patents, which we shall refer to as the Martin and French patents.

The examiner's final rejection, on February 13, 1962, was that claims 1-5 and 8-13 were "unpatentable over" Martin, and "unpatentable over" each of the French and Swedish patents, and claims 6-7 were "unpatentable over" the French patent. "To reiterate," he said, "the claimed compounds are deemed clearly obvious to one of ordinary skill in the art."

The examiner's answer before the board, on August 14, 1962, said, "upon reconsideration claim 7 is deemed allowable," no reason being stated. The examiner also expressly withdrew the rejection of claims 8-12 on Martin, no reason being stated. He added the Swedish *280 patent to the rejection of claim 6. This left the situation as reported in the board opinion, April 30, 1963: claims 1-5 and 13 rejected on Martin and claims 1-6 and 8-13 rejected on the French or Swedish patent.

We mention the dates because our decision in In re Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43, which we think has a bearing on this case, was handed down March 20, 1963. It was, therefore, not considered by the examiner but was considered by the board, to the extent of summarily distinguishing it on its facts, in ten lines. The solicitor also suggests that the Papesch case is factually distinguishable from the situation here.

The board opinion states at the outset, and the solicitor in his oral argument said it is "significant history," that claim 3 was the count in an interference, No. 89,009, and claim 13 was the count in another interference, No. 89,010, [FN6] both interferences having been dissolved by the examiner on his own motion on the ground of unpatentability over the references used here. While this is of interest, we fail to see that it has any bearing on the patentability issue before us except to emphasize its importance and the possible effect of this decision on others than the appellants. It does incidentally explain the presence in our record of Dr. Dumas' affidavit (from Interference No. 89,010) and other interference papers. [2] Since interferences are set up only on allowable applications (Rule 203), it would also indicate that at one time the examiner must have considered claims 3 and 13 to be patentable, subsequent to which (on July 20, 1961) fourteen new references were cited including the three relied on here. This may be more interesting to those who know the situation than it is to us. We do sense, however, that we are participating in but one scene of a much larger drama.

The examiner and the solicitor, on the one hand, took a somewhat more restricted view of the ground of rejection on the Geigy company's patents than did the board, on the other hand. The examiner restricted himself to the view that appellants' claimed compounds are unpatentable because they are obvious under section 103. The solicitor took the same view, which he summed up in his brief as follows:

> Clearly, then the compounds defined by subgeneric claim 2 are obvious as compounds in view of the French patent disclosure. The sole issue, then is whether such compounds are obvious within the meaning of 35 U.S.C. 103, as that term in that section of the statute has been interpreted by this Court in In re Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43; In re Petering, supra, [49 CCPA 993, 301 F.2d 676, 133 USPQ 275], and In re Lambooy, 49 CCPA 985, 300 F.2d 950, 133 USPQ 270.

The board position, however, goes beyond that of the examiner, and beyond what the solicitor chose to argue in this court, in that

its opinion makes the following statement:

> If the specific examples exemplifying the generic disclosure [of the French patent] are looked to, the possible combinations are quite small and include several compounds disclosed by appellants and within the scope of claims 1 and 2. Following In re Petering, 133 USPQ 275, these claims can even be said to be anticipated. [Emphasis ours.]

Speaking of the Martin patent, the board opinion includes this statement:

> Thus there are disclosed the making of several compounds which [within?] the scope of claims 1 and 2 and over which claims 3 to 5 and 13 are considered obvious. [Emphasis ours.]

[3] To say that prior art compounds are "within the scope of" appealed claims is to say that those claims are "anticipated" and the board, therefore, appears to have taken the position that, "Following In re Petering," claims 1 and 2 read on the prior art and are unpatentable for want of novelty under 35 U.S.C. 102, though the board made no reference to that section of the statute. In Petering, however, we did, expressly resting the rejection on section 102(b) on the ground the disclosure was such that it described the compound claimed. In "Following In re Petering," the intent of the board to rely on section 102 seems clear.

In this situation we have two different issues to deal with, anticipation under section 102 and obviousness under section 103. To keep matters clear, we shall deal with them separately.

*281 Opinion

Notwithstanding the two statements of the board just quoted, counsel for appellants made three statements, both in their brief and at oral argument, which the Patent Office has not controverted and which we find to accord with the record. They are:

"There is no specific example in any reference of the making of any compound within even the broadest claim here sought."

"There is no disclosure in any reference of any blood sugar lowering action or any compound that is said to have blood sugar lowering action."

"No reference contains a specific utility disclosure of any sort, or states that any particular compound or compounds have any particular utility."

In regard to the last statement, we will quote what the references say about utility from which it will be seen that the disclosures are very general. Martin refers to "valuable sulphonamide derivatives" and contains the statement that "The claimed new sulphonamide derivatives are remarkably suitable for therapeutical purposes." [FN7] Each of the four product or compound claims ends with the phrase, "being a colorless compound of therapeutical properties." (Perhaps that is what the examiner had in mind in his reference to "the necessity for this conjunction of utility and product in the claims," but if he did, we fail to see the point of it. [FN8]) We note in passing that these compounds claimed by Martin, said to have unidentified "therapeutical" suitability are all sulfonyl urethanes, not ureas, and are not in the class claimed by appellants. It is suggested by appellants that perhaps they have "sulfa" drug antibacterial activity, since they contain the amino-benzene- sulfonyl-NH-structural unit of sulfanilamide, an early "sulfa" drug, which is the activity appellants specifically wish to avoid in oral anti-diabetic drugs.

The French (and corresponding Swedish) patent contains a "basket" statement of utility as follows:

> The said procedure [for making N-substituted ureas] has general applications and furnishes products utilizable for the preparation of auxiliary products in the textile industry, for preservatives, disinfectants, anti-parasite agents such for example as anti-mite [moth in Swedish patent] products, or again the products can

be used as plasticizers in the lacquer industry, and in the synthetic plastics industry. Some of these materials have therapeutic properties or they can be used in the industry as intermediate products.

We agree with appellants' statement that "There is no indication of which of the endless [meaning at least 130] possible products have which of these possible uses."

Our concept of appellants' invention, as gathered from their specification and the surrounding supporting evidence from the prosecution history, is central to our thinking. What appellants invented, discovered, found out, or developed through research, is a group of particular substituted benzenesulfonyl ureas having hypoglycemic activity without antibacterial activity and which are non-toxic, so that they have superior properties as oral anti-diabetic drugs. They are, perforce, chemical compounds in which the aforesaid useful properties inhere.

Certain it is, and it has not been argued to the contrary, that this invention is not even hinted at in any reference. Nevertheless the Patent Office has refused a patent on this invention (which, indeed, is a "conjunction of utility and product," though claimed as new compounds found to have the desired biological effect) because the examiner and the board thought the compounds, looked upon as mere chemical formulae, would have been obvious; and the board, "Following in re Petering," additionally thought claims 1 and 2 would be "anticipated."

The Board's Own Anticipation Rejection

We shall first consider the board's view of claims 1 and 2 as "anticipated." The board opinion makes quite clear what it meant by the expression "Following In re Petering" in the passage quoted supra, namely, to take the specific illustrative examples of the French patent, dissect them into their chemical *282 R subl , R sub2 , and R sub3 components, and reassemble those components in all possible combinations to see whether any such combination, thus synthesized, falls within an appealed claim. This game is called "Following In re Petering," and that it is. But we disagree with the board since our view is that In re Petering should not be followed in this case because Petering involved a very special situation which we do not consider comparable to the situation at bar.

In Petering we came to the conclusion that a specific compound, 6,7,- dimethyl- 9 - [beta - monohydroxethyl] - isoalloxazine, named in claim 10 and included in four other claims the rejection of which we affirmed, was actually described in the Karrer reference patent by reason of the particular disclosure of that patent which we felt would be recognized by those of ordinary skill in the art as a description of some 20 compounds in a limited class, the members of which were very similar to one another in structure and all of which possessed the same properties. The class was isoalloxazines, three-ring compounds on which there were, in the small class, three variable substituents, Y, Z, and R. But both Y and Z were limited to variation only as between hydrogen (H) and methyl (CH sub3), giving the four possible combinations H,H; H,CH sub3 ; CH sub3 ,H; and CH sub3 ,CH sub3 . R in every case was a hydroxyalkyl radical which might vary in length from -CH sub2 OH to -CH sub2 (CHOH) sub4 CH sub2 OH, a total of only five members of that series being included in the small class description, disregarding isomerism. The four possible Y and Z combinations times the five hydroxyalkyl possibilities made a total of 20 possible compounds. Furthermore, the patent attributed the vitamin activity of these compounds to the presence of a hydroxyalkyl radical at R and showed that the vitamin activity was the same whether Y and Z were hydrogen or methyl. On these facts we concluded, 133 USPQ at 280:

> It is our opinion that one skilled in this art would, on reading the Karrer patent, at once envisage each member of this limited class, even though this skilled person might not at once define in his mind the formal boundaries of the class as we have done here.

We put great emphasis in that opinion on the total circumstances in the case "including such factors as the limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus."

[5] We did not intend our Petering opinion or decision to become a precedent for the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant's disclosures, on the theory that such reconstructed disclosures describe specific compounds within the meaning of section 102. Furthermore, we do not find the present case to be of the type we had before us in Petering. Even if we take the 10 examples of the Franch or the 12 examples of the Swedish reference, take them apart and recombine them into different compounds than those named, we do not get a small recognizable class with common properties. We would apparently get from the French patent some 130 and from the Swedish some 156 compounds. And in doing this we are not dealing with such closely related units as the H and CH sub3 and the five hydroxyalkyl components in Petering but with such widely differing R super1 choices as p-acylaminobenzene, diphenyl, beta-naphthalene and dimethylbenzene, to name a few from the thirteen possible choices. And for the R super3 choices there are such diverse radicals as ethyl, dodecyl, benzyl, and alpha- naphthyl. We will not apply the Petering type of analysis to such a situation. We therefore disagree with the view of the board (which the solicitor has not urged on us) that claims 1 and 1 "can even to said to be anticipated." We note that the board seems to have originated its use of Petering. Although the examiner specifically considered that case on another point for which appellants cited it, his only comment about it was that it was "not deemed controlling." We also note that the board gave no indication that it intended to make a new ground of rejection (under section 102, for example, pursuant to Rule 196(b)) different from the ground relied on by the examiner which was limited to obviousness, a section 103 rejection.

We hold similar views as to the board's indication that a specific description of compounds within claims 1 and 2 can be made out of the Martin disclosure. To do this the board selects p-chloro- and p-bromo- for R (as used in appellants' claim 2, supra) and ethyl or isoamyl for R sub2 to create, ex post facto, four undisclosed specific compounds out of a possible 259, according to appellants' apparently valid calculations. This is not the kind of description we found in Petering and we do not find here any "anticipation" by the Martin patent of claims 1 and 2.

***283** The Obviousness Rejection

This leaves for consideration the original examiner's rejection of all claims on appeal as unpatentable over the references because of obviousness. As to this rejection, we proceed on the correlative postulate that none of appellants' claimed compounds is in the prior art and on the basis that the Patent Office contends that the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious * * * to a person having ordinary skill in the art * * *." 35 U.S.C. 103.

To make out the case most favorable to the Patent Office, in which the structural differences between the appealed claims and the prior art are as small as possible, the solicitor takes for comparison a compound within appellants' claims 1 and 2 (not specifically claimed) which he finds in the affidavit of Dr. Dorzbach, who made pharmacological tests on various compounds for appellants. Using the affidavit numbering, he calls this compound "(2)" and first compares it with compound "(7)", also from the affidavit. To these he then adds examples 8, 9, and 10 of the French patent and, with the same numbering, we name these five compounds as follows (our emphasis):

(2) N-(4-chloro-benzenesulfonyl)-N'-ethyl urea

(claimed)

(7) N-(4-chloro-benzenesulfonyl)-N'-methyl urea (affidavit)

(8) N-(4-chloro-benzenesulfonyl)-N'-benzyl urea (prior art)

(9) N-(4-methyl -benzenesulfonyl)-N'-phenyl urea (prior art)

(10) N-(4-methyl -benzenesulfonyl)-N'-dodecyl urea (prior art)

For varying reasons, none of the above compounds listed, other than (2), is within appellants' claims: (7) because the N' - methyl has only one carbon, (8) because N' - benzyl is excluded, (9) because the claims require a chloro- or bromobenzene group and there is none and also because N' - phenyl is excluded, and (10) because there is no chloro- or bromobenzene and N' - dodecyl is excluded, having 12 carbons, the limit being 7. Some of these differences which distinguish the claimed group of compounds from the prior art may appear small but they are significant.

Compound (7) occupies a unique position. We have noted that it is from an affidavit. That affidavit indicates that it is from the French patent but it is not; the affidavit was simply in error in that assumption but lists it as a "known" compound and thus the solicitor's brief lists it. The solicitor took some pains at the oral argument to point out that (7) is not to be found in the French patent and is not derivable from it for want of any disclosed reactant that would produce an N' - methyl. Though (7) is not statutory "prior art" in this case, it illustrates an important fact. Compound (2), here claimed, was shown by tests on rabbits to have hypoglycemic (blood sugar lowering) activity, though not as much as the second higher homolog with N' - butyl instead of ethyl. Compound (7), the next lower homolog, having an N'- methyl, was found by Dr. Dorzbach to have no hypoglycemic activity. And we here note that the compound which is the same except for having N' - propyl, intermediate ethyl and butyl in the series, described in claim 13, is effective enough to be on the market as "Diabinese."

[6] We think that, by his own admissions, the solicitor does not have the right to rely on compound (7) as prior art but according to our views it would make no difference if he could. He relies on it as a "next lower homologue" of claimed compounds and appellants have shown unexpected advantageous properties it does not possess. His next reliance is on compound (8) as one "analogous to the compounds, within the scope of claim 1, where the R sub2 substituent is a cyclo-group," the reference being to such compounds as those named in claim 6 and allowed claim 7 where the N' substituent is cyclohexyl or cyclohexyl- methyl, which are cyclo-alkyl, saturated substituents, not unsaturated aromatic substituents. The analogy is not close, in general; but the record here shows, as to compounds identical except that one has N' - cyclohexyl and the other N' - phenyl (compound (9) supra), that the latter has very high toxicity so as to be wholly unusable as a drug whereas the former has hypoglycemic activity and is non-toxic. (We have found no test of record on compound (8). We know nothing specific of its properties.)

The solicitor does not place any particular reliance on compound (10) beyond displaying its formula. Notwithstanding its structural similarities to the claimed compounds, the evidence is that upon test it proved to have no hypoglycemic activity at all.

Summarizing on the French and Swedish patents, the Patent Office position is that they disclose compounds which are homologs of or analogous to appellants' compounds, wherefore the latter are obvious. At the same time it *284 is admitted that these references do "not teach that any of the compounds have the property of lowering blood sugar," to quote the board.

The Patent Office also urges that appellants' compounds, though not named in the Martin patent, would be obvious therefrom, insofar as they are defined in claims 1-5 and 13. That position is based on the contention that there

is enough in Martin to teach one how to make compounds of the formula, R- benzenesulfonyl-R'-urea (to paraphrase the examiner) where R is p-chloro and p- bromo and R' is ethyl or isoamyl, which would fall within the claims aforesaid, through no such compounds are shown in Martin. This reference from beginning to end is concerned with compounds wherein R is a nitrogen-containing group in para position, p-nitro (NO sub2), p-amino (NH sub2), or p-acetylamino (CH sub3 -CO-NH), all outside of appellants' claims. The patent shows how to convert nitro to amino by catalytic reduction and acetylamino to amino by hydrogenation. All specific examples end up with, and all product claims are directed to, amino compounds.

One of Martin's processes is to cause "salts of sulphonamides of the benzene series, which contain in the p-position a nitrogen-containing group or a substituent replaceable by such a group, to react with carbonic acid derivatives capable of reaction." (Emphasis ours.) As examples of sulfonamides, salts of which may be used, he includes among four named salts "p-chloro- or bromobenzene sulphonamide." It is this disclosure which the Patent Office relies on. This appears from the record before us to be an anomalous disclosure for the reason that Martin expressly states, twice, that he wants a substituent in the para position replaceable by a nitrogen-containing group if it is not one, and the proofs here show, what the examiner expressly admitted, that p- chloro and p-bromo cannot be converted to a nitrogen-containing group, "by any of the known processes available in the prior art." The examiner felt this fact was immaterial and so did the board. Strictly speaking, perhaps it is; but we think one skilled in the art trying to follow Martin's processes to obtain his products would not be likely to use p-chloro- or bromobenzene sulfonamide salts. Martin did not in any of the 24 reactions he describes.

Summarizing on the Martin patent, there is no disclosure or description in it of any of appellants' compounds and, a fortiori, no description of their properties but at most disclosures of processes by which some of them might be made. As we understand this record, it is not contended that those skilled in the art would not know how to make the claimed compounds. Appellants' specification says, "The compounds of the above general formula [as in claim 1] are made by methods known for making sulphonyl-ureas." The Martin disclosure, therefore, is no closer to appellants' compounds than a next adjacent homolog or an analogous compound would be and contains no more information about properties of the compounds it does disclose than the French or Swedish patents.

As to all references, the solicitor, when asked at oral argument whether they contain anything that would help in the treatment of diabetes, replied, "No. I unhesitatingly say no."

[7] For a score of years a consistent line of decisions has emanated from this court refusing to sustain rejections in fact situations essentially like that here. In the passage we quoted above from the solicitor's brief he correctly stated that the issue is obviousness as we have propounded the nature of that issue in the Lambooy, Petering, and Papesch cases. In Papesch we tried to make it clear that in our opinion the use of the term "obvious" in section 103, a section whose history shows it was intended to ameliorate the effect of certain harsh court decisions on patentability, does not make unpatentable chemical compounds which would have been patentable under decisions antedating the enactment of that section, reviewed in Papesch. We also dealt with the contention that a compound was so obvious that we should pay no attention to its unforeseeable beneficial or advantageous properties in determining patentability, rejecting that proposition, saying: "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."

The board and the solicitor (the examiner did not have the case before him) attempt to distinguish this case from Papesch. The board said:

> The situation here is not considered to be the same, in particular, it is pointed out that there are no comparative tests, or even allegations, that the compounds of the reference used as the basis of rejection do not possess the property involved, nor did the reference in Papesch disclose the variety of uses disclosed by the reference here, in fact it did not report any biological tests or disclose any use.

[8] *285 We cannot positively identify what the board had in mind as the compounds "used as the basis of rejection" but if we look to those selected by the solicitor for inclusion in his brief as the closest prior art, the board would seem to be in error in saying there were no comparative tests and that there is no evidence they "do not possess the property involved * * *." We discussed above comparative tests which do show that the prior art compounds relied on do not possess the properties we find to be an integral part of appellants' invention. If, perchance, the board is referring to the compounds within the appealed claims which it was able to reconstruct from the dissected examples of the references, our answer is that we rejected that approach and also that the board is patently asking for proof of the impossible. As to what the Robins et al. reference in Papesch may or may not have disclosed by way of uses, we think that is no ground of distinction because our decision in that case rested on what the appellant disclosed which was not disclosed in the reference. Our deci-
[8] sion here rests on similar ground. On the obviousness issue, the vague "basket" disclosure of possible uses in the French and Swedish patents and the equally vague disclosure of the Martin patent are unimportant. What is important is the fact that the utility discovered by appellants is not disclosed in the prior art. We see no factual ground on which to distinguish the Papesch case. This is also our answer to the solicitor's attempt to distinguish that case in saying:

> In the instant case, the French patent discloses utilities for the compounds disclosed therein, and to this extent, the factual situation here differs from that of the Papesch case * * *.

He went a bit further, however, in asserting that the compound of Example 9 of the French patent was shown by evidence in the Dorzbach affidavit to have the utility "described for appellants' compounds * * *." While the evidence does show that the compound had a blood sugar level lowering property, it also disclosed that it was lethal, a fact omitted from the solicitor's argument. Very high toxicity, in our view, cancels out any notion of anti- diabetic "tuility." Furthermore, it was appellants who disclosed the property to which the solicitor refers. It was not known to the prior art.

For the foregoing reasons, we think this case is clearly within the principles of the Papesch case and we see no need to repeat anything there stated. That is not a case that stands alone, having been predicated on the ten or so cases reviewed therein. We have also followed it or applied the same principles without referring to it in In re Riden, Jr., 50 CCPA 1411, 318 F.2d 761, 138 USPQ 112, 114, where Judge Almond, speaking for the court, said:

> Chemical cases should not be decided solely on the basis of homology or analogy in structural formulae. The determination of obviousness is not the mechanistic overlaying of chemical formulae to observe whether a difference greater than a methylene group or a chlorine atom exists.

and in In re Lunsford, 51 CCPA 1000, 327 F.2d 526, 140 USPQ 425, 427, wherein Judge Martin, speaking for the court, finding an "unobvious property inherent in the claimed compounds" sufficient to overcome a showing of very close structural obviousness, said "there is no basis in law for ignoring any property," and in In re Ward, 51 CCPA 1132, 329 F.2d 1021, 141 USPQ 227, 228, wherein the court said:

> * * * claims to chemical compounds are drawn to more than structural formulae. They define the compounds themselves and

compounds possess properties which must be considered along with the formulae.

Here the esters might appear to be obvious in terms of the concept of their structure but that is only half the game. There remains the consideration of the properties of the esters. * * * That unexpected property cannot be ignored in the determination of obviousness of the claimed esters as substances and not as structural formulae.

Of course, we made the same sort of holding in the Lambooy case and in the Petering case as to some claims, yet the Patent Office has continued to present the identical issue to us. We hope our view of the law has now become clear.

There remains one point to consider. The board opinion presents an argument as to why our view of the law is wrong, in the following passage:

The French patent mentions textile treating agents, disinfectants, parasiticides, plasticizers and intermediates. If someone made compounds coming within the scope of the claims for any such purposes or used them for such purposes, the claims would be infringed, but what would lowering blood sugar have to do with the matter? The argument based on this property would of course be germane to at least some of the non*286 -elected claims [process of lowering blood sugar in the treatment of diabetes?] which are so restricted that this property has significance, but to allow any claim by reason of this property when it will dominate activity wholly unrelated to the property argued does seem somewhat irrational.

We have given full consideration to the foregoing. We do not think our holdings are irrational and we have made them with our eyes open. The solicitor put the question flatly before us at the conclusion of his oral argument saying that, while he did not deny that appellants had made an important invention in the field of diabetic medication, the question for this court is, "Is this the way to claim it in this case? Should it be claimed so that the property or the invention or the discovery that the appellants made here is defined in the claim and not merely set forth in the record? That's our position."

[9] Again, we considered the same position in Papesch and answered it by approving claims to compounds, recognizing the practical advantages product claims have from the standpoint of protection. As we have indicated above, where we are concerned with new compounds in which unobvious properties have been found, the properties being inherent in the compounds, one could even say it is "somewhat irrational" to say the "invention" is not in the compounds. Semantics aside, the hard facts were stated by appellants' counsel in response to court questioning at the end of his argument:

The process claims that the Patent Office would like to drive us to are of very, very little value as a real live honest-to-goodness matter. We all know that. So we simply have to ask for product claims and that's why we're here. * * * The difficulty is this: section 271 of the Patent Code helped out immensely with respect to this problem of misuse but it does not make a method claim the equivalent of a product claim, and that is the fundamental difficulty.

[10] Our view, in brief, is that the basic principle of the patent system is to protect inventions which meet the statutory requirements. Valuable inventions should be given protection of value in the real world of business and the courts. We do not share the board's theoretical fear that allowing the compound claims on appeal will "dominate activity" with respect to the use of the claimed compounds for purposes such as those disclosed in the French patent, or any purposes other than the treatment of diabetes, to put it as broadly as possible. For one thing, the claims here will give no domination whatever over the compounds disclosed in the references. For another, balancing the alternatives of providing adequate protection to appellants' limited group of anti-diabetic agents against the

mere possibility that someone might wish to use some of them for some such purpose as making a textile size, we favor the former.

For the foregoing reasons and others stated in Papesch and later cases following its principles, the decision of the board is reversed.

FN1 This application is not of record here and we know nothing more about it.

FN2 Appellants' brief states that this was another of their developments and that they have obtained U.S. patent 2,968,158 thereon, not of record.

FN3 The corresponding broad description of the specification says that Rsub2 stands for the various named radicals, rather than "atoms" and the use of the latter term in claim 1 would appear to be inadvertent error.

FN4 Article by Samuel J. N. Sugar, M.D., et al. in AMA Archives of Internal Medicine for September, 1959, pages 360-364; article by L. L. Pennock, M.D., in the Pennsylvania Medical Journal for October, 1959, pages 1537-1539.

FN5 The examiner and the board give this patent a date of Dec. 27, 1945, but according to the translation of record that was the filing date of the French application. The patent was granted 25 Nov. 1946 and published 10 March 1947. We state this merely for accuracy. No one has made a point of it.

FN6 The record shows that claim 13 was suggested to appellants under Rule 203 in an office action of July 25, 1957, and was made by them on September 25, 1957. This probably explains why claim 13 does not correspond to any specific example in appellants' application. The other party to the interference, now dissolved, was William M. McLamore of Chas. Pfizer and Co. Another party was added later, Frederick J. Marshall and Max V. Sigal, but was dissolved out Dec. 2, 1959, before the interference was dissolved on June 20, 1960.

FN7 "Therapeutic" per Webster's 7th New Collegiate Dictionary, means "of or relating to the treatment of disease or disorders by remedial agents or methods." Gould's Medical Dictionary (5th ed.), says: "therapeutics. The branch of medical science dealing with the treatment of disease."

FN8 [4] We are aware that attorneys often write compound claims including a statement of some inherent property, general or specific, for example the product claims of the Martin patent just quoted from, or the claims of the Karrer patent quoted in our opinion in the Petering case. Where the balance of the claim fully identifies the compound, as is true in both instances, and the property is inherent, we fail to see that such statements add anything to the claim definition of the named compound.

MARTIN, Judge, concurring.

I agree with the majority opinion except insofar as it finds a section 102 rejection in the board's decision. I do not think the board's passing reference to In re Petering, 49 CCPA 993, 301 F.2d 676, 133 USPQ 275, i.e., by following Petering claims 1 and 2 "can even be said to be anticipated," can properly be taken as a section 102 rejection. If the board meant such a passing comment to be a rejection under section 102, it should have so stated.

As the majority opinion notes, the examiner and solicitor restrict themselves to the view that the rejection is one of obviousness under section 103. In connection with the obviousness rejection, In re Petering, supra, is correctly cited by the majority since the second issue in that case was one of obviousness. The board affirmed "the decision of the examiner rejecting the claims * * *." Appellants did not notify this court in their reasons of appeal of any appeal from an affirmance of a rejection based on section 102.

Thus as the author of the Petering case, I must view as dictum the discussion in the majority opinion, under the heading "The Board's Own Anticipation Rejection," of that portion of In re Petering which relates to the section 102 issue. The appeal before us does not present a clear opportunity to indicate either the limits of the Petering case or its place within the scope of enabling disclosures of section 102.

Cust. & Pat.App.

145 U.S.P.Q. 274

END OF DOCUMENT

Schering Corporation
v.
Precision-Cosmet Co., Inc.

District Court, D. Delaware

No. 83-829

Decided July 2, 1985

United States Patents Quarterly Headnotes

PATENTS
[1] Pleading and practice in courts -- Motions -- For summary judgment -- Issues determined (§ 53.6335)
Trial court, when considering motion for judgment n.o.v. concerning jury verdict of patent validity, may not review issue of validity de novo, but is limited by standard of review and guidelines set forth in Connell v. Sears, Roebuck & Co., 220 USPQ 193, and Weiner v. Rollform, Inc., 223 USPQ 369.

PATENTS
[2] Patentability -- New use or function -- Composition of matter (§ 51.555)
Use of tertiary butyl styrene (TBS), which is old composition, to create gas permeable hard contact lens constitutes significant modification and thus precludes assertion that claim is invalid as simply new use for old substance.

PATENTS
[3] Accounting -- Increased or treble damages or profits (§ 11.35)
Double damages, rather than treble damages, should be awarded against infringer, in view of evidence which demonstrated willful infringement but which also demonstrated that infringing product had been, to significant degree, developed independently, and which demonstrated that infringer had not litigated in bad faith.

***278** Action by Schering Corporation, against Precision-Cosmet Co., Inc., for patent infringement. On plaintiff's motion for award of prejudgment interest, increased damages, and attorney's fees, and on defendant's motion for judgment n.o.v. or for new trial. Plaintiff's motion granted.

Bruce M. Stargatt, Richard H. Morse, and Young, Conaway, Stargatt & Taylor, all of Wilmington, Del., and John O. Tramontine, Eric C. Woglom, Jesse J. Jenner, Richard M. Barnes, Douglas J. Gilbert, and Fish & Neave, all of New York, N.Y., for plaintiff.

Paul E. Crawford, and Connolly, Bove, Lodge & Hutz, both of Wilmington, Del., and Douglas J. Williams, Mark J. DiPietro, and Merchant, Gould, Smith, Edell, Welter & Schmidt, all of Minneapolis, Minn., for defendant.

Stapleton, Circuit Judge. [FN1]

This is a patent infringement action brought by plaintiff Schering Corporation against defendant Precision-Cosmet Co., Inc. ("P-C"). On March 11, 1985, a jury returned a general ***279** verdict for Schering in the amount of $1,263,482, along with answers to a number of interrogatories. Currently before the Court are motions by both parties. P-C has moved for Judgment Notwithstanding the Verdict ("JNOV") and, in the alternative, for a new trial. Schering has moved for an award of prejudgment interest, increased damages, and reasonable attorney's fees.

I. MOTION FOR JNOV

The moving party is entitled to a JNOV when the Court is convinced:

(1) that reasonable persons could not in light of . . . [the] evidence have found the facts necessary to support the jury's verdict; or (2) that the facts properly found cannot in law support that verdict. If, on the other hand, the court is convinced that reasonable persons could have found in light of. . . [the] evidence the facts necessary to support in law the jury's verdict, denial of the motion for JNOV is required.

Weinar v. Rollform, Inc., 744 F.2d 797, 805, 223 USPQ 369, 373 (Fed. Cir. 1984) (citing Connell v. Sears, Roebuck & Co., 722 F.2d

1542, 220 USPQ 193 (Fed. Cir. 1983)).

The Federal Circuit has also set forth guidelines that a court must follow in considering a motion for JNOV. Under these guidelines, a court must:

(1) consider all the evidence; (2) in a light most favorable to the non- mover; (3) drawing reasonable inferences favorable to the nonmover; (4) without determining credibility of witnesses, and (5) without substituting its choice for that of the jury between conflicting elements in the evidence.

Connell v. Sears, 722 F.2d at 1546, 220 USPQ at 197. Further, where as here the issue raised is validity, "the true question is whether [defendant], which bore the burden, 35 U.S.C. §282, submitted such evidence as would preclude a reasonable jury from reaching a verdict of validity."Weinar v. Rollform, 744 F.2d at 805, 223 USPQ at 373. In this regard, it is well to note that the question presented by a motion for JNOV is not whether the district court would have found the invention obvious as though there had been no trial before a jury. Id. Rather, the question is whether the jury's verdict that the Schering patent is valid (i.e. has not been proved invalid) is supported by substantial evidence. Id. (citing Bio-Rad Laboratories, Inc. v. Nicolet Instrument Corp., 739 F.2d 604, 222 USPQ 654 (Fed. Cir. 1984)).

[1] Notwithstanding these principles, P-C argues that the trial court may review the issue of validity de novo. In so doing, P-C relies upon the Federal Circuit's recent statement in E.W.P. Corp. v. Reliance Universal, Inc., 755 F.2d 898, 905, 225 USPQ 20, 24 (Fed. Cir. 1985), that validity "is a question of law and that question is freely reviewable by this court."E.W.P. Corp., however, was not tried before a jury. In Connell v. Sears, the court explained that though obviousness is indeed a question of law, it is an issue that may properly be submitted to a jury, in the same manner that other legal questions, such as negligence, are regularly submitted to juries in personal injury cases. 722 F.2d at 1547, 220 USPQ at 197; Railroad Dynamics, Inc. v. A. Stucki Co., 727 F.2d 1506, 1514-15, 220 USPQ 929, 937 (Fed. Cir. 1984). Thus, though P-C is clearly correct that obviousness is a question of law, it is equally clear that when faced with a motion for JNOV concerning a verdict of validity, consideration of that motion by the trial court is limited by the standard of review and guidelines set forth in Connell v. Sears and Weinar v. Rollform.

A. The Obviousness Issue

The parties agree, for purposes of the motion for JNOV and a new trial, that the claimed invention is a gas permeable hard contact lens made principally of tertiary butyl styrene ("TBS"). P-C contends that such an invention would have been obvious to one with ordinary skill in the art in light of seven items of prior art, only one of which was before the Patent Examiner: (1) the Fatt article (DX-212AG); (2) Larke & Tighe U.K. Patent No. 1,394,056 (DX-212M); (3) Gaiser U.S. Patent No. 2,674,743 (DX-212B); (4) the Salame article (DX-212H); (5) Lundberg U.S. Patent No. 4,057,598 (DX-212C); (6) the Dow brochures (DX- 212AH, DX-212AI), and (7) Larke U.K. Patent No. 1,395,501 (DX-212N).

Defendants contend that the above prior art paved a clear path to the inventor's decision to substitute the higher alkyl styrenes, including TBS, in a hard contact lens formulation, in order to provide improved gas permeability.

I conclude, however, that there is substantial evidence in the record supporting the conclusion that the subject matter of the invention of the Schering patent taken as a whole would not have been obvious at the time the invention was made to a person of ordinary skill in the art.

A principal contention made by P-C with respect to the question of obviousness is that the high gas permeability of a TBS lens would be predicted in 1977 on the theory that the addition of bulkier side groups to a polymer creates a more "open structure" (lower density) for the passage of oxygen. P-C presented *280 the testimony of Dr. Salame

for purposes of explicating this theory. Both of Schering's experts, however, expressly opined that the higher permeability of TBS would not have been predictable and provided reasons for their opinions. Dr. Hoehn expressly stated that the permeability of TBS was not predictable. (Tr. 1620). He explained that, contrary to Dr. Salame's theory, permeability of a material is not a property of the polymer; it is instead a property of the article made from the polymer. (Tr. 1618). According to Dr. Hoehn, predicting permeability with any degree of success depends on whether one has studied the article made from the polymer. Id.

Dr. Fatt testified that he would not be able to predict increased permeability of a polymer merely on the basis that bulkier side groups were added. (Tr. 343). Dr. Fatt opined that gas permeability was predicted upon two components -- the speed at which the molecule traveled through the plastic and the solubility of the gas in the plastic -- and that these components could offset one another with the result that addition of a bulkier group would not necessarily lead to increased permeability. (Tr. 343). He also indicated that the lower density of a polymer did not always lead to increased permeability. (Tr. 342).

Dr. Fatt further testified that the increased permeability of ethyl, isopropyl and tertiary butyl styrene over stryene and methyl styrene was unexpected. (Tr. 270-71). Mr. Deichert of Bausch & Lomb also acknowledged that the permeability of TBS was "surprising and unexpected". (Tr. 1093).

P-C contends that the Larke & Tighe patent (DX-212M) teaches one skilled in the art that the addition of bulkier side groups, by providing more open space, will improve oxygen permeability. P-C's reference here is not to any teaching concerning the compositions claimed in the Schering patent but, rather, to the following language of the Larke & Tighe patent:

> Although the invention is not limited to any particular theory, it is believed that the bulky side groups attached to the polymer chain disrupt the chain symmetry and regularity of the polymer giving a more open structure having increased gas permeability.

Given the contrary testimony of Dr. Fatt and Dr. Hoehn as to the understanding of those working in the art at the relevant time, the jury was not bound to conclude that the artisan of ordinary skill would take this theoretical speculation at face value. Testimony to the contrary by Drs. Hoehn and Fatt represented substantial evidence that increased permeability was not predictable.

Dr. Fatt further testified that the use of TBS in a hard contact lens would not have been obvious to him from the Lundberg patent (DX-212C). He explained that the patent disclosed TBS as one of 25 to 30 monomers for the hydrophobic block of a copolymer and that one of the 25 possible uses for the copolymer was a soft, not hard, contact lens. He indicated that there was no mention of gas permeability in Lundberg. (Tr. 279-293). He explained that out of the many possible combinations of uses with different monomers, disclosed by Lundberg, it would not have been obvious to pick out the use of TBS in a soft lens, let alone in a hard one. (Tr. 292).

As to the Gaiser patent (DX-212B), Dr. Fatt indicated that neither TBS nor any other alkyl styrene claimed in the Schering patent is mentioned in Gaiser. (Tr. 297). Moreover, both Drs. Fatt and Salame testified that the substituted styrenes referred to by Gaiser constituted a class of more than one hundred compounds. (Fatt Tr. 297-98; Salame Tr. 1271-72). Most significantly, Fatt testified that Gaiser did not mention anything with respect to the improved gas permeability that resulted from the use of certain substituted styrenes. (Tr. 297).

While Dr. Salame testified that the increased permeability of TBS would have been obvious, the jury was entitled to reject his testimony if they did not find it credible. And it is not the province of this Court to weigh the credibility of Salame's testimony against the testimonies of Hoehn and Fatt. Connell v. Sears, 722 F.2d at 1546-47, 220 USPQ at 196-97.

The question here is whether P-C, in light of its burden to prove invalidity by clear and convincing evidence, submitted such evidence as would preclude a reasonable jury from reaching a verdict of validity. I conclude that it did not and that the jury's conclusion on obviousness was supported by substantial evidence.

B. Anticipation

P-C argues that the Gaiser patent, which teaches that contact lenses can be made of styrene or substituted styrenes, anticipates a number of the asserted claims of the Schering patent. P-C points to the testimony of Dr. Fatt and Dr. Loshaek. Dr. Fatt testified that he would have understood the reference to substituted styrenes in the Gaiser patent to mean divinyl benzene. (Tr. 295- 296). He also indicated that a contact lens of divinyl benzene, having a substantial amount of ethyl styrene as an impurity, would come within the language of claim 1 of the patent-in-suit. Dr. Loshaek testified that the term "substituted styrenes" could mean the styrenes he had been testifying about, including TBS. (Tr. 1460-61).

*281 Dr. Fatt also testified, however, that neither TBS, isopropyl styrene, ethyl styrene, nor any other substituted styrene are mentioned in the Gaiser patent. (Fatt 295-297). Dr. Fatt also stated that Gaiser did not mention gas permeability with respect to substituted styrenes. (Tr. 297). In addition, both Drs. Fatt and Salame testified that the class of substituted styrenes includes more than one hundred compounds. (Fatt Tr. 297-298; Salame Tr. 1271- 72).

As recently stated by the Federal Circuit:

> A party asserting that a patent claim is anticipated under 35 U.S.C. 102 must demonstrate . . . identity of invention. In cases like this, identity of invention is a question of fact, and one who seeks such a finding must show that each element of the claim in issue is found, either expressly described or under principles of inherency, in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device or practice . . . . (citations omitted).

Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771-72, 218 USPQ 781, 789 (Fed. Cir. 1983), cert. denied, ---------- U.S. ----------, 224 USPQ 520 (1984).

The general rule is that a prior genus does not anticipate a later species. I Chisum, Patents § 3.02[2] (1985); see In re Ruschig, 343 F.2d 965, 145 USPQ 274 (C.C.P.A. 1965). If, however, it is possible to derive a class of compounds of lesser scope than the genus disclosed in a prior art reference on the basis of preferences ascertainable from the remainder of the reference, anticipation may be found. E.g., Application of Schaumann, 572 F.2d 312, 316, 197 USPQ 5, 9 (C.C.P.A. 1978); In re Petering, 301 F.2d 676, 681, 133 USPQ 275, 279-80 (C.C.P.A. 1962). The anticipating reference must contain within its four corners a sufficient description to enable one to practice the invention without experimentation or inventive skill. Phillips Elec. & Pharmaceutical Indus. Corp. v. Thermal & Elec. Indus., Inc., 450 F.2d 1164, 1169, 171 USPQ 641, 644-45 (2d Cir. 1971); Dewey & Almy Chem. Co. v. Mimex Co., 124 F.2d 986, 990, 52 USPQ 138, 142-43 (2d Cir. 1942); I Chisum, Patents § 3.04[1][6] (1985). See CBS v. Sylvania Electric Prod., Inc., 415 F.2d 719, 725, 162 USPQ 577, 581 (1st Cir. 1969) (test is whether the prior art reference "describes the invention with sufficient clarity and specificity so that one skilled in the art may practice the invention without assistance from the patent claimed to have been anticipated.")

Based on these principles, I conclude that there was substantial evidence in the present case from which a reasonable jury could conclude that Gaiser did not anticipate the various claims of the Schering patent. Indeed, given the text of the Gaiser patent and the undisputed evidence with respect to the number of compounds coming within the class of substituted styrenes, it is difficult to understand how the jury could have concluded otherwise. Gaiser does not mention any particular substituted styrene, makes no

references to the permeability of specific substituted styrenes, and provides no basis whatever for preferring any sub-group of substitute styrenes over other substituted styrenes for use in making contact lenses. Given the fact that substituted styrenes comprise a class in excess of one hundred compounds, it seems clear that the elements of the claimed invention, namely TBS, were not adequately described by Gaiser for purposes of identification; and that one of ordinary skill in the art would have had to engage in extensive experimentation to get from Gaiser to the Schering invention.

In re Petering and In re Schaumann, cases relied on by P-C, both involved situations where a reference disclosing a broader group of compounds was narrowed to a small, definite and limited class of compounds by preferences expressed in the remainder of the disclosure. In the present case, there was evidence indicating that Gaiser would not have pointed one toward a more limited class of substituted styrenes, such as, for example, the alkyl styrenes disclosed by the patent-in-suit.

C. New Use For Old Substance Issue

P-C argues that as a matter of law claims 1, 15, 18, 21, 25 and 27 are invalid as reading on a homopolymer of TBS, which is admittedly an old composition. P-C predicates its argument upon the well-established doctrine that a new use for an old substance is not patentable. In re Thuau, 135 F.2d 344, 57 USPQ 324 (C.C.P.A. 1943). Thus, P-C argues that the terms "contact lens" and "buttons" appearing in the preambles of the various challenged claims merely describe a new use for TBS.

[2] I conclude, however, that rather than merely claiming a new use for TBS, the Schering patent discloses a new composition made from TBS, i.e., a hard gas permeable contact lens or button. In Thuau, the applicant attempted to claim a compound that he had failed to "change in any way."Id. at 347, 57 USPQ at 326. Here, the Schering patent discloses more than the mere chemical composition TBS; it claims contact lenses that have been cut and shaped from the raw compound itself. Such a modification is legally significant and prevents the challenged claims from falling under the doctrine of In re Thuau.

"The rule that no product patent may issue for discovery of a new use for an old product or *282 process is tempered by the 'doctrine of slight changes.' " Chisum, I Patents § 1.03[8][b] at 1-171 (1985). The doctrine of slight changes extends to the area of chemical compounds. Id. at 1-174. That the modification of an old compound into a new patentable one may indeed be slight is illustrated by Application of Wiggins, 397 F.2d 356, 158 USPQ 199 (C.C.P.A. 1968).

Wiggins sought to patent a compound (referred to by the court as Osub2) because of its analgesic and pain relieving activity in humans. One of Wiggins' claims rejected by the examiner and Board of Appeals prescribed a dosage of Osub2 from "about 10 milligrams to about 1000 milligrams."Id. at 358, 158 USPQ at 201. The prior art consisted of an article by Wolf describing the exact same compound and its use in protecting mice from x-ray radiation. Wolf did not suggest the use for Osub2 discovered by Wiggins, nor did Wolf suggest administering Osub2 in the 10 to 1000 milligram range disclosed by Wiggins. The Board of Appeals rejected the application on the ground that Wiggins had "discovered a new use for an old composition."Id. at 359 n.5, 158 USPQ at 201-02 n.5 (emphasis supplied by Board). The court disagreed, finding that Wiggins had discovered a few composition since the amounts of Osub2 employed by Wiggins in his composition were different from the amounts that Wolf had administered in his experiments. Id. at 359-60, 158 USPQ at 201-02.

In light of Wiggins, wherein a mere change in the amount of a compound was deemed sufficient to change an old composition into a new one, it would appear to follow that the transformation of TBS into a contact lens involves the creation of a new composition.

In arguing to the contrary, defendants rely heavily upon Application of Benner, 174 F.2d 938, 82 USPQ 49 (C.C.P.A. 1949). In that case, the applicant argued that he had changed the shape of the compound at issue. The court rejected this argument because the applicant had failed to describe the purported change in shape in the claims of the patent. Id. at 942-43, 82 USPQ at 54. Moreover, the court refused to recognize the introductory phrases of the challenged claims -- which recited a "ball mill lining element" -- for purposes of showing that the compound described in the claims had been shaped into a particular article, i.e., a new composition. P-C similarly argues that the challenged claims of the Schering patent, as distinct from their preambles, merely describe TBS, and that Schering cannot use the preambles, which describe contact lenses and buttons, to further limit what is already defined by the claims themselves.

After Benner, the Court of Claims and Patent Appeals in Kropa v. Robie, 187 F.2d 150, 88 USPQ 478 (C.C.P.A. 1951), set down guidelines for determining when the introductory phrase of a claim would be permitted to limit the claim itself. The court indicated that the preamble would be permited to limit a claim where it "was deemed essential to point out the invention defined by the claim or count," that is, where "the preamble was considered necessary to give life, meaning and vitality to the claims or counts."Id. at 152, 88 USPQ at 481. The court performed an exhaustive analysis of prior precedent and found inter alia:

> The preamble is a limitation where it specifies an article or composition in which there inheres a field of specific use, and the constituents of the article which are recited in the portion of the count following the preamble are old compounds not theretofore known to be useful in such an article.

Id. at 159, 88 USPQ at 487. The Court of Appeals for the Federal Circuit has continued to look to the preamble when "necessary to give meaning to the claim and properly define the invention."Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 896, 221 USPQ 669, 675 (Fed. Cir. 1984), cert. denied, 53 U.S.L.W. 3239, 225 USPQ 795 (October 1, 1984).

In the present case, the words "contact lens" and "button" are essential to point out the invention defined by the claims. It is only by reference to the introductory phrase of the challenged claims that it can be known that the subject matter defined by the claims is comprised as a contact lens or as a button adapted to be formed into a lens. In so holding, I note that "claims should be so construed, if possible, as to sustain their validity."ACS Hosp. Systems, Inc. v. Montifiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 932 (Fed. Cir. 1984).

D. Structural Similarity

P-C contends that a hard contact lens of TBS was obvious because TBS is an "isomeric homolog" of the prior art styrene or methyl styrene hard contact lenses.

While it is true that close structural similarity between prior art compounds and those that are claimed may be an indicia of obviousness, the subject matter of the invention as a whole may be non-obvious if the claimed compound has unexpected properties. Application of Payne, 606 F.2d 303, 314, 203 USPQ 245, 255 (C.C.P.A. 1979); In Re Papesch, 315 F.2d 381, 137 USPQ 43 (C.C.P.A. 1963).

In the present case, the jury was presented with substantial evidence upon which it could *283 reasonably have concluded that a lens of TBS had such unexpected properties as to rebut any inference that might be drawn from structural similarity. Dr. Fatt, for example, testified that the two alkyl styrenes preferred by the Schering patent, TBS and isopropyl styrene, as well as ethyl styrene, all demonstrated unexpected increases in gas permeability over the prior art styrene and methyl styrene. (Fatt Tr. 270-71).

II. MOTION FOR A NEW TRIAL

P-C moves in the alternatives for a new trial on the grounds that (1) the verdict with respect to a number of issues is against the weight of the evidence; (2) the damages are excessive; and (3) errors in certain of the jury instructions prejudiced defendant's case.

A motion for a new trial differs from a motion for JNOV in that:

> A motion for a directed verdict or for judgment n.o.v. raises the legal sufficiency of the evidence, and is to be sharply distinguished form a motion for a new trial on the ground that the verdict is against the weight of the evidence. The latter motion is addressed to the sound discretion of the trial court, which may set aside the verdict as contrary to the preponderance of the evidence although a directed verdict or judgment n.o.v. is not justified (footnote omitted).

6A J. Moore, Moore's Federal practice § 59.08(5) (2d ed. 1984) (hereinafter Moore, supra). The standard of review in considering a motion for a new trial is most often formulated in one of three ways. Thus, a new trial will be granted if the verdict is against the clear weight of the evidence, Shatterproof Glass Corp. v. Libbey-Owens Food Co., 758 F.2d 613, 626, 225 USPQ 634, 643 (Fed. Cir. 1985); 6A Moore, supra, § 59.08(5) (emphasis added), or if the court is convinced the jury has reached a "seriously erroneous result," Herman v. Hess Oil Virgin Islands Corp., 379 F.Sup. 1268, 1271 (D.V.I. 1974), aff'd, 524 F.2d 767 (3d Cir. 1975), 6A Moore, supra, § 59.08(5), or if there has been a miscarriage of justice. Parsons v. Doctors For Emergency Services, 81 F.R.D. 660, 662 (D.Del. 1979); Moore, supra § 59.08(5).

A. Infringement By Saturn II Lens

P-C contends that the jury's finding of infringement of the Schering patent by the Saturn II lens is against the weight of the evidence. P-C argues that the Saturn II, because of its soft skirt, is fundamentally different from the hard contact lens claimed by the Schering patent and could not have infringed the Schering patent either literally or under the doctrine of equivalents. I conclude, however, that the clear weight of the evidence does not warrant overturning the jury's finding of infringement with respect to the Saturn II.

P.C. admits that the Saturn II lens is characterized by a hard center. Dr. Fatt testified that the portion of the Saturn lens that its wearer looks through is hard, and that, as far as vision is concerned, the Saturn II is a hard contact lens. (Fatt Tr. 385). P-C admits (Def. Br. 36) that the hard portion of the Saturn II functions to correct astigmatism and there was testimony during trial that one of the advantages of the hard lens over the soft is that the hard lens corrects astigmatism.

Since the asserted claims of the Schering patent are not closed, the addition of the soft skirt to the hard center of Saturn II did not preclude a finding of literal infringement by the jury. In addition, the jury was entitled to conclude that Saturn II infringed under the doctrine of equivalents -- especially in light of Dr. Fatt's testimony.

I am not persuaded that the verdict of infringement was clearly not based upon a preponderance of the evidence, or that there has been a miscarriage of justice with respect to this issue.

B. The Question Of Validity

P-C submits that for the same reasons it is entitled to a JNOV on the issues of obviousness and anticipation, it is alternatively entitled to a new trial on those issues on the ground that the jury's verdict is against the weight of the evidence. Having already discussed much of the relevant testimony and evidence with respect to this matter, I need not repeat it here.

Suffice it to say that I am unable to conclude that the jury's determination respecting validity was contrary to the clear weight of the evidence.

C. Damages

P-C contends that Schering failed to satisfy its burden of showing what a reasonable royalty would be, and that the jury's award is excessive and against the weight of the evidence.

Schering introduced evidence as to what would be a reasonable royalty for P- C's infringement through the testimony of Dudley Smith, an expert on patent licensing. Basically, Mr. Smith concluded that after a hypothetical licensing negotiation, the parties would have agreed to a 50/50 split of profits which he translated into a royalty based upon 30% of the *284 gross projected sales prices for all lenses made by P-C. P-C did not challenge Mr. Smith's credentials or experience at trial and he is clearly a well qualified expert on licensing. Notably, P-C did not offer the expert testimony of any licensing witness of its own.

Mr. Smith provided extensive testimony explaining how he arrived at his recommended reasonable royalty. He explained that the procedure for determining a reasonable royalty is to assume a hypothetical negotiation between a willing licensor and willing licensee who are attempting to agree on a reasonable royalty rate for a license under the patent-in-suit. Smith constructed the hypothetical negotiation by using what he considered a generally recognized royalty rate for patent licenses and then considering the effect of numerous factors that might increase or decrease the initially chosen rate. Smith evaluated the effect of approximately seventeen factors in forming his opinion as to an appropriate royalty. (Tr. 584-618).

Defendant argues essentially that Smith's opinion is unsupportable when viewed against the evidence relating to (1) other licenses in the contact lens field; (2) established royalty rates in the optical and chemical industries; and (3) other gas permeable lenses on the market.

P-C's first argument is that it produced uncontroverted evidence of royalty rates currently in place in the contact lens industry, i.e., the Erickson agreement (DX-256), [FN2] which provides a royalty rate of 5% on net sales, and the Bausch & Lomb agreement, which provides a 10% royalty of net sales on the sale of Saturn II lenses by B & L (5% to P-C and 5% to Erickson). (DX-135). P-C further points to a number of statements by Smith that P-C claims undermine his opinion concerning the royalty that ought to apply to the present case. According to P-C, Smith allegedly agreed with a statement from the Finnegan article that most royalty rates are 5 to 6% based on net sales, he admitted that seldom do licensees use profit as a basis for calculating royalties, and also agreed with a statement that in the optics and chemical fields royalties are based upon net sales,, not gross profits, and that royalties range from 2% to 5%.

With respect to the Erickson agreement, upon which P-C particularly relies in pressing its motion for a new trial on the issue of damages, Smith testified that it was not "analogous" to the agreement that would have been hypothetically negotiated between Schering and P-C. Smith indicated that under the Georgia Pacific analysis the patent at issue is assumed valid and infringed during negotiations. The consequence of this assumption is that the royalty tends to increase. (Tr. 587, 687). Smith distinguished Erickson on the ground that it did not involve a patent presumed to be "invalid and infringed." (Tr. 687).

Moreover, while the Erickson agreement licensed P-C under Erickson's patent, it did so at a time (1977) when the Saturn lens had a PMMA center and was years away from being ready for submission to the FDA with a TBS center (which P-C did not do until 1984), and thus was far less valuable to P-C than a license in July 1981 under Schering's patent. In addition, the royalty under the Erickson agreement was accompanied by a substantial fixed payment (DTX-256), and there is no evidene that Erickson was ever a gas permeable hard contact lens supplier so that P-C would be a competitor of Erickson. Smith indicated that each of these factors would have a substantial impact on the royalty rate.

P-C's claims that Smith agreed with actual statements from the Finnegan article relating to the rate of typical industry royalties and the rate of royalties in the field of optics and chemicals are belied by the record. Smith testified that he could not agree with the proposition that common industry royalty rates were 5-6% of net sales for two reasons. First, he had not seen the survey on which the statement was based, and second he explained that the statement of typical rates does not show whether a patent license is involved "let alone a patent that had been held valid and infringed." (Tr. 272). Smith was also unable to agree with the statement concerning typical royalty rates in the chemical and optics industries. He explained that the statement was too broad, and that he would need to know what type of license was being referred to, since royalty rates varied according to the nature of the license. (Tr. 677-78).

Moreover, there was testimony by Smith relating to the Finnegan article that actually supported his calculations of a reasonable royalty. He indicated that the 5% royalty rates based on net sales referred to in the Finnegan article related to "commercial cases where . . . none of the patents have been held valid and infringed." He pointed out on the other hand that Finnegan described a case where "the Court awarded a reasonable royalty which equalled forty-eight percent of the patent infringer's profits." (Tr. 714).

Smith also testified at several points explaining why he calculated his royalty based *285 on projected gross sales of all manufactured lenses rather than net sale of units sold as advocated by P-C. (Tr. 706-709; 1805- 1807).

Finally, P-C argues that the rate recommended by Smith was unjustifiably high since the Airlens did not constitute an extraordinarily unique product giving a competitive advantage to the licensee. This factor was, of course, one of many that the jury was free to consider in determining the appropriate royalty. But even if, as P-C contends, the value of the Airlens to a hypothetical license was reduced in 1981 because the lens market was occupied by numerous competitors, I am not persuaded that this factor, alone or in combination with any others cited by P-C, constituted evidence that clearly rebutted Smith's testimony.

Thus, while the burden was on Schering to prove damages by a "reasonable probability", Gyromat Corp. v. Champion Spark Plug Co., 735 F.2d 549, 555, 222 USPQ 4, 8 (Fed. Cir. 1984), I conclude from the foregoing that Schering successfully and persuasively carried this burden. Virtually all of the arguments that P-C now raises with respect to the evidence were addressed and rebutted by Smith. The jury was free to credit his testimony and it is not surprising that it did so given the fact that no expert testimony was offered to contradict his views. [FN3]

D. Jury Instructions

In support of its motion for a new trial, P-C asserts that there were a number of errors of omission and commission in the instructions given to the jury. I remain of the view that the jury was adequately and correctly instructed regarding the applicable law and further conclude that, in the one area open to reasonable debate, any error that may have crept into the charge would not warrant a new trial.

The parties are in agreement as to the standard of review of jury instructions on a motion for a new trial:

> Instructions must be viewed in their entirety. A new trial is permissible when it is clear that error in the instructions as a whole was such as to have misled the jury.

Railroad Dynamics, Inc. v. A. Stucki Co., 727 F.2d 1506, 1518, 220 USPQ 929, 940 (Fed. Cir. 1984). In addition, the error must prejudice the defendant's case. Shatterproof Glass, 758 F.2d at 627, 225 USPQ at 642.

1. "Likely To Carry Burden"

I declined to give the following instruction requested by P-C:

If you find that the additional prior art relied on by defendants is more pertinent than the prior art referred to by the Patent Office during the consideration of the application for the Schering patent, then defendants are more likely to carry their burden of proof that the patent is invalid.

This requested instruction takes a comment of the Federal Circuit regarding what juries are likely to do in certain situations and attempts to convert it into a proposition of law. In my judgment, it would have been more likely to confuse the jury than to help it understand the applicable law.

In addition to being given an explanation of the patent system and what happens in the Patent Office, the jury was correctly instructed that it was required to determine, with respect to each claim, whether the evidence as a whole showed clearly and convincingly that the subject matter of the invention would have been obvious to one of ordinary skill in the art given the prior art. The vast majority of the evidence tendered at trial was relevant to this issue. One piece of such evidence was that certain of defendant's prior art references were not before the Patent Office when it decided that the statutory requirement of nonobviousness had been met. While P-C chose not to do so, it was free to stress this particular fact to the jury in closing argument. It was not entitled, however, to have the judge single this fact out and tell the members of the jury that it meant that P-C was "more likely" to have carried its burden of proving obviousness. The relevance and importance in any particular case of evidence tending to show that some prior art references were not before the PTO will depend upon the jury's view of the other evidence bearing on the obviousness issue.

2. Presumed Knowledge

P-C complains that the Court failed to charge the jury regarding a presumption that "a hypothetical ordinary person skilled in the art has knowledge of all the art relied on at trial even if the patentees were actually unaware of that art." One problem with this contention is that it does not appear that P-C actually requested an instruction to this effect.

Defendant's "Request For Instruction 19A" requested the following: "You must presume the inventors were aware of all the art, whether or not they were in fact aware of it at *286 that time." In a letter to the Court dated March 7, 1985, P-C requested a slightly different construction: "You must presume that the inventors were aware of all of the relevant art which existed at the time they made the invention, irrespective of whether they personally knew of it." The presumption that the inventor has knowledge of all the art has been rejected by the Court of Appeals for the Federal Circuit. Kimberly-Clark v. Johnson & Johnson, 745 F.2d 1437, 1454, 223 USPQ 603, 614 (Fed. Cir. 1984) ("We hereby declare the presumption that the inventor has knowledge of all material prior art to be dead.") There can, therefore, be no error in this Court's failure to adopt the above two requested instructions.

Second, at the prayer conference P-C failed to make any request with regard to knowledge of the ordinary person skilled in the art. Under F.R. Civ. P. 51, P-C has waived any objection based on that omitted instruction.

Finally, even if the instruction had been properly requested and improperly denied, I would be unable to conclude that the error was such as to mislead the jury and prejudice the defendant. P-C is specifically concerned about Salame's Permachor System, since there was testimony from some of Schering witnesses that persons in the art may not have been aware of that system. (Tr. 176-77, 1613). However, the jury was specifically instructed that Salame's Permachor system was part of the "stipulated or agreed upon prior art." (Charge to the Jury, p. 16). The jury was further instructed that, on the issues of obviousness and anticipation, they were to "consider each patent or publication which has been agreed to be prior art." (Charge to the Jury, p. 25). Finally, the Court defined prior art for the jury as "the knowledge that was previously available to the public" (id. at 15) -- not art available to only certain individuals.

[FN4]

Based on the above, I am confident that the jury was not misled as to the scope and content of the prior art or as to their duty to compare each claim of the patent-in-suit with all of P-C's prior art references.

3. Old Composition For New Use

In addition to claiming as a matter of law that six claims of the Schering patent are invalid because they merely disclose a new use for an old compound, see section I.C., supra, P-C also contends that it was entitled to an instruction submitting this defense to the jury.

I have already concluded, however, that as a matter of law the Schering claims disclose a new composition. Therefore, P-C was not entitled to an instruction submitting this defense to the jury.

4. Deichert's Work

In support of its motion for a new trial, P-C complains of the instruction of the Court regarding claims 18, 27 and 29 of the Schering patent and the issues of whether they were anticipated by Mr. Deichert's work at Bausch & Lomb during August and September of 1977. In support of this contention, P-C relies upon the assertion that "an inventor need only appreciate the existence of the subject matter of his invention, but need not fully appreciate all of the functions or advantages that make it patentable." I do not disagree with this proposition; I do not think it applicable, however, to the issues of whether Deichert's work anticipates claims 18, 27 and 29.

The subject matter of claims 18, 27 and 29 is "an optically clear, non- hydrophilic contact lens" (or a "button adapted to machine" such a lens) having "a gas permeability constant of at least about 10x10-11" and being made of a polymer produced by polymerizing 70% to 100% TBS monomer, 0% to 10% "compatible cross-linking monomer" and 0% to 20% "compatible plasticizer." [FN5] While I acknowledge, in retrospect, that the matter is not free from doubt, I charged as I did with respect to these claims because, on the record before me, I regarded the presence of a DK value of at least 10 as well as the presence of at least 70% TBS to be part of the definition of the subject matter of these claims and not an inherent characteristic of an invention defined by the other portions of the claims. From this perspective, in *287 order to find the inventions of these claims anticipated by Deichert, the jury would have to conclude not only that Deichert made a lens coming within the scope of the claims, but also that he appreciated that he had done so. This would include an appreciation that his 70% plus TBS lens had a DK value in excess of 10. This was significant because there was evidence that Deichert had never tested his lens for gas permeability.

The charge as given was intended to comport with the teachings of Silvestri v. Grant, 496 F.2d 593, 181 USPQ 706 (C.C.P.A. 1974) and Knorr v. Pearson, 671 F.2d 1368, 213 USPQ 196 (C.C.P.A. 1982). If the gas permeability constant of 10x10-11 be regarded as an inherent characteristic of the invention otherwise defined in claims 18, 27 and 29 and these cases are to be distinguished on that basis, it still wold not follow, however, that P-C is entitled to a new trial with respect to these claims. I say this because if the jury found, as it did, that P-C- had not carried its burden of proving that Deichert's work anticipated the broader subject matter of the other claims-in- suit, it follows, a fortiori, that it did not carry its burden with respect to claim 18, 27 and 29. In this connection, it seems to me that the jury's finding of no anticipation of the other claims strongly suggests, and perhaps requires, a finding that the subject matter of the claims of the Schering patent are limited to hard contact lenses and that Deichert was found by the jury to have worked solely with soft contact lenses.

5. Infringement

P-C's final objection to the Court's charge is that it was erroneous to permit the jury to consider the performance characteristics of Schering AIRlens.

The Court's charge stated that Schering had

the burden of proving that the accused lenses and buttons infringe the claims of the Schering patent. (Tr. 1901). The Court further instructed the jury at least four times that they should determine infringement by comparing the claims with the accused product. (Tr. 1896, 1901, 1902 and 1904.)

With regard to the doctrine of equivalents, the Court instructed the jury:

> In order for the doctrine of equivalents to apply, however, each element of the claimed invention or its substantial equivalent must be found in the accused product. And the claimed invention and the accused product must perform substantially the same function in substantially the same way to yield substantially the same result.
>
> Now, as I have already explained to you, the test of infringement is whether the claims of the patent cover the accused device so that the accused products are to be compared with the claims of the Schering patent and not with the plaintiff's product, the AIRlens.
>
> However, if you reach this issue of whether the accused product and the claimed invention perform substantially the same function in substantially the same way to yield substantially the same result, and if you believe that the AIRlens, the plaintiff's product, comes within the scope of the claims of the patent, you may consider the evidence of Schering which compared the performance characteristics of the AIRlens with those of the Opus III and Saturn II.

Id., p. II, Tr. 1904-05.

In this context, it was not error to give the jury permission to consider the performance characteristics of the AIRlens on the issue of equivalents in the event it concluded that the AIRlens was an embodiment of the invention described in the claims of the Schering patent.

III. SCHERING'S MOTIONS

A. Increased Damages

In addition to its general verdict for Schering, the jury answered a number of interrogatories and found, inter alia, that P-C had willfully infringed each of the asserted patent claims. Schering now moves for an award of increased damages pursuant to 35 U.S.C. §284.

In Underwater Devices, Inc. v. Morrison-Knudson Co., 717 F.2d 1380, 1389- 90, 219 USPQ 569, 576 (Fed. Cir. 1983), the court upheld a treble damage award based on a finding of willful infringement and stated:

> Where, as here, a potential infringer has actual notice of another's patent rights, he has an affirmative duty to exercise due care to determine whether or not he is infringing. Such an affirmative duty includes, inter alia, the duty to seek and obtain competent legal advice from counsel before the initiation of any possible infringing activity. (Citations omitted).

More recently, the Federal Circuit has recognized that while counsel's opinion with respect to a patent is evidence of good faith, it is not dispositive, and it is necessary to look at the totality of circumstances presented by a case in determining whether infringement is willful. Central Soya Co., Inc. v. Geo. A. Hormel & *288 Co., 723 F.2d 1573, 1577, 220 USPQ 490, 492 (Fed. Cir. 1983). The Federal Circuit has also indicated that "willfulness may include a determination that the infringer had no reasonable basis for believing it had a right to do the acts."Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1548, 221 USPQ 1, 8 (Fed. Cir. 1984) (citing Stickle v. Heublein, Inc., 716 F.2d 1550, 1565, 219 USPQ 377, 388 (Fed. Cir. 1983)).

In the present case, the jury had before it the following evidence of willfulness. P-C knew of Schering's patent prior to P-C's application to the FDA in July 1981 for approval to sell the Opus III contact lenses. (Tr. 898- 899). P-C had consulted with counsel concerning the question of infringement of the Schering patent prior to the July 1981 FDA application. (Tr. 432-435). The issue of infringement was discussed at the July 1981 meeting of

Frigitronic's Board of Directors and is reflected in the following statement taken from the minutes of that meeting:

> Mr. West presented an article stating the opinion that gas permeable hard lenses are the product of the future. Our OP346[**] has the highest oxygen permeability of all lenses aside from the silicones. It can be manufactured in our present facility. However, we may be infringing a patent application.

(PTX-84, p.4). Mr. Ralph E. Crump, President of Frigitronics, Inc., testified that he "assume[d]" that the patent application referred to in these minutes was the Wesley-Jessen (Schering) patent. (Tr. 437-39). [FN6] There was also evidence that in May-June 1981, P-C made a "blind inquiry" to determine whether Schering would be willing to grant a license under its patent. To conceal its identity while making this inquiry, P-C hired a lawyer from Chicago to contact Schering, so that Schering would not suspect that the call came from P-C to P- C's counsel, both of whom were located in Minneapolis. (PX-51, 52, 53; Schmidt Tr. 1700; West Tr. 1699). Finally, there was evidence that as of May 1984, P-C continued to receive advice from counsel that it was infringing the patent-in- suit. As stated in the May 15, 1984 minutes of the Board of Directors:

> Our attorneys have said we must invalidate the Schering patent in order to win this case, since otherwise we would be infringing. They say we have a 60- 70% chance based on prior art. (PX-88).

Notwithstanding this evidence that P-C knew it might be infringing Schering's patent, P-C tendered no evidence that it had obtained an opinion from competent counsel analyzing and evaluating the validity of the Schering patent.

In light of the foregoing, my views are in accordance with those of the jury respecting the issue of willful infringement. P-C was on notice from mid-1981 that it was probably infringing the Schering patent. Yet, P-C came forward with little in the way of demonstrating that it relied in good faith upon competent opinion of counsel as to the invalidity of the Schering patent. While P-C apparently had been advised by its attorneys that there was a "60-70% chance" of invalidating Schering's patent, this opinion does not satisfy the criteria for reasonable reliance spelled out in Underwater Devices, 717 F.2d at 1390, 219 USPQ at 577 (Memorandum containing "only bold, conclusory, and unsupported remarks regarding validity" is inadequate). Additionally, the May 1984 Statement would appear to have come too late for purposes of demonstrating good faith. An organization on notice that it is infringing another's patent should inquire into the validity of the patent before rather than after the alleged infringing activities begin. Underwater Devices, 717 F.2d at 1390, 219 USPQ at 576 (emphasis supplied by court).

[3] Since I am in agreement with the jury that Schering made out its case of willful infringement, I will award Schering double damages. I have decided to double the damages rather than treble them for three reasons. First, this is not a case where a successful patented product is introduced to the market and is later copied by the alleged infringer. P-C presented testimony that it had been developing its contact lenses for approximately two years before becoming aware of the Schering patent. The same testimony indicated that P-C began working with TBS without knowledge that TBS had ever been used in a contact lens. (Tr. 823-836). "Multiplication of damages depends upon the degree of bad faith exhibited by the defendant,"Trio Process Corp. v. L. Goldstein's Sons, Inc., 638 F.2d 661, 662-63 (3d Cir. 1981), and the fact that P-C developed its lenses independently significantly diminishes the degree of its culpability.

Second, while P-C did not satisfy its affirmative duty to obtain some reasonable basis for believing in the invalidity of the Shering patent before commencing production of its lenses, it has not litigated this case in

bad faith. By the time of trial, counsel for P-C, based upon the prior art and the testimony of a highly qualified *289 expert, Mr. Salame, had developed litigable issues with respect to validity and I am confident that P-C and its counsel believed in the merits of its defense at trial.

Finally, while wholly justified given the record before it, I believe the jury's evaluation of damages was on the high side of the permissible range.

B. Attorney's Fees

Schering moves for an award of reasonable attorney's fees pursuant to 35 U.S.C. §285. Such an award is appropriate where, as here, there has been a finding of willful infringement. E.G., Kori Corp. v. Wilco Marsh Buggies & Draglines, Inc., 761 F.2d 649, 225 USPQ 985, 989, Appeal No. 84-1143 (Fed. Cir. 1985); Central Soya Co., Inc. v. Geo. A. Hormel & Co., 723 F.2d 1573, 1577-78, 220 USPQ 490, 493 (Fed. Cir. 1983); Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 221 USPQ 1 (Fed. Cir. 1984).

C. Prejudgment Interest

Schering has moved pursuant to 35 U.S.C. § 284 for an award of prejudgment interest.

There can be little doubt that Schering is entitled to such an award. The Supreme Court has recently construed 35 U.S.C. § 284 to require that prejudgment interest ordinarily be awarded:

> The standard governing the award of prejudgment interest under §284 should be consistent with Congress' overriding purpose of affording patent owners complete compensation. In light of that purpose, we conclude that prejudgment interest should ordinarily be awarded. In the typical case an award of prejudgment interest is necessary to ensure that the patent owner is placed in as good a position as he would have been in had the infringer entered into a reasonable royalty agreement. An award of interest from the time that the royalty payments would have been received merely serves to make the patent owner whole, since his damages consist not only of the value of the royalty payments but also of the foregone use of the money between the time of infringement and the date of the judgment. (footnote omitted)

General Motors Corp. v. Devex Corp., 461 U.S. 648, 655-56, 217 USPQ 1185, 1188 (1983). P-C has not alleged any facts demonstrating that a prejudgment award would be inappropriate in this case.

Schering relies upon Lam, Inc. v. Johns-Manville Corp., 718 F.2d 1056, 1066, 219 USPQ 670, 676 (Fed. Cir. 1983) for the proposition that this Court may adopt for prejudgment interest a rate above the Treasury bill rate set by 28 U.S.C. § 1961 for post-judgment, namely the prime interest rate or the corporate bond rate. However, the court in that case stated:

> The district court may "fix" the interest and select an award above the statutory rate, or select an award at the prime rate. Once the claimant has affirmatively demonstrated that a higher rate should be used, the district court may fix the interest or that higher rate. (citations omitted).

718 F.2d at 1066, 219 USPQ at 676 (emphasis added). In the present case, Schering offered no evidence which would support an award above the statutory rate. In Lam, Inc. v. Johns-Manville Corp., the claimant 'affirmatively demonstrated and the district court found that Lam borrowed money at or above the prime rate in order to continue its operations."Id. A comparable showing has not been made by Schering here. Accordingly, an award of prejudgment interest will be made at the Treasury bill rate as set forth in 28 U.S.C. § 1961, compounded annually. I also endorse the method by which Schering has calculated the prejudgment interest which it seeks.

IV. CONCLUSION

P-C's motion for a JNOV or a new trial will be denied. Schering will promptly submit an

amended form of final judgment which will double the damages found by the jury and will include interest from the time each reasonable royalty payment would have been made until the date of judgment. This final judgment will also award counsel fees in an amount to be hereafter agreed upon or fixed by the Court.

FN1 Honorable Walter K. Stapleton, United States Circuit Judge for the Third Circuit, sitting by designation.

FN2 This agreement provided for the transfer to PC of the Saturn lens technology from Erikson.

FN3 See Hanson v. Alpine Valley Ski Area, Inc., 718 F.2d 1075, 1079, 219 USPQ 679, 682-83 (Fed. Cir. 1983) (discussing the failure of defendant to counter plaintiff's expert license witness with one of its own).

FN4 The Court had previously instructed the jury at the outset of the trial as follows:

So when we ask ourselves whether the invention described in the patent is new and whether it was obvious, given what had been learned earlier by others, we compare the patent with the prior art, we compare the patent with the pre-existing patents and publications in the same area that reflect what others had learned and discovered before.

The prior part is what was previously available to the public and those practicing this art, and this is what is important. It does not matter whether or not it is shown that the inventor of a patent knew about or received aid from the prior art and what others had discovered.

In order to have a valid patent, somebody has to be able to show that they added something of value to what was previously available to the public.

FN5 As is clear from the wording of the claims, the percentage of TBS and cross-linking monomer are based on the total weight of the polymer and the percentage of plasticizer is based on the total weight of the polymer and plasticizer.

FN6 The parties agreed that any statement or admission made by Frigitronics would be binding on P-C as if it had been made by P-C itself (see Charge To The Jury, March 11, 1985, p. 2).

D.Del.

227 U.S.P.Q. 278

END OF DOCUMENT

Warner-Jenkinson Company et al.
v.
Allied Chemical Corporation et al.

District Court, S.D. New York

No. 76 Civ. 2744

Decided July 31, 1979

United States Patents Quarterly Headnotes

PATENTS
[1] Patentability -- In general (§ 51.01)
Inventions that are useful, novel, and non-obvious are patentable.

PATENTS
[2] Pleading and practice in courts -- Burden of proof -- Validity (§ 53.138)
Presumption from patent grant -- In general (§ 55.1)
Presumption from patent grant -- Patent Office consideration of prior art (§ 55.5)
Court's inquiry into patent's validity begins with statutory "presumption of validity" of patents granted by Patent Office; parties alleging invalidity have burden to overcome presumption by clear and convincing evidence, and every reasonable doubt should be decided in favor of patent's validity; presumption is strongest where Patent Office has granted patent with knowledge of prior art; on other hand, presumption does not apply to novelty issue that was not considered by examiner; as to this claim, burden rests upon patentees to establish de novo validity of their patents.

PATENTS
[3] Patentability -- Anticipation -- In general (§ 51.201)
Patentability -- Anticipation -- Combining references (§ 51.205)
Patentability -- Composition of matter (§ 51.30)
Invention that was known or used by others in this country, or patented or described in printed publication in this or foreign country, before its invention by patent applicant is "anticipated," and therefore is not patentable, since it is not novel; anticipation is narrow and technical attack on patentability; as consequence, standards of anticipation are strict; invention must be disclosed within four corners of single reference; in case of chemical compounds, mere recitation of structural formula is insufficient to be anticipation, as disclosure must also recite means of preparing compound and at least one significant useful property.

PATENTS
[4] Patentability -- Anticipation -- In general (§ 51.201)
Patentability -- Anticipation -- Combining references (§ 51.205)
Patentability -- Anticipation -- Modifying references (§ 51.217)
It is not anticipation where one would have to experiment with large number of possible intermediates referred to in allegedly anticipatory foreign patent and successfully piece together necessary ones to come up with one generic formula out of total of twenty-seven generic formulae and then would have to experiment further to discover specific formula of claimed compound.

PATENTS
[5] Patentability -- Anticipation -- Combining references (§ 51.205)
Patentability -- Anticipation -- Publications -- In general (§ 51.2271)
Legal accuracy of argument that description in printed publication that imparts to person of ordinary skill sufficient information that, coupled with disclosures of prior art, would enable him to devise invention without further genuine inspiration or undue experimentation anticipates patented product is dubious.

PATENTS
[6] Patentability -- Anticipation -- Patents -- Foreign (§ 51.2215)
Patentability -- Anticipation -- Patents -- Old patents (§ 51.2217)
Common sense, which is not altogether irrelevant even in patent cases, generates doubts that relatively obscure one-hundred year old foreign patent that only indirectly discloses composition of food dye compound

and does not clearly disclose its properties describes that compound to dye chemist skilled in art in 1965.

PATENTS
[7] Evidence -- Expert testimony (§ 36.10)
Foreign patents (§ 38)
Patentability -- Evidence of -- In general (§ 51.451)
Prior adjudication -- In general (§ 56.01)
Both German and Dutch Patent Offices are strict in enforcing rule that anticipation by prior patent or publication precludes patentability; while decisions of these two foreign patent offices are in no way controlling upon U.S. court considering same issue, they are valuable as opinions of trained experts in inventor's country and where art is best understood; opinions of such men, learned, able, and disinterested, officially expressed after thorough examination, are persuasive to say least; their expert judgment is considered since it is recognized that in applying standards of novelty and nonobviousness, patent offices of Germany and Holland are among strictest in world, on par with, if not superior to, American office.

PATENTS
[8] Patentability -- Evidence of -- In general (§ 51.451)
Patentability -- Invention -- In general (§ 51.501)
Patentability -- Tests of -- In general (§ 51.701)
Invention is "obvious," and therefore not patentable, if differences between subject matter sought to be patented and prior art are such that subject matter as whole would have been obvious at time invention was made to person having ordinary skill in art to which that subject matter pertains; although test laid down is indeed misty enough, Supreme Court has given direction by setting forth "primary factors" always relevant to inquiry into obviousness, which are scope and content of prior art, differences between prior art and claims at issue, and level of ordinary skill in pertinent art, as well as certain secondary considerations, which are, commercial success, long felt but unsolved needs, failure of others, etc., that might be utilized to give light to circumstances surrounding origin of subject matter sought to be patented.

PATENTS
[9] Patentability -- Composition of matter (§ 51.30)
Obvious molecular modification coupled with showing of novel properties or superiority over known properties can establish patentability.

PATENTS
[10] Patentability -- Evidence of -- State of art (§ 51.467)
Patentability -- Invention -- Specific cases -- Chemical (§ 51.5093)
State of food dye art in 1965 was such that nontoxicity was essentially not predictable in azo dye compound; and nontoxicity would only be established by trial and error and animal testing.

PATENTS
[11] Patentability -- Composition of matter (§ 51.30)
Patentability -- Evidence of -- In general (§ 51.451)
Patents meet standards for patentability where essential unpredictability of most important properties negates claim of obviousness; various secondary considerations noted by Supreme Court can tip scales in favor of patentability in close cases.

PATENTS
[12] Defenses -- Fraud (§ 30.05)
Defenses -- Unclean hands (§ 30.25)
Patent grant -- Nature of patent rights -- In general (§ 50.201)
Pleading and practice in courts -- Judgments (§ 53.53)
Pleading and practice in Patent Office -- In general (§ 54.1)
Declaration of "unenforceability" of patents would not prejudice patent owners' ability to reapply to Patent Office and acquire new patent; declaration of invalidity would preclude reapplication; court shares concern of party that contends that where nondisclosures are serious, material, and reckless, subsequently granted patents should be declared invalid or, at least, unenforceable; since Patent Office, flooded with applications

and at times lacking adequate resources, is unable to check all facts and investigate all relevant prior art, it must rely on applicants for many of facts upon which its decisions are based; highest standards of honesty and candor on part of applicants in presenting such facts to Office are thus necessary elements in working patent system; accordingly, "unclean hands" occasioned by failure to disclose such facts can operate to invalidate patent or render it unenforceable.

PATENTS
[13] Defenses – Fraud (§ 30.05)
Patentability – Tests of – Skill of art (§ 51.707)
Pleading and practice in Patent Office – In general (§ 54.1)
Specification – Sufficiency of disclosure (§ 62.7)

Finding that patentee acted in good faith in disclosing best method does not conclude matter when disclosure is so generalized or unhelpful as to withhold effective use of patented discovery from public; proper test is one indicated by statute's words – would person skilled in art, be able, with reasonable effort, to synthesize patented compound?; ordinary dye chemist would automatically know to use alcohol-wash step to guarantee requisite dye purity.

PATENTS
[14] Defenses – Fraud (§ 30.05)
Defenses – Unclean hands (§ 30.25)
Pleading and practice in Patent Office – In general (§ 54.1)

Patents procured where misrepresentations are made in atmosphere of gross negligence as to their truth will not be enforced, even where there is no finding that withheld material would have caused Patent Office to deny application; public interest demands that all facts relevant to such matters be submitted formally or informally to Patent Office, which can then pass upon evidence's sufficiency; applicant has duty to disclose matters that are relevant.

PATENTS
[15] Pleading and practice in Patent Office – In general (§ 54.1)

Applicant who knows of prior art that plainly describes his claimed invention or comes so close that reasonable man would say that invention was not original but had been anticipated will not be excused for failure to disclose his knowledge.

PATENTS
[16] Misuse of patents – In general (§ 45.01)
Patent grant – Nature of patent rights – In general (§ 50.201)
Title – Licenses – Royalty provisions – In general (§ 66.4231)

Patent empowers owner to exact royalties as high as he can negotiate with leverage of that monopoly; 17 1/2 percent royalty does not alone constitute patent misuse.

PATENTS
[17] Misuse of patents – In general (§ 45.01)

Fact that delisting of competitive food dye by FDA, almost year after parties agreed upon royalty rate, had made patented food dye only major red food color on market, is no ground upon which to charge patent owners with patent misuse.

PATENTS
[18] Misuse of patents – In general (§ 45.01)

Patent licensee's decision not to absorb but to pass on testing surcharge to their customers by including it in their billings of patented product falling under license agreement that pegged 17 1/2 percent rate to invoice price at which licensee sold product does not constitute patent misuse.

PATENTS
[19] Estoppel – As to validity – Licensor or license (§ 35.156)
Infringement – In general (§ 39.01)
Title – Licenses – In general (§ 66.401)

Patent owners' claim of infringement fails in case in which settlement agreements under which accused infringers pay royalties are in effect and accuseds have paid royalty from time agreements were made to present and thus are authorized licensees; provision in license agreement that patent owners shall

not commence another litigation in less than two years may, by itself present question of enforceability in light of Lear Inc. v. Adkins, 162 USPQ 1.

PATENTS
[20] Costs -- Attorney's fees (§ 25.5)
Maneuvering by parties, each of which is at fault for involving courts second time with their hard-fought controversy when it could have been resolved in first action, does not create "exceptional case" warranting allowance of counsel fees.

PATENTS
Particular patents -- Food Dyes
3,519,617, Rast and Steiner, Red Phenyl-Azo-Naphthol Dyestuff for Edible Compositions, valid and not infringed.
3,640,733, Rast and Steiner, Edible Substrates Colored with Monoazo Dyestuffs, valid and not infringed.

***839** On remand from Court of Appeals, Second Circuit; 193 USPQ 753.

Action by Warner-Jenkinson Company, a Division of The Seven-Up Company, and H. Kohnstamm & Company, Inc., against Allied Chemical Corporation and Buffalo Color Corporation, for declaratory judgment of patent invalidity, noninfringement, and unenforceability, in which defendant counterclaims for infringement and breach of contract. Claims and counterclaims dismissed.

Francis T. Carr, Paul Lempel, Edwin Baranowski, and Kenyon & Kenyon, all of New York, N.Y., (Donald G. Leavitt, and Koenig, Senniger, Powers & Leavitt, both of St. Louis, Mo., of counsel for Warner-Jenkinson Company, and Patrick J. Joyce, Stamford, Conn., of counsel for H. Kohnstamm & Company, Inc.) for plaintiffs.

William K. Kerr, William J. Gilbreth, John E. Nathan, Hugh C. Barrett, David J. Lee, Alan M. Gordon, and Fish & Neave, all of New York, N.Y. (Battle, Fowler, Lidston, Pierce & Kheel, of counsel for Buffalo Color Corporation) for defendants.

Weinfeld, District Judge.

Plaintiffs Warner-Jenkinson Co. ("Warner") and H. Kohnstamm & Co. "'Kohnstamm"), two commercial manufacturers ***840** of synthetic food colors, brought this action against defendants Allied Chemical Corporation ("Allied" or "Allied Chemical") and Buffalo Color Corporation ("Buffalo Color"), the patentee and assignee, respectively, [FN1] of two patents relating to a red food dye known as FD & C No. 40 ("Red 40"), the leading red food color now on the market. This is the second such action commenced by plaintiffs. The first lawsuits were brought against Allied Chemical in January 1972 (and were subsequently consolidated for trial purposes), seeking a declaratory judgment of invalidity, noninfringement, and unenforceability of Allied's patents for Red 40. [FN2] Allied counterclaimed for infringement.

After extensive pretrial discovery over a three-year period, during which twenty-seven witnesses were deposed and more than 30,000 pages of documents were produced, the trial commenced before Judge William Conner of this Court, with each side prepared to proceed with an array of fact and expert witnesses. On the second day of trial, after cross-examination of plaintiffs' first witness, settlement negotiations were initiated; discussions continued over a period of four months. The settlement reached by the parties provided for a $200,000 payment by plaintiffs to Allied; release of plaintiffs by Allied from all liability for infringement based upon their activities prior to March 1, 1975; release of Allied by plaintiffs from charges of unfair competition prior to March 1, 1975; and the grant to each plaintiff of a manufacturing license by Allied Chemical, with provision for a royalty charge of 17- 1/2 % of the sales price of all quantities of Red 40 manufactured and sold by plaintiffs. Based on the parties' stipulation, an order was entered on July 23, 1975 by Judge Conner, dismissing the plaintiffs' claims of patent invalidity without prejudice, their unfair competition claims with prejudice, and defendants' infringement claims without prejudice.

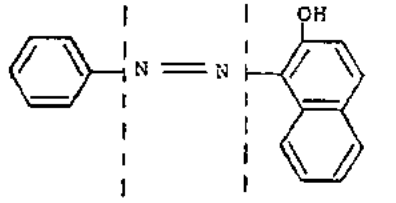
The instant complaint was filed shortly after another, competing, red food dye was banned by the Food & Drug Administration ("FDA") in February 1976. Plaintiffs again request a declaratory judgment that the Red 40 patents are invalid, unenforceable, and not infringed by plaintiffs and as a consequence further seek invalidation of the licensing agreements, restitution of royalties paid to defendants under those agreements, and damages resulting from defendants' alleged unfair competition subsequent to March 1, 1975. Defendants deny plaintiffs' averments and counterclaim against each plaintiff for patent infringement in the event that plaintiffs are held to be unlicensed because the existing agreements are void. In addition, Allied alleges a counterclaim against plaintiffs for breach of the settlement agreement. After a line-by-line review and study of the 2500-page trial record, the several thousands of pages of exhibits received into evidence, and the Court's daily trial notes, which include a contemporaneous appraisal of each witness and his demeanor, the Court finds that plaintiffs have failed to sustain their burden of proof on the claims asserted in their complaint and, similarly, that defendants have not established their counterclaims.

I.

The patents in suit, numbered 3,519,617 ('617) and 3,640,733 ('733), were granted by the United States Patent Office to Allied for an invention, the main object of which was to provide "highly soluble non-toxic monoazo dye combinations which are useful in the coloring of edible substrates." [FN3] "Manifestly, the validity of each of these patents turns on the facts"; [FN4] background facts bearing on the issues in this case include the history of the food dye industry, the circumstances under which the chemical compositions were synthesized and patented, and the impact of the patent on the industry.

A.

At least since the 1880s, the marketplace has recognized the usefulness of artificial *841 color in foods, primarily to correct for natural variations in food color and to make edibles more visually appealing and palatable. [FN5] By 1900 most of the food dyes used in this country were synthetic "coal-tar dyes," that is, dyes prepared from derivatives of compounds recovered in the distillation of coal (particularly benzene and naphthalene). [FN6] Among the most common coal-tar dyes were the simplest -- "phenyl-azonaphthol dyes" having the following general chemical structure: [FN7]



Such dyestuffs are prepared by diazotizing the "phenyl intermediate" and then bonding it with the "naphthol intermediate," a process in use for over 100 years. [FN8]

At the turn of the century, Dr. Bernhard C. Hesse, a German dye expert, was retained by the United States Department of Agriculture to investigate the safety of coaltar dyes. In his classic study, Dr. Hesse described several desired characteristics of coal-tar food dyes: (1) nontoxicity and safety for human consumption; (2) desirable shade and brightness, together with high tinctorial strength; (3) stability of the color when subjected to great heat, light, reducing agents, and acids that are used in the preparation of foods; (4) solubility in water and other liquids; (5) suitability for mixing or blending with other colors; and (6) lack of taste, odor, or other potentially offensive characteristics. [FN9] Hesse's research focused on the first desideratum, safety and nontoxicity, and sifted through dozens of coal-tar dyes to select seven that were certified for general food use under the Pure Food and Drug Act of 1906. [FN10] Hesse's choices -- including three red dyes, Ponceau 3R (now known as "Red 1"), Amaranth ("Red 2"), Erythrosine ("Red 3") [FN11] -- were made only after extensive physiological testing on dogs, rabbits, humans,

since "[i]t has been known since 1888 that it is unsafe to attempt to predict the harmfulness or the harmlessness of coal-tar colors by analogy" to other, chemically similar, dyes. [FN12]

Accordingly, what the food color industry strives for, and indeed must seek to achieve under exacting statutory standards, is, first and foremost, nontoxicity and safety of the product for human consumption. But to achieve commercial success other properties are also of importance. Between 1907 and 1938, due to industry demand for additional shades and further safety testing, other new colors were added to the approved list. One such dye, now known as "Red 4" (a scarlet color slightly less blue than Red 1), was developed by plaintiff Warner and added to the list in 1929. [FN13] At the same time, continued concern over the safety of food colors *842 led to the passage of the Food, Drug and Cosmetic Act of 1938, which made certification mandatory and required toxicological data based on animal tests for continued or new listings of food colors. [FN14] As of 1951 there were nineteen coal-tar colors authorized for unrestricted food use, after public hearings required by the Act.

In the 1950s, however, the FDA, after conducting animal tests to reassess the toxicity of food colors, "delisted," or removed from the certified lists, no less than seven colors. Pursuant to the Color Additive Amendment of 1960, [FN15] the FDA in 1963 promulgated stringent and detailed regulations outlining the type of experimentation and other data to be submitted to establish grounds for permanent listing of food colors. [FN16] Concomitant with the FDA's heightened concern over toxicity, the red dye industry faced a "crisis" because of the delistment of Red 1 in 1960 (on the ground that it produced liver damage in test animals) and Red 4 in 1964 (on the ground of adverse pathological findings). [FN17] The delistments, which considerably narrowed the approved coal-tar additives, created an urgent need in the industry for a bright scarlet food color that could pass the FDA's ever more stringent toxicity tests and that had the vital "application properties" of a good food dye -- useful shade and tinctorial strength, stability, solubility, suitability for blends, tastelessness and odorlessness. [FN18]

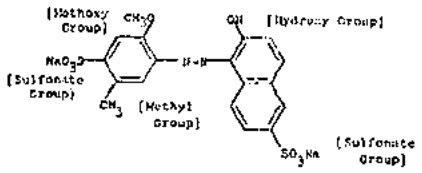
B.

Defendant Allied and plaintiffs Warner and Kohnstamm were in the early 1960s major manufacturers of food dyes, and red dyes constituted a large segment of their business. The crisis in red dyes produced an immediate reaction. In August or September 1964, Raymond Leary, Allied's Food Colors Product Manager, requested the Company's Analytical Laboratory to determine whether "any foreign food reds or any present as well as obsolete D&C or Ext. D&C colors might offer a suitable substitute" for Red 4. [FN19] The laboratory was unable to find such a substitute, and Leary turned to Allied's Research Department, specifically to Dr. Russell Steiner, a noted organic chemist with substantial theoretical and practical knowledge of coal-tar dye synthesis; [FN20] Steiner selected as his assistant Gustav Rast, a senior dye chemist. The object of their research, which extended over a period of two and one-half years, was to find a red food color dye that had a shade between that of Red 1 and Red 4, was nontoxic, and had the many specific application properties necessary for general food use. [FN21]

Upon synthesis and testing of existing compounds, Steiner and Rast in December 1964 realized that no existing food color would meet the need; a new dye would have to be invented. Prior to returning to the laboratory, Steiner and Rast discussed certain empirical criteria which they believed might bear on the toxicological acceptability of such compounds: the dye should (1) have water-solubilizing groups (such as sulfonic acid groups, -SOsub3) on both sides of the azo linkage, (2) not contain exotic groups or be prepared from intermediates which were known carcinogens, (3) and substitute methoxy groups (-OCHsub3) for methyl groups *843 (-CHsub3) wherever possible. These "guidelines" represented the state of the art of food dye chemistry in 1964 and early 1965 [FN22] and were, by and large,

reaffirmed in a conference with Kelly Ferber of Allied Chemical's Production Department. [FN23] On the other hand, the history of FDA delistments through 1964 suggested that such criteria were not reliable in predicting nontoxicity; [FN24] so, too, it was all but impossible to predict most application properties of dye compounds based solely upon an analysis of their structures, except that sulfonic acid groups made a compound water soluble and methyl and methoxy groups shifted dye shade in a "batho-chromic" (toward bluer hues) direction. Accordingly, the researchers did not follow the guidelines dogmatically but, instead, synthesized a wide range of azo compounds, followed by further experimentation and comparison testing.

Steiner and Rast actually began synthesizing dyes in December 1964 -- first, existing dyes and, then, new ones that they hypothesized. Each dye was applied to a wool swatch for shade comparison with swatches dyed with Red 1 and Red 4; of the more than 90 colors synthesized, nine were found close enough in color to justify application testing in early 1965. One of the nine was a compound synthesized by Steiner and Rast in December; it was prepared by coupling para- cresidine monosulfonic acid (the phenyl intermediate) with Schaeffer's Salt (the naphthol intermediate):



This dye, later to be approved by the FDA as Red 40 and patented by Allied, was at first not considered a leading candidate to replace Red 1 and Red 4, because it had a methyl group, which was questionable on toxicity grounds; an initial application test (stability to sulfur dioxide) was disappointing; it did not have the exact shade desired; and there were potential difficulties in preparing the compound because paracresidine monosulfonic acid was not available commercially. [FN25]

After synthesizing further dyes and conducting numerous application tests, [FN26] the researchers narrowed the list of promising candidates to five by July 1965, and Allied engaged Hazelton Laboratories ("Hazelton") to conduct toxicological tests on these "finalists." Upon reviewing Hazelton's results of short-term feeding of large doses of the dyes to dogs, Allied in December 1965 eliminated one of the five compounds from consideration. In February 1966 it sent Hazelton ten-pound samples of the remaining four finalists for six-week feeding tests with dogs and rats and commenced a new series of application tests. Two of the dyes were eliminated from consideration after the tests revealed liver and thyroid abnormalities in animals, leaving two potential dyes. For purposes of Allied's internal identification, the compounds were denoted as "Z-4576" and "Z-4578," the latter being a disazo compound.

During 1966 the Company subjected the two remaining candidates (Z-4576 and Z- 4578) to side-by-side comparison tests with Red 4, including solubility in water, ethyl alcohol, and glycerine; stability as to heat, pH, acid, sugar, and sodium hydroxide; tinctorial strength as applied to sugar patties, milk tints, wool; the effect of metals on shade; and fastness and substantivity (resistence to "bleeding" off of the food). The "[c]onsensus was that Non-Toxic Red Z-4576 was superior in most properties and is most similar to the delisted FD & C Red #4" [FN27] Accordingly, Z-4576 was selected for ***844** long-term toxicological testing by Hazelton, consisting mainly of feeding studies on rats and dogs, dermal application tests on rabbits and mice, and reproduction studies. In March 1970 Hazelton reported that the compound was entirely nontoxic, and on April 22 Allied petitioned the FDA for listing the color additive as suitable and safe for use in foods and drugs. The FDA listed the dye as FD & C No. 40 on April 10, 1971, based in part on animal studies conducted by the agency that established that the dye did not have the toxicity exhibited by Red 4. Indeed, the FDA's toxicologist found that "[t]he slight differences in structures of [Red 40] from that of FD & C Red No. 4 apparently are responsible for the

difference in toxicity." [FN28]

C.

Because of its proven nontoxicity and superior application properties, Z-4576 was viewed as a desirable successor color to Red 4 and, therefore, a valuable project for Allied Chemical. To protect its heavy investment in the development and testing of the dye over an extended period, Allied took steps to obtain a patent, especially since those persons at Allied who were engaged in the project considered that the product had a good chance of being patented. As a result, an "invention record" was prepared by M.D. Edelman of Allied's Industrial Chemicals Division for "a novel monoazo dyestuff obtained by coupling diazolitized 3-methoxy-6-methyl sulfonic acid in alkaline media, into Schaeffer's Salt," to be used "as a satisfactory substitute for FD&C Red #4" since it had analogous properties and was surprisingly more soluble in water than Red 4. [FN29] In his thorough search of American and foreign patent records, Edelman found that a German patent, D.R.P. 12,451, was, "perhaps, the most pertinent reference" to the prior art.

This German patent concerned "the preparation of red and violet azo dyes which are formed by the reaction of diazoanisoles and their sulfonic acids with naphthols and their sulfonic acids." [FN30] Among the dozens of generic formulae disclosed in the patent is the one derived from combining the methyl ether of amino cresol sulfonic acid with beta-naphthol monosulfonic acid which theoretically would embrace Z-4576. [FN31] But Edelman concluded that since "[t]his art which was published in 1879, does not particularly identify the components" of the various generic formulae, and "no mention is made of their lack of toxicity and suitability for coloring edible substrate," it was no barrier to patentability. [FN32]

The invention record prepared by Edelman was forwarded to Dr. A. Victor Erkkila, the Chief Patent Liaison Officer of the Industrial Chemicals Division, in February 1967. Dr. Erkkila -- who received his doctorate in physical chemistry from the Technical University in Stuttgart, Germany in 1935 -- studied the German patent and the other patented chemicals cited by Edelman's report. He, too, concluded that Z-4576 was not specifically disclosed in any of the references and that it was patentable. [FN33] Erkkila thereupon forwarded the invention record to Michael S. Jarocz, Patent Counsel for the laboratories of the National Aniline Division of Allied, who also studied the German Patent thoroughly. He felt that the "shotgun disclosure" of D.R.P. 12,451 could in "no possible way * * * be construed as disclosing Red 40 unless [by] resort[ing] to incredible hindsight." [FN34] In particular, he considered the unique properties of Z-4576 -- nontoxicity, surprisingly high solubility, and other excellent application properties -- to be the basis for patentability, and these were in no way disclosed by the arcane teutonic patent.

*845 On May 18, 1967, Jarocz filed Allied's application with the United States Patent Office. The "Abstract of Disclosure" provided, in part, as follows:

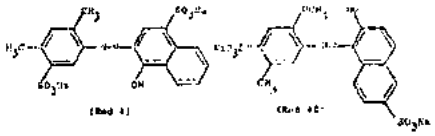
> Monoazo compounds of this invention, which may be termed 1-([2-alkoxy-5- alkyl-4-sulfophe-nyl]azo) -2-naphthol-6-sulfonic acids and physiologically acceptable salts thereof are prepared by conventional procedures, e.g. coupling diazotized 5-alkoxy-2-alkylsulfanilic acid, in alkaline media, into 2-naphthol-6-sodium sulfonate. The monoazo compounds of the invention are useful as dyestuffs for various substrates and especially for edible substrates, such as foodstuffs or pharmaceutical compositions.
>
> This invention relates to the production of novel red monoazo dyestuffs. More particularly, the present invention is directed to highly soluble red monoazo dyestuffs and to their use as colorants, especially in dyeing of edible substrates.
>
> Certain red dyes have found use in the past in various coloring or dyeing applications, especially in the coloring of foodstuffs or other edible substrates. One such dyestuff

(F.D. & C. Red No. 4) recently has been delisted for essentially all edible uses by the Food and Drug Administration, thereby creating a need for a red dye particularly useful in the coloring of edible substrates.

Accordingly, one object of the present invention is to provide new and useful dye compositions.

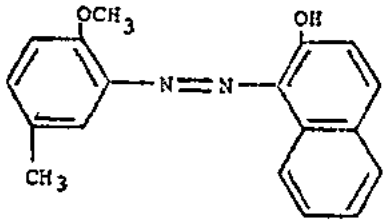
A further object of the present invention is to provide highly soluble non- toxic monoazo dye compositions which are useful in the coloring of edible substrates.

Relying on his own prior experience as a Patent Examiner (1960 to 1964), Jarocz did not cite D.R.P. 12,451 as the most pertinent prior art because he believed, in good faith, that the German Patent was irrelevant and would only confuse the Examiner; as prior art, he cited Red 4:



One year later, in May 1968, Allied filed applications for a "use" patent with the Dutch Patent Office and a "composition" patent with the German Patent Office, based on substantially the same claims.

On April 9, 1969, the American Patent Examiner made an initial determination rejecting the claims asserted in the application, primarily because the applicants did not sufficiently describe the utility of their invention and because a prior patent was structurally so similar that the invention was obvious to the ordinary dye chemist. The latter is the "Elley Patent": [FN35]



Allied petitioned for a reconsideration of the Examiner's decision on the ground that the invention's usefulness in coloring edible substrates and its surprising properties, including nontoxicity and high solubility, justified patentability. The applicant also distinguished the Elley Patent as a red to bluish-red water-insoluble color useful for dyeing petroleum products, which had never been noted for food dye uses and was particularly unsuitable therefor because of its undesirable "bronzy fluorescence." These arguments were apparently persuasive to the Patent Office, since it granted the '617 patent on July 7, 1970, and the '733 patent on February 8, 1972. [FN36]

Allied also encountered problems in its foreign applications. Thus in 1973, Dr. Muhlbauer, the German Examiner, questioned "the existence of inventive level" because of the large number of red dyes of excellent solubility already on the market and requested the applicant to submit a more complete statement of the prior art. In response, Allied narrowed its application somewhat but defended the inventive contribution: "The advance of the art represented by the new dyestuffs results primarily from their lack of toxicity. * * * The inventive level of the object of the application results from the fact that dyes of similar structure * * * are toxic and/or have other undesired properties. * * * It is surprising that by such a slight change in the chemical structure the toxicity could be so strongly reduced." [FN37] Also included in the response ***846** was a list of "literature references," including citations to the Elley Patent, D.R.P. 12,451, the "Widmer Patent," [FN38] and the "Baum Patent." [FN39] The German Examiner obtained and examined the references and concluded that none rendered

Red 40 unpatentable. Hence, on October 11, 1974, the German Patent Office announced that Allied's application would be published for opposition; as no opposition was filed, the Office granted the patent on June 16, 1975.

Of all the authorities passing upon Allied Chemical's application, the most stringent scrutiny was carried out by the Dutch Patent Office, which in 1973 had been the first to mention, after its own search, the relevance of D.R.P. 12,451. Allied in 1975 narrowed its claims before the Dutch Office to embrace the use of the compounds only for dyeing foods, drugs, and beverages. [FN40] Although the Office found that a patentable invention did reside in the more circumscribed claim, it raised further questions to distinguish the use of Red 40 from that of D.R.P. 12,451 and other red dyes listed in the various indices. On November 30, 1978, the Application Department announced that the application was acceptable and would be published for opposition; no opposition has been received as of the date of this opinion, with the prospect that the Dutch patent will issue in due course.

D.

Allied began manufacture of Red 40 in 1971, at which time there was only one other major red food dye on the market, Red 2. Red 40 was an immediate and enormous commercial success: the dye certified by the FDA rose from 26,000 pounds in the third quarter of 1971 to an average in excess of 160,000 pounds per quarter in the years 1973 to 1975. [FN41]

Although Red 2 continued to hold a sizeable share of the market, the established nontoxicity (combined with FDA publicized doubts about the nontoxicity of Red 2), bright scarlet hue, surprisingly high solubility, and other application properties of Red 40 made it more than just a replacement for Red 4. For example, in 1973 Allied's development of Red 40 received "Top Honors" in the "Ingredients Category" of the Putman Food Awards, based on Red 40's novelty, breadth of application, and significance to the food color industry. This success, moreover, stimulated competitors to try to develop new red food dyes, though without result as of this date. Indeed, Warner, a plaintiff in this action, contracted with St. Louis University for research "to synthesize purified laboratory quantities of novel water-soluble dyes * * * for possible use as food colors" [FN42] and entered into a three-year $3,000,000 contract with Dynapol Corporation for the latter to invent a new red dye using advanced polymer technology. [FN43]

Recognizing the utility of Red 40, and not having a suitable alternative at hand, Warner and Kohnstamm, after failing to obtain licenses from Allied, commenced manufacture of the dye. In 1972 they instituted the lawsuits, discussed above, to declare the patents invalid. Upon settlement of that litigation, plaintiffs entered into "License Agreements" with Allied, pursuant to which the licensees were to pay a royalty of 17 1/2 % on the "net sales price," or invoice price, of Red 40 sold and were precluded from terminating the Agreements at any time before the second anniversary of the licenses on March 1, 1977. However, before that date, on February 12, 1976, the FDA delisted Red 2, leaving Red 40 as the only significant red food color on the market; the immediate result was an increase in the sales (to an average of over 400,000 pounds per quarter for the years 1976 through 1978) and corresponding increases in the total royalties collected by Allied.

*847 In June 1976, plaintiffs instituted this second action to declare the patents invalid or unenforceable and to recover royalty payments made under the License Agreements. Judge Marvin Frankel, to whom the case was assigned, dismissed the complaint on the ground that the License Agreements precluded suit before the termination of the two-year period, but the Court of Appeals reversed and remanded, holding that the two-year nontermination period did not bar the action. [FN44] Upon Judge Frankel's resignation from the Bench, the case was assigned to this Court and proceeded to trial.

II.

While contractual and other ancillary claims are advanced by both sides, the hard core of the case is whether the '617 and '733 patents are valid and enforceable. To determine these issues, the Court must assess, first, the inventive contribution made by Allied's red dye and, second, the substantial accuracy and completeness of disclosures made in its patent application and the use defendants have made of the patents in suit.

A.

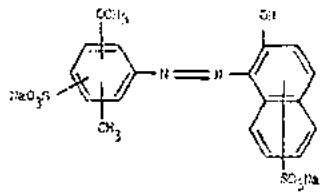
[1] Inventions that are useful, novel, and nonobvious are patentable. Plaintiffs contend that the patents in suit are invalid because they fail the latter two litmus tests for patentability. Defendants, on the other hand, argue, in the unadorned language of their counsel, that what Steiner and Rast did -- "what lies at the heart of their inventive contribution" -- was "to invent a novel and unobvious scarlet red food color -- a specific monoazo dye (bearing particular substituents in precise locations) and one which possessed the myriad of unpredictable application and toxicological properties demanded of a safe, general use, food color." [FN45]

[2] The Court's inquiry begins with the statutory "presumption of validity" of the patents granted by the Patent Office. Plaintiffs have the burden of proof to overcome the presumption by clear and convincing evidence, and every reasonable doubt should be decided in favor of the patents' validity. [FN46] The presumption is strongest where the Patent Office has granted the patent with knowledge of the prior art [FN47] -- here, the Elley Patent, the Baum Patent, and FD & C Yellow No. 6 ("Yellow 6") were considered by the Patent Examiner, and plaintiffs' remaining citations to the prior art are largely cumulative. [FN48] On the other hand, the presumption does not apply to the issue of novelty, since plaintiffs' attack focuses on the German Patent -- D.R.P. 12,451 -- not considered by the Examiner. As to this claim, the burden rests upon defendants to establish de novo the validity of their patents. [FN49] Based on the recent intensive refresher course in organic chemistry afforded by the charts and written submissions prepared by the parties, its assessment of the credibility and study of the testimony of the expert witnesses presented by each side, and an exhaustive review of the record, the Court is persuaded that the patents are valid.

1.

[3] An invention is "anticipated," and therefore not patentable because not novel, if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." [FN50] Anticipation is a narrow and technical attack on patentability; as a consequence, "the *848 standards of anticipation are strict. The invention must be disclosed within the four corners of a single reference." [FN51] In the case of chemical compounds, the mere recitation of a structural formula is insufficient to be an anticipation: the disclosure must also recite means of preparing the compound and at least one significant useful property. [FN52]

[4] Plaintiffs argue that Claim 3 of D.R.P. 12,451 (the "German Patent") anticipates the patents in suit. Claim 3 reads: "The above described processes for the production of yellow and red dyes by action * * * of diazo anisole sulfonic acids from the anisoles named under [Claims] 1 and 2 on naphthols, naphthol monosulfonic acids, and naphthol disulfonic acids." Claims 1 and 2 list no less than nine diazoanisole sulfonic acids; three separate naphthol sulfonic acids are possible. Claim 3 thus embraces over twenty-seven generic formulae, one of which is produced by the action of "methyl ether of amino cresol sulfonic acid on betanaphthol monosulfonic acid." The structural formula for this product is [FN53]



This structure theoretically embraces over 100 separate isomers [compounds having the same elemental composition (the same number of carbon, hydrogen, etc., atoms in the compound) but different structures], each having different properties. Plaintiffs' own expert conceded that the German Patent contained no description of Red 40 either in specific words or by specific structure, which in this instance was in accord with the views of defendants' experts. Accordingly, an initial response to plaintiffs' argument is that the German Patent does not disclose Red 40 with the requisite specificity; one would have to experiment with a large number of possible intermediates referred to in the German Patent and successfully piece together the necessary ones to come up with the one generic formula out of a total of twenty-seven generic formulae and then would have to experiment further to discover the specific structure of Red 40. This is not anticipation. [FN54]

*849 The argument, however, is more complex and relies on other references. Thus counsel for plaintiffs contend that (1) if "the description in the printed publication impart[s] to the person of ordinary skill sufficient information which, coupled with the disclosures of the prior art, would enable him to devise the invention without further genuine inspiration or undue experimentation," then the description anticipates the patented product, [FN55] and (2) the "person of ordinary skill" in the food dye industry would be aware of the editor's comment on D.R.P. 12,451 in the Friedlander edition of German patents and the Colour Index and would deduce from these references that a dyestuff having the same structural formula as Red 40 was the most natural disclosure of that patent. The "Friedlander Comment" reads in relevant part: [FN56]

> The aminophenol ethers stated in the patent to be used for the preparation of azo dyes came chiefly from ortho- and para-anisidine and their sulfonic acids, as well as amino cresol ether. The ortho compound yields in combination with B-naphthol and its sulfonic acids, yield essentially yellower derivatives, as contrasted to the corresponding para compounds.
>
> One prepared from o-anisidine and Schaefer-B-naphthol monosulfonic acid, gives a scarlet red dye which falls under the designation "Anisole red"; one somewhat yellower from anisidine sulfonic acid and B-naphthol is known as "Ponceau 3G" (3J or Scarlet 3J) in the Trade.

In more detail, plaintiffs' argument runs thus: The German Patent describes scarlet red dyestuffs produced by the action of "diazoanisole sulfonic acids" on "betanaphthol monosulfonic acid." A diazoanisole sulfonic acid described in the German Patent and highlighted in the Friedlander Comment is "methyl ether of amino cresol sulfonic acid," and the only "methyl ether of amino cresol sulphonic acid" shown in the 1956 edition of the Colour Index is orthotoluene sulfonic acid, 4-amino-5-methoxy, which is the same intermediate used to make Z-4576. The argument continues: The only beta-naphthol monosulfonic acid mentioned in the Friedlander reference is Schaeffer's Salt, the same naphthol coupling intermediate used to make Z-4576. Thus plaintiffs by this three-reference process argue that one skilled in the art would have been led to and known of Red 40. While this convoluted argument appears to have a surface logic, in fact it is reconstructed, brilliant hindsight that is not convincing on the issue to anticipation. [FN57]

[5] To begin with, given Judge Learned. Hand's admonition that "a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated," the Court is dubious of the legal accuracy of step one in the general argument. [FN58] But even if the anticipatory *850 reference could be pieced together from several sources as suggested by plaintiffs, the Court finds that the patents in suit would not have been disclosed to a cognizant artisan in the field of dye chemistry in 1964.

[6] One is led to inquire if, as plaintiffs contend, the German Patent together with

the Friedlander Comment so obviously describes Red 40, why Warner did not come across it in 1929 when it sought and created a new scarlet red food color -- the now delisted Red 4. Common sense, not altogether irrelevant even in patent cases, generates doubts that a relatively obscure one-hundred year old foreign patent, which only indirectly discloses the composition of Red 40 and does not clearly disclose its properties, describes the compound to a dye chemist skilled in the art in 1965. [FN59] This common sense view is confirmed by the reliable expert testimony in this case. Thus Dr. Erkkila, a highly experienced dye chemist, testified upon his deposition that although the German Patent theoretically embraced Red 40, it was not even a pertinent prior art reference because Red 40 was only one of several hundred compounds described. "If a person had to devise a molecule which had these [food color] properties, even if he knew about the German patent," it was the view of Dr. Erkkila that the patent would in no way "lead him to that at all. It was such a broad disclosure. This is something like telling you that there is oil in Texas, but you go, and find where it is. * * * The German patent did not specifically disclose it and its teaching was so broad that it would encompass hundreds, if not, who knows how many, possible structures." [FN60]

Dr. Kenneth Freeman, an analytical food color chemist who, after many years service with the FDA, was the Director of its Division of Color Certification and Evaluation, testified that within the "generic terminology" of D.R.P. 12,451 are included "several thousand dyes." More important, Dr. Freeman, who impressed the Court with his knowledge of dye chemistry and his candor, stated that he found no specific description of Red 40 in the German patent, as read with the Friedlander Comment. Dr. Freeman's parsing of the language of the Comment as it would be read by a dye chemist rebuts the testimony of plaintiffs' expert witness, Dr. Bernard Rottschaefer, that the Comment describes Red 40 with particularity. Thus he pointed out that the Friedlander Comment mentions Schaeffer's Salt only as a coupler with ortho-anisidine and anisidine sulfonic acid, both of which lack methyl groups, and nowhere does Friedlander suggest Red 40's phenyl component, the closest reference being amino cresol ether, without any mention of its sulfonic acids, which Dr. Freeman interpreted as excluding the amino cresol ether sulfonic acid component of Red 40. [FN61] Moreover, he testified that there is no indication that Friedlander meant to key the reader to a combination of Schaeffer's Salt in the second paragraph and the phenyl components listed in the first paragraph of the Comment, nor would a dye chemist so interpret.

Defendants' contention that the ordinary dye chemist would be confused, rather than enlightened, by the German Patent is supported too by incidents involving plaintiffs' own expert Dr. Rottschaefer. His declarations about the clarity of the German Patent's disclosures were delivered with an air of result-oriented assurance, and so it is not without significance that despite Dr. Rottschaefer's intense study of the patent, he too was sometimes confounded by its broadside mode of disclosure. For example, when he was asked to circle sections of the German Patent that defined the two moieties of Red 40, and after a recess to afford him the opportunity to reflect, Dr. Rottschaefer circled the wrong sections. Later, he erred in stating that Claim 2, not Claim 3, of the patent embraces the patents in suit. [FN62] The Court would find itself strained *851 to accept plaintiffs' theory that D.R.P. 12,451 discloses the structure of Red 40 when their own expert is so easily tripped up in its teutonic maze.

[7] A final factor supports the Court's judgment that the D.R.P. 12,451 does not anticipate Red 40. The German and Dutch Patent Offices had the German Patent before them when they allowed the Red 40 patents to be published for opposition. Trial evidence abundantly establishes that both offices are strict in enforcing the rule that anticipation by prior patent or publication precludes patentability, [FN63] and the issue of anticipation was directly considered by each. Indeed, in a lengthy letter to the German Office, Allied raised the same argument it

now presses before the Court, that "[i]t would require informed hindsight to select the single relevant structural formula * * * from the 40 to 60 broad and generalized structural formulae of the German patent." [FN64] While the decisions of the two foreign patent offices "are in no way controlling upon this court, * * * they are valuable as opinions of trained experts in the country of the inventor and where the art is best understood. The opinions of such men, learned, able and disinterested, officially expressed after thorough examination, are persuasive to say the least." [FN65] Their expert judgment is considered probative since it is recognized that in applying standards of novelty and nonobviousness, the patent offices of "Germany and Holland are among the strictest in the world," on a par with, if not superior to, the American office. [FN66] They found no anticipation by D.R.P. 12,451; this Court finds none.

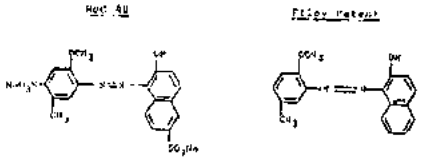
2.

[8] The Court next considers plaintiffs' contention that the subject matter of the claims was obvious to a dye chemist of ordinary skill in 1964-68. An invention is "obvious," and therefore not patentable, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." [FN67] Though the "test laid down is indeed misty enough," [FN68] the Supreme Court has given direction by setting forth "primary factors" always relevant to an inquiry into obviousness -- "the scope and content of the prior art," "differences between the prior art and the claims at issue," and "the level of ordinary skill in the pertinent art" -- as well as certain secondary considerations -- "commercial success, long felt but unsolved needs, failure of others, etc." -- that "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." [FN69]

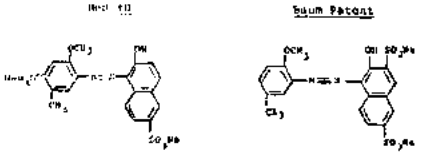
[9] Because "the enormous number of known organic compounds gives rise to a situation in which absolutely unique and *852 unknown groupings of atoms in a completely new chemical compound is a rare occurrence," courts have generally held that such compounds are patentable even though similar compounds or isomers are well-known in the field. "Obvious molecular modification coupled with a showing of novel properties or superiority [over] known properties can establish patentability." [FN70] Since Judge Rich's celebrated decision of In re Papesch, [FN71] courts have been moving to a test of "essential predictability," balancing the significance of unexpected properties resulting from minor chemical manipulations of existing compounds against the desirable properties that would be expected from such alterations. [FN72]

At trial, plaintiffs mounted a technically powerful case in support of their claim that any one of several well-known dyestuffs could, with certain minimal changes, be transformed into Red 40 and that a dye chemist of ordinary skill would have known to make those alterations to achieve the desirable properties of Red 40. It may be accepted that a dye chemist in 1965 would have been aware of the appropriate literature and the main patents on which plaintiffs rely: the Elley Patent, which covers a compound which is reddish to bluish-red in shade; the Widmer Patent, a deep or bluish-red hue; the Baum Patent, a cherry red tint; and Yellow 6, a reddish-yellow (or yellowish-orange) color. Plaintiffs are also correct that such a chemist would have been familiar with certain molecular modifications and their effects on properties: sulfonation is highly desirable because it increases solubility in water and may decrease dangers of toxicity, and methyl and methoxy groups will shift the shade of the dye in a bathochromic direction, though for toxicity purposes methoxy groups should be preferred over methyl ones. According to plaintiffs' theory, a few simple changes in existing dyes, checked by routine experimentation in a laboratory available to our hypothetical chemist, [FN73] would yield a nontoxic scarlet red color having the structure of Red 40.

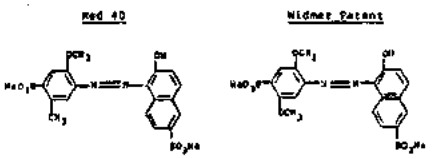
Thus plaintiffs stress that by merely adding sulfonic acid groups to the Elley Patent,



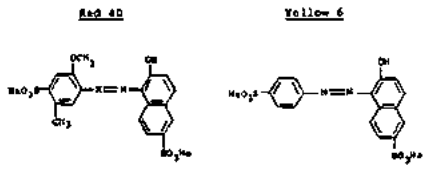
or shifting one sulfonic acid group of the Baum Patent from the naphthol to the phenyl component,



Red 40's structure would be created and that these manipulations would have been obvious to a dye chemist who wanted a nontoxic *853 water soluble red dye because addition of sulfonic acid groups guarantees water solubility and reduces risks of toxicity. As to the Widmer Patent, the only shift would be to replace a methoxy group with a methyl one,



And Yellow 6 is claimed to render the patents in suit obvious since the addition of methyl and methoxy groups would shift its shade from reddish yellow to a deeper shade of red,



Thus by these simple changes plaintiffs argue that a dye chemist in 1965, after consultation with one skilled in the toxicology of food colors, would know that a food color should be monoazo and sulfonated on both sides, and that change from methyl to methoxy auxochrome groups reduced toxicity -- all of which would lead him to the structure of a scarlet red food color.

Again, plaintiffs' logical step-by-step argument relies on retrospective brilliance. Yet their analysis does not satisfactorily explain why the United States Patent Office, whose own careful search embraced the Elley and Baum Patents and Yellow 6, nonetheless granted the patents in suit. [FN74] Nor does it explain how these structural similarities failed to prevent the German and Dutch Patent Offices from giving their imprimatur, after an even more searching scrutiny of the prior art. The conclusion is warranted that, relying on the case law progeny of Papesch, these offices found the structural changes to be nonobvious ones in the light of Red 40's surprising and unexpected properties -- proven and unquestioned nontoxicity, very high water solubility, and excellent application properties.

Indeed the state of the art in 1965 indicates that the molecular manipulations suggested by plaintiffs were not necessarily the most obvious ones to make in order to produce a nontoxic scarlet food dye. Thus the Elley Patent "relates to the production of colored gasolines and petroleum distillates, such as motor fuels, which are reddish to bluish-red in shade, have a bronzy fluorescence and are stable to the action of sunlight." [FN75] From the point of view of a food dye chemist in 1965, any variation of this compound would appear undesirable, since the patent not only suggests gasoline and other petroleum uses, but the "bronzy fluorescence" property would be highly undesirable in a food color; the Elley Patent would, if anything, "lead away" from the structure of Red 40 as a potential food dye. Even if the patent were itself more inviting, the direction of the prior art would not result in Red 40. Based on the nontoxicity principles that sulfonation is desirable and methoxy groups should substitute for methyl groups, the "obvious" alterations would be to replace the methyl group in Elley's phenyl moiety with a methoxy group and then experiment

with different arrangements of sulfonic acid groups. This would tend, also, to lead away from Red 40.

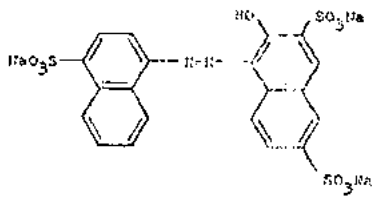
The Baum Patent, differing from the patents in suit only in the placement of a sulfonic acid group, is a dye "which will give to wool and silk a deep crimson shade." [FN76] The Colour Index indicates that the Baum dyestuff is "cherry red," arguably the same hue as Red 4, the desired shade in the Steiner and Rast search. But neither reference mentions any use of the dye to color food. More importantly, to maximize the probability of nontoxicity based on the state of the art in 1965, the obvious manipulations would be to add one or more sulfonic groups to the left-hand moiety, without subtracting one from the right-hand moiety, and to strike the methyl group on the right-hand side. Again, the established principles of the art in 1965 would not have led the dye chemist ineluctably to Red 40. In addition, the credible expert evidence establishes that adding or shifting the position of sulfonate substituents would have a *854 definite but unpredictable effect on the color of the resulting dye. Thus the manipulation suggested by plaintiffs (shifting the position) or that suggested by the prior art (adding a third group) would likely yield an unacceptable shade.

Likewise, the Widmer Patent describing "complex chromium compounds of monoazo dyestuffs" for wool and other fibers, appears entirely inapposite to the 1965 search for a nontoxic food dye. [FN77] Moreover, the state of the art would militate against substituting a methyl for a methoxy group (which would be necessary to lead the chemist to Red 40), since such substitution would increase risks of toxicity, rather than reduce them.

From the perspective of a food dye chemist in 1965, and not from the wisdom bred of hindsight, the most relevant prior art on which plaintiffs rely is Yellow 6, which was extensively used as a water-soluble food color. An initial problem with reliance on Yellow 6, however, is that there was in 1965 some concern that it, like Red 4 and Red 1, might run into toxicity problems with the FDA. [FN78] Such a concern, even though it has proven unfounded in retrospect, would not have made Yellow 6 the obvious starting point for synthesizing a safe red dye. To the contrary, the uncertainty in the industry growing out of the FDA's numerous delistings in the late 1950s and early 1960s and the prospect of future delistings of existing colors, well-known in the trade and to food dye chemists, justifies the approach taken by Steiner and Rast -- to seek out new structures and make their choice based on extensive chemical and pharmacological experimentation. Indeed, the approach pressed by plaintiffs -- making structural manipulations in the myriad reddish dyes whose nontoxicity was far from established under the crisis circumstances in 1965 -- would not have been the prudent, or obvious, means of discovering a safe food dye such as Red 40.

[10] Moreover, if the chemist did start with Yellow 6, the obvious changes he would make would be to add one, two, or three methoxy groups to the left- hand moiety to shift the shade in a bathochromic direction; the prior art would lead away from the structure of Red 40 because of the belief prevailing in 1965 that methoxy groups were preferred over methyl ones. The fact is that in 1965 dye chemists had scarce and unreliable information upon which to make predictions about toxicity. Many of their basic assumptions, in fact, have been cast into doubt. For example, the view that substituting methoxy groups for methyl groups as a way to reduce the risk of toxicity, accepted by dye chemists and toxicologists in 1964 and 1965, was severely questioned by an article published in 1965-66 by Dr. Jack Radomski, one of plaintiffs' own expert witnesses. [FN79] Similarly, the assumed wisdom that azo dyes that were bilaterally sulfonated would be nontoxic [FN80] is undermined by the delisting of Red 2, which has the following structure:

*855



The Court finds that the state of the art in 1965 was such that nontoxicity was essentially not predictable in an azo dye compound. Nontoxicity would only be established by trial and error and animal testing, which is precisely what Allied engaged in over an extended period.

Not only was Red 40's nontoxicity essentially unpredictable, but so too were its excellent application properties. While plaintiffs vigorously contend that Red 40 is quite an ordinary dyestuff having few qualities to recommend it other than its monopoly of the market, their position is belied by the testimony and documentation produced by one of their own witnesses, Dr. Samuel Zuckerman, the Vice-President of plaintiff Kohnstamm and General Manager of its Color Division. In a pamphlet on food colors published by the National Academy of Sciences and verified by Dr. Zuckerman as a reliable source on the subject, is a table of "Physical and Chemical Properties of Certified Food Colors," which yields the following information: [FN81]

Properties	Red 40	Red 2	Yellow 6
Stability to			
Light	very good	moderate	moderate
Oxidation	fair	fair	fair
pH change	good	good	good
Compatibility with			
Good Components	very good	good	moderate
Tinctorial strength	very good	good	good
Solubility			

(g/100 ml)			
Water	25	20	19
EtOH	9.5	7	10
Glycerin	3	18	20
Overall Rating	good	moderate	moderate

Plaintiffs have offered no evidence to refute the information in this chart, nor any explanation why in 1965 a dye chemist would have expected such superior application properties for Red 40. Indeed, plaintiffs' expert, Dr. Rottschaefer, acknowledged that, except for shade and solubility, he "wouldn't have enough knowledge from their structures to predict * * * at least on a tentative basis, the relative chemical properties" of Red 40 and Yellow 6. [FN82] In general, plaintiffs' argument with respect to the Elley, Widmer, and Baum Patents and Yellow 6, that with slight manipulation those with ordinary skill in the art of color research would have known of Red 40, utterly ignores an item of prime consideration in the search for a food dye -- its application properties. Although they do refer to toxicity, water solubility, and shade, they ignore these other essential matters.

[11] Even if the Court were to accept plaintiffs' position that the general shade of Red 40 was moderately predictable, with routine experimentation, its important application properties and nontoxicity were not. The patents in suit clearly meet the standards for patentability, since the essential unpredictability of the most important properties negates the claim of obviousness. This conclusion is bolstered by the various secondary considerations noted by the Supreme Court, which can tip the scales in favor of patentability in cases where the issue is closer than in the instant case. [FN83] Red 40 was developed to fill the serious void created by the delistment of Red 4; on filling this void, it has been a phenomenal commercial success; although in some measure it is due to the delisting of Red 2 in 1976, Red 40's success independent of the demise of Red 2 cannot be disputed. [FN84] The compound has also been acclaimed by the industry, winning the Putman Food Award for its inventive contribution. Warner itself paid tribute to Allied for its "bravado" in paying all the expenses for the pharmacology and testing for the development of Red 40 and thereby "scooping the rest of the industry." [FN85] Most compelling is the fact that despite plaintiffs' confident assertions that a safe red dye could easily be derived by performing certain simple manipulations on the structure of Yellow 6 (adding methoxy ***856** radicals), no such dyestuff has been forthcoming despite their concentrated efforts to develop a safe substitute red food color, and the leaders in the industry have tacitly acknowledged the uniqueness of Red 40 by entering into licensing agreements with Allied.

B.

The Court's finding that the patents in suit were not anticipated or obvious at the time of the invention does not end the inquiry, for plaintiffs argue that the patents are invalid or unenforceable on policy grounds, because of (1) Allied's failure to disclose pertinent prior art and the best mode of preparation in prosecuting its application before the Patent Office and (2) defendants' misuse of the "patent monopoly" to extort unreasonable sums from plaintiffs or drive them out of the dye market. The Court finds their claims to be without substance.

1.

[12] The first set of collateral attacks on the validity or enforceability of the patents is that Allied Chemical failed to disclose material matters in prosecuting its application before the Patent Office: (a) the

"best mode" for preparing the dyes and (b) the most relevant prior art. While stopping short of alleging fraud on the Patent Office, plaintiffs contend that where nondisclosures are serious, material, and reckless the subsequently granted patents should be declared invalid or, at least, unenforceable. [FN86] The Court shares this concern. Because a patent grants a monopoly, and because the Patent Office, flooded with applications and at times lacking adequate resources, is unable to check all facts and investigate all relevant prior art, "it must rely on applicants for many of the facts upon which its decisions are based. The highest standards of honesty and candor on the part of applicants in presenting such facts to the office are thus necessary elements in a working patent system." [FN87] Accordingly, "unclean hands" occasioned by failure to disclose such facts can operate to invalidate a patent or render it unenforceable. [FN88] Although Allied's disclosures were not all-inclusive, the Court finds that they were presented in good faith and without reckless disregard of the applicant's duties of disclosure.

The first challenge is that Allied failed to meet the statutory requirement that "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains * * * to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." [FN89] Plaintiffs do not dispute that the Red 40 specification clearly and accurately describes a mode that will yield the compound but charges that it is not the "best mode" because it omits an "alcohol-wash" purification step that is necessary to produce a batch with the 85% dye purity mandated by the FDA. As a result, the argument goes, the inventive contribution of the patent is insufficiently revealed to the public.

[13] Defendants, acknowledging that "[a] patentee must disclose the best method known to him to carry out the invention," contend that "[i]t is enough that [the applicant] act in good faith in his patent disclosure." [FN90] Although Allied did act in good faith, such a finding does not conclude the matter when the disclosure is so generalized or unhelpful so as to withhold effective use of the patented discovery from the public; the more recent case law sternly counsels that "[u]nintentional obtuseness or obfuscation might be a reason not to penalize someone; ***857** we do not see it as a reason for granting a seventeen year monopoly." [FN91] The proper test is the one indicated by the words of the statute: would a person skilled in the art be able, with a reasonable effort, to synthesize the patented compound?

While it appears that there were several possible means of increasing dye purity, the evidence before the Court conclusively establishes that the ordinary dye chemist would automatically know to use the alcohol-wash step to guarantee the requisite purity. This fact was dramatically demonstrated on defendants' examination of chemists employed by the two plaintiff companies. Fred Hope, a chemist at Kohnstamm, testified that he had no difficulty preparing Red 40 and used the alcohol-wash technique to increase the purity; he stated that the procedure was "something that almost any organic chemist should know." [FN92] More important, Richard Falk, Warner's Manager of Color Production, conclusively testified that a chemist of ordinary skill in the manufacture of food colors could pick up the Red 40 patents, read the disclosed method of preparation, and have no problem in preparing the product with the degree of purity required for FDA certification. [FN93] Although it would have been better to have included the alcohol-wash step in the patent's specification, its omission was neither reckless nor uninformed, but rather based on the correct perception that dye chemists would utilize the method in any event.

[14] Plaintiffs' second challenge is that Allied's failure to cite D.R.P. 12,451 and Yellow 6 to the Patent Office as relevant prior art constitutes unclean hands that should equitably estop it from enforcing its

patents. [FN94] Courts have agreed that where "misrepresentations [are] made in an atmosphere of gross negligence as to their truth," patents thereby procured will not be enforced, even where there is no finding that the withheld material would have caused the Patent Office to deny the application. [FN95]"Public interest demands that all facts relevant to such matters be submitted formally or informally to the Patent Office, which can then pass upon the sufficiency of the evidence": [FN96] the applicant has a duty to disclose matters that are relevant.

Though the Court is persuaded that Allied and its agents did not act in bad faith in failing to make these disclosures and there was no purpose to deceive, the issue remains as to whether Allied acted with a reckless disregard of its duty of full disclosure. Defendant's disclosure in its application was, arguably, self-serving, since the only citation to prior art was to Red 4, which was unlikely to render the patents in suit obvious in the light of applicant's representation that Red 4 "recently has been delisted for essentially all edible uses by the Food and Drug Administration, thereby creating a need for a red dye particularly useful in the coloring of edible substrates." But its failure to disclose Yellow 6 was not wrongful conduct, since there is no evidence that anyone associated with the patent application -- attorney Jarocz, expert Erkkila, inventor Steiner, or researcher Edelman -- found Yellow 6 relevant to patentability.

[15] The issue is sharper with respect to the failure to disclose D.R.P. 12,451. It is clear that "[i]f an applicant knows of prior art which plainly describes his claimed invention or comes so close that a reasonable man would say that the invention was not original but had been anticipated, he will not be excused for failure to disclose his knowledge." [FN97] And Edelman's invention *858 record listed the German Patent as "perhaps, the most pertinent reference." Nonetheless, the Court is persuaded that Allied's failure to disclose was not purposeful or designed to mislead nor did it constitute gross or reckless disregard of its duty of disclosure.

From an objective perspective, of course, Jarocz's judgment was the correct one, since this Court, and both the German and Dutch Patent Offices, carefully considered D.R.P. 12,451 in affirming the novelty of the Red 40 patents. And the judgment of Jarocz, a former Patent Examiner, that the antiquated German Patent might prove confusing was not without substance. His decision not to cite the patent came only after much study and discussion with others more knowledgeable than he, primarily Dr. Erkkila, whose characterization of D.R.P. 12,451 as an impossibly broad generic disclosure is probative. In sum, even assuming that the German Patent would have been pertinent in the proceedings before the United States Patent Office, Allied was reasonably diligent and not reckless in not citing the German Patent as prior art or as a possible anticipation. [FN98]

2.

Plaintiffs' further argument is that defendants have misused their patents (a) by charging an exhorbitant royalty rate that has allegedly priced Kohnstamm out of the market and is oppressive to Warner and (b) by applying the rate to the "testing surcharge" that since December 1976 has been included in the invoice price of food colors sold by both plaintiffs. [FN99] Plaintiffs' charge that the 17 1/2 % rate is exhorbitant, rests upon two events that took place after the parties had agreed upon the royalty rate: the delisting of Red 2 in February 1976 gave defendants a unique monopoly position by in effect closing the market to all other red food colors, and in December 1976 industry members agreed to share among themselves the expense of a testing program. As a result, it is urged that the patents are unenforceable and that defendants are engaged in unfair competition.

[16] With respect to the broader charge that the 17 1/2 % rate constituted patent misuse, the legal authorities on which plaintiffs rely in no way support their far-fetched position. The main cases cited by plaintiffs support the proposition that "conditioning the grant of a patent license upon payment of royalties on products which do not use the teaching of the

patent does amount to patent misuse." [FN100] There is no such tie-in product in this case. Instead, the facts of the case fall squarely under the equally established principle that "[a] patent empowers the owner to exact royalties as high as he can negotiate with the leverage of that monopoly," [FN101] and rates well in excess of 17 1/2 % charged here have been upheld against charges of patent misuse. [FN102]

Plaintiffs' position is further undermined, if not conclusively rebutted, by the fact that the 17 1/2 % rate was the result of bargaining among giants in the food dye industry. Of the six leading food color manufacturers four -- the two plaintiff companies, the Hilton-Davis Chemical Company, and defendant Buffalo Color -- manufacture and sell Red 40; the first three are licensed at the 17 1/2 % rate, pursuant to agreements freely negotiated and entered. [FN103] Plaintiffs engaged in arm's length bargaining with Allied over a four-month period, after the *859 first trial was underway. One of the bargained- for provisions of the License Agreement was the royalty of 17 1/2 % of the invoice price charged to customers; if plaintiffs were dissatisfied with the provision, they were under no compulsion to accept the contract -- the door of the courthouse was open for them to continue the trial and seek a final determination of the validity of the patents, and if successful they would have been free of any royalty payment. Their choice to agree to the 17 1/2 % rate binds them now.

[17] The fact that the delisting of Red 2, almost a year after the parties agreed upon the royalty rate, had made Red 40 the only major red food color on the market, is no ground upon which to charge defendants with patent misuse. This was a result of the action of the FDA, which acted under a public duty to guard against potentially harmful food components. This action by an official agency did not convert the previously agreed upon royalty rate into an exhorbitant or coercive rate. More important, the likely delisting of Red 2 was known to plaintiffs, as it was to the entire industry, almost four years before entry into the Licensing Agreements. Finally, it is not without significance that Hilton-Davis entered into its licensing agreement, containing the same 17 1/2 % royalty provision, after the FDA's action in February 1976.

Plaintiffs make the further claim that Kohnstamm was forced to give up the manufacture of Red 40 because the royalty rate was too high. The fact is that Kohnstamm manufactured and sold Red 40 under its license from March 1975 to November 1978 and paid almost $500,000 in royalties. Kohnstamm's decision not to manufacture Red 40 was a calculated business judgment based on its view that it was more profitable to concentrate on and expand production of another dye, Red 3, in which it had a strong market position and to buy Red 40 rather than to make it under the royalty license. Moreover, Kohnstamm's claim that the royalty rate forced it to discontinue the manufacture of Red 40 is seriously undermined by a study specifically undertaken by its cost accountant to evaluate whether it was cheaper to buy Red 40 at prevailing market prices or to manufacture it under the License Agreement from Allied at the 17 1/2 % royalty rate. The cost accountant's conclusion based upon a study and analysis of significant factors was that it was more profitable to manufacture Red 40 even after the royalty payment than to purchase the product in the market. However, Kohnstamm's executives decided otherwise. But whatever influenced their decision it was a deliberate business judgment. The claim here advanced that Kohnstamm was foreclosed from the market because of the royalty rate borders on the frivolous.

Any suggestion that the rate of royalty is excessive or excludes competitors from the market is also negated by the continued viability of Warner, Kohnstamm's co-plaintiff in this action, and Hilton-Davis as competitors in the Red 40 market which includes Buffalo Color. The evidence establishes that Warner has made a profit on its sale and manufacture of the patented item, on which it has paid (through February 1979) royalties of $2,500,000. Hilton- Davis, from the time it

was licensed through February 1979, has paid almost $1,500,000 in royalties. Plaintiffs' contention that because of the ban on Red 2 and the increased sales of Red 40 with the consequent dollar increase in royalty payments the stipulated 17 1/2 % royalty rate thereby became "economically oppressive, unreasonable and excessively high," stands economics on its head.

[18] With respect to the further claim that the royalty is unfairly applied to the testing surcharge, plaintiffs' argument is equally weak. The License Agreements expressly pegged the 17 1/2 % rate to the "invoice price at which Licensed Food Color was sold by Licensee," for the business convenience of the parties. [FN104] The plaintiffs' decision not to absorb but to pass on the surcharge to their customers by including it in their billings of Red 40 should not deprive defendants of their claimed right to receive royalties based upon the billings. [FN105] Defendants' calculation of the royalty from the full invoice price, including the surcharge, is based upon an assertion of their right to receive 17 1/2 % as royalty as defined in the agreement. [FN106] Accordingly, the Court holds that defendants have engaged in no unfair business conduct constituting misuse of their patents, unfair competition, or violation of the antitrust laws, since defendants' royalties are fully justified under the terms of the Licensing Agreements, which were ***860** fully negotiated and entered into without coercion.

[19] The Court next considers defendants' counterclaims of infringement of the patents and breach of contract of the settlement agreements. These are somewhat interrelated. If the settlement agreements under which the plaintiffs pay the 17 1/2 % royalty are in effect, then defendants' claim of infringement must fail since plaintiffs have paid the royalty from the time the agreements were made to the present and thus are authorized licensees. Thus the primary thrust of the breach of contract claim is that plaintiffs' commencement of this action within fifteen months after the first action had been settled, in the face of a provision in the agreement that the "licensee [plaintiffs] shall have the right to terminate this agreement at any time after the second anniversary thereof," violated the agreement. The defendants contend that the two-year provision was a period of mandatory "repose" from litigation and that the commencement of this suit prior thereto was a material breach which terminated the agreement; as a consequence, defendants assert that plaintiffs no longer were licensees and their continued manufacture of Red 40 makes them infringers. While defendants' desire for a period of repose is understandable, the simple fact is that the settlement agreements do not contain any specific provision that plaintiffs shall not commence another litigation in less than two years -- a provision which by itself may present a question of its enforceability in the light of Lear Inc. v. Adkins. [FN107]

But, more important, the matter appears to have been put at rest by the decision of the Court of Appeals in this very case, where the basis of the defendants' motion to dismiss this action is the alleged breach here advanced to support defendants' claim. The majority of the Court, based in large measure upon the underlying rationale of Lear of the public interest in challenges to alleged invalid patent monopolies, held that "[t]he plaintiffs should not be barred from declaratory relief simply because the licensing agreement is not terminable by the licensee for two years" and that "a two-year moratorium on litigation is not implicit in every two-year nontermination provision." [FN108] Thus the commencement of this action before the two-year period did not constitute a breach of the parties' agreement, and since plaintiffs admittedly are current in meeting the royalty payments under the Licensing Agreements, there is no basis for the infringement claim.

One final matter remains to be decided. Defendants, the prevailing party in this lawsuit, strongly urge the Court to grant it counsel fees for its defense of this action. They argue that this is an "exceptional case" in which courts are empowered to grant such fees because of what they term are "extraordinary circumstances" surrounding the case, to wit: [FN109] plaintiffs "slavishly" copied the

patented item before instituting their first action in this Court, disregarded the period of repose of the Licensing Agreements when they commenced this second action attacking defendants' patents, attempted to avoid payment of royalties during the litigation by petitioning the Court to place all such funds in an escrow account, and stubbornly persisted in their contention that unlicensed manufacture of Red 40 would not infringe the patents in suit, even if they were held to be valid.

The Court concurs that, depending upon one's point of view, this case has been "exceptional," in that it has arisen out of "extraordinary circumstances." There is no doubt that both parties have engaged in extensive and burdensome litigation and that each has incurred very substantial legal and other expenses in the course of the two sharply contested lawsuits. But this has been of their own choosing. Each had the opportunity for a binding judicial determination of their respective claims four years ago when the first case actually proceeded to trial. The parties opted instead for a settlement which their very experienced lawyers knew would not conclusively and finally resolve their controversy. Plaintiffs, instead of pressing their claims of invalidity, noninfringement, and unenforceability of the patents, preferred to pay the agreed-upon royalty with a right of termination after a two-year period.

[20] Defendant Allied had a similar opportunity to present its counterclaim for infringement for judicial and binding determination but decided to settle for the royalty payments to it plus a payment of $200,000. Moreover, Allied could have cut off the *861 prospect of a second lawsuit by insistence upon a consent decree of validity and enforceability of its patents (plaintiffs refused to enter into such a decree), failing which it was still free to continue the still-pending trial and secure an adjudication of its counterclaim upon the merits which would have had res judicata force. [FN110] That renewal of litigation was a distinct likelihood, whether openly stated or not, is evident from the order of dismissal without prejudice of plaintiffs' claims in the first action. Thus each party, defendants no less than plaintiffs, shares the responsibility for this second action with its consequent burdens and expenses. Indeed, each is at fault for involving the Courts a second time with their hard-fought controversy when it could have been resolved in the first action. While settlement of actions is to be encouraged, those which are but a temporary truce in the parties' continued warfare and present only the facade but not the reality of settlement should not be encouraged. Such maneuvering does not create the "exceptional case" warranting the allowance of counsel fees. Each litigant will bear its own fees.

In sum, judgment may be entered dismissing upon the merits plaintiffs' claims of invalidity, noninfringement and unenforceability of the patents and their other claims; dismissing upon the merits defendants' counterclaims of breach of contract and infringement and denying defendants' application for attorneys' fees.

The foregoing shall constitute the Court's Findings of Fact and Conclusions of Law.

So ordered.

FN1 In June 1977, Allied assigned to Buffalo Color all its right, title, and interest to each of the patents in suit. Buffalo, under a supplemental complaint, is named as a defendant and asserts a counterclaim for infringement from the time it acquired the patents.

FN2 Jurisdiction in these cases is based on 28 U.S.C. §1338.

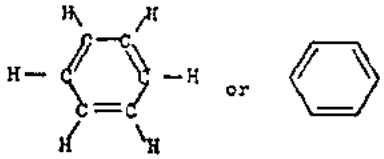
FN3 Exh. 3. Initially, Allied applied for only one patent, but after the Patent Examiner required separation of dyestuff claims and claims directed to edible substrates colored with such dyestuffs, a second application was filed, based on the same disclosures. The '617 "composition of matter" patent embraces nine claims, and the subsequently issues '733 "use" patent includes ten claims. Defendants' averments of infringement at trial were limited to claim 6 of the '617 patent and claim 7 of the '733 patent (describing the structure of Red 40); plaintiffs' averments of invalidity, noninfringement, and unenforceability were directed to all claims of both

patents. The Court's opinion focuses on claims relating to Red 40.

FN4 Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 5, 148 USPQ 459, 462 (1966).

FN5 National Academy of Sciences (Committee on Food Protection, Food & Nutrition Board, Division of Biology & Agriculture, National Research Council), Food Colors 9 (1971) (Exh. BB) [hereinafter cited as Food Colors Study].

FN6 The basic building block of coal-tar dyes is benzene, which is an organic compound consisting of six carbon atoms ("C") and six hydrogen atoms ("H") in a molecular ring containing three alternating double bonds:



Naphthalene is an aromatic organic compound composed of two benzene rings conjoined at one of the double bonds.

FN7 The phenyl group is a benzene ring absent one of its hydrogen atoms; the naphthol group is a naphthyl group absent two of its hydrogen atoms, one of which has been replaced by a hydroxyl radical ("OH"). The azo group is the main chromophoric component of the compound and consists of two nitrogen atoms ("N").

FN8 An "intermediate" is any one of the starting materials in a chemical reaction to make another compound.

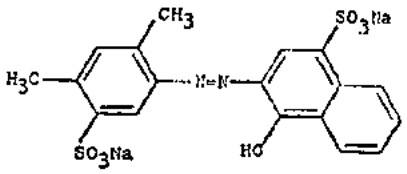
FN9 B. Hesse, Coal-Tar Colors Used in Food Products 2-3, 25-30 (1912) (Exh. AZ). These same properties are the ones considered to be the essential desiderata today, see Food Colors Study, supra note 5, at 36-37.

FN10 Act of June 30, 1906, ch. 3915, 40 Stat. 273. In Food Inspection Decision 76, issued on July 13, 1907, the Federal Government listed the seven colors chosen by Hesse and provided that use of other dyes would be grounds for prosecution. Calvery, Coal-Tar Colors: Their Use in Foods, Drugs & Cosmetics, 114 Am. J. Pharmacology 1, 4-5 (1942) (Exh. BA) (quoting from F.I.D. 76).

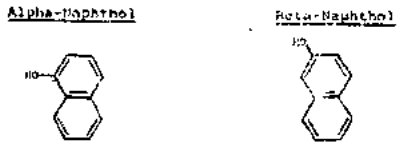
FN11 The shorthand notations derive from the subsequent listing of these compounds by the FDA as "FD & C" ("Food, Drug & Cosmetic") Color Nos. 1, 2, and 3.

FN12 B. Hesse, supra note 9, at 11.

FN13 The structural formula for Red 4 is as follows:



The naphthol component for Red 4 is an "alpha - naphthol," not the "beta- naphthol" used in the prototype in the text at note 7 supra.



FN14 Act of June 25, 1938, ch. 675, 52 Stat. 1040, codified at 21 U.S.C. §§301-392. For the impact of the Act on the dye industry, see Calvery, supra note 10.

FN15 Pub. L. No. 86-618, tit. I, 74 Stat. 397 (1960), codified at 21 U.S.C. §§321, 331, 333, 342, 343, 346, 351, 361, 362, 371, 376.

FN16 28 Fed. Reg. 6439 (June 23, 1962).

FN17 Red 4 was relisted in 1965 for the limited use of dying maraschino cherries but in 1976 was delisted for all food use purposes.

FN18 See Exh. D (1965 Steiner request for research authorization: "Thus there is an urgent need for a bright yellowish-red to replace Reds #1 and #4."); Exh. EZ (December 1964 letter from Warner's Director of Sales: "Unfortunately there is no entirely satisfactory single replacement for FD & C Red No. 4.")

FN19 Exh. 501 (laboratory report evaluating various possibilities).

FN20 Dr. Steiner received his Ph.D. in organic chemistry in 1956. Since 1974, he has been on the Editorial Board of the Colour Index, a prestigious position held by few American chemists. His reputation in the dye chemist community was acknowledged by all witnesses.

FN21 Trial Record ("T.R.") 2122.

FN22 See T.R. 754-60 (testimony of Dr. Jack Radomski, plaintiffs' expert); id. 2158-59, 2179-80 (testimony of Dr. Steiner); Exhs. 102-104, 106 (scholarly articles); Exh. 505 (1965 Progress Report on Steiner & Rast research); Exh. 540 (1967 Allied memo); Exh. 603(6).

FN23 Exh. 503. But cf. T.R. 2163-67 (Steiner testimony that some of Ferber's suggestions were self-contradictory).

FN24 Thus dyes, including Red 1 and Red 4, that had been long accepted as nontoxic through the 1950s suddenly, in the 1960s, were subject to delistment as unsafe. Food dye chemists in the 1960s were, moreover, unsure as to the reasons some compounds, such as beta-naphthylamine, were toxic and others, such as the structurally similar alpha-naphthylamine, were not. See notes 79-80 infra.

FN25 See T.R. 2152-55, 2158-59, 2178-82 (testimony of Dr. Steiner); Exh. 603(6) (Rast memorandum, Jan. 7, 1965).

FN26 These included tests with respect to solubility; tinctorial strength on various types of foodstuffs, including cherries and wieners; stability to sulfur dioxide, heat, pH changes, ascorbic acid. Exh. 513 (Progress Report of Steiner & Rast research, Aug. 1965).

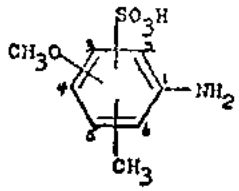
FN27 Exh. 531 P4.3 (minutes of Allied Industrial Chemicals meeting Feb. 2, 1967). As indicated in a report by Dr. Steiner written in late 1966 or early 1967, Exh. AB, the researchers found Z-4576 to be substantially more soluble in water and glycerine than either of the other two dyes, stronger than Z-4578 in sugar platting tests, and considerably less inclined to "bleed" from cherries than Red 1, Red 4, or Z-4578. See also T.R. 2202-10 (testimony of Dr. Steiner).

FN28 Exh. FI, at 20.

FN29 Exh. 533 (invention record, Feb. 13, 1967).

FN30 Exh. 10T.

FN31 Amino cresol is methyl-amino-benzene, and the term methyl ether denotes a methoxy radical. Thus the "methyl ether of amino cresol sulfonic acid," has the following formula,



One specific formula included in that generic formula is that of the phenyl component of Red 40: the methyl group is fixed in the # 5 position, the sulfonic acid group in the # 4 position, and the methoxy group in the # 2 position (numbered counterclockwise from the azo linkage). Similarly, the naphthol component of Red 40 is one of the variations on the general formula denoted in "beta-naphthol monosulfonic acid," with the sulfonic acid group in the # 6 position on the naphthol ring (if numbered clockwise from the azo linkage).

FN32 Exh. 533 P6.3 (invention record).

FN33 See T.R. 1688-93 (testimony of Dr. Erkkila).

FN34 T.R. 1224-25.

FN35 United States Patent No. 2,224,904 (Dec. 17, 1940) ("Coloring of Petroleum Distillates") (Exh. 49).

FN36 Allied disclaimed the "terminal portion" of the '733 patent -- the portion which would have extended beyond the expiration of the '617 patent -- so that both patents will expire on the same date (July 6, 1987).

FN37 Exh. GE, at 42-43. In response to Examiner Muhlbauer's citation to many red dyes listed in the

Colour Index, the letter stated that "none of the above-mentioned known red dyes is sufficiently suitable for use as a food dye. In particular none of these dyes has the combination of properties that it is nontoxic, stable to sulfur dioxide and of yellowish-red color. Some of them are furthermore precipitated by acid or not completely fast to light." Id. at 48-49. See also Exh. 575 (letter of Oct. 30, 1973 to German Patent Office).

FN38 United States Patent No. 2,606,184 (Aug. 5, 1952) ("Chromiferous Monoazo-Dyestuffs") (Exh. 51).

FN39 United States Patent No. 250,038 (Nov. 22, 1881) ("Manufacture of Crimson Coloring Matter") (Exh. 44) The Baum Patent is identical to Colour Index No. 16160.

FN40 Exh. GC, at 89 (new claim: "A method of coloring foods, beverages and pharmaceutical and cosmetic preparations as well as labels coming into contact with the same, characterized by the use as coloring substance of a compound of [claim 1 of the '617 patent] * * *.")

FN41 Exhs. DS & 405. Although plaintiffs contend that Red 40's success was entirely contingent on the misfortunes of Red 2, the Court's examination of the FDA's statistics persuades it that Red 40 had consumer appeal independent of the demand for Red 2.

FN42 Exh. EA P1 (agreement between Warner and University).

FN43 T.R. 1099-1102, 1130, 1721-22, 1729-30.

FN44 Warner-Jenkinson Co. v. Allied Chem. Corp., 567 F.2d 184, 187- 88, 193 USPQ 753, 755-757 (2d Cir. 1977).

FN45 Defendants' Brief after Trial, at 34.

FN46 35 U.S.C. §282; Santa Fe-Pomeroy, Inc. v. P&Z Co., 569 F.2d 1084, 1091, 197 USPQ 449, 454-455 (9th Cir. 1978).

FN47 Champion Spark Plug Co. v. Gyromat Corp., No. 78-7556, slip op. at 3584 n.11, 202 USPQ 785, 788 n.11 (2d Cir. July 2, 1979); Georgia- Pacific Corp. v. United States Plywood Corp., 258 F.2d 124, 133, 118 USPQ 122, 129-130 (2d Cir. 1958); Dennison Mfg. Co. v. Ben Clements & Sons, Inc., 467 F.Supp. 391, 406-07 (S.D.N.Y. 1979); Lerner v. Child Guidance Prods., Inc., 406 F.Supp. 560, 563, 189 USPQ 83, 86-87 (S.D.N.Y. 1975), aff'd, 547 F.2d 29, 193 USPQ 329 (2d Cir. 1976); cf. Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 164, 116 USPQ 484, 490 (4th Cir. 1958) (Haynsworth, J.) ("That presumption of validity, however, should not be disregarded especially in a case of this sort where the intricate questions of bio-chemistry involved are peculiarly within the particular competence of the experts of the Patent Office.")

FN48 See note 74 infra.

FN49 Cathodic Protection Serv. v. American Smelting & Refining Co., 594 F.2d 499, 505, 203 USPQ 102, 106-107 (5th Cir. 1979); Republic Indus., Inc. v. Schlage Lock Co., 592 F.2d 963, 972, 200 USPQ 769, 779 (7th Cir. 1979) (even one prior art reference not considered by Patent Office may undermine presumption of validity); Julie Research Laboratories, Inc. v. Guildline Instruments, Inc., 501 F.2d 1131, 183 USPQ 1 (2d Cir. 1974).

FN50 35 U.S.C. §102(a); see id. §102(b).

FN51 General Tire & Rubber Co. v. Firestone Tire & Rubber Co., 349 F.Supp. 345, 356, 174 USPQ 427, 442-443 (N.D. Ohio 1972), aff'd in relevant part, 489 F.2d 1105, 180 USPQ 98 (6th Cir. 1973), cert. denied, 417 U.S. 932, 182 USPQ 1 (1974) (citing cases); accord, General Elec. Co. v. United States, 572 F.2d 745, 768, 198 USPQ 65, 84-85 (Ct. Cl. 1978) ("To anticipate a claim, a prior art reference must show each and every element claimed."); Tights, Inc. v. Acme-McCrary Corp., 541 F.2d 1047, 1056, 191 USPQ 305, 310-311 (4th Cir.), cert. denied, 429 U.S. 980, 192 USPQ 64 (1976); Saf-Gard Prods., Inc. v. Service Parts, Inc., 532 F.2d 1266, 1270, 190 USPQ 455, 457-458 (9th Cir.), cert. denied, 429 U.S. 896 (1976) (quoting and following Stauffer v. Slenderella Sys. of Calif., 254 F.2d 127, 128, 115 USPQ 347, 348- 349 (9th Cir. 1957)); Shanklin Corp. v. Springfield Photo Mount Co., 521 F.2d 609, 616-17, 187 USPQ 129, 133-135 (1st Cir.), cert. denied, 424 U.S. 914, 188 USPQ 720 (1975); In re Royka, 490 F.2d 981, 984, 180 USPQ 580 (C.C.P.A. 1974); Shelco, Inc. v. Dow Chem. Co., 466 F.2d 613, 614, 173 USPQ

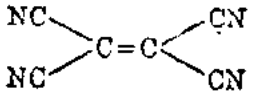
451, 452 (7th Cir.), cert. denied, 409 U.S. 876, 175 USPQ 385 (1972) (quoting and following Illinois Tool Works, Inc. v. Sweetheart Plastics, Inc., 436 F.2d 1180, 1182-83, 168 USPQ 451, 453- 454 (7th Cir. 1971)); Ling-Temco-Voght, Inc. v. Kollsman Instrument Corp., 372 F.2d 263, 267, 152 USPQ 446, 449-450 (2d Cir. 1967) (Medina, J.)

FN52 In re Samour, 571 F.2d 559, 197 USPQ 1 (C.C.P.A. 1978) (citing cases); E.I. DuPont de Nemours & Co. v. Ladd, 328 F.2d 547, 140 USPQ 297 (D.C. Cir. 1964).

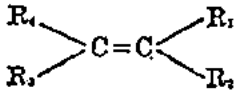
FN53 For the chemical explanation of this formula, see note 31 supra.

FN54 Cf. Rich Prods. Corp. v. Mitchell Foods, Inc., 357 F.2d 176, 180, 148 USPQ 522, 524-525 (2d Cir. 1966); Taussig v. Jack & Jill One Hour Cleaners, No. 12, Inc., 462 F.Supp. 1026, 1035-36, 200 USPQ 579, (N.D. Ohio 1978); Technical Tape Corp. v. Minnesota Mining & Mfg Co., 143 F.Supp. 429, 435-36, 110 USPQ 260, 265-266 (S.D.N.Y. 1956), aff'd, 247 F.2d 343, 114 USPQ 422 (2d Cir. 1957).

A similar argument was squarely rejected in E.I. DuPont de Nemours & Co. v. Ladd, 328 F.2d 547, 140 USPQ 297 (D.C. Cir. 1964), which involved the patent for the chemical tetracyanoethylene,



The validity of the patent was attacked as anticipated by the following patent,



"wherein Rsub1 and Rsub2 stand for a member of the group consisting of CN, acyl and an esterified carboxylic acid group,

Rsub3 stands for a member of the group consisting of hydrogen, CN, acyl and an esterified carboxylic acid group and

Rsub4 stands for a member of the group consisting of alkyl, oxalkyl, aryl, CN, acyl and an esterified carboxylic acid group."

The testimony at trial was to the effect that a trained expert would have chosen tetracyano-ethylene as one of the most evident disclosures of that generic patent. Yet the Court held nonetheless that the earlier patent, "allowing as it did an infinite number of possibilities, would be minimally described as an 'implicit' publication of theoretical lists of hundreds or thousands of possible compounds; and thus would not be an appropriate anticipation of a later patent application for a specific compound." Id. at 553, 140 USPQ at 302.

FN55 Struthers Scientific & Int'l Corp. v. Rappl & Hoenig Co., 453 F.2d 250, 255, 172 USPQ 257, 260-261 (2d Cir. 1971).

FN56 Exh. 11T, at 9 (emphasis added by plaintiffs' expert witness). The Friedlander edition was a leading collection of German patents earlier in this century; the editor reported various patents and then commented upon their most useful applications.

FN57 See General Tire & Rubber Co. v. Firestone Tire & Rubber Co., 349 F.Supp. 345, 356, 174 USPQ 427, 442-443 (N.D. Ohio 1972), aff'd in relevant part, 489 F.2d 1105, 180 USPQ 98 (6th Cir. 1973), cert. denied, 417 U.S. 932, 182 USPQ 1 (1974) ("An anticipating reference must teach the invention; it is not sufficient to point to its silence or ambiguity after the invention and argue that the invention could be made out from the reference * * *. A patented combination cannot be anticipated piecemeal by finding individual features separately in the prior art.")

FN58 Dewey & Almy Chem. Co. v. Mimex Co., 124 F.2d 986, 989, 52 USPQ 138, 141-142 (2d Cir. 1942); see cases cited in notes 51 & 54 supra. The portion of the Struthers opinion quoted by plaintiffs, see text as note 55 supra, cites only one case in support of the proposition, In re Palmquist, 319 F.2d 547, 138 USPQ 234 (C.C.P.A. 1963), a case analyzing standards of "obviousness" under 35 U.S.C. §103, not "anticipation" under id. §102. Palmquist, moreover, has been overruled by the Court of Customs & Patent Appeals, see In re Foster, 343 F.2d 980, 989, 145 USPQ 166, 173-174

(C.C.P.A. 1965), and no court in this or other circuits has ever cited or followed the Struthers case. Plaintiffs' citation to In re Samour, 571 F.2d 559, 197 USPQ 1 (C.C.P.A. 1978), is inapposite, for that case involved publication of a precise structural formula, and the Court found the patent anticipated even though one would have to turn to a second source for a method of preparing the disclosed structure. See In re Marshall, 578 F.2d 301, 304, 198 USPQ 344, 346- 347 (C.C.P.A. 1978).

FN59 Cf. Imhaeuser v. Buerk, 101 U.S. 647, 660 (1880) (patented combination cannot be anticipated piecemeal); Duplan Corp. v. Deering Milliken, Inc., 444 F.Supp. 648, 708, 197 USPQ 342, 394-395 (D.S.C. 1977).

FN60 T.R. 1688-89.

FN61 Id. 1561:

A. * * * Then the final part of the sentence [in paragraph one of the Friedlander Comment] appears to me to exclude the aminocresol ether sulfonic acids.

Q. And on what do you base that conclusion, that latter conclusion?

A. Well, because in the first portion he is talking about the ortho- and para-anisidine and their sulfonic acids but in the next phrase, he just mentions aminocresol ether without any reference at all to their sulfonic acids.

FN62 See T.R. 448-51, 113, 1558-59, 2229-2300; cf. Exh. 11T, at 4 (copy of German Patent on which Dr. Rottschaefer circled wrong portion).

FN63 See T.R. 1958-60 (expert testimony of Delvalle Goldsmith, international patent attorney) (Dutch standards of novelty are, if anything, stricter than those in America); id. 1967-68 (German standards of novelty similar to those in United States and applied at least as strictly). See also American Infra-Red Radiant Co. v. Lambert Indus., Inc., 360 F.2d 977, 991-94, 149 USPQ 722, 731-734 (8th Cir. 1966), cert. denied, 385 U.S. 920, 151 USPQ 757 (1966).

FN64 Exh. 575, at 5.

FN65 Badische Anilin & Soda Fabrik v. Kalle, 94 F. 163, 176 (S.D.N.Y. 1899) (Coxe, J.), aff'd, 104 F. 802 (2d Cir. 1900) (relying on decision of German Patent Office); see American Infra-Red Radiant Co. v. Lambert Indus., Inc., 360 F.2d 977, 987, 149 USPQ 722, 731-734 (8th Cir. 1966), cert. denied, 385 U.S. 920, 151 USPQ 757 (1966); Faraday, Inc. v. Audio Devices, Inc., 165 USPQ 634, 637 (S.D.N.Y. 1970).

FN66 T.R. 1660. Thus the Court finds Timely Prods. Corp. v. Arron, 523 F.2d 288, 295-96, 187 USPQ 257, 261-263 (2d Cir. 1975), relied upon heavily by plaintiffs, to be distinguishable. There, Judge Conner upheld the exclusion of evidence of foreign patent grants, since there was no evidentiary basis to indicate that similar standards were applied to patentability in the foreign offices relied upon by appellant: "the standards of patentability vary widely from country to country; some countries, including France, one of the nine countries here, have only what amounts to a registration system with no examination given as to novelty, much less to level of ingenuity." Id. at 295, 187 USPQ at 262.

FN67 35 U.S.C. §103.

FN68 Reiner v. I. Leon Co., 285 F.2d 501, 503-04, 128 USPQ 25, 27- 28 (2d Cir. 1960) (L. Hand, J.), cert. denied, 366 U.S. 939, 129 USPQ 502 (1961).

FN69 Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18, 148 USPQ 459, 466-467 (1966); see Dann v. Johnston, 425 U.S. 219, 226-30, 189 USPQ 257, 260-262 (1976); Eltra Corp. v. Basic, Inc., No. 77-3364, 202 USPQ 630 (6th Cir. May 21, 1979); Cathodic Protection Serv. v. American Smelting & Refining Co., 594 F.2d 499, 505-07, 203 USPQ 102, 107-108 (5th Cir. 1979) (reviewing Supreme Court cases); Digitronics Corp. v. New York Racing Ass'n, 553 F.2d 740, 745, 193 USPQ 577, 581- 582 (2d Cir.), cert. denied, 434 U.S. 860 (1977) ("the court must look, in light of both the training of the patentee and the elements in the claimed invention which give it its novel quality, at what arts the patentee could reasonably be expected to consult in doing the inventing").

FN70 Commissioner of Patents v. Deutsche Gold-und-Silber Scheideanstalt Vormals Roessler, 397 F.2d 656, 661, 157 USPQ 549, 553-554 (D.C. Cir. 1968) (Burger, J.) (footnotes omitted).

FN71 315 F.2d 281, 137 USPQ 43 (C.C.P.A. 1963) (courts have determined the nonobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties).

FN72 The test of essential predictability has been developed primarily in the Court of Customs & Patent Appeals, see In re May, 574 F.2d 1082, 1092, 197 USPQ 601, 608-609 (C.C.P.A. 1978); In re Wilder, 563 F.2d 457, 460, 195 USPQ 426, 429-430 (C.C.P.A. 1977); In re Albrecht, 514 F.2d 1389, 185 USPQ 590 (C.C.P.A. 1975); In re Hoch, 428 F.2d 1341, 166 USPQ 406 (C.C.P.A. 1970), but has also been favorably received by several circuit courts analyzing patentability of chemical compositions. See Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1101, 174 USPQ 65, 68-69 (5th Cir. 1972); Commissioner of Patents v. Deutsche Gold-und-Silber Scheideanstalt Vormals Roessler, 397 F.2d 656, 661, 157 USPQ 549, 553-554 (D.C. Cir. 1968) (Burger, J.); Note, Standards of Obviousness & the Patentability of Chemical Compounds, 87 Harv. L. Rev. 607 (1974); cf. General Tire & Rubber Co. v. Jefferson Chem. Co., 497 F.2d 1283, 1287-88, 182 USPQ 70, 72-74 (2d Cir. 1974) (Friendly, J.), cert. denied, 419 U.S. 968, 183 USPQ 513 (1974) (reserving question but citing Harvard Law Review Note with approval). Two district courts have expressed reservations with the Court of Patent Appeals' approach, but their judgments have been affirmed on other grounds in decisions citing and discussing Papesch with approval. See Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 341 F.Supp. 1303, 173 USPQ 65 (E.D.N.Y.), aff'd sub nom. Carter-Wallace, Inc. v. Otte, 474 F.2d 529, 540, 176 USPQ 452 (2d Cir. 1972) (Friendly, J.), cert. denied, 412 U.S. 929, 178 USPQ 65 (1973); Monsanto Co. v. Rohm & Haas Co., 312 F.Supp. 778, 164 USPQ 556 (E.D. Pa. 1971), aff'd, 456 F.2d 592, 599-600, 172 USPQ 323, 327- 329 (3d Cir.), cert. denied, 407 U.S. 934, 174 USPQ 129 (1972).

FN73 Cf. Indiana General Corp. v. Krystinel Corp., 421 F.2d 1023, 1030-31, 164 USPQ 321, 326-327 (2d Cir. 170), cert. denied, 398 U.S. 928, 165 USPQ 609 (1970) (Medina, J.) (routine degree of experimentation is part of ordinary skill in the art).

FN74 It is clear from his initial rejection that the Examiner had carefully examined the Elley Patent; that he also considered Yellow 6 and the Baum Patent is apparent from his "Searched" notation, which embraced portions of the Colour Index that included Yellow 6 (C.I. 15985) and the Baum Patent (C.I. 16160). The thoroughness of the Examiner's search is attested to by the fact that he noted an error in the 1956 edition of the Colour Index, upon which Allied had relied, that had been corrected in the 1963 Supplement.

FN75 Exh. 49.

FN76 Exh. 44.

FN77 Exh. 51.

FN78 Thus in public memorandum of December 14, 1964, the very time when Steiner and Rast were conducting their early experiments, Warner's Director of Sales stated that seven-year dog studies were in progress to evaluate Red 2 and Yellow 6. Though the report to Warner's customers was understandably optimistic, it does indicate at least a temporary FDA cloud over these two colors, one of which was later delisted. Exh. EZ.

FN79 T.R. at 755 (testimony of Dr. Radomski):

Q. At any time in the past was it thought that methoxy groups were less toxic, the methoxy groups on the phenyl moiety, were less toxic than methyl groups?

A. Yes. It was thought that when FD & C Red No. 32 was found to be toxic and cathartic, a substitute dye, Citrus Red No. 2, was developed.

Citrus Red No. 2 is exactly the same dye as Red 32 except it has two methoxy groups on it instead of two methyl groups.

And when this dye was first developed and in the initial testing it seemed to be less toxic than Red 32. However, certain long term testing, which is the most critical thing, showed it to be a very toxic and acid substance.

FN80 The accepted view in the science of dye chemistry in the 1950s was "that all water-soluble sulphonated azo colourings should be free from

carcinogenic activity," a view that was undermined when Red 1 and Red 4 proved to have toxic effects. In its place a new hypothesis took form: "It may be that sulphonation on both sides of the azo linkage reduces the chance of carcinogenic effect by permitting more rapid elimination of the metabolites formed by the reductive cleavage of the monoazo colourings." Mannell, Further Investigations on Production of Liver Tumours in Rats by Ponceau 3R, 2 Food Cosmetics Toxicology 169, 173 (1964) (Exh. 107); see Daniel, The Excretion & Metabolism of Edible Food Colors, 4 Toxicology & Applied Pharmacology 572, 589-90 (1962) (Exh. 106) (indicating uncertain state of art); Radomski & Deichmann, Cathartic Action & Metabolism of Certain Coal Tar Food Dyes, 118 J. Pharmacology & Experimental Therapeudics 322, 327 (1956) (Exh. 103) ("[C]atharsis seems to be associated with derivation from beta-naphthylamine or alpha- or beta-naphthol. Sulfonation of the naphthalene ring destroys the cathartic properties.")

FN81 Food Colors Study, supra note 5, at 38 (Table 16).

FN82 T.R. 610-11.

FN83 See United States v. Adams, 383 U.S. 39, 148 USPQ 479 (1966); Photo Electronics Corp. v. England, 581 F.2d 772, 781-82, 199 USPQ 710, 718-720 (9th Cir. 1978) (secondary considerations especially helpful where evidence is highly technical); Dennison Mfg. Co. v. Ben Clements & Sons, Inc., 467 F.Supp. 391, 416-19, 203 USPQ 895, 915-921 (S.D.N.Y. 1979) (examining commercial success, failure of others, industry recognition as important factors supporting patentability); cf. Safety Car Heating & Lighting Co. v. General Elec. Co., 155 F.2d 937, 939, 69 USPQ 401, 402-403 (2d Cir. 1946) (L. Hand, J.)

FN84 See note 41 supra.

FN85 Exh. EM.

FN86 A declaration of "unenforceability" of the patents in suit would not prejudice defendants' ability to reapply to the Patent Office and acquire a new patent; a declaration of invalidity would preclude reapplication. Cf. Timely Prods. Co. v. Arron, 523 F.2d 288, 297-98, 187 USPQ 257, 263- 265 (2d Cir. 1975) (distinguishing between two terms but questioning practical difference).

FN87 Norton v. Curtiss, 433 F.2d 779, 793-94, 167 USPQ 532, 543- 544 (C.C.P.A. 1970).

FN88 See True Temper Corp. v. CF & I Steel Corp., Nos. 76-2106, 76-2107, 202 USPQ 412 (10th Cir. May 31, 1979); Union Carbide Corp. v. Borg-Warner Corp., 550 F.2d 355, 363 n.8, 193 USPQ 1, 8 n.8 (6th Cir. 1977); Turzillo v. P&Z Mergentime, 532 F.2d 1393, 189 USPQ 783 (D.C. Cir. 1976), cert. denied, 429 U.S. 897, 191 USPQ 655 (1977); Frantz Mfg Co. v. Phenix Mfg Co., 457 F.2d 314, 325, 173 USPQ 266, 274-275 (7th Cir. 1972); cf. Kingsland v. Dorsey, 338 U.S. 318, 319, 83 USPQ 330, 330-331 (1949) ("By reason of the nature of an application for patent, the relationship of attorneys to the Patent Office requires the highest degree of candor and good faith . . . .")

FN89 35 U.S.C. §112.

FN90 Benger Laboratories Ltd. v. R.K. Laros Co., 209 F.Supp. 639, 644, 135 USPQ 11, 15-16 (E.D. Pa. 1962), aff'd per curiam, 317 F.2d 455, 137 USPQ 693 (3d Cir.), cert. denied, 375 U.S. 833, 139 USPQ 566 (1963); accord, Illinois Tool Works, Inc. v. Solo Cup Co., 179 USPQ 322, 366-69 (N.D. Ill. 1973).

FN91 Dale Electronics, Inc. v. R.C.L. Electronics, Inc., 488 F.2d 382, 389, 180 USPQ 225, 229-230 (1st Cir. 1973); accord, Union Carbide Corp. v. Borg-Warner Corp., 550 F.2d 355, 363, 193 USPQ 1, 7-8 (6th Cir. 1977); Frantz Mfg Co. v. Phenix Mfg Co., 457 F.2d 314, 325, 173 USPQ 266, 274-275 (7th Cir. 1972).

FN92 T.R. 1915; see id. 1912-14; Exh. NA.

FN93 T.R. 2071-72.

FN94 Plaintiffs appear to have abandoned their claim that Allied misrepresented the "surprisingly high solubility" of Red 40 in its application. Indeed, the credible evidence introduced at trial fully supported Allied's claims. See Exh. BB, at 38 (table reproduced in text at note 81 supra).

FN95 Norton v. Curtiss, 433 F.2d 779, 796, 167 USPQ 532, 545-546 (C.C.P.A. 1970); accord, True Temper Corp. v. CF & I Steel Corp., Nos. 76-

2106, 76-2107, 202 USPQ 412 (10th Cir. May 31, 1979); Turzillo v. P&Z Mergentime, 532 F.2d 1393, 1400, 189 USPQ 783, 788-789 (D.C. Cir. 1976), cert. denied, 429 U.S. 897, 191 USPQ 655 (1977); Monsanto Co. v. Rohm & Haas Co., 456 F.2d 592, 597-600, 172 USPQ 323, 326-329 (3d Cir. 1972), cert. denied, 407 U.S. 934, 174 USPQ 129 (1973); Carter- Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 881, 169 USPQ 625, 634-635 (2d Cir. 1971) (Friendly, J.), cert. denied, 412 U.S. 929 (1973); Beckman Instruments, Inc. v. Chemtronics, Inc., 428 F.2d 555, 565, 165 USPQ 355, 363-364 (5th Cir.), cert. denied, 400 U.S. 956, 168 USPQ 1 (1970).

FN96 Precision Instrument Mfg Co. v. Automotive Maintenance Mach. Co., 324 U.S. 806, 818, 65 USPQ 133, 139 (1945).

FN97 True Temper Corp. v. CF & I Steel Corp., Nos. 76-2106, 76-2107, 202 USPQ 412 (10th Cir. May 31, 1979).

FN98 Cf. Walker Process Equip., Inc. v. Food Mach. & Chem. Corp., 382 F.2d 172, 177, 147 USPQ 404, 407 (1965) ("honest mistake as to the effect of prior [art] on patentability" will not strip patentee of its patent); Xerox Corp. v. Dennison Mfg Co., 322 F.Supp. 963, 968-69, 168 USPQ 700, 704-706 (S.D.N.Y. 1971) (applicant justified in relying on reasonable and good faith judgment "in deciding what matters are and are not of sufficient relevance and materiality to require disclosure").

FN99 Plaintiffs, defendants, and other members of the industry agreed, with the approval of the FDA, to share among themselves the cost of a temporary program of toxicological testing for FD & C colors. Exh. 202.

FN100 Zenith Radio Corp. v. Hazeltine Research, Inc., 395 U.S. 100, 135, 161 USPQ 577, 591 (1969); see Morton Salt Co. v. G.S. Suppiger Co., 314 U.S. 488, 493, 52 USPQ 30, 33 (1942); Glen Mfg, Inc. v. Perfect Fit Indus., 420 F.2d 319, 164 USPQ 257 (2d Cir. 1970); Duplan Corp. v. Deering Milliken, Inc., 444 F.Supp. 648, 693-705, 197 USPQ 342, 382-393 (D.S.C. 1977).

FN101 Brulotte v. Thys Co., 379 U.S. 29, 33, 143 USPQ 264, 266 (1964).

FN102 E.g., W.L. Gore & Assocs., Inc. v. Carlisle Co., 529 F.2d 614, 623, 189 USPQ 129, 136-137 (3d Cir. 1976) (30% royalty); Georgia-Pacific Corp. v. United States Plywood-Champion Papers Inc., 446 F.2d 295, 170 USPQ 369 (2d Cir. 1971) (22% royalty).

FN103 The record does not disclose any objection of Hilton-Davis to the royalty payments, though it has paid approximately $1,500,000 in royalties over the last three years. There is trial testimony that Hilton-Davis, invited by plaintiffs to join in this action, declined to do so and that its counsel was of the view that the Red 40 patents were valid and would be infringed if the dye were manufactured without a license. T.R. 1068-69. In addition, to secure the license Hilton-Davis paid Allied $100,000.

FN104 Exh. CH PP1.6, 3.1(a).

FN105 T.R. 1105-07. Defendant Buffalo Color does not include the testing charge in its invoice price; on its sales of Red 40, it invoices the "temporary testing surcharge" as a separate invoice item.

FN106 Plaintiffs were free to challenge defendants' interpretation by a declaratory judgment suit but have failed to do so.

FN107 395 U.S. 653, 162 USPQ 1 (1967).

FN108 Warner-Jenkinson Co. v. Allied Chemical Corp., 567 F.2d 184, 188, 193 USPQ 753, 756-757 (2d Cir. 1977).

FN109 35 U.S.C. §285; see Kahn v. Dynamics Corp. of Am., 508 F.2d 939, 945, 184 USPQ 260, 264 (2d Cir. 1974), cert. denied, 421 U.S. 930, 185 USPQ 505 (1975); Louis Marx & Co. v. Buddy L Corp., 453 F.Supp. 392, 398, 202 USPQ 277, 281-282 (S.D.N.Y. 1978).

FN110 Wallace Clark & Co. v. Acheson Indus., 394 F.Supp. 393, 399- 400, 186 USPQ 138, 141-143 (S.D.N.Y. 1975), aff'd, 532 F.2d 846, 190 USPQ 321 (2d Cir.), cert. denied, 425 U.S. 976 (1976); Addressograph-Multigraph Corp. v. Cooper, 156 F.2d 483, 70 USPQ 272 (2d Cir. 1946).

S.D.N.Y.

206 U.S.P.Q. 837

END OF DOCUMENT

E. I. DU PONT DE NEMOURS AND COMPANY
v.
LADD, Comr. Pats., et al.

Court of Appeals, District of Columbia

No. 17883

Decided Jan. 30, 1964

United States Patents Quarterly Headnotes

PATENTS
[1] Evidence--Expert testimony (§ 36.10)
Patentability -- Anticipation -- Patents--In general (§ 51.2211)
It is significant, in determining whether prior art patent included tetracyanoethylene, that abstract of patent, which was prepared by chemist and which appeared in Chemical Abstracts, did not mention tetracyanoethylene but described family of compounds in language which would not include tetracyanoethylene within its scope.

PATENTS
[2] Patentability--Composition of matter (§ 51.30)
Patent which implicitly discloses theoretical list of hundreds or thousands of possible compounds is not anticipation of application for a specific compound; latter compound is patentable since it differs in kind, rather than degree, from general formula of patent or any of its possible substituent combinations.

PATENTS
[3] Claims--Indefinite--Chemical (§ 20.553)
Claim, reading "tetracyanoethylene," defines an invention within meaning of 35 U.S.C. 112 since "tetracyanoethylene" is little more than structural formula of compound converted into utterable combination of letters; chemical formula would adequately describe claimed compound; since "tetracyanoethylene" is equally descriptive of compound as a line-and-symbol formula, it is sufficient for purposes of statutory particularity.

PATENTS
[4] Prior adjudication -- Applications for patent (§ 56.05)
In determining whether claim complies with 35 U.S.C. 112, court is persuaded somewhat by history of Patent Office in granting patents for claims having same descriptive nature as instant claim.

PATENTS
[5] Claims--Indefinite -- Chemical (§ 20.553)
Specification -- Sufficiency of disclosure (§ 62.7)
It is important, in determining whether name of compound, as stated in claim, complies with 35 U.S.C. 112 that expert testimony establishes that name does describe compound and that one skilled in the art would understand what was indicated by use of name.

PATENTS
Particular patents--Nitrile
Cairns and Graef, Polymerizable Nitrile and Polymer Product Therefrom, claims 1 and 3 of application allowed.

***298** Appeal from District Court for District of Columbia, Jackson, J.

Action under 35 U.S.C. 145 by E. I. du Pont de Nemours and Company (assignee of Theodore Le Seuer Cairns and Edith M. Graef, Serial No. 382,842, filed Sept. 28, 1953; Patent Office Division 50) against David L. Ladd, Commissioner of Patents, and Luther H. Hodges, Secretary of Commerce. From judgment for defendants, plaintiff appeals. Reversed; Edgerton, Senior Circuit Judge, dissenting without opinion.

M. PHILIP CHURCHILL, New York, N.Y. (C. HAROLD HERR, Wilmington, Del., and FREDERICK SCHAFER, Washington, D.C., on the brief) for appellant.

J. SCHIMMEL (CLARENCE W. MOORE on the brief) for appellees.

Before EDGERTON, Senior Circuit Judge, and MILLER and BASTIAN, Circuit Judges.

BASTIAN, Circuit Judge.

In September 1952, two employees of appellant, E. I. Du Pont de Nemours and Company, filed with the United States Patent Office a patent application entitled "Polymerizable Nitrile and Polymeric Product Obtained Therefrom." [FN1] Subsequently, Du Pont, applicants' assignee, duly prosecuted the application in accordance with the requirements of law and the rules of the Patent Office. On September 27, 1957, the Primary Examiner of the Patent Office entered a Final Rejection of all claims included in the application. Du Pont thereupon appealed the final rejection of claim 1 and, in amended form, claims 3 and 4, to the Board of Appeals of the Patent Office, which, on October 17, 1960, rendered a decision affirming the Primary Examiner's rejection of claims 1, 3 and 4. The Board subsequently denied Du Pont's petition for reconsideration.

Appellant then filed its complaint against the Commissioner of Patents and the Secretary of Commerce, appellees here, in the United States District Court for the District of Columbis pursuant to 35 U.S.C. § 145, [FN2] seeking a decree authorizing the Commissioner of Patents to issue Letters Patent on the rejected claims of the patent application. A trial on the merits was had and, on March 20, 1963, the District Court entered an order dismissing the complaint, finding that appellant was not entitled to a patent containing claims 1 and 3. [FN3] This appeal followed.

Essentially, two issues are presented: (1) whether the compound represented by claims 1 and 3 is unpatentable under *299 35 U.S.C. § 102; [FN4] and (2) whether claim 1 is further unpatentable for failure to meet the standards of particularity and distinctness required by 35 U.S.C. § 112. [FN5]

I

The claims involved here read as follows:

"Tetracyanoethylene.

"3. White crystalline monomeric tetracyanothylene characterized (1) by melting within the range of 195-200 degrees C. in a sealed tube, (2) by being sublimable in air at 120-150 degreesC., (3) by having infrared absorption spectrum with a divided band characteristic of conjugated unsaturated nitriles, and (4) by formation with toluene of an orange-colored 1:1 complex having a light absorption maximum 4060A when dissolved therein."

Tetracyanoethylene is described as an organic chemical compound having extraordinary properties. As indicated by the application, the substance reacts with certain other chemicals to produce strong permanent dyes for synthetic fibers, and its polymers and co-polymers are highly useful as insecticides, as well as motor coil and transformer wire insulation where high temperatures are encountered. The compound itself has the following structural formula:

NC CN

C=C

NC CN

The tribunals of the Patent Office rejected both claims 1 and 3 on the ground that they had been anticipated, and hence precluded from patentability, by a prior patent (No. 2,264,354) issued to Alder et al. in 1941 entitled "Addition Products of Dienes and Unsaturated Esters, Ketones, or Nitriles." Included in that patent was the following formula:

Rsub4 Rsub1

C=C

Rsub3 Rsub2

"wherein R sub1 and R sub2 stand for a member of the group consisting of CN,acyl and an esterified carboxylic acid group,

R sub3 stands for a member of the group consisting of hydrogen, CN, acyl and anesterified carboxylic acid group and

R sub4 stands for a member of the group consisting of alkyl, oxalkyl, aryl, CN,acyl and an esterified carboxylic acid group."

A second reference in the Alder patent found to be significant by the District Court, and indicated on appeal is the following sentence:

"Examples for the other reaction components falling within the above definition are the products of the condensation of aldehydes and acetyl acetic acid esters or malonic acid esters, furthermore, ethylene-tetra-carboxylic acid esters, the corresponding nitriles, and furthermore, the products of the condensation of aldehydes and 1.3-diketones such as acetylacetone."

The Patent Office argued, and the District Court agreed, that the disclosures made by the earlier Alder patent "would clearly teach a person of ordinary skill in the art that certain chemical structures would be obtained by making directed substitutions in a general formula specifically disclosed" and that, consequently, the disclosures of the Alder patent were "sufficient under the law to bar a later applicant from *300 obtaining a claim to said chemical structure." Accordingly, on the basis of Application of Baranauckas, 43 CCPA 727, 228 F.2d 413, 108 USPQ 226 (1955), the District Court held that appellant was not entitled to a patent on claim 1. Further, while noting that the "pure compound" of claim 3 was not suggested by the Alder patent, the court reasoned that its unique properties could be ascertained only after having successfully produced the compound of claim 1. Thus, claim 1 having been determined to be implicit in the Alder patent, claim 3 was considered merely "an increase in knowledge of a prior disclosure," and therefore unpatentable under National Lead Co. v. Marzall, 91 U.S.App.D.C. 63, 198 F.2d 296, 93 USPQ 353 (1952).

Claim 1

In Shell Development Co. v. Watson, 102 U.S.App.D.C. 297, 252 F.2d 861, 116 USPQ 428 (1958), this court adopted the District Court holding that, in order to defeat a patent

application on the basis of 35 U.S.C. § 102(a), [FN6] a prior publication must "exhibit the thing claimed in such an intelligible manner as to enable persons skilled in the art to which the invention is related to comprehend it." Moreover in Application of LeGrice, 49 CCPA 1124, 1138, 301 F.2d 929, 939, 133 USPQ 365, 374 (1962), it was said:

> "[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. Unless this condition prevails, the description in the printed publication is inadequate as a statutory bar to patentability under section 102(b)."

In the case before us, three of the four expert witnesses who testified regarding the anticipation of claims 1 and 3 by the earlier Alder patent [Theodore L. Cairns, Louis F. Fieser and Arthur C. Cope] stated that the general R sub1 , R sub2 , R sub3 , R sub4 , formula gives rise to an infinite number of possible compounds inasmuch as the acyl, alkyl, aryl, ox-alkyl and esterified carboxylic acid groups mentioned in the formula represent classes or groups of substituents, within each of which are an infinite (or at least an indefinite) number of specific elements. Hence, even if one were to pick and hold constant a substituent for R sub1 , R sub2 and R sub3 in the general formula, an infinite number of specific compounds would be suggested each time one of the above-named substituents was substituted for R sub4 . The unequivocal testimony of these three witnesses was that, as a consequence of the vast scope of the general formula, this disclosure in the Alder patent would not suggest tetracyanoethylene to one skilled in the art of organic chemistry. As graphically stated by Dr. Cope:

> "Taking all of the possible combinations and permutations of R sub1 and R sub2 , and R sub3 and R sub4 , and recognizing how many of them may be of infinite scope, that formula is just about as broad as the universe; and, in my opinion, it is so broad that it would lead no chemist to the selection of any specific compound falling within that area. * * * I would say that this is so broad that for a chemist to be led to any specific compound by this formula would be just about the same as being led to a specific Chinese baby being born at this moment."

The District Court, however, based its decisions on the cross-examination testimony of Donald J. Cram, the fourth of appellant's experts to testify regarding the scope of the Alder patent. The court stated:

> "It appears in the record that Dr. Cram, an expert testifying on behalf of plaintiff stated that if the directions shown by the reference for making the substitutions in the general formula are made 'you would encounter tetracyanoethylene as the eighth compound', and, accordingly, it would appear that the holding of the Baranaukas case, supra, is clearly pertinent and would teach a person of ordinary skill in the art that a structure would be obtained by making directed substitutions, which is exactly equivalent to one in which compounds are actually illustrated."

The court was therefore of the view that since the formula for tetracyanoethylene could be arrived at by a mechanical application of the named substituents in the Alder formula, the earlier patent was an anticipation under 35 U.S.C. § 102, and the present application was properly rejected.

*301 We are of the opinion that a close reading of the entire deposition of Dr. Cram clearly indicates a contrary conclusion. On direct examination, Dr. Cram was shown the Alder patent and asked whether, as a chemist, he would find in the general formula and language of that patent "any description of tetracyanoethylene that is meaningful to you as a chemist?" His answer was:

"If I had never heard the term 'tetracyanoethylene' or seen its formula written down and I read this patent I would not consider that I had heard of tetracyanoethylene."

He further testified:

"I don't see anything here that would lead me to the structure of tetracyanoethylene in reading of this.

* * *

"I can't conceive of predicting the properties of tetracyanoethylene as I know them today from anything that is written down in this patent."

Under cross-examination by counsel for the Patent Office, Dr. Cram testified that although the cyano (CN) group was the first one mentioned for R sub1 and R sub2 , it did not stand out from the other groups also mentioned by Alder for R sub1 and R sub2 . His testimony continued:

"Q. Isn't it reasonable to assume that one skilled in the art would select the first one mentioned?

"A. Not necessarily. I think he might well pick the one with which he had had the most experience."

Dr. Cram was then directed by the cross-examiner to assume first that R sub1 , R sub2 of the general formula were both CN groups, and then to make the substitutions for R sub3 and R sub4 in the order mentioned in the patent. [FN7] It was only in answer to this restrictive question, relating more to statistical probabilities than to a chemist's usage of the Alder formula, that Dr. Cram testified:

"Then I believe that you would encounter tetracyanoethylene as the eighth compound."

Dr. Cram's testimony on re-direct examination is explanatory of that statement. When asked how many different organic chemical compounds would be be covered if he started with CN groups substituted for R sub1 , R sub2 and R sub3 , and then went through all the possible variations for R sub4 he stated:

"You could conceive of arriving at this tetracyano compound after listing an infinite number of--almost an infinite number of other compounds, but you would arrive at the tetracyano compound eighth if you are willing to use family structures of compounds and not particular compounds; and that is a thought that my questioner on cross-examination was referring to classes of organic compounds when I arrived at that number eight or eighth, and not to particular compounds." [Emphasis added.]

It seems clear, therefore, that Dr. Cram's testimony, viewed in its entirety, indicates his complete accord with the other three expert witnesses regarding the infinite breadth of the Alder formula and the resultant improbability of a skilled chemist being led by that formula to tetracyanoethylene as a specific compound.

A second reference in the Alder patent, "ethylene-tetra-carboxylic acid esters, the corresponding nitriles," was also urged as a disclosure sufficient to preclude patentability inasmuch as one of the corresponding nitriles of ethylene-tetra-carboxylic acid esters would be tetracyanoethylene. On this point all the expert testimony was uniform that the entire sentence (set forth supra in full) was ambiguous, and that the words "corresponding nitriles" referred not only to ethylene-tetra-carboxylic acid esters, but to all the prior references in the sentence. In the words of Dr. Cope:

"I have read this sentence many times, and I find it completely ambiguous. I do not know what is meant by 'corresponding nitriles.' * * * I don't know what a nitrile is corresponding to in any of these classes. That is not a chemically precise definition and my conclusion would be that, whatever it means, it is of the same infinite scope essentially as the R sub1 , R sub2 , R sub3 , R sub4 formula."

Based on this ambiguity, and the fact that this reference, like the general formula, allows of innumerable possibilities, the expert testimony indicated clearly that tetracyanoethylene would *302 not be suggested to one skilled in the art.

[1] Additional testimony established that a scientific article published in 1939 by Alder and Rickert, covering essentially the same subject-matter at the 1941 patent and using many of the same examples, did not include tetracyanoethylene directly, indirectly, by implication or otherwise. Moreover, in 1942 an abstract of the Alder patent, prepared by a trained chemist, appeared in Chemical Abstracts (a publication of the American Chemical Society) summarizing for chemists what the Alder patent described. It is significant that, according to Dr. Cairns's testimony, this abstract not only did not mention tetracyanoethylene, but described the ethylene family of compounds used in the Alder process in language which would not even include tetracyanoethylene within its scope.

It seems clear to us, therefore, from a reading of the entire record, that the disclosures in the Alder patent would not have taught one skilled in the art the subject-matter of claim 1. It follows that claim 1 is not rendered unpatentable by 35 U.S.C. § 102.

The cases of Shell Development Co. v. Watson, supra, and Application of Baranauckas, supra, are cited by appellee as authority compelling a contrary result. We disagree.

In Shell Development, the prior publication, unlike the Alder patent, gave in detail the specific formula of the specific compound in question and was part of the standard chemical literature understood to describe already known compounds. Also, there was testimony in that case that one skilled in the art could easily have arrived at the claimed compound from a reading of the earlier publication.

In Baranauckas, the prior publication relied upon was one of the standard authoritative German publications of chemical literature. This publication described a bromine compound which exactly corresponded to the chlorine compound claimed by the applicant except for the difference between bromine and chlorine atoms. In addition, the publication described how to make these compounds and stated that chlorine and bromine behaved identically in the process of making the compound. The court reasoned there that it was a simple procedure to substitute chlorine for bromine in the process set out in the prior publication, and hence "would clearly teach a person of ordinary skill in the art" the claimed compounds.

Contrasting with the two cases cited by appellees, the testimony in the case before us is clear and specific that one skilled in the art would not be led to tetracyanoethylene by the Alder patent. Hence those cases are inapposite to the facts here.

It should be noted also that the court in Baranauckas stated:

> "* * * though our decision is compelled by the existing law, we feel constrained to point out that there are limits to the doctrine of those cases. What the precise boundary lines are, we are unable to discern. Certainly they do not extend so far as to permit publication of theoretical lists of hundreds or thousands of possible compounds to deny patent protection on such compounds to those who actually discovered them later. * * *" 43 CCPA at 731, 228 F.2d at 416, 108 USPQ at 228.

[2] Even if there were some doubt that the Alder patent was not an implicit disclosure of tetracyanoethylene, within the meaning of the Baranauckas holding, the policy considerations suggested by that court would compel the same result. Certainly the Alder patent, allowing as it did an infinite number of possibilities, would be minimally described as an implicit "publication of theoretical lists of hundreds or thousands of possible compounds," and thus would not be an appropriate anticipation of a later patent

application for a specific compound.

Finally, the following language of the District Court in Phillips Petroleum Co. v. Ladd, 219 F.Supp. 366, 369, 138 USPQ 421, 423 (D.D.C. 1963), is singularly applicable:

"When, by reason of a combination of properties and characteristics, a new product constitutes a substantial improvement, providing unforeseen uses and results, the product represents a difference in kind and not merely in result. [Citing cases.] As distinguished from difference in degree, difference in kind exists when a product possesses a unique combination of extraordinary and novel properties and characteristics of which the prior art was not aware." [Citing cases.]

In the present case, the expert testimony established tetracyanoethylene as an organic chemical compound having extraordinary properties. The substance exhibits an unusual stability to oxidation but, when it does burn, produces an extremely hot flame. It reacts uniquely with certain aromatic solvents to produce various color complexes. *303 The compound enters into substitution reactions with nucleophiles, evidences an unusually stable radical anion, and is possessed of many other unusual characteristics. Perhaps most striking is the fact that the compound is composed entirely of carbon and nitrogen atoms, unlike ninety-nine per cent or more of the known organic compounds, which contain hydrogen.

Dr. Cairns stated that tetracyanoethylene possessed properties shared by none of the other chemical groupings included in the Alder substituents. Similarly, Dr. Fieser testified:

"Q. Do you consider that this was a material the properties or characteristics of which could have been predicted by skilled chemists from looking at the formula or the name on a piece of paper?

"A. No, I certainly don't think so at that time without any knowledge of the compound or even closely related compounds. I don't think one could have predicted the substance was capable of existence. * * *"

It seems clear, therefore, that tetracyanoethylene differs in kind, rather than merely in degree, from the general Alder formula or any of its other possible substituent combinations. Consequently, on this additional ground, the prior patent would not be an anticipation sufficient to preclude the granting of letters patent on the instant application. [FN8]

Claim 3

While claims 1 and 3 were dealt with jointly by the Patent Office tribunals, the District Court correctly considered the claims separately, noting that claim 1 was the broader, while claim 3 was limited to an "essentially pure compound." The court went on:

"Counsel [for the Patent Office] admits that the Alder et al. patent does not suggest the claimed properties set out in claim 3. Furthermore, both parties agree that the properties expressed in claim 3 are not predictable, and that such properties could be ascertained only after successfully producing the compound."

Notwithstanding, the court held:

"[I]n accordance with the holding in National Lead Co. v. Marzall, 91 U.S.App.D.C. 63, 198 F.2d 296, 93 USPQ 353, an increase in knowledge of a prior disclosure or the discovery of new properties thereof does not justify the grant of a patent."

While we do not dispute the District Court's interpretation of the National Lead decision, we feel that case is not applicable here. In the National Lead case, the patent applicant was seeking to patent a drilling fluid having a certain combination of chemical ingredients which would determine its viscosity. In affirming the denial of letters patent, this

court pointed out that well-drilling fluid containing the ingredients included in the application was known, and that the mere novel proportion of the chemical additives was insufficient to warrant a patent. Roberts v. Ryer, 91 U.S. 150 (1875), cited in the National Lead opinion, dealt with a slight modification of the design of a refrigerator, also a well-known product.

Hence those cases are not controlling where, as here, a novel or unique product is involved. It is significant that, while the Primary Examiner stated that the properties recited in claim 3 were inherent in the compound suggested by Alder, the District Court found as a fact that there was not the slightest suggestion of these properties in the Alder patent. We hold that the District Court's finding on this point compelled a result contrary to that which the court reached, for the same reasons set forth supra relating to claim 1.

II

[3] The second major issue, raised by appellees after the trial and urged on appeal, is that claim 1 does not meet the standard of particularity required by 35 U.S.C. § 112, [FN9] and hence is not patentable. In short, appellees argue that the word "tetracyanoethylene" does not define an invention within the meaning of the statute. We think that a contrary conclusion is compelled.

Preliminarily it should be noted that the so-called "Geneva" system of nomenclature, from which the name tetracyanoethylene is derived, is a standard system of identification for various chemical compounds. The compound here involved is called an ethylene, or derivative of ethylene, because of the central nucleus of the two carbonation (C-C); the tetracyano part of part of the name means that four cyano (CN) groups are attached to the ethylene nucleus. It seems, therefore, that the word tetracyanoethylene is little more than the structural formula *304 of the compound converted into an utterable combination of letters. We do not understand appellees to assert that a chemical formula would not adequately describe a compound claimed in a patent application, and since it seems apparent that the name here is as equally descriptive of the compound as a line-and-symbol formula, it is as sufficient for purposes of statutory particularity. [FN10]

More important, however, the ultimate factor controlling a question of the sufficiency of a claim is well stated in Application of Nelson, 47 CCPA 1031, 1045, 280 F.2d 172, 181, 126 USPQ 242, 251 (1960):

> "The descriptions in patents are not addressed to the public generally, to lawyers or to judges, but, as section 112 says, to those skilled in the art to which the invention pertains or with which it is most nearly connected. The sufficiency of a specification must be tested in the light of this fact and judged by what it conveys to those who are skilled in the art."

[5] In the District Court proceedings, uncontroverted expert testimony established that the name of the compound tetracyanoethylene did describe the compound, and that one skilled in the art would understand what was indicated by the use of the name. [FN11] Consequently, we are of the opinion that claim 1 is not defective for lack of statutory particularity.

For the above reasons, the order of the District Court must be reversed, and the case remanded to that court with instructions to enter an order authorizing the Commissioner of Patents to issue a patent to appellant on Claims 1 and 3.

So ordered.

FN1 Serial No. 311,544, subsequently Serial No. 382,842 as a continuation-in-part application.

FN2 66 Stat. 803 (1952), 35 U.S.C. § 145 (1958).

FN3 Claim 4 was likewise dismissed, appellant having abandoned that claim at the trial.

FN4 66 Stat. 797 (1952), 35 U.S.C. § 102 (1958): "Conditions for patentability; novelty and loss of

right to patent. A person shall be entitled to a patent unless(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States * * *."

FN5 66 Stat. 798 (1952), 35 U.S.C. § 112 (1958): "Specification. " The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof."

FN6 Note 4, supra.

FN7 Significant is the testimony of Dr. Fieser concerning the substitution of more than two cyano groups in the general Alder formula: "* * * I feel that as a chemist I couldn't interpret this general formula with a cyano-hydrocarbon beyond those containing 1 and 2 cyano groups, because there are no other examples but those included in the patent, and in Alder's original paper no mention is made of anything having more than two cyano groups and I think I would have to stop at that point."

FN8 Cf. Application of Papesch, 50 C.C.P.A. 1084, 315 F.2d 381, 137 USPQ 43 (1963); Mathieson Alkali Works, Inc. v. Coe, 69 App.D.C. 210, 99 F.2d 443, 39 USPQ 96 (1938); Rem-Cru Titanium, Inc. v. Watson, 147 F.Supp. 915, 112 USPQ 88 (D.D.C. 1956).

FN9 Note 5, supra.

FN10 [4] We are also persuaded somewhat by the history of the Patent Office in granting letters patent for application claims having the same descriptive nature as claim 1 herein.

FN11 E.g., by Dr. Fieser:"Q. * * * In your opinion, is the naming of a compound per se and only that a sufficient and proper identification of that compound?* * *"A. Well, it depends. Are you talking about tetracyanoethylene?"Q. I will ask you that question directly. Is that a sufficient and complete definition of a new product?"A. Either the name or the formula in that case, it seems to me, is a sufficient description.

EDGERTON, Senior Circuit Judge, dissents.

C.A.D.C.

140 U.S.P.Q. 297

END OF DOCUMENT

Chapter 18: the Chen presentation

P. 257: Acetyl chloride (Lewis acid) opens the oxetane ring and leads to A-ring contraction (related to Greene conditions 9-11): this shows that using conditions 9-11 to try to remove methoxy from the claimed compounds would dramatically alter the structure and lead to inactive compounds, based on prior research

P. 258: Hcl/trifluoroacetic acid: similar, unavoidable A ring contraction (related to Greene condition 5); oxetane ring opening

P. 258: Boron tribromide or trimethylsilyl bromide (Lewis acid:nuceleophiles): A ring contracted products (related to Greene conditions 2-11): oxetane ring opening.

Discussion of Greene Conditions: See the Taxane Literature

Taxane Anticancer Agents: March 1994 ACS Symposium

Presentations: made by Professors Kingston and Holton

Also presentations: Dr. Commerçon and Dr. Chen (BMS)

Dr. Commerçon will explain how Dr. Chen's presentation demonstrates the unacceptableness of the Greene conditions for removing alkoxy groups from taxanes of the type claimed.

Greene's Eleven Conditions: Unacceptable for Taxanes

Would Disturb:

- The Ester Linkage
- Other Substituents of the Taxane Intermediate
- Break Rings (Rearrangements) and/or
- Generate Epimerization

Greene's Teachings (15-17) on Methoxy Protecting Group

- Dr. Commerçon will discuss the conditions Greene reports for cleavage (deprotection) of a methoxy in general.

Eleven conditions are reported.

- Require: the presence of a nucleophile and, if necessary, Lewis acid assistance.

THE HOLTON PATENT

- Col. 6, lines 23-40: discusses hydroxyl protecting groups

Lines 35-40: The hydroxyl protecting group selected should be easily removed under conditions that are sufficiently mild, e.g., in 48% HF, acetonitrile, pyridine, or 0.5% Hcl/water/ethanol and/or zinc, acetic acid so as not to disturb the ester linkage or other substituents of the taxol intermediate (emphasis added).

The purpose of today's interview: have Dr. Commerçon

-- an inventor,

--one of the world's leading taxane chemists, with about 60 paper/patents on the subject and a frequent lecturer, and

--the Director of New Lead generation for the assignee, Rhône-Poulenc Rorer,

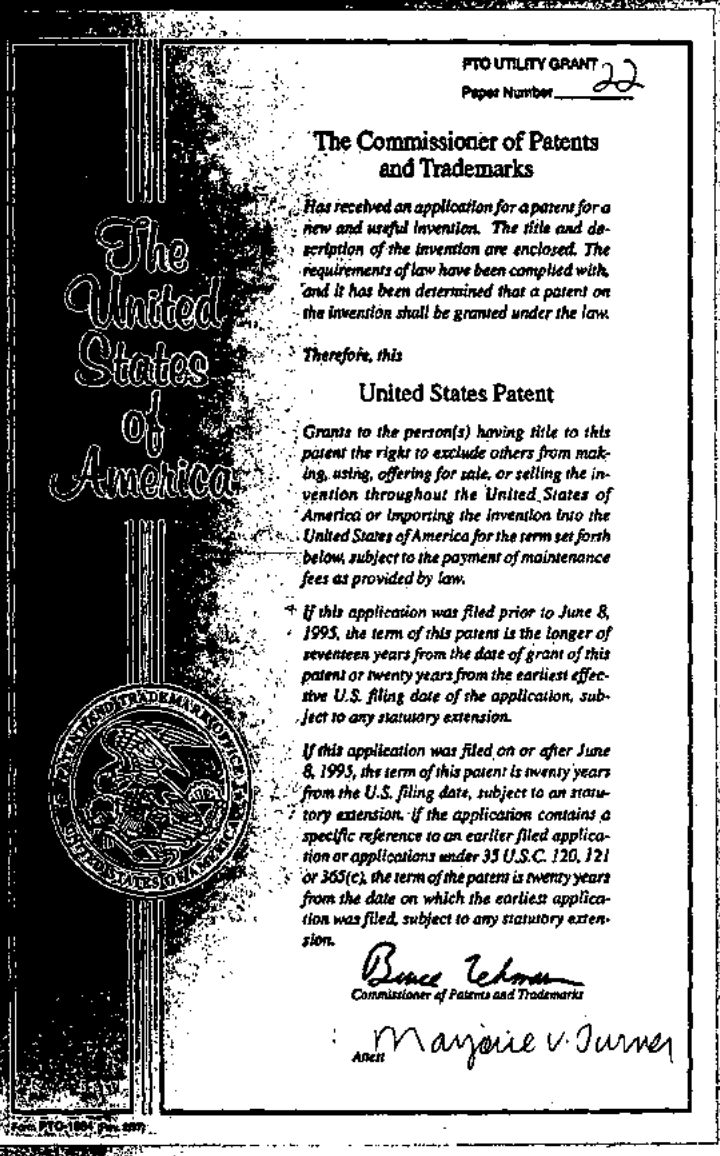
discuss in detail with you the teachings of Holton and Kingston to demonstrate although alkoxy radicals can be hydroxy protecting groups in certain molecules, the alkoxy radicals at the 7 and 10 position of the claimed compounds are not hydroxy protecting groups.

INTERVIEW SN 08/622,011: OCTOBER 2, 1997

As discussed in the first interview, all "product" claims will be amended to recite that R_4 (10-Position) and R_5 (7-position) represent a C_{1-6} alkoxy radical.

Although not required, it has been decided to narrow the allowed process claims to be commensurate in scope with the "product" claims.

An open issue: are the 7- and 10-position alkoxys hydroxy protecting groups?



PTO UTILITY GRANT
Paper Number 22

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to an statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extension.

Bruce Lehman
Commissioner of Patents and Trademarks

Attest Marjorie V. Turner

(RIGHT INSIDE)

US005847170A

United States Patent [19]

Bouchard et al.

[11] Patent Number: 5,847,170

[45] Date of Patent: Dec. 8, 1998

[54] **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Hervé Bouchard**, Ivry-sur-Seine; **Jean-Dominique Bourzat**, Vincennes; **Alain Commerçon**, Vitry-sur-Seine, all of France

[73] Assignee: **Rhône-Poulenc Rorer, S.A.**, Antony Cedex, France

[21] Appl. No.: **622,011**

[22] Filed: **Mar. 26, 1996**

Related U.S. Application Data

[60] Provisional application No. 60/010,144, Jan. 17, 1996.

[30] **Foreign Application Priority Data**

Mar. 27, 1995 [FR] France 95 03545
Dec. 22, 1995 [FR] France 95 15381

[51] **Int. Cl.**[6] **C07D 305/14**
[52] **U.S. Cl.** **549/510**; 549/511
[58] **Field of Search** 549/510, 511

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,229,526	7/1993	Holton et al.	549/213
5,319,112	6/1994	Kingston et al.	549/510
5,486,601	1/1996	Holton et al.	514/337
5,739,362	4/1998	Holton et al.	549/510

FOREIGN PATENT DOCUMENTS

0 336 841	10/1989	European Pat. Off. .
604910	7/1994	European Pat. Off. .
0 639 577	2/1995	European Pat. Off. .
694539	1/1996	European Pat. Off. .
WO 92/09589	6/1992	WIPO .
WO 94/07878	4/1994	WIPO .
WO 94/18164	8/1994	WIPO .
WO96/00724	1/1996	WIPO .

OTHER PUBLICATIONS

Greene et al, "Protective Groups in Organic Synthesis", pp. 10–14, 2nd edition, 1991.

M.L. Shelanski et al., "Microtubule Assembly in the Absence of Added Nucleotides", Proc. Natl. Acad. Sci. vol. 70, No. 3,pp. 765–768 (1973).

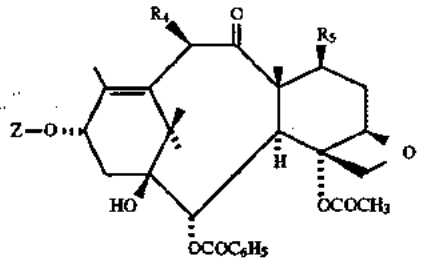
G. Chauvière et al., "Analyse structurable et etude biochimique de produits isoles de l'if: Taxus baccata L. (Taxaces)", C.R. Acad. Sc. Paris, t.293, pp. 501–503 (1981).

J. Kant et al., "A Chemoselective Approach to Functionalize the C–10 Position of 10–Deacetylbaccatin III. Synthesis and Biological Properties of Novel C–10 Taxol Analogues", Tetrahedron Letters, vol. 35, No. 31, pp. 5543–5546, 1994.

Primary Examiner—Ba K. Trinh
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

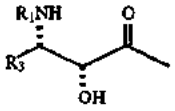
[57] **ABSTRACT**

New taxoids of general formula (I):



(I)

their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):



(II)

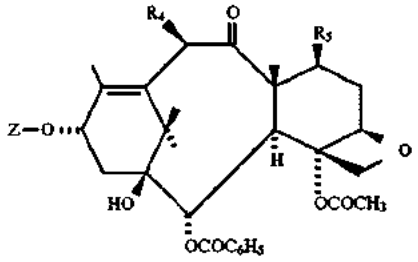
display noteworthy antitumour and antileukaemic properties.

22 Claims, No Drawings

TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the priority of U.S. provisional application 60/010.144 filed Jan. 17, 1996.

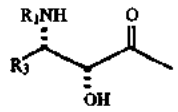
The present invention relates to new taxoids of general formula (I)



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):



(II)

in which:

R_1 represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical preferably selected from furyl and thienyl radicals,

or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

R_3 represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

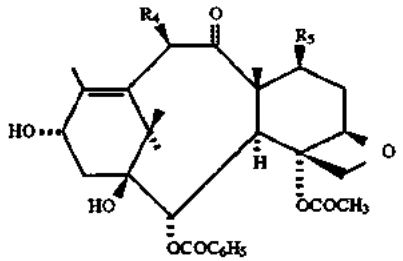
Preferably, the radicals R_4 and R_5, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2—O—CO— in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

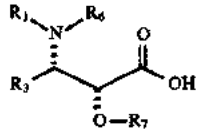
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):



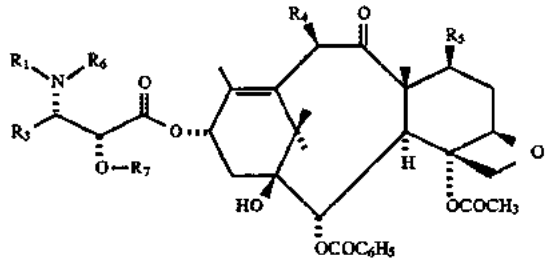
(III)

in which R_4 and R_5 are defined as above, by means of an acid of general formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, followed by replacement of the protective groups represented by R_7 and/or R_6 and R_7 by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from −10° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitrites, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 80° C.

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

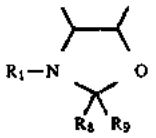
When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the following manner:

1) when R_8 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from −10° to 60° C., or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

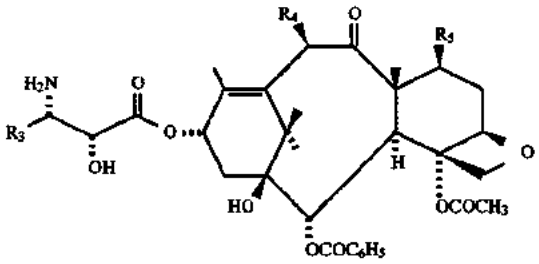
2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and R_9 represents a hydrogen atom, or alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms may be performed, depending on the meanings of R_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or alternatively R_8 and R_9 together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):



(VII)

in which R_3, R_4 and R_5 are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2—O—CO—X \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

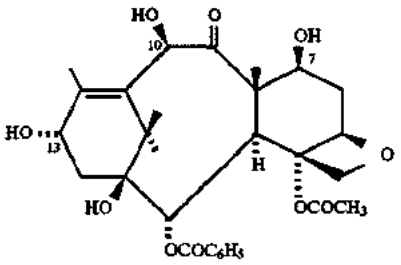
Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20° C. to yield the product of general formula (VII).

Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent

chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0° to 50° C., and preferably at about 20° C.

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C., and preferably from 15° to 30° C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and R_4 and R_5 are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):

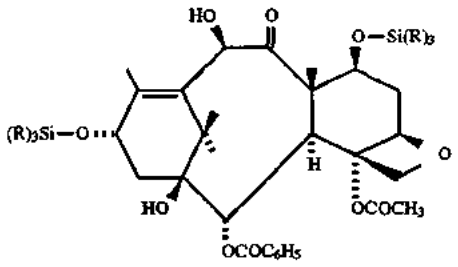


(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:

$$(R)_3—Si—Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):

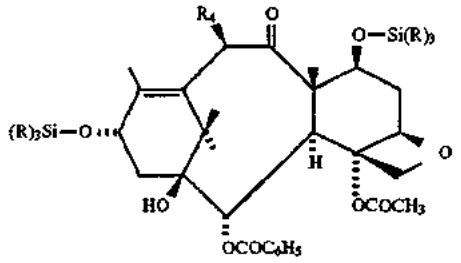


(XI)

in which R is defined as above, followed by the action of a product of general formula:

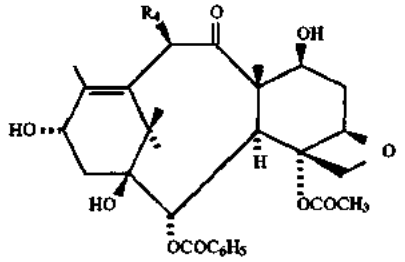
$$R'_4—X_1 \qquad (XII)$$

in which R'_4 represents a radical such that $R'_4—O$ is identical to R_4 defined as above and X_1 represents a reactive ester residue such as a sulphuric or sulphonic ester residue or a halogen atom, to obtain a product of general formula (XIII):



(XIII)

in which R and R_4 are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):



(XIV)

in which R_4 is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

$$R'_5—X_2 \qquad (XV)$$

in which R'_5 represents a radical such that $R'_5—O$ is identical to R_5 defined as above and X_2 represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonic ester residue, to give the product of general formula (III).

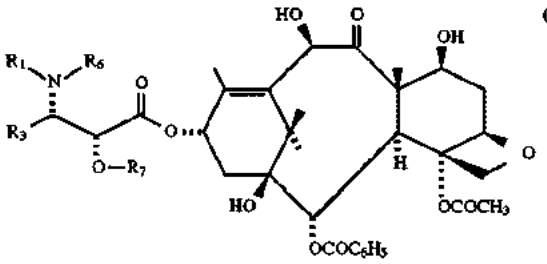
Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0° C. and the refluxing temperature of the reaction mixture.

Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0° to 50° C.

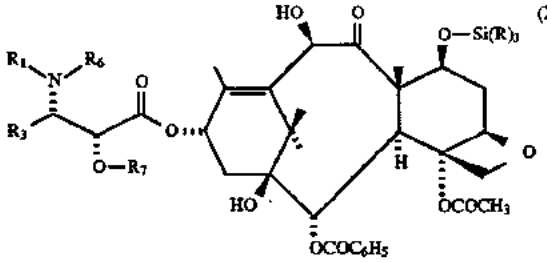
Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0° to 80° C.

Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

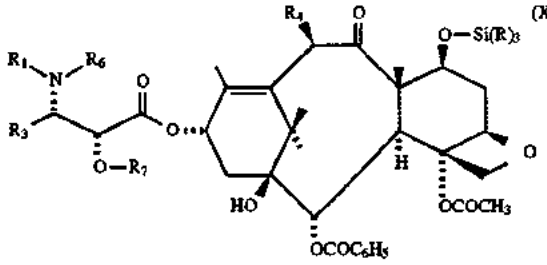
According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4 is defined as above and R_5 is defined as above may be obtained from a product of general formula (XVI):


(XVI)

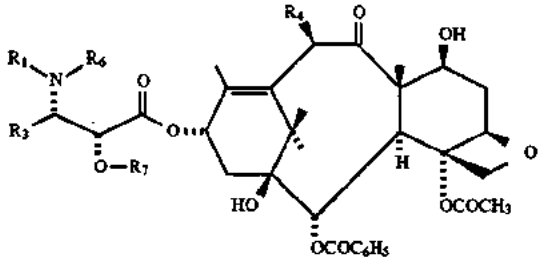
in which R_1, R_3, R_6 and R_7 are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):


(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):


(XVIII)

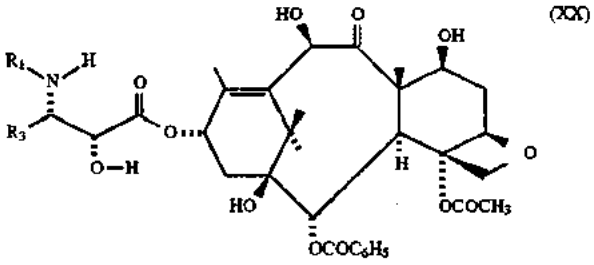
in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):


(XIX)

which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

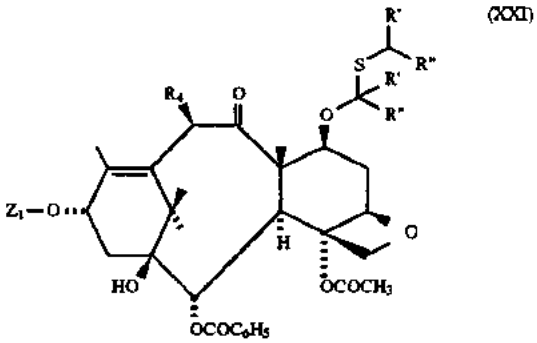
The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336,841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):

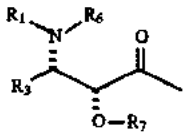

(XX)

in which R_1 and R_3 are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

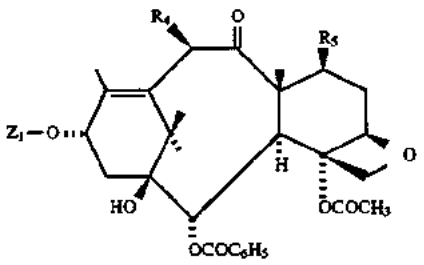
According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):


(XXI)

in which R_4 is defined as above and R' and R", which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of general formula (XXII):


(XXII)

in which R_1, R_3, R_6 and R_7 are defined as above, and, to obtain a product of general formula (XXIII):

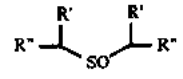


(XXIII)

followed, when Z_1 represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by R_6 and/or R_6 and R_7 by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from −10° to 60° C.

According to the invention, the product of general formula (XXI) in which Z_1 and R_4 are defined as above may be obtained by the action of a sulphoxide of general formula (XXIV):



(XXIV)

in which R' and R" are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50° C., and preferably at about 25° C.

The new products of general formula (I) obtained by carrying out the processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M. L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765–768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501–503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 2 cm^3 of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 10:90 to 40:60 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$ with a few drops of CD_3OD-d_4; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.63 (s, 3H: CH_3); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; CH_2 at position 6); 1.78 (unres. comp., 3H: CH_3); 2.02 and 2.15 (2 dd, J=14 and 9, 1H each: CH_2 at position 14); 2.14 (s, 3H: CH_3); 3.22 and 3.35 (2 s, 3H each: OCH_3); 3.64 (d, J=7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: $ArOCH_3$); 4.06 and 4.16 (2 d, J=8.5, 1H each; CH_2 at position 20); 4.53 (d, J=5, 1H: H at position 2'); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J=10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J=7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J=8, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to OCH_3); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.58 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 7.96 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 cm^3 of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0° C. for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 cm^3 of dichloromethane and 5 cm^3 of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 cm^3 of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatog-

raphy [12 Merck preparative silica gel $60F_{254}$ plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40° C., 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

optical rotation $[\alpha]_{20}^{D}$=−32.9 (c=0.5; methanol)

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.39 (s, 9H: $C(CH_3)_3$); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: CH_3); 1.82 and 2.72 (2 mts, 1H each: CH_2 at position 6); 1.91 (s, 3H: CH_3); 2.31 (limiting AB, 2H: CH_2 at position 14); 2.39 (s, 3H: $COCH_3$); 3.33 and 3.48 (2 s, 3H each: OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: H 3); 3.88 (dd, J=11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J=10, 1H: H at position 5); 5.30 (broad d, J=10, 11H: H at position 3'); 5.47 (d, J=10, 1H: CONH); 5.66 (d, J=7, 1H: H at position 2); 6.24 (broad t, J=9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene in 5 cm^3 of iodomethane and 0.5 cm^3 of dimethylformamide. After 45 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 50 cm^3 of ethyl acetate and 8 cm^3 of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene were thereby obtained in the form of a pale yellow solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; with a few drops of CD_3OD-d_4, chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: CH_3); 1.11 (s, 3H: CH_3); 1.65 (s, 3H: CH_3); 1.72 and 2.67 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.21 (limiting AB, J=14 and 9, 2H: CH_2 at position 14); 2.25 (s, 3H: $COCH_3$); 3.26 and 3.40 (2 s, 3H each: OCH_3); 3.85 (d, J=7, 1H: H at position 3); 3.89 (dd, J=11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.78 (broad t, J=9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.53 (d, J=7, 1H: H at position 2); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.56 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.05 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyoxy)-11-taxene in 30 cm^3 of dichloromethane. After 48 hours at a temperature in the region of 20° C., the reaction mixture was poured into a suspension of 100 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 cm^3 of dichloromethane and then twice 80 cm^3 of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm: coupling constants J in Hz): 1.10 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.48 (d, J=8.5, 1H: OH at position 13); 1.70 (s, 3H: CH_3); 1.81 and 2.61 (2 mts, 1H each: CH_2 at position 6); 2.09 (d, J=5, 1H: OH at position 7); 2.11 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J=9; 2H: CH_2 at position 14); 3.48 (s, 3H: OCH_3); 3.97 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J=10, 1H: H at position 5); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl) baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-

bis(triethylsilyloxy)-11-taxene in 25 cm^3 of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0° C., and then for 5 hours 30 minutes at a temperature in the region of 20° C. The reaction mixture was cooled again to a temperature in the region of 0° C., and 125 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise. After 1 hour at 20° C. and then 18 hours at 5° C., the reaction mixture was diluted by adding 50 cm^3 of dichloromethane and poured into 50 cm^3 of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 cm^3 of dichloroemethane, and the organic phases were then combined, washed with 10 cm^3 of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 5.15 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063–0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^{1}H NMR spectrum (600 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl CH_2); 0.97 and 1.04 (2 t, J=7.5, 9H each: ethyl CH_3); 1.15 (s, 3H: CH_3); 1.18 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: CH_3); 1.89 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.04 (s, 3H: CH_3); 2.15 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.29 (s, 3H: $COCH_3$); 3.40 (s, 3H: OCH_3); 3.83 (d, J=7, 1H: H: H at position 13); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 7, 1H: H at position 7); 4.91 (s 1H: H at position 10); 4.96 (broad d, J=10, 1H at position 5); 5.01 (broad t, J=9, 1H: H at position 13); 5.62 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 cm^3 of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetylbaccatin III) in 50 cm^3 of anhydrous pyridine. After 17 hours at a temperature in the region of 20° C., the reaction mixture was brought to a temperature in the region of 115° C. and 10.8 cm^3 of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115° C., the reaction mixture was brought back to a temperature in the region of 20° C. and diluted with 30 cm^3 of ethyl acetate and 100 cm^3 of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 cm^3 of ethyl acetate. The organic phases were combined, washed with 50 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063–0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.08 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.91 and 2.57 (2 mts, 1H each: CH_2 at position 2); 2.04 (s, 3H: CH_3); 2.12 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.88 (d, J=7, 1H: H at position 3); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.27 (d, J=1, 1H: OH at position 10); 4.40 (dd, J=11 and 7, 1H: H at position 7); 4.95 (broad d, J=10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13); 5.16 (d, J=1, 1H: H at position 10); 5.60 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 2

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 cm^3 of a 0.1N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20° C. and then for 80 hours at 4° C., and 20 cm^3 of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 cm^3 of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates is 20×20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 cm^3 of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. A white foam was obtained, which was repurified according to the same technique [3 plates; 20×20×1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)]. 205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

optical rotation: $[\alpha]_{20}^{D}$=–33 (c=0.5; methanol).

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: —CH_3); 1.25 (s, 3H: —CH_3); 1.39 [s, 9H: —$C(CH_3)_3$]; 1.70 (s, 1H: —OH at position 1); 1.75 (s, 3H: —CH_3); 1.82 and 2.72 (2 mts, 1H each: —CH_2 at position 6); 1.91 (s, 3H: —CH_3);

2.31 (limiting AB, 2H: —CH_2 at position 14); 2.39 (s, 3H: —$COCH_3$); 3.33 and 3.48 (2 s, 3H each: —OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: —H at position 3); 3.88 (dd, J=11 and 7, 1H: —H at position 7); 4.20 and 4.33 (2d, J=8.5, 1H each: —CH_2 at position 20); 4.65 (mt, 1H: —H at position 2'); 4.83 (s, 1H: —H at position 10); 5.00 (broad d, J=10, 1H: —H at position 5); 5.30 (broad d, J=10, 1H: —H at position 3'); 5.47 (d, J=10, 1H: —CONH—); 5.66 (d, J=7, 1H: —H at position 2); 6.24 (broad t, J=9, 1H: —H at position 13); from 7.30 to 7.50 (mt, 5H: —C_6H_5 at position 3'); 7.52 [t, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 3 and H at position 5)]; 7.63 [t, J=7.5, 1H: —$OCOC_6H_5$ (—H at position 4)]; 8.12 [d, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 2 and H at position 6)].

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 cm^3 of an ethanolic suspension of activated nickel according to Raney (obtained from 80 cm^3 of the approximately 50% commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 cm^3 of distilled water and with 5 times 100 cm^3 of ethanol) were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm^3 of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20° C. and then filtered through sintered glass. The sintered glass was washed with 4 times 80 cm^3 of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-cm^3 fractions. Fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 350 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxy-phenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 cm^3 of acetic acid and 7.55 cm^3 of acetic anhydride were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 cm^3 of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20° C., and then poured into a mixture of 500 cm^3 of distilled water and 250 cm^3 of dichloromethane. 30 cm^3 of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with twice 250 cm^3 of dichloromethane. The organic phases were combined, washed with 250 cm^3 of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063–0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 1.25 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 cm^3 of methanol and 100 cm^3 of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60° C., and 10 g of powdered zinc were then added. The reaction mixture was then stirred for 15 minutes at 60° C., thereafter cooled to a temperature in the region of 20° C. and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 cm^3 of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 50 cm^3 of ethyl acetate and 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution and with 25 cm^3 of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy-carbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

EXAMPLE 3

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 135 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at

a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

^{1}H NMR spectrum (600 MHz; $CDCl_3$; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: $C(CH_3)_3$; 1.19 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.27 (t, J=7, 3H: ethyl CH_3); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: CH_3); 1.68 (s, 3H: CH_3); 1.77 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.86 (s, 3H: $COCH_3$); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.27 (s, 3H: OCH_3); 3.45 and 3.68 (2 mts, 1H each: ethyl CH_2); 3.76 (d, J=7, 1H: H3); 3.81 (s, 3H: $ArOCH_3$); 3.85 (dd, J=11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.58 (d, J=4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.46 (d, J=4.5, 1H: H at position 3'); 5.60 (d, J=7 Hz, 1H: H2); 6.13 (broad t, J=9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.50 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ H at the meta position); 7.59 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm^3 of ethyl acetate and 0.004 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.32 (t, J=7, 3H: ethyl CH_3); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H; CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each ethyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 cm^3 of iodomethane and 1 cm^3 of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 6 cm^3 of distilled water and 8 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$ with the addition of a few drops of CD_3OD-d_4; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: CH_3); 1.09 (s, 3H: CH_3); 1.22 (t, J=7, 3H: ethyl CH_3); 1.62 (s, 3H: CH_3); 1.68 and 2.66 (2 mts, 1H each: CH_26); 2.03 (s, 3H, CH_3); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.23 (s, 3H: $COCH_3$); 3.23 (s, 3H: OCH_3); from 3.40 to 3.65 (mt, 2H: ethyl CH_2); 3.84 (d, J=7.5, 1H: H at position 3); 3.88 (dd, J=10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J=8.5, 1H each: CH_2 20); 4.75 (broad t, J=9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J=10, 1H: H at position 5); 5.51 (d, J=7.5, 1H: H at position 2); 7.42 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position);

7.53 (t, J=7.5, 1H: $OCOC_6H_5$ at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β, hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 21 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 40 cm^3 of dichloromethane and poured into a suspension of 40 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: ethyl CH_3); 1.38 (d, J=9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: CH_3); 1.82 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.02 (d, J=5, 1H: OH at position 13); 2.08 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$).; 2.32 (d, J=9, 2H: CH_2 at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl OCH_2); 3.98 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5 Hz, 1H each: CH_220); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J=10 and 1.5, 1H: H at position 5); 5.05 (s, 1H: H at position 10); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.2 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

^1H NMR spectrum (400 MHz, $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl CH_2); 0.97 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 1.13 (s, 3H: CH_3); 1.20 (s, 3H: CH_3); 1.29 (t, J=7.5, 3H: CH_3 of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: CH_3); 1.89 and 2.58 (2 mts, 1H each: CH_2 at position 2); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.53 (mt, 2H: CH_2 of ethoxy at position 10); 3.84 (d, J=7, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.43 (dd, J=11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5), 5.01 (s, 1H: H at position 10); 5.61 (d, J=7, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20° C. to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through

cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 84.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.97 (t, J=7, 3H: propyl CH_3); 1.07 (s, 9H: $C(CH_3)_3$); 1.19 (s, 6H: CH_3); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central CH_2 of propyl); 1.60 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.78 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.82 (unres. comp. 3H: $COCH_3$); 2.07 and 2.19 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 3.26 (s, 3H: OCH_3); 3.30 and 3.58 (2 mts, 1H each: propyl OCH_2); 3.73 (d, J=7.5, 1H: H at position 3); 3.81 (s, 3H: $ArOCH_3$); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.57 (d, J=4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J=7.5, 1H: H at position 2); 6.13 (broad t, J=9, 1H: H at position 13); 6.40 (spread unres. comp 1H: H at position 5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ meta H); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm^3 of ethyl acetate and 0.0071 cm^3 of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 27 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate were obtained in the form of a white foam, the characteristics of which are as follows:

^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.99 (t, J=7, 3H: propyl CH_3); 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central CH_2 of propyl); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H: CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.36 and 3.64 (2 mts, 1H each: propyl OCH_2); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J=7.5, Hz, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-7β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 165 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene in 1.7 cm^3 of iodomethane and 1 cm^3 of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 5 cm^3 of distilled water and 7 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 cm^3 of distilled water and then 7 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 117.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white foam, the characteristics of which were as follows:

^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.98 (t, J=7, 3H: propyl CH_3); 1.05 (s, 3H: CH_3), 1.19 (s, 3H: CH_3); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: CH_2 at position 6); 1.72 (s, 3H: CH_3); 2.10 (s, 3H: CH_3); from 2.05 to 2.35 (mt, 2H: CH_2 at position 14); 2.28 (s, 3H: $COCH_3$); 3.32 (s, 3H: OCH_3); 3.45 and 3.65 (2 mts, 1H each: propyl OCH_2); 3.92 (d, J=7.5, 1H: H3); 3.93 (dd, J=11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J=10, 1H: H at position 5); 5.60 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.11 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 585 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis

(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 24 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 30 cm^3 of dichloromethane and poured into a suspension of 30 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

^1H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J=7, 3H: propyl CH_3); 1.06 (s, 3H: CH_3); 1.22 (s, 3H: CH_3); 1.45 (d, J=7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); 1.67 (s, 3H: CH_3); 1.83 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: CH_2 at position 4); 2.28 (s, 3H: $COCH_3$); 3.40 and 3.57 (2 mts, 1H each: propyl OCH_2); 3.97 (d, J=7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J=10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J=7.5, 1H: H at position 2); 7.50 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.00 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethyl-silyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis (triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz); 0.57 and 0.70 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl CH_3); 0.94 (t, J=7.5, 3H: propyl CH_3); 1.14 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.67 (s, 3H: CH_3); 1.69 (mt, 2H: central CH_2 of propyl); 1.88 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.40 (mt, 2H: propyl OCH_2); 3.84 (d, J=7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J=8.5, 1H each: CH_2 at position 20); 4.44 (dd, J=11 and 6.5, 1H: H at position 7); 4.96 (broad d, J=10 Hz, 1H: H5); 4.97 (s, 1H: H 10), 4.99 (broad t, J=9 Hz, 1H: H at position 13); 5.62 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared

according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained.

For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to 100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

The example which follows illustrates a composition according to the invention.

EXAMPLE

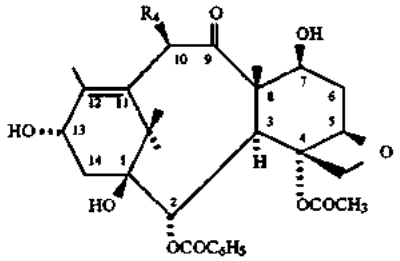
40 mg of the product obtained in Example 1 are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

We claim:

1. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

3. A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):



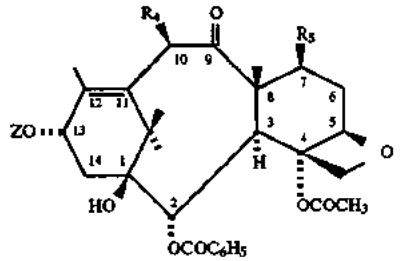
(XIV)

wherein R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

with a compound of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and X_2 represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

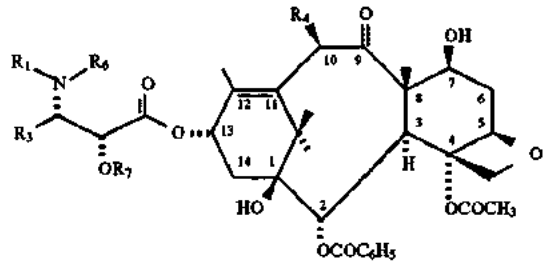
wherein Z is hydrogen, R_4 is as defined above, and R_5 is identical to R'_5 as defined above.

4. A method comprising the step of reacting a product of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein R'_5 represents a radical such that R'_5—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, and X_2 represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

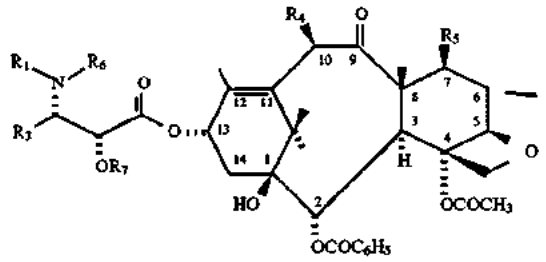
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

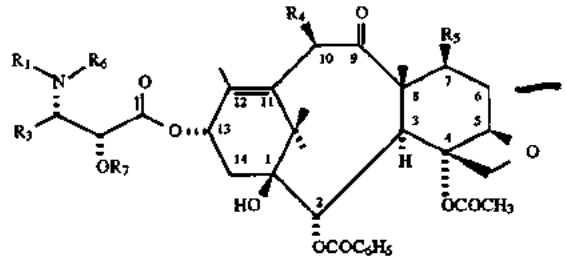
either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to form a compound of the formula (V):



wherein R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and R_1, R_3, R_4, R_6, and R_7 are as defined above.

5. A method comprising the step of replacing with hydrogen atom(s) group(s) R_6 and R_7 in a compound of the formula (V):



wherein:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

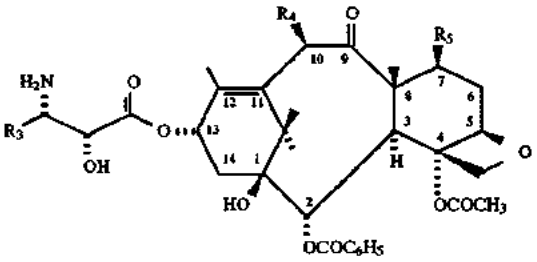
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, optionally in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein R_3, R_4, and R_5 are as defined above.

6. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-

taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

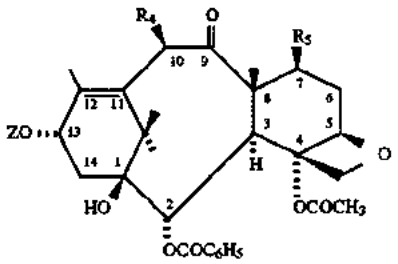
7. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tertbutoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

(c) reacting the product obtained in (b) with an acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

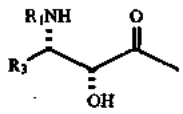
8. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

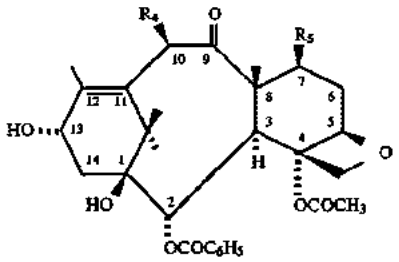
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

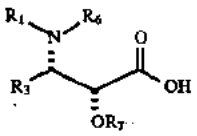
esterifying a product of formula (III):



(III)

in which R_4 and R_5 are defined as above

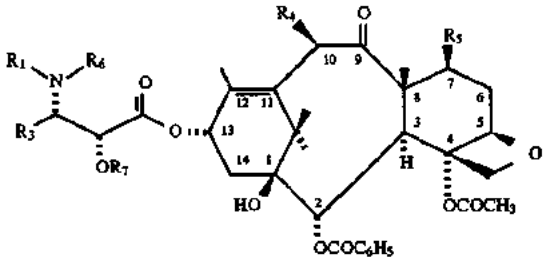
with an acid of formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or

with a derivative of said acid, to obtain an ester of formula (V):

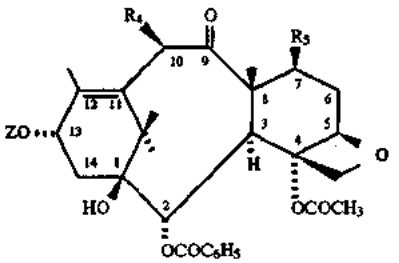


(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, and

replacing the protective group(s) of said ester of formula (V), represented by R_7 or R_6 and R_7 together, by hydrogen atoms.

9. A process for preparing a new taxoid of the following formula (I):



(I)

in which:

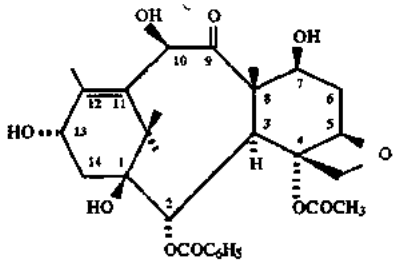
Z represents a hydrogen atom,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating 10-deacetylbaccatin III of formula (IX):

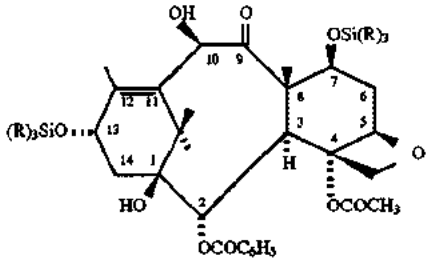


(IX)

with a silyl halide of formula:

$$(R)_3—Si—Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



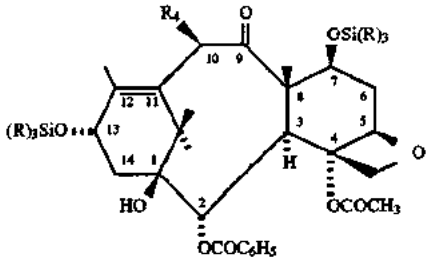
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4—X_1 \qquad (XII)$$

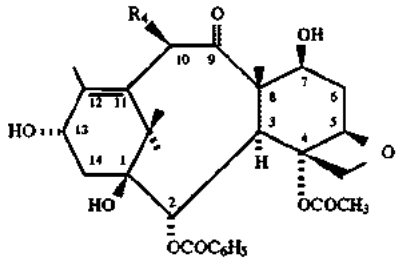
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined above and X_1 represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):



(XIII)

in which R and R_4 are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):



(XIV)

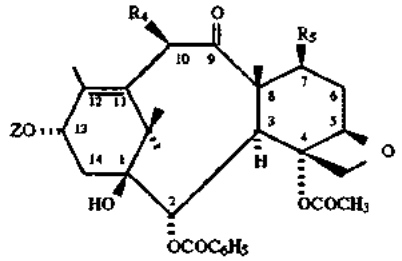
in which R_4 is defined as above, and

etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

in which R'_5 represents a radical such that $R'_5—O$ is identical to R_5 defined as above and X_2 represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

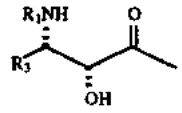
10. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2—O—CO—$ in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

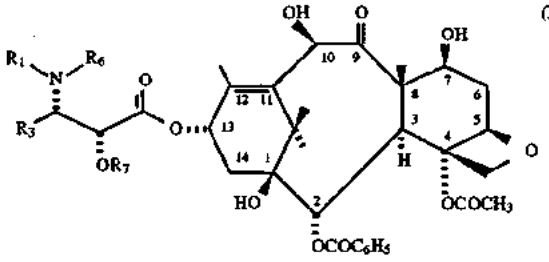
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating a product of formula (XVI):

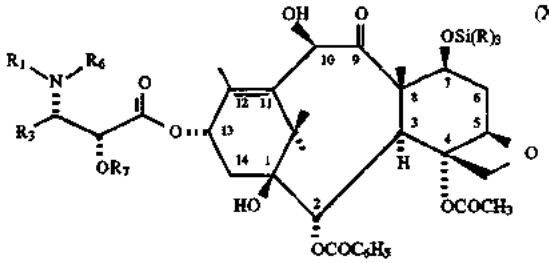


(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, with a product of formula (X):

$$(R)_3Si—Hal \quad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



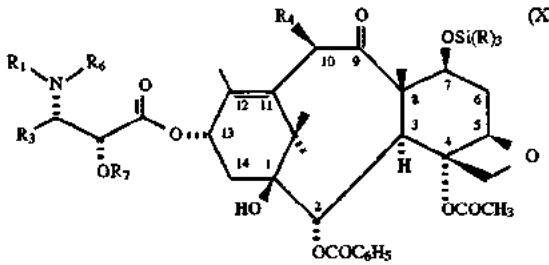
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:

$$R'_4—X_1 \quad (XII)$$

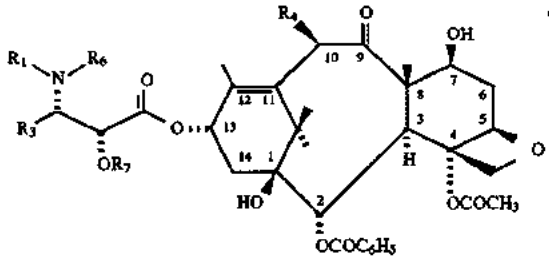
in which R'_4 represents a radical such that R'_4—O is identical to R_4 defined as above and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



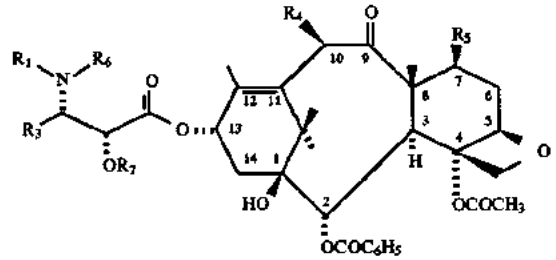
(XIX)

in which R_1, R_3, R_4, R_6 and R_7 are defined as above which, when reacted with a product of formula (XV):

$$R'_5—X_2 \quad (XV)$$

in which R'_5 represents a radical such that R'_5O is identical to R_5 defined above and X_2 represents a reactive ester residue or a halogen atom,

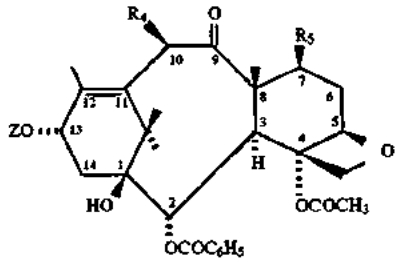
yields the product of formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

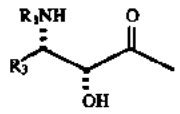
11. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2—O—CO— in which R_2 represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an

alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

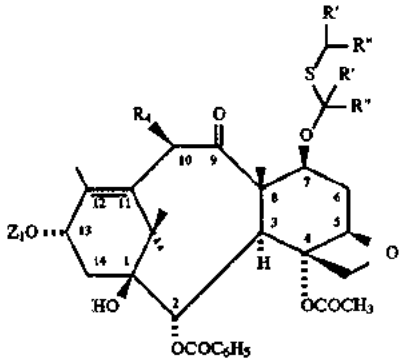
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

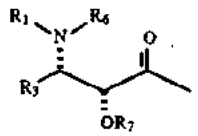
said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):



(XXI)

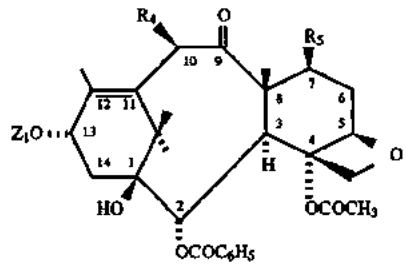
in which R_4 is defined as above, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of formula (XXII):



(XXII)

in which R_1 and R_3 are defined as above and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, to obtain a product of formula (XXIII):



(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 together by hydrogen atoms under the following conditions:

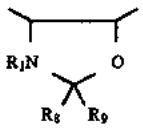
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation, or

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring,

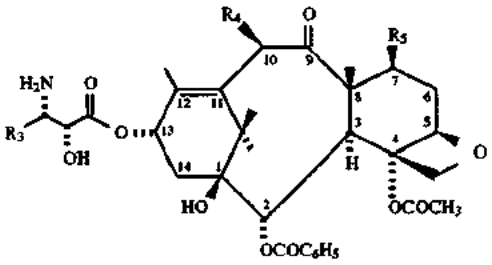
and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring, said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



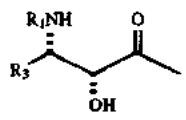
(VII)

in which R_3, R_4 and R_5 are defined as in claim 1, and acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):

$$R_2—O—CO—X \qquad \text{(VII)}$$

in which R_2 is defined as above and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

or

b) R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

said replacing of the protective group formed by R_6 and R_7 together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from −10° to 60° C.

12. A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from −10° to 90° C.

13. A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0° to 90° C.

14. A process according to claim **8**, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0° to 80° C.

15. A process according to claim **8**, further comprising replacing the protective group(s) R_7 or R_6 and R_7 together by hydrogen atoms, wherein:

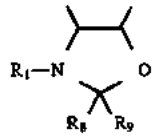
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI),



(VI)

in which R^1 is defined as in claim **8** and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together with the carbon atom to which they are linked, form a 4- to 7-membered ring,

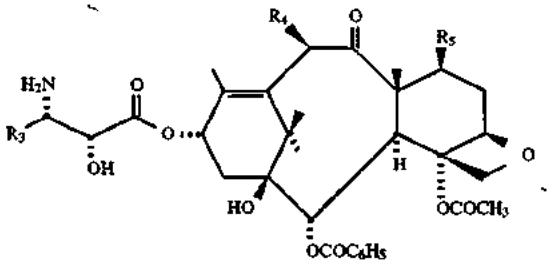
and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_6 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, and optionally, in an organic solvent, to obtain the product of formula (VII):



(VII)

in which

R_3, R_4 and R_5 are defined in claim 8, and

said product of formula (VII) is acylated with benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):

$$R_2—O—CO—X \qquad \text{(VIII)}$$

in which R_2 is defined in claim 8 and X represents a halogen atom or a residue —O—R_2 or —O—CO—O—R_2, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O—CO— in which R_2 is defined as above, R_6 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

the protective group formed by R_6 and R_7 is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C.

16. A process according to claim **15**, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9 which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

17. A process according to claim **15**, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

18. A process according to claim **15**, wherein said temperature ranges from 15° to 30° C.

19. A process according to claim **15**, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

20. A process according to claim **15**, wherein said trihalomethyl radical is trichloromethyl.

21. A process according to claim **15**, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

22. A process according to claim **7**, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

* * * * *

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/822,011	03/26/96	BOUCHARD	30126.0367-00

HM42/0826

FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
TRINH, B	
ART UNIT	**PAPER NUMBER**
1612	21

DATE MAILED: 08/26/98

A. ☐ The petition filed _____ under 37 CFR 1.312(b) is granted.
The paper has been forwarded to the examiner for consideration on the merits.

B. ☑ The amendment filed 6-18-98 under 37 CFR 1.312 has been considered, and has been:

1. ☑ entered
2. ☐ entered as directed to matters of form not affecting the scope of the invention (0.3311).
3. ☐ disapproved. A report appears below.
4. ☐ entered in part. A report appears below.

Report: claims 29, 30, 31, 34 are renumbered as claims 19, 20, 21, 22.

BA K. TRINH
PRIMARY EXAMINER
GROUP 1600
1612

* PTO 1449

PLEASE FURNISH YOUR ZIP CODE IN ALL CORRESPONDENCE

(703) 308-4545

FORM PTOL-271 (REV. 7/80)

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Complete and mail this form, together with [illegible] fees, to: **Box ISSUE FEE**
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T-1

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1/2/320

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CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

HM42/0609
FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

PATENT AND TRADEMARK OFFICE JUL 21 1998 JC4

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(Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/622,011	03/26/96	023	TRINH, B 1612	06/09/98

First Named Applicant: BOUCHARD, HERVE

TITLE OF INVENTION: NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 3806.0367-00	549-510.000	F17	UTILITY	NO	$1320.00	09/09/98

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 FINNEGAN, HENDERSON,
2 FARABOW, GARRETT &
3 DUNNER, L.L.P.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE Rhône-Poulenc Rorer, S.A.

(B) RESIDENCE: (CITY & STATE OR COUNTRY) Antony Cedex, FRANCE

Please check the appropriate assignee category indicated below (will not be printed on the patent)

☐ Individual ☒ corporation or other private group entity ☐ government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):

☒ Issue Fee

☐ Advance Order - # of Copies _____

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The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

(Authorized Signature) Thalia V. Warnement (Date) 07/21/98

Thalia V. Warnement, Reg. No. 39,064

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

07/23/1998 ASEARFRT 00000194 08622011

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PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011

Filed: March 26, 1996

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Notice of Allowance Dated June 9, 1998 Batch No. F17

Group Art Unit: 1612

Examiner: B. Trinh

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1. 312
AND REQUEST FOR RETURN OF INITIALED PTO-1449's

Pursuant to 37 C.F.R. § 1.312 and subject to the recommendation of the Examiner and the approval of the Commissioner, and without withdrawing the case from issue, kindly amend this application as follows:

In the Claims:

Please cancel claim 16 without prejudice or disclaimer.

(original claim 16) **Remarks**

The above-identified application was allowed in the Office Action mailed June 9, 1998. The issue fee has not yet been paid.

Subsequent to allowance, Applicants noted that because the October 29, 1997, amendment to claim 15 (later rewritten as claim 39 in the April 23, 1998,

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202-408-4000

amendment) incorporated the temperature range "-10 to 60°C" into claim 15, dependent claim 16 no longer further limited claim 15, and was thus redundant. Accordingly, Applicants propose to cancel claim 16. No new matter is introduced by this amendment, and no new issues are raised.

Thus, since they are in compliance with 37 C.F.R. § 1.312 and M.P.E.P. § 714.16, Applicants respectfully request that this Amendment be entered.

In addition, Applicants respectfully request that the Examiner initial and return to Applicants the PTO-1449 forms filed with the Information Disclosure Statements (IDS's) of (1) April 24, 1998, (2) May 21, 1998, and (3) May 28, 1998. The Notice of Allowability (PTOL-37) indicated that the PTO-1449's for both of the May IDS's were attached thereto; however, there were no attachments to the PTOL-37. Applicants accordingly await the receipt of all three initialed PTO-1449 forms from the Examiner.

Conclusion

In light of the above, pending claims 17, 40, 26-34, 36-39, and 6-12 are in condition for allowance. An early and favorable action is earnestly solicited.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Amendment, such extension is hereby requested. If there are

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any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Date: June 18, 1998

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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM42/0609
FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/622,011	03/26/96	023	TRINH, B. 1612	06/09/98

First Named Applicant: BOUCHARD, HERVE

TITLE OF INVENTION: NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
3806.0367-00	549-510.000	F17	UTILITY	NO	$1320.00	09/09/98

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

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III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 10-96) Approved for use through 06/30/99. (0651-0033)

*U.S. GPO: 1998-437-639/80023

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/[illegible] 1	03/2[illegible]	BOUCHARD	0367-00

HM42/0609
FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
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EXAMINER	
TRINH, B	

ART UNIT	PAPER NUMBER
1612	9

DATE MAILED: 06/09/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☑ This communication is responsive to amendment filed 5-21-98, 5-28-98

☑ The allowed claim(s) is/are 17,20,24-28,32-39,6-12,16,29-31 and 34 renumbered as claims 1-23

☐ The drawings filed on _____ are acceptable.

☑ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☑ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☑ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 16, 17 5-21-98 5-28-98

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

BA K. TRINH
PRIMARY EXAMINER
GROUP 1200
1612

PTOL-37 (Rev. 10/95)

*U.S. GPO: 1997-417-381/62707

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Attorney Docket No. 3806.0367

Attorney Docket No. 3806.0367	Serial No. 08/622,011
Applicant Hervé BOUCHARD et al.	
Filing Date March 26, 1996	Group ~~1203~~ 1612

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date
BT	5,739,362	04/14/98	Holton et al.	549	510	

FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Sub Class	Trans. Yes	Trans. No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

Examiner	Date Considered
	6-98

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Form PTO 1449 Patent and Trademark Office - U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Attorney Docket No. 3806.0367

Attorney Docket No. 3806.0367	Serial No. 08/622,011
Applicant Hervé BOUCHARD et al.	
Filing Date March 26, 1996	Group 1612

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date

FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Sub Class	Trans. Yes	Trans. No
BT	WO96/00724	11 Jan 96	WIPO				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

Examiner	Date Considered
	6 98

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INFORMATION DISCLOSURE CITATION
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Attorney Docket No. 3806.0367

Attorney Docket No. 3806.0367	Serial No. 08/622,011
Applicant Hervé BOUCHARD et al.	
Filing Date March 26, 1996	Group 1612

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date

FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Sub Class	Trans. Yes	Trans. No
	EP604910	6 Jul 94	European				
	EP694539	31 Jan 96	European				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

Examiner	Date Considered 6-98

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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7/18

PATENT
Attorney Docket No. 3806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hervé BOUCHARD et al.	
Serial No.: 08/622,011	Group Art Unit: 1612
Filed: March 26, 1996	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), Applicants bring to the attention of the Examiner the document listed on the attached PTO 1449. This Information Disclosure Statement is being filed after the events recited in Section 1.97(b) but, to the undersigned's knowledge, before the mailing date of either a Final Action or a Notice of Allowance. Under the provisions of 37 C.F.R. § 1.97(c), this Information Disclosure Statement is accompanied by a fee of $240.00 as specified by Section 1.17(p).

A copy of the listed document is attached. Applicant respectfully requests that the Examiner consider the listed document and indicate that it was considered by making appropriate notation on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed

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better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claims in the application and Applicants determine that the cited document does not constitute "prior art" under United States law, Applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the document be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Date: May 28, 1998

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PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: 1612

Filed: March 26, 1996 — Examiner: B. Trinh

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

FURTHER SUPPLEMENTAL REMARKS

In response to the Office Action dated February 25, 1998, Applicants filed an Amendment on April 23, 1998. Following the interview with Examiner Trinh and Supervisory Primary Examiner Kight held on May 21, 1998, Applicants prepared and filed a Supplemental Amendment and an Information Disclosure Statement, also on May 21, 1998. The discussion in the Supplemental Amendment demonstrates that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups.

In view of the above-mentioned papers and in view of the Supplemental Remarks set forth below, Applicants respectfully request reconsideration of this application. The purpose of the Supplemental Remarks is two-fold:

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(1) To bring additional evidence to the Examiner's attention to further support Applicants' position that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups; and

(2) To complete the record reflecting a summary of the interview by providing further detail from the interview that demonstrates the patentability of compound claim 17 and pharmaceutical composition claim 40.

Additional Evidence

After the interview and after the Supplemental Amendment under 37 C.F.R. § 1.115 was filed on May 21, 1998, Applicants considered the issues in this case further. As a result of that consideration, Applicants file the accompanying Information Disclosure Statement citing two published European patent applications: EP 684 539 A1 (EP '539) and EP 604 910 A1 (EP '910). The disclosures of these two EP applications are quite similar to the disclosures of EP 639 577 (EP '577) and the Kant article in *Tetrahedron Letters* which were cited in an Information Disclosure Statement on June 26, 1996. These EP applications are also quite similar to the Upjohn publication, WO96/00724, cited in the May 21, 1998, Supplemental Amendment in support of Applicants' position that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups. EP '539 and EP '910 are brought to the Examiner's attention because, like the disclosures of EP 639 577,

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the Kant article in *Tetrahedron Letters*, and the Upjohn publication previously cited, they further support Applicants' position that the methyl groups at the 7- and 10-position of the compound recited in claim 17 are not hydroxy protecting groups.[1]

EP '539 and EP '910

The disclosure of EP '539, like that of Upjohn, contains no suggestion that methyl at the 7-position, i.e., when R^1 is H, is a hydroxy protecting group. In fact, the contrary is suggested. At page 3, line 40 et seq., "hydroxy protecting group" is defined broadly to include methyl ether. However, when EP '539 deems a group to be a hydroxy protecting group, the symbol "P" is used. *See, e.g.*, page 5, structures (IV) and (V) considered in view of page 7, line 1, which expressly defines "P" as a hydroxy protecting group.

The EP '910 disclosure relates to phosphonoxymethyl ethers of taxane derivatives and pharmaceutically acceptable salts thereof. There is a disclosure at page 5, lines 20-25 of a formula wherein there could be a methyl at the 10-position. As

[1] Even if it they are prior art, EP '539 and EP '910, just like the Upjohn application (WO 96/00724) raise no issues under 35 U.S.C. §§ 102 and 103 with respect to claims 17 and 40. Neither of these applications, nor any other art of record, remotely teaches or suggests the compound recited in present claim 17 which recites methoxy groups at **both** the 7- and 10-positions. In these references, the 7- and 10-positions are defined in a mutually exclusive way, *i.e.*, the substituents recited at the 7- and 10-positions do not overlap. Thus, there is no suggestion in these applications that the substituents at the 7- and 10-positions can be the same, let alone that they can **both** be methoxy. Indeed, these documents are very similar to the teachings of EP '577 and the Kant article, which have been before the Examiner for almost two years.

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in EP '539, at page 5, line 43 et seq. of EP '910, "hydroxy protecting group" is defined broadly to include methyl ether. However, the 7-position is expressly defined so as to exclude the possibility of a methyl. As with EP '539, when EP '910 deems a group to be a hydroxy protecting group, the symbol "P" is used. *See, e.g.*, page 9, lines 35-38, Scheme 4, considered in view of page 9, lines 40-41, which expressly defines "P" as a hydroxy protecting group.

Further, both EP '539 and EP '910 (as well as EP '577) expressly recognize that a particular moiety may or may not be a hydroxy protecting group in a taxane molecule depending on the circumstances. For example, at page 7, line 24 et seq., EP '539 points out that the suitable carbonates might be either hydroxy protecting groups or part of the final product. The critical distinction is explained by EP '539 at page 7, lines 25-27:

> . . . thus, when a carbonate is used as a hydroxy protecting group, it is intended to be removed in a later step to generate the free hydroxy group; otherwise, the carbonate moiety remains as part of the final product.

This explanation appears in identical language at page 10, lines 19-22 of EP '910 and at page 11, lines 8-12 of EP '577.

As explained in the May 21, 1998, Supplemental Amendment and numerous other places in this record, the methyl groups at the 7- and 10-positions of the compound recited in claim 17 are not intended to be removed, i.e., converted to an H. Moreover, Dr. Commerçon, in his Declarations filed in October 1997 and April 1998,

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has proven that under the traditional deprotection conditions of the taxane art previously relied on by the Examiner, as well as of the Holton '362 patent, the methyl groups at the 7- and 10-positions of the compound recited in present claim 17 are not removed, i.e., are not converted to an H.

Therefore, EP '539 and EP '910 support Applicants' position that the methyl groups at the 7- and 10-positions of the compound of claim 17 are not hydroxy protecting groups. The foregoing clearly establishes that there are at least five documents of record, two of which have been of record for almost two years, that support Applicants' position.[2]

Holton '362

Similarly, Holton '362, discussed in the May 21, 1998, Supplemental Amendment, raises no issues under 35 U.S.C. § 102 or 103. Although Holton '362 generally teaches that methyl ether can be present at the 7- and 10-positions, the methyl ether is solely described as a hydroxy protecting group. Because Applicants have established that the methoxy groups in the 7- and 10-positions of the claimed compound <u>are not</u> hydroxy protecting groups, Holton '362 in no way teaches or *prima facie* suggests the claimed invention. Further, based on the disclosure of Holton '362, there is no predictability that any group generally described as a hydroxy protecting

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[2] The five documents are EP '539, EP '577, EP '910, the Kant article, and the Upjohn application all of which are discussed above.

group would be a hydroxy protecting group in a specific taxane molecule, let alone at any specific position thereof.

CONCLUSION

In view of the foregoing remarks and those set forth in the May 21, 1998, Supplemental Amendment, it is urged that all of the pending claims are in condition for allowance. An early and favorable action is earnestly solicited.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of these Remarks, such extension is hereby requested. If there are any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Reg. No. 41,449
for Thalia V. Warnement
Reg. No. 39,064

David M. Maiorana
Reg. No. 41,449

Dated: May 28, 1998

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PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hervé BOUCHARD et al.	
Serial No.: 08/622,011	Group Art Unit: 1612
Filed: March 26, 1996	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.115

In response to the Office Action dated February 25, 1998, Applicants filed an Amendment on April 23, 1998. After further consideration and an interview with Examiner Trinh and Supervisory Primary Examiner Kight held on May 21, 1998, Applicants respectfully request reconsideration of this application in view of the amendment and remarks below.

IN THE CLAIMS:

Please add new claim 40 as follows:

--40. A pharmaceutical composition comprising at least the product according to claim 17 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.--

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REMARKS

Applicants thank Examiner Trinh and Supervisory Primary Examiner Kight for the helpful interview conducted with Mme. Magali Le Pennec and their other representatives, Thalia Warnement, Tom Irving, Charlie Van Horn, and David Maiorana on May 21, 1998. The following remarks reflect the substance of the interview.

Status of Claims

Claims 6-12, 16-17, 26-34, 36-39 and new claim 40 are now pending. Claim 40 is identical to original claim 21, which was inadvertently previously canceled without prejudice or disclaimer. As explained at the interview, claim 40 is drawn to the pharmaceutical composition containing the compound of claim 17, so Applicants take the position that it should be considered together with the compound claim. No new matter has been added by this amendment.

Summary of the Interview

At the interview, it was stated that the Office is withdrawing reliance on Holton '526, Kingston '112, and Holton '601. Although there is no rejection of record, Applicants discussed in detail at the interview Holton '362 which was filed in an Information Disclosure Statement in April 1998, and WO96/00724

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("Upjohn") which is filed in an Information Disclosure Statement submitted herewith.

As reflected in the Examiner Interview Summary Record, Applicants provided evidence and argument that the methyl groups at the 7- and 10-positions of the compound in claim 17 are not hydroxy protecting groups. Applicants have no desire for those methyl groups to be hydroxy protecting groups. Exhibit 1 shows the structures of the compound in claim 17 and of the Taxotere® product, which is a commercial product approved by the FDA for cancer treatment and marketed by the assignee, Rhône-Poulenc Rorer . As established in the April 1998 declaration of Dr. Commerçon, which is of record, the compound of claim 17 appears to have improved multi-drug resistance properties as compared to the Taxotere® product. Therefore, conversion of the compound of claim 17 to the Taxotere® product would defeat the purpose of the claimed invention.

A central discussion at the interview involved the proposition that just because a group is recited generally to be a hydroxy protecting group does not necessarily mean that the group will be a hydroxy protecting group at any specific position in a specific taxane molecule. Examiner Trinh has recognized this unpredictability in an Office Action dated December 1, 1994, during the prosecution history of the Holton '362 patent, stating:

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> Due to the bulky and complex structure of the tetracyclic ring, to remove or to attach a chemical group to the ring is unique, it can only be carried out by a specific reaction, not by assertion or assumption and is not within the capacity of an artisan in the absence of the prior art teachings. Each modification on a specific position of the baccatin ring must be supported by a representative working example, not by mere allegation.

The evidence of record supports this unpredictability. It is true that the Holton '362 patent generally identifies methyl ethers, benzoyl esters and acetyl esters as hydroxy protecting groups. Column 4, lines 4-10. However, as clearly established at the interview, the Holton '362 patent itself supports the proposition that this general disclosure does not mean that any particular group identified is a hydroxy protecting group at a particular position in a particular taxane molecule. Exhibit 2, which was discussed at the interview, summarizes hydroxy protecting groups and removal conditions of the patent art discussed at the interview.

As seen therein, even though Holton '362 has 121 synthetic examples, the only real hydroxy protecting group at either the 7- or 10-position was triethylsilyl (TES). In Example 1, a 7-TES protected taxol compound was exposed to acetonitrile, pyridine and HF, which as explained in Holton '526, is one of the three classic conditions for deprotection of the hydroxy group in the type of taxane molecules disclosed in these patents. The structure of the resultant product is shown in Example 1. The TES was converted to hydrogen to

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result in a hydroxy group at the 7-position. However, at each of the 4- and 10-positions, the acetyl (Ac) group was not removed, and the benzoyl group was not removed at the 2 position. Yet, in his general discussion, Holton identified acetyl and benzoyl as hydroxy protecting groups. Clearly, he understood, as evidenced by Example 1, that acetyl and benzoyl will not be hydroxy protecting groups in every taxane molecule or at every position of a taxane molecule. A similar analysis can be applied to Examples 2-121 of Holton '362. Therefore, one skilled in the art could not reasonably predict that a known hydroxy protecting group will be a taxane hydroxy protecting group, let alone a hydroxy protecting group at any specific taxane position. Rather, as in Holton '362, experimentation must be conducted to make the determination.

In fact, as established at the interview, a methyl group is not a hydroxy protecting group at the 7- and 10-positions of the compound of claim 17. At the interview, Applicants presented the Upjohn publication which contains taxane molecules that can have methoxy at the 7-position and either hydrogen, hydroxy or acetyloxy at the 10-position. See page 9, line 21 and see compounds 47 and 56 at pages 99 and 102, respectively.

There is no suggestion in Upjohn that at the 7-position, methyl is a hydroxy protecting group. In fact, the contrary is suggested because Upjohn distinguishes the Holton '526 compounds as using 7-O protecting groups,

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whereas Upjohn calls its compounds "7-ether taxol analogs."[1] It is implicit from this statement that Upjohn does not consider its 7-ether substituents to be hydroxy protecting groups at the 7-position.

In addition, Applicants have proven, via the October 1997 Commerçon declaration, that the methyl groups at the 7- and 10-positions of the claimed molecule are not hydroxy protecting groups. Exhibit 2 demonstrates that the conditions for removing hydroxy protecting groups taught by the '362 patent and by all of the patents relied on by the Office include the following:

(1) HF, acetonitrile, pyridine;

(2) HCl/water/ethanol; and/or

(3) zinc, acetic acid.

Dr. Commerçon tested the claimed compound under each of these conditions. In each case, analyses of the results were consistent with the claimed compound being the only taxane compound present. Commerçon, October 1997 declaration, ¶ 8. These results demonstrate that when the claimed

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[1] Even if it is prior art, Upjohn raises no issues under 35 U.S.C. §§ 102 and 103 with respect to claims 17 and 21. As noted above, the only possibilities at the 10-position are hydrogen, hydroxy and acetyloxy. There is not even the remotest suggestion of using methoxy. Further, the 7- and 10-positions are defined in a mutually exclusive way. Thus, there is not even a remote suggestion of a compound such as the compound of claim 17, which recites methoxy at both the 7- and 10-positions.

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compound is subjected to the deprotection conditions described in the four patents recited in Exhibit 2, no conversion of the methyl groups to hydrogens is observed. Accordingly, one skilled in the art would conclude that the methyl groups in the 7- and 10-positions of the claimed compound cannot be considered to be hydroxy protecting groups under the art recognized conditions for removal of hydroxy protecting groups from taxane compounds.

Applicants have thus shown that the methyl groups at the 7- and 10-positions of the claimed compound are not hydroxy protecting groups. Accordingly, Holton '362 in no way teaches or *prima facie* suggests the claimed invention nor is there predictability that any group generally described as a hydroxy protecting group would be a hydroxy protecting group in a specific taxane molecule, let alone at any specific position thereof. Applicants respectfully submit that the present claims are in condition for allowance and request the Office to specifically enter into the record that Applicants have proven that methyl groups are not hydroxy protecting groups at the 7- and 10-positions in the claimed compound.

CONCLUSION

In view of the foregoing, it is urged that all of the pending claims are in condition for allowance. An early and favorable action is earnestly solicited. If

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the Examiner has any questions or concerns, the he is requested to contact the undersigned.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this amendment, such extension is hereby requested. If there are any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Thalia V. Warnement Reg No. 39,064
for Thomas L. Irving
Thomas L. Irving
Reg. No. 28,619

Dated: May 21, 1998

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	15

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Tom Irving (Reg. No. 38,548) (3) Mr. Charles Van Horn, Mr. David Maiorana, Ms. Lubinecki

(2) Ms Thalia Warnement (4) Ex. Trinh, SPE John Kight

Date of interview 5-21-98

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: 17

Identification of prior art discussed: art of record US 5,739,362

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant had provided evidence and argument, suggesting that the CH_2 groups at the 7 and 10- positions are not hydroxy protecting groups. Examiner will consider the same upon submission.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Examiner's Signature

PTOL-413 (REV. 1-84)

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#17

PATENT
Attorney Docket No. 3806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: 1203

Filed: March 26, 1996 — Examiner: B. Trinh

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed is a response to the Office Action of February 25, 1998. The items checked below are appropriate:

[ ] Applicants hereby petition for a three-month extension of time to respond to the above Office Action. The fee of $950.00 for the Extension is enclosed.

The claims are calculated below:

	Claims Remaining After Amendment		Highest Number Previously Paid	Present Extra	Rate	Additional Fee
Total	23	-	31	0	x $ 22	$ 00.00
Indep.	10	-	9	1	x $ 82	82.00
[ ] First Presentation of Multiple Dep. Claim(s)					+ $270	
					Subtotal	$
					Reduction by ½ if small entity	-
					TOTAL	$ 82.00

[ ] A fee of $_____ to cover the cost of the additional claims added by this response is enclosed.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

[X] Please charge our Deposit Account No. 06-0916 to cover the cost of additional claims added by this response.

To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this response, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Date: May 21, 1998

By: Thalia V. Warnement

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#17

PATENT

Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hervé BOUCHARD et al.	
Serial No.: 08/622,011	Group Art Unit: 1203
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For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

LETTER

Further to the telephone conference between Examiner Trinh and Applicants' representative, Tom Irving, on April 30, 1998, Applicants hereby submit, as requested by the Examiner, copies of the court cases discussed with respect to anticipation of species by a genus, along with a copy of M.P.E.P. § 2144.08, which sets forth guidelines regarding obviousness of species when prior art teaches a genus.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Dated: April 30, 1998

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2144.08 Obviousness of Species When Prior Art Teaches Genus [R-3]

**>I. Interim Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference

These "Genus-Species Guidelines" are to assist Office personnel in the examination of applications which contain claims to species or a subgenus of chemical compositions for compliance with 35 U.S.C. 103 based upon a single prior art reference which discloses a genus encompassing the claimed species or subgenus but does not expressly disclose the particular claimed species or subgenus. Office personnel should attempt to find additional prior art to show that the differences between the prior art primary reference and the claimed invention as a whole would have been obvious. Where such additional prior art is not found, Office personnel should follow these guidelines to determine whether a single reference 35 U.S.C. 103 rejection would be appropriate. The guidelines are based on the Office's current understanding of the law and are believed to be fully consistent with binding precedent of the Supreme Court, the Federal Circuit, and the Federal Circuit's predecessor courts.

The analysis of the guidelines begins at the point during examination after a single prior art reference is found disclosing a genus encompassing the claimed species or subgenus. Before reaching this point, Office personnel should follow normal examination procedures. Accordingly, Office personnel should first analyze the claims as a whole in light of and consistent with the written description, considering all claim limitations. When evaluating the scope of a claim, every limitation in the claim must be considered. See, e.g., *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995). However, the claimed invention may not be dissected into discrete elements to be analyzed in isolation, but must be considered as a whole. See, e.g., *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1983) ("treating the advantage as the invention disregards the statutory requirement that the invention be viewed 'as a whole' "). Next, Office personnel should conduct a thorough search of the prior art and identify all relevant references. Both claimed and unclaimed aspects of the invention should be searched if there is a reasonable expectation that the unclaimed aspects may be later claimed. If the most relevant prior art consists of a single prior art reference disclosing a genus encompassing the claimed species or subgenus, Office personnel should follow the guidelines set forth herein.

These guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. Rather, they are to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Thus, rejections must be based upon the substantive law, and it is these rejections which are appealable, not any failure by Office personnel to follow these guidelines.

Office personnel are to rely on these guidelines in the event of any inconsistent treatment of issues between these guidelines and any earlier provided guidance from the Office.

II. Determine Whether the Claimed Species or Subgenus Would Have Been Obvious to One of Ordinary Skill in the Pertinent Art at the Time the Invention Was Made

The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103. "The section 103 requirement of unobviousness is no different in chemical cases than with respect to other categories of patentable inventions." *In re Papesch*, 315 F.2d 381, 385, 137 USPQ 43, 47 (CCPA 1963). A determination of patentability under 35 U.S.C. 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*), *cert. denied*, 500 U.S. 904 (1991). Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103. See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d

347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck [& Co.* v. *Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that . . . regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). *See also In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

A proper obviousness analysis involves a three-step process. First, Office personnel should establish a *prima facie* case of unpatentability considering the factors set out by the Supreme Court in *Graham* v. *John Deere*. See, e.g., *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993) ("The PTO bears the burden of establishing a case of *prima facie* obviousness."); *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966), requires that to make out a case of obviousness, one must: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims in issue; (3) determine the level of skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. If a *prima facie* case is established, the burden shifts to applicant to come forward with rebuttal evidence or argument to overcome the *prima facie* case. See, e.g., *Bell*, 991 F.2d at 783-84, 26 USPQ2d at 1531; *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956; *Oetiker*, 977 F.2d at 1445, 24 USPQ2d at 1444. Finally, Office personnel should evaluate the totality of the facts and all of the evidence to determine whether they still support a conclusion that the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. *Id.*

A. Establishing a *Prima Facie* Case of Obviousness

To establish a *prima facie* case of obviousness in a genus-species chemical composition situation, as in any other 35 U.S.C. § 103 case, it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art teachings. See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996) ("[T]he mere possibility that one of the esters or the active methylene group-containing compounds . . . could be modified or replaced such that its use would lead to the specific sulfoalkylated resin recited in claim 8 does not make the process recited in claim 8 obvious "unless the prior art suggested the desirability of [such a] modification' or replacement.") (quoting *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) ("[A] proper analysis under § 103 requires, *inter alia*, consideration of . . . whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process."). In order to find such motivation or suggestion there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings. The prior art disclosure may be express, implicit, or inherent. Regardless of the type of disclosure, the prior art must provide some motivation to one of ordinary skill in the art to make the claimed invention in order to support a conclusion of obviousness. See, e.g., *Vaeck*, 947 F.2d at 493, 20 USPQ2d at 1442 (A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success."); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."); *Hodosh* v. *Block Drug Co.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir.), *cert. denied*, 479 U.S. 827 (1986). These disclosed findings should be made with a complete understanding of the first three "Graham factors." When evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a *prima facie* case of obviousness. The determination as to whether a *prima facie* case exists should be made on the full record before the Office at the time of the determination. Thus, Office personnel should (1) determine the "scope and content of the prior art"; (2) ascertain the "differences between the prior art and the claims at issue"; and (3) determine "the level of ordinary skill in the pertinent art." *Graham* v. *John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). *Accord*, e.g., *In re Paulsen*, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994).

1. Determine The Scope and Content of the Prior Art

As an initial matter, Office personnel should determine the scope and content of the relevant prior art. Each reference must qualify as prior art under 35 U.S.C. 102 (e.g., *Panduit Corp.* v. *Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.) ("Before answering *Graham's* 'content' inquiry, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102."), *cert. denied*, 481 U.S. 1052 (1987)), and should be in the field of applicant's endeavor, or be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). *Accord;* e.g., *In re Clay*, 966 F.2d 656, 658–59, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992).

In the case of a prior art reference disclosing a genus, Office personnel should make findings as to (1) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus; (2) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; (3) the predictability of the technology; and (4) the number of species encompassed by the genus taking into consideration all of the variables possible.

2. Ascertain The Differences Between the Prior Art Genus and the Claimed Species or Subgenus

Once a relevant prior art genus is identified, Office personnel should compare it to the claimed species or subgenus to determine the differences. Through this comparison, the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed. Office personnel should make explicit findings on the similarities and differences between the closest prior art reference and the claimed species or subgenus including findings relating to similarity of structure, chemical properties and utilities. In *Stratoflex, Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530, 1537, 218 USPQ 871, 877 (Fed. Cir. 1983), the Court noted that "the question under 35 U.S.C. § 103 is not whether the differences [between the claimed invention and the prior art] would have been obvious" but "whether the claimed invention *as a whole* would have been obvious." (emphasis in original).

3. Determine the Level of Skill in the Art

Office personnel should evaluate the prior art from the standpoint of the hypothetical person having ordinary skill in the art at the time the claimed invention was made. See, *Ryko Manufacturing Co.* v. *Nu-Star Inc.*, 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991) ("The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry."); *Uniroyal Inc.* v. *Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050, 5 USPQ2d 1434, 1438 (Fed. Cir.), *cert. denied*, 488 U.S. 825 (1988) (evidence must be viewed from position of ordinary skill, not of an expert). In most cases, the only facts of record pertaining to the level of skill in the art will be found within the prior art reference. However, any additional evidence presented by applicant should be evaluated.

4. Determine Whether One of Ordinary Skill in the Art Would Have Been Motivated to Select the Claimed Species or Subgenus

In light of the findings made relating to the three *Graham* factors, Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. See, e.g., *Ochiai*, 71 F.3d at 1569–70, 37 USPQ2d at 1131; *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943–44 (Fed. Cir. 1992); *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901; *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). See also *In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996) (discussing motivation to combine). To address this key issue, Office personnel should consider all relevant prior art teachings, focusing on the following, where present.

(a) Consider the Size of the Genus

Consider the size of the prior art genus, bearing in mind that size alone cannot support an obviousness rejection. See, e.g., *Baird*, 16 F.3d at 383, 29 USPQ2d at 1552 (observing that "it is not the mere number of

compounds in this limited class which is significant here but, rather, the total circumstances involved"). There is no absolute correlation between the size of the prior art genus and a conclusion of obviousness. *Id.* Thus, the mere fact that a prior art genus contains a small number of members does not create a *per se* rule of obviousness. Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., *Deuel*, 51 F.3d at 1558–59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); *Baird*, 16 F.3d at 382–83, 29 USPQ2d at 1552; *Bell*, 991 F.2d at 784, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."). However, a genus may be so small that it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds inherently anticipated a claimed species within the genus because "one skilled in [the] art would...envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original). *Accord In re Schaumann*, 572 F.2d 312, 316, 197 USPQ 5, 9 (CCPA 1978) (prior art genus encompassing claimed species which disclosed preference for lower alkyl secondary amines and properties possessed by the claimed compound constituted description of claimed compound for purposes of 35 U.S.C. § 102(b)). *C.f., In re Ruschig*, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965) (Rejection of claimed compound in light of prior art genus based on *Petering* is not appropriate where the prior art does not disclose a small recognizable class of compounds with common properties.).

(b) Consider the Express Teachings

If the prior art reference expressly teaches a particular reason to select the claimed species or subgenus, Office personnel should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed invention. An express teaching may be based on a statement in the prior art reference such as an art recognized equivalence. For example, see *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807, 10 USPQ2d 1843, 1846 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989) (holding claims directed to diuretic compositions comprising a specific mixture of amiloride and hydrochlorothiazide were obvious over a prior art reference expressly teaching that amiloride was a pyrazinoylguanidine which could be coadministered with potassium excreting diuretic agents, including hydrochlorothiazide which was a named example, to produce a diuretic with desirable sodium and potassium eliminating properties). See also, *In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1312 (Fed. Cir. 1996) (holding there is sufficient motivation to combine teachings of prior art to achieve claimed invention where one reference specifically refers to the other).

(c) Consider the Teachings of Structural Similarity

Consider any teachings of a "typical," "preferred," or "optimum" species or subgenus within the disclosed genus. If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."). The utility of such properties will normally provide some motivation to make the claimed species or subgenus. See *Id.*

In making an obviousness determination, Office personnel should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention. See, e.g., *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic); *In re Susi*, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (the difference from the particularly preferred subgenus of the prior art was a hydroxyl group, a difference conceded by applicant "to be of little importance."). In the area of biotechnology, an exemplified species may differ from a claimed species by a

conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid . . . [which] is generally expected to lead to either no change or only a small change in the properties of the protein." *Dictionary of Biochemistry and Molecular Biology 97* (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., *Molecular Cell Biology 51* (2d ed. 1990).

The closer the physical and chemical similarities between the claimed species or subgenus and any exemplary species or subgenus disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner to the genus. See, e.g., *Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (and cases cited therein). *C.f. Baird*, 16 F.3d at 382–83, 29 USPQ2d at 1552 (disclosure of dissimilar species can provide teaching away).

Similarly, consider any teaching or suggestion in the reference of a preferred species or subgenus that is significantly different in structure from the claimed species or subgenus. Such a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness. *Baird*, 16 F.3d at 382–83, 29 USPQ2d at 1552 (reversing obviousness rejection of species in view of large size of genus and disclosed "optimum" species which differed greatly from and were more complex than the claimed species); *Jones*, 958 F.2d at 350, 21 USPQ2d at 1943 (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic). For example, teachings of preferred species of a complex nature within a disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus. *Baird*, 16 F.3d at 382, 29 USPQ2d at 1552. See also *Jones*, 958 F.2d at 350, 21 USPQ2d at 1943 (disclosed salts of genus held not sufficiently similar in structure to render claimed species *prima facie* obvious).

Concepts used to analyze the structural similarity of chemical compounds in other types of chemical cases are equally useful in analyzing genus–species cases. For example, a claimed tetra–orthoester fuel composition was held to be obvious in light of a prior art tri–orthoester fuel composition based on their structural and chemical similarity and similar use as fuel additives. *Dillon*, 919 F.2d at 692–93, 16 USPQ2d at 1900–02. Likewise, claims to amitriptyline used as an antidepressant were held obvious in light of the structural similarity to imipramine, a known antidepressant prior art compound, where both compounds were tricyclic dibenzo compounds and differed structurally only in the replacement of the unsaturated carbon atom in the center ring of amitriptyline with a nitrogen atom in imipramine. *In re Merck & Co.*, 800 F.2d 1091, 1096–97, 231 USPQ 375, 378–79 (Fed. Cir. 1986). Similarly, a claimed protein compound having an amino acid sequence including Met–Phe–Pro–Leu–$(Asp)_4$–Lys–Y was held to be obvious in light of structural similarities to the prior art. One reference provided motivation to create fusion proteins in the forms X–$(Asp)_4$–Lys–Y. Other references taught positioning Met at the start of the amino acid sequence and that the sequences Phe–Pro–Ile or Leu–Pro–Leu could serve as X in the basic formula. The known structural similarity of Ile and Leu meant that appellants merely substituted one element known in the art for a known equivalent. Thus, the substitution was held to be obvious. *In re Mayne*, 104 F.3d 1339, 1342–43, 41 USPQ2d 1451, 1454–55 (Fed. Cir. 1997). Other structural similarities have been found to support a *prima facie* case of obviousness; e.g., *In re May*, 574 F.2d 1082, 1093–95, 197 USPQ 601, 610–11 (CCPA 1978) (stereoisomers); *In re Wilder*, 563 F.2d 457, 460, 195 USPQ 426, 429 (CCPA 1977) (adjacent homologs and structural isomers); *In re Hoch*, 428 F.2d 1341, 1344, 166 USPQ 406, 409 (CCPA 1970) (acid and ethyl ester); *In re Druey*, 319 F.2d 237, 240, 138 USPQ 39, 41 (CCPA 1963) (omission of methyl group from pyrazole ring). Generally, some teaching of a structural similarity will be necessary to suggest selection of the claimed species or subgenus. *Id.*

(d) Consider the Teachings of Similar Properties or Uses

Consider the properties and utilities of the structurally similar prior art species or subgenus. It is the properties and utilities that provide real world motivation for a person of ordinary skill to make species structurally similar to those in the prior art. *Dillon*, 919 F.2d at 697, 16 USPQ2d at 1905; *In re Stemniski*, 444 F.2d 581, 586, 170 USPQ 343, 348 (CCPA 1971). Conversely, lack of

any known useful properties weighs against a finding of motivation to make or select a species or subgenus. *In re Albrecht*, 514 F.2d 1389, 1392, 1395–96, 185 USPQ 585, 587, 590 (CCPA 1975) (The prior art compound so irritated the skin that it could not be regarded as useful for the disclosed anesthetic purpose, and therefore a person skilled in the art would not have been motivated to make related compounds.); *Stemniski*, 444 F.2d at 586, 170 USPQ at 348 (close structural similarity alone is not sufficient to create a *prima facie* case of obviousness when the reference compounds lack utility, and thus there is no motivation to make related compounds.). However, the prior art need not disclose a newly discovered property in order for there to be a *prima facie* case of obviousness. *Dillon*, 919 F.2d at 697, 16 USPQ2d at 1904–05 (and cases cited therein). If the claimed invention and the structurally similar prior art species share a useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species: e.g., *id.* For example, based on a finding that a tri–orthoester and a tetra–orthoester behave similarly in certain chemical reactions, it has been held that one of ordinary skill in the relevant art would have been motivated to select either structure. *Id.* at 692, 16 USPQ2d at 1900–01. In fact, similar properties may normally be presumed when compounds are very close in structure. *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have 'very close' structural similarities and similar utilities, without more a *prima facie* case may be made."). Thus, evidence of similar properties weighs in favor of a conclusion that the claimed invention would have been obvious. *Dillon*, 919 F.2d at 697–98, 16 USPQ2d at 1905; *In re Wilder*, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

(e) Consider the Predictability of the Technology

Consider the predictability of the technology. See, e.g., *Dillon, 919 F.2d at 692–97, 16 USPQ2d at 1901–05; In re Grabiak*, 769 F.2d 729, 732–33, 226 USPQ 870, 872 (Fed. Cir. 1985). If the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious because it may not be reasonable to infer that they would share similar properties. See, e.g., *In re May*, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA 1978) (*prima facie* obviousness of claimed analgesic compound based on structurally similar prior art isomer was rebutted with evidence demonstrating that analgesia and addiction properties could not be reliably predicted on the basis of chemical structure); *In re Schechter*, 205 F.2d 185, 191, 98 USPQ 144, 150 (CCPA 1953) (unpredictability in the insecticide field, with homologs, isomers and analogs of known effective insecticides having proven ineffective as insecticides, was considered as a factor weighing against a conclusion of obviousness of the claimed compounds). However, obviousness does not require absolute predictability, only a reasonable expectation of success; *i.e.*, a reasonable expectation of obtaining similar properties. See, e.g., *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

(f) Consider Any Other Teaching to Support the Selection of the Species or Subgenus

The categories of relevant teachings enumerated above are those most frequently encountered in a genus–species case, but they are not exclusive. Office personnel should consider the totality of the evidence in each case. In unusual cases, there may be other relevant teachings sufficient to support the selection of the species or subgenus and, therefore, a conclusion of obviousness.

5. Make Express Fact–Findings And Determine Whether They Support A *Prima Facie* Case of Obviousness

Based on the evidence as a whole (*In re Bell*, 991 F.2d 781,784, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990)), Office personnel should make express fact–findings relating to the *Graham* factors, focusing primarily on the prior art teachings discussed above. The fact–findings should specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus. *Kulling*, 897 F.2d at 1149, 14 USPQ2d at 1058; *Panduit Corp.* v. *Dennison Mfg. Co.*, 810 F.2d 1561, 1579 n.42, 1 USQP2d 1593, 1606 n.42 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Thereafter, it should be determined whether these findings, considered as a whole, support a *prima facie* case that the claimed invention would have been obvious to one of ordinary skill in the relevant art at the time the invention was made.

B. Determining Whether Rebuttal Evidence Is Sufficient To Overcome the *Prima Facie* Case of Obviousness

If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901. Rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094–95 (Fed. Cir. 1995), or by way of an affidavit or declaration under 37 CFR 1.132, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687; *In re Piasecki*, 745 F.2d 1468, 1474, 223 USPQ 785, 789–90 (Fed. Cir. 1984). However, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139–40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Office personnel should consider all rebuttal arguments and evidence presented by applicants. See, e.g., *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995) (error not to consider evidence presented in the specification). *C.f., In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996) (error not to consider factual evidence submitted to counter a 35 U.S.C. 112 rejection); *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042–43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.); *Piasecki*, 745 F.2d at 1472, 223 USPQ at 788 ("[Rebuttal evidence] may relate to any of the *Graham* factors including the so–called secondary considerations."). Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others." *Graham* v. *John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. See also, e.g., *In re Piasecki*, 745 F.2d 1468, 1473, 223 USPQ 785, 788 (Fed. Cir. 1984) (commercial success). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692–93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343–44, 41 USPQ2d 1451, 1455 (Fed. Cir. 1997) (conclusory statements that claimed compound posesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome *prima facie* case of obviousness).Rebuttal evidence may include evidence that the claimed invention was copied by others. See, e.g., *In re GPAC*, 57 F.3d 1573, 1580, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Hybritech Inc.* v. *Monoclonal* Antibodies, 802 F.2d 1367, 1380, 231 USPQ 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). It may also include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich*, 579 F.2d 86, 91–92, 198 USPQ 210, 214 (CCPA 1978) (Expert opinions regarding the level of skill in the art were probative of the nonobviousness of the claimed invention.); *Piasecki*, 745 F.2d at 1471, 1473–74, 223 USPQ at 790 (Evidence of nontechnological nature is pertinent to the conclusion of obviousness. The declarations of those skilled in the art regarding the need for the invention and its reception by the art were improperly discounted by the Board); *Beattie*, 974 F.2d at 1313, 24 USPQ2d at 1042–43 (Seven declarations provided by music teachers opining that the art teaches away from the claimed invention must be considered, but were not probative because they did not contain facts and did not deal with the specific prior art that was the subject of the rejection.).

Consideration of rebuttal evidence and arguments requires Office personnel to weigh the proffered evidence and arguments. Office personnel should avoid giving evidence no weight, except in rare circumstances. *Id.* See also *In re Alton*, 76 F.3d 1168, 1174–75, 37 USPQ2d 1578, 1582–83 (Fed. Cir. 1996). However, to be entitled to substantial weight, the applicant should establish a nexus between the rebuttal evidence and the claimed invention, *i.e.*, objective evidence of nonobviousness must be attributable to the claimed invention. The Federal Circuit has acknowledged that applicant bears the burden of establishing nexus, stating:

> In the ex parte process of examining a patent application, however, the PTO lacks the means or resources to gather evidence which supports or refutes the applicant's assertion that the sales constitute commercial success. C.f. Ex parte Remark, 15 USPQ2d 1498, 1503 ([BPAI] 1990) (evidentiary routine of shifting burdens in civil proceedings inappropriate in ex parte prosecution proceedings because examiner has no available means for adducing evidence). Consequently, the PTO must rely upon the applicant to provide hard evidence of commercial success.

In re Huang, 100 F.3d 135, 139–40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996). See also *GPAC*, 57 F.3d at 1580, 35 USPQ2d at 1121; In re Paulsen, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994) (Evidence of commercial success of articles not covered by the claims subject to the 35 U.S.C. 103 rejection was not probative of nonobviousness). Additionally, the evidence must be reasonably commensurate in scope with the claimed invention. See also, e.g., *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). *In re Soni*, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995) does not change this analysis. In *Soni*, the Court declined to consider the Office's argument that the evidence of nonobviousness was not commensurate in scope with the claim because it had not been raised by the Examiner (54 F.3d at 751, 34 USPQ2d at 1688).

When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. *Id.*

For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.). But see, *Grasselli*, 713 F.2d at 743, 218 USPQ at 778 (evidence of superior properties for sodium containing composition insufficient to establish the non–obviousness of broad claims for a catalyst with "an alkali metal" where it was well known in the catalyst art that different alkali metals were not interchangeable and applicant had shown unexpected results only for sodium containing materials); *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (evidence of superior properties in one species insufficient to establish the nonobviousness of a subgenus containing hundreds of compounds); *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (one test not sufficient where there was no adequate basis for concluding the other claimed compounds would behave the same way). However, an exemplary showing may be sufficient to establish a reasonable correlation between the showing and the entire scope of the claim, when viewed by a skilled artisan. See, e.g., *Chupp*, 816 F.2d at 646, 2 USPQ2d at 1439; *Clemens*, 622 F.2d at 1036, 206 USPQ at 296. On the other hand, evidence of an unexpected property may not be sufficient regardless of the scope of the showing. Where the claims are not limited to a particular use, and where the prior art provides other motivation to select a particular species or subgenus, a showing of a new use may not be sufficient to confer patentability. See *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1900–01. Accordingly, each case should be evaluated individually based on the totality of the circumstances.

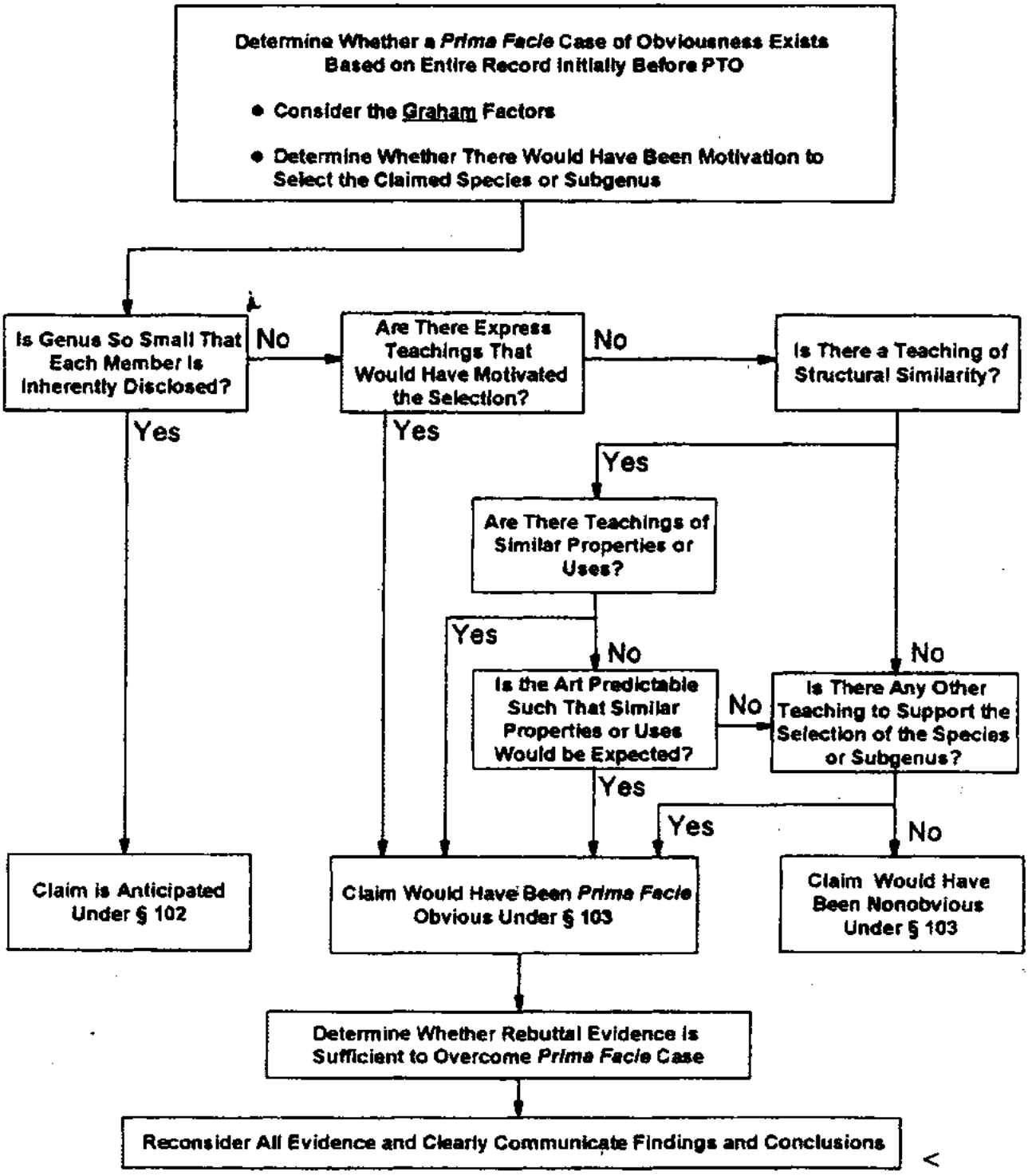
Office personnel should not evaluate rebuttal evidence for its "knockdown" value against the *prima facie* case, *Piasecki*, 745 F.2d at 1473, 223 USPQ at 788, or summarily dismiss it as not compelling or insufficient. If the evidence is deemed insufficient to rebut the *prima facie* case of obviousness, Office personnel should specifically set forth the facts and reasoning that justify this conclusion.

III. Reconsider All Evidence and Clearly Communicate Findings and Conclusions

A determination under 35 U.S.C. 103 should rest on all the evidence and should not be influenced by any earlier conclusion. See, e.g., *Piasecki*, 745 F.2d at 1472–73, 223 USPQ at 788; *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Thus, once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. See, e.g., *Piasecki*, 745 F.2d at 1472, 223 USPQ at 788; *Eli Lilly*, 902 F.2d at 945, 14 USPQ2d at 1743. All the proposed rejections and their bases should be reviewed to confirm their correctness. Only then should any rejection be imposed in an Office action. The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings.

Where applicable, the findings should clearly articulate which portions of the reference support any rejection. Explicit findings on motivation or suggestion to select the claimed invention should also be articulated in order to support a 35 U.S.C. 103 ground of rejection. *Dillon*, 919 F.2d at 693, 16 USPQ2d at 1901; *In re Mills*, 916 F.2d 680, 683, 16 USPQ2d 1430, 1433 (Fed. Cir. 1990). Conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute sufficient factual findings.

If the closest prior art is a single reference disclosing a genus, determine whether the claimed species or subgenus would have been obvious to one of ordinary skill in the pertinent art at the time the invention was made by performing the following analysis...



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161 Trinh

GAU 1203 1617

PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#14/Suppl. Response M. Watts 5/12/98

In re Application of:	)	
Hervé BOUCHARD et al.	)	
Serial No.: 08/622,011	)	Group Art Unit: 1203
Filed: March 26, 1996	)	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

APR 27 1998 RECEIVED

Sir:

SUPPLEMENTAL RESPONSE

In response to the Office Action dated February 25, 1998, Applicants filed an Amendment, along with a Declaration of Dr. Commerçon, on April 23, 1998, following an interview of the same date. Since the Examiner suggested hand delivery of the papers during the afternoon of April 23, Applicants diligently prepared the same on an expedited basis following the interview. Although it is believed to be clear from the April 23 papers, Applicants wish to emphasize one point discussed at the interview just to make sure the record is complete.

Specifically, Applicants made clear at the interview that, in accord with their position of record, referenced in the April 23 papers and particularly as set forth in the Amendment filed October 28, 1997, and Dr. Commerçon's

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Declaration, submitted therewith, an alkoxy group, such as methoxy, is not, in view of the teachings as a whole of the art of record, a hydroxy-protecting group at the 7- and 10-positions of the claimed compound recited in pending product claim 17 or in any of the other compound claims that have been canceled without prejudice or disclaimer. This conclusion is dictated by the requirement of the art of record that hydroxy protecting groups are groups that can be "hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents." *See, e.g.*, Col. 9, lines 19-21 of the '601 patent. Dr. Commerçon's October 1997 declaration demonstrated that in the claimed compound, the methoxy group at each of the 7- and 10- positions is not removed by the mild conditions described in the art of record. As explained at the interview, the comparative testing presented in the Commerçon declaration of April 23, 1998, is simply in support of an alternative argument that assumes *arguendo* the correctness of the statement in Holton '601 that such a methoxy group is a hydroxy protecting group. Neither the Commerçon declaration of April 23, 1998 nor the remarks in the accompanying amendment in any way constitutes an admission that in the context of the claimed compound and the compounds in the canceled claims, an alkoxy group at the 7- and 10-positions is a hydroxy protective group. For the reasons presented in the papers hand-delivered to the Examiner or, independently, for the reasons presented in

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papers filed in October 1997, the claimed compound is patentable over all the art of record.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this response, such extension is hereby requested. If there are any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Thalia V. Warnement, Reg. No. 39064
for Thomas L. Irving
Thomas L. Irving
Reg. No. 28,619

Dated: April 24, 1998

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#13/ IDS
M. Watts
5/2/98

PATENT
Attorney Docket No. 3806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: 1203

Filed: March 26, 1996 — Examiner: B. Trinh

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), Applicants bring to the attention of the Examiner the document listed on the attached PTO 1449. This Information Disclosure Statement is being filed after the events recited in Section 1.97(b) but, to the undersigned's knowledge, before the mailing date of either a Final Action or a Notice of Allowance. Under the provisions of 37 C.F.R. § 1.97(c), this Information Disclosure Statement is accompanied by a fee of $240.00 as specified by Section 1.17(p).

A copy of the listed document is attached. Applicant respectfully requests that the Examiner consider the listed document and indicate that it was considered by making appropriate notation on the attached form.

This submission does not represent that a search has been made or that no

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better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claims in the application and Applicants determine that the cited document does not constitute "prior art" under United States law, Applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the document be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Date: April 24, 1998

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 305/14, 409/12, 407/12, A61K 31/335 — A1

(11) International Publication Number: **WO 96/00724**

(43) International Publication Date: 11 January 1996 (11.01.96)

(21) International Application Number: PCT/US95/06595

(22) International Filing Date: 7 June 1995 (07.06.95)

(30) Priority Data:
08/268,179 28 June 1994 (28.06.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/268,179 (CIP)
Filed on 28 June 1994 (28.06.94)

(71) Applicant *(for all designated States except US)*: THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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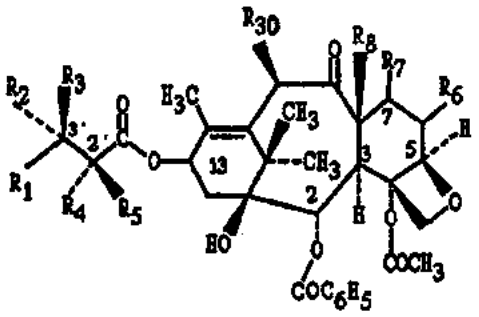
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 7-ETHER-TAXOL ANALOGS, ANTINEOPLASTIC USE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

This invention provides 7-ether-taxol analogs of formula (I). The compounds of formula (I) are useful for the treatment of the same cancers for which taxol has been shown active, including human ovarian cancer, breast cancer, and malignant melanoma as well as lung cancer, gastric cancer, colon cancer, head and neck cancer, and leukemia.



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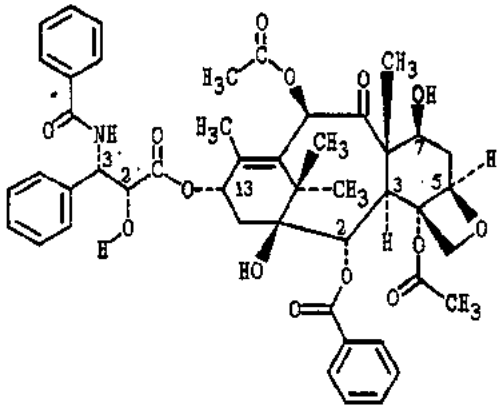
7-ETHER-TAXOL ANALOGS, ANTINEOPLASTIC USE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

Taxol is a member of the taxane family of diterpenes, having the structure shown below:



The numbering system shown for taxol is that recommended by IUPAC (IUPAC, Commission on the Nomenclature of Organic Chemistry, 1978).

The chemistry of the potent anticancer diterpenoid taxol and analogs thereof is reviewed, with an emphasis on isolation and analysis, structural modifications, partial synthesis, and structure-activity relationships by David G.I. Kingston, The Chemistry of Taxol, Pharmac. Ther., Vol 52, pp 1-34, 1991.

The clinical pharmacology of taxol is reviewed by Eric K. Rowinsky and Ross C. Donehower, The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics, Pharmac. Ther., Vol 52, pp 35-84, 1991. Clinical and preclinical studies with taxol are reviewed by William J. Slichenmyer and Daniel D. Von Hoff, Taxol: A New and Effective Anti-cancer Drug, Anti-Cancer Drugs, Vol. 2, pp 519-530, 1991.

Taxol and analogs thereof are the subject of various patents including, for example, U.S. Patent Nos. 4,814,470; 4,857,653; 4,942,184; 4,924,011; 4,924,012; 4,960,790; 5,015,744; 5,157,049; 5,059,699; 5,136,060; 4,876,399; 5,227,400; 5,248,796 as well as PCT Publication No. WO 92/09589, European Patent Application 90305845.1 (Publication No. A2 0 400 971), 90312366.9 (Publication No.

A1 0 428 376), 89400935.6 (Publication No. A1 0 366 841) and 90402333.0 (Publication No. 0 414 610 A1), 87401669.4 (A1 0 253 739), 92308608.6 (A1 0 534 708), 92308609.4 (A1 534 709) and PCT Publication Nos. WO 91/17977, WO 91/17976, WO 91/13066, WO 91/13053.

Various processes for the preparation of taxol (and intermediates and analogs thereof) are described in Tetrahedron Letters, 1992, 33, 5185; J. Org. Chem., 1991, 56, 1681 and J. Org. Chem., 1991, 56, 5114.

Chen et al., Serendipitous Synthesis of a Cyclopropane-Containing Taxol Analog via Anchimeric Participation of an Unactivated Angular Methyl Group, Advance ACS Abstracts, Vol 1, No. 2., July 15, 1993 reported the treatment of a 7-*epi* taxol derivative with DAST in dichloromethane led to an unexpected reaction involving participation of the C-19 methyl group and clean formation of a cyclopropane ring. See also J. Org. Chem., 1993, 58, 4520 (August 13, 1993) and U.S. Patent 5,254,580 (granted 19 October 1993).

U.S. Patent 5,248,796 (granted 28 September 1993) relates to 10-desacetoxy-11,12-dihydrotaxol-10,12(18)-diene derivatives and the preparation of 10-desacetoxytaxol.

EP Application 0 558 959 A1 discloses various phosphonooxy and carbonate 2' taxol derivatives of taxol with increased water solubility.

Water-soluble pro-taxol analogs are disclosed in Nicolaou, K.C.; Riemer, C.; Kerr, M.A.; Rideout, D.; Wrasidlo, W., Nature 364:464-66 (1993).

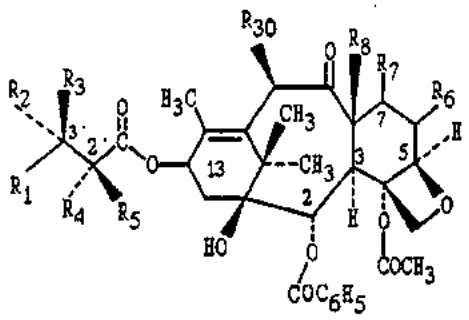
J. Am. Chem. Soc., Vol. 116, No. 4, 1599-1600 (1994) decribes the production of 7-BOM baccatin III. The 7-BOM baccatin III was treated with lithium hexamethyl disilazide and the resulting alkoxide reacted with (3R,4S)-N-benzoyl-3-O-TES-4-phenyl-2-azetedinone to give 7-BOM-2'-TES-taxol. This was reacted with HF-pyridine to give 7-BOM-taxol.

At the 207 Annual Meeting of the American Chemical Society, L. Klein described the "surprisingly good activity" of 7-ether analogs of 9-OH-taxotere, in particular the 7-OMe and the 7-allyl analogs. No method of synthesis was described.

U.S. Patent 5,229,526 (Holton) describes the use of 7-O-protecting groups (namely T^1, including triethylsilyl and ethoxyethyl) in the the preparation of various biologically active derivatives of baccatin III and 10-deacetyl baccatin III wherein the C-7 and C-2' hydroxyl protecting groups are hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents.

SUMMARY OF THE INVENTION

This invention provides taxol analogs of Formula I:



I

The compounds of Formula I are useful for the treatment of the same cancers for which taxol has been shown active, including human ovarian cancer, breast cancer, and malignant melanoma as well as lung cancer, gastric cancer, colon cancer, head and neck cancer, and leukemia.

CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula CH_3-C(=Z_1)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as taxol, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6

represents the 6 position or carbon atom number in the nucleus as traditionally designated by those skilled in the art.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by N^*=C(CH_3)-CH=CCl-CH=C^*H with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by -N^*-$(CH_2)_2$-N(C_2H_5)-CH_2-C^*H_2. Similarly, 2-furyl can be represented by -C*-O-CH=CH-C*H= and 2-thienyl represented by -C*-S-CH=CH-C*H=.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X_1)(X_2)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (β) configuration and is indicated by an unbroken line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as -C(=R_i)- might be bivalent and be defined as oxo or keto (thus forming a carbonyl group (-CO-) or as two separately attached monovalent

variable substituents α-R_{i-j} and β-R_{i-k}. When a bivalent variable, R_i, is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form "α-R_{i-j}:β-R_{i-k}" or some variant thereof. In such a case both α-R_{i-j} and β-R_{i-k} are attached to the carbon atom to give -C(α-R_{i-j})(β-R_{i-k}). For example, when the bivalent variable R_6, -C(=R_6)- is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are α-R_{6-1}:β-R_{6-2}, ... α-R_{6-9}:β-R_{6-10}, etc, giving -C(α-R_{6-1})(β-R_{6-2})-, ... -C(α-R_{6-9})(β-R_{6-10})-, etc. Likewise, for the bivalent variable R_{11}, -C(=R_{11})-, two monovalent variable substituents are α-R_{11-1}:β-R_{11-2}. For a ring substituent for which separate α and β orientations do not exist (e.g. due to the presence of a carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and β designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula -C_1(R_i)H-C_2(R_j)H- (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group -X-Y-, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form -CH_2-CH_2-O-CO- ..." means a lactone in which the carbonyl is bonded to C_2. However, when designated "... R_j and R_i are taken together to form -CO-O-CH_2-CH_2-the convention means a lactone in which the carbonyl is bonded to C_1.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C_1-C_4", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-(CH_2)$_n$-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no

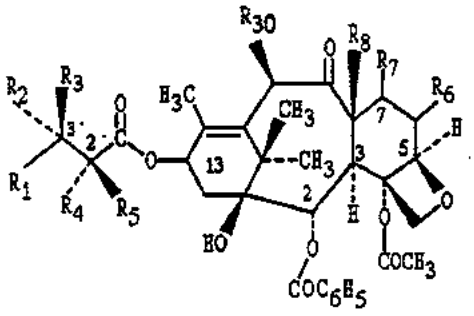
intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS/FIGURES which will also set forth the chemical structural formula of that particular substituent.

The term "Boc" refers to C(O)O-t-butyl, "Troc" refers to C(O))CH_2CCl_3, TES refers to $Si(Et)_3$, Ph refers to phenyl, Ac refers to $C(O)CH_3$, Bz refers to C(O)Ph, and Cbz refers to $C(O)OCH_2C_6H_5$.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, this invention provides 7-ether-taxol analogs of general Formula I



I

wherein:

R_1 is selected from the group consisting of

$-CH_3$,

$-C_6H_5$ or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino,

hydroxy or nitro,

-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or

3,4-methylenedioxyphenyl;

R_2 is selected from the group consisting of -H, -NHC(O)H,-NHC(O)C_1-C_{10}alkyl (preferably -NHC(O)C_4-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -NHC(O)C(CH$_3$)=CHCH$_3$, -NHC(O)OC(CH$_3$)$_3$, -NHC(O)OCH$_2$phenyl, -NH$_2$, -NHSO$_2$-4-methylphenyl, -NHC(O)(CH$_2$)$_3$COOH, -NHC(O)-4-(SO$_3$H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH$_2$C(CH$_3$)$_3$, -NHC(O)C(CH$_3$)$_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -NHC(O)C_3-C_8cycloalkyl, -NHC(O)OC(CH$_2$CH$_3$)$_2$CH$_3$, -NHC(O)OC(CH$_3$)$_2$CH$_2$Cl, -NHC(O)OC(CH$_3$)$_2$CH$_2$CH$_3$, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH$_3$)$_3$ or -NHC(O)NHC(CH$_3$)$_3$;

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH$_3$)$_3$, with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH$_3$), -OC(O)OCH$_2$C(Cl)$_3$, -OCOCH$_2$CH$_2$NH$_3^+$ HCOO$^-$, -NHC(O)phenyl, -NHC(O)OC(CH$_3$)$_3$, -OCOCH$_2$CH$_2$COOH and pharmaceutically acceptable salts thereof, -OCO(CH$_2$)$_3$COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH$_2$CH$_2$-), propylene (-CH$_2$CH$_2$CH$_2$-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -NR'$_2$R'$_3$, -OR'$_3$, -SR'$_3$, -OCH$_2$C(O)NR'$_4$R'$_5$ where R'$_2$ is -H or -CH$_3$, R'$_3$ is -(CH$_2$)$_n$NR'$_6$R'$_7$ or (CH$_2$)$_n$N$^+$R'$_6$R'$_7$R'$_8$ X$^-$ where n is 1-3, R'$_4$ is -H or -C_1-C_4alkyl, R'$_5$ is -H, -C_1-C_4alkyl, benzyl, hydroxyethyl, -CH$_2$CO$_2$H or dimethylaminoethyl, R'$_6$ and R'$_7$ are -CH$_3$, -CH$_2$CH$_3$, benzyl or R'$_6$ and R'$_7$ together with the nitrogen of NR'$_6$R'$_7$ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'$_8$ is -CH$_3$, -CH$_2$CH$_3$ or benzyl , X$^-$ is halide, and base is NH$_3$, (HOC$_2$H$_4$)$_3$N, N(CH$_3$)$_3$, CH$_3$N(C$_2$H$_4$)$_2$NH, NH$_2$(CH$_2$)$_6$NH$_2$, N-methylglucamine, NaOH or KOH], -OC(O)(CH$_2$)$_n$NR^{2}R^3 [where n is 1-3, R^2 is -H or -C_1-C_3alkyl and R^3 -H or -C_1-C_3alkyl], -OC(O)CH(R")NH$_2$ [where R" is selected from the group consisting of -H, -CH$_3$, -CH$_2$CH(CH$_3$)$_2$, -CH(CH$_3$)CH$_2$CH$_3$, -CH(CH$_3$)$_2$, -CH$_2$phenyl, -(CH$_2$)$_4$NH$_2$, -CH$_2$CH$_2$COOH, -(CH$_2$)$_3$NHC(=NH)NH$_2$], the residue of the amino acid proline,

$-OC(O)CH=CH_2$, $-C(O)CH_2CH_2C(O)NHCH_2CH_2SO_3^- Y^+$,
$-OC(O)CH_2CH_2C(O)NHCH_2CH_2CH_2SO_3^-Y^+$ wherein Y^+ is Na^+ or $N^+(Bu)_4$,
$-OC(O)CH_2CH_2C(O)OCH_2\ CH_2OH$;

R_5 is -H or -OH, with the overall proviso that when R_5 is -OH, R_4 is -H and with the further proviso that when R_5 is -H, R_4 is other than -H;

R_6 is -H:-H;

R_7 is α-R_{91}:β-R_{92} where one of R_{91} and R_{92} is -H and the other of R_{91} and R_{92} is -W where W is selected from the group consisting of

$-O-C_1-C_{10}$alkyl,

$-O-C_3-C_{10}$ unsaturated alkyl (preferably allyl and crotyl),

$-O-C_5-C_{15}$ heteroalkyl [e.g. $-OCH_2$(2- or 3-furyl), $-OCH_2$(2- or 3-pyrrolyl), $-OCH_2$(2-, 3- or 4-pyridyl), $-OCH_2$(2-, 3-, 4-, 5-, 6, 7- or 8-quinolinyl), $-OCH_2$(1-, 3-, 4-, 5-, 6, 7- or 8-isoquinolinyl), $-OCH_2$(2-, 4- or 5-imidazoyl), $-OCH_2$(3-, 4- or 5-pyrazolyl), $-OCH_2$(2-pyrazinyl), $-OCH_2$(2-, 4-, 5- or 6-pyrimidinyl), $-OCH_2$(2-, 3-, 4-, 5-, 6- or 7-indolyl), $-OCH_2$(3-, 4- or 5-isoxazolyl); preferably $-OCH_2$(2- or 3-furyl), $-OCH_2$(2- or 3-pyrrolyl), $-OCH_2$(2-, 3- or 4-pyridyl), $-OCH_2$(2-, 4- or 5-imidazoyl) or $-OCH_2$(3-, 4- or 5-isoxazolyl)],

$-O-CH(R^{21})OR^{22}$ where

R^{21} is -H or $-C_1-C_6$ alkyl, and

R^{22} is $-C_1-C_{10}$alkyl, $-C_3-C_{10}$ unsaturated alkyl (preferably allyl and crotyl), $-C_5-C_{15}$ heteroalkyl [e.g. CH_2-(2- or 3-furyl), CH_2(2- or 3-pyrrolyl), CH_2(2-, 3, or 4-pyridyl), CH_2(2-, 3-, 4-, 5-, 6, 7- or 8-quinolinyl), CH_2(1-, 3-, 4-, 5-, 6, 7- or 8-isoquinolinyl), CH_2(2-, 4- or 5-imidazoyl), CH_2(3-, 4- or 5-pyrazolyl), CH_2(2-pyrazinyl), CH_2(2-, 4-, 5- or 6-pyrimidinyl), CH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl), CH_2(3-, 4- or 5-isoxazolyl); preferably CH_2-(2- or 3-furyl), CH_2(2- or 3-pyrrolyl), CH_2(2-, 3, or 4-pyridyl), CH_2(2-, 4- or 5-imidazoyl), CH_2(3-, 4- or 5-isoxazolyl); preferably CH_2-(2- or 3-furyl), CH_2(2- or 3-pyrrolyl), CH_2(2-, 3, or 4-pyridyl), CH_2(2-, 4- or 5-imidazoyl) or CH_2(3-, 4- or 5-isoxazolyl)],

or when R^{21} and R^{22} are taken together to form a ring with 4 to 6 carbon atoms (preferably a ring with 5 or 6 carbon atoms),

$-CH(R^{28})S(O)_mAr$

where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

$-CH(R^{28})S(O)_mCH_2R^{28}$ where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (preferably allyl and crotyl),

-$(CH_2)_q$phenyl where q is 0-6,

-$(CH_2)_q$phenyl where q is 0-6 and substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-naphthyl,

-naphthyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-C_5-C_{15} heteroalkyl [e.g. -(2- or 3-furyl), (2- or 3-pyrrolyl), (2-, 3, or 4-pyridyl), (2-, 3-, 4-, 5-, 6, 7- or 8-quinolinyl), (1-, 3-, 4-, 5-, 6, 7- or 8-isoquinolinyl), (2-, 4- or 5-imidazoyl), (3-, 4- or 5-pyrazolyl), (2-pyrazinyl), (2-, 4-, 5- or 6-pyrimidinyl), (2-, 3-, 4-, 5-, 6- or 7-indolyl), (3-, 4- or 5-isoxazolyl); preferably -(2- or 3-furyl), (2- or 3-pyrrolyl), (2-, 3, or 4-pyridyl), (2-, 4- or 5-imidazoyl), (3-, 4- or 5-isoxazolyl)],

or when R^{28} and R^{28} are taken together to form a ring with 4 to 6 carbon atoms (preferably a ring with 5 or 6 carbon atoms);

m is O to 2;

R_8 is $-CH_3$;

R_{30} is -H, OH, or $-OC(O)CH_3$; and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

An embodiment of the subject invention are compounds of Formula I where position 2 is $-OR_{40}$ (where R_{40} is -C(O)phenyl substituted with one, 2 or 3 azido, cyano, methoxy, or halo; preferably -C(O)-3-azidophenyl) rather than -O-C(O)phenyl.

A preferred embodiment of the subject invention is compounds of Formula I where R_1 is phenyl or phenyl substituted with halo, R_2 is $-NHC(O)C_6H_5$, R_3 and R_5 are -H, R_4 is -OH, and R_{30} is -OH or $-OC(O)CH_3$. Another preferred embodiment of the subject invention is compounds of Formula I where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is $-NHC(O)OC(CH_3)_3$, R_3 and R_5 are -H, R_4 is -OH, and R_{30} is -H or $-COCH_3$. A preferred embodiment of the subject invention is compounds of Formula I where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is $-NHC(O)NHC(CH_3)_3$, R_3 and R_5 are -H, R_4 is -OH, and R_{30} is -OH or $-OCOCH_3$.

W is preferably selected from the group consisting of:

-O-C_1-C_{10}alkyl (more preferably -O-C_1-C_{10}alkyl);

-O-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-O-CH(R^{21})OR^{22} where

R^{21} is H or C_1-C_6 alkyl, and

R^{22} is preferably -C_1-C_6alkyl or -C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-CH(R^{28})S(O)$_m$Ar where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

-CH(R^{28})S(O)$_m$CH_2R^{28}

where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl), or

-(CH_2)$_q$phenyl where q is 0-3; and

m is 0.

An embodiment of the subject invention are compounds of Formula I where R_2 is -NHC(O)C_6H_5, R_4 is hydroxy, R_3 and R_5 are -H, R_1 is phenyl or substituted phenyl, and -W is selected from the group consisting of:

-O-C_1-C_{10}alkyl (more preferably -O-C_1-C_{10}alkyl);

-O-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-O-CH(R^{21})OR^{22} where

R^{21} is H or C_1-C_6 alkyl, and

R^{22} is preferably -C_1-C_6alkyl or -C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-CH(R^{28})S(O)$_m$Ar where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

-CH(R^{28})S(O)$_m$CH_2R^{28}

where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl), or

-(CH_2)$_q$phenyl where q is 0-3; and

m is 0.

Another embodiment of the subject invention are compounds of Formula I

where R_2 is -NHC(O)OC$(CH_3)_3$, R_1 is phenyl or substituted phenyl, R_4 is hydroxy, R_3 and R_5 are -H, and -W is selected from the group consisting of:

-O-C_1-C_{10}alkyl (more preferably -O-C_1-C_{10}alkyl);

-O-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-O-CH(R^{21})OR^{22} where

R^{21} is H or C_1-C_6 alkyl, and

R^{22} is preferably -C_1-C_6alkyl or -C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl);

-CH(R^{28})S(O)$_m$Ar where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

-CH(R^{28})S(O)$_m$$CH_2R^{28}$

where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (more preferably -O-C_3-C_4 unsaturated alkyl), or

-$(CH_2)_q$phenyl where q is 0-3; and

m is 0.

An embodiment of the subject invention are compounds of Formula I where R_1 is selected from the group consisting of -CH_3, -C_6H_5 or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro and R_2 is selected from the group consisting of -H, -NHC(O)H,-NHC(O)C_1-C_{10}alkyl (preferably -NHC(O)C_4-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -NHC(O)C(CH_3)=$CHCH_3$, -NHC(O)OC$(CH_3)_3$, -NHC(O)OCH_2phenyl, -NH_2, -$NHSO_2$-4-methylphenyl, -NHC(O)$(CH_2)_3$COOH, -NHC(O)-4-(SO_3H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH_2C$(CH_3)_3$, -NHC(O)C$(CH_3)_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -NHC(O)C_3-C_8cycloalkyl, -NHC(O)OC$(CH_2CH_3)_2CH_3$, -NHC(O)OC$(CH_3)_2CH_2$Cl, -NHC(O)OC$(CH_3)_2CH_2CH_3$, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC$(CH_3)_3$ or -NHC(O)NHC$(CH_3)_3$.

Additional preferred embodiments of Formula I include:

7-(O-ethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (4),

7-(O-methoxyethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (6),

7-(O-methoxymethyl)-13-(N-Boc-2'-β-phenyl isoserinyl)-baccatin III (8),

7-(O-benzyloxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (10),

7-[O-(2,2,2-trichloroethoxy)methyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (21),

7-[O-(2,2,2-trichloroethoxy)methoxymethyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (22),

7-(O-methylthiomethyl) taxol (42),

7-(O-methylthiomethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (44) and

7-(O-phenylthiomethyl) taxol (46);

7-O-methyl Taxol (47)

7-[O-ethyl(1-thioethyl)] Taxol (49)

13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (55)

13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56)

13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (58)

more preferably:

7-(O-ethoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (14) and

7-(O-methoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (27).

A preferred embodiment of the subject invention are compounds of Formula I where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is $-NHC(O)NHC(CH_3)_3$, R_3 and R_5 are -H, R_4 is -OH, and R_{30} is -OH or $-OCOCH_3$.

The compounds of Formula I include both the 7-α and 7-β configuration of the 7-ether substitution.

Preferred members of the moiety $-O-C_5-C_{15}$ heteroalkyl include:

OCH_2-(2- or 3-furyl), OCH_2(2- or 3-pyrrolyl), OCH_2(2-, 3, or 4-pyridyl),. OCH_2(2-, 4- or 5-imidazoyl) and OCH_2(3-, 4- or 5-isoxazolyl).

An embodiment of the present invention are 7-deoxy-7-W-taxol analogs of general Formula I wherein:

R_1 is selected from the group consisting of $-CH_3$, $-C_6H_5$ or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro;

R_2 is selected from the group consisting of -H, $-NHC(O)C_1$-C_{10}alkyl

(preferably -NHC(O)C_4-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -NHC(O)$C(CH_3)$=$CHCH_3$, -NHC(O)$OC(CH_3)_3$, -NH_2, -$NHSO_2$-4-methylphenyl, -NHC(O)$(CH_2)_3$COOH, -NHC(O)-4-(SO_3H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)$CH_2C(CH_3)_3$, -NHC(O)$C(CH_3)_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, -NHC(O)$NHC(CH_3)_3$, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -NHC(O)C_3-C_8cycloalkyl;

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)$OC(CH_3)_3$; with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH_3), -OC(O)$OCH_2C(Cl)_3$, -$OCOCH_2CH_2NH_3^+$ $HCOO^-$, -NHC(O)phenyl, -NHC(O)$OC(CH_3)_3$, -$OCOCH_2CH_2COOH$ and pharmaceutically acceptable salts thereof, -$OCO(CH_2)_3$COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -$NR'_2R'_3$, -OR'_3, -SR'_3, -$OCH_2C(O)NR'_4R'_5$ where R'_2 is -H or -CH_3, R'_3 is -$(CH_2)_nNR'_6R'_7$ or $(CH_2)_nN^+R'_6R'_7R'_8$ X^- where n is 1-3, R'_4 is -H or -C_1-C_4alkyl, R'_5 is -H, -C_1-C_4alkyl, benzyl, hydroxyethyl, -CH_2CO_2H or dimethylaminoethyl, R'_6 and R'_7 are -CH_3, -CH_2CH_3, benzyl or R'_6 and R'_7 together with the nitrogen of $NR'_6R'_7$ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'_8 is -CH_3, -CH_2CH_3 or benzyl , X^- is halide, and base is NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4)_2NH$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH or KOH], -OC(O)$(CH_2)_nNR^2R^3$ [where n is 1-3, R^2 is -H or -C_1-C_3alkyl and R^3 -H or -C_1-C_3alkyl], -OC(O)$CH(R'')NH_2$ [where R'' is selected from the group consisting of -H, -CH_3, -CH_2CH $(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -$CH(CH_3)_2$, -CH_2phenyl, -$(CH_2)_4NH_2$, -CH_2CH_2COOH, -$(CH_2)_3$ $NHC(=NH)NH_2$], the residue of the amino acid proline, -OC(O)CH=CH_2, -$C(O)CH_2CH_2C(O)NHCH_2CH_2SO_3^-$ Y^+, -OC(O)CH_2 $CH_2C(O)NHCH_2CH_2CH_2SO_3^-Y^+$ wherein Y^+ is Na^+ or $N^+(Bu)_4$, -OC(O)$CH_2CH_2C(O)OCH_2$ CH_2OH;

R_5 is -H or -OH, with the overall proviso that when R_5 is -OH, R_4 is -H and with the further proviso that when R_5 is -H, R_4 is other than -H;

R_{30} is -H, -OH or -OC(O)CH_3; and

pharmaceutically acceptable salts thereof when the compound contains either an

acidic or basic functional group.

Another embodiment of the present invention are 7-deoxy-7-W-taxol analogs of general Formula I wherein:

R_1 is selected from the group consisting of $-CH_3$, $-C_6H_5$ or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro;

R_2 is selected from the group consisting of -H, $-NHC(O)C_1$-C_{10}alkyl (preferably $-NHC(O)C_4$-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, $-NHC(O)C(CH_3)=CHCH_3$, $-NHC(O)OC(CH_3)_3$, $-NH_2$, $-NHSO_2$-4-methylphenyl, $-NHC(O)(CH_2)_3COOH$, -NHC(O)-4-(SO_3H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, $-NHC(O)CH_2C(CH_3)_3$, $-NHC(O)C(CH_3)_3$, $-NHC(O)OC_1$-C_{10}alkyl, $-NHC(O)NHC_1$-C_{10}alkyl, $-NHC(O)NHC(CH_3)_3$, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, $-NHC(O)C_3$-C_8cycloalkyl; and

W is selected from the group consisting of

O-methyl;

O-propyl;

O-allyl;

O-methoxymethyl;

O-ethoxymethyl;

O-methoxyethoxymethyl;

O-benzyloxymethyl;

O-(2,2,2-trichloroethoxy)methyl;

O-(2,2,2-trichloroethoxy)methoxymethyl;

O-methylthiomethyl; and

O-phenylthiomethyl

R_3, R_4, R_5 and R_{30} are as defined above.

A further preferred embodiment of the present invention are 7-deoxy-7-W-taxol analogs of general Formula I wherein:

R_1 is selected from the group consisting of $-CH_3$, $-C_6H_5$ or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro;

R_2 is selected from the group consisting of -H, $-NHC(O)C_1$-C_{10}alkyl (preferably $-NHC(O)C_4$-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with

one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -NHC(O)C(CH_3)=$CHCH_3$, -NHC(O)OC(CH_3)$_3$, -NH_2, -$NHSO_2$-4-methylphenyl, -NHC(O)(CH_2)$_3$COOH, -NHC(O)-4-(SO_3H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH_2C(CH_3)$_3$, -NHC(O)C(CH_3)$_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, NHC(O)NHC(CH_3)$_3$, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -NHC(O)C_3-C_8cycloalkyl;

W is selected from the group consisting of

O-ethoxymethyl;

O-methoxyethoxymethyl;

O-benzyloxymethyl;

O-(2,2,2-trichloroethoxy)methyl;

O-(2,2,2-trichloroethoxy)methoxymethyl;

O-methylthiomethyl; and

O-phenylthiomethyl;

and

R_3, R_4, R_5 and R_{30} are as defined above.

In compounds of Formula I, W is preferably selected from the group consisting of

O-methyl;

O-propyl;

O-allyl;

O-methoxymethyl;

O-ethoxymethyl;

O-methoxyethoxymethyl;

O-benzyloxymethyl;

O-(2,2,2-trichloroethoxy)methyl;

O-(2,2,2-trichloroethoxy)methoxymethyl;

O-methylthiomethyl; and

O-phenylthiomethyl;

more preferably

O-methoxymethyl;

O-ethoxymethyl;

O-methoxyethoxymethyl;

O-benzyloxymethyl;

O-(2,2,2-trichloroethoxy)methyl;

O-(2,2,2-trichloroethoxy)methoxymethyl;

O-methylthiomethyl; and

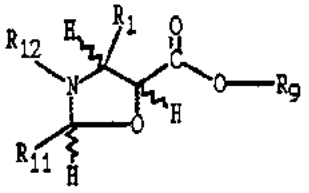
O-phenylthiomethyl.

Examples of -O-C_5-C_{15} heteroalkyl include: -OCH_2(2- or 3-furyl), -OCH_2(2- or 3-pyrrolyl), -OCH_2(2-, 3- or 4-pyridyl), -OCH_2(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -OCH_2(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -OCH_2(2-, 4- or 5-imidazoyl), -OCH_2(3-, 4- or 5-pyrazolyl), -OCH_2(2-pyrazinyl), -OCH_2(2-, 4-, 5- or 6-pyrimidinyl), -OCH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl) and -OCH_2(3-, 4- or 5-isoxazolyl).

Examples of C_1-C_6 alkyl include straight and branched alkyl chains, including for example methyl, ethyl, isopropyl, t-butyl, isobutyl and 2-methyl-pentyl.

Examples of C_1-C_3 alkoxy are methoxy, ethoxy, propoxy and isomeric forms thereof.

The present invention also provides a process for preparing oxazolidines of Formula 5



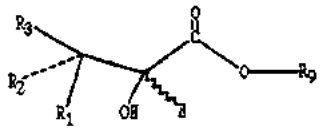
in which

R_1 is as defined above;

R_9 is selected from C_1-C_6alkyl; R_{11} is phenyl substituted with -(OC_1-C_2alkyl)$_n$ where n is 1 to 3;

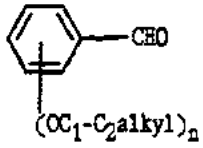
R_{12} is selected from the group consisting of -C(O)H, -C(O)C_1-C_{10}alkyl (preferably -C(O)C_4-C_6alkyl), -C(O)phenyl, -C(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -C(O)C(CH_3)=$CHCH_3$, -C(O)O$C(CH_3)_3$, -C(O)OCH_2phenyl, -SO_2-4-methylphenyl, -C(O)$(CH_2)_3$COOH, -C(O)-4-(SO_3H)phenyl, -C(O)-1-adamantyl, -C(O)O-3-tetrahydrofuranyl, -C(O)O-4-tetrahydropyranyl, -C(O)$CH_2C(CH_3)_3$, -C(O)$C(CH_3)_3$, -C(O)OC_1-C_{10}alkyl, -C(O)NHC_1-C_{10}alkyl, -C(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, or -C(O)C_3-C_8cycloalkyl, -C(O)$C(CH_2CH_3)_2CH_3$, -C(O)$C(CH_3)_2CH_2Cl$, -C(O)$C(CH_3)_2CH_2CH_3$, -C(O)-1-phenyl-1-cyclopentyl, -C(O)-1-methyl-1-cyclohexyl, -C(S)NH$C(CH_3)_3$, -C(O)NH$C(CH_3)_3$ or -C(O)NHPh;

which comprises reacting a hydroxy-amine of Formula 3

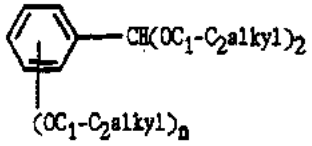


in which R_1 and R_3 are as defined above and R_2 is selected from the group consisting of -NHC(O)H,-NHC(O)C_1-C_{10}alkyl (preferably -NHC(O)C_4-C_6alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -NHC(O)C(CH_3)=$CHCH_3$, -NHC(O)OC(CH_3)$_3$, -NHC(O)OCH_2phenyl, -NHSO_2-4-methylphenyl, -NHC(O)(CH_2)$_3$COOH, -NHC(O)-4-(SO_3H)phenyl, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH_2C(CH_3)$_3$, -NHC(O)C(CH_3)$_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, or -NHC(O)C_3-C_8cycloalkyl, -NHC(O)C(CH_2CH_3)$_2CH_3$, -NHC(O)C(CH_3)$_2CH_2$Cl, -NHC(O)C(CH_3)$_2CH_2CH_3$, -NHC(O)-1-phenyl-1-cyclo-pentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH_3)$_3$, -NHC(O)NHC(CH_3)$_3$ or -NHC(O)NHPh;

with (1) an electron rich benzaldehyde of Formula 4A

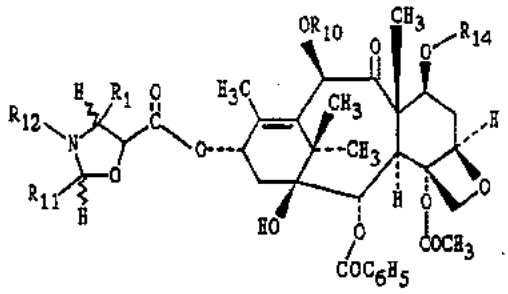


or (2) an electron rich acetal of Formula 4

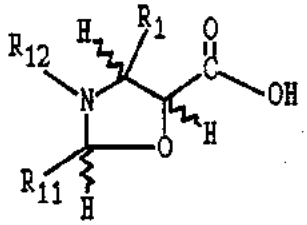


where n is 1-3.

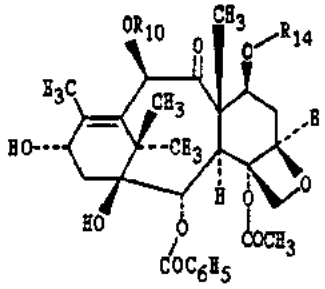
In addition, the present invention provides a process of preparing



which comprises reacting an oxazolidine free acid of Formula 7



with a baccatin compound of Formula 8



in the presence of a dehydrating agent. Wherein R_{10} and R_{14}, being the same or different, are selected from the group consisting of -C(O)C_1-C_6alkyl (preferably -$C(O)CH_3$), -C(O)OC_1-C_6alkyl, -$C(O)OCH_2CX_3$ where X is Halo, -$C(O)OCH_2CH_2SiR_{20}$ (where R_{20} is C_1-C_6 alkyl), or -$Si(R_{20})_3$ or R_{14} is is selected from the group consisting of

-C_1-C_{10}alkyl,

-C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl),

-C_5-C_{15} heteroalkyl [e.g. -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -CH_2(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-pyrazolyl), -CH_2(2-pyrazinyl), -CH_2(2-, 4-, 5- or 6-pyrimidinyl), -CH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl),

-CH_2(3-, 4- or 5-isoxazolyl); preferably -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3- or 4-pyridyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-isoxazolyl)],

-O-CH(R^{21})OR^{22} where

R^{21} is -H, -C_1-C_6 alkyl, and

R^{22} is -C_1-C_{10}alkyl, -C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl), -C_5-C_{15} heteroalkyl [e.g. -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -CH_2(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-pyrazolyl), -CH_2(2-pyrazinyl), -CH_2(2-, 4-, 5- or 6-pyrimidinyl), -CH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl), -CH_2(3-, 4- or 5-isoxazolyl); preferably -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-isoxazolyl)]

or when R^{21} and R^{22} are taken together to form a ring with 4 to 6 carbon atoms,

-CH(R^{28})S(O)$_m$Ar

where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

or

-CH(R^{28})S(O)$_m$$CH_2$$R^{28}$

where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl),

-(CH$_2$)$_q$phenyl where q is 1-6,

-(CH$_2$)$_q$phenyl where q is 1-6 and substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-naphthyl,

-naphthyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-C_5-C_{15} heteroalkyl [e.g. -(2- or 3-furyl), -(2- or 3-pyrrolyl), -(2-, 3, or 4-pyridyl), -(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -(2-, 4- or 5-imidazoyl), -(3-, 4- or 5-pyrazolyl), - (2-pyrazinyl), (2-, 4-, 5- or 6-pyrimidinyl), -(2-, 3-, 4-, 5-, 6- or 7-indolyl), -(3-, 4- or 5-isoxazolyl); preferably -(2- or 3-furyl), -(2- or 3-pyrrolyl), -(2-, 3, or 4-pyridyl), -(2-, 4- or 5-imidazoyl), -(3-, 4- or 5-isoxazolyl)]

or when R^{28} and R^{28} are taken together to form a ring with 4 to 6 carbon

atoms;

m is O to 2; and

R_{11} and R_{12} are as defined above.

The compounds of this invention (Formula I) may be prepared by the procedure(s) as shown in Charts A', A", A'" and B.

As used in Charts 2-20, the terms R_{20}, R_{23}, R_{24}, R_{25}, R_{26} and R_{27} are defined as follows:

R_{20} is selected from the group consisting of

-C_1-C_{10}alkyl,

-C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl),

-C_5-C_{15} heteroalkyl [e.g. -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -CH_2(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-pyrazolyl), -CH_2(2-pyrazinyl), -CH_2(2-, 4-, 5- or 6-pyrimidinyl), -CH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl), -CH_2(3-, 4- or 5-isoxazolyl); preferably -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3- or 4-pyridyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-isoxazolyl)],

-O-CH(R^{21})OR^{22} where

R^{21} is -H, -C_1-C_6 alkyl, and

R^{22} is -C_1-C_{10}alkyl, -C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl), -C_5-C_{15} heteroalkyl [e.g. -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -CH_2(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-pyrazolyl), -CH_2(2-pyrazinyl), -CH_2(2-, 4-, 5- or 6-pyrimidinyl), -CH_2(2-, 3-, 4-, 5-, 6- or 7-indolyl), -CH_2(3-, 4- or 5-isoxazolyl); preferably -CH_2(2- or 3-furyl), -CH_2(2- or 3-pyrrolyl), -CH_2(2-, 3, or 4-pyridyl), -CH_2(2-, 4- or 5-imidazoyl), -CH_2(3-, 4- or 5-isoxazolyl)]

or when R^{21} and R^{22} are taken together to form a ring with 4 to 6 carbon atoms,

-CH(R^{28})S(O)$_m$Ar

where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

or

-CH(R^{28})S(O)$_m$$CH_2$$R^{28}$

where R^{28} is

C_1-C_6 alkyl,

-C_3-C_{10} unsaturated alkyl (preferably allyl, crotyl),

-$(CH_2)_q$phenyl where q is 1-6,

-$(CH_2)_q$phenyl where q is 1-6 and substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-naphthyl,

-naphthyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -C_5-C_{15} heteroalkyl [e.g. -(2- or 3-furyl), -(2- or 3-pyrrolyl), -(2-, 3, or 4-pyridyl), -(2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl), -(1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl), -(2-, 4- or 5-imidazoyl), -(3-, 4- or 5-pyrazolyl), - (2-pyrazinyl), (2-, 4-, 5- or 6-pyrimidinyl), -(2-, 3-, 4-, 5-, 6- or 7-indolyl), -(3-, 4- or 5-isoxazolyl); preferably -(2- or 3-furyl), -(2- or 3-pyrrolyl), -(2-, 3, or 4-pyridyl), -(2-, 4- or 5-imidazoyl), -(3-, 4- or 5-isoxazolyl)]

or when R^{28} and R^{28} are taken together to form a ring with 4 to 6 carbon atoms;

m is 0 to 2;

R_{23} is selected from the group consisting of -H, -C_1-C_{10}alkyl (preferably -C_4-C_6alkyl), -phenyl, -phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, -$C(CH_3)$=$CHCH_3$, -$OC(CH_3)_3$, -OCH_2phenyl, -SO_2-4-methylphenyl, -$(CH_2)_3COOH$, -4-(SO_3H)phenyl, -1-adamantyl, -O-3-tetrahydrofuranyl, -O-4-tetrahydropyranyl, -$CH_2C(CH_3)_3$, -$C(CH_3)_3$, -OC_1-C_{10}alkyl, -NHC_1-C_{10}alkyl, -NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, or -C_3-C_8cycloalkyl, -$C(CH_2CH_3)_2CH_3$, -$C(CH_3)_2CH_2Cl$, -$C(CH_3)_2CH_2CH_3$, --1-phenyl-1-cyclopentyl, -1-methyl-1-cyclohexyl, -C(S)$NHC(CH_3)_3$, -$NHC(CH_3)_3$ or -NHPh.

R_{24} is preferably Troc and TES.

R_{25} is phenyl substituted with -$(OC_1$-C_2alkyl$)_n$ where n is 1 to 3;

R_{26} is -H; and

R_{27} is selected from the group consisting of -$C(O)C_1$-C_6alkyl (preferably -$C(O)CH_3$), -$C(O)OC_1$-C_6alkyl, -$C(O)OCH_2CX_3$ where X is Halo, -$C(O)OCH_2CH_2SiR_{20}$ (where R_{20} is C_1-C_6 alkyl), or -$Si(R_{20})_3$, preferably Troc and TES.

The preparation of 3-azido-2-hydroxy-carboxylic acid esters 1 may be prepared as described in the literature (see Denis, J-N.; Correa, A.; Greene, A. E. J.

Org. Chem., 1990, *55*, 1957). These materials are readily hydrogenated to the free amines 2, even though the literature intentionally avoids this intermediate by preparing the hydroxy-acylated intermediate prior to the reduction of the azide. The amine 2 is sufficiently stable that no problem is encountered in isolating it and directly using it to prepare the N-acylated free hydroxy compounds 3. Compounds 3 have been utilized by protection of the hydroxy group, hydrolysis of the ester to the acid, and condensation directly with a baccatin III derivative or after conversion to the oxazinone (European Patent 0 428 376 A1, US 436235). These procedures are distinctly inferior because they require large excesses of the acylating agent and generally do not proceed beyond about 60% completion. Procedures have also been described using a beta-lactam intermediate but these also require large excesses of reagent or the introduction of very strong bases such as LDA which makes them more difficult to perform and unsuitable for certain analogs (Ojima, I.; Habus, I.; Zhao, M.; George, G. I.; Jayasinghe, L. R. *J. Org. Chem.*, 1991, *56*, 1681, EP 0 400 971 A2). A very effective condensation procedure involving the conversion of the hydroxy-amine derivative 3 to an oxazolidine with 2 non hydrogen substituents at the 2 position was described by Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. in *Tetrahedron Lett.*, 1992, *33*, 5185 and Patent WO 92/09589. The condensation proceeds in very high yield but the removal of the protecting group requires sufficiently strong acid that sensitive taxol analogs are destroyed under the deprotection conditions. We have modified and improved this procedure by formation of the oxazolidines 5 not with a ketone, as the above workers have used but, with an electron rich benzaldehyde 4.

Such chemistry was recently described by Didier, E.; Fouque, E.; Taillepied, I, Commercon, A. Tetrahedron Lett. 1994, 35, 2349. The oxazolidines derived from the benzaldehyde 4 are produced as a mixture of diastereomers but these have been separated in some cases and the diastereomers have been shown to be equally useful when carried on in the synthesis. The oxazolidines 5 are readily hydrolyzed to the salts 6 and the acids 7. The acid is labile and needs to be used shortly after preparation. Both oxazolidine isomers are equally effective in the condensation reaction with the protected baccatins 8 giving an excellent yield of the oxazolidine protected taxol analogs 9. More importantly, both oxazolidine isomers from these electron rich benzaldehydes are readily hydrolyzed under very mild acid conditions allowing deprotection without causing undesired transformations of highly acid sensitive taxol derivatives such as 10 which are the subject of this invention. There are references to the use of electron rich aldehydes for the protection of 1,2-diols as

dioxolanes but no previous reference to the use of such aldehydes for the protection of 2-hydroxy protected amines except for the Didier reference cited above. The deprotection may be carried out such that both the oxazolidine and the 7 protected hydroxyl of 9 are removed at the same time or each may be removed independently. Additionally described is the deprotection of selected urethane analogs 10 to the free amine 11 (Chart B). These are then reconverted to a variety of amine acylated analogs 10.

The conversion of azide 1 to the amine 2 is effected by reduction as is known in the art. Thus, the reaction may be carried out by hydrogenation in the presence of a variety of hydrogenation catalysts such as palladium, platinum, rhodium, or ruthenium. Alternatively, the azide may be reduced by treatment with a phosphine such as triphenyl or tributyl phosphine or by an acid such as hydrochloric, sulfuric, trifluoroacetic or hydrobromic in the presence of a metal such as zinc, iron, or tin. These reactions may be effected in a solvent such as ethanol, methanol, ethyl acetate, methyl t-butyl ether or tetrahydrofuran and the like. The conversion of amine 2 to its acylated derivative 3 is effected by treatment of the amine in pyridine or a non basic solvent such as methylene chloride or tetrahydrofuran containing a tertiary amine such as triethyl amine or ethyl diisopropyl amine with an acylation agent. If 3 is a urethane, 2 is treated with an agent such as benzylchloroformate, 2,2,2-trichloroethoxycarbonyl chloride, di-tert-butyldicarbonate, or other urethane forming agent as is known in the art. If 3 is an amide, 2 is treated with an acylating agent such as an acyl halide, and acyl anhydride, or other acylating agent as is known in the art. If 3 is a urea or a thiourea, 2 is treated with an agent such as alkyl or aryl isocyanate, alkyl or aryl isothiocyanate, or other urea or thiourea forming agent as is known in the art.

An alternate method for the preparation of compounds of formula 3 (where $R_2 = R_{12}NH$-, R_3 = -H, and R_9 = -H) is shown in Chart A". The penultimate compound shown in Chart A" is a compound of formula 3 wherein $R_2 = R_{12}NH$-, R_3 = -H, and R_9 = -*t*-Bu. In Chart A", TMS is a trimethylsilyl group, TMSCl is chlorotrimethylsilane, and LDA is lithium diisopropyl amide.

Another alternate method for the preparation of compounds of formula 3 (where $R_2 = R_{12}NH$-, R_3 = -H, and R_9 = -H) is shown in Chart A'". In Chart A'", Ts is a *p*-toluenesulfonyl (tosyl) group.

The hydroxy acids prepared in Charts A" and A'" may further be converted to compounds of formula 3 where $R_2 = R_{12}NH$-, R_3 = -H, and $R_9 = -CH_3$ by reaction with diazomethane or esterification by other methods known in the art.

The hydroxy amide or urethane 3 is converted to the oxazolidine 5 by treatment with an electron rich benzaldehyde or its acetal such as dimethyl or diethyl acetal 4 and an acid catalyst such as p-toluene sulfonic acid, pyridinium p-toluene sulfonate or other acid catalysts known in the art in a solvent such as tetrahydrofuran, toluene, methylene chloride, or other aprotic solvent. Examples of electron rich benzaldehydes include but are not limited to 2-, 3-, 4-methoxybenzaldehyde; 2,4-, 3,5-, 2,5-dimethoxybenzaldehyde; 2,4,6-trimethoxybenzaldehyde; and 4-ethoxybenzaldehyde. The preferred benzaldehyde is 2,4-dimethoxybenzaldehyde. The oxazolidine formation is generally carried out by heating to reflux to distill both the solvent and to carry off the evolved water or alcohol. The ester of 5 is hydrolyzed to the salt 6 by treatment with an alkali or quaternerary amine hydroxide or by an alkali carbonate or other base as known in the art in a solvent such as water, methanol, ethanol, or other protic solvent. The reaction may by carried out from -78°C to 100°C. The product 6 is stable and may be isolated by evaporation of the solvents and stored as a solid or the reaction may be used directly to convert 6 to the acid 7 by treatment with acid. Generally, 7 is obtained by treating an aqueous solution of 6 in a separatory funnel with sufficient acid such as hydrochloric, sulfuric, potassium hydrogen sulfate, or the like, and partitioning the desired acid into an organic solvent such as ethyl acetate, methylene chloride, ether, or the like and evaporation of the solvent. The resultant acid 7 is sufficiently pure and stable for use in the next reaction but in general is not sufficiently stable for long term storage. The acid 7 is condensed with the baccatin derivative 8 to form the ester 9 with a dehydrating agent. Most preferred for this procedure is a carbodiimide such as dicyclohexyl carbodiimide, diisopropyl carbodiimide, di-p-tolyl carbodiimide, ethyl dimethylaminopropyl carbodiimide hydrochloride salt, or the like, and a basic catalyst, preferably 4-dimethylamino-pyridine. The reaction is generally carried out in an aprotic solvent such as toluene, benzene, tetrahydrofuran, dioxane, or the like at 25°C to 100°C. Other dehydration procedures for the formation of 9 may be used such as conversion of 7 to its mixed ester with a sulfonic acid such as with toluenesulfonyl chloride or benzenesulfonyl chloride, or formation of the acid halide from the dried 6 in the presence of oxalyl chloride as is known in the art for acid sensitive carboxylic acids. The oxazolidines 9 may be deprotected so that the protecting oxazolidine and the groups blocking the hydroxyl at the baccatin 7 position are individually removed in either order or both removed together depending on the protecting group at the 7 position and on the reaction conditions. If R_{14} is an acid labile group such as a silyl ether, then

hydrolysis of the oxazolidine may be run under mild acid conditions and leads to the 7 position deprotection as well, giving 10MZ directly. Conditions for such conversions include hydrolysis in aqueous acetic acid, aqueous alcoholic acid of 0.01 to 0.1 N at 0°C to 50°C, or alcoholic acid of 0.01 to 0.1 N at 0°C to 50°C.

Alternatively, the protection at the 7 position could be removed at a second step if it is not acid labile. For example, the trichloroethoxycarbonyl group at position 7 could be removed from 10MY (Chart B) by reduction as is known in the art to give 10MZ. Depending on the nature of the protecting group on the nitrogen (i.e. R_2 or R_3) of 10MZ (Chart B) the protecting group can be removed to give 11Z. For example, when R_2 is $PhCH_2OC(O)NH$, it may be removed by mild hydrogenolysis. Conditions for such conversions include reduction with hydrogen over a metal catalyst such as palladium in a solvent such as ethanol or ethyl acetate at room temperature and from one to three atmospheres of pressure. Other methods are known in the art. The resultant amine 11Z may be reconverted to a amide or urethane 10MZ (Chart B) by acylation procedures as described for the conversion of 2 to 3 above. The product 10MZ may be protected on the 2' hydroxyl to give 12MZ (Chart B). For example, the 2' hydroxyl may be acylated with trichloroethoxycarbonyl chloride in pyridine or other aromatic amine solvents, or in a non basic solvent such as toluene, methylene chloride, or tetrahydrofuran containing a tertiary amine base. The reaction may be run at -50°C to 100°C. Other methods for such acylations are well known in the art.

The reaction of taxol, taxol analogs 10MZ (R_{10} is acetate or other suitable acyl moiety), baccatin III, or baccatin III analogs 8 (R_{10} is acetate or other suitable acyl moiety) with hydrazine comprises a particularly advantageous method for preparation of 10-deacetyl taxol, 10-deacyl taxol analogs (10MZ, R_{10} = H), 10-deacetyl baccatin III, and 10-deacyl baccatin III analogs (8, R_{10} = H). Whereas the reported method (Samaranayake, G.; *et. al., J. Org. Chem.*, 1991, *56*, 5114) for removal of the acyl group from this position of taxol and baccatin structures, i.e., zinc bromide in methanol, gives a number of other products in addition to the desired deacylation product, the reaction with hydrazine gives almost exclusively the desired deacylation product. The reaction may be performed at room temperature in an organic solvent and usually requires as little time as 15 min or as much as 24 hr, depending on the substrate. The preferred solvent for the reaction is 95% ethanol and 98% hydrazine is the preferred form of the reagent.

The compounds Formula I of this invention [where R_{40} is not equal to $-C(O)C_6H_5$)] can be prepared by the procedure shown in Chart D according to the

method of Chaudhary, A. G.; *et.al.*, J. Am. Chem. Soc., 1994, *116*, 4097-8.)

A general procedure for synthesizing the compounds of Formula I is set forth below.

The taxol analog III of chart 2 may be converted to a 2'- protected derivative IV by reaction with a trialkylchlorosilane in an aprotic solvent such THF, pyridine or DMF in the presence of a base such as imidazole or pyridine or with an alkoxy-carbonylchloride such as trichloroethylchloroformate, benzyloxychloroformate or allyloxychloroformate in an aprotic solvent such as methylene chloride or pyridine and an added base such as pyridine, triethyl amine or diisopropyl ethyl amine. A taxol analog III may be converted to a 2',3'-oxazolidine derivative V as described in Chart A' for the conversion of 3 to 5.

The baccatin analog VI of chart 3 may be converted to the 7-protected baccatin VII by reaction with a trialkylchlorosilane in an aprotic solvent such THF, pyridine or DMF in the presence of a base such as imidazole or pyridine or with an alkoxycarbonylchloride such as trichloroethylchloroformate, benzyloxychloroformate or allyloxychloroformate in an aprotic solvent such as methylene chloride or pyridine and an added base such as pyridine, triethyl amine or diisopropyl ethyl amine. The 7-protected baccatin VII of chart 3 may condensed with the oxazolidine acid VIII to form the ester IX with a dehydrating agent. Most preferred for this procedure is a carbodiimide such as dicyclohexyl carbodiimide, diisopropyl carbodiimide, di-p-tolyl carbodiimide, ethyl dimethylaminopropyl carbodiimide hydrochloride salt, or the like, and a basic catalyst, preferably 4-dimethylaminopyridine. The reaction is generally carried out in an aprotic solvent such as toluene, benzene, tetrahydro-furan, dioxane, or the like at 25°C to 100°C. Other dehydration procedures for the formation of IX may be used such as conversion of VIII to its mixed ester with a sulfonic acid such as with toluenesulfonyl chloride or benzenesulfonyl chloride, or formation of the acid halide from an dried alkali metal salt of VIII in the presence of oxalyl chloride as is known in the art for acid sensitive carboxylic acids. The 7-protected oxazolidine IX may be selectively deprotected to the 7-hydroxy oxazolidine V. If R^{27} is a trialkyl silyl group the conversion of IX to V may be effected with a fluoride such as tetrabutyl ammonium fluoride, pyridinium fluoride or triethyl ammonium trihydrofluoride in an inert solvent such as THF or methylene chloride. If R^{27} is a protecting group such as trichloroethoxycarbonyl it may be removed by reduction with zinc or other metal in the presence of a weak acid such a acetic acid or ammonium chloride in an solvent such as acetic acid or methanol or aqueous mixtures of such solvents.

A 2'-protected taxol analog X of Chart 4 with R^{20} as an alkoxymethyl- or aryloxymethyl ether may be made from an 2'-protected-7-hydroxy-taxol IV by reaction with a chloromethyl alkyl or chloromethylaryl ether as is known in the art (Braun, H.; Hild, W. Angew. Chem. Int. Ed. Eng. 1984, 23, 723; Danishefsky, S.; Barbachyn, M. J. Am. Chem. Soc. 1985, 107, 7761; McCarvey, G. J.; Bajiva, J. S. J. Org. Chem. 1984, 49, 409; Falck, J. R.; Yadageri, P. J. Org. Chem. 1989, 54, 5851; Andreev, V. M.; Fonchenko, Z. V.; Cherkayev, G. V.; Mochalin, V. B.; Kheifits, L. A. Khim. Farm. Zh. 1990, 24, 50; Swindel, C. S.; Kraus, N. E.; Horwitz, S. B.; Ringel, I. J. Med. Chem. 1991, 34, 1176; Wu, Z. F.; Fraserreid, B.; Mootoo, D. R. Tetrahedron Lett. 1988, 29, 6549). A 2'-protected taxol analog X of Chart 4 with R^{20} as an alkyl-, allyl, or alkarylether may be made from an 2'-protected-7-hydroxy-taxol IV by the methods shown is charts 7-20 or by reaction with a diazo alkane or aryl diazo compound in the presence of a transition metal catalyst such as rhodium, ruthenium or palladium in an aprotic solvent such as THF, dioxane, or DMF at a temperature of -20 °C to 150 °C. A taxol analog XI may be prepared from the 2'-protected analog X by deprotection of the 2'-protecting group as is known in the art.

An oxazolidinyl-taxol analog XII of Chart 5 with R^{20} as an alkoxymethyl- or aryloxymethyl ether may be made from an oxazolidinyl-7-hydroxy-taxol V by reaction with a chloromethyl alkyl or chloromethylaryl ether as is known in the art (Braun, H.; Hild, W. Angew. Chem. Int. Ed. Eng. 1984, 23, 723; Danishefsky, S.; Barbachyn, M. J. Am. Chem. Soc. 1985, 107, 7761; McCarvey, G. J.; Bajiva, J. S. J. Org. Chem. 1984, 49, 409; Falck, J. R.; Yadageri, P. J. Org. Chem. 1989, 54, 5851; Andreev, V. M.; Fonchenko, Z. V.; Cherkayev, G. V.; Mochalin, V. B.; Kheifits, L. A. Khim. Farm. Zh. 1990, 24, 50; Swindel, C. S.; Kraus, N. E.; Horwitz, S. B.; Ringel, I. J. Med. Chem. 1991, 34, 1176; Wu, Z. F.; Fraserreid, B.; Mootoo, D. R. Tetrahedron Lett. 1988, 29, 6549.). An oxazolidinyl taxol or analog XII of Chart 5 with R^{20} as an alkyl-, allyl, or alkarylether may be made from an oxazolidinyl-7-hydroxy-taxol V by the methods shown in charts 7-20 or by reaction with a diazo alkane or aryl diazo compound in the presence of a transition metal catalyst such as rhodium, ruthenium or palladium in an aprotic solvent such as THF, dioxane, or DMF at a temperature of -20 °C to 150 °C. A taxol analog XI may be prepared from an oxazolidinyl analog XII by hydrolysis in aqueous acetic acid, aqueous alcoholic acid of 0.01 to 0.1 N at 0°C to 50°C, or alcoholic acid of 0.01 to 0.1 N at 0°C to 50° C or other method as is known in the art.

The baccatin analog VI of chart 6 may be converted to the 7-ether baccatin XIII in the same manner that IV of chart 4 is converted to X. The 7-ether baccatin

XIII of chart 6 may condensed with the oxazolidine acid VIII to form the ester XII with a dehydrating agent as described for the condensation of VII with VIII of chart 3. The oxazolidine XII may be deprotected to the analog XI as described for Chart 5.

A 2'-protected taxol 7-ether XIV of chart 7 can be prepared from a 2-protected taxol analog IV by reaction with a dialkyl sulfide and benzoyl peroxide (Medina, J. C.; Soloman, M.; Kyler, K. S. Tetrahedron Lett. 1988, 29, 3773.) or by reaction with a chloroalkylthioalkyl ether in the presence of a strong base such as sodium hydride or silver nitrate and a tertiary base such as triethyl amine or diisopropyl ethyl amine in an aprotic solvent such as THF, dioxane, or methylene chloride (Holton, R. A.; Davis, R. G. Tetrahedron Lett. 1977, 533, Suzuki, K.; Inanaga, J.; Yamaguchi, M. Chem. Lett. 1979, 1277). Similarly, a 2'-protected taxol 7-arythioalkyl ether XV of chart 7 can be prepared from a 2-protected taxol analog IV by reaction with a aryl alkyl sulfide and benzoyl peroxide (Medina, J. C.; Soloman, M.; Kyler, K. S. Tetrahedron Lett. 1988, 29, 3773.) or by reaction with a chloroalkylthioaryl ether in the presence of a strong base such as sodium hydride or silver nitrate and a tertiary base such as triethyl amine or diisopropyl ethyl amine in an aprotic solvent such as THF, dioxane, or methylene chloride (Holton, R. A.; Davis, R. G. Tetrahedron Lett. 1977, 533, Suzuki, K.; Inanaga, J.; Yamaguchi, M. Chem. Lett. 1979, 1277).

A 2'-protected taxol 7-alkylthioalkyl XIV of Chart 8 may be oxidized to a sulfoxide XVI by sodium metaperiodate and alcoholic solvent or by other method known in the art (Carrasco, M.; Jones, R. J.; Kamel S.; Rapoport, H.; Truong, T. Org. Syn. 1991, 20 29; Johnson, C.; Keiser, L. Org. Syn. Coll Vol V , 1973, 791) or by other methods known in the art. Similarly, a 2'-protected taxol 7-arythioalkyl ether XV of Chart 9 may be oxidized to a sulfoxide XVIII by sodium metaperiodate and alcoholic solvent or by other method known in the art (Carrasco, M.; Jones, R. J.; Kamel S.; Rapoport, H.; Truong, T. Org. Syn. 1991, 20 29; Johnson, C.; Keiser, L. Org. Syn. Coll Vol V , 1973, 791) or by other methods known in the art.

A 2'-protected taxol 7-alkylthioalkyl ether XIV of Chart 8 may be oxidized to a sulfone XVII by meta chloroperbenzoic acid in aprotic solvents such as methylene chloride or THF or by hydrogen peroxide in aprotic or protic solvents such as methylene chloride, methanol, or ethanol (Carpino, L. A.; McAdams, L. V. Org. Syn. Coll. Vol. VI, 1988, 403; Paquette, L. A.; Carr, R. V. C. Org. Syn, 1985, 64, 157) or by other methods known in the art. Similarly, a 2'-protected taxol 7-arylthioalkyl XV of Chart 9 may be oxidized to a sulfone XIX by meta chloroperbenzoic acid in aprotic solvents such as methylene chloride or THF or by hydrogen peroxide in

aprotic or protic solvents such as methylene chloride, methanol, or ethanol (Carpino, L. A.; McAdams, L. V. Org. Syn. Coll. Vol. VI, 1988, 403; Paquette, L. A.; Carr, R. V. C. Org. Syn, 1985, 64, 157) or by other methods known in the art.

A 2'-protected taxol 7-arylthiooxomethylether XVIII (R^{28} = H) of Chart 10 may be alkylated to a 2'-protected taxol 7-arylthiooxoalkylether XVIII (R^{28} = alkyl) by treatment with a strong base such as sodium hydride, lithium diethyl amide, lithium hexamethyl disilazide or similar strong base in an aprotic solvent such as THF, ether, dioxane or 1,2-dimethoxyethane followed by treatment with an alkylating agent such as an alkyl iodide, alkyl bromide, or alkyl alcohol sulfonate ester. Similarly, a 2'-protected taxol 7-arylthiodioxomethylether XIX (R^{28} = H) of Chart 11 may be alkylated to a 2'-protected taxol 7-arylthiodioxoalkylether XIX (R^{28} = alkyl) by treatment with a strong base such as sodium hydride, lithium diethyl amide, lithium hexamethyl disilazide or similar strong base in an aprotic solvent such as THF, ether, dioxane or 1,2-dimethoxyethane followed by treatment with an alkylating agent such as an alkyl iodide, alkyl bromide, or alkyl alcohol sulfonate ester.

A 2',3'-oxazolidine protected taxol 7-ether XXII of chart 12 can be prepared from a 2',3'-oxazolidine protected taxol analog V by reaction with a dialkyl sulfide and benzoyl peroxide (Medina, J. C.; Soloman, M.; Kyler, K. S. Tetrahedron Lett. 1988, 29, 3773.) or by reaction with a chloroalkylthioalkyl ether and a tertiary base such as triethyl amine or diisopropyl ethyl amine in an aprotic solvent such as THF, dioxane, or methylene chloride. Similarly, a 2',3'-oxazolidine protected taxol 7-arythioalkyl ether XXIII of chart 12 can be prepared from a 2',3'-oxazolidine protected taxol analog V by reaction with a aryl alkyl sulfide and benzoyl peroxide (Medina, J. C.; Soloman, M.; Kyler, K. S. Tetrahedron Lett. 1988, 29, 3773.) or by reaction with a chloroalkylthioaryl ether and a tertiary base such as triethyl amine or diisopropyl ethyl amine in an aprotic solvent such as THF, dioxane, or methylene chloride. A 2',3'-oxazolidine taxol 7-alkylthioalkyl XXII of Chart 13 may be oxidized to a sulfoxide XXIV by sodium metaperiodate and alcoholic solvent or by other method known in the art (Carrasco, M.; Jones, R. J.; Kamel S.; Rapoport, H.; Truong, T. Org. Syn. 1991, 20 29; Johnson, C.; Keiser, L. Org. Syn. Coll Vol V , 1973, 791) or by other methods known in the art. Similarly a 2',3'-oxazolidine taxol 7-arythioalkyl ether XXXIII of Chart 14 may be oxidized to a sulfoxide XXVI by sodium metaperiodate and alcoholic solvent or by other method known in the art (Carrasco, M.; Jones, R. J.; Kamel S.; Rapoport, H.; Truong, T. Org. Syn. 1991, 20 29; Johnson, C.; Keiser, L. Org. Syn. Coll Vol V , 1973, 791) or by other methods

known in the art.

A 2',3'-oxazolidine protected taxol 7-alkylthioalkyl ether XXII of Chart 13 may be oxidized to a sulfone XXV by meta chloroperbenzoic acid in aprotic solvents such as methylene chloride or THF or by hydrogen peroxide in aprotic or protic solvents such as methylene chloride, methanol, or ethanol (Carpino, L. A.; McAdams, L. V. Org. Syn. Coll. Vol. VI, 1988, 403; Paquette, L. A.; Carr, R. V. C. Org. Syn, 1985, 64, 157) or by other methods known in the art. Similarly, a 2',3'-oxazolidine protected taxol 7-arylthioalkyl XXIII of Chart 14 may be oxidized to a sulfone XXVII by meta chloroperbenzoic acid in aprotic solvents such as methylene chloride or THF or by hydrogen peroxide in aprotic or protic solvents such as methylene chloride, methanol, or ethanol (Carpino, L. A.; McAdams, L. V. Org. Syn. Coll. Vol. VI, 1988, 403; Paquette, L. A.; Carr, R. V. C. Org. Syn, 1985, 64, 157) or by other methods known in the art.

A 2',3'-oxazolidine protected taxol 7-arylthiooxomethylether XXVI (R^{28} = H) of Chart 15 may be alkylated to a 2',3'-oxazolidine protected taxol 7-arylthio-oxoalkylether XXVI (R^{28} = alkyl) by treatment with a strong base such as sodium hydride, lithium diethyl amide, lithium hexamethyl disilazide or similar strong base in an aprotic solvent such as THF, ether, dioxane or 1,2-dimethoxyethane followed by treatment with an alkylating agent such as an alkyl iodide, alkyl bromide, or alkyl alcohol sulfonate ester. Similarly, a 2',3'-oxazolidine protected taxol 7-arylthiodioxomethylether XXVII (R^{28} = H) of Chart 16 may be alkylated to a 2',3'-oxazolidine protected taxol 7-arylthiodioxoalkylether XXVII (R^{28} = alkyl) by treatment with a strong base such as sodium hydride, lithium diethyl amide, lithium hexamethyl disilazide or similar strong base in an aprotic solvent such as THF, ether, dioxane or 1,2-dimethoxyethane followed by treatment with an alkylating agent such as an alkyl iodide, alkyl bromide, or alkyl alcohol sulfonate ester.

A 2'-protected taxol 7-alkylthioalkyl XIV (Chart 17), 2'-protected taxol 7-arythioalkyl ether XV (Chart 18), 7-methylthiooxomethylether XVI (Chart 8, R^{28} = H), 7-alkylthiooxoalkylether XVI (Chart 8, R^{28} = alkyl), 7-methylthiodioxo-methylether XVII (Chart 8, R^{28} = H), 7-alkylthiodioxoalkylether XVII (R^{28} = alkyl), 7-arylthiooxomethylether XVIII (Chart 9, R^{28} = H), 7-arylthiooxoalkylether XVIII (Chart 10, R^{28} = alkyl) , 7-arylthiodioxomethylether XIX (Chart 9, R^{28} = H), or a 7-arylthiodioxoalkylether XIX (Chart 11, R^{28} = alkyl) may be desulfurized with Raney Ni (Pettit, G. R.; Van Tamelen, E. E. Organic Reactions, 1962, 12, 356) to the respective 2-protected taxol ethers XX. The 2'-protected taxol ethers XX may be deprotected to the taxol 7 ether analogs as described earlier for the conversion of XII

to XI (Chart 5).

A 2',3'-oxazolidine protected taxol 7-alkylthioalkyl XXII (Chart 19), 2',3'-oxazolidine protected taxol 7-arythioalkyl ether XXIII (Chart 20), 2',3'-oxazolidine protected taxol 7-methylthiooxomethylether XXIV (Chart 13, R^{28} = H), 2',3'-oxazolidine protected taxol 7-alkylthiooxoalkylether XXIV (Chart 13, R^{28} = alkyl), 2',3'-oxazolidine protected taxol 7-methylthiodioxomethylether XXV (Chart 13, R^{28} = H), 2',3'-oxazolidine protected taxol 7-alkylthiodioxoalkylether XXV (Chart 13, R^{28} = alkyl), 2',3'-oxazolidine protected taxol 7-arylthiooxomethylether XXVI (Chart 14, R^{28} = H), 2',3'-oxazolidine protected taxol 7-arylthiooxoalkylether XXVI (Chart 15, R^{28} = alkyl), 2',3'-oxazolidine protected taxol 7-arylthiodioxomethylether XXVII (Chart 14, R^{28} = H), or a 2',3'-oxazolidine protected taxol 7-arylthiodioxoalkylether XXVII (Chart 16, R^{28} = alkyl) may be desulfurized with Raney Ni (Pettit, G. R.; Van Tamelen, E. E. Organic Reactions, 1962, 12, 356) to the respective 2',3'-oxazolidine protected taxol ethers XXVIII. The 2',3'-oxazolidine protected taxol ethers XXVIII may be deprotected to a 7-ether analog XXI as described earlier for the conversion of XII to XI (Chart 6).

Example 1 Preparation of 13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2)

13-(N-Boc-β-phenyl isoserinyl)-baccatin III (1, 1.36 g, 1.6 mmol) is dissolved in dry pyridine (16 mL) and the solution cooled to 0°C. To this is added chlorotriethylsilane (0.3 mL, 1.76 mmol). The reaction is allowed to stir at 0°C for 2 hrs. After stirring overnight at room temperature TLC still shows the presence of some starting material. The reaction is recooled to 0°C and chlorotriethylsilane (0. 3 mL, 1.76 mmol) is added again. After each of three more two h periods additions of chlorotriethylsilane (0.2 mL, 0.25 mL, and 0.20 mL) is repeated. The reaction is then warmed to room temperature and stirred overnight. TLC then shows no starting material remaining. The solution is extracted twice with saturated $CuSO_4$. The aqueous layers are re-extracted with ethyl acetate. The organic layers are combined, filtered through sodium sulfate, and concentrated in vacuo. The residue is chromatographed over a column of silica gel (150 g) packed in 1:9 EtOAc: Hexane. The column is eluted with (1:9) EtOAc: Hexane (300 mL), (1:4) EtOAc: Hexane (1 L), (1:3) EtOAc: Hexane (500 mL), and (1:1) EtOAc: Hexane (1 L) collecting 70 mL fractions. 13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 1.24 g 80% yield) as a white solid is found on evaporation of fractions 53-69.

Proton NMR ($CDCl_3$; TMS): δ 0.39 (m, 6H); 0.78 (m, 9H); 1.90 (m, 4H); 2.25 (s, 3H); 2.39 (m); 2.53 (s); 2.50-2.63 (m); 3.83 (d, 1H); 4.20 (d, 1H); 4.34 (d, 1H); 4.47

(m, 1H); 4.55 s, 1H); 5.00 (d, 1H); 5.28 (m, 1H); 5.49 (m, 1H); 5.68 (d, 1H); 6.30 (m, 2H); 7.28 (m); 7.37 (m, 2H); 7.50 (m, 2H); 7.61 (m, 1H); 8.12 (d, 2H)

Mass Spec (FAB-High Res.) Theory: 964.4514 Found: 964.4528

Example 2 Preparation of 7-(O-ethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (3)

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 100mg, 0.104mM) is stirred at RT under nitrogen in methylene chloride (1 mL). To the solution are added chloromethyl ethyl ether (58 mL, 0.624 mM) and diisopropylethyl amine (109 mL, 0.624 mM). After 2 days the reaction is found to be complete by TLC. The reaction is then partitioned between methylene chloride-water. The layers are separated and the water layer re-extracted with methylene chloride. The organic layers are dried over sodium sulfate, combined and evaporated under vacuum. The crude product is chromatographed over silica gel (10 g), eluting with (20-80) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 13-28, which upon combining and evaporating under vacuum leave 7-(O-ethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (3, 104 mg, 98% yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.48

Proton NMR ($CDCl_3$; TMS): δ 0.3-0.50 (m, 6H); 0.74-0.84 (t, 9H); 1.10-1.20 (t, 3H); 1.21 (s, 3H); 1.26 (s, 3H); 1.33 (s, 9H); 1.76 (s, 3H); 1.96 (s, 3H); 2.21 (s, 3H); 2.33-2.46 (m, 1H); 2.52 (s, 3H); 2.78-2.94 (m, 1H); 3.35-3.48 (m, 1H); 3.60-3.74 (m, 1H); 3.85-3.94 (d, 1H); 4.10-4.20 (m, 1H); 4.15-4.23 (d, 1H); 4.30-4.37 (d, 1H); 4.56 (s, 1H); 4.75 (s, 2H); 4.92-5.00 (d, 1H); 5.20-5.33 (bd, 1H); 5.43-5.55 (bd, 1H); 5.64-5.73 (d, 1H); 6.20-6.31 (t, 1H); 6.37 (s, 1H); 7.14-7.34 (m, 3H); 7.34-7.43 (t, 2H); 7.43-7.55 (t, 2H); 7.55-7.64 (t, 1H); 8.08-8.16 (d, 2H).

Example 3 Preparation of 7-(O-ethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (4)

7-(O-ethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (3, 104 mg, 0.102mM) is stirred at RT under nitrogen in 0.1N HCl in MeOH (1 mL, prepared from 71 mL acetyl chloride and 10 mL MeOH). TLC after 15 min shows no starting material to be present. The reaction is then partitioned between ethyl acetate-5% sodium bicarbonate. The layers are separated and the water layer re-extracted with ethyl acetate. The organic layers are dried over sodium sulfate, combined and evaporated under vacuum. The crude product is chromatographed

over 10g silica gel, eluting with (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 17-29, which upon combining and evaporating under vacuum leave 7-(O-ethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (4, 71mg, 77% yield) as a white solid.

TLC (silica gel): 40-60 acetone-hexane; R_f: 0.64

Proton NMR ($CDCl_3$; TMS): δ 1.10-1.20 (t, 3H); 1.21 (s, 3H); 1.22 (s, 3H); 1.35 (s, 9H); 1.75 (s, 3H); 1.88 (s, 3H); 2.21 (s, 3H); 2.36 (s, 3H); 2.76-2.90 (m, 1H); 3.33-3.49 (m, 1H); 3.55 (bs, 1H); 3.59-3.73 (m, 1H); 3.80-3.90 (d, 1H); 4.03-4.22 (m, 2H); 4.24-4.34 (d, 1H); 4.61 (bs, 1H); 4.73 (s, 2H); 4.86-4.96 (d, 1H); 5.19-5.31 (bd, 1H); 5.41-5.54 (bd, 1H); 5.60-5.70 (d, 1H); 6.09-6.23 (t, 1H); 6.34 (s, 1H); 7.25-7.43 (m, 5H); 7.43-7.54 (t, 2H); 7.54-7.65 (t, 1H); 8.00-8.13 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 908.4089; theory for $C_{48}H_{62}N_1O_{18}$ is 908.4068; 908, 627, 585, 105, 59, 57.

Example 4 Preparation of 7-(O-methoxyethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (5)

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 100mg, 0.104mM) is stirred at RT under nitrogen in methylene chloride (1 mL) and the solution treated with MEM chloride (71 mL, 0.624 mM) and diisopropylethyl amine (109 mL, 0.624 mM). The reaction is allowed to react for 2 days, at which point it is still incomplete. Additional MEM chloride (71 mL, 0.624 mM) and disopropylethyl amine (109 mL, 0.624 mM) is added. The reaction is allowed to react for 3 more days, when reaction is found to be complete. The reaction is partitioned between methylene chloride-water. The layers are separated and the water layer re-extracted with methylene chloride. The organic layers are dried over sodium sulfate, combined and evaporated under vacuum. The crude product is chromatographed over silica gel (11 g), eluting with 20-80 acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. 7-(O-methoxyethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (5, 101 mg, 93% yield) as a white solid is found in fractions 17-37 after combining and evaporating under vacuum.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.44

Proton NMR ($CDCl_3$; TMS): δ 0.3-0.51 (m, 6H); 0.75-0.85 (t, 9H); 1.21 (s, 3H); 1.26 (s, 3H); 1.33 (s, 9H); 1.76 (s, 3H); 1.95 (s, 3H); 2.20 (s, 3H); 2.31-2.45 (m, 1H); 2.52 (s, 3H); 2.80-2.95 (m, 1H); 3.35 (s, 3H); 3.47-3.60 (m, 1H); 3.51 (s, 2H); 3.70-3.82 (m, 1H); 3.86-3.95 (d, 1H); 4.13-4.24 (m, 2H); 4.29-4.37 (d, 1H); 4.55 (s, 1H); 4.75-4.87 (q, 2H); 4.92-5.00 (d, 1H); 5.20-5.34 (bd, 1H); 5.44-5.56 (bd, 1H); 5.65-

5.73 (d, 1H); 6.19-6.33 (t, 1H); 6.36 (s, 1H); 7.23-7.43 (m, 5H); 7.44-7.54 (t, 2H); 7.54-7.64 (t, 1H); 8.06-8.16 (d, 2H).

Example 5 Preparation of 7-(O-methoxyethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (6)

7-(O-methoxyethoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (5, 101 mg, 0.096mM) is stirred at RT under nitrogen in (80-20) HOAc-water (2 mL). The reaction is found to be complete by TLC in 5 hours. The reaction mixture is then freeze-dried. The crude product is chromatographed over silica gel (10g), eluting with (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. 7-(O-methoxyethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (6, 90 mg, 100 % yield) as a white solid is found in fractions 23-48 upon combining and evaporating under vacuum.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.27

Proton NMR ($CDCl_3$; TMS): δ 1.20 (s, 3H); 1.24 (s, 3H); 1.35 (s, 9H); 1.75 (s, 3H); 1.87 (s, 3H); 2.21 (s, 3H); 2.36 (s, 3H); 2.81-2.96 (m, 1H); 3.34 (s, 3H); 3.50 (s, 2H); 3.46-3.60 (m, 1H); 3.66 (bs, 1H); 3.72-3.82 (m, 1H); 3.82-3.91 (d, 1H); 4.08-4.23 (m, 2H); 4.26-4.36 (d, 1H); 4.63 (bs, 1H); 4.73-4.85 (m, 2H); 4.88-4.98 (d, 1H); 5.21-5.34 (bd, 1H); 5.52-5.62 (bd, 1H); 5.62-5.71 (d, 1H); 6.14-6.26 (t, 1H); 6.33 (s, 1H); 7.28-7.43 (m, 5H); 7.43-7.55 (t, 2H); 7.56-7.68 (t, 1H); 8.02-8.16 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 938.4166; theory for $C_{49}H_{64}N_1O_{17}$ is 938.4174; 938, 882, 878, 657, 105, 89, 59, 57.

Example 6 Preparation of 7-(O-methoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (7)

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 100 mg, 0.104mM) is stirred at RT under nitrogen in dry THF (1 mL) and the solution treated with chloromethyl methyl ether (47 mL, 0.624 mM) and diisopropylethyl amine (109 mL, 0.624 mM). The reaction is allowed to stand at RT overnight, during which the THF evaporates to about one half volume and a precipitate forms. The precipitate is redissolved by the addition of methylene chloride (0.5 mL). The reaction is found to be incomplete at this point by TLC, so it is concentrated to one half volume and treated with chloromethyl methyl ether (47 mL, 0.624 mM) and diisopropylethyl amine (109 mL, 0.624 mM). The reaction is then allowed to proceed an additional 4 days, when reaction is complete. The reaction is partitioned between methylene chloride-water. The layers are separated and the water layer re-extracted with

methylene chloride. The organic layers are dried over sodium sulfate, combined and evaporated under vacuum. The crude product is chromatographed over silica gel (10 g), eluting with (20-80) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 15-26, which upon combining and evaporating under vacuum leave 7-(O-methoxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (7, 76 mg, 72 % yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.44

Proton NMR ($CDCl_3$; TMS): δ 0.3-0.52 (m, 6H); 0.74-0.85 (t, 9H); 1.22 (s, 3H); 1.26 (s, 3H); 1.33 (s, 9H); 1.77 (s, 3H); 1.97 (s, 3H); 2.21 (s, 3H); 2.32-2.47 (m, 1H); 2.53 (s, 3H); 2.75-2.90 (m, 1H); 3.30 (s, 3H); 3.86-3.94 (d, 1H); 4.10-4.20 (m, 1H); 4.15-4.24 (d, 1H); 4.30-4.36 (d, 1H); 4.56 (s, 1H); 4.63-4.70 (d, 1H); 4.70-4.79 (d, 1H); 4.92-5.02 (d, 1H); 5.22-5.34 (bd, 1H); 5.44-5.56 (bd, 1H); 5.67-5.74 (d, 1H); 6.20-6.30 (t, 1H); 6.39 (s, 1H); 7.24-7.34 (m, 3H); 7.34-7.44 (t, 2H); 7.45-7.55 (t, 2H); 7.56-7.65 (t, 1H); 8.07-8.16 (d, 2H).

Example 7 Preparation of 7-(O-methoxymethyl)-13-(N-Boc-2'-β-phenyl isoserinyl)-baccatin III (8)

7-(O-Methoxymethy)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (7, 76 mg, 0.075mM) is dissolved at RT under nitrogen in (80-20) HOAc-water (2 mL). After a few minutes, a precipitate forms. The precepitate is redissolved by the addition of THF (2 ml). The reaction is allowed to stand for 1.5 days, some of the THF evaporating. At this point the reaction if found to be complete by TLC. The reaction mixture is then freeze-dried. The crude product is chromatographed over silica gel (10 g) silica gel, eluting with (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 15-29, which upon combining and evaporating under vacuum leave 7-(O-methoxymethyl)-13-(N-Boc-2'-β-phenyl isoserinyl)-baccatin III (8, 63 mg, 94 % yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.28

Proton NMR ($CDCl_3$; TMS): δ 1.21 (s, 3H); 1.23 (s, 3H); 1.35 (s, 9H); 1.76 (s, 3H); 1.90 (s, 3H); 2.21 (s, 3H); 2.37 (s, 3H); 2.72-2.87 (m, 1H); 3.29 (s, 3H); 3.56 (bs, 1H); 3.80-3.90 (d, 1H); 4.04-4.20 (m, 2H); 4.25-4.34 (d, 1H); 4.54-4.68 (d, 1H); 4.58 (bs, 1H); 4.68-4.75 (d, 1H); 4.87-4.96 (d, 1H); 5.20-5.31 (bd, 1H); 5.42-5.56 (bd, 1H); 5.62-5.70 (d, 1H); 6.10-6.23 (t, 1H); 6.36 (s, 1H); 7.24-7.44 (m, 5H); 7.44-7.54 (t, 2H); 7.54-7.66 (t, 1H); 8.01-8.13 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 894.3943; theory for $C_{47}H_{60}N_1O_{16}$ is 894.3912; 894, 838, 613, 571, 553, 105, 57.

Example 8 Preparation of 7-Benzyloxymethyl-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (9)

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 100mg, 0.104mM) is stirred at RT under nitrogen in methylene chloride (1 ML) and the solution treated with benzyl chloromethyl ether (104 mL, 0.624 mM, 80% pure) and diisopropylethyl amine (109 mL, 0.624 mM). The reaction is allowed to stand for 2 days, when it is complete as found by TLC. The reaction is then partitioned between methylene chloride-water. The layers are separated and the water layer re-extracted with methylene chloride. The organic layers are dried over sodium sulfate, combined and evaporated under vacuum. The crude product is chromatographed over silica gel (15 g), eluting with (20-80) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 19-33, which upon combining and evaporating under vacuum leave 7-(O-benzyloxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (9, 92 mg, 81 % yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f 0.50

Proton NMR ($CDCl_3$; TMS): δ 0.3-0.53 (m, 6H); 0.70-0.85 (t, 9H); 1.22 (s, 3H); 1.26 (s, 3H); 1.33 (s, 9H); 1.79 (s, 3H); 1.95 (s, 3H); 2.20 (s, 3H); 2.33-2.46 (m, 1H); 2.51 (s, 3H); 2.83-2.98 (m, 1H); 3.88-3.96 (d, 1H); 4.15-4.29 (m, 2H); 4.30-4.38 (d, 1H); 4.40-4.49 (d, 1H); 4.55 (s, 1H); 4.64-4.74 (d, 1H); 4.86 (s, 2H); 4.90-5.00 (d, 1H); 5.21-5.34 (bd, 1H); 5.44-5.58 (bd, 1H); 5.67-5.76 (d, 1H); 6.21-6.32 (t, 1H); 6.40 (s, 1H); 7.20-7.44 (m, 5H); 7.44-7.54 (t, 2H); 7.54-7.64 (t, 1H); 8.06-8.15 (d, 2H).

Example 9 Preparation of 7-(O-benzyloxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (10)

7-(O-benzyloxymethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (9, 92 mg, 0.085mM) is dissolved at RT under nitrogen in (80-20) HOAc-water (2 mL). A precipitate forms after a few minutes, and this is redissolved by the addition of THF (2 mL). The reaction is allowed to stand at RT for 1.5 days and at 45° C for 3 days. The reaction is found to be nearly complete at this point by TLC. The reaction mixture is then freeze-dried. The crude product is chromatographed over silica gel (10 g), eluting with (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 15-26, which upon combining and evaporating under vacuum leave 7-(O-benzyloxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (10, 70 mg, 85 % yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f 0.30

Proton NMR ($CDCl_3$; TMS): δ 1.22 (s, 3H); 1.23 (s, 3H); 1.35 (s, 9H); 1.78 (s,

3H); 1.87 (s, 3H); 1.95-2.10 (m, 1H); 2.21 (s, 3H); 2.36 (s, 3H); 2.82-2.96 (m, 1H); 3.48-3.58 (bd, 1H); 3.82-3.92 (d, 1H); 4.13-4.24 (m, 2H); 4.28-4.36 (d, 1H); 4.39-4.48 (d, 1H); 4.64 (bs, 1H); 4.65-4.72 (d, 1H); 4.81-4.90 (m, 2H); 4.90-4.98 (d, 1H); 5.22-5.32 (bd, 1H); 5.42-5.54 (bd, 1H); 5.62-5.71 (d, 1H); 6.12-6.24 (t, 1H); 6.37 (s, 1H); 7.21-7.43 (m, 10H); 7.43-7.54 (t, 2H); 7.55-7.65 (t, 1H); 8.04-8.15 (d, 2H).

Mass Spec (FAB, m/z) $(M+H)^+$ measured at 970.4242; theory for $C_{53}H_{64}N_1O_{16}$ is 970.4225; 970, 914, 689, 647, 105, 57, 43.

Example 9a Preparation of 7-TES-Baccatin III-(4S,5R)-N-t-buylurea-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (11)

Crude (4S,5R)-N-t-butyl urea-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (475mg,1.07mM) is dissolved in methanol (10mL), water (0.4mL) and K_2CO_3 (190mg) is added. After stirring overnight TLC shows only a spot at the origin. The solution is concentrated in vacuo and the residue partitioned between CH_2Cl_2 and 5% $NaHSO_4$ solution. The layers are separated and the aqueous layer extracted with EtOAc. The combined organic layers are filtered through anhydrous sodium sulfate and concentrated in vacuo leaving (4S,5R)-N-t-butyl urea-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine-carboxylic acid. 7-TES-baccatin III (500mg, 0.71 mM) is dissolved in toluene (7ml). All of the (4S,5R)-N-t-butyl urea-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine-carboxylic acid from above is added in a solution of CH_2Cl_2. The solution is heated to 80° C driving off the CH_2Cl_2 after which DCC (240mg, 1.15 mM) and DMAP (45mg, 0.36mM) are added. After 0.5 hr TLC shows little starting material so the slurry is cooled. The reaction is filtered through Celite and the filtrate concentrated in vacuo and chromatographed over a column of silica gel (80 g) in (1:3) EtOAc:hexane. The column is eluted with (1:3) EtOAc:hexane (200ml) and (1:2) EtOAc:hexane (1L) collecting 40 ml fractions. 7-TES-Baccatin III-(4S,5R)-N-t-buylurea-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (11, 906 mg) is found in fractions 28-47.

Mass Spec: Theory 1111.5198 Found 1111.5189

Proton NMR ($CDCl_3$; TMS): δ 0.59 (m, 6H); 0.92 (m,9H); 1.20 (m); 1.92 (s, 3H); 2.13 (s, 3H); 2.19 (s, 3H); 2.50 (m, 1H); 3.84 (m); 3.92 (s, 3H); 4.13 (d, 1H); 4.26 (d, 1H); 4.48 (m, 2H); 4.88 (d, 1H); 4.95 (d, 1H); 5.55 (d, 1H); 5.69 (d, 1H); 6.50 (m); 6.72 (m); 7.27-7.64 (m, 10H); 8.06 (d, 2H)

Example 10 Preparation of baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-

dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12) and 7-epi-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester

Baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (11, 198 mg, 0.178mM) is stirred at RT under nitrogen in dry THF (3 mL). To this solution is added tetra-n-butyl ammonium fluoride (56 mg, 0.178 mM). The reaction is followed by TLC which indicates the starting material is consumed in 45 minutes, giving two more polar products. The reaction mixture is then partitioned between ethyl acetate-5% sodium bicarbonate-brine. The aqueous layer is re-extracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (20 g), eluting with (50-50) ethyl acetate-hexane. Mixed fractions are rechromatographed. Fractions of 3 mL are collected, analyzing them by TLC. Baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12, 61 mg, 34 % yield) is found as a white solid on evaporation of fractions 42-56 and 7-epi-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (68 mg, 38 % yield) is found as a white solid on evaporation of fractions 24-31.

Data for 7-epi-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester:

TLC (silica gel): (50-50) ethyl acetate-hexane; R_f: 0.39

Proton NMR ($CDCl_3$; TMS): δ 1.16 (s, 12H); 1.23 (s, 3H); 1.65 (s, 3H); 2.00 (s, 3H); 2.04 (s, 3H); 2.22 (s, 3H); 3.65-3.74 (bd, 1H); 3.86 (s, 3H); 3.90 (s, 3H);4.34 (s, 2H); 4.57 (s 1H); 4.80-4.92 (m, 2H); 4.94-4.98 (d, 1H); 5.58-5.61 (d, 1H); 5.73-5.78 (d, 1H); 6.23-6.33 (t, 1H); 6.49-6.56 (d, 1H); 6.53 (s, 1H); 6.70 (s, 1H); 6.86 (s, 1H); 7.26-7.58 (m, 8H); 7.58-7.66 (t, 1H); 8.01-8.09 (d, 2H).

Data for baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12):

TLC (silica gel): (50-50) ethyl acetate-hexane; Rf: 0.24

Proton NMR ($CDCl_3$; TMS): δ 1.16 (s, 12H); 1.28 (s, 3H); 1.66 (s, 3H); 1.90 (s, 3H); 1.98 (s, 3H); 2.26 (s, 3H); 2.43-2.55 (m, 2H); 3.73-3.81 (d, 1H); 3.84 (s, 3H); 3.91 (s, 3H); 4.11-4.16 (d, 1H); 4.21-4.27 (d, 1H); 4.36-4.47 (m, 1H); 4.50 (s 1H); 4.82-4.92 (bd, 1H); 4.92-4.96 (d, 1H); 5.50-5.55 (d, 1H); 5.61-5.68 (d, 1H); 6.25-6.37 (m, 2H); 6.47-6.55 (m, 2H); 6.71 (s, 1H); 7.23-7.57 (m, 8H); 7.57-7.64 (t, 1H); 8.00-8.07 (d, 2H).

Preparation of baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12)

Baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (11, 3.41 g, 3.07 mM) is stirred at RT under nitrogen in dry acetonitrile (30 mL) and the solution treated with triethyl amine trihydrofluoride (5 mL), resulting in a thick slurry which dissolves over a 7 h period. The reaction is followed by TLC and found to be essentially finished in 7.5 hr. At this point the reaction is diluted with ethyl acetate and washed with 5% sodium bicarbonate, 5% sodium bisulfate and brine. The organic layer is dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (300 g), eluting with (25-75, 1.5 L), (30-70, 1 L), and (40-60, 2 L) acetone-hexane. Fractions of 40 mL are collected, analyzing them by TLC. Fractions 74-92 were combined and evaporated under vacuum to give baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12, 2.26 g, 74% yield) as a white solid.

TLC (silica gel): (50-50) ethyl acetate-hexane; R_f: 0.24

Proton NMR ($CDCl_3$; TMS): δ 1.16 (s, 12H); 1.28 (s, 3H); 1.66 (s, 3H); 1.90 (s, 3H); 1.98 (s, 3H); 2.26 (s, 3H); 2.43-2.55 (m, 2H); 3.73-3.81 (d, 1H); 3.84 (s, 3H); 3.91 (s, 3H); 4.11-4.16 (d, 1H); 4.21-4.27 (d, 1H); 4.36-4.47 (m, 1H); 4.50 (s 1H); 4.82-4.92 (bd, 1H); 4.92-4.96 (d, 1H); 5.50-5.55 (d, 1H); 5.61-5.68 (d, 1H); 6.25-6.37 (m, 2H); 6.47-6.55 (m, 2H); 6.71 (s, 1H); 7.23-7.57 (m, 8H); 7.57-7.64 (t, 1H); 8.00-8.07 (d, 2H).

Example 11 Preparation of 7-(O-ethoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (13)

Baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12, 61 mg, 0.061 mM) is stirred at RT under nitrogen in methylene chloride (1 mL). To this solution is added chloromethyl ethyl ether (28 mL, 0.306 mM) and diisopropyl ethyl amine (53 mL, 0.306 mM). The reaction is followed by TLC which shows the reaction to be incomplete in two days. At this time chloromethyl ethyl ether (28 mL, 0.306 mM) and diisopropyl ethyl amine (53 mL, 0.306 mM) are again added. After 5 days, the reaction is partitioned between methylene chloride-water. The aqueous layer is re-extracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated. The crude product is chromatographed over silica gel (10 g), eluting with a gradient

of (20-80) to (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. Fractions 35-57 are combined and evaporated under vacuum to give 7-(O-ethoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (13, 44 mg, 69% yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.67

Proton NMR ($CDCl_3$; TMS): δ 1.08-1.18 (t, 3H); 1.18 (s, 9H); 1.21 (s, 3H); 1.26 (s, 3H); 1.74 (s, 3H); 1.98 (s, 3H); 2.06 (s, 3H); 2.26 (s, 3H); 2.74-2.88 (m, 1H); 3.38-3.48 (m, 1H); 3.62-3.73 (m, 1H); 3.82-3.94 (d, 1H); 3.84 (s, 3H);3.92 (s, 3H);4.10-4.21 (m 2H); 4.21-4.30 (d, 1H); 4.58 (s 1H); 4.74 (s, 2H); 4.82-4.92 (d, 1H); 4.94-4.98 (d, 1H); 5.55-5.59 (d, 1H); 5.62-5.70 (d, 1H); 6.26-6.37 (t, 1H); 6.37 (s, 1H); 6.47-6.56 (m, 2H); 6.75 (s, 1H); 7.25-7.66 (m, 9H); 8.02-8.11 (d, 2H).

Example 12 Preparation of 7-(O-ethoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (14)

7-(O-ethoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (13, 44 mg, 0.042 mM) is stirred at RT under nitrogen in (80-20) acetic acid-water (2 mL). The reaction is followed by TLC and found to be complete in 4 hours. The reaction is then freeze-dried. The crude product is purified by chromatography over silica gel (10 g), eluting with (30-70) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC. The product is found in fractions 17-32, which are combined and evaporated under vacuum to give 7-(O-ethoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (14, 26 mg 68 % yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.39

Proton NMR ($CDCl_3$; TMS): δ 1.09-1.17 (t, 3H); 1.20 (s, 3H); 1.21 (s, 3H); 1.23 (s, 9H); 1.75 (s, 3H); 1.87 (s, 3H); 1.88-2.01 (t, 1H); 2.20 (s, 3H); 2.23-2.32 (d, 2H); 2.39 (s, 3H); 2.75-2.88 (m, 1H); 3.34-3.45 (m, 1H); 3.58-3.70 (m, 1H); 3.81 (s, 1H); 3.81-3.87 (d, 1H); 4.05-4.15 (dd, 1H); 4.15-4.20 (d, 1H); 4.27-4.31 (d, 1H); 4.59-4.65 (m, 2H); 4.72 (s, 2H); 4.89-4.97 (d, 1H); 5.17-5.22 (d, 1H); 5.30-5.36 (dd, 1H); 5.63-5.70 (d, 1H); 6.09-6.19 (t, 1H); 6.33 (s, 1H); 7.27-7.41 (m, 5H); 7.43-7.54 (t, 2H); 7.57-7.65 (t, 1H); 8.06-8.12 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 907.4240; theory for $C_{48}H_{62}N_2O_{15}$ is 907.4228; 907, 627, 567, 281, 263, 235, 205, 136, 105, 59, 43.

Example 17 Preparation of 7-[O-(2,2,2-trichloroethoxy)methyl]-13-(N-Boc-β-phenyl

isoserinyl)-baccatin III (21) and 7-[O-(2,2,2-trichloroethoxy)methoxymethyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (22)

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 95 mg, 0.099mM) is stirred at RT under nitrogen in methylene chloride (1 mL) and the solution treated with a (1-1)-mixture of chloromethyl-(2,2,2-trichloroethyl) ether and chloromethyl-(2,2,2-trichloroethoxy)methyl ether (98 mL) and diisopropyl ethyl amine (109 mL, 0.624 mM). The reaction is followed by TLC, which shows the reaction not to be complete after 22 days. Thus, additional (1-1)-mixture of chloromethyl-(2,2,2-trichloroethyl) ether and chloromethyl-(2,2,2-trichloroethoxy)methyl ether (98 mL) are added as well as 1,2-dichloroethane (1 mL). The reaction is then heated in a 4 day cycle to 75°C for 8 h and allowed to stand at RT for 16 h. The reaction is then heated to 75°C continuously for 24 hours. The reaction mixture is then chromatographed over silica gel (15 g), eluting with (25-75) acetone-hexane. Fractions of 3 mL are collected, analyzing them by TLC, which indicates the presence of four compounds. The two less polar compounds are found in fractions 10-13 and the two more polar compounds in fractions 14-33. Evaporation of fractions 10-13 leaves a residue which is treated with (80-20) acetic acid water (3 mL). This reaction is then freeze dried. TLC shows the products of this reaction to be the same as the products found in fractions 14-33 above. Thus, all the residues are combined and chromatographed over an E. Merck size A HPLC silica gel column, eluting with a gradient of (20-80) to (40-60) ethyl acetate-hexane. 7-[O-(2,2,2-trichloroethoxy)methyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (21, 23mg, 23% yield) is found on evaporation of fractions 52-66 as a white solid and 7-[O-(2,2,2-trichloroethoxy)methoxymethyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (22, 23 mg, 22% yield) is found on evaporation of fractions 68-88 as a white solid.

Data for 7-[O-(2,2,2-trichloroethoxy)methyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (21):

TLC (silica gel): (25-75) ethyl acetate-hexane; R_f 0.25

Proton NMR ($CDCl_3$; TMS): δ 1.20 (s, 3H); 1.24 (s, 3H); 1.35 (s, 9H); 1.76 (s, 3H); 1.87 (s, 3H); 1.92-2.03 (t, 1H); 2.22 (s, 3H); 2.26-2.34 (d, 2H); 2.37 (s, 3H); 2.85-2.99 (m, 1H); 3.37-3.53 (bs, 1H); 3.80-3.89 (d, 1H); 3.97-4.06 (d, 1H); 4.12-4.25 (m, 3H); 4.27-4.34 (d, 1H); 4.63 (bs, 1H); 4.87-5.03 (m, 3H); 5.18-5.30 (bd, 1H); 5.37-5.47 (bd, 1H); 5.61-5.70 (d, 1H); 6.12-6.23 (t, 1H); 6.32 (s, 1H); 7.27-7.45 (m, 5H); 7.45-7.54 (t, 2H); 7.57-7.65 (t, 1H); 8.05-8.15 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 908.4089; theory for $C_{48}H_{62}N_1O_{16}$ is 908.4068; 908, 627, 585, 105, 59, 57.

Data for 7-[O-(2,2,2-trichloroethoxy)methoxymethyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (22):

TLC (silica gel): (25-75) ethyl acetate-hexane; R_f 0.17

Proton NMR ($CDCl_3$; TMS): δ 1.22 (s, 6H); 1.35 (s, 9H); 1.75 (s, 3H); 1.91 (s, 3H); 2.21 (s, 3H); 2.25-2.32 (d, 2H); 2.37 (s, 3H); 2.69-2.82 (m, 1H); 3.35-3.48 (bs, 1H); 3.80-3.86 (d, 1H); 4.13-4.26 (m, 4H); 4.26-4.34 (d, 1H); 4.63 (bs, 1H); 4.73-4.80 (d, 1H); 4.83-5.04 (m, 4H); 5.21-5.32 (d, 1H); 5.40-5.47 (d, 1H); 5.64-5.70 (d, 1H); 6.14-6.24 (t, 1H); 6.39 (s, 1H); 7.30-7.45 (m, 5H); 7.45-7.57 (t, 2H); 7.57-7.66 (t, 1H); 8.07-8.15 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 908.4089; theory for $C_{48}H_{62}N_1O_{16}$ is 908.4068; 908, 627, 585, 105, 59, 57.

Example 21 Preparation of 7-(O-methoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (26)

Baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (12, 610 mg, 0.612 mM) is stirred at RT under nitrogen in methylene chloride (3 mL) and the solution treated with chloromethyl methyl ether (232 mL, 3.06 mM) and diisopropyl ethyl amine (530 mL, 3.06 mM). The reaction is followed by TLC. After 24 hours the reaction is found to be complete. The reaction is then diluted with methylene chloride and washed with 5% sodium bisulfate and 5% sodium bicarbonate, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (70 g), eluting with a gradient of (25-75) to (30-70) acetone-hexane. Fractions of 20 mL are collected, analyzing them by TLC. 7-(O-methoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (less polar isomer 26a, 532 mg, 84% yield) is found on evaporation of fractions 31-47 as a white solid and methoxymethyl-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (more polar isomer 26b, 62 mg, 10% yield) is found on evaporation of fractions 48-57 as a white solid.

Data for 7-(O-methoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (26a):

TLC (silica gel): (30-70) acetone-hexane; R_f 0.42

Proton NMR ($CDCl_3$; TMS): δ 1.17 (s, 12H); 1.23 (s, 3H); 1.75 (s, 3H); 1.93 (s, 3H); 2.07 (s, 3H); 2.21 (s, 3H); 2.66-2.83 (m, 1H); 3.29 (s, 3H); 3.78-3.90 (m, 1H);

3.82 (s, 3H); 3.91 (s, 3H); 4.06-4.30 (m, 3H); 4.56-4.76 (m, 3H); 4.81-4.91 (d, 1H); 4.97 (s, 1H); 5.58 (s, 1H); 5.62-5.70 (d, 1H); 6.24-6.36 (t, 1H); 6.39 (s, 1H); 6.45-6.57 (m, 2H); 6.75 (s, 1H); 7.24-7.64 (m, 9H); 7.96-8.08 (d, 2H).

Data for 7-(O-methoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (26b):

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.35

Proton NMR ($CDCl_3$; TMS): δ 0.96 (s, 9H); 1.16 (s, 3H); 1.20 (s, 3H); 1.66 (s, 3H); 1.70 (s, 3H); 1.81 (s, 3H); 2.20 (s, 3H); 2.67-2.82 (m, 1H); 3.28 (s, 3H); 3.72-3.78 (d, 1H); 3.82 (s, 3H); 3.90 (s, 3H); 4.03-4.17 (m, 2H); 4.20-4.25 (d, 1H); 4.50-4.54 (d, 1H); 4.58-4.65 (d, 1H); 4.65-4.70 (d, 1H); 4.80-4.88 (d, 1H); 5.40-5.46 (d, 1H); 5.58-5.64 (d, 1H); 6.03-6.13 (t, 1H); 6.27 (s, 1H); 6.48-6.58 (m, 2H); 6.73 (s, 1H); 7.33-7.58 (m, 8H); 7.58-7.65 (t, 1H); 7.99-8.05 (d, 2H).

Example 22 Preparation of 7-(O-methoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (27)

7-(O-Methoxymethyl)-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (594 mg, 26a and 26b from example 21, 0.57 mM) is stirred at RT under nitrogen in (80-20) acetic acid-water (25 mL). The reaction is followed by TLC and found to be complete in 4 hours. The reaction is then freeze-dried. The crude residue is purified over a silica gel column (60 g), eluting with (35-65) acetone-hexane. Fractions of 15 mL are collected, analyzing them by TLC. The product is found in fractions 27-45 which are combined and evaporated under vacuum to give 7-(O-methoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (27, 385 mg, 75% yield) as a white solid.

TLC (silica gel): (30-70) acetone-hexane; R_f: 0.23

Proton NMR ($CDCl_3$; TMS): δ 1.22 (s, 3H); 1.24 (s, 12H); 1.76 (s, 3H); 1.89 (s, 3H); 2.20 (s, 3H); 2.25-2.34 (d, 2H); 2.40 (s, 3H); 2.72-2.86 (m, 1H); 3.29 (s 2H); 3.68 (bs, 1H); 3.81-3.88 (d, 1H); 4.07-4.15 (dd, 1H); 4.15-4.22 (d, 1H); 4.26-4.34 (d, 1H); 4.55 (bs, 1H); 4.60-4.74 (m, 3H); 4.89-4.96 (d, 1H); 5.06-5.16 (bd, 1H); 5.30-5.37 (dd, 1H); 5.64-5.70 (d, 1H); 6.10-6.20 (t, 1H); 6.36 (s, 1H); 7.27-7.40 (m, 5H); 7.45-7.55 (t, 2H); 7.58-7.66 (t, 1H); 8.06-8.14 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 893.4095; theory for $C_{47}H_{61}N_2O_{15}$ is 893.4072; 969, 893, 613, 281, 263, 235, 205, 136, 105.

Example 35 Preparation of 2'-TES-7-(O-methylthiomethyl) taxol (41).

2'-TES-taxol (40, 100 mg, 0.103 mM) is stirred at 0° C under nitrogen in 0.4 mL of dry acetonitrile and the solution treated with dimethyl sulfide (58 mL) and benzoyl peroxide (25 mg) 4 times at 5 minute intervals. The reaction is allowed to proceed at 0° C for 3.5 hours. It is then diluted with ethyl acetate and washed with 5% sodium bicarbonate, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (10g), eluting with (30-70) ethyl acetate-hexane. Fractions of 3 mL are collected analyzing them by TLC. Fractions 24-46 contained the pure product and are combined and evaporated, leaving 2'-TES-7-methyl thiomethyl taxol (41, 54 mg, 51%) as a white solid.

TLC (silica gel): (30-70) ethyl acetate-hexane; Rf: 0.31

Proton NMR ($CDCl_3$; TMS): δ 0.34-0.58 (m, 6H); 0.77-0.85 (t, 9H); 1.26 (s, 3H); 1.27 (s, 3H); 1.78 (s, 3H); 1.80-1.94 (m, 2H); 2.08 (s, 3H); 2.12 (s, 3H); 2.19 (s, 3H); 2.35-2.50 (m, 1H); 2.56 (s, 3H); 2.76-2.90 (m, 1H); 3.86-3.96 (d, 1H); 4.18-4.39 (2d+1m, 3H); 4.68 (s, 2H); 4.70-4.75 (d, 1H); 4.93-5.03 (d, 1H); 5.68-5.79 (m, 2H); 6.20-6.32 (t, 1H); 6.58 (s, 1H); 7.13-7.23 (d, 1H); 7.30-7.60 (m, 10H); 7.71-7.80 (d, 2H); 7.90-7.97 (d, 1H); 8.06-8.17(d, 2H).

Example 36 Preparation of 7-(O-methylthiomethyl) taxol (42)

2'-TES-7-(O-methylthiomethyl) taxol (41, 54 mg, 0.053mM) is stirred at RT under nitrogen in (80-20) acetic acid-water (6 mL) for 3 hours, when it is found to be complete by TLC. The reaction is then freeze-dried. The crude product is chromatographed over 5g silica gel, eluting with 50-50 ethyl acetate-hexane. Fractions of 1 mL are collected analyzing them by TLC. Fractions 11-35 contained the pure product and are combined and evaporated, leaving 7-(O-methylthiomethyl) taxol (42, 42 mg, 88% yield) as a white solid.

TLC (silica gel): (40-60) ethyl acetate-hexane; Rf: 0.23

Proton NMR ($CDCl_3$; TMS): δ 1.10 (s, 3H); 1.14 (s, 3H); 1.68 (s, 3H); 1.85 (s, 3H); 2.04 (s, 3H); 2.11 (s, 3H); 2.20-2.28 (d, 2H); 2.30 (s, 3H); 2.64-2.80 (m, 1H); 3.74-3.82 (d, 1H); 4.07-4.15 (d, 1H); 4.15-4.30 (d+m, 2H); 4.58 (s, 2H); 4.70-4.75 (d, 1H); 4.82-4.92 (d, 1H); 5.55-5.64 (d, 1H); 5.68-5.76 (d, 1H); 6.04-6.15 (t, 1H); 6.44 (s, 1H); 6.99-7.09 (d, 1H); 7.23-7.49 (m, 10H); 7.64-7.74 (d, 2H); 8.00-8.08(d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 914.3429; theory for $C_{49}H_{56}N_1O_{14}S_1$ is 914.3421; 990, 914, 836, 629, 286, 268, 240, 210, 121, 105, 61, 43.

Example 37 Preparation of 7-(O-methylthiomethyl)-13-(N-Boc-2'-TES-β-phenyl

isoserinyl)-baccatin III (43).

13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (2, 287 mg, 0.298 mM) is stirred at 0° C under nitrogen in dry acetonitrile (1.2 mL) and the solution treated with dimethyl sulfide (170 mL) and benzoyl peroxide (73 mg) 4 times at 5 minute intervals. The reaction is allowed to proceed at 0° C for 4 hours, when TLC shows it to be complete. It is then diluted with ethyl acetate and washed with 5% sodium bicarbonate-brine, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (35g), eluting with (30-70) ethyl acetate-hexane. Fractions of 4 mL are collected analyzing them by TLC. Fractions 26-51 contained the pure product and are combined and evaporated leaving 7-(O-methylthiomethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (43, 273 mg, 90% yield) as a white solid.

TLC (silica gel): (30-70) ethyl acetate-hexane; Rf: 0.46

Proton NMR ($CDCl_3$; TMS): δ 0.30-0.49 (m, 6H); 0.71-0.84 (t, 9H); 1.26 (s, 3H); 1.32 (s, 9H); 1.77 (s, 3H); 1.80-1.93 (t, 2H); 2.05 (s, 3H); 2.12 (s, 3H); 2.15 (s, 3H); 2.19 (s, 3H); 2.33-2.44 (m, 1H); 2.53 (s, 3H); 2.78-2.89 (m, 1H); 3.87-3.95 (d, 1H); 4.16-4.23 (d, H); 4.25-4.35 (d+m, 2H); 4.57 (s, 1H); 4.67 (s, 1H); 4.93-5.01 (d, 1H); 5.23-5.35 (bs, 1H); 5.46-5.56 (d, 1H); 5.67-5.75 (d, 1H); 6.23-6.32 (t, 1H); 6.57 (s, 1H); 7.23-7.33 (m, 3H); 7.33-7.41 (t, 2H); 7.43-7.53 (t, 2H); 7.53-7.63 (t, 1H); 8.06-8.14(d, 2H).

Example 38 Preparation of 7-(O-methylthiomethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (44).

7-(O-Methylthiomethyl)-13-(N-Boc-2'-TES-β-phenyl isoserinyl)-baccatin III (43, 273 mg, 0.267mM) is stirred at RT under nitrogen in (80-20) acetic acid-water (30 mL) for 4.5 hours, when it is found to be complete by TLC. The reaction is then freeze-dried. The crude product is chromatographed over silica gel (30 g), eluting with (70-30) ethyl acetate-hexane. Fractions of 4 mL are collected analyzing them by TLC. Fractions 15-25 contained the pure product and are combined and evaporated, leaving 7-(O-methylthiomethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (44, 225 mg, 93% yield) as a white solid.

TLC (silica gel): (30-70) ethyl acetate-hexane; Rf: 0.26

Proton NMR ($CDCl_3$; TMS): δ 1.20 (s, 3H); 1.34 (s, 9H); 1.75 (s, 3H); 1.79-1.96 (m, 2H); 1.89 (s, 3H); 2.11 (s, 3H); 2.14 (s, 3H); 2.18 (s, 3H); 2.23-2.32 (d, 2H); 2.36 (s, 3H); 2.73-2.85 (m, 1H); 3.54-3.63 (d, 1H); 3.83-3.91 (d, 1H); 4.13-4.21 (d, 1H); 4.25-4.34 (d+m, 2H); 4.55-4.70 (m, 3H); 4.90-4.98 (d, 1H); 5.20-5.32 (bd, 1H);

5.44-5.56 (bd, 1H); 5.64-5.72 (d, 1H); 6.14-6.24 (t, 1H); 6.54 (s, 1H); 7.24-7.44 (m, 5H); 7.44-7.53 (t, 2H); 7.54-7.64 (t, 1H); 8.04-8.14(d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 910.3697; theory for $C_{47}H_{60}N_1O_{15}S_1$ is 910.3683; 910, 629, 587, 569, 105, 61, 57, 43.

Example 39 Preparation of 2'-TES-7-(O-phenylthiomethyl) taxol (45).

2'-TES-taxol (40, 104 mg, 0.107 mM) is stirred at 0° C under nitrogen in dry acetonitrile (0.4 mL) and the solution treated with thioanisol (97 mL) and benzoyl peroxide (25 mg) 4 times at 5 minute intervals. The reaction is allowed to proceed at 0° C for 5 hours and in the refrigerator overnight, when TLC shows it to be complete. It is then diluted with ethyl acetate and washed with 5% sodium bicarbonate, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over silica gel (12 g), eluting with (30-70) ethyl acetate-hexane. Fractions of 4 mL are collected analyzing them by TLC. Fractions 18-43 contain the pure product and are combined and evaporated leaving 2'-TES-7-(O-phenylthiomethyl) taxol (45, 91 mg, 78% yield) as a white solid.

TLC (silica gel): (30-70) ethyl acetate-hexane; Rf: 0.47

Proton NMR ($CDCl_3$; TMS): δ 0.37-0.59 (m, 6H); 0.78-0.90 (t, 9H); 0.88 (s, 3H); 1.16 (s, 3H); 1.79 (s, 3H); 1.95 (s, 3H); 2.09 (s, 3H); 2.35-2.48 (m, 1H); 2.56 (s, 3H); 2.74-2.87 (m, 1H); 3.89-3.97 (d, 1H); 4.20-4.28 (d, 1H); 4.30-4.44 (m, 2H); 4.70-4.75 (d, 1H); 4.90-4.99 (d, 1H); 5.05 (s, 2H); 5.69-5.76 (m, 2H); 6.18-6.30 (t, 1H); 6.52 (s, 1H); 7.11-7.63 (m, 16H); 7.72-7.80 (d, 2H); 8.07-8.17(d, 2H).

Example 40 Preparation of 7-(O-phenylthiomethyl) taxol (46).

2'-TES-7-(O-phenylhiomethyl) taxol (45, 91 mg) is stirred at RT under nitrogen in (80-20) acetic acid-water (10 mL) for 2 hours, when it is found to be complete by TLC. The reaction is then freeze-dried. The crude product is chromatographed over silica gel (10g), eluting with (70-30) ethyl acetate-hexane. Fractions of 3 mL are collected analyzing them by TLC. Fractions 10-33 contain the pure product and are combined and evaporated, leaving 7-phenylthiomethyl taxol (46, 62 mg, 77%) as a white solid.

TLC (silica gel): (40-60) ethyl acetate-hexane; R_f 0.26.

Proton NMR ($CDCl_3$; TMS): δ 1.06 (s, 3H); 1.11 (s, 3H); 1.69 (s, 3H); 1.86 (s, 3H); 1.89 (s, 3H); 2.18-2.27 (d, 2H); 2.30 (s, 3H); 2.60-2.76 (m, 1H); 3.74-3.83 (d, 1H); 4.07-4.14 (d, 1H); 4.16-4.30 (m, 2H); 4.69-4.74 (d, 1H); 4.77-4.86 (d, 1H); 4.95 (s, 2H); 5.55-5.64 (d, 1H); 5.68-5.76 (dd, 1H); 6.04-6.14 (t, 1H); 6.36 (s, 1H); 7.04-7.14 (t, 2H);

7.14-7.47 (m, 14H); 7.47-7.56 (t, 1H); 7.62-7.70 (d, 2H); 7.97-8.07 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 976.3557; theory for $C_{54}H_{58}O_{14}N_1S_1$ is 976.3578; 1052, 976, 836, 691, 286, 268, 240, 210, 123, 105, 77, 43.

Example 41 Preparation of 7-O-methyl Taxol (47)

7-(O-phenylthiomethyl) taxol (46, 50 mg, 0.051 mM) is stirred at 0° C under nitrogen in 2 mL abs. EtOH and the solution treated with 0.5 mL Raney Nickel in 1 mL abs. EtOH (the Raney Nickel is washed with water (5x), acetone and ethanol before use). After a few minutes the reaction is warmed to RT. The reaction is followed by TLC. After 40 minutes the reaction, is filtered through Celite, washing well with abs. EtOH. The filtrate and wash are combined and evaporated under vacuum. The crude product is chromatographed over silica gel (5 g), eluting with a gradient of (30-70) to (70-30) ethyl acetate-hexane. Fractions of 1 mL are collected, analyzing them by TLC. Fractions 55-78 contained impure product and are combined and evaporated under vacuum. Rechromatographing the impure product on HPLC grade silica gel, using (35-65) acetone-hexane as eluant, gives 7-OMe Taxol (47, 13 mg, 30% yield) as a white solid.

TLC (silica gel): (35-65) ethyl acetate-hexane; R_f:0.44.

Proton NMR ($CDCl_3$; TMS): δ 1.20 (s, 6H); 1.68 (s, 3H); 1.82 (s, 3H); 2.22 (s, 3H); 2.25-2.34 (dd, 2H); 2.38 (s, 3H); 2.64-2.80 (m, 1H); 3.34 (s, 3H); 3.63-3.74 (d, 1H); 3.74-3.91 (m, 2H); 4.12-4.22 (d, 1H); 4.25-4.34 (d, 1H); 4.74-4.84 bs, 1H); 4.90-5.01 (d, 1H); 5.60-5.70 (d, 1H); 5.74-5.84 (dd, 1H); 6.12-6.24 (t, 1H); 6.39 (s, 1H); 7.06-7.14 (d, 1H); 7.30-7.56 (m, 10H); 7.56-7.66 (t, 1H); 7.21-7.32 (d, 2H); 8.04-8.16 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 868.3534; theory for $C_{48}H_{54}O_{14}N_1$ is 868.3544; 868, 583, 286, 268, 240, 210, 121, 105, 43.

Example 42 Preparation of 7-[O-ethyl(1-thioethyl)] Taxol (49)

2'-TES-taxol (40, 200 mg, 0.207 mM) is stirred at 0° C under nitrogen in dry acetonitrile (0.8 mL) and the solution treated with diethyl sulfide (0.178 mL) and benzoyl peroxide (50 mg) 4 times at 5 minute intervals. The reaction is allowed to proceed at 0° C for 3 hours, in the freezer for 5 hours and in the refrigerator overnight,

following the reaction by TLC. The reaction is then diluted with ethyl acetate and washed with 5% sodium bicarbonate. The organic layer is dried over sodium sulfate and evaporated under vaccum. The resultant crude product is chromatographed over silica gel (25 g), eluting with a gradient of (30-70) to (90-10) ethyl acetate-hexane. Fractions of 5 mL are collected, analyzing them by TLC. Fractions containing 2'-TES-7-ethylthioethyl Taxol (48) are combined and evaporated under vacuum. The impure product is stirred at RT under nitrogen in (80-20) HOAc-water (3 mL) and the reaction followed by TLC and is found to be complete after 2 hours. The reaction is then freeze-dried. The product is chromatographed over HPLC grade silica gel, eluting with (45-55) ethyl acetate hexane. This still gives impure product so the chromatography is repeated using a gradient of (30-70) to (40-60) ethyl acetate-toluene. This gives 7-[O-ethyl(1-thioethyl)] Taxol (49, 17 mg) as a white solid.

TLC (silica gel): (50-50) ethyl acetate-hexane; R_f:0.50.

Proton NMR ($CDCl_3$; TMS): δ 1.12-1.32 (2s+1t, 9H); 1.50-1.56 (d, 3H); 1.67-1.84 (m, 5H); 1.92 (s, 3H); 2.18 (s, 3H); 2.38 (s, 3H); 2.54-2.70 (m, 1H); 2.70-2.84 (m, 1H); 3.68-3.74 (d, 1H); 3.82-3.90 (d, 1H); 4.13-4.23 (d, 1H); 4.26-4.35 (d, 1H); 4.50-4.60 (dd, 1H); 4.64-4.74 (q, 1H); 4.80 (bs, 1H); 4.92-5.01 (d, 1H); 5.62-5.70 (d, 1H); 5.75-5.84 (dd, 1H); 6.13-6.24 (t, 1H); 6.55 (s, 1H); 7.05-7.14 (d, 1H); 7.30-7.57 (m, 10H); 7.57-7.66 (t, 1H); 7.72-7.78 (d, 2H); 8.07-8.16 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 942.3713; theory for $C_{51}H_{60}O_{14}N_1S_1$ is 942.3734; 942, 880, 854, 836, 286, 268, 240, 210, 122, 105, 89, 77, 43.

Example 44 Preparation of 13-(N-Cbz-2'-TES-b-phenyl isoserinyl)-baccatin III (51)

This material is prepared from 13-(N-Cbz-b-phenyl isoserinyl)-baccatin III (50, See U.S. Serial No. PCT/US 93/11827 filed 12/13/93 and WO 94/13655 published 06/23/94 which are incorporated herein by reference) in the same manner as 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III is prepared from 13-(N-Boc-b-phenyl isoserinyl)-baccatin III in Example 1.

Example 45 Preparation of 13-(2'-TES-b-phenyl isoserinyl)-baccatin III (52)

13-(N-Cbz-2'-TES-b-phenyl isoserinyl)-baccatin III (51, 217 mg, 0.217 mM) is

stirred at RT under nitrogen in 2 mL dry THF-3 mL methanol. To the solution is added 100 mg ammonium formate and 60 mg 10% Pd/C. The reaction is allowed to proceed for 30 minutes when TLC showed the reaction to be complete. The reaction is filtered through Celite, washing with ethyl acetate. The combined filtrate and wash is washed with 5% sodium bicarbonate, dried over sodium sulfate and evaporated under vacuum. The residue is reevaporated twice with toluene and once with ethyl acetate-hexane to give 13-(2'-TES-b-phenyl isoserinyl)-baccatin III (52, 186 mg) as a white solid.

TLC: silica gel; 50-50 ethyl acetate-hexane; R_f:0.36.

^{1}H NMR ($CDCL_3$; TMS): d 0.43-0.57 (m, 6H); 0.78-0.92 (t, 9H); 1.03 (s, 3H); 1.14 (s, 3H); 1.54 (s, 3H); 1.73 (s, 3H); 2.08 (s, 3H); 2.21 (s, 3H); 2.38-2.52 (m, 1H); 3.61-3.69 (d, 1H); 4.01-4.12 (2d, 2H); 4.13-4.24 (2d, 2H); 4.24-4.35 (dd, 1H); 4.81-4.89 (d, 1H); 5.49-5.56 (d, 1H); 5.93-6.05 (t, 1H); 6.18 (s, 1H); 7.03-7.30 (m, 5H); 7.40-7.50 (t, 2H); 7.54-7.63 (t, 1H); 7.90-7.98 (d, 2H).

Example 46 Preparation of 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III (53)

13-(2'-TES-b-phenyl isoserinyl)-baccatin III (52, 186 mg, 0.215 mM) is stirred at 0°C under nitrogen in 2 mL dry THF. To this is added by syringe t-butyl isocyanate (0.03 mL). After 5 minutes, the reaction is warmed to RT, following the reaction by TLC. After 2 hours more t-butyl isocyanate (0.01 mL) is added. After a total reaction time of 4.5 hours, the reaction is found to me essentially complete by TLC. The reaction is evaporated under vaccum and the crude residue chromatographed over 20 g silica gel, eluting with 40-60 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 20-72 contain pure product and are combined and evaporated under vacuum to give 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III (53, 193 mg) as a white solid.

TLC: silica gel; 50-50 ethyl acetate-hexane; R

$_f$:0.61.

^{1}H NMR ($CDCL_3$; TMS): d 0.14-0.38 (m, 6H); 0.64-0.74 (t, 9H); 1.08 (s, 3H); 1.15 (s. 9H); 1.20 (s, 3H); 1.63 (s, 3H); 1.86 (s, 3H); 2.16 (s, 3H); 2.52 (s, 3H); 2.60-2.66 (d, 1H); 3.72-3.79 (d, 1H); 4.11-4.18 (d, 1H); 4.20-4.28 (d, 1H); 4.28-4.38 (m, 1H); 4.46-4.50 (d, 1H); 4.88-4.96 (m, 2H); 5.10-5.18 (d, 1H); 5.22-5.30 (d, 1H); 5.58-5.64 (d, 1H); 6.12-6.24 (t, 1H); 6.26 (s, 1H); 7.15-7.33 (m, 5H); 7.36-7.66 (t, 2H);

7.47-7.55 (t, 1H); 7.99-8.06 (d, 2H).

Example 47 Preparation of 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (54)

13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III (53, 193 mg, 0.203 mM) is stirred at 0°C under nitrogen in 2 mL acetonitlile. To this is added by syringe dimethyl sulfide (0.115 mL) followed by four additions 5 minutes apart of benzoyl peroxide (50 mg portions). After 30 minutes everything is in solution and after 2 hours the reaction is complete by TLC. The reaction is partitioned between ethyl acetate-5% sodium bicarbonate. The organic layer is dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over 20 g silica gel, eluting with 30-70 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 25-61 contain pure product and are combined and evaporated under vacuum to give 13-(N-(t-butylamino-carbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (54, 178 mg) as a white solid.

TLC: silica gel; 50-50 ethyl acetate-hexane; R_f:0.34.

^{1}H NMR ($CDCL_3$; TMS): d 0.14-0.40 (m, 6H); 0.64-0.76 (t, 9H); 1.16 (s, 3H); 1.17 (s. 12H); 1.70 (s, 3H); 1.74-1.88 (m, 1H); 2.00 (s, 3H); 2.03 (s, 3H); 2.11 (s, 3H); 2.14-2.24 (m, 1H); 2.30-2.44 (m, 1H); 2.54 (s, 3H); 2.71-2.86 (m, 1H); 3.79-3.88 (d, 1H); 4.10-4.23 (m, 2H); 4.23-4.29 (d, 1H); 4.47-4.51 (d, 1H); 4.54-4.61 (d, 1H); 4.87-4.95 (d+s, 2H); 5.12-5.20 (d, 1H); 5.24-5.30 (d, 1H); 5.60-5.68 (d, 1H); 6.09-6.21 (t, 1H); 6.49 (s, 1H); 7.17-7.34 (m, 5H); 7.38-7.46 (t, 2H); 7.48-7.56 (t, 1H); 7.99-8.08 (d, 2H).

Example 48 Preparation of 13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (55)

13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (54, 178 mg, 0.174mM) is stirred at RT under nitrogen in 25 ml 80-20 acetic acid-water. TLC after 5 minutes shows the reaction to be complete.The reaction is freeze-dried overnight. The crude product is chromatographed over 20 g silica gel, eluting with 50-50 ethyl acetate-hexane. Fractions of 3 mL are collected, analyzing them by TLC. Fractions 30-60 are found to contain 13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (55)

as a white solid.

TLC: silica gel; 50-50 ethyl acetate-hexane; R_f:0.47.

^{1}H NMR ($CDCL_3$; TMS): d 1.20 (s, 3H); 1.24 (s, 12H); 1.71 (s, 3H); 2.00 (s, 3H); 2.12 (s, 3H); 2.20 (s, 3H); 2.27-2.35 (d, 2H); 2.40 (s, 3H); 2.74-2.88 (m, 1H); 3.72-3.79 (d, 1H); 3.84-3.90 (d, 1H); 4.15-4.22 (d, 1H); 4.26-4.35 (m, 2H); 4.54(s, 1H); 4.61-4.70 (m, 2H); 4.93-4.99 (d, 1H); 5.10-5.16 (d, 1H); 5.33-5.40 (dd, 1H); 5.67-5.74 (d, 1H); 6.10-6.21 (t, 1H); 6.54 (s, 1H); 7.28-7.42 (m, 5H); 7.45-7.54 (t, 2H); 7.58-7.65 (t, 1H); 8.08-8.14 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 909.3822; theory for $C_{47}H_{61}O_{14}N_2S_1$ is 942.3734; 281, 263, 235, 205, 182, 136, 105, 61, 43.

Example 49 Preparation of 13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56)

A 4 mL quantity Raney Nickel wetted with absolute ethanol is stirred at 0^0C under nitrogen. To this is added by syringe 13-(N-(t-butylamino-carbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (55, 52 mg, 0.057 mM) in 2 mL absolute ethanol. The temperature is kept at 0^oC throughout the reaction and the washing process. The reaction is followed by TLC and left to go for 5 hours. The Raney Nickel is allowed to settle and the supernatant removed by suction. Repeating four times, THF (20 mL) is added, stirred 2 min and removed by suction. The combined washing are evaporated under vacuum, leaving 50 mg solid. The crude product is chromatographed over 5g HPLC grade silica gel, eluting with 50-50 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 29-40 are found to contain 13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56, 18 mg) as a white solid.

TLC: silica gel; 50-50 ethyl acetate-hexane; R_f:0.32.

^{1}H NMR ($CDCL_3$; TMS): d 1.19 (s, 3H); 1.22 (s, 9H); 1.71 (s, 3H); 1.88 (s, 3H); 2.16 (s, 3H); 2.21 (s, 3H); 2.23-2.33 (d, 2H); 2.41 (s, 3H); 2.63-2.78 (m, 1H); 3.32 (s, 3H); 3.78-3.91 (m, 2H); 4.07-4.20 (m, 2H); 4.23-4.32 (d, 1H); 4.59 (bs, 1H); 4.91 (s, 1H); 4.93-5.01 (d, 1H); 5.24-5.34 (dd, 1H); 5.39-5.49 (d, 1H); 5.62-5.70 (d, 1H); 6.04-6.18 (t, 1H); 6.40 (s, 1H); 7.22-7.40 (m, 5H); 7.42-7.53 (t, 2H); 7.54-7.64 (t, 1H); 8.00-8.12 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 863.3992; theory for $C_{46}H_{59}O_{14}N_2$

is 863.3966; 583, 523, 281, 263, 235, 205, 182, 136, 105.

Example 50 Preparation of 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (57)

A 8 mL quantity Raney Nickel wetted with absolute ethanol is stirred at 0^0C under nitrogen. To this is added by syringe 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (54, 100 mg (0.098 mM) in 2 mL absolute ethanol. The temperature is kept at 0^oC throughout the reaction and the washing process. The reaction is followed by TLC and left to go for 3 hours, when it is mostly complete. The Raney Nickel is then allowed to settle and the supernatant removed by suction. Repeating nine times, THF (40 mL) is added, stirred 2 min and removed by suction. All the washings are combined and evaporated under vacuum, leaving 60 mg solid. The crude product is chromatographed over 10g silica gel, eluting with 30-70 ethyl acetate-hexane. Fractions of 3 mL are collected, analyzing them by TLC. Fractions 15-44 are combined and evaporated under vacuum to give 13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (57, 56 mg) as a white solid.

TLC: silica gel; 30-70 ethyl acetate-hexane; R_f:0.29.

^{1}H NMR ($CDCL_3$; TMS): d 0.19-0.46 (m, 6H); 0.70-0.82 (t, 9H); 1.22 (s, 3H); 1.25 (s, 3H); 1.27 (s, 9H); 1.75 (s, 3H); 2.00 (s, 3H); 2.22 (s, 3H); 2.36-2.50 (m, 1H); 2.65 (s, 3H); 3.37 (s, 3H); 3.86-3.95 (m, 2H); 4.19-4.26 (d, 1H); 4.30-4.38 (d, 1H); 4.54-4.60 (d, 1H); 4.96-5.06 (d, 1H); 5.16 (s, 1H); 5.18 (s, 1H); 5.26-5.35 (d, 1H); 5.65-5.74 (d, 1H); 6.20-6.30 (t, 1H); 6.46 (s, 1H); 7.24-7.40 (m, 5H); 7.44-7.55 (t, 2H); 7.57-7.65 (t, 1H); 8.07-8.16 (d, 2H).

Example 51 Preparation of 13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56)

13-(N-(t-butylaminocarbonyl)-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (57, 56 mg, 0.057mM) is stirred at RT under nitrogen in 2 ml 80-20 acetic acid-water. TLC after 10 minutes shows the reaction to be complete. The reaction is then freeze-dried. The crude residue is chromatographed over 7 g HPLC grade silica gel, eluting with 50 mL each of 50-50 and 60-40 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 22-35 are found to contained 13-

(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56, 38 mg) as a white solid upon evaporation.

TLC: silica gel; 60-40 ethyl acetate-hexane; R_f:0.42.

^{1}H NMR ($CDCL_3$; TMS): d 1.20 (s, 3H); 1.22 (s, 3H); 1.23 (s, 9H); 1.72 (s, 3H); 1.89 (s, 3H); 2.21 (s, 3H); 2.23-2.32 (d, 1H); 2.41 (s, 3H); 2.63-2.78 (m, 1H); 2.78-2.92 (m, 3H); 4.12-4.20 (d, 1H); 4.26-4.33 (d, 1H); 4.57-4.63 (m, 1H); 4.70 (s, 1H); 4.92-5.00 (d, 1H); 5.20-5.34 (m, 2H); 5.60-5.68 (d, 1H); 6.07-6.17 (t, 1H); 6.41 (s, 1H); 7.24-7.40 (m, 5H); 7.44-7.53 (t, 2H); 7.56-7.65 (t, 1H); 8.05-8.11 (d, 2H).

Example 52 Preparation of 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III (2)

13-(2'-TES-b-phenyl isoserinyl)-baccatin III (52, 360 mg, 0.401 mM) is stirred at RT under nitrogen in 2 mL dry THF. To this is added di-t-butyldicarbonate (90 mg) dissolved in 1 mL dry THF containing .06 mL triethylamine. The reaction is allowed to proceed for 20 hours, when TLC shows it to be complete. The reaction is evaporated under vaccum and the crude residue chromatographed over 40 g silica gel, eluting with 40-60 ethyl acetate-hexane. Fractions of 15 mL are collected, analyzing them by TLC. Fractions 11-23 are found to contain 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III (2, 360 mg) as a white solid.

TLC: silica gel; 40-60 ethyl acetate-hexane; R_f:0.46.

^{1}H NMR ($CDCL_3$; TMS): d 0.28-0.52 (m, 6H); 0.74-0.85 (t, 9H); 1.16 (s, 3H); 1.30 (s. 3H); 1.31 (s, 9H); 1.69 (s, 3H); 1.90 (s, 3H); 2.24 (s, 3H); 2.33-2.45 (m, 1); 2.53 (s, 3H); 3.80-3.88 (d, 1H); 4.15-4.23 (d, 1H); 4.28-4.37 (d, 1H); 4.39-4.50 (m, 1H); 4.55 (s, 1H); 4.94-5.04 (d, 1H); 5.21-5.34 (bd, 1H); 5.40-5.54 (bd, 1H); 5.65-5.74 (d, 1H); 6.23-6.35 (m, 2H); 7.21-7.43 (m, 5H); 7.43-7.55 (t, 2H); 7.55-7.65 (t, 1H); 8.04-8.16 (d, 2H).

Example 53 Preparation of 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (58)

A 5 mL quantity Raney Nickel wetted with absolute ethanol is stirred at 0^0C under nitrogen. To this is added by syring 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (44, 50 mg , 0.055 mM) dissolved in 2 mL absolute ethanol. The temperature is kept at 0^oC throughout the reaction and the washing process. The reaction is followed by TLC, no starting material remains after 30

minutes. The Raney Nickel is allowed to settle and the the supernatant removed by suction. Repeating eleven times, absolute ethanol (10 mL) is added, stirred 2 min and removed by suction. All the washings are combined and evaporated under vacuum, leaving 33 mg solid. The crude residue is chromatographed over 5g HPLC grade silica gel, eluting with a gradient of 40-60 to 60-40 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 27-40 are found to contain 13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (58, 21mg) as a white solid.

TLC: silica gel; 40-60 ethyl acetate-hexane; R_f:0.25.

^{1}H NMR ($CDCL_3$; TMS): d 1.16 (s, 6H); 1.28 (s, 9H); 1.65 (s, 3H); 1.83 (s, 3H); 2.15 (s, 3H); 2.30 (s, 3H); 2.57-2.75 (m, 1H); 3.28 (s, 3H); 3.32-3.48 (m, 1H); 3.70-3.88 (m, 2H); 4.01-4.16 (d, 1H); 4.18-4.30 (d, 1H); 4.56 (s, 1H); 4.83-4.98 (d, 1H); 5.13-5.27 (d, 1H); 5.32-5.44 (d, 1H); 5.53-5.65 (d, 1H); 6.04-6.19 (t, 1H); 6.36 (s, 1H); 7.13-7.37 (m, 5H); 7.37-7.48 (t, 2H); 7.48-7.60 (t, 1H); 7.94-8.08 (d, 2H).

Mass Spec (FAB, *m/z*) $(M+H)^+$ measured at 864.3805; theory for $C_{46}H_{58}O_{15}N_1$ is 864.3806; 808, 730, 583, 541, 523, 105, 77, 57, 43.

Preparation 1 Preparation of 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III

A solution of 13-(N-Boc-β-phenyl isoserinyl)-baccatin III (2, 1 mmol) in methylene chloride is treated with allyl trichloroacetimidate (2 mmol) and trifluoromethane sulfonic acid (25 mL) and the reaction stirred 48 h at rt. The reaction is filtered and the filtrate washed with 5% aqueous sodium bicarbonate solution. The organic layer is then dried ($MgSO_4$) and the solvent evaporated under vacuum. The residue is purified by chromatography over silica gel, leaving 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III.

Analogous to Kloosterman, M.; de Nijs, M. P.; van Boom, J. H. *J. Carbohyd. Chem.* 1986, *5*, 2247.

Preparation 2 Preparation of 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III

Sodium hydride (55% dispersion in mineral oil, 43 mg, 1 mmol) is washed three times, by decantation, with anhydrous n-hexane. A solution of 13-(N-Boc-β-phenyl isoserinyl)-baccatin III (2, 1 mmol) in anhydrous DMF (6 mL) is add at 0° C and the resulting mixture stirred at rt for 30 min. The resulting mixture is then treated with allyl bromide (1.3 mmol) and stirred for an additional 60 min. The reaction is then quenched with 5% aqueous ammonium chloride solution and extracted with ether. The

organic layer is dried ($MgSO_4$) and the solvent evaporated under vacuum. The residue is purified by chromatography over silica gel, leaving 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III.

Analogous to Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* 1989, *30*, 4669.

Preparation 3 Preparation of 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III

Under an argon atmosphere, tris(dibenzylidineacetone)dipalladium (0.025 mmol), and 1,4-bis(biphenylphosphino)butane (0.1 mmol) are added to tetrahydrofuran (2 mL). This solution is treated with13-(N-Boc-β-phenyl isoserinyl)-baccatin III (2, 1 mmol) and allyl ethyl carbonate in tetrahydrofuran (2 mL). After stirring at 65° C for 4 h, the solvent is evaporated under vacuum. The residue is purified by chromatography over silica gel, leaving 7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III.

Following the procedure described in example 40, 41 and 42 and preparations 1, 2 and 3 but using the appropriate starting material of examples 2 and 11 the following 7-ether-taxol analogs are prepared:

7-(O-methyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III;

7-(O-methyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III;

7-(O-ethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III;

7-(O-ethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III;

7-(O-propyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III;

7-(O-propyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III;

7-(O-allyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III;

7-(O-allyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III;

7-(O-benzyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III;

7-(O-benzyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III;

Taxol and the other starting taxol analogs are known or can be readily prepared by known methods. See The Chemistry of Taxol, Pharmac. Ther., Vol 52, pp 1-34, 1991 as well as:

U.S. Patent Nos. 4,814,470; 4,857,653; 4,942,184; 4,924,011; 4,924,012; 4,960,790; 5,015,744; 5,059,699; 5,136,060; 5,157,049; 4,876,399; 5,227,400, 5,254,580 as well as PCT Publication No. WO 92/09589, European Patent Application 90305845.1 (Publication No. A2 0 400 971), 89400935.6

(Publication No. A1 0 366 841) and 90402333.0 (Publication No. 0 414 610 A1), 87401669.4 (A1 0 253 739), 92308608.6 (A1 0 534 708), 92308609.4 (A1 534 709), and PCT Publication Nos. WO 91/17977, WO 91/17976, WO 91/13066, WO 91/13053 all of which are incorporated herein by reference.

The compounds of the invention can be formulated per se in pharmaceutical preparations or formulated in the form of pharmaceutically acceptable salts thereof, particularly as nontoxic pharmaceutically acceptable addition salts or acceptable basic salts. These salts can be prepared from those compounds of the invention which contain acidic or basic groups according to conventional chemical methods.

Normally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess thereof of the desired salt forming inorganic or organic acid in a suitable solvent or various combination of solvents. As an example, the free base can be dissolved in an aqueous solution of the appropriate acid and the salt recovered by standard techniques, for example, by evaporation of the solution. Alternatively, the free base can be dissolved in an organic solvent such as a lower alkanoyl, an ether, an alkyl ester, or mixtures thereof, for example, methanol, ethanol, ether, ethylacetate, an ethylacetate-ether solution, and the like, whereafter it is treated with the appropriate acid to form the corresponding salt. The salt is recovered by standard recovery techniques, for example, by filtration of the desired salt on spontaneous separation from the solution or it can be precipitated by the addition of a solvent in which the salt is insoluble and recovered therefrom.

The taxol derivatives of the invention can be utilized in the treatment of cancers, due to their cytotoxic, antitumor activity. The new compounds are administrable in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable form. The pharmaceutical preparation which contains the compound is conveniently admixed with a nontoxic pharmaceutical organic carrier or a nontoxic pharmaceutical inorganic carrier, usually about 0.01 mg up to 2500 mg, or higher per dosage unit, preferably 50-500 mg. Typical of pharmaceutically acceptable carriers are, for example, mannitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid, and other conventionally employed acceptable carriers. The

pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

Exemplary of a typical method for preparing a tablet containing the active agents is to first mix the agent with a nontoxic binder such as gelatin, acacia mucilage, ethyl cellulose, or the like. The mixing is suitably carried out in a standard V-blender and usually under anhydrous conditions. Next, the just prepared mixture can be slugged through conventional tablet machines and the slugs fabricated into tablets. The freshly prepared tablets can be coated, or they can be left uncoated. Representative of suitable coatings are the nontoxic coatings including shellac, methylcellulose, carnauba wax, styrene-maleic acid copolymers, and the like. For oral administration, compressed tablets containing 0.01 milligram, 5 milligrams, 25 milligrams, 50 milligrams, 500 milligrams, etc., up to 2500 milligrams are manufactured in the light of the above disclosure and by art known fabrication techniques well known to the art and set forth in Remington's Pharmaceutical Science, Chapter 39, Mack Publishing Co., 1965.

To formulate the tablet, the active compound, cornstarch, lactose, dicalcium phosphate and calcium carbonate are uniformly blended under dry conditions in a conventional V-blender until all the ingredients are uniformly mixed together. Next, the cornstarch paste is prepared as a 10% paste and it is blended with the just prepared mixture until a uniform mixture is obtained. The mixture is then passed through a standard light mesh screen, dried in an anhydrous atmosphere and then blended with calcium stearate, and compressed into tablets, and coated if desired. Other tablets containing 10, 50, 100, 150 mgs, etc., are prepared in a like fashion.

The following Formulation I is an example of a tablet formulation comprising a compound of the invention.

FORMULATION I	
Ingredients:	Per tablet, mg.
Active compound	50.0
Cornstarch	15.0
Cornstarch paste	4.5
Calcium carbonate	15.0
Lactose	67.0
Calcium stearate	2.0
Dicalcium phosphate	50.0

The manufacture of capsules containing 10 milligrams to 2500 milligrams for oral use consists essentially of mixing the active compound with a nontoxic carrier and enclosing the mixture in a polymeric sheath, usually gelatin or the like. The capsules can be in the art known soft form of a capsule made by enclosing the compound in intimate dispersion within an edible, compatible carrier, or the capsule can be a hard capsule consisting essentially of the novel compound mixed with a nontoxic solid such as talc, calcium stearate, calcium carbonate, or the like. Capsules containing 25 mg, 75 mg, 125 mg, and the like, of the novel compound, singularly or mixtures of two or more of the novel compounds are prepared, for example, as follows:

FORMULATION II	
Ingredients	Per Capsule, mg.
Active compound	50.0
Calcium carbonate	100.0
Lactose, U.S.P.	200.0
Starch	130.0
Magnesium stearate	4.5

The above ingredients are blended together in a standard blender and then discharged into commercially available capsules. When higher concentrations of the active agent is used, a corresponding reduction is made in the amount of lactose.

The compounds of the invention can also be freeze dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations suitable for parenteral, injectable administration. For such administration, the formulation can be reconstituted in water (normal, saline), or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like.

The dose administered, whether a single dose, multiple dose, or a daily dose, will of course, vary with the particular compound of the invention employed because of the varying potency of the compound, the chosen route of administration, the size of the recipient and the nature of the patient's condition. The dosage administered is not subject to definite bounds, but it will usually be an effective amount, or the equivalent on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active drug to achieve its desired pharmacological and physiological effects.

Typically the compounds of the invention can be administered by intravenous injection at doses of 1-500 mg per patient per course of treatment, preferable with doses of 2-100 mg, the exact dosage being dependent on the age, weight, and condition of the patient. An example of a suitable formulation for injection is using a solution of the compound of the invention in a mixture of polysorbate alcohol and dehydrated alcohol (e.g., 1:1) followed by dilution with 5% dextrose in water prior to infusion or injection.

The compounds of Formula I are useful for the same cancers for which taxol has been shown active, including human ovarian tumors, mammary tumors, and malignant

melanoma, lung tumors, gastric tumors, colon tumors, head and neck tumors, and leukemia. See, e.g., the clinical pharmacology of taxol is reviewed by Eric K. Rowinsky and Ross C. Donehower, The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics, Pharmac. Ther., Vol 52, pp 35-84, 1991. Clinical and preclinical studies with taxol are reviewed by William J. Slichenmyer and Daniel D. Von Hoff, Taxol: A New and Effective Anti-cancer Drug, Anti-Cancer Drugs, Vol. 2, pp 519-530, 1991.

The biological activity of the 7-deoxy-7-ether-taxol compounds (Formula I) of the invention has been confirmed using well known procedures. For example, comparison of the cytotoxicity of Cpd 8 with taxol itself in L1210 mouse leukemia carcinoma cells in culture indicated that the IC_{90} (90% growth inhibitory concentration) for 7-(O-methoxymethyl)-13-(N-Boc-2'-β-phenyl isoserinyl)-baccatin III (8) was 0.0011 micrograms/ml and for taxol was 0.017 micrograms/ml. In an *in vitro* tubulin polymerization assay, conducted after the manner of F. Gaskin, et al., J. Mol. Biol., 89:737, 1974, 7-(O-ethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (4) and 7-(O-methoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (27) were was able to induce tubulin polymerization *in vitro* at 20°C in a manner very similar to taxol.

The biological activity of the compounds of this invention has been further confirmed using well known procedures against L1210 leukemia and the results set forth in Table I. The results were obtained using standard well known procedure (Li, L.H.; Kuentzel, S.L.; Murch, L.L.; Pschigoga, L.M.; and W.C. Krueger, "Comparative biological and biochemical effects of nogalamycin and its analogs on L1210 leukemia," Cancer Res. 39:4816-4822 (1979)). The results are expressed as an IC_{50} which is the drug concentration required to inhibit cell proliferation to 50% of that of untreated control cells. Lower numbers indicated greater activity.

TABLE I

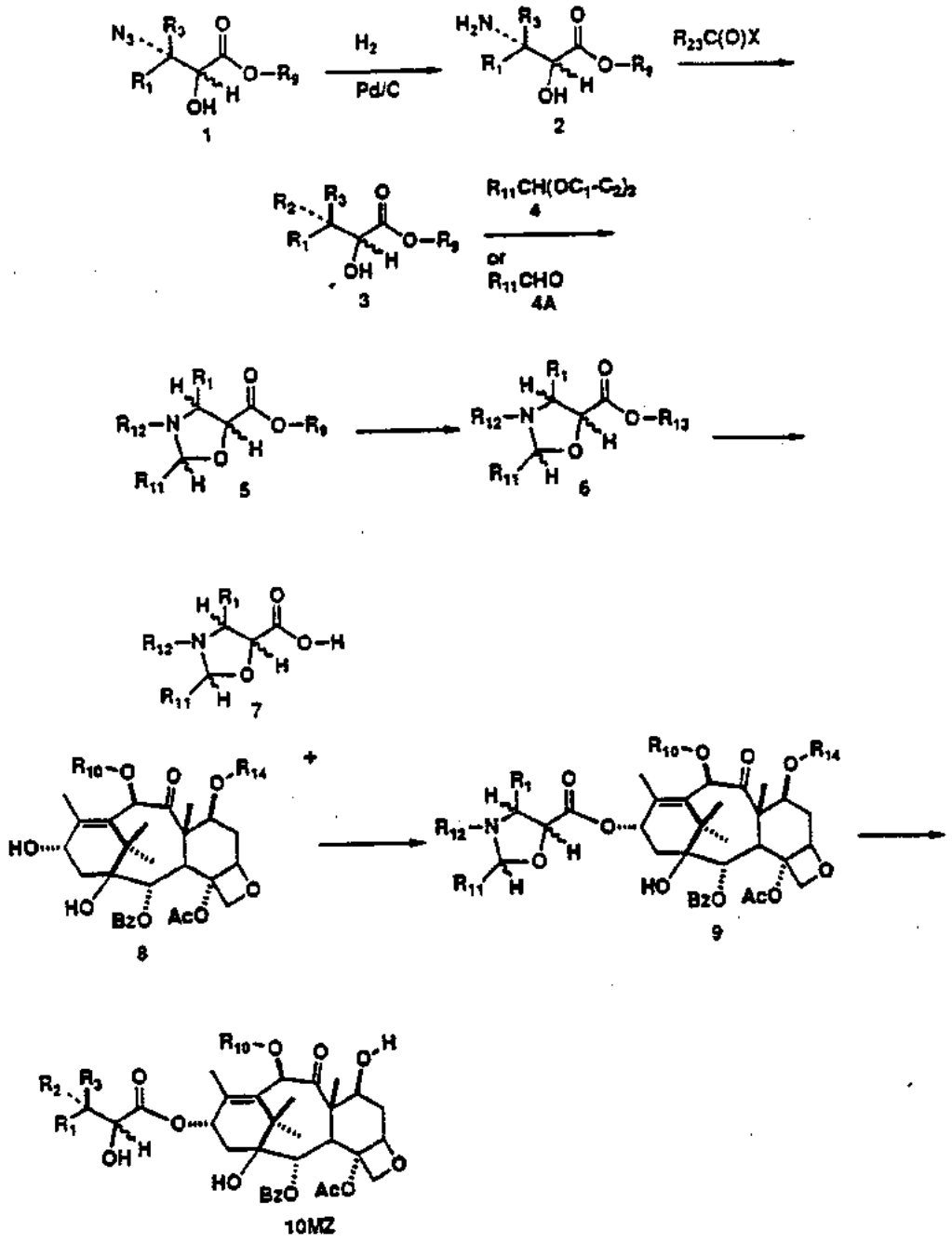
Compound	L1210 (IC_{50} ug/ml)
taxol	0.017
taxotere	0.004
6	0.0023
8	0.0011
10	0.001
14	0.0014
21	0.0024
22	0.0047

The biological activity of the compounds of this invention has been further confirmed using well known procedures against A2780 human ovarian carcinoma and the results set forth in Table II. The results were obtained using standard well known procedure (Perez, R. P.; O'Dwyer, P. J.; Handel, L. M.; Ozols, R. F.; Hamilton, T. C. Int. J. Cancer 1991, 48, 265, Alley, M.C.; Scudiero, D. A.; Monks, A.; Hursey, M. L; Czerwinski, M. J.; Fine, D. L.; et al. Cancer Res 1988, 48, 589).

TABLE II

Compound	A2780 (IC_{50} μg/ml)
taxol	0.0018
taxotere	0.0007
4	0.0007
14	0.00007
27	0.00004
42	0.00047
44	0.00037
46	0.0016
47	0.0007 0.00044 (retest)
49	0.0057
55	0.00025
56	0.00034
58	0.00038

CHART A'



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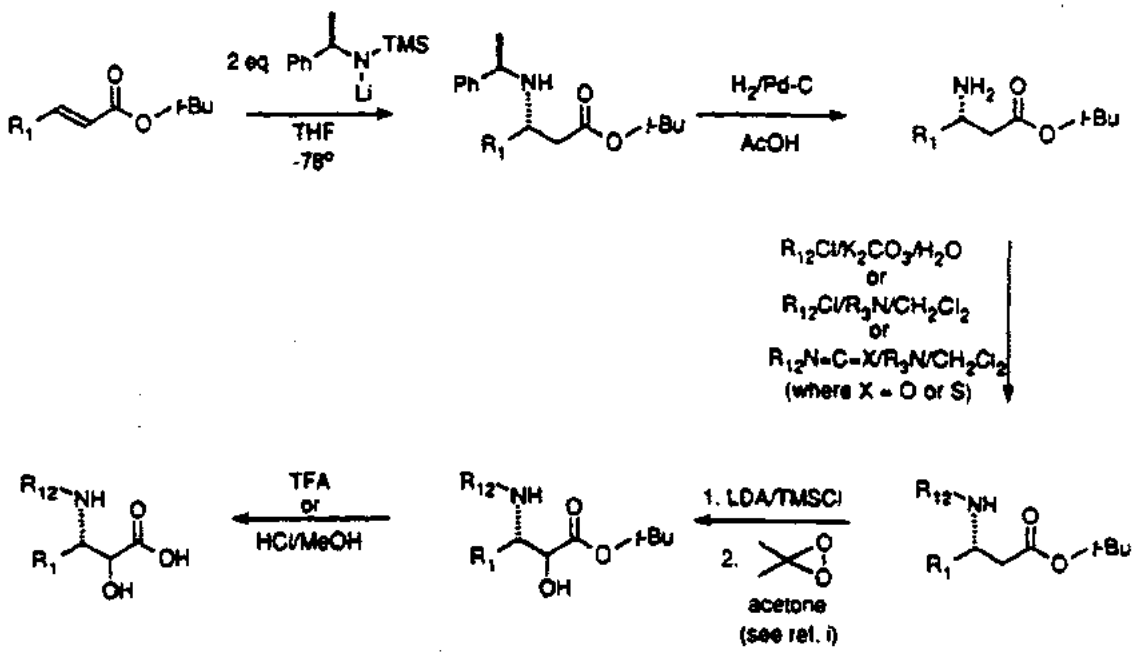
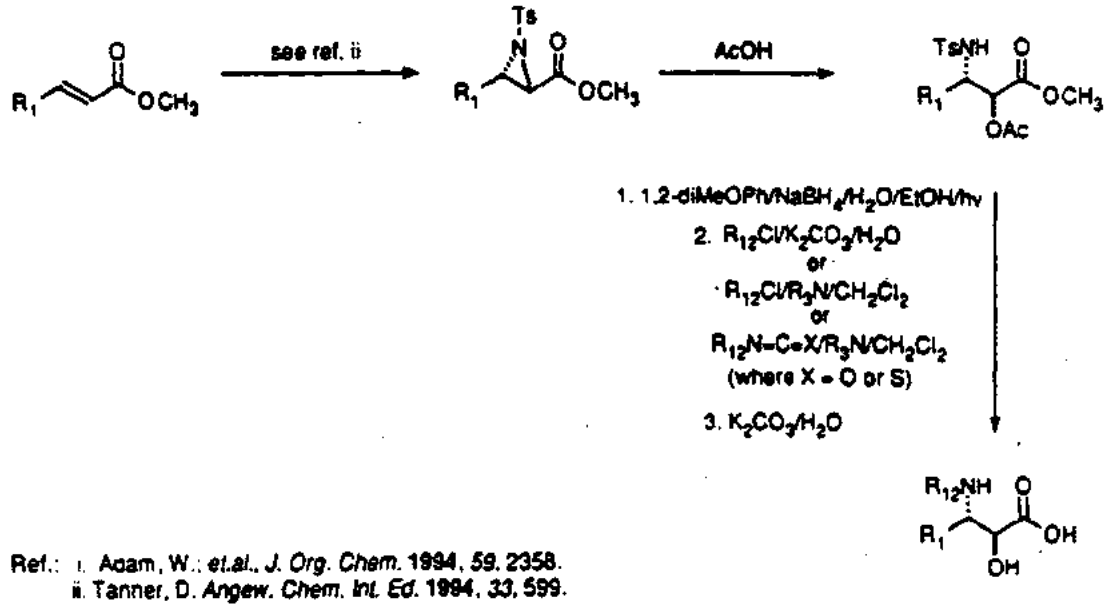
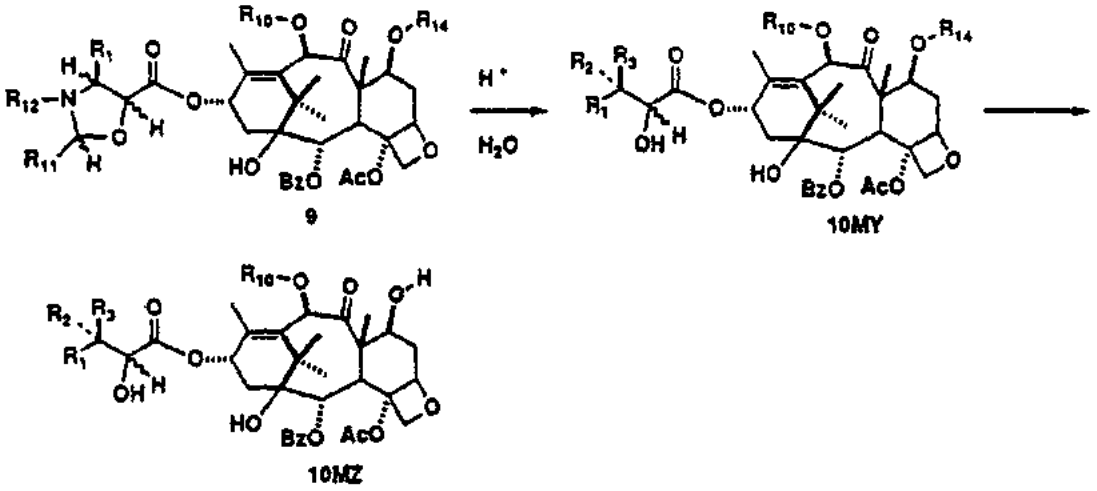


Chart A''



Ref.: i. Adam, W.; *et.al., J. Org. Chem.* **1994**, *59*, 2358.
ii. Tanner, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 599.

CHART B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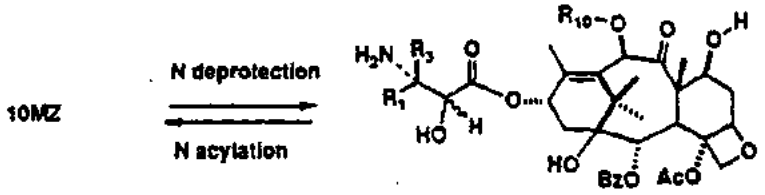
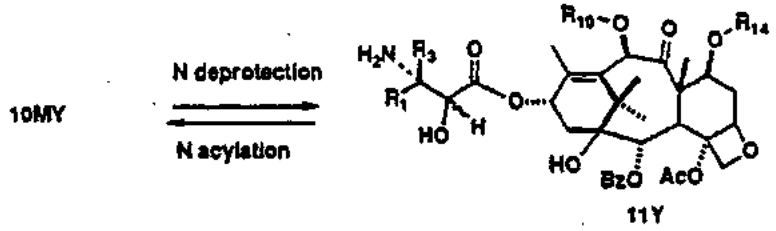

10MZ
N deprotection
N acylation
11Z


10MY
N deprotection
N acylation
11Y

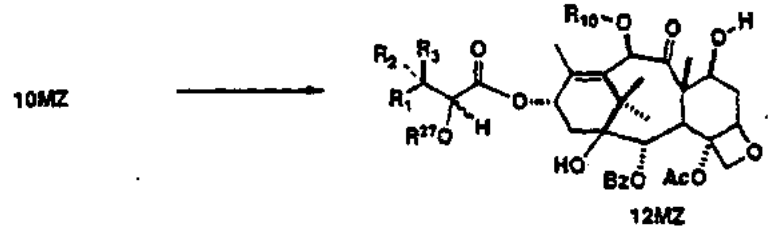

10MZ
12MZ

CHART D

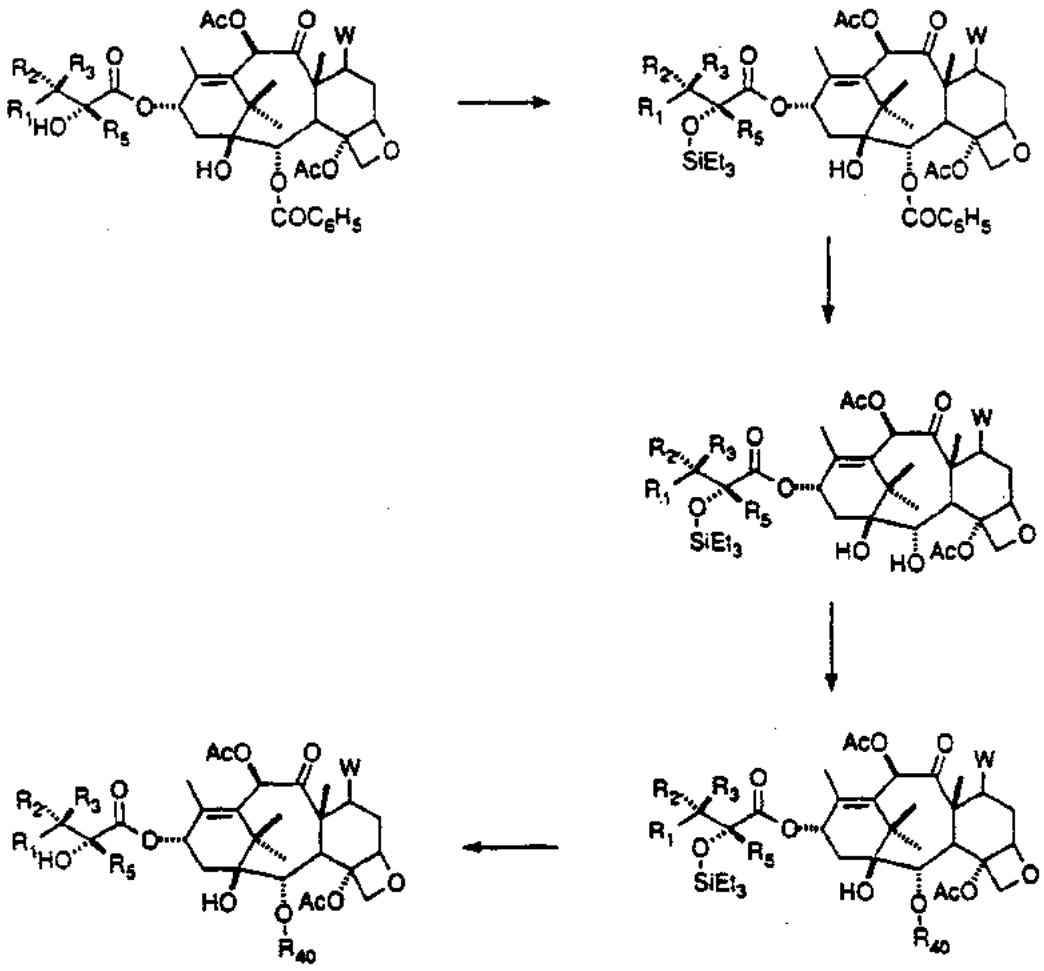
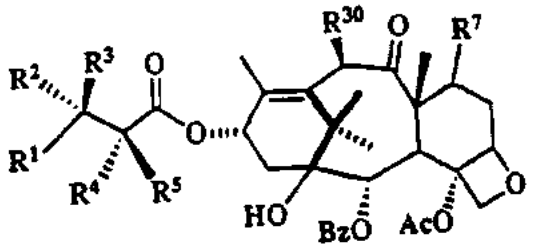
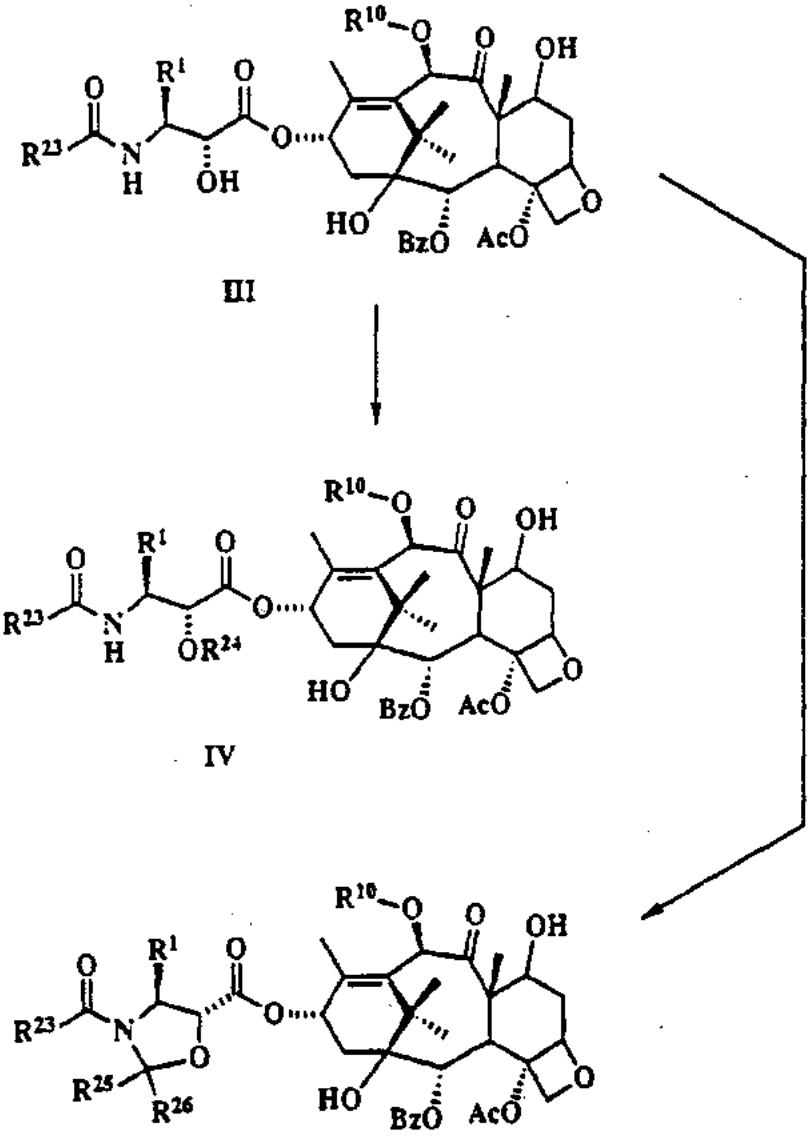


CHART 1



I

CHART 2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O
O
OH
R1
O
O
R23
N
H
OH
HO
BzO
AcO
O
III
R10
O
O
OH
R1
O
O
R23
N
H
OR24
HO
BzO
AcO
O
IV
R10
O
O
OH
R1
O
O
R23
N
R25
R26
O
HO
BzO
AcO
O
V

CHART 3

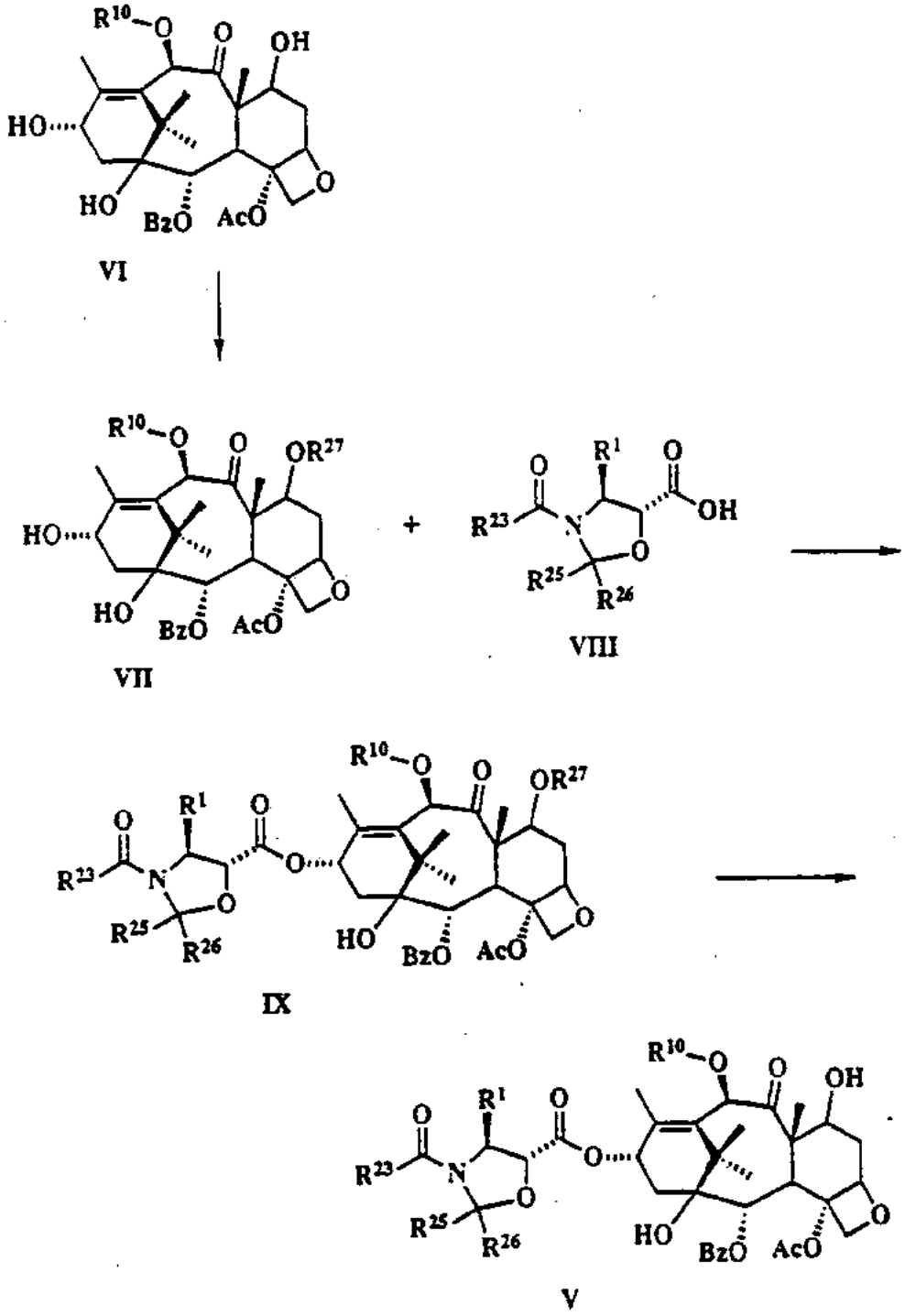
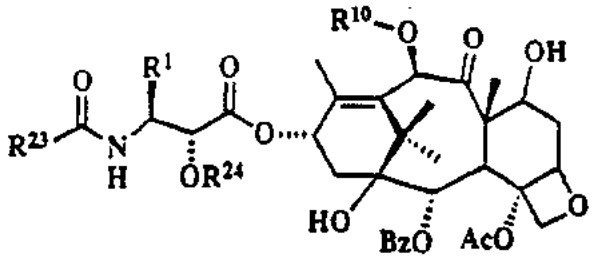
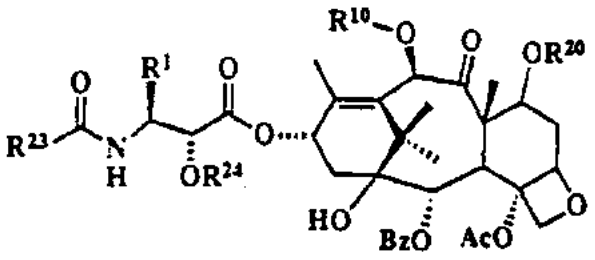

R10
O
O
OH
HO
HO
BzO
AcO
VI
R10
O
O
OR27
HO
HO
BzO
AcO
VII
+
R1
O
O
R23
N
OH
O
R25
R26
VIII
R10
O
O
OR27
R1
O
O
R23
N
O
R25
R26
O
HO
BzO
AcO
IX
R10
O
O
OH
R1
O
O
R23
N
O
R25
R26
O
HO
BzO
AcO
V

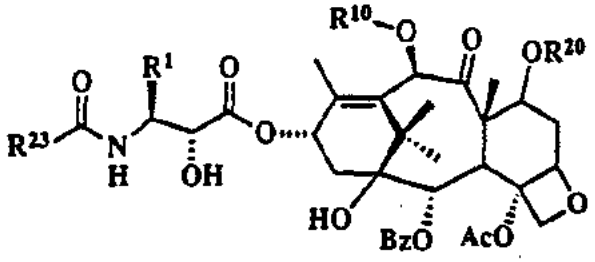
CHART 4



IV

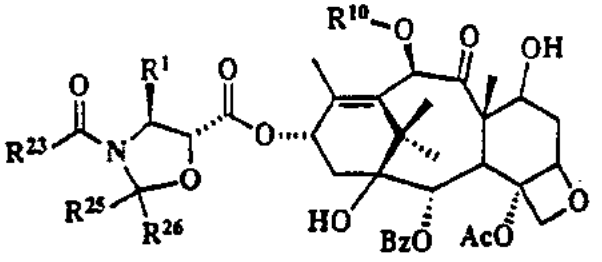


X

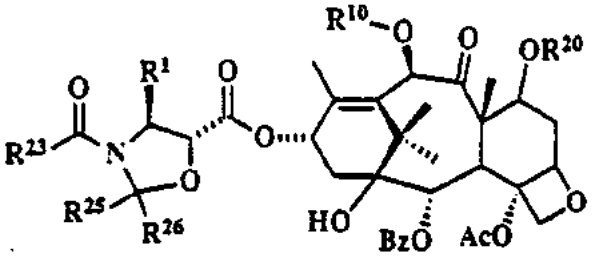


XI

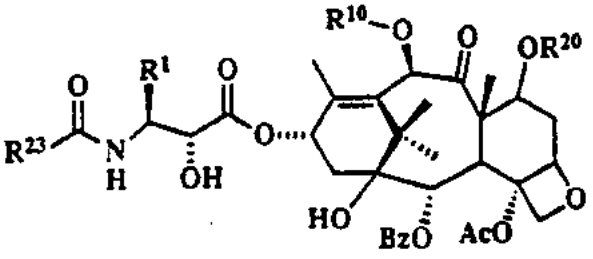
CHART 5



V



XII



XI

CHART 6

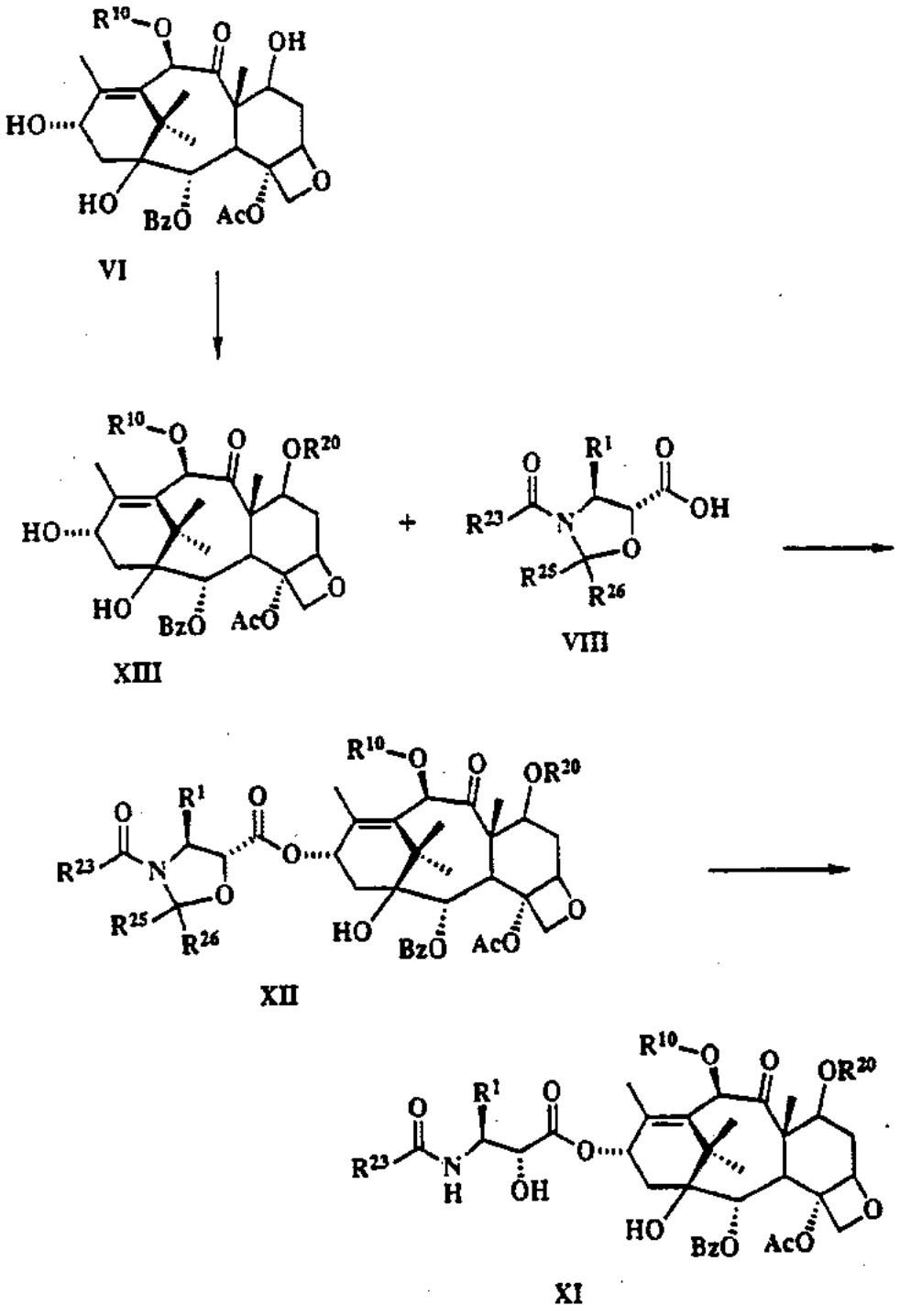


CHART 7

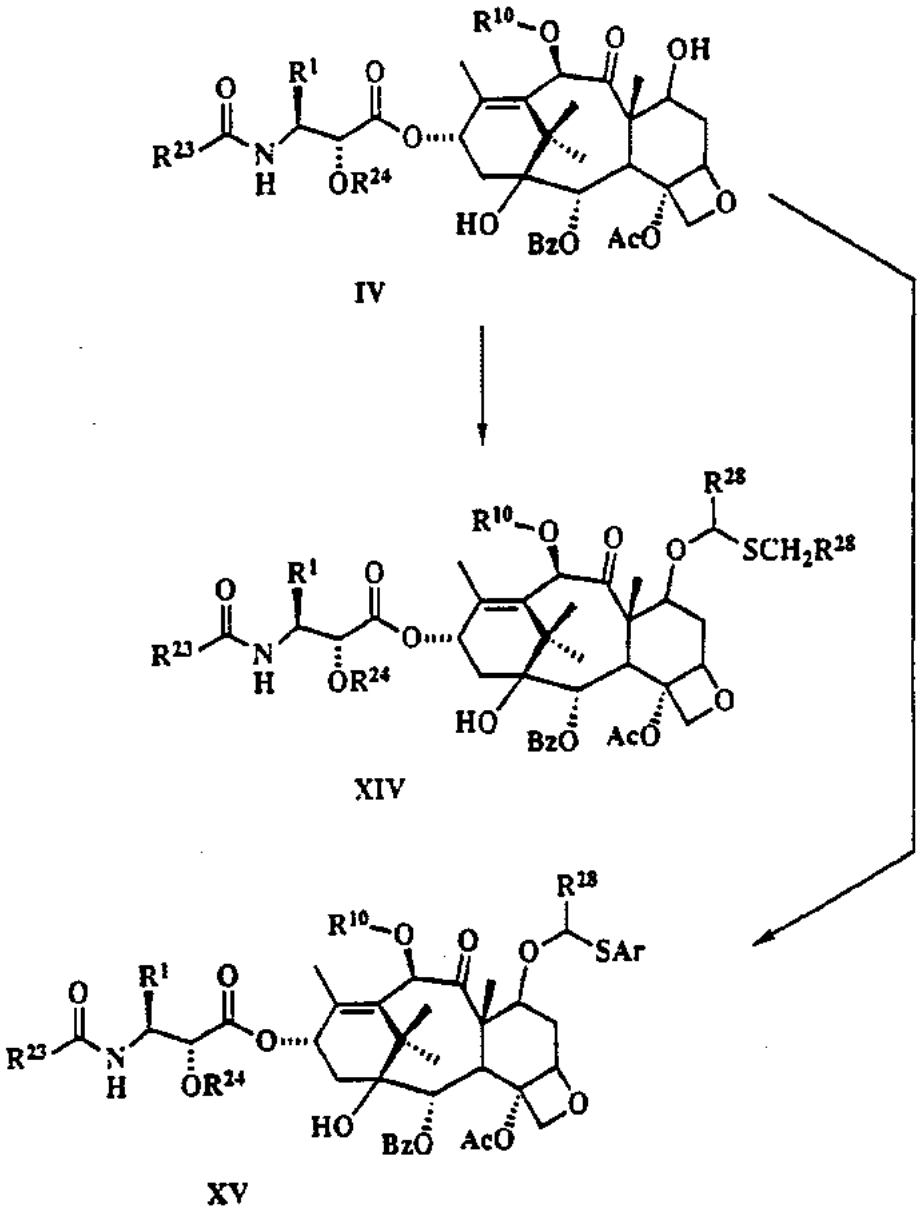


CHART 8

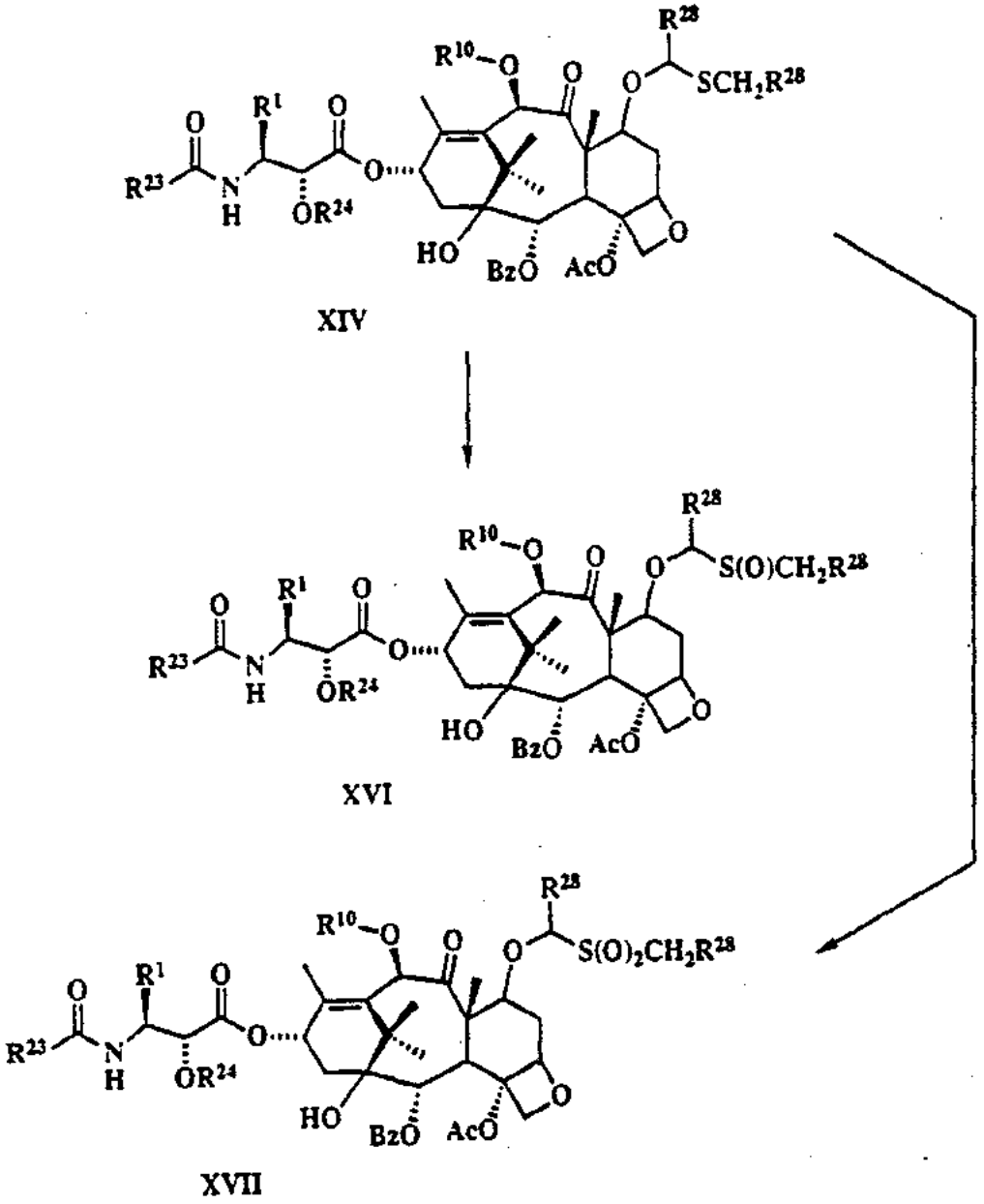


CHART 9

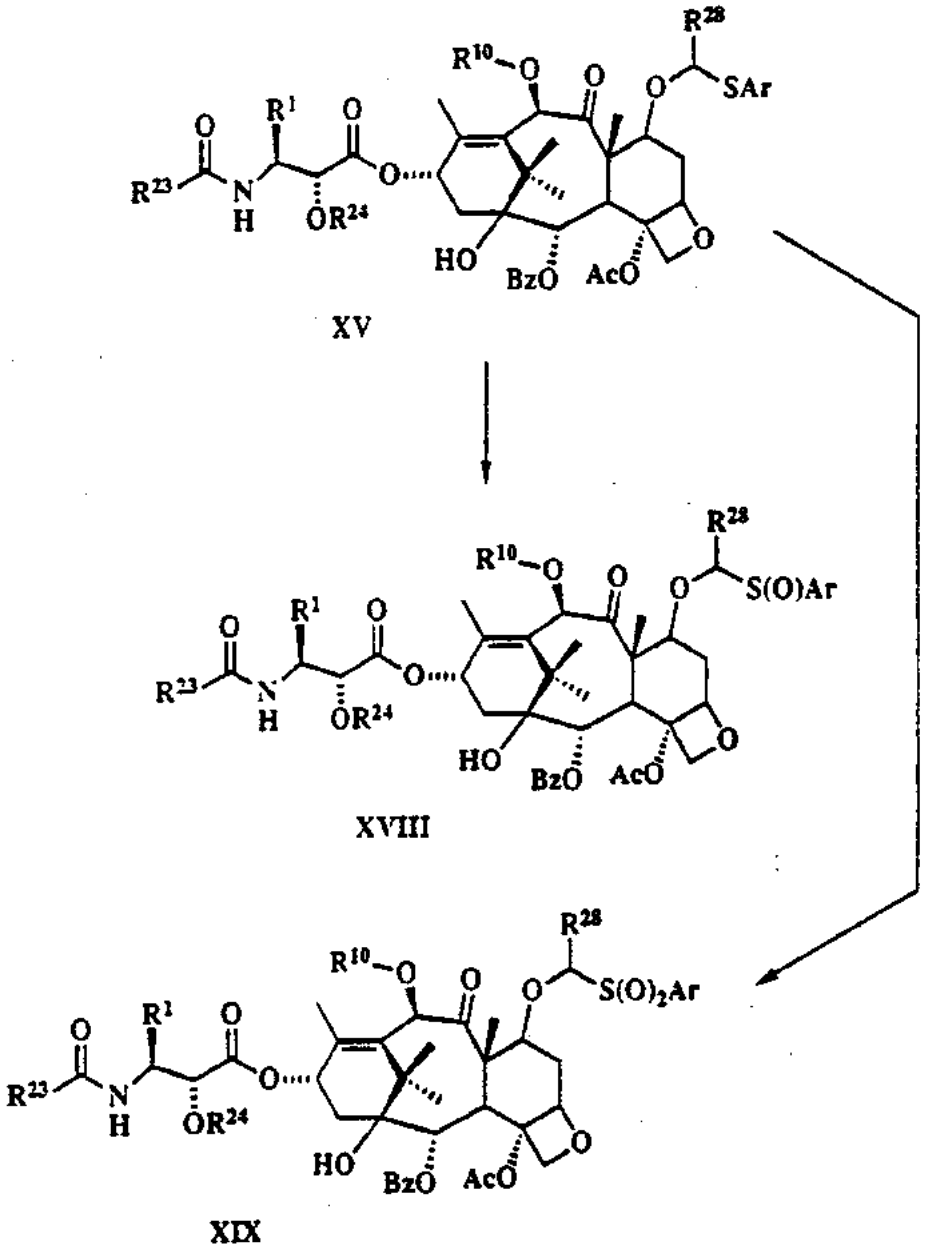
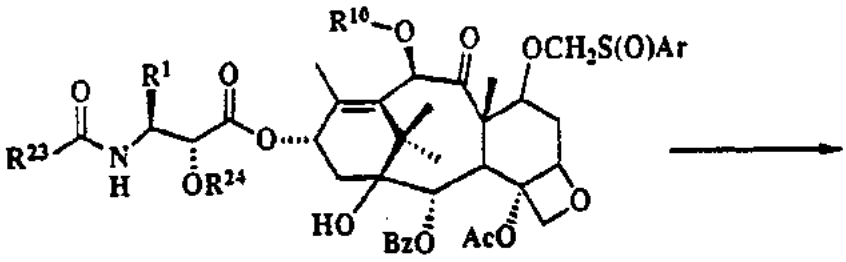
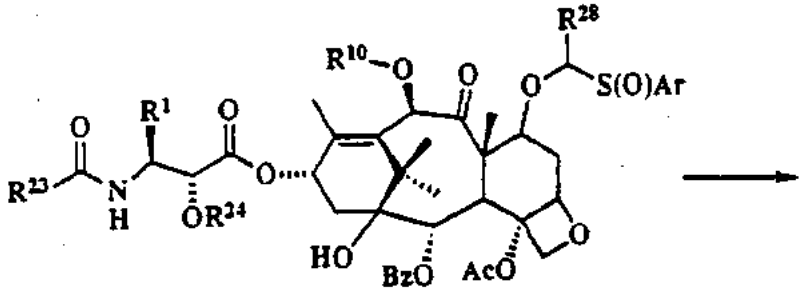

R28
R10
O
O
O
SAr
R1
O
O
R23
N
H
OR24
O
HO
BzO
AcO
O
XV
R28
R10
O
O
O
S(O)Ar
R1
O
O
R23
N
H
OR24
O
HO
BzO
AcO
O
XVIII
R28
R10
O
O
O
S(O)2Ar
R1
O
O
R23
N
H
OR24
O
HO
BzO
AcO
O
XIX

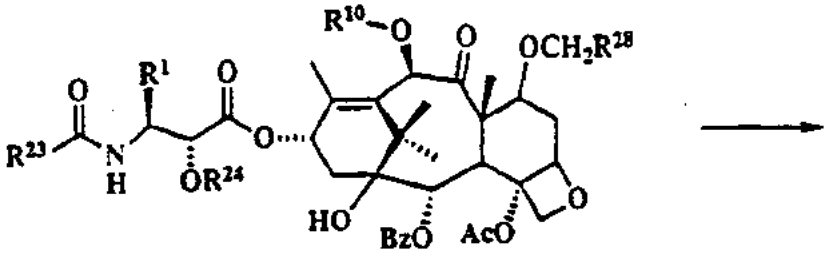
CHART 10



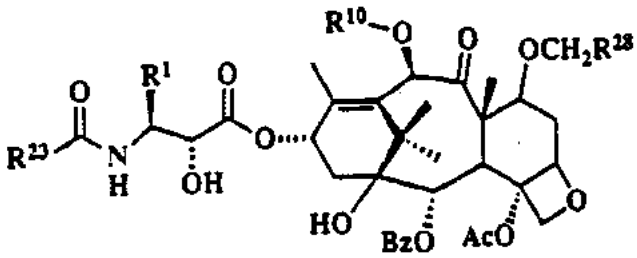
XVIII, R^{28} = H



XVIII, R^{28} not H

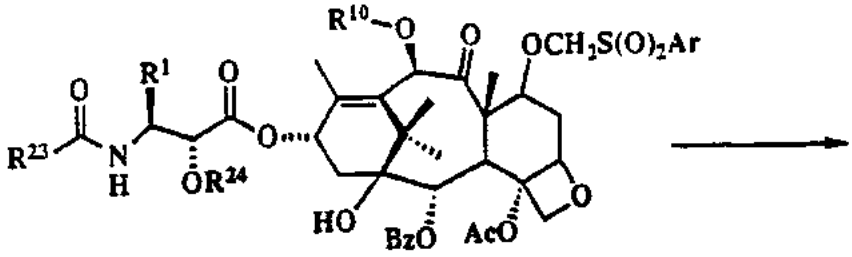


XX

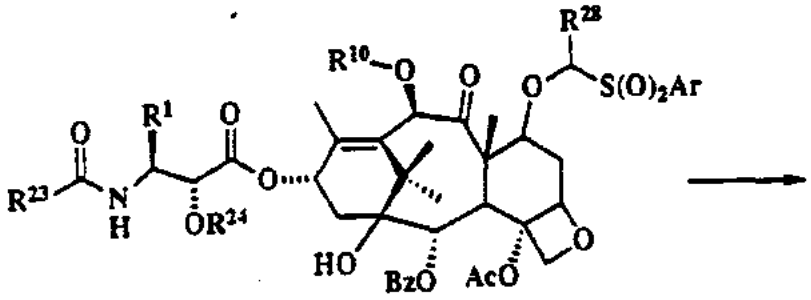


XXI

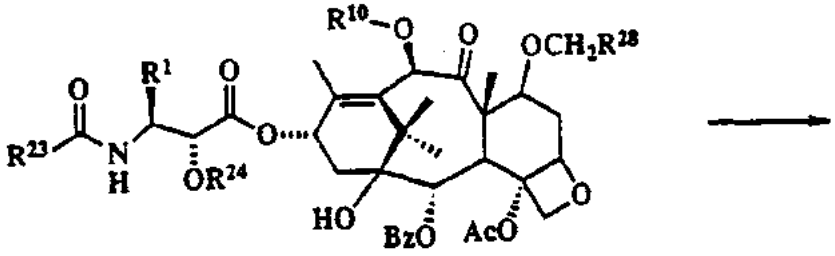
CHART 11



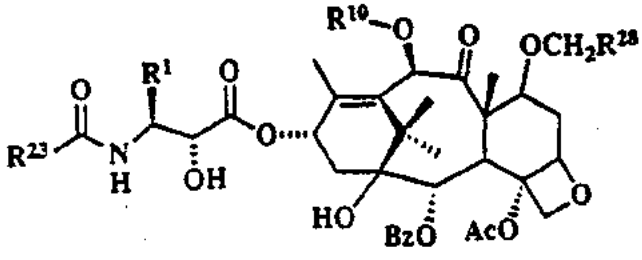
XIX, R^{28} = H



XIX, R^{28} not H



XX



XXI

CHART 12

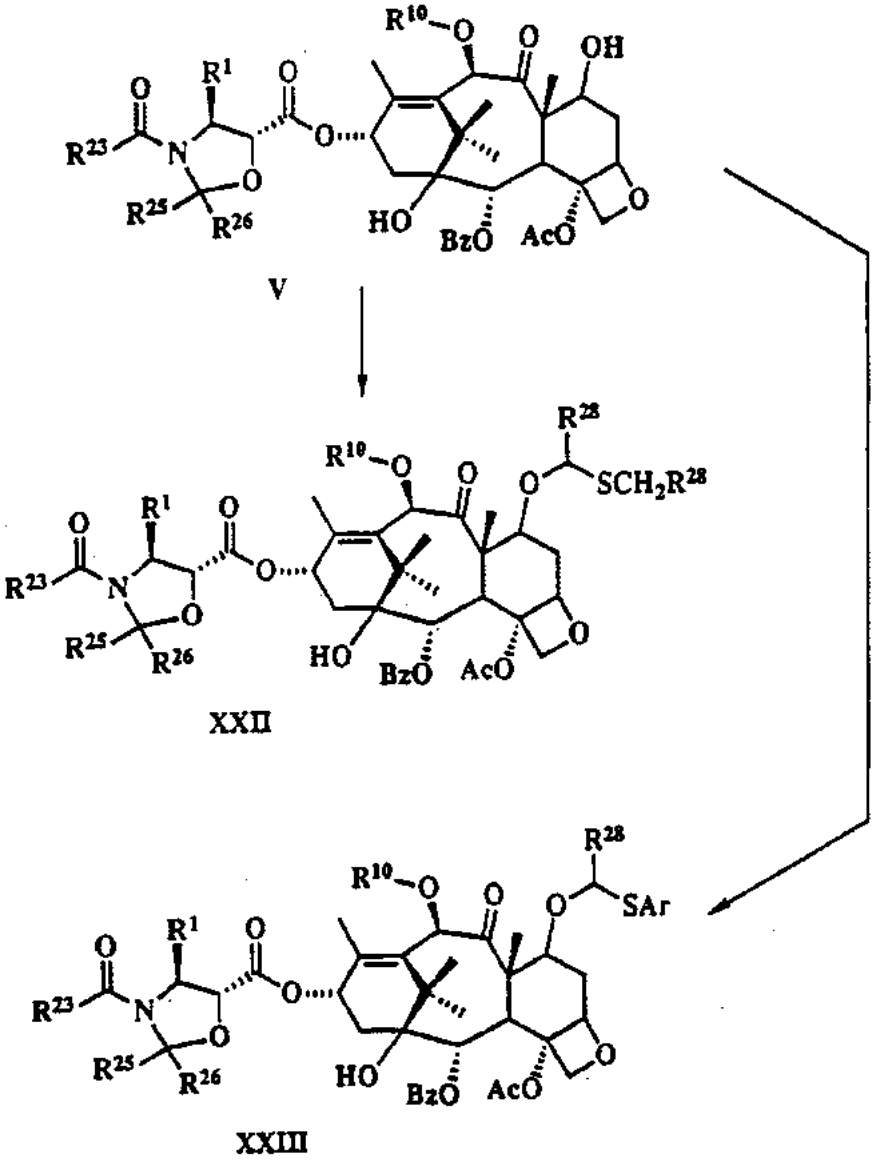

R10
O
O
OH
R1
O
R23
N
O
O
R25
R26
HO
BzO
AcO
V
R28
SCH2R28
XXII
SAr
XXIII

CHART 13

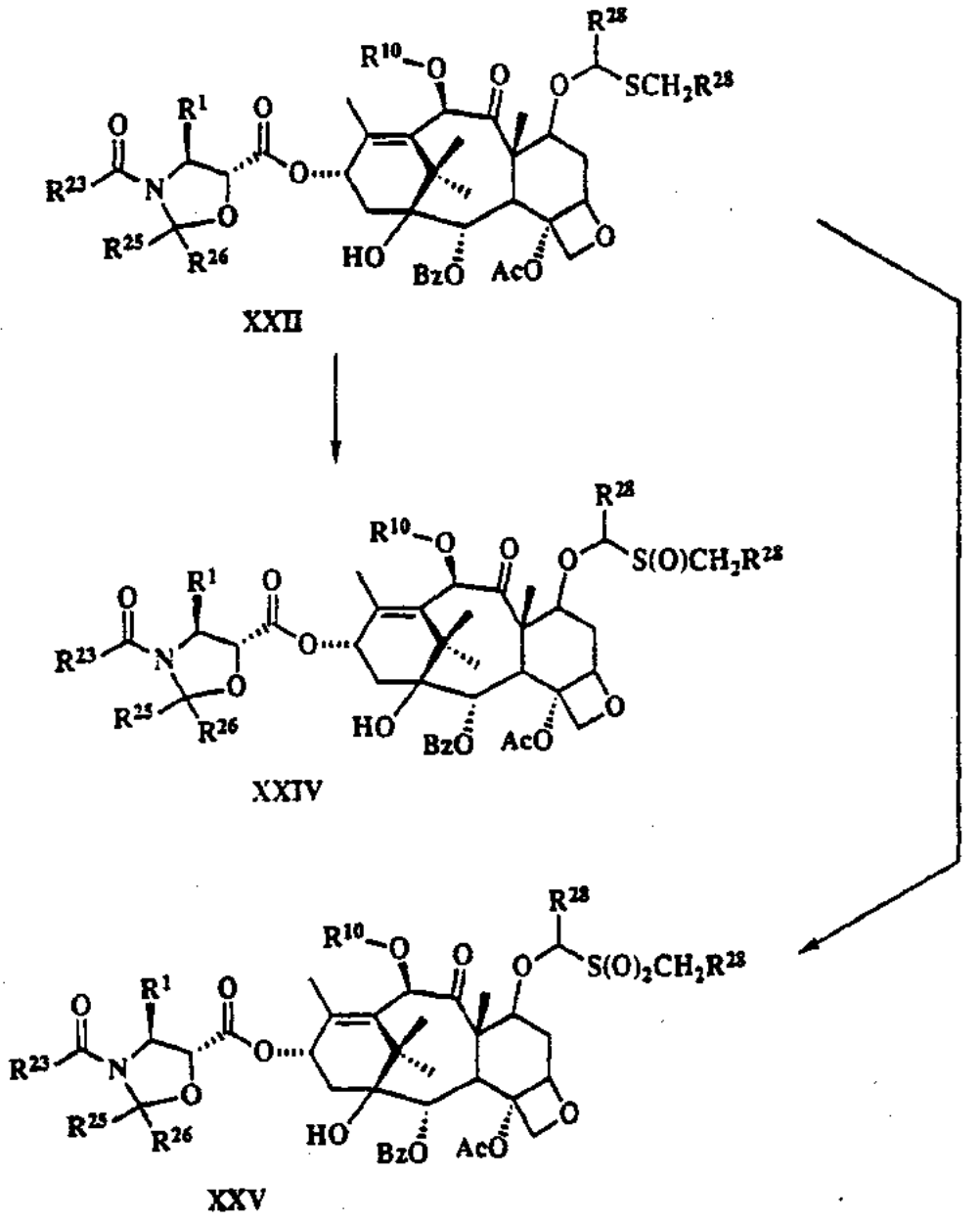
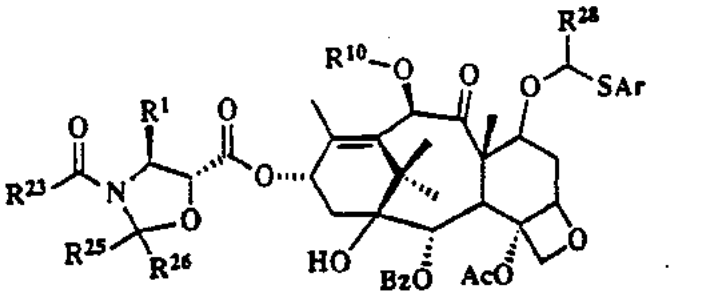
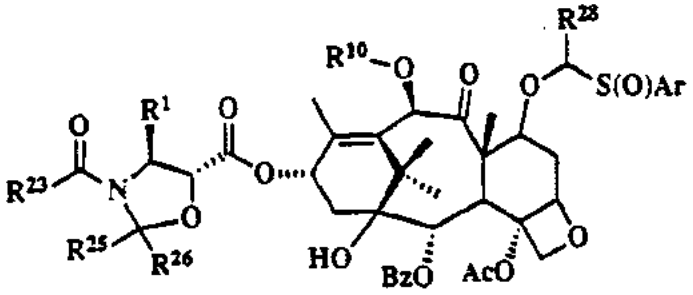


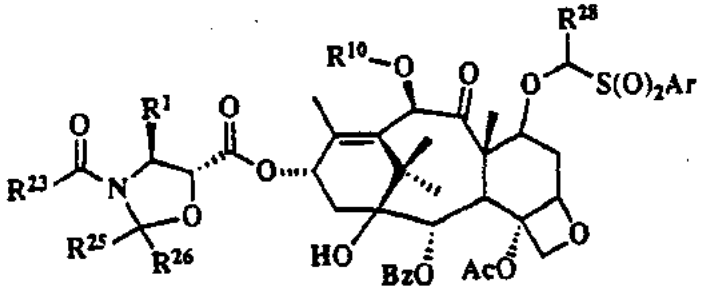
CHART 14



XXIII

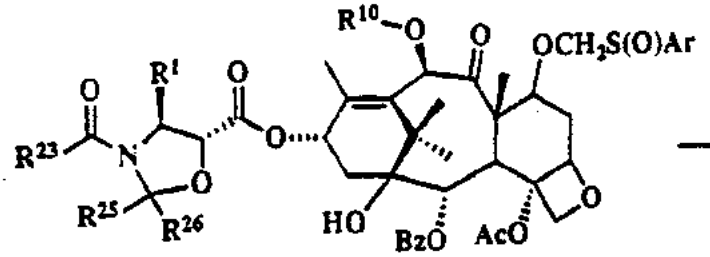


XXVI

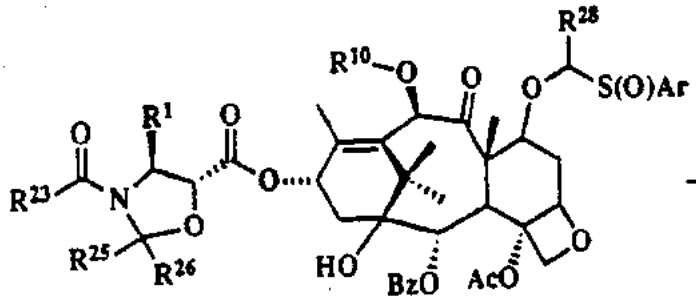


XXVII

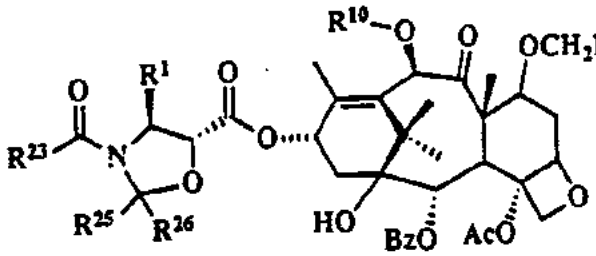
CHART 15



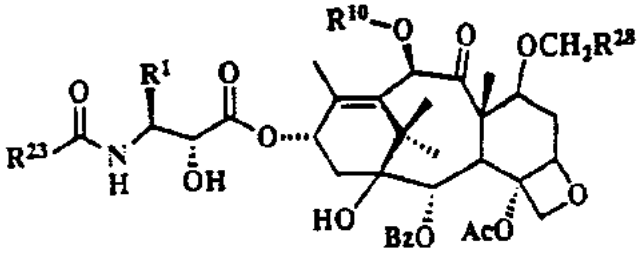
XXVI, R^{28} = H



XXVI, R^{28} not H

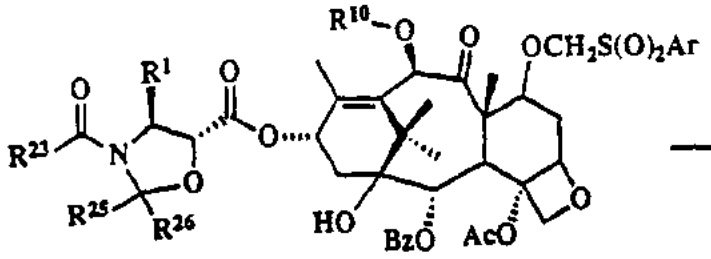


XXVIII

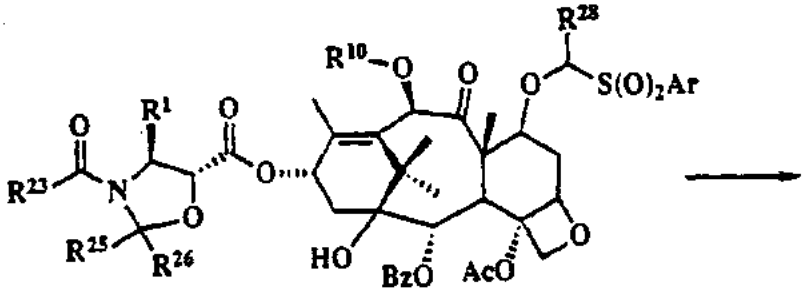


XXI

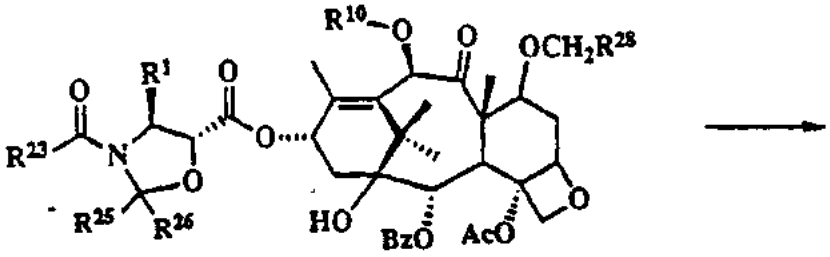
CHART 16



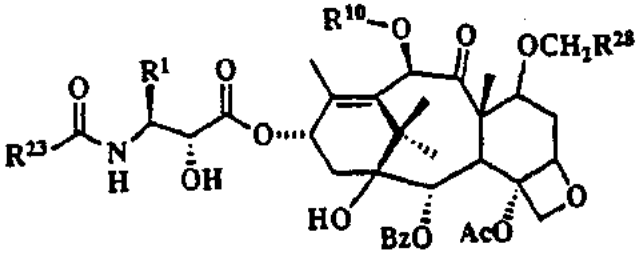
XXVII, R^{28} = H



XXVII, R^{28} not H

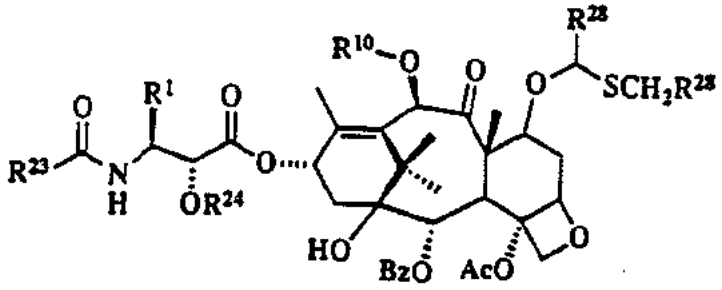


XXVIII

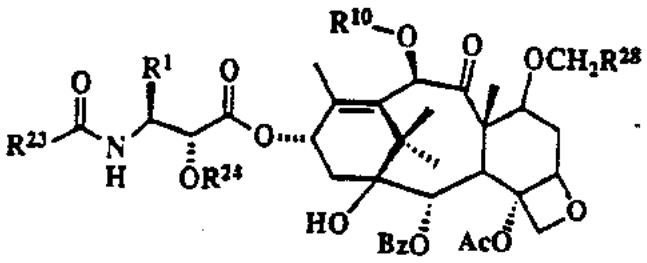


XXI

CHART 17

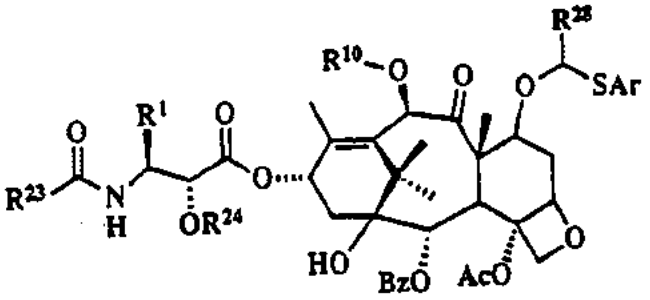


XIV

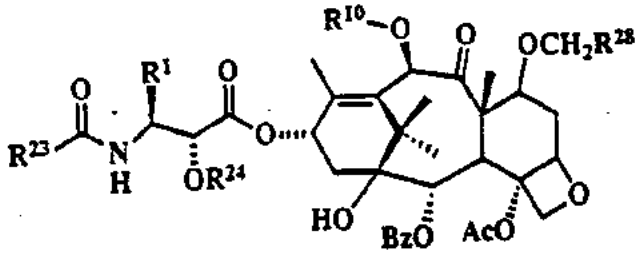


XX

CHART 18

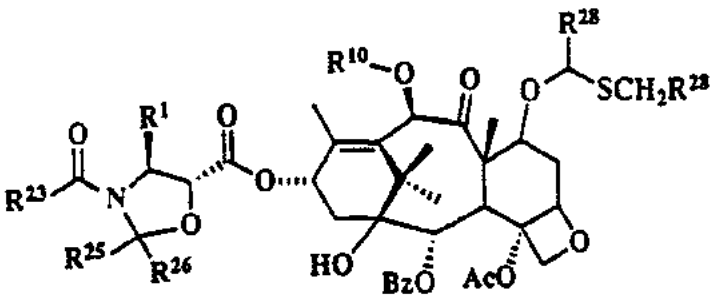


XV

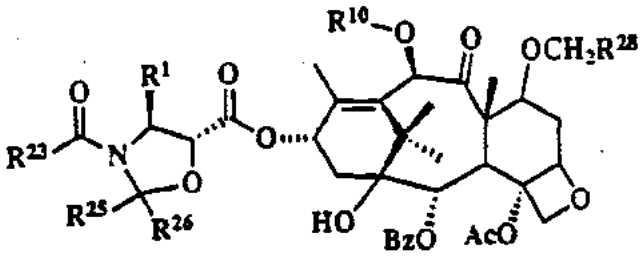


XX

CHART 19

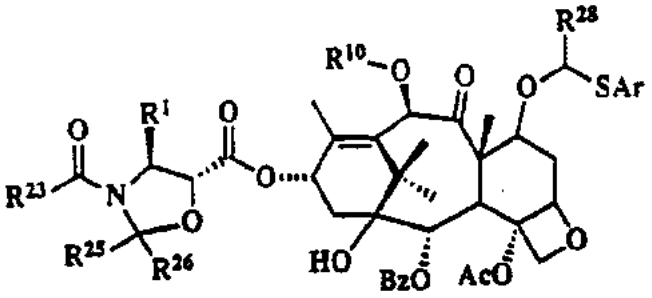


XXII

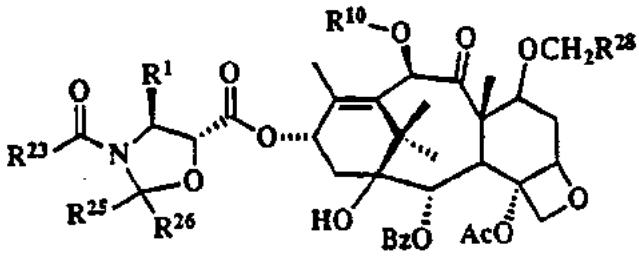


XXVIII

CHART 20

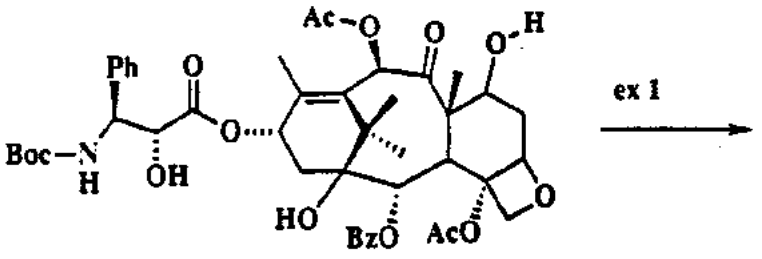


XXIII



XXVIII

FORMULA CHART: 1



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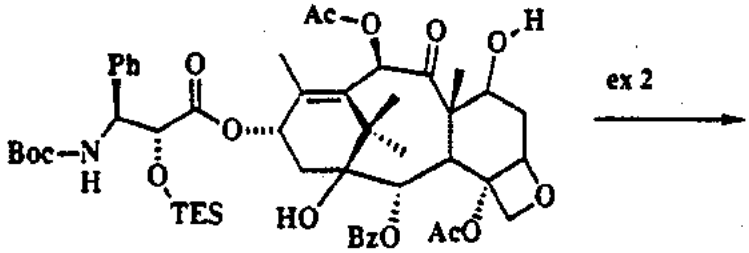

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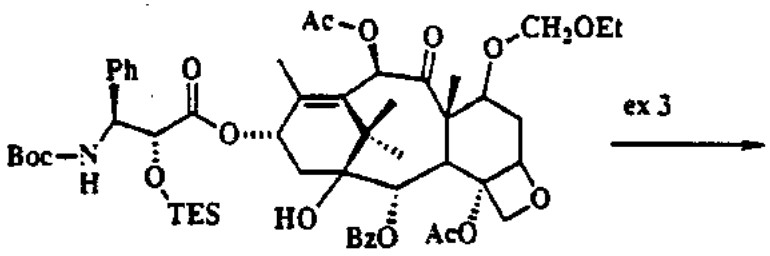

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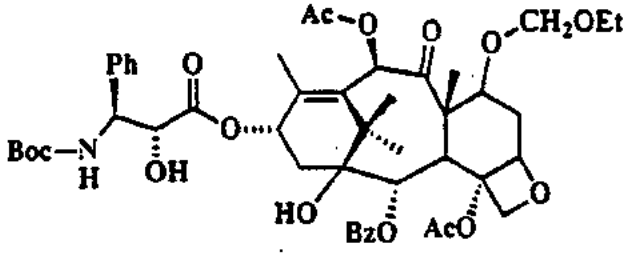

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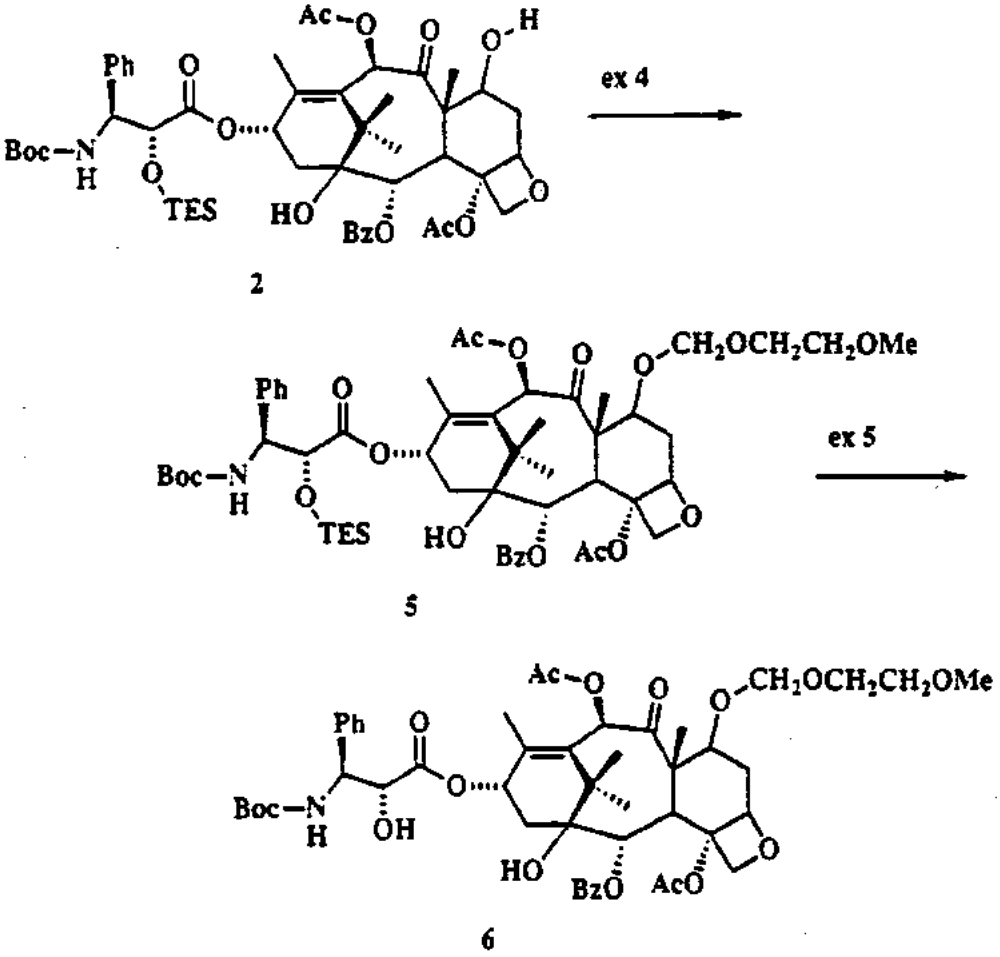

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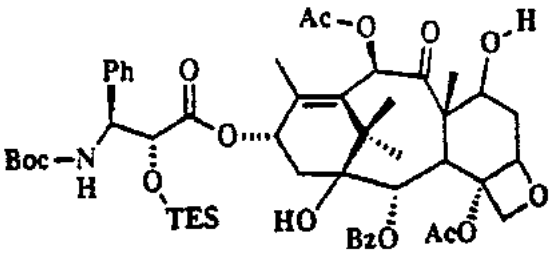

ex 6

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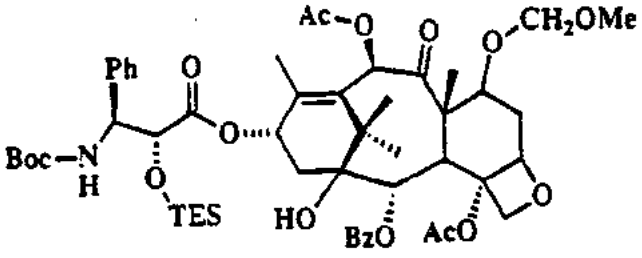

ex 7

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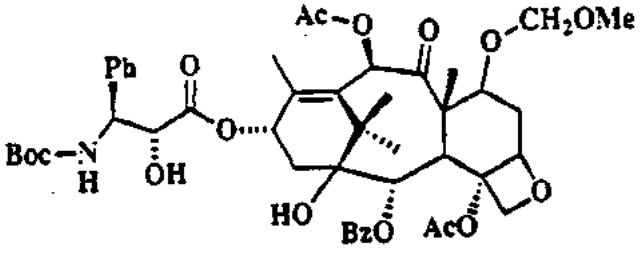

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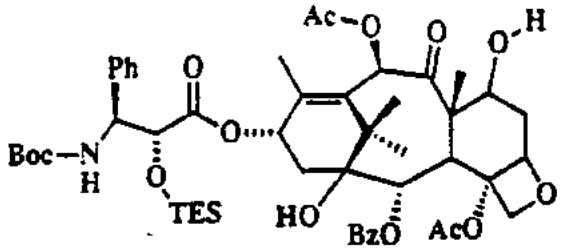

ex 8

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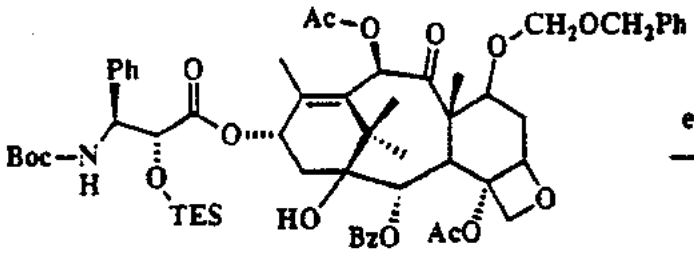
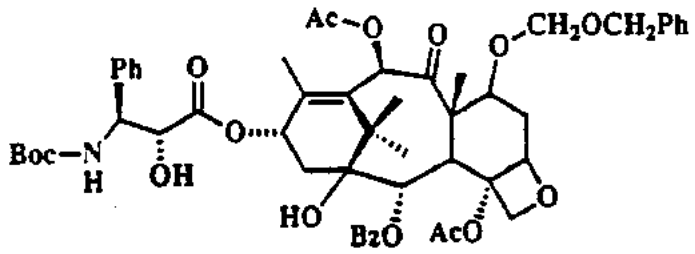


ex 9

9



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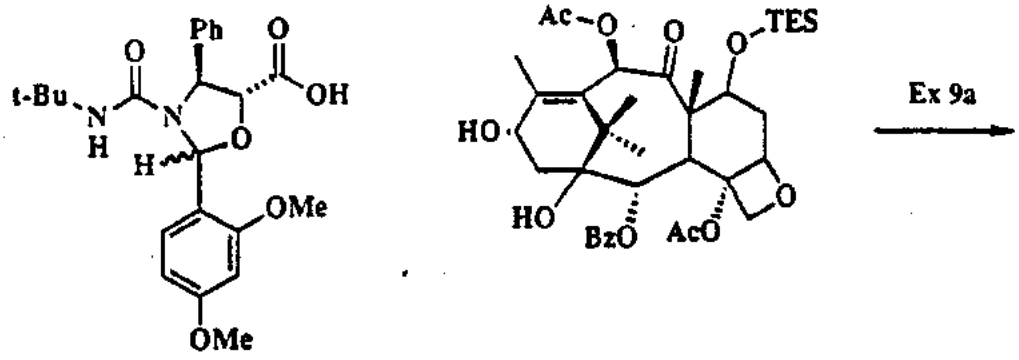

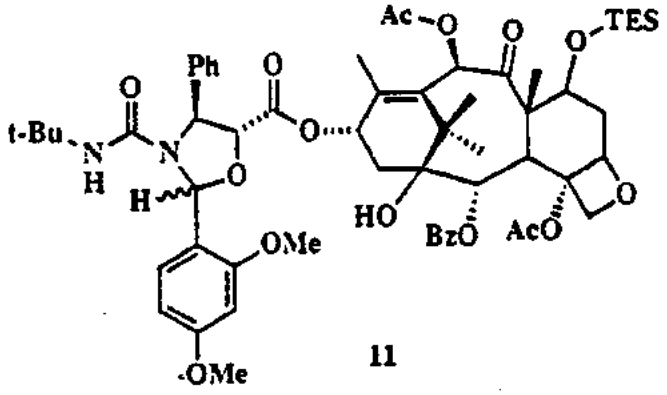

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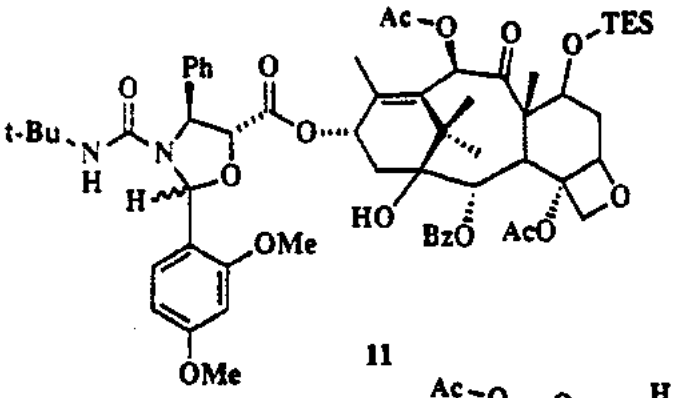

Ex 10

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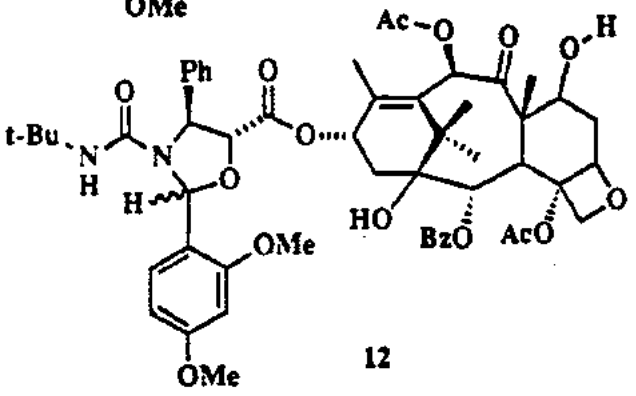
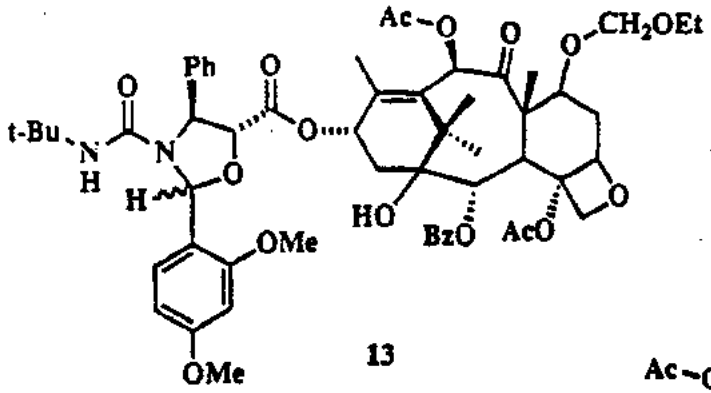


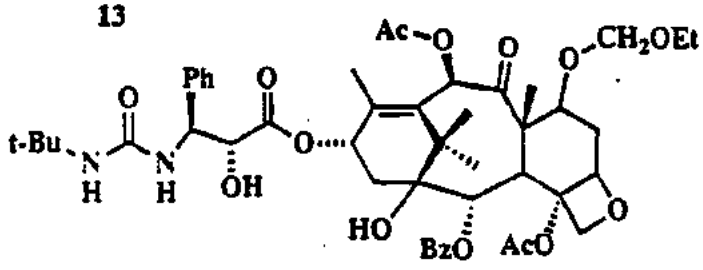
Ex 11

12



Ex 12

13



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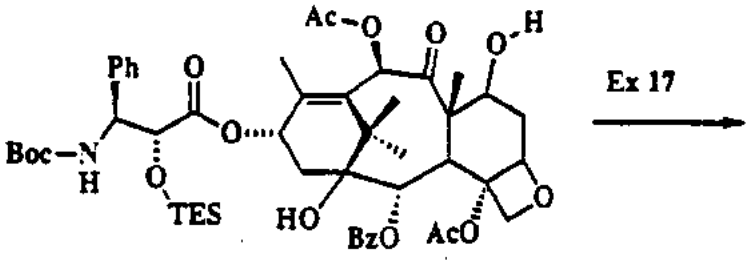

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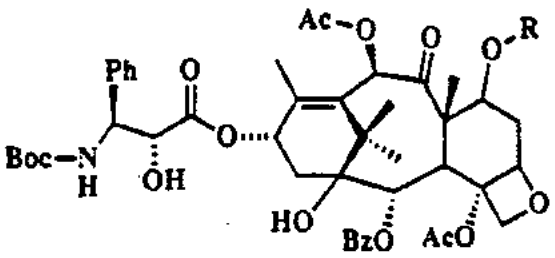
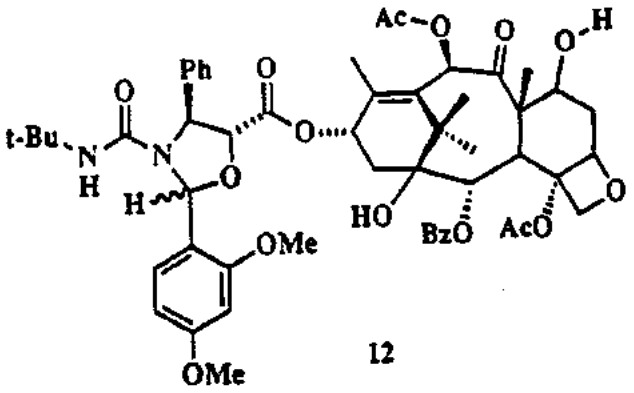


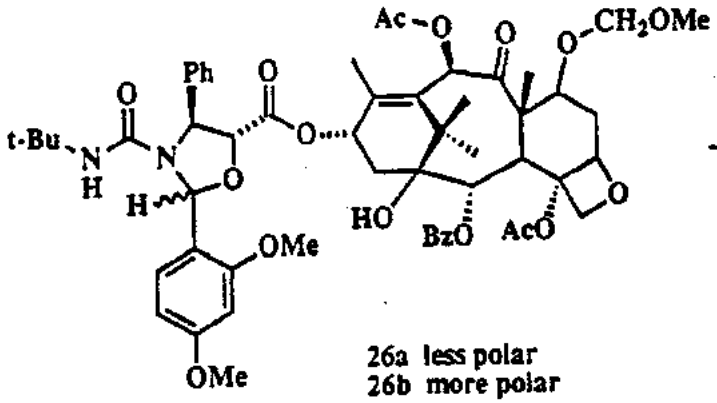
21 R = $CH_2OCH_2CCl_3$
22 R = $CH_2OCH_2OCH_2CCl_3$

FORMULA CHART: 10



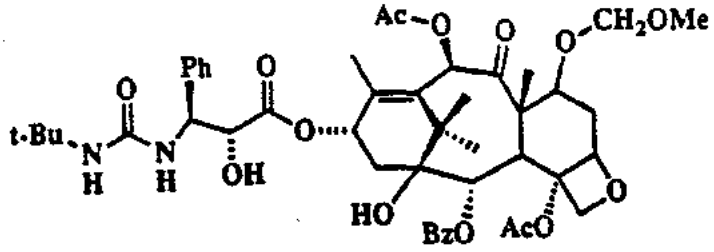
Ex 21

12



Ex 22

26a less polar
26b more polar



27

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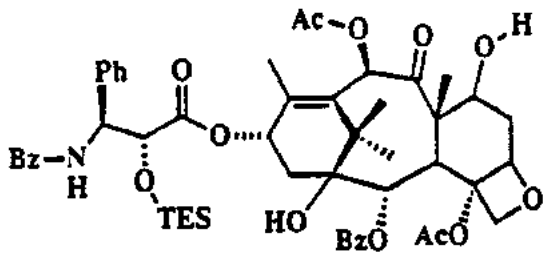
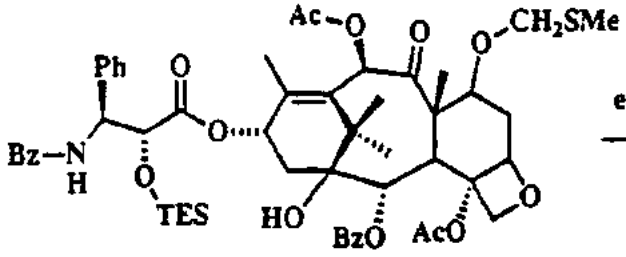


ex 35

40



ex 36

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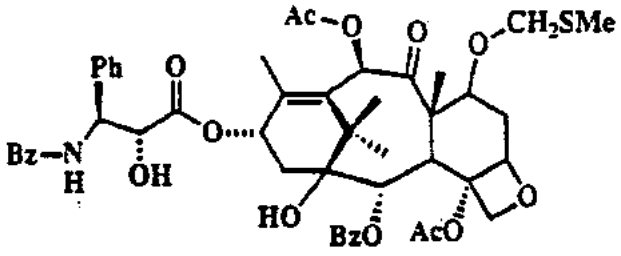

42

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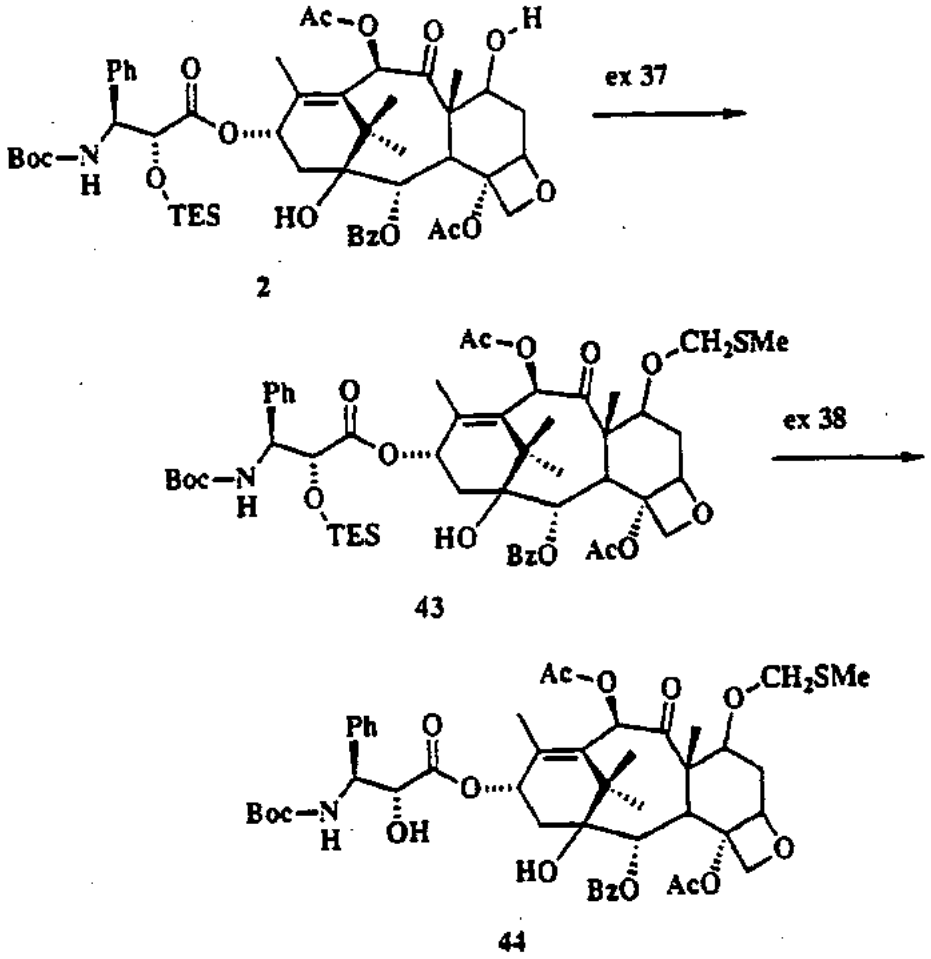

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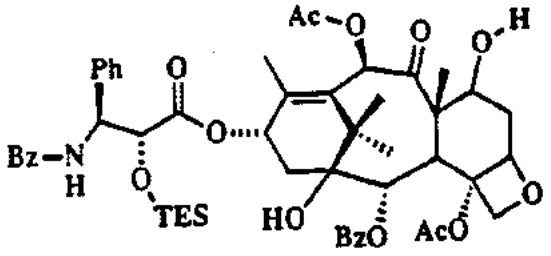

ex 39

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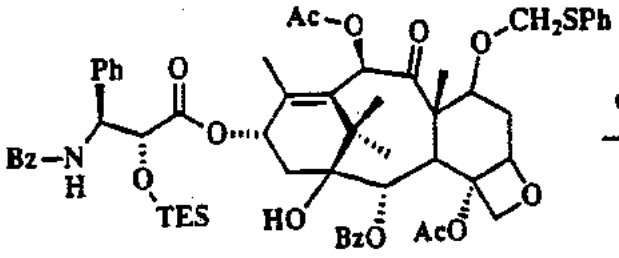

ex 40

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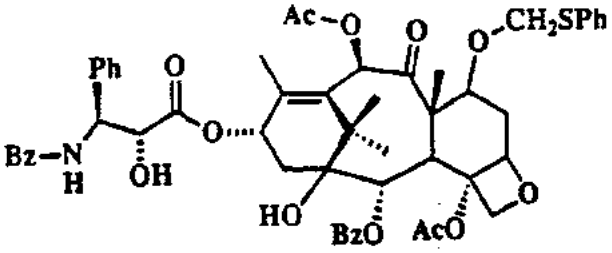

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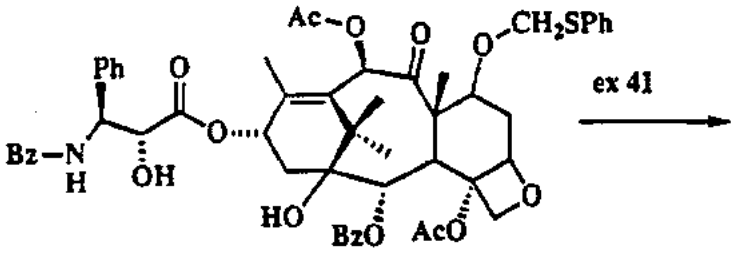

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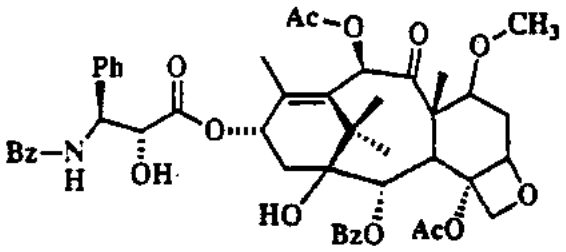

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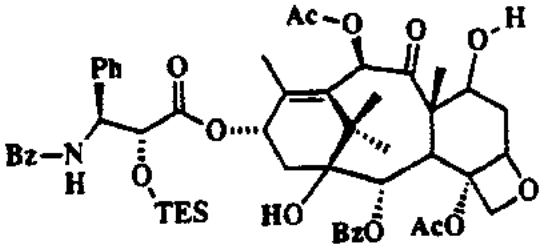

ex 42

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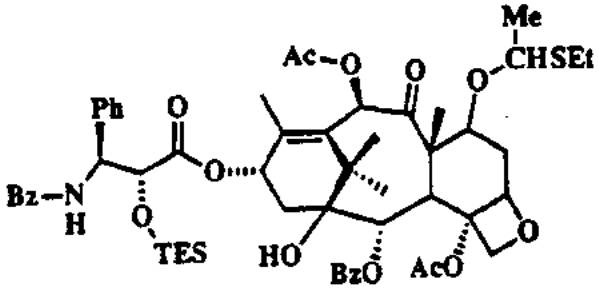

ex 42

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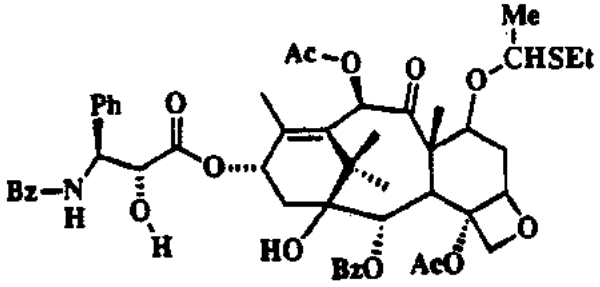

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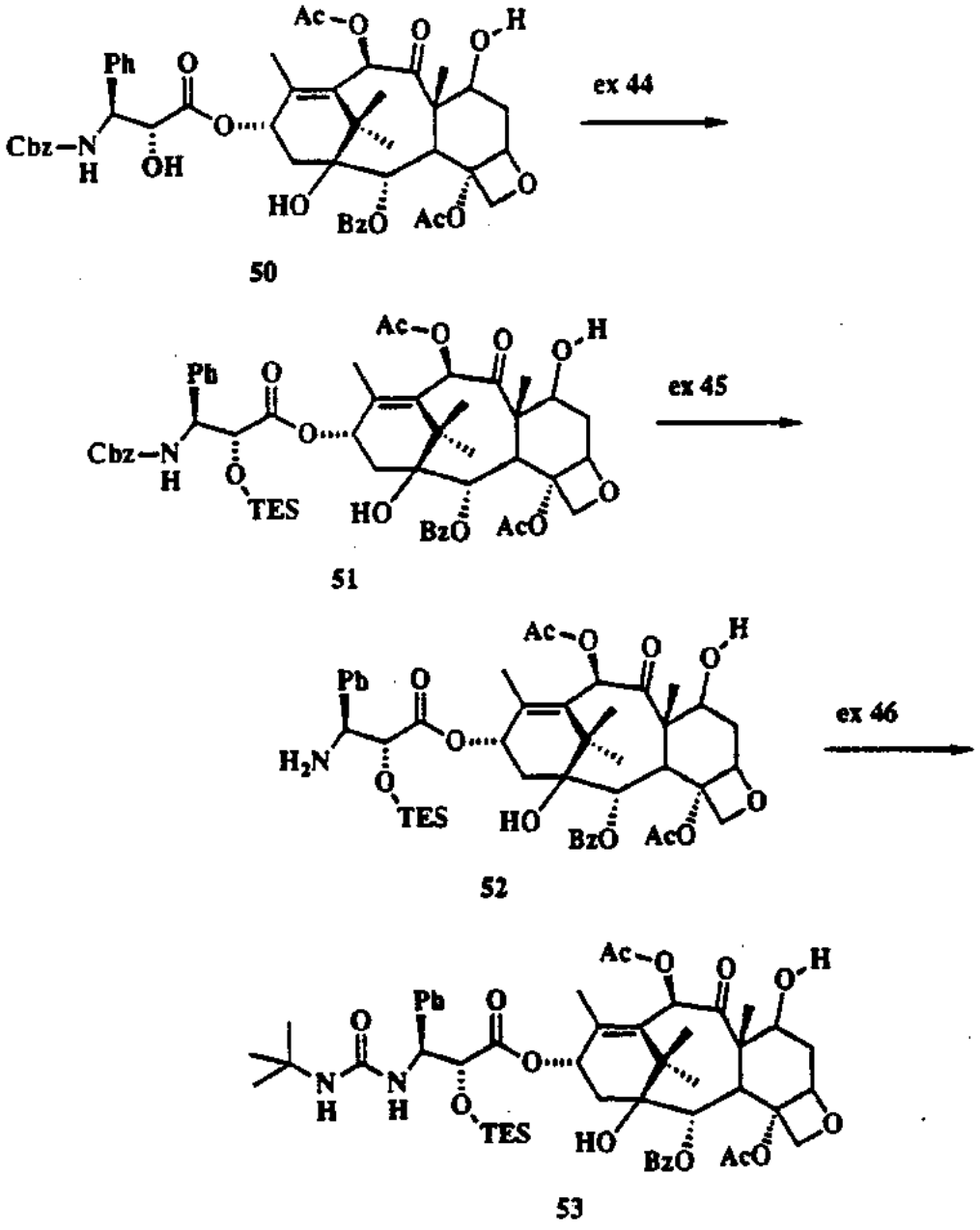
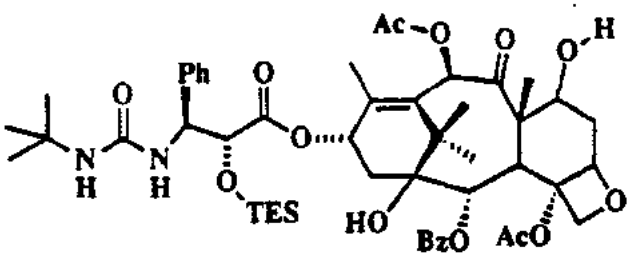
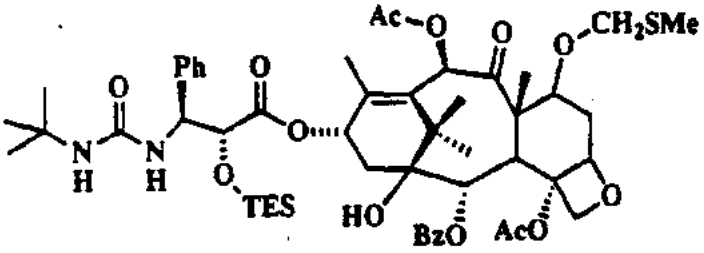


FORMULA CHART: 24



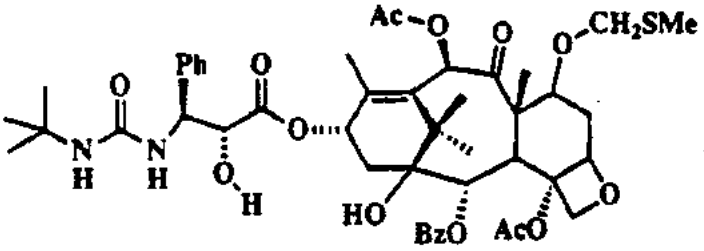
ex 47

53



ex 48

54



ex 49

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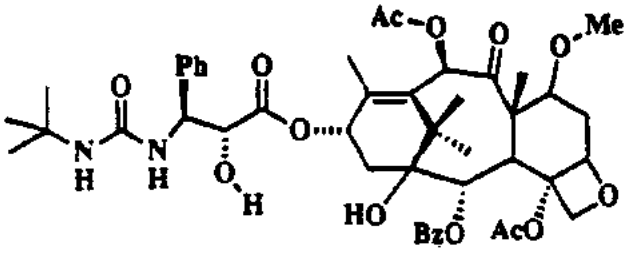

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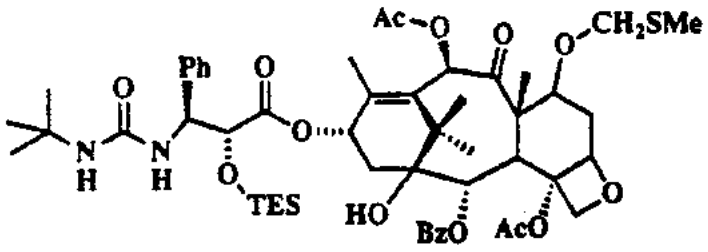
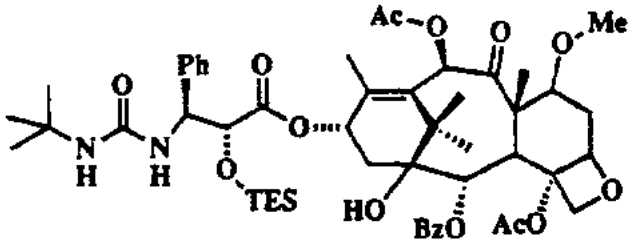


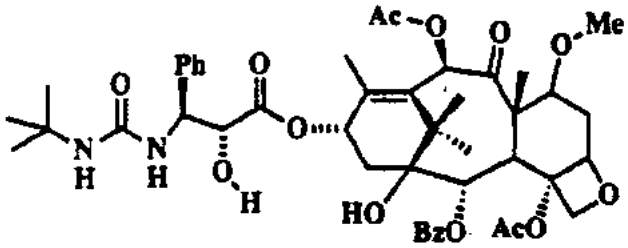
ex 50

54



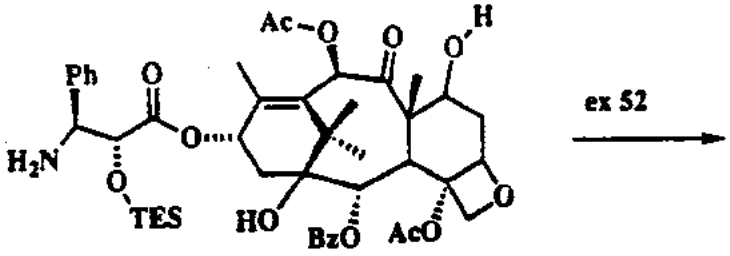
ex 51

57



56

FORMULA CHART: 26



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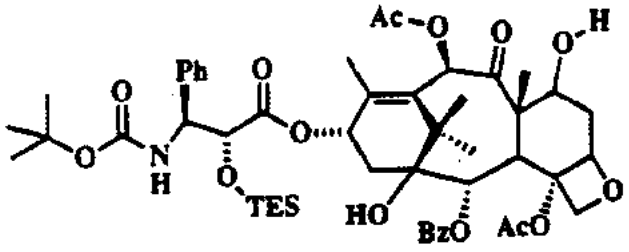

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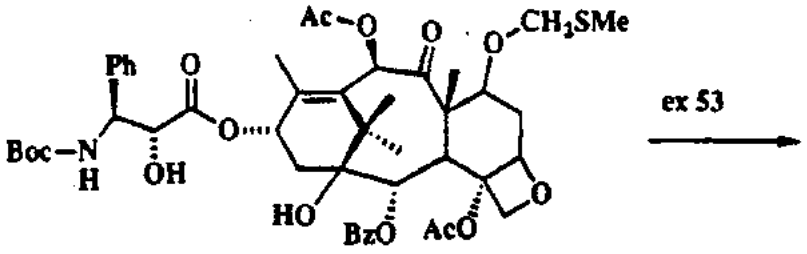

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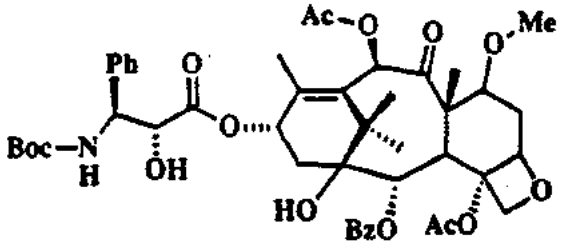
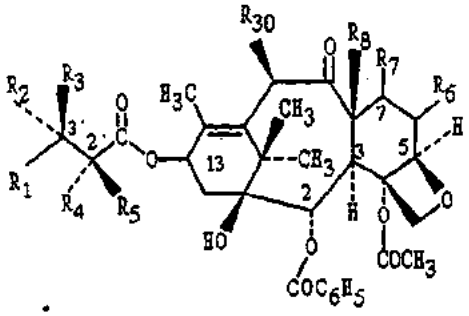


58

CLAIMS

1. A compound of the Formula I:



I

wherein:

R_1 is selected from the group consisting of

$-CH_3$,

$-C_6H_5$ or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro,

-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;

R_2 is selected from the group consisting of -H, -NHC(O)H,-NHC(O)C_1-C_{10}alkyl, -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, $-NHC(O)C(CH_3)=CHCH_3$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_2$phenyl, $-NH_2$, $-NHSO_2$-4-methylphenyl, $-NHC(O)(CH_2)_3COOH$, -NHC(O)-4-(SO_3H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, $-NHC(O)CH_2C(CH_3)_3$, $-NHC(O)C(CH_3)_3$, -NHC(O)OC_1-C_{10}alkyl, -NHC(O)NHC_1-C_{10}alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, -NHC(O)C_3-C_8cycloalkyl, $-NHC(O)OC(CH_2CH_3)_2CH_3$, $-NHC(O)OC(CH_3)_2CH_2Cl$, $-NHC(O)OC(CH_3)_2CH_2CH_3$, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, $-NHC(S)NHC(CH_3)_3$ or $-NHC(O)NHC(CH_3)_3$;

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or $-NHC(O)OC(CH_3)_3$, with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3

are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-$OC(O)CH_3$), -$OC(O)OCH_2C(Cl)_3$, -$OCOCH_2CH_2NH_3^+$ $HCOO^-$, -NHC(O)phenyl, -$NHC(O)OC(CH_3)_3$, -$OCOCH_2CH_2COOH$ and pharmaceutically acceptable salts thereof, -$OCO(CH_2)_3COOH$ and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -$NR'_2R'_3$, -OR'_3, -SR'_3, -$OCH_2C(O)NR'_4R'_5$ where R'_2 is -H or -CH_3, R'_3 is -$(CH_2)_nNR'_6R'_7$ or $(CH_2)_nN^+R'_6R'_7R'_8$ X^- where n is 1-3, R'_4 is -H or -C_1-C_4alkyl, R'_5 is -H, -C_1-C_4alkyl, benzyl, hydroxyethyl, -CH_2CO_2H or dimethylaminoethyl, R'_6 and R'_7 are -CH_3, -CH_2CH_3, benzyl or R'_6 and R'_7 together with the nitrogen of $NR'_6R'_7$ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'_8 is -CH_3, -CH_2CH_3 or benzyl , X^- is halide, and base is NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4)_2NH$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH or KOH], -$OC(O)(CH_2)_nNR^2R^3$ [where n is 1-3, R^2 is -H or -C_1-C_3alkyl and R^3 -H or -C_1-C_3alkyl], -$OC(O)CH(R'')NH_2$ [where R'' is selected from the group consisting of -H, -CH_3, -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -$CH(CH_3)_2$, -CH_2phenyl, -$(CH_2)_4NH_2$, -CH_2CH_2COOH, -$(CH_2)_3NHC(=NH)NH_2$], the residue of the amino acid proline, -OC(O)CH=CH_2, -$C(O)CH_2CH_2C(O)NHCH_2CH_2SO_3^-$ Y^+, -$OC(O)CH_2CH_2C(O)NHCH_2CH_2CH_2SO_3^-Y^+$ wherein Y^+ is Na^+ or $N^+(Bu)_4$, -$OC(O)CH_2CH_2C(O)OCH_2$ CH_2OH;

R_5 is -H or -OH, with the overall proviso that when R_5 is -OH, R_4 is -H and with the further proviso that when R_5 is -H, R_4 is other than -H;

R_6 is -H:-H;

R_7 is α-R_{91}:β-R_{92} where one of R_{91} and R_{92} is -H and the other of R_{91} and R_{92} is -W where W is selected from the group consisting of

-O-C_1-C_{10}alkyl,

-O-C_3-C_{10} unsaturated alkyl,

-O-C_5-C_{15} heteroalkyl,

-$O\text{-}CH(R^{21})OR^{22}$ where

R^{21} is -H or -C_1-C_6 alkyl, and

R^{22} is -C_1-C_{10}alkyl, -C_3-C_{10} unsaturated alkyl or -C_5-C_{15} heteroalkyl; or when R^{21} and R^{22} are taken together to form a ring with 4 to 6 carbon atoms;

$-CH(R^{28})S(O)_mAr$ where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

or $-CH(R^{28})S(O)_mCH_2R^{28}$

where R^{28} is

$-C_1$-C_6 alkyl,

$-C_3$-C_{10} unsaturated alkyl,

$-(CH_2)_q$phenyl where q is 0-6,

$-(CH_2)_q$phenyl where q is 0-6 and substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

-naphthyl,

-naphthyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro,

$-C_5$-C_{15} heteroalkyl,

or when R^{28} and R^{28} are taken together to form a ring with 4 to 6 carbon atoms;

m is O to 2;

R_8 is $-CH_3$;

R_{30} is -H, OH, or $-OC(O)CH_3$; and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

2. A compound according to Claim 1 wherein R_2 is $-NHC(O)C_6H_5$, R_4 is hydroxy, R_3 and R_5 are -H, and R_1 is phenyl or substituted phenyl.

3. A compound according to Claim 1 wherein R_2 is $-NHC(O)OC(CH_3)_3$, R_1 is phenyl or substituted phenyl, R_4 is hydroxy, and R_3 and R_5 are -H.

4. A compound according to Claim 1 wherein R_2 is $-NHC(O)NHC(CH_3)_3$, R_1 is phenyl or substituted phenyl, R_4 is hydroxy, and R_3 and R_5 are -H.

5. A compound according to Claim 1 wherein W is $-O$-C_1-C_{10}alkyl.

-O-C_3-C_{10} unsaturated alkyl or -O-C_5-C_{15} heteroalkyl.

6. A compound according to Claim 1 wherein -W is -O-CH(R^{21})OR^{22} where
R^{21} is -H or -C_1-C_6 alkyl, and
R^{22} is -C_1-C_{10}alkyl or -C_3-C_{10} unsaturated alkyl.

7. A compound according to Claim 1 wherein -W is -O-CH(R^{21})OR^{22} and R^{22} is selected from the group consisting of CH_2-(2- or 3-furyl), CH_2(2- or 3-pyrrolyl), CH_2(2-, 3, or 4-pyridyl), CH_2(2-, 4- or 5-imidazoyl) or CH_2(3-, 4- or 5-isoxazolyl).

8. A compound according to Claim 1 wherein -W is -CH(R^{28})S(O)$_m$$CH_2R^{28}$ and R^{28} is -C_1-C_6 alkyl, -C_3-C_{10} unsaturated alkyl or -$(CH_2)_q$phenyl where q is 0-6.

9. A compound according to Claim 1 wherein -W is -CH(R^{28})S(O)$_m$$CH_2R^{28}$ and R^{28} is selected from the group consisting of CH_2-(2- or 3-furyl), CH_2(2- or 3-pyrrolyl), CH_2(2-, 3, or 4-pyridyl), CH_2(2-, 4- or 5-imidazoyl) or CH_2(3-, 4- or 5-isoxazolyl).

10. A compound according to Claim 1 wherein -W is -CH(R^{28})S(O)$_m$Ar where R^{28} is -C_1-C_6 alkyl, -C_3-C_{10} unsaturated alkyl or -$(CH_2)_q$phenyl where q is 0-6.

11. A compound according to Claim 1 wherein R_2 is -NHC(O)C_6H_5, R_4 is hydroxy, R_3 and R_5 are -H, R_1 is phenyl or substituted phenyl, and -W is selected from the group consisting of:

-O-C_1-C_{10}alkyl;

-O-C_3-C_{10} unsaturated alkyl;

-O-CH(R^{21})OR^{22} where
R^{21} is H or C_1-C_6 alkyl, and
R^{22} is -C_1-C_6alkyl or -C_3-C_{10} unsaturated alkyl;

-CH(R^{28})S(O)$_m$Ar where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; or

-CH(R^{28})S(O)$_m$$CH_2R^{28}$
where R^{28} is

$-C_1$-C_6 alkyl,

$-C_3$-C_{10} unsaturated alkyl, or

$-(CH_2)_q$phenyl where q is 0-3; and

m is 0.

12. A compound according to Claim 1 wherein R_2 is $-NHC(O)OC(CH_3)_3$, R_1 is phenyl or substituted phenyl, R_4 is hydroxy, R_3 and R_5 are -H, and -W is selected from the group consisting of:

$-O-C_1$-C_{10}alkyl;

$-O-C_3$-C_{10} unsaturated alkyl;

$-O-CH(R^{21})OR^{22}$ where

R^{21} is H or C_1-C_6 alkyl, and

R^{22} is $-C_1$-C_6alkyl or $-C_3$-C_{10} unsaturated alkyl;

$-CH(R^{28})S(O)_mAr$ where Ar is phenyl or phenyl substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; or

$-CH(R^{28})S(O)_mCH_2R^{28}$

where R^{28} is

$-C_1$-C_6 alkyl,

$-C_3$-C_{10} unsaturated alkyl, or

$-(CH_2)_q$phenyl where q is 0-3; and

m is 0.

13. A compound according to Claim 1 wherein R_2 is $-NHC(O)NHC(CH_3)_3$.

14. A compound according to Claim 13 wherein -W is selected from the group consisting of:

O-methyl;

O-propyl;

O-allyl;

O-methoxymethyl;

O-ethoxymethyl;

O-methoxyethoxymethyl;

O-benzyloxymethyl;

O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

15. A compound according to Claim 13 wherein -W is selected from the group consisting of:

O-methoxymethyl;
O-ethoxymethyl;
O-methoxyethoxymethyl;
O-benzyloxymethyl;
O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

16. A compound according to Claim 12 wherein -W is selected from the group consisting of:

O-methyl;
O-propyl;
O-allyl;
O-methoxymethyl;
O-ethoxymethyl;
O-methoxyethoxymethyl;
O-benzyloxymethyl;
O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

17. A compound according to Claim 12 wherein -W is selected from the group consisting of:

O-methoxymethyl;

O-ethoxymethyl;
O-methoxyethoxymethyl;
O-benzyloxymethyl;
O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

18. A compound according to Claim 1 wherein -W is selected from the group consisting of:

O-methyl;
O-propyl;
O-allyl;
O-methoxymethyl;
O-ethoxymethyl;
O-methoxyethoxymethyl;
O-benzyloxymethyl;
O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

19. A compound according to Claim 1 wherein -W is selected from the group consisting of:

O-methoxymethyl;
O-ethoxymethyl;
O-methoxyethoxymethyl;
O-benzyloxymethyl;
O-(2,2,2-trichloroethoxy)methyl;
O-(2,2,2-trichloroethoxy)methoxymethyl;
O-methylthiomethyl; and
O-phenylthiomethyl.

20. A compound according to Claim 1 selected from the group consisting of:

7-(O-ethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (4),

7-(O-methoxyethoxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (6),

7-(O-methoxymethyl)-13-(N-Boc-2'-β-phenyl isoserinyl)-baccatin III (8),

7-(O-benzyloxymethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (10),

7-(O-ethoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (14),

7-[O-(2,2,2-trichloroethoxy)methyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (21),

7-[O-(2,2,2-trichloroethoxy)methoxymethyl]-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (22),

7-(O-methoxymethyl)-13-(N-(t-butylaminocarbonyl)-β-phenyl isoserinyl)-baccatin III (27),

7-(O-methylthiomethyl) taxol (42),

7-(O-methylthiomethyl)-13-(N-Boc-β-phenyl isoserinyl)-baccatin III (44),

7-(O-phenylthiomethyl) taxol (46),

7-O-methyl Taxol (47),

7-[O-ethyl(1-thioethyl)] Taxol (49),

13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methylthiomethyl ether (55),

13-(N-(t-butylaminocarbonyl)-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (56), and

13-(N-Boc-2'-TES-b-phenyl isoserinyl)-baccatin III 7-O-methyl ether (58).

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/06595

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D305/14 C07D409/12 C07D407/12 A61K31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 960 790 (V. STELLA) 2 October 1990 see the whole document	1
E	WO,A,95 20582 (UPJOHN) 3 August 1995 see claims	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 1995	- 2. 11. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Francois, J

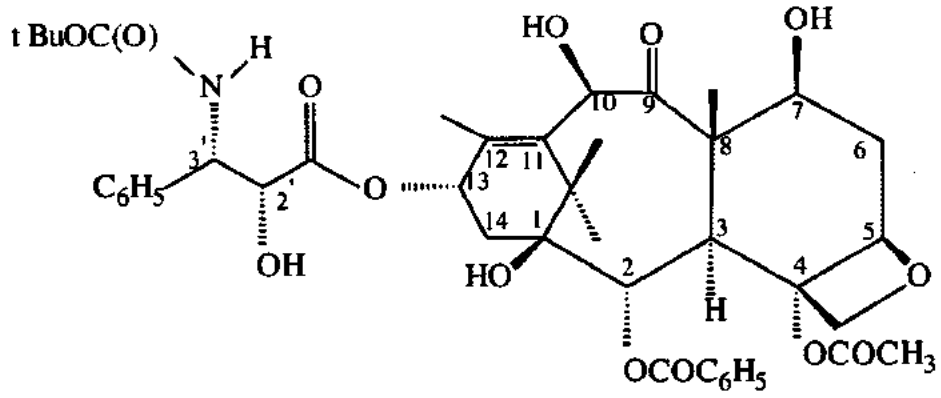
Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/06595

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4960790	02-10-90	AU-B-	628161	10-09-92
		AU-B-	5271590	09-10-90
		CA-A-	2028096	10-09-90
		EP-A-	0419653	03-04-91
		GR-B-	1000684	08-10-92
		JP-T-	4504845	27-08-92
		WO-A-	9010443	20-09-90
WO-A-9520582	03-08-95	AU-B-	1680695	15-08-95

Form PCT/ISA/210 (patent family annex) (July 1992)



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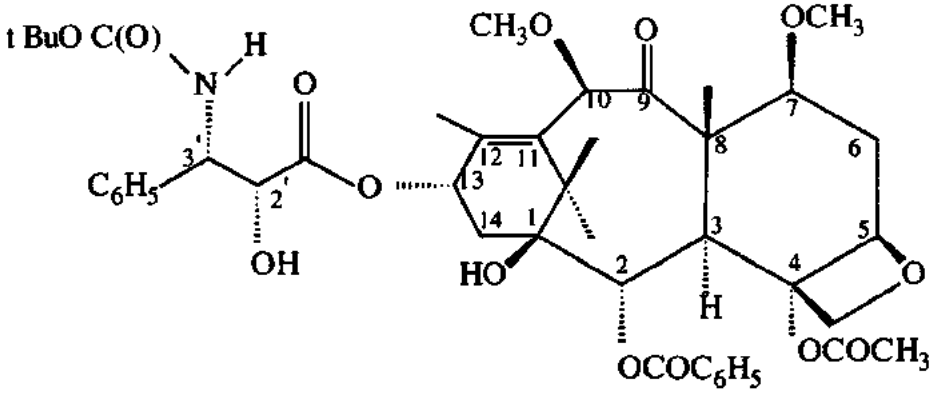


CLAIMED COMPOUND : DIMETHOXY

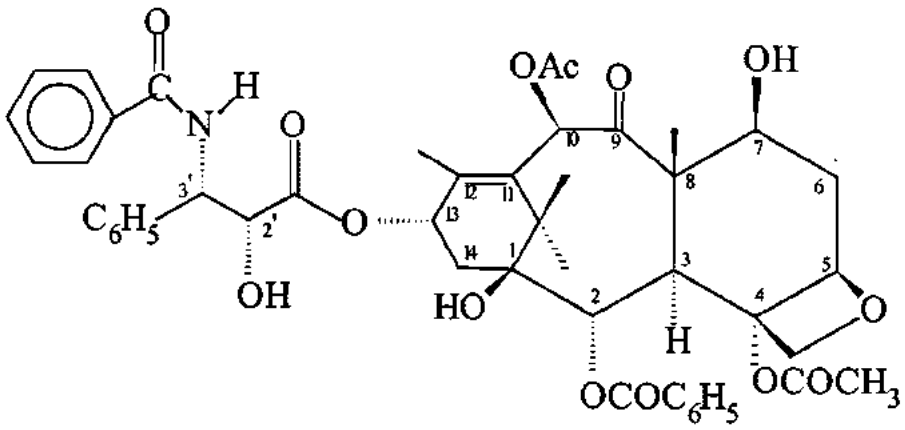
SUMMARY OF HYDROXY PROTECTING GROUPS AND REMOVAL CONDITIONS OF THE ART CITED BY THE EXAMINER EXCEPT FOR GREENE

Document	Inventor	Hydroxy Protecting Groups Generally Disclosed	Exemplified Hydroxy Protecting Groups at 7 and 10 Positions	EXAMPLES*	7, 10 POSITION	CONDITIONS FOR REMOVING HYDROXY PROTECTING GROUP
US5,229,526 (PTO has withdrawn reliance on this document)	Holton	ethers ; esters such as acetate (these are only described as being on the β-lactam- regarding the baccatin is disclosed "hydroxy protecting group")	triethylsilyl	1, 2, 4-15	7 position: TES 10 position: Ac (Ac is not a hydroxy protecting group in this molecule)	The hydroxyl protecting group selected should be easily removed under conditions that are sufficiently mild, e.g., in 48% HF, acetonitrile, pyridine (Ex. 2-15), or 0.5% HCl/water/ethanol (Ex. 1), and/or zinc, acetic acid (no Ex.) so as not to disturb the ester linkage or other substituents of the taxol intermediate.
				3	7 position: TES 10 position: TES	
US5,319,112 (PTO has withdrawn reliance on this document)	Kingston et al.	2,2,2-trichloroethyl-oxycarbonyl or other protecting group derivative	2,2,2-trichloroethyl-oxycarbonyl (Troc)	1	7 position: Troc 10 position: Ac (Ac is not a hydroxy protecting group in this molecule)	The hydroxyl protecting groups are removed using appropriate reagents, e.g., zinc in acetic acid
US5,489,601 (PTO has withdrawn reliance on this document)	Holton et al.	broadly defined; includes ethers such as methyl; esters such as acetyl and benzoyl	triethylsilyl (TES)	1, 2, 3	7 position: TES 10 position: Ac (Ac is not a hydroxy protecting group in this molecule)	The protecting groups are hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents. Conditions are shown as HF, pyridine, and acetonitrile. Column 9 and Examples 1-3.

Document	Inventor	Hydroxy Protecting Groups Generally Disclosed	Exemplified Hydroxy Protecting Groups at 7 and 10 Positions	EXAMPLES*	7, 10 POSITION	CONDITIONS FOR REMOVING HYDROXY PROTECTING GROUP
US5,739,362	Holton et al.	broadly defined; includes ethers such as methyl; esters such as acetyl and benzoyl	triethylsilyl	1-35, 69, 70-101, 103-121	7 position: TES 10 position: Ac (Ac is not a hydroxy protecting group in this molecule)	The protecting groups are hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents. Conditions are shown as HF, pyridine, and acetonitrile. Column 10 and Examples 1-121.
				36, 55-68, 102	7 position: TES 10 position: TES	
				37, 42, 43, 44	7 position: TES 10 position: H	
				38, 39, 45, 46, 50, 51	7 position: TES 10 position: oxo	
				40, 52, 53, 54	7 position: H 10 position: Ac (Ac is not a hydroxy protecting group in this molecule)	
				41, 47, 48, 49	7 position: H 10 position: H	

* Analysis of the examples is based on the written description of the protected taxane intermediate in the examples, not necessarily the chemical structure disclosed

TAXOL



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 604 910 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **93120801.1**

(22) Date of filing: **23.12.93**

(51) Int. Cl.[5]: **C07F 9/655**, A61K 31/675, C07F 9/6558, C07D 305/14, C07D 407/12, C07F 7/18

A request for correction of the description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

(30) Priority: **24.12.92 US 996455**
17.08.93 US 108015
24.11.93 US 154840

(43) Date of publication of application:
06.07.94 Bulletin 94/27

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

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(54) Phosphonooxymethyl ethers of taxane derivatives.

(57) The present invention concerns novel water-soluble phosphonooxymethyl ethers of taxane derivatives, their use as antitumor agents, and pharmaceutical compositions containing the novel compounds.

EP 0 604 910 A1

BACKGROUND OF THE INVENTION

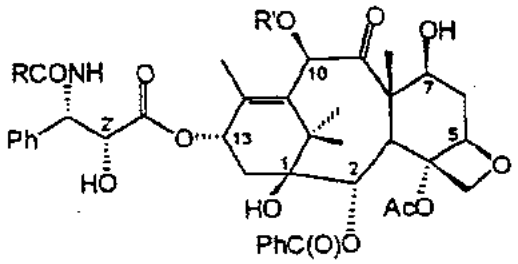
1. Field of the Invention

The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

2. Background Art

Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is currently undergoing clinical trials against ovarian, breast and other types of cancer in the United States and France and preliminary results have confirmed it as a most promising chemotherapeutic agent. The results of paclitaxel clinical studies are reviewed in Rowinsky and Donehower, "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics" Pharmac. Ther., 52:35-84, 1991.

Recently, a semi-synthetic analog of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models. Taxotere® is also currently undergoing clinical trials in Europe and the United States. The structures of paclitaxel and Taxotere® are shown below; the conventional numbering system of the paclitaxel molecule is provided.



Taxol®: R = Ph; R' = acetyl

Taxotere®: R = t-butoxy; R' = hydrogen

One drawback of paclitaxel is its very limited water solubility requiring it to be formulated in nonaqueous pharmaceutical vehicles. One commonly used carrier is Cremophor EL which may itself have undesirable side effects in man. Accordingly, a number of research teams have prepared water-soluble derivatives of paclitaxel which are disclosed in the following references:

(a) Haugwitz et al, U.S. Patent No. 4,942,184;

(b) Kingston et al, U.S. Patent No. 5,059,699;

(c) Stella et al, U.S. Patent No. 4,960,790;

(d) European Patent Application 0,558,959 A1 published September 8, 1993.

(e) Vyas et al, Bioorganic & Medicinal Chemistry Letters, 1993, 3:1357-1360.

and

(f) Nicolaou et al, Nature, 1993, 364:464-466

Compounds of the present invention are phosphonooxymethyl ethers of taxane derivatives and pharmaceutically acceptable salts thereof. The water solubility of the salts facilitates preparation of pharmaceutical formulations.

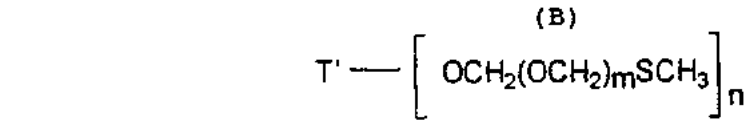
SUMMARY OF THE INVENTION

The present invention relates to taxane derivatives having the formula (A):

$$T \text{---} \left[OCH_2(OCH_2)_mOP(O)(OH)_2 \right]_n \qquad (A)$$

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is 1, 2 or 3; m is 0 or an integer from 1 to 6 inclusive; or a pharmaceutically acceptable salt thereof.

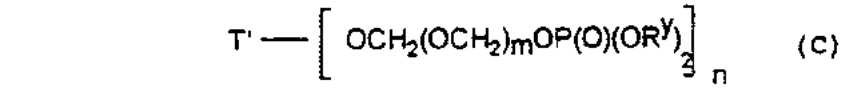
Another aspect of the present invention provides taxane derivatives having the formula (B):



(B)

wherein T' is T in which non-reacting hydroxy groups have been blocked, m and n are as defined under formula (A).

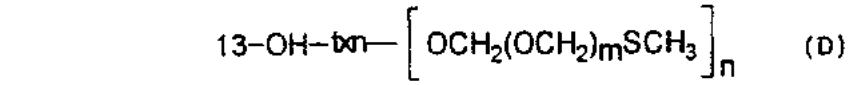
Yet another aspect of the present invention provides intermediates having the formula (C):



(C)

wherein T', m and n are as defined under formula (A), and R^y is a phosphono protecting group.

Another aspect of the present invention provides compounds of the formula (D):



(D)

wherein m and n are as defined above; and txn is a taxane moiety; or a C13 metal alkoxide thereof.

Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula (A).

Yet another aspect of the present invention provides a pharmaceutical composition which comprises an antitumor effective amount of a compound of formula (A) and a pharmaceutically acceptable carrier.

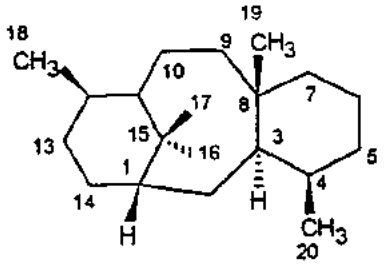
DETAILED DESCRIPTION OF THE INVENTION

In the application, unless otherwise specified explicitly or in context, the following definitions apply. "Alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. "Alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. "Alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

"Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl substituted with at least one group selected from C_{1-6} alkanoyloxy, hydroxy, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, aryl, C_{2-6} alkenyl, C_{1-6} alkanoyl, nitro, amino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

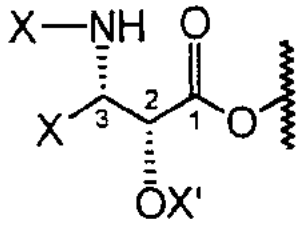
"Phosphono-" means the group $-P(O)(OH)_2$ and "phosphonooxymethoxy" or "phosphonooxymethyl ether" means generically the group $-OCH_2(OCH_2)_mOP(O)(OH)_2$. "(Methylthio)thiocarbonyl" means the group $-C(S)SCH_3$. "Methylthiomethyl" (also abbreviated as MTM) generically refers to the group $-CH_2SCH_3$.

"Taxane moiety" (also abbreviated as txn) denotes moieties containing the twenty carbon taxane core framework represented by the structural formula shown below with the absolute configuration.



The numbering system shown above is one used in conventional taxane nomenclature, and is followed throughout the application. For example, the notation C1 refers to the carbon atom labelled as "1"; C5-C20 oxetane refers to an oxetane ring formed by the carbon atoms labelled as 4, 5 and 20 with an oxygen atom; and C9 oxy refers to an oxygen atom attached to the carbon atom labelled as "9", said oxygen atom may be an oxo group, α- or β-hydroxy, or α- or β-acyloxy.

"Substituted 3-amino-2-hydroxypropanoyloxy" denotes a residue represented by the formula



(X is a nonhydrogen group and X' is hydrogen or a non-hydrogen group.) The stereochemistry of this residue is the same as the paclitaxel sidechain. This group is sometimes referred to in the application as the "C13 sidechain."

"Taxane derivative" (abbreviated as T) refers to a compound having a taxane moiety bearing a C13 sidechain.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Phosphono protecting groups" means moieties which can be employed to block or protect the phosphono functional group; preferably such protecting groups are those that can be removed by methods that do not appreciably affect the rest of the molecule. Suitable phosphonooxy protecting groups are well known to those skilled in the art and include for example benzyl and allyl groups.

"Hydroxy protecting groups" include, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether and t-butyl-dimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl.

Additional examples of hydroxy and phosphono protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., 1991, John Wiley & Sons, and McOmie, Protective Groups in Organic Chemistry, 1975, Plenum Press. Methods for introducing and removing protecting groups are also found in such textbooks.

"Pharmaceutically acceptable salt" means a metal or an amine salt of the acidic phosphono group in which the cation does not contribute significantly to the toxicity or biological activity of the active compound. Suitable metal salts include lithium, sodium, potassium, calcium, barium, magnesium, zinc, and aluminum salts. Preferred metal salts are sodium and potassium salts. Suitable amine salts are for example, ammonia, tromethamine (TRIS), triethylamine, procaine, benzathine, dibenzylamine, chloroprocaine, choline, diethanolamine, triethanolamine, ethylenediamine, glucamine, N-methylglucamine, lysine, arginine,

ethanolamine, to name but a few. Preferred amine salts are lysine, arginine and N-methylglucamine salts.

In the specification and in the claims, the term $-OCH_2(OCH_2)_mOP(O)(OH)_2$ is intended to emcompass both the free acid and its pharmaceutically acceptable salts, unless the context indicates specifically that the free acid is meant.

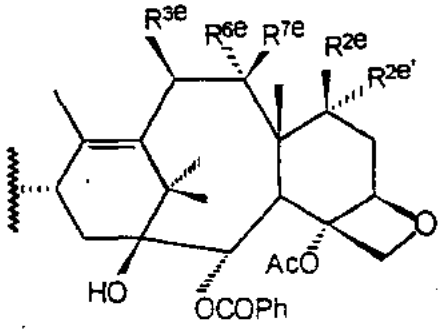
One aspect of the present invention provides taxane derivatives of the formula (A)

$$T\text{---}\left[OCH_2(OCH_2)_mOP(O)(OH)_2\right]_n \quad (A)$$

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is an 1, 2 or 3; m is 0, or an integer from 1 to 6 inclusive, or a pharmaceutically acceptable salt thereof.

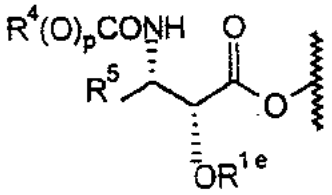
In one embodiment the taxane moiety contains at least the following functionalities: C1-hydroxy, C2-benzoyloxy, C4-acetyloxy, C5-C20 oxetane, C9-oxy, and C11-C12 double bond.

In a preferred embodiment the taxane moiety is derived from a residue having the formula

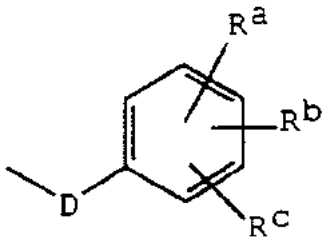


wherein $R^{2e'}$ is hydrogen and R^{2e} is hydrogen, hydroxy, - $OC(O)R^x$, or $-OC(O)OR^x$; or R^{2e} is hydrogen and $R^{2e'}$ is fluoro; R^{3e} is hydrogen, hydroxy, $-OC(O)R^x$, C_{1-6}alkyloxy, or $-OC(O)OR^x$; one of R^{6e} or R^{7e} is hydrogen and the other is hydroxy or $-OC(O)R^x$; or R^{6e} and R^{7e} together form an oxo group; R^x is as defined below.

In another embodiment, the C13 sidechain is derived from a residue having the formula



wherein R^{1e} is hydrogen or $-C(O)R^x$, $-C(O)OR^x$; R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-Z-R^6$; Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl; R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl, or heteroaryl; and R^x is C_{1-6} alkyl optionally substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or a radical of the formula

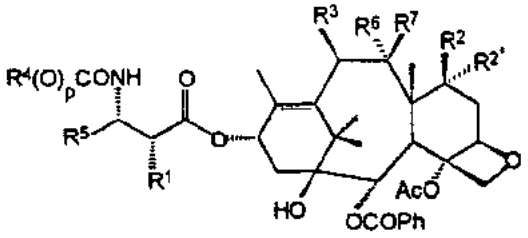


wherein D is a bond or C_{1-6} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-6} alkylamino, di-C_{1-6} alkylamino, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy; p is 0 or 1.

In a preferred embodiment, R^4 is C_{1-6} alkyl and p is 1, or R^4 is or -Z-R^6 and p is 0. More preferably, $R^4(O)_p$ is t-butoxy, phenyl, isopropyloxy, n-propyloxy, or n-butoxy.

In another preferred embodiment R^5 is C_{2-6} alkenyl or -Z-R^6 and Z and R^6 are as previously defined. More preferably, R^5 is phenyl, 2-furyl, 2-thienyl, isobutenyl, 2-propenyl, or C_{3-6} cycloalkyl.

In another embodiment, compound of formula (A) may be more specifically represented by the formula (I)



(I)

wherein R^1 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; or $R^{2'}$ is fluoro, and R^2 is hydrogen; R^3 is hydrogen, hydroxy, acetoxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; one of R^5 or R^7 is hydrogen and the other is hydroxy, C_{1-6} alkanoyloxy, or $-OCH_2(OCH_2)_mOP(O)(OH)_2$; or R^6 and R^7 together form an oxo group; with the proviso that at least one of R^1, R^2, R^3, R^6 or R^7 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^4, R^5, R^x, m and p are as previously defined; or a pharmaceutically acceptable salt thereof.

In compounds of formula (I), examples of R^x include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, chloromethyl, 2,2,2-trichloroethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, 2-propenyl, phenyl, benzyl, bromophenyl, 4-aminophenyl, 4-methylaminophenyl, 4-methylphenyl, 4-methoxyphenyl and the like. Examples of R^4 and R^5 include 2-propenyl, isobutenyl, 3-furanyl (3-furyl), 3-thienyl, phenyl, naphthyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, ethenyl, 2-propenyl, 2-propynyl, benzyl, phenethyl, phenylethenyl, 3,4-dimethoxyphenyl, 2-furanyl (2-furyl), 2-thienyl, 2-(2-furanyl)ethenyl, 2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl and the like.

In one preferred embodiment, the present invention provides compounds of formula (I) in which R^5 is C_{2-6} alkenyl or -Z-R^6 and Z and R^6 are as previously defined. More preferably, R^5 is phenyl, 3-furyl, 3-thienyl, 2-propenyl, isobutenyl, 2-furyl, 2-thienyl, or C_{3-6} cycloalkyl.

In another preferred embodiment R^4 of compounds of formula (I) is C_{1-6} alkyl in which case p is 1; or R^4 is -Z-R^6 and Z and R^6 are as previously defined, and in which case p is 0. More preferably $R^4(O)_p$- is t-butoxy, phenyl, isopropyloxy, n-propyloxy, n-butoxy.

In another preferred embodiment, the present invention provides compounds of formula (I) in which R^1 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$. In a more preferred embodiment, R^2 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, or $-OC(O)R^x$, and R^x is preferably C_{1-6} alkyl. In another more preferred embodiment, R^3 is hydroxy or acetoxy.

In another preferred embodiment, the present invention provides compound of formula (I) in which R^2 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^1 is hydroxy or $-OC(O)OR^x$; and R^3 is hydrogen, hydroxy, acetoxy, $-OCH_2-(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; and R^x is as previously defined. In a more preferred embodiment R^1 is hydroxy or $-OC(O)OR^x$ and R^x is preferably C_{1-6} alkyl; and R^3 is hydroxy or acetoxy.

In another preferred embodiment, the present invention provides compound of formula (I) in which R^3 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^1 is hydroxy or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy or $-OC(O)OR^x$; or $R^{2'}$ is fluoro and R^2 is hydrogen; and R^x is as previously defined. In a more preferred embodiment, R^1 is hydroxy or $-OC(O)OR^x$, and R^x is preferably C_{1-6} alkyl. In another more preferred embodiment, R^2 is hydroxy.

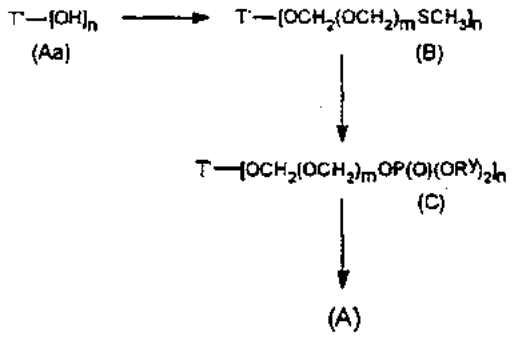
In another preferred embodiment, m is 0 or 1 when the phosphonooxymethoxy group is present on the C7 of the taxane moiety.

The preferred pharmaceutically acceptable salts of a compound of formula (A) are alkali metal salts including lithium, sodium and potassium salts; and amine salts including triethylamine, triethanolamine, ethanolamine, arginine, lysine and N-methylglucamine salts. Even more preferred salts are arginine, lysine and N-methylglucamine salts.

The most preferred embodiments of taxane derivatives of formula (A) include the following compounds: (1) 7-O-phosphonooxymethylpaclitaxel, (2) 2'-O-(ethyloxycarbonyl)-7-O-phosphonooxymethylpaclitaxel; (3) 2'-O-phosphonooxymethylpaclitaxel; (4) 2',7-bis-O-(phosphonooxymethyl)paclitaxel; (5) 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel; (6) 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel; (7) 10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel; (8) 2'-O-phosphonooxymethoxymethylpaclitaxel and their respective pharmaceutically acceptable salts, particularly the sodium, potassium, arginine, lysine, N-methylglucamine, ethanolamine, triethylamine and triethanolamine salts.

Compounds of formula (A) may be prepared from a taxane derivative starting material $T\text{-}[OH]_n$ wherein T and n are as previously defined. The identity of $T\text{-}[OH]_n$ is not particularly limited so long as there is at least one reactive hydroxy group present on either the taxane moiety or the C13 side chain to allow the formation of phosphonooxymethyl ether linkage. It is to be understood that the reactive hydroxy group may be directly attached to the C13 propanoyloxy backbone (e.g. the 2'-hydroxy group of paclitaxel) or to the taxane core framework (e.g. the 7-hydroxy group of paclitaxel); or it may be present on a substituent on the C13 sidechain, or on a substituent on the taxane core. The reaction sequence shown in Scheme I may be used to prepare compounds of formula (A)

Scheme I



In Scheme I T' is a taxane derivative in which non-reacting hydroxy groups have been blocked; R^Y is a phosphono protecting group; n and m are as previously defined. Thus an appropriately protected T' having one or more reactive hydroxy groups is first converted to a corresponding methylthiomethyl ether of formula (B). Using paclitaxel as an example, T' may be paclitaxel itself (to effect 2',7-bismethylthiomethylation), 7-O-triethylsilylpaclitaxel, or 2'-O-ethoxycarbonylpaclitaxel. A compound of formula (B) where m is 0 may be prepared by treating $T'\text{-}[OH]_n$ with dimethylsulfoxide/acetic anhydride, or with dimethylsulfide and an organic peroxide. These reactions are discussed more fully in a subsequent section.

The MTM ether having one intervening methyleneoxy unit (i.e. compounds of formula (B) where m = 1) may be prepared by several possible routes. In one a compound of formula (B) where m = 0 is reacted with N-iodosuccinimide (NIS) and methylthiomethanol to extend the chain by one methyleneoxy unit.

$$T'—[OCH_2SCH_3]_n + n\ CH_3SCH_2—OH \xrightarrow{NIS} T'—[OCH_2OCH_2SCH_3]_n$$

The compound of methylthiomethanol and its preparation is reported in Syn. Comm., 1986, 16 (13): 1607-1610.

In an alternative method, the T-alkoxide (Ad) generated by treating a compound of formula (Aa) with a base such as n-butyl lithium, lithium diisopropylamide or lithium hexamethyldisilazide, is reacted with chloromethyl methylthiomethyl ether to provide a compound of formula (B) in which m = 1.

$$\underset{(Ad)}{T'—[O^-]_n} + n\ \underset{(Ae)}{CH_3SCH_2—OCH_2Cl} \longrightarrow T'—[OCH_2OCH_2SCH_3]_n$$

Compound (Ae) is prepared by reacting methylthiomethoxide (obtained from methylthiomethanol by treatment with a base such as n-butyl lithium, lithium diisopropylamide or lithium hexamethyldisilazide) with chloroiodomethane. Compound (Ae) may also be prepared by treating 1,1'-dichlorodimethylether ($ClCH_2OCH_2Cl$) with a stoichiometric amount or less (e.g. about 0.8 equivalent) of sodium iodide followed by sodium thiomethoxide. 1,1'-Dichlorodimethyl ether is reported in Ind. J. Chem., 1989, 28B, pp. 454-456.

In another method, a compound of formula (Aa) is reacted with bis(MTM)ether, $CH_3SCH_2OCH_2SCH_3$, and NIS to give a compound of formula (B) in which m = 1.

$$T'-[OH]_n + n\ CH_3SCH_2OCH_2SCH_3 \rightarrow T'-[OCH_2OCH_2SCH_3]_n$$

Bis(MTM)ether is prepared by reacting 1,1'-dichlorodimethyl ether with sodium iodide followed by sodium thiomethoxide.

The procedure described above using methylthiomethanol and NIS may be applied to any reagent having an MTM group to extend the chain by one methyleneoxy unit at a time. For example, a compound of formula (B) wherein m = 1 can be reacted with methylthiomethanol and NIS to provide a compound of formula (B) wherein m = 2. The process may be repeated to provide compounds of formula (B) in which m is 3, 4, 5 or 6.

In the second step shown in Scheme I, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether. This is accomplished by treating the MTM ether with NIS and protected phosphate $HOP(O)(OR^Y)_2$. In the third step, the phosphono protecting group and any hydroxy protecting group(s) are removed to provide a compound of formula (A). For example, a suitable phosphono protecting group is benzyl which may be removed by catalytic hydrogenolysis; hydroxy protecting groups such as trialkysilyl may be removed by fluoride ion, trichloroethoxycarbonyl may be removed by zinc. Removal of protecting groups are taught in textbooks such as Green and Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991; and McOmie, Protective in Organic Chemistry, Plenum Press, 1973. Both steps are discussed in detail in a later section in the specification.

A variation of the reaction sequence shown in Scheme I is provided in Scheme II.

Scheme II

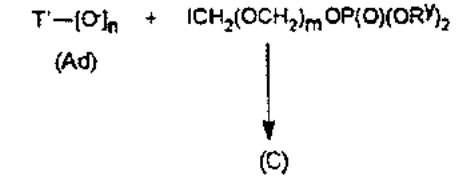
$$\underset{(Aa)}{T'—[OH]_n} + n\ \underset{(Ca)}{CH_3SCH_2(OCH_2)_mOP(O)(OR^Y)_2} \longrightarrow (C)$$

In Scheme II, a compound of formula (Aa) is reacted with a compound of formula (Ca) and NIS to give a compound of formula (C), which is then deblocked to give a compound of formula (A). Compounds of formula (Ca) in which m is 0 may be prepared by first treating methylthiomethanol with a base such as Na,

Li or K hexamethyldisilazide to give methylthiomethoxide; the methoxide is then reacted with a protected chlorophosphate such as dibenzyl chlorophosphate to provide the desired compound. Compounds of formula (Ca) in which m is 1 may be prepared by treating $CH_3SCH_2OCH_2Cl$ with a diprotected phosphate salt, e.g. sodium, potassium, tetra(n-butyl)ammonium salts of dibenzyl phosphate; or $CH_3SCH_2OCH_2Cl$ may be first converted to the corresponding iodo compound using sodium iodide prior to reacting with the phosphate salt. Alternatively, compounds of formula (Ca) in which m is 1 may be prepared by treating $ClCH_2OCH_2Cl$ with sodium iodide followed by sodium thiomethoxide to provide $CH_3SCH_2OCH_2SCH_3$; this compound is then treated with NIS and a diprotected phosphate such as dibenzyl phosphate to give the desired product. Any of the previously mentioned reagents having a MTM group may be extended one methyleneoxy unit at a time by reacting said reagent with methylthiomethanol and NIS.

In another method for preparing a compound of formula (A), T-alkoxide (Ad) is reacted with an iodophosphate as shown in Scheme III.

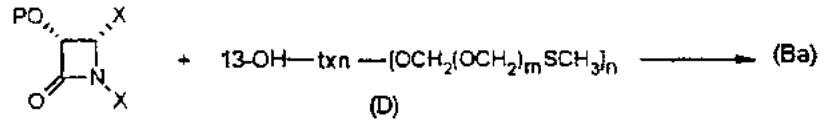
Scheme III



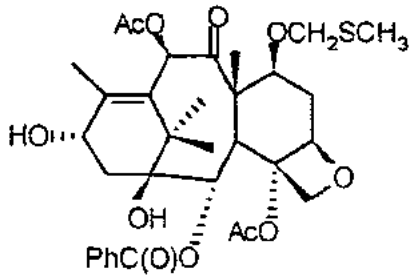
In Scheme III, the iodophosphate compound is obtained by reacting $ClCH_2(OCH_2)_mCl$ with a diprotected phosphate salt to give $ClCH_2(OCH_2)_mOP(O)(OR^Y)_2$ which is then treated with sodium iodide to give the desired product.

Yet another method suitable for preparing a subset of compounds of formula (A) in which at least one of the phosphonooxymethoxy groups is linked to the taxane moiety is shown in Scheme IV.

Scheme IV



In Scheme IV, m and n are as previously defined; X is a non-hydrogen group, P is a hydroxy protecting group; txn is a taxane moiety. Compounds of formula (D) are taxanes having a 13α-hydroxy group and one or more methylthiomethyl ether linked directly or indirectly to the taxane core; also included are C13 metal alkoxides of formula (D). An example of a compound of formula (D) is 7-O-methylthiomethylbaccatin III:



The coupling of the taxane (D) with the azetidinone is analogous to the one shown in Scheme VI, infra; thus the procedure described there for the preparation of a compound of formula (Id) is also applicable to the preparation of a compound of formula (Ba) [i.e. a compound of formula (B) in which at least one of the MTM

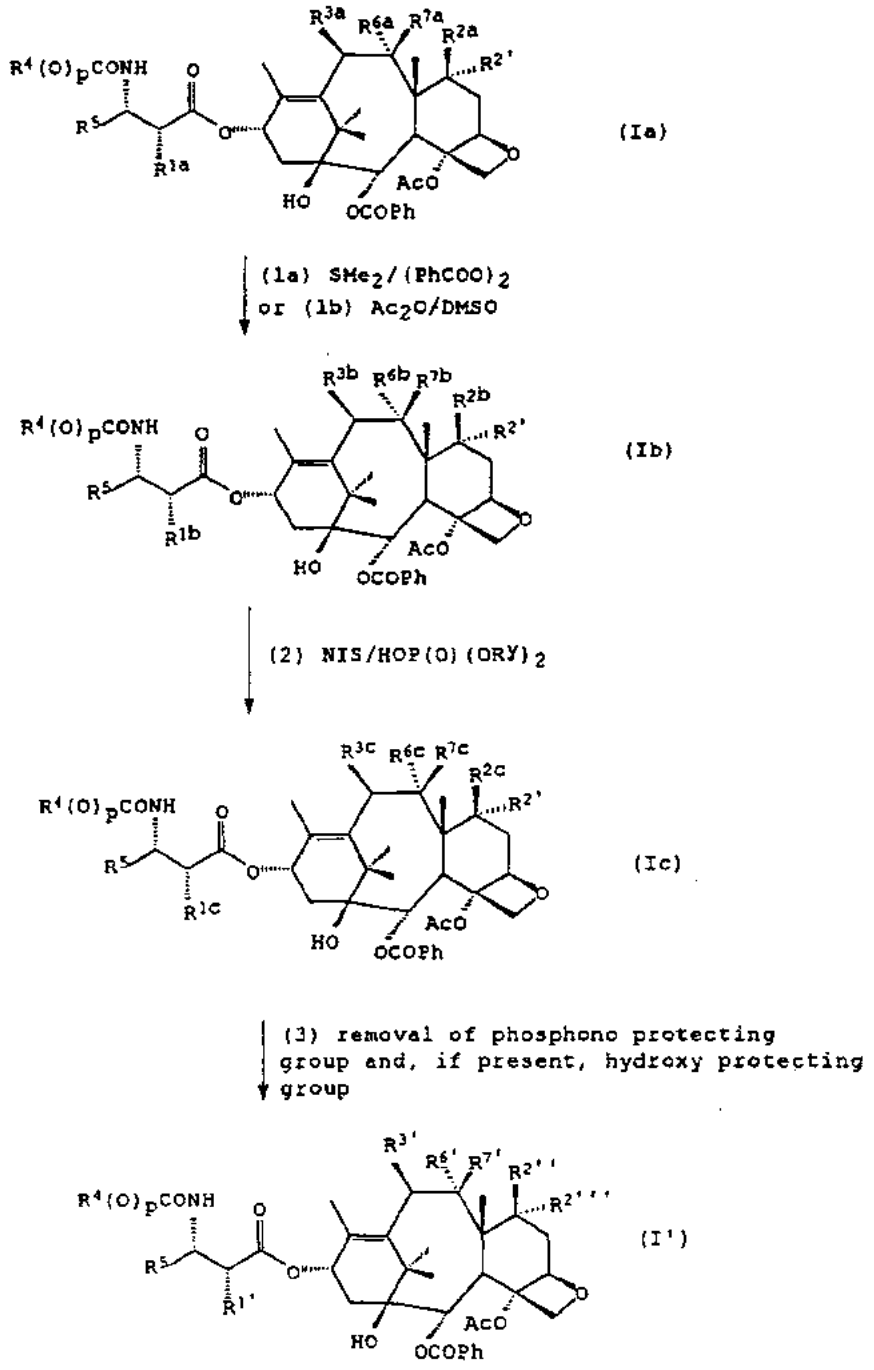
group is linked directly or indirectly to the taxane moiety], if a compound of formula (D) is used in place of a compound of formula (II) in Scheme VI. The taxane (D) is preferably first converted to a C13 metal alkoxide such as sodium, potassium or lithium alkoxide; lithium alkoxide is preferred. The azetidinone serves as the precursor of the C13 sidechain. After the coupling reaction with a taxane, the hydroxy protecting group P is removed, and if desired, the free hydroxy group on the sidechain may be converted to the MTM ether or derivatized to an ester or a carbonate as herein described.

The azetidinone may be prepared by methods described later which are also methods generally known in the art. Compounds of formula (D) may be prepared by the general procedure described above for the preparation of compounds of formula (B) using a suitably protected taxane. However, more conveniently, they can be obtained from a compound of formula (Ba) by cleaving the 13-sidechain using a borohydride such as sodium or tetrabutylammonium borohydride; for example, 7-O-MTM of paclitaxel is treated with tetrabutylammonium borohydride to give 7-O-MTM baccatin III.

The general process of Scheme I for the preparation of a compound of formula (A) is more particularly exemplified in Scheme V which illustrates the preparation of a compound of formula (I') (i.e. a compound of formula (I) in which m is 0). The procedure employed in this synthetic sequence is generally applicable to other taxane derivatives not specifically encompassed by formula (I). Furthermore, the procedure in Scheme (V) may be modified in accordance with teachings contained herein by one skilled in the art to arrive at taxane derivatives of formula (A) in which m is 1 or 2.

It is to be understood that in Scheme V as well as elsewhere in the specification, the term "hydroxy protecting group" may encompass carbonates (-OC(O)OR^x);thus, when a carbonate is used as a hydroxy protecting group, it is intended to be removed in a later step to generate the free hydroxy group, otherwise, the carbonate moiety remains as part of the final product.

Scheme V



In Scheme V, R^{1a} is hydroxy, protected hydroxy, -OC(O)R^X or -OC(O)OR^X; $R^{2'}$ is hydrogen, and R^{2a} ishydrogen, hydroxy, protected hydroxy, or -OC(O)OR^X; or $R^{2'}$ is fluoro, and R^{2a} is hydrogen; R^{3a} is hydrogen, hydroxy, protected hydroxy, acetoxy, or -OC(O)OR^X; one of R^{6a} or R^{7a} is hydrogen and the other is hydroxy, protected hydroxy or C_{1-6} alkanoyloxy; or R^{6a} and R^{7a} together form an oxo group; with the proviso that at least one of R^{1a}, R^{2a} or R^{3a}, R^{6a} or R^{7a} is hydroxy. R^{1b} is hydroxy, protected hydroxy, -OCH_2SCH_3, -OC(O)R^X or -OC(O)OR^X; $R^{2'}$ is hydrogen, and R^{2b} is hydrogen, hydroxy, protected hydroxy, -OCH_2SCH_3 or -OC(O)OR^X; or $R^{2'}$ is fluoro, and R^{2b} is hydrogen; R^{3b} is hydrogen, hydroxy, protected hydroxy, acetoxy, -OCH_2SCH_3 or -OC(O)OR^X; one of R^{6b} or R^{7b} is hydrogen and the other is hydroxy,

protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2SCH_3$; or R^{6b} and R^{7b} together form an oxo group; with the proviso that at least one of R^{1b}, R^{2b}, R^{3b}, R^{6b} or R^{7b} is $-OCH_2SCH_3$. R^{1c} is hydroxy, protected hydroxy, $-OCH_2OP(O)(OR^y)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2c} ishydrogen, hydroxy, protected hydroxy, $-OCH_2OP(O)(OR^y)_2$ or $-OC(O)OR^x$; or $R^{2'}$ is fluoro, and R^{2c} is hydrogen; R^{3c} is hydrogen, hydroxy, protected hydroxy, acetoxy, $-OCH_2OP(O)(OR^y)_2$ or $-OC(O)OR^x$; one of R^{6c} or R^{7c} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2OP(O)(OR^y)_2$; with the proviso that at least one of R^{1c}, R^{2c}, R^{3c}, R^{6c} or R^{7c} is $-OCH_2OP(O)(OR^y)_2$. $R^{1'}$is hydroxy, $-OCH_2OP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'''}$ is hydrogen, and $R^{2''}$ is hydrogen, hydroxy, $-OCH_2OP(O)(OH)_2$ or $-OC(O)OR^x$; or $R^{2''}$ is fluoro, and $R^{2'''}$ is hydrogen; $R^{3'}$ is hydrogen, hydroxy, acetoxy, $-OCH_2OP(O)(OH)_2$ or $-OC(O)OR^x$; one of $R^{6'}$ or $R^{7'}$ is hydrogen and the other is hydroxy, C_{1-6}alkanoyloxy or $-OCH_2P(O)(OH)_2$; with the proviso that at least one of $R^{1'}$, $R^{2''}$, $R^{3'}$, $R^{6'}$ or $R^{7'}$ is $-OCH_2OP(O)(OH)_2$.R^4, R^5 and R^x are as defined previously, and R^y is a phosphono protecting group.

In the first step, the free hydroxy group of a compound of formula (Ia) is converted to the corresponding methylthiomethyl ether ($-OCH_2SCH_3$) group. This conversion may be accomplished by either one of the two procedures (1a - the dimethylsulfide method) and (1b - the dimethylsulfoxide method). The dimethylsulfide method for converting alcohols to methylthiomethyl ethers is reported in Medina et al, Tet. Lett., 1988, pp. 3773-3776, the relevant portions thereof are hereby incorporated by reference. The dimethylsulfoxide method is the well-known reaction commonly known as the Pummerer reaction.

It should be noted that the reactivity of a hydroxy group differs depending on its location on the taxane derivative starting material of formula (Ia). Although in general the 2'-hydroxy group is more reactive in acylation reactions than the 7-hydroxy group which in turn is more reactive than the 10-hydroxy group, it has been found that, surprisingly, the 7-hydroxy is more readily converted into the methylthiomethyl ether than the 2'-hydroxy group. The tertiary hydroxy group at C-1 is usually the least reactive. The difference in hydroxy reactivity may be exploited in controlling the site and degree of methylthiomethylation.

Thus with a compound of formula (Ia) wherein R^{1a} and R^{2a} are both hydroxy, the predominant methylthiomethylation product is the corresponding 7-O-methylthiomethyl ether. In order to obtain a compound of formula (Ib) wherein R^{1b} is methylthiomethoxy, without also converting the 7-hydroxy group, if present, into a methylthiomethyl ether, the 7-hydroxy group is blocked with a conventional hydroxy protecting group such as triethylsilyl. Similarly, 10-methylthiomethyl ether may be obtained without also converting the 7- and/or 2'-hydroxy groups, if present, when the latter groups are blocked by the same of different hydroxy protecting groups. Even though the 7-hydroxy is the preferential methylthiomethylation site, it is still preferable to protect the 2'-hydroxy group if the 7-monomethylthiomethyl ether is the desired product.

Moreover, the reaction conditions may be manipulated to favor the formation of bis- or tris-methylthiomethyl ether taxane derivatives. For example, in the case of paclitaxel, increasing reaction time or using a larger excess of the methylthiomethylating reagents can result in a higher ratio of 2',7-bis-(methylthiomethyl) ether paclitaxel in the product mixture.

Returning now to Scheme V, in procedure (1a) a compound of formula (Ia) is treated with dimethylsulfide and an organic peroxide such as benzoyl peroxide. The reaction is carried out in an inert organic solvent such as acetonitrile, methylene chloride and the like at a temperature conducive to product formation; typically the reaction is carried at a temperature range of from about -40°C to about ambient temperature. Dimethylsulfide and benzoyl peroxide are used in excess relative to the taxane derivative starting material (Ia), and dimethylsulfide is used in excess relative to benzoyl peroxide.

The relative amounts of starting materials used will depend on the degree of methylthiomethylation to be achieved. Thus when one free hydroxy group of the taxane derivative starting material (Ia) is to be converted to the methylthiomethyl ether, dimethylsulfide and benzoyl peroxide may be used in up to 10 fold excess relative to taxane derivative (Ia); and preferably, dimethylsulfide is used in about two to three fold excess relative to benzoyl peroxide. In the case where the starting material (Ia) has both 2'- and 7-hydroxy groups, the amount of 2',7-bis(methylthiomethyl)ether obtained increases with the relative amounts of dimethylsulfide and benzoyl peroxide. When 2',7-bis(methylthiomethyl) ether is the desired product, dimethylsulfide is preferably used in about 15 to about 20 fold excess of the taxane derivative starting material; and benzoyl peroxide is used in about 5 to about 10 fold excess relative to the taxane derivative starting material.

Alternatively, a compound of formula (Ib) may be prepared by reacting a compound of formula (Ia) with dimethylsulfoxide and acetic anhydride (procedure 1b). This procedure is suitable for derivatizing a non-2'-hydroxy group into its methylthiomethyl ether. In procedure (1b), a compound of formula (Ia) is dissolved in dimethylsulfoxide and acetic anhydride is added to the solution. The reaction is usually carried out at room temperature, and for 18-24 hours to produce the monomethylthiomethyl ether.

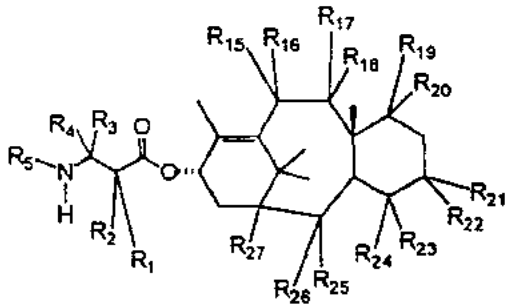
In the second step of the reaction sequence, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether. The methylthiomethyl to protected phosphonooxymethyl conversion may be accomplished by the general method reported in Veeneman et al, Tetrahedron, 1991, v47, pp. 1547-1562, the relevant portions thereof are hereby incorporated by reference. Thus, a compound of formula (Ib) with at least one methylthiomethyl ether group is treated with N-iodosuccinimide and a protected phosphoric acid such as dibenzyl phosphate. The reaction is carried out in an inert organic solvent such as tetrahydrofuran or a halogenated hydrocarbon such as 1,2-dichloroethane or methylene chloride, and optionally in the presence of a dehydrating agent such as molecular sieves. A catalyst such as silver trifluoromethanesulfonate may also be added to accelerate the reaction. The reaction is carried out at a temperature ranging from about 0°C to about room temperature, preferably at room temperature. N-Iodosuccinimide and the protected phosphoric acid are used in about the same molar equivalent as the methylthiomethylether (Ib), but preferably they are used in slight excess, for example about 1.3 to about 1.5 equivalents relative to compound of formula (Ib).

In the third step of the reaction sequence, the phosphono protecting group and hydroxy protecting group, if present, are removed. The deblocking is accomplished by conventional methods well known in the art such as acid- or base-catalyzed hydrolysis, hydrogenolysis, reduction, and the like. For example, catalytic hydrogenolysis can be used to remove the benzyl phosphono protecting group as well as the benzyloxycarbonyl hydroxy protecting group. Deprotecting methodologies may be found in standard texts such as Greene and Wutz, or McOmie, supra.

The base salts of a compound of formula (I) may be formed by conventional techniques involving contacting a compound of formula (I) free acid with a metal base or with an amine. Suitable metal bases include hydroxides, carbonates and bicarbonates of sodium, potassium, lithium, calcium, barium, magnesium, zinc, and aluminum; and suitable amines include triethylamine, ammonia, lysine, arginine, N-methylglucamine, ethanolamine, procaine, benzathine, dibenzylamine, tromethamine (TRIS), chloroprocaine, choline, diethanolamine, triethanolamine and the like. The base salts may be further purified by chromatography followed by lyophilization or crystallization.

TAXANE DERIVATIVES STARTING MATERIALS

The processes described above may be applied to any taxane derivatives of the formula T-$[OH]_n$ to form compounds of formula (A). Many examples of T-$[OH]_n$ have been reported in the literature and some of which are listed below. (a) paclitaxel; (b) Taxotere®; (c) 10-desacetylpaclitaxel; (d) taxane derivatives disclosed in PCT application 93/06079 (published April 1, 1993) having the formula



wherein R_1 is $-OR_6$, $-SR_7$, or $-NR_8R_9$; R_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; R_3 and R_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or acyl, provided, however, that R_3 and R_4 are not both acyl; R_5 is $-COR_{10}$, $-COOR_{10}$, $-COSR_{10}$, $-CONR_8R_{10}$, $-SO_2R_{11}$, or $-POR_{12}R_{13}$;R_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative; R_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group; R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_9 is an amino protecting group; R_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OR_{10}$, or $-NR_8R_{14}$; R_{12} and R_{13} are independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OR_{10}$, or $-NR_8R_{14}$; R_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_{15} and R_{16} are independently hydrogen, hydroxy, lower alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy or R_{15} and R_{16} together form an oxo; R_{17} and R_{18} are independently hydrogen, hydroxy, lower alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy or

R_{17} and R_{18} together form an oxo; R_{19} and R_{20} are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; R_{21} and R_{22} are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or R_{21} and R_{22} together form an oxo; R_{24} is hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{23} and R_{24} together form an oxo or methylene or R_{23} and R_{24} together with the carbon atom to which they are attached form an oxirane ring or R_{23} and R_{22} together with the carbon atom to which they are attached form an oxetane ring; R_{25} is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{26} is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{26} and R_{25} taken together form an oxo; and R_{27} is hydrogen, hydroxy or lower alkoxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; (e) taxane derivatives disclosed in U.S. Patent 5,227,400 3'-desphenyl-3'-(2-furyl) or 3'-(2-thienyl) derivatives of paclitaxel, Taxotere®; (f) taxane derivatives disclosed in EP 534,709 published March 31, 1993 (paclitaxel derivatives in which the sidechain phenyl groups are independently replaced with naphthyl, styryl or substituted phenyl). See also PCT 92/09589 published June 11, 1992; (g) taxane derivatives disclosed in EP 534,707 published March 31, 1993 (paclitaxel derivatives in which the 3'-N-benzoyl group is replaced with ethoxycarbonyl or methoxycarbonyl); (h) PCT Application 93/06093 published April 1, 1993 (10-desacetoxy derivatives of paclitaxel and Taxotere®); (i) EP 524,093 published January 20, 1993 (10-, 7-, or 7,10-bis-O-(N-substituted carbamoyl taxane derivatives); (j) 9-α-hydroxy analog of paclitaxel is disclosed in Klein, "Synthesis of 9-Dihydrotaxol: A New Bioactive Taxane," Tetrahedron Letters, 1993, 34(13):2047-2050; (k) 14-β-hydroxy analog of paclitaxel and Taxotere® prepared from 14β-hydroxy-10-deacetylbaccatin III are disclosed at the 205th ACS National Meeting in Colorado, 1993. (Med. Chem. Division, Abstract No. 28); and (l) other taxanes, such as C7-fluorotaxanes and various C10-substituted taxanes, as disclosed in our copending U.S. patent application U.S.S.N. 08/062,687 filed May 20, 1993 which is herein incorporated by reference in its entirety.

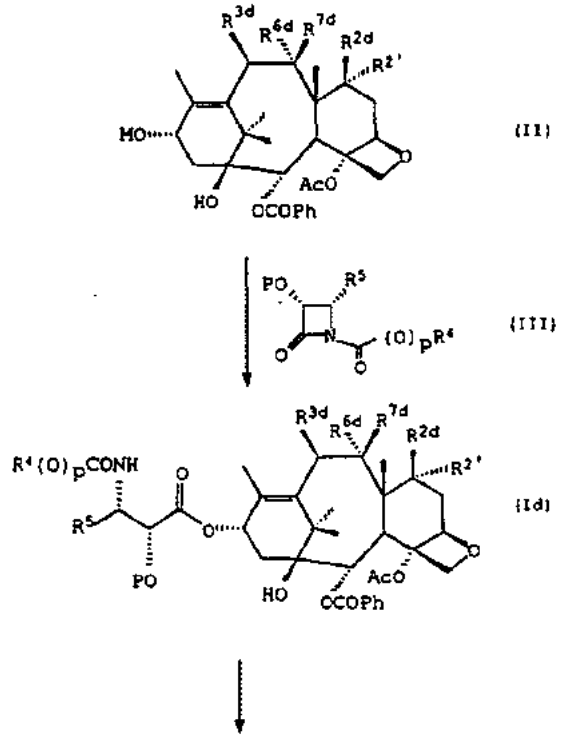
The free hydroxy group or groups of taxane derivatives may be converted by conventional methods to the corresponding ester or carbonate; for example in compounds of formula (Ia) one of R^{1a}, R^{2a} or R^{3a} is $-OC(O)R^x$ or $-OC(O)OR^x$ and R^x is as previously defined. Thus, a taxane derivative T-OH may be reacted with a compound of the formula $L\text{-}C(O)OR^x$ (L being a leaving group) such as a chloroformate in the presence of a base such as tertiary amine to give the corresponding carbonate; for example, paclitaxel reacts with ethyl chloroformate in the presence of diisopropylethylamine to provide 2'-O-ethyloxycarbonyl-paclitaxel. T-OH may also react with a carboxylic acid R^xCO_2H or an acylating equivalent thereof (e.g. an anhydride, active ester or an acyl halide) to provide the corresponding ester.

Additionally, taxane derivatives $T\text{-}[OH]_n$ may be prepared by acylating a taxane moiety having a C13-hydroxy group with an appropriately substituted 3-amino-2-hydroxypropanoic acid, an acylating equivalent thereof, or a precursor thereof. Suitable precursors of substitutd 3-amino-2-hydroxypropanoic acid are for example azetidinones of formula (III). This acylation reaction is exemplified in the coupling of hydroxy protected baccatin III or hydroxy protected 10-deacetylbaccatin III and a phenylisoserine derivative to give paclitaxel derivatives as disclosed in e.g. Denis et al, U.S. Patents 4,924,011 and 4,924,012; and in the coupling of a protected baccatin III and an azetidinone to give paclitaxel and derivatives thereof as disclosed in EP Published Application 400,971 published December 5, 1990 (now U.S. Patent 5,175,315) and U.S. Patent 5,229,526.

The process as disclosed in EP 400,971 (the Holton process) involves reacting 1-benzoyl-3-(1-ethoxy)-ethoxy-4-phenyl-2-azetidinone with 7-O-triethylsilylbaccatin III in the presence of N,N-dimethylaminopyridine and pyridine at 25°C for 12 hours; paclitaxel is obtained after the various hydroxy protecting groups are removed. An improvement of the Holton process is reported by Ojima et al in "New and Efficient Approaches to the Semisynthesis of Taxol and its C-13 Side Chain Analogs by Means of β-Lactam Synthon Method" Tetrahedron, 1992, 48(34):6985-7012. Ojima's process involves first generating the sodium salt of 7-triethylsilylbaccatin III with sodium hydride; this salt is then reacted with chiral 1-benzoyl-3-(1-ethyoxy)-ethoxy-4-phenyl-2-azetidinone to provide paclitaxel after removal of the hydroxy protecting groups. In U.S. 5,229,526 Holton discloses the coupling of a metal alkoxide of baccatin III or a derivative thereof with a 2-azetidinone to provide taxanes with C13 sidechain. This process is said to be highly diastereoselective; therefore racemic mixtures of the sidechain precursor 2-azetidinone may be used. Recently, Ojima et al reported in "A Highly Efficient Route to Taxotere by the β-Lactam Synthon Method," Tetrahedron Letters, 1993, 34(26):4149-4152, the coupling of metal alkoxides of 7,10-bis-O-(trichloroethoxycarbonyl)-10-deacetyl-baccatin III with chiral 1-(t-butoxycarbonyl)-4-phenyl-3-(protected hydroxy)-2-azetidinone to give Taxotere® after deprotection. The relevant portions of all references cited above are hereby incorporated by reference.

The baccatin/azetidinone process generalized to the preparation of compounds of formula (Ia) is illustrated in Scheme VI. Again, other taxane derivatives not specifically encompassed within the formula (Ia) may also be prepared by this process by employing appropriate starting materials.

Scheme VI



In Scheme VI, $R^{2'}$ is hydrogen, and R^{2d} is hydrogen, protected hydroxy, or -OC(O)OR^x; or $R^{2'}$ is fluoro, and R^{2d} is hydrogen; R^{3d} is hydrogen, acetoxy, protected hydroxy or -OC(O)OR^x; one of R^{6d} or R^{7d} is hydrogen and the other is hydroxy, protected hydroxy or C_{1-6} alkanoyloxy; or R^{6d} and R^{7d} together form an oxo group; P is a hydroxy protecting group; M is hydrogen or a Group IA metal such as lithium, sodium or potassium; and p, R^4, R^5 and R^x are as previously defined. The reaction may be conducted according to the procedure disclosed in EP 400,971 wherein the baccatin III derivative of formula (II) wherein M is hydrogen is reacted with an azetidinone of formula (III) in the presence of an organic base such as N,N-dimethylaminopyridine. Preferably, however, the baccatin III derivative is first converted to a 13-alkoxide by treating the former with a strong base such as hydrides, alkylamides, and bis(trialkylsilyl)amides of Group IA metals as disclosed in U.S. Patent 5,229,526 and the Ojima references, supra. More preferably, the 13-alkoxide is a lithium alkoxide. The formation of a lithium salt may be achieved by reacting a compound of formula (II) wherein M is hydrogen with a strong metal base, such as lithium diisopropylamide, C_{1-6} alkyllithium, lithium bis(trimethylsilyl)amide, phenyllithium, lithium hydride, or the like base.

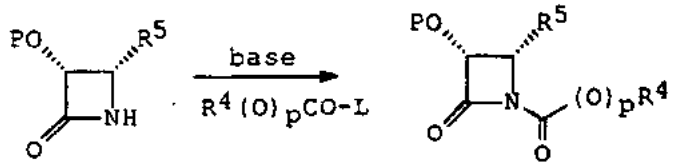
The coupling reaction between a taxane of formula (II) and an azetidinone of formula (III) is conducted in an inert organic solvent such as tetrahydrofuran at reduced temperature in the range of about 0°C to about -78°C. The azetidinones of formula (III) may be used as a racemic mixture to couple with taxane metal alkoxides of formula (II) in which M is a group 1A metal; in such case, the azetidinone reactant is preferably used in at least 2 equivalents relative to the taxane reactant, and more preferably from about 3 to about 6 equivalents. Chiral azetidinones may also be used, and in such case one equivalent of the azetidinone relative to the taxane may be sufficient, but preferably the azetidinone is used in slight excess, for example up to 1.5 equivalents.

The hydroxy protecting groups may be the same or they may be chosen in a manner to allow the selective removal of one or more protecting groups without substantially affecting the others; for example, in a compound of formula (Id), R^{2d} and PO may be both triethylsilyloxy, and R^{3d} may be benzyloxycarbonyl; catalytic hydrogenolysis in the presence of palladium on carbon removes the benzyloxycarbonyl protecting group without removing the triethylsilyl group. Thus, the hydroxy protecting groups of a compound of

formula (Id) may be selectively removed to provide a compound of formula (Ia).

Compounds of formula (II) are either known in the literature, e.g baccatin III, 10-deacetylbaccatin III and their hydroxy protected derivatives, or can be prepared from the known compounds by conventional conventional methods, e.g converting a hydroxy group to a carbonate. Additional compounds of formula (II) may be prepared according to procedures described hereinbelow in the section PREPARATION OF STARTING MATERIALS.

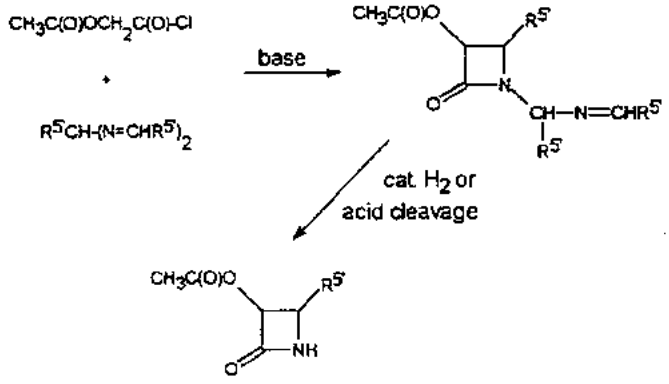
Compounds of formula (III) can be prepared from a compound of (IIIa) according to the general method described in EP 400,971 and Ojima et al. Tetrahedron, 48:6985-7012, 1992.



(IIIa) (III)

Thus a compound of formula (IIIa) is first treated with a base such as n-butyllithium or triethylamine, and then followed by a compound of the formula $R^4(O)_pCO$-L where L is a leaving group to provide a compound of formula (III).

Compounds of (IIIa) may be prepared according to the general method disclosed in EP 400,971 by going through an intermediate compound 3-acetoxy-4-substituted-2-azetidinone (IIIb); or by the method disclosed in US5,229,526 by going through an intermediate compound 3-triethylsilyloxy-4-substituted-2-azetidinone. In an improved process a compound (IIIb) may be obtained by condensing acetoxyacetyl chloride with a bis-imine followed by hydrogenolysis or acid cleavage to remove the N-imine group; this process is shown in the following scheme in which R^5 is an optionally substituted aryl or a heteroaryl group such as furyl or thienyl. This process is disclosed in co-pending application U.S.S.N 08/052,434 filed April 23, 1993 which is hereby incorporated by reference.



The products (IIIb) obtained from these cycloaddition reactions are usually a racemic mixture of the two cis-azetidinones. The racemic mixture may be resolved by conventional methods such as conversion to diastereomers, differential absorption on column packed with chiral adsorbents, or enzymatically. For example, a racemic mixture of compounds of formula (IIIb) may be contacted with an enzyme that catalyzes the hydrolysis of an ester, for example an esterase or a lipase, to selectively cleave the 3-acyl group of one enantiomer without affecting the other. (See e.g. Brieva et al, J. Org. Chem., 1993, 58:1068-1075; also co-pending application U.S.S.N. 092,170 filed July 14, 1993, European Patent Application Number 552041, published July 29, 1993). Alternatively, the racemic mixture may be first subjected to base-catalyzed hydrolysis to remove the 3-acyl group and to generate a racemic mixture of the corresponding 3-hydroxy β-lactam; the racemic mixture of 3-hydroxy β-lactam is then contacted with an enzyme capable of catalyzing acylation of an hydroxy group to selectively acylate the hydroxy group of one enantiomer without affecting the other. Or the racemic mixture of 3-hydroxy β-lactam may be acylated with a chiral carboxylic acid, and

the resulting diastereomeric mixture may then be separated using methods known in the art, and the chiral auxiliary removed to provide the desired enantiomer.

Ojima et al, in J. Org. Chem., 56:1681-1683, 1991; Tet. Lett., 33:5737-5740, 1992; and Tetrahedron, 48:6985-7012, 1992 reported the synthesis of a number of chiral azetidinones of formula (IIIa) and/or the corresponing N-(p-methoxyphenyl) congener; wherein P is the hydroxy protecting group triisopropylsilyl; and R^5 is 4-methoxyphenyl, 3,4-dimethyoxyphenyl, phenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-furyl, 2-phenylethenyl, 2-(2-furyl)ethenyl, 2-methylpropyl, cyclohexylmethyl, isopropyl, phenethyl, 2-cyclohexylethyl, or n-propyl. The relevant portions of these references are hereby incorporated by reference. Other azetidinones within the definition of formula (III) but are not specifically disclosed in these references may be prepared by a person skilled in the art following the methodologies generally known in the art.

BIOLOGICAL EVALUATION

Compounds of the present invention are novel antitumor agents; representative compounds of formula (A) have been evaluated in in vitro cytotoxicity assays and in vivo animal tumor models.

In vitro cytotoxicity data

Compounds of the present invention showed in vitro cytoxicity activity against human colon carcinoma cells HCT-116 and HCT-116/VM46. The HCT-116/VM46 cells are cells that have been previously selected for teniposide resistance and express the multi-drug resistance phenotype, including resistance to paclitaxel. Cytotoxicity was assessed in HCT-116 human colon carcinoma cells by XTT (2,3-bis(2-methoxy-4-nitro-5-sulfphenyl)-5-[(phenylamino)carbonyl]2H-tetrazolium hydroxide) assay as reported in D.A. Scudiero, et al., "Evaluation of soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines," Cancer Res. 48:4827-4833, 1988. Cells were plated at 4000 cells/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37°C for 72 hours at which time the tetrazolium dye, XTT, was added. A dehydrogenase enzyme in live cells reduces the XTT to a form that absorbs light at 450 nm which can be quantitated spectrophotometrically. The greater the absorbance, the greater the number of live cells. The results are expressed as an IC_{50}, which is the drug concentration required to inhibit cell proliferation (i.e., absorbance at 450 nm) to 50% of that of untreated control cells. The IC_{50} values for compounds evaluated in this assay are given in Table I.

Table I

In vitro cytotoxicity data against human colon carcinoma cells.		
Compound	IC_{50} (μM)	
	HCT-116	HCT-116/VM46[1]
Taxotere®	0.004	0.213 (53)
paclitaxel	0.004	0.44 (124)
Example 1	0.020	1.30 (66)
Example 3	0.266	6.67 (25)
Example 4	0.044	5.36 (122)

[1]Value is parenthesis is fold resistance relative to HCT-116 cells.

The compound 7-O-methylthiomethylpaclitaxel (Example 1 (a) was also tested in the cytotoxicity assay and it showed IC_{50} of 0.003 μM against HCT-116 and 0.025 μM against HCT-116/VM46.

In vivo antitumor activity

Balb/c x DBA_2 F_1 (CDF_1) hybrid mice were implanted subcutaneously (sc) with 0.1 ml of a 2% (w/v) brei of M109 lung carcinoma (as described in W. Rose "Evaluation of Madison 109 Lung Carcinoma as a Model for Screening Antitumor Drugs," Cancer Treatment Reports, 65, No. 3-4 pp. 299-312 (1981). The test compounds and reference drug, paclitaxel, were administered intravenously to groups of mice; each group received a compound at a different dose level, and three or four different dose levels were evaluated per

compound. Mice were followed daily for survival until their death or about day 75 post-tumor implant, whichever occurred first. One group of mice per experiment remained untreated and served as the control. Tumors were also measured once or twice weekly and the size in mm was used to estimate tumor weight according to the published procedure (ibid).

Median survival times of compound-treated (T) mice were compared to the median survival time of parallel control (C) mice. The ratio of the two values for each compound-treated group of mice was multiplied by 100 and expressed as a percentage (i.e., % T/C) in Table II for representative compounds. Additionally, the difference between the median time for treated groups and that for the control group to grow tumor to 1 gm, expressed as T-C values in days, is also shown in Table II. The greater the T-C value, the greater the delay in primary tumor growth. Compounds showing % T/C ≥ 125% and/or T-C ≥ 4.0 days are considered to be active in the M109 SC model.

Table II

Compound	Maximum Effect		Opt. Dose
	% T/C	T-C (days)	(mg/kg/inj;)
Example 1	131	14.0	45[a]
paclitaxel	134	14	48/24[a,c]
Example 3	160	18.8	24[b]
paclitaxel	151	15	18[b]

[a]Compound was administered i.v. once daily, on days 4, 5, 6, 7 and 8 post-tumor implant.

[b]Compound was administered i.v. once daily, on days 5, 6, 7, 8 and 9 post-tumor implant.

[c]Higher dose achieved maximum increase in lifespan; lower dose associated with causing maximum delay in tumor growth.

Compound of Example 3 (as the triethanolamine salt) was further evaluated in murine and human xenograft tumor models (M109, A2780/cDDP - human ovarian carcinoma resistant to cisplatin, and HCT-116 - human colon carcinoma) against paclitaxel as positive control. The A2780/cDDP moel is described in Rose and Basler, In Vivo, 1990, 4:391-396; the HCT-116 model is described in Rose and Basler, In Vivo, 1989, 3:249-254. M109 was passaged sc biweekly in Balb/C mice and implanted sc into CDF1 mice for antitumor evaluation. A2780/cDDP and HCT-116 were grown in athymic mice for both passage (every two to three weeks) and therapy experiments. Compound of Example 3 was administered iv in water, or orally in water with a few drops of Tween 80, while paclitaxel was either suspended in water plus Tween 80, or dissolved in cremophore/ethanol (50%/50%) and diluted with saline. The treatment regimen for the sc M109 tumor tests was once daily for 5 consecutive days beginning on Day 4 post tumor implant. For the human tumor xenograft tests, compounds were given once daily every other day for five administrations beginning when the tumors were staged to between 50 to 100 mg.

In one M109 experiment, compound of Example 3 administered iv achieved max. %T/C of 155 (T-C of 19 days) at 36 mg/kg/inj. (cf. paclitaxel max. %T/C of 132 (T-C of 13 days) at 36 or 18 mg/kg/inj.). In the same experiment, compound of Example 3 administered orally achieved a max. %T/C of 158 (T-C of 22.8 days) at a dose of 160 mg/kg/adm. while paclitaxel at the same dose (highest tested) suspended in water and Tween 80 did not show activity. In another M109 experiment, iv administered compound of Example 3 produced max. %T/C of 170 (T-C of 17 days) at 48 mg/kg/inj. (cf. paclitaxel max.%T/C of 167 (T-C of 14 days) at 48 or 36 mg/kg/inj.). In the same experiment, orally administered compound of Example 3 produced max. %T/C of 172 (T-C of 17 days) at a dose of 200 mg/kg/adm. while paclitaxel dissolved in cremophore/ethanol/saline did not show activity at 60/mg/kg/inj. In this experiment, paclitaxel dissolved in cremophore/ethanol/saline could not be administered at greater than 60/mg/kg/inj. due to solubility and toxicity constraints.

In the A2780/cDDP experiment, iv administered compounds of Example 3 showed max. T-C value of 29.8 days at 36 mg/kg/inj (cf. paclitaxel max. T-C of 26.3 days at 36 mg/kg/inj.). Orally administered compound of Example 3 produced max. T-C of 20 days at a dose of 160 mg/kg/adm. In the HCT-116 experiment, iv treatment with 24 or 36 mg/kg/inj. of paclitaxel produced 6 cures of 7 or 6 cures of 8 treated mice, respectively, and 160 or 240 mg/kg/adm. of oral compound of Example 3 cured 6 or 7 of 8 treated

mice, respectively. Cure means tumor-free on Day 80 post tumor implant.

Compounds of the present invention are phosphonooxymethyl ethers of taxane derivatives. The pharmaceutically acceptable salt forms exhibit improved water solubility over paclitaxel thereby allowing more convenient pharmaceutical formulations. Without being bound by theory, it is believed that the phosphonooxymethyl ethers of the present invention are prodrugs of paclitaxel or derivative thereof; the phosphonooxymethyl moiety being cleaved upon contact with phosphatase in vivo to generate subsequently the parent compound. As shown above, compounds of the instant invention are effective tumor inhibiting agents. Thus, another aspect of the instant invention concerns a method for inhibiting mammalian tumors which comprises administering to a tumor bearing host an antitumor effective amount of a compound of formula (A).

Compounds of formula (A) of the present invention may be used in a manner similar to that of paclitaxel; therefore, an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering a compound of the present invention. The dosage, mode and schedule of administration for compounds of this invention are not particularly restricted, and will vary with the particular compound employed. Thus a compound of the present invention may be administered via any suitable route of administration, preferably parenterally; the dosage may be, for example, in the range of about 1 to about 100 mg/kg of body weight, or about 20 to about 500 mg/m^2. Compounds of formula (A) may also be administered orally; oral dosage may be in the range of about 5 to about 500 mg/kg of body weight. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient.

The present invention also provides pharmaceutical compositions containing an antitumor effective amount of a compound of formula (A) in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. Examples of formulating paclitaxel or derivatives thereof may be found in, for example, United States Patents Nos. 4,960,790 and 4,814,470. For example, compounds of the present invention may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. They may also be manufactured in the form of sterile solid compositions, for example, freeze dried and, if desired, combined with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use for parenteral administration.

Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly-(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), broad doublet (bd), broad triplet (bt), broad quartet (bq), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d_6 (deuterated acetone), DMSO-d_6 (perdeuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuterochloroform) and other conventional deuterated solvents. The infrared (IR) spectral description include only absorption wave numbers (cm^{-1}) having functional group identification value.

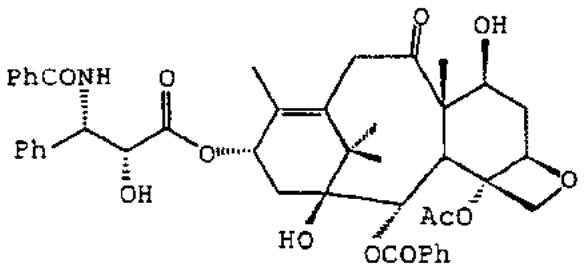
Celite is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); v/v (volume/volume); FAB (fast atom bombardment); NOBA (m-nitrobenzyl alcohol); min (minute(s)); h or hr-(s) (hour(s)); NIS (N-iodosuccinimide); BOC (t-butoxycarbonyl); CBZ (benzyloxycarbonyl); Bn (benzyl); Bz (benzoyl); TES (triethylsilyl); DMSO (dimethylsulfoxide); THF (tetrahydrofuran); HMDS (hexamethyl-disilazane).

PREPARATION OF STARTING MATERIALS

The preparations of several specific starting materials useful in the preparation of compounds of formula (A) are exemplified below.

Preparation 1. 10-Desacetoxypaclitaxel



(a) 2',7-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetyl paclitaxel

10-Deacetyl paclitaxel (140 mg, 0.173 mmol) in dry dichloromethane (3.5 mL) was treated at 0°C with pyridine (0.028 mL, 0.346 mmol) and trichloroethyl chloroformate (0.0724 mL, 0.260 mmol). After 1h at this temperature, the cold bath was removed and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue chromatographed on silica gel (30-50% ethyl acetate in hexane) to afford the title compound as a foam (92.3 mg, 46%). Further elution afforded unreacted starting material (35 mg, 25%), and 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetylpaclitaxel in 16% yield.

(b) 2',7-O-bis(2,2,2-trichloroethoxycarbonyl)-10-desacetoxy-11,12-dihydropaclitaxel-10,12(18)-diene

The product obtained in step (a) (92.3 mg, 0.079 mmol) in dry dichloromethane (2 mL) was treated at room temperature with 1,1,2-trifluoro-2-chlorotriethylamine (0.0384 mL, 0.238 mmol). The solution was stirred overnight. The solvent was evaporated and the residue purified by column chromatography (25% ethyl acetate in hexane) to afford the title compound as a white powder (42.8 mg, 47.3%).

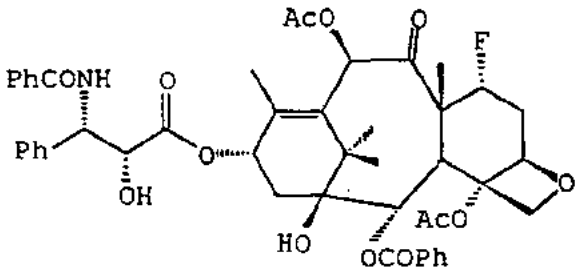
(c) 10-Desacetoxy-11,12-dihydropaclitaxel-10,12(18)-diene

The product of step (b) (39 mg, 0.034 mmol) was dissolved in methanol (0.5 mL) and acetic acid (0.5 mL), and treated with acid-washed zinc dust (66.4 mg, 1.020 mmol). The slurry was heated at 40°C for 1h, filtered and the filtrate evaporated. Chromatography of the residue with 60% ethyl acetate/hexane gave the title compound as a foam (22 mg, 81%).

(c) 10-Desacetoxypaclitaxel

The product of step (c) (22 mg, 0.028 mmol) in ethyl acetate (0.7 mL) was hydrogenated at atmospheric pressure in the presence of palladium on charcoal (10%, 14.7 mg, 0.014 mmol Pd) After 5.5 h at RT, filtration (rinsing with ethyl acetate), evaporation and chromatography (60% ethyl acetate in hexane) gave the title product (15.0 mg, 68%) as a white foam.

Preparation 2. 7-Deoxy-7α-fluoropaclitaxel



(a) 2'-O-Benzyloxycarbonyl-7-deoxy-7α-fluoropaclitaxel

Diethylaminosulfur trifluoride (DAST, 18.7 μL, 0.141 mmol) was dissolved in dry dichloromethane (0.5 mL), and this solution was cooled to 0°C. A solution of 2'-O-(benzyloxycarbonyl)paclitaxel (71 mg, 0.072 mmol) in dichloromethane (1 mL) was added and the resulting solution was kept at 0°C for 30 min and at room temperature for 4 h. Then, water (0.15 mL) was added to the reaction mixture in order to quench the reaction and the resultant mixture was concentrated to leave a residue. The residue was chromatographed on a silica gel column (being eluted with 40% ethyl acetate in hexane) to yield 61 mg (Y: 85.7%) of a 1:1 mixture of the title compound and 2'-O-benzyloxycarbonyl-8-desmethyl-7,8-cyclopropapaclitaxel.

(b) 7-Deoxy-7α-fluoropaclitaxel

The product mixture obtained in Step (a) (89 mg) was dissolved in ethyl acetate (3 mL) and the mixture was stirred under slightly over one atmospheric pressure of hydrogen in the presence of palladium on charcoal (10% Pd, 29mg, 0.027 mmol). After 12 h, the solvent was removed, and the residue was purified by silica gel chromatography (being eluted with 40% ethyl acetate in hexane) to afford 67.7 mg of the title compound, along with 8-desmethyl-7,8-cyclopropapaclitaxel.

The following HPLC method was used to separate the 7-deoxy-7α-fluoropaclitaxel and 8-desmethyl-7,8-cyclopropapaclitaxel.

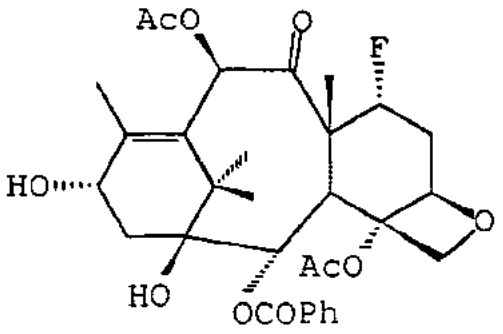
Equipment

Pump:	PE Series 4
Column:	Shandon Hypercarb (graphitized carbon), 7μ, 100 x 4.6 mm, #59864750 (information on preparative size columns may be obtained from Keystone Scientific, Bellefonte, PA)
Injector:	PE ISS-100
Detector:	HP-1040M

Conditions

Mobile Phase:	85:15 methylene chloride: hexane Separation not lost at 80:19:1 methylene chloride: hexane: isopropyl alcohol
Flow Rate:	2.5 mL/min
Detector:	254nm
Diluent:	Sample dissolved in methylene chloride

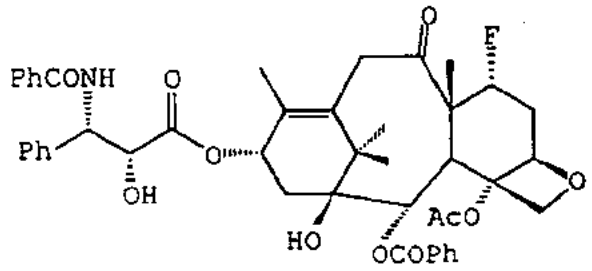
Preparation 3. 7-Deoxy-7α-fluorobaccatin III



To a dry flask under an inert atmosphere was added 2'-O-(benzyloxycarbonyl)paclitaxel (4 g, 4 mmol) and dry toluene (80 mL). The resulting slurry was stirred at ambient temperature while dry tetrahydrofuran (16 mL) was added dropwise until a colorless solution resulted. The above solution was cooled to -78°C in a dry ice/acetone bath then treated with diethylaminosulfur trifluoride (DAST, 1.2 mL, 2.5 eq.). The reaction mixture was allowed to stir for 16h as it gradually warmed to ambient temperature. The resulting suspension was filtered and the filtrate (diluted with ethyl acetate (30 mL)) was washed with saturated aqueous sodium bicarbonate followed by brine. The organic fraction was dried ($MgSO_4$) and concentrated to give a crude product as a white foam. The crude material was partially purified by silica gel column chromatography (eluted with 10% CH_3CN in CH_2Cl_2) to afford 1.45 g of a mixture of 2'-O-(benzyloxycarbonyl)-7-deoxy-7α-fluoropaclitaxeland 2'-O-(benzyloxycarbonyl)-8-desmethyl-7,8-cyclopropapaclitaxel (82:18 mixture by ^{1}H-NMR).

The above mixture (1.45 g) was taken up in ethyl acetate (60 mL) and treated with palladium on carbon (300 mg). After shaking for 4 h under 50 pounds per square inch (psi) of hydrogen, the reaction was vented and filtered through a short plug of silica gel and concentrated. This furnished the desired product mixture, 7-deoxy-7α-fluoropaclitaxel and 8-desmethyl-7,8-cyclopropapaclitaxel, as a white foam (1.24 g, Y: 99%, 90:10 mixture by ^{1}H-NMR). This mixture was taken up in dry methylene chloride (30 mL) and treated with tetrabutylammonium borohydride (745 mg, 2.9 mmol, 2 eq) and allowed to stir for 6 h. The reaction was then quenched with acetic acid (1 mL), diluted with additional methylene chloride (30 mL) and washed with saturated aqueous sodium bicarbonate solution. The organic fraction was dried ($MgSO_4$) and concentrated. The crude, substituted taxane core mixture was partially purified by silica gel column chromatography (eluted with 10% CH_3CN in CH_2Cl_2) to give a 90:10 mixture (as determined by ^{1}H-NMR) of 7-deoxy-7-α-fluorobaccatin III and 8-desmethyl-7,8-cyclopropabaccatin III (510 mg, 60%) as a white foam. The resulting foam was crystallized from hot isopropanol to give 7-deoxy-7α-fluorobaccatin III (as small white needles (Y: 410 mg); m.p. 234-236°C (decomposition).

Preparation 4. 10-Desacetoxy-7-deoxy-7α-fluoropaclitaxel



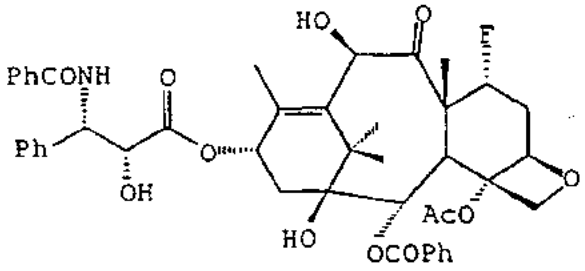
(a) 2'-O-Benzyloxycarbonyl-10-desacetoxypaclitaxel

10-Desacetoxypaclitaxel (27 mg, 0.034 mmol) in dichloromethane (1 mL) was treated with benzyl chloroformate (0.0146 mL, 0.102 mmol), followed by diisopropylethylamine (0.0177 mL, 0.102 mmol). The reaction mixture was stirred at 0 °C for 45 min, and at rt for 12 h. Evaporation of the solvent and silica gel chromatography (being eluted with 40% ethyl acetate in hexane) gave 25.5 mg (Y: 81%) of the title compound as a foam.

(b) 10-Desacetoxy-7-deoxy-7α-fluoropaclitaxel

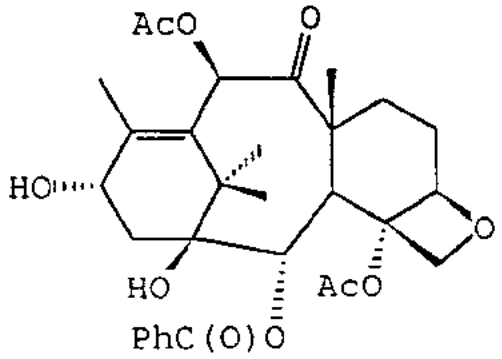
The product obtained in Step (a) (25.5 mg, 0.028 mmol) in dichloromethane (0.8 mL) at 0 °C was treated with DAST (0.0071 mL, 0.055 mmol). After 45 min at 0 °C, the reaction was allowed to proceed for 5 h at rt. Evaporation of the solvent and chromatography gave 2'-O-benzyloxycarbonyl-7-deoxy-7α-fluoropaclitaxel as a crude foam. This compound was dissolved in ethyl acetate (1 mL) and was stirred under slightly over one atmosphere of hydrogen in the presence of palladium on charcoal (10%, 8.9 mg) for 12 h at rt. The catalyst was removed by filtration and silica gel chromatography of the product gave 10 mg (Y: 40% over two steps) of the title product as a foam.

Preparation 5. 10-Deacetyl-7-deoxy-7α-fluoropaclitaxel



A solution of 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetylpaclitaxel (120 mg, 0.103 mmol) in dichloromethane (2 mL) was cooled at 0 °C and treated with DAST (0.0266 mL, 0.207 mmol). The solution was stirred at 0 °C for 30 min and at rt for 4 h. The reaction was quenched by adding water (0.05 mL). The reaction mixture was concentrated and the residue was purified by silica gel chromatography (being eluted with 30% ethyl acetate in hexane) to afford 81 mg (Y: 68%) of 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-7-deoxy-7α-fluoropaclitaxel as a foam. This compound (63 mg, 0.054 mmol) was dissolved in methanol (0.5 mL) and acetic acid (0.5 mL) and treated with zinc dust (104 mg, 1.62 mmol) for 90 min at 45 °C. The reaction mixture was filtered and the filtrate was concentrated. Silica gel chromatography (being eluted with 40% hexane in 60% ethyl acetate) of the residue afforded 38 mg (Y: 86%) of the title compound as a white solid.

Preparation 6. 7-Deoxybaccatin III



(a) 7-O-[(Methylthio)thiocarbonyl]baccatin III

Baccatin III (750 mg, 1.278 mmol) was dissolved in dry tetrahydrofuran (20 mL) and imidazole (8.7 mg, 0.128 mmol) was added in one lot. Sodium hydride (50% in mineral oil, 77 mg, 1.597 mmol) was added at room temperature. When gas evolution had ceased (10 min), carbon disulfide (4.6 mL) was added at once. After 3 h at room temperature, the yellow solution was treated with methyl iodide (0.238 mL, 3.835 mmol) and stirred overnight. Work-up with ethyl acetate and water gave the title compound as a crude oil.

Alternate Run:

Baccatin III (394 mg, 0.672 mmol) was dissolved in tetrahydrofuran (5 mL) and carbon disulfide (1 mL). To this solution was added sodium hydride (40.3 mg, 60%, 1.009 mmol). A catalytic amount of imidazole was also added. The reaction mixture was stirred at room temperature for 1.5 h. and then methyl iodide (122.8 µL, 2.016 mmol) was added. After 40 min, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (eluted with 20%-50%-60% ethyl acetate in hexanes) to afford the title product (260 mg, Y: 57.2%) together with 7-epi baccatin (98.5 mg, 25%).

(b) 7-O-[(Methylthio)thiocarbonyl]-13-O-triethylsilylbaccatin III

The product of step (a) as a crude oil was dissolved in dry dimethylformamide (5 mL) and treated with imidazole (870 mg, 12.78 mmol) and triethylsilyl chloride (2.10 mL, 12.78 mmol) at room temperature for 15 h. Addition of water was followed by extraction into ethyl acetate. The organic layer was washed extensively with water, and then dried. Silica gel flash chromatography (being eluted with 20% ethyl acetate in hexanes) gave the title compound as a glassy solid (Y: 209 mg, 20% yield over two steps).

Alternate Run:

The product of step (a) (193.4 mg, 0.286 mmol) was dissolved in dry dimethylformamide (2.86 mL). To this solution was added imidazole (77.9 mg, 1.14 mmol), followed by triethylsilyl chloride (192 µL, 1.14 mmol). The reaction mixture was stirred overnight at room temperature. After 12 h, the reaction mixture was diluted with ethyl acetate (150 mL). The organic layer was washed with water (3 X 10 mL) and brine (1 X 10 mL), dried, and concentrated in vacuo. The residue was chromatographed on silica gel (eluted with 20% Ethyl acetate in hexanes) to afford the title product (163 mg,Y: 72.0%).

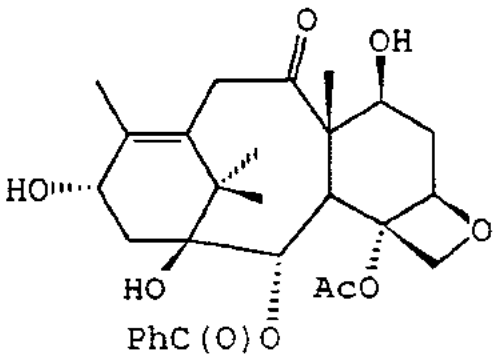
(c) 7-Deoxy-13-O-triethylsilylbaccatin III

The product of step (b) (182 mg, 0.230 mmol) in dry benzene (5 mL) was heated to 80°C in the presence of tributyltin hydride (0.310 mL, 1.150 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 10 mg). After 3h the solution was allowed to cool, and the solvent evaporated in vacuo. Silica gel chromatography of the residue (being eluted with 20% ethyl acetate in hexane) gave the title compound as an oil.

(d) 7-Deoxybaccatin III

The product of step (c) was dissolved in tetrahydrofuran (5 mL) and treated with tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.50 mL, 0.50 mmol) for 2h at room temperature. Dilution with ethyl acetate and washing with water and brine, followed by silica gel chromatography (being eluted with 1:1 ethyl acetate/hexane) gave the title compound as a white glassy solid (63 mg, Y: 58% over two steps).

Preparation 7. 10-Desacetoxybaccatin III



(a) 10-Deacetyl-10-O-(pentafluorophenoxy)thiocarbonyl-7-O-triethylsilylbaccatin III

7-O-Triethylsilyl-10-deacetylbaccatin III (see Greene et al, J. Am. Chem. Soc., 110, p. 5917, 1988) (319 mg, 0.485 mmol) was dissolved in dry tetrahydrofuran (5 mL), cooled to -40°C, and treated with n-butyllithium (1.58M in hexanes, 0.384 mL, 0.606 mmol). After 40 min at this temperature, pentafluorophenyl chlorothionoformate (0.086 mL, 0.536 mmol) was added neat by syringe. The reaction mixture was stirred at -20°C for 90 min, quenched with saturated ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated. The residue was purified by silica gel chromatography (being eluted with 40% ethyl acetate in hexane) to afford the title compound as a foam (320 mg, Y: 74%).

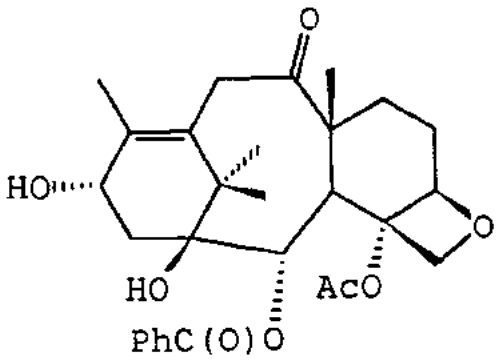
(b) 10-Desacetoxy-7-O-triethylsilylbacctain III

The product of step (a) (119 mg, 0.135 mmol) was dissolved in dry toluene (3 mL) and treated with AIBN (2 mg). The solution was degassed with dry nitrogen, then tributyltin hydride (0.055 mL, 0.202 mmol) was added. Subsequently, the solution was heated at 90°C for 1 h. The solvent was then evaporated and silica gel chromatography of the residue (being eluted with 40% ethyl acetate in hexane) gave the title compound (87 mg, Y: 99%) as a colorless foam.

(c) 10-Desacetoxybaccatin III

The product of step (b) (120 mg, 0.187 mmol) was dissolved in acetonitrile (3.5 mL) and the solution was cooled to -10°C. Concentrated HCl (36%, 0.060 mL) was added, and the solution was stirred for 30 min. The mixture was diluted with ethyl acetate (75 mL), and washed with saturated aqueous sodium bicarbonate and brine, then dried and concentrated. The residue was purified by flash silica chromatography (being eluted with 70% ethyl acetate in hexane) to afford 10-deacetyloxybaccatin III as a foam (75 mg, Y: 76%).

Preparation 8. 10-Desacetoxy-7-deoxybaccatin III



(a) 7-O-[(Methylthio)thiocarbonyl]-10-desacetoxybaccatin III

10-Desacetoxybaccatin III (75 mg, 0.142 mmol) was dissolved in dry tetrahydrofuran (2 mL) and carbon disulfide (0.5 mL). Sodium hydride (60% in mineral oil, 8.5 mg, 0.213 mmol) was then added, and the mixture was stirred at room temperature for 2 h. Iodomethane (0.026 mL, 0.426 mmol) was added, and the reaction was allowed to proceed overnight. The solvent was then removed and the residue was purified by silica gel chromatography (being eluted with 50-70% ethyl acetate in hexane) to give the title compound as a foam (46.4 mg, Y: 53%).

(b) 10-desacetoxy-7-deoxy-baccatin III

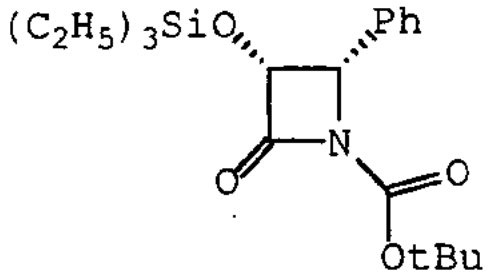
The product of step (a) (36 mg, 0.058 mmol) was refluxed in benzene (1 mL) in the presence of AIBN (2 mg) and tributyltin hydride (0.079 mL, 0.290 mmol) under an argon atmosphere for 3h. Concentration of the reaction mixture and flash silica gel chromatography of the residue (being eluted with 40% ethyl acetate in hexanes) followed by HPLC (high pressure liquid chromatography) separation from other components afforded the title compound as a foam (16.8 mg, Y: 56%).

Alternate Run:

To a solution of 7-O-[(methylthio)carbonothioyl]-13-O-triethylsilylbaccatin III (product of preparation I, step (b), 416.3 mg, 0.527 mmol) in dry toluene (10.5 mL) was added catalytic amount of AIBN, and the resulting solution was degassed with dry N_2 for 5 min. Tributyltin hydride (708.7 uL, 2.63 mmol) was the added and the reaction mixture was heated at 100°C for 2 h., after which another portion of tributyltin hydride (425.3 uL, 1.581 mmol) was added. The reaction mixture was heated for 5.5 h at 100°C, and then allowed to cool to room temperature. Silica gel chromatography (eluted with 20% ethyl acetate in hexanes) afforded 7-deoxy-10-desacetoxy-13-O-(triethysilyl)baccatin III (320 mg, Y: 97%).

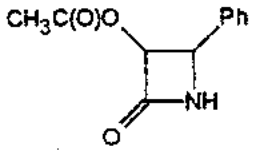
To a solution of the product of the above step (160 mg, 0.255 mmol) in dry tetrahydrofuran (2 mL) at room temperature was added tetrabutylammonium fluoride (766 uL, 1 M, 0.766 mmol). The reaction mixture was stirred for 1 h at room temperature. The solvent was removed and the residue was chromatographed on silica gel (eluted with 50-70% ethyl acetate in hexanes) to afford the desired title product (115 mg, Y: 87.9%).

Preparation 9. (3R, 4S)-1-t-Butoxycarbonyl-4-phenyl-3-triethylsilyloxy-2-azetidinone



To a stirred solution of (3R,4S)-4-phenyl-3-triethylsilyloxy-2-azetidinone (2.200 g, 7.92 mmol) in dry tetrahydrofuran (25 mL) was added N,N-diisopropylethylamine (1.65 mL, 9.510 mmol, 1.2 equiv) at 0 °C under an argon atmosphere. The solution was stirred for 5 min followed by the addition of di-t-butyl carbonate (2.080 g, 9.510 mmol, 1.2 equiv) and 4-dimethylaminopyridine (193.6 mg, 1.581 mmol, 0.20 equiv). The reaction mixture was stirred at 0 °C for 60 min., then diluted with ethyl acetate (25 mL). The resulting solution was washed with brine, 10% $NaHCO_3$, 10% HCl solution, dried ($MgSO_4$), and concentrated to give a crude compound (oil). The compound was further purified by silica gel flash chromatography (being eluted with 15% ethyl acetate in hexanes) to afford the title compound as a white solid (2.4 g, Y: 83%).

Preparation 10. (±)-cis-3-Acetyloxy-4-phenylazetidin-2-one

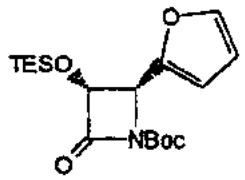


(a) To a 1 L, 3-necked round bottom flask equipped with a thermometer, magnetic stirrer and dropping funnel was added hydrobenzamide (30.00 g, 100.5 mmol) and ethyl acetate (150 mL). With stirring and under a blanket of argon, the reaction mixture was cooled to 5 °C and triethylamine (16.8 mL, 121 mmol) was added. A solution of acetoxyacetyl chloride (12.4 mL, 116 mmol) in ethyl acetate (300 mL) was then added dropwise over a 90 min period. After 16 h at this temperature, the reaction mixture was allowed to warm to 20 °C (1.5 h) and transferred to a separatory funnel. The organic layer was washed successively with aqueous NH_4Cl (sat) (150 mL, 100 mL), aqueous $NaHCO_3$ (saturated) (120 mL) and brine (120 mL). For purposes of characterization, the title compound can be isolated at this stage by drying the organic phase over $MgSO_4$, filtering, and removing the solvent in vacuo. This provided (±)-cis-3-acetyloxy-1-[-(phenyl)(benzylidenimino)methyl]-4-phenylazetidin-2-one in quantitative crude yield as a red glass.

(b) A solution of the compound obtained in part (a) in ethyl acetate (500 mL) was carefully transferred, under a stream of argon, to a 2.0 L Parr flask containing 10% palladium on activated charcoal (6.00 g). This mixture was treated with hydrogen (4 atm) for 20 h whereupon the catalyst was removed by filtration through a pad of Celite. The filter cake was slurried in ethyl acetate (200 mL), stirred (10 min) and filtered. The filter cake was rinsed with ethyl acetate (100 mL) and the filtrates combined. The organic layer was washed with 10% HCl (300 mL) and both layers filtered through a sintered glass funnel to remove the white precipitate (dibenzylamine•HCl) which was rinsed with ethyl acetate (100 mL). The phases were separated and the organic layer was washed with another portion of 10% HCl (200 mL). The combined 10% HCl washes were re-extracted with ethyl acetate (200 mL) and the combined organic layers were washed with aqueous $NaHCO_3$ (saturated) (300 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a final volume of 75 mL. This mixture was cooled to 4 °C and the precipitated product isolated by filtration. The filter cake was washed with hexane (200 mL) to provide 16.12 g (78.1% overall yield from hydrobenzamide) of the title compound as white

needles.
mp = 150-151 °C

Preparation 11. (±)- cis-3-Triethylsilyloxy-4-(2-furyl)-N-t-butoxycarbonylazetidin-2-one



(a) The procedure described in Preparation 10, part (a), was followed except that hydrofuramide [i.e. 2-furyl-CH-(N=CH-2-furyl)$_2$] was used instead of hydrobenzamide and the reaction was performed on 18.6 mmol (vs 100 mmol) scale. Thus, hydrofuramide (5.00 g, 18.6 mmol), triethylamine (3.11 mL, 22.3 mmol) and acetoxyacetyl chloride (2.30 mL, 21.4 mmol) gave 6.192 g (Y: 90.4%) of (±)-cis-3-acetyloxy-1-[(2-furyl)(2-furylmethylenimino)methyl]-4-(2-furyl)azetidin-2-one as a pale red syrup.

(b) The procedure described in Preparation 10, part (b), was followed except that the product was isolated by preparative TLC and the reaction was performed on the 2.7 mmol scale based on the original amount of hydrofuramide. Thus, the crude product obtained in part (a) above was re-dissolved in ethyl acetate (50 mL) and added to 10% palladium on activated charcoal (150 mg). Purification of the crude solid by preparative TLC (2 mm silica gel, eluted with 1:1 ethyl acetate/hexane) gave 386 mg (65.8% corrected overall yield from hydrofuramide) (±)-cis-3-(acetyloxy)-4-(2-furyl)azetidin-2-one as a yellow solid. This was recrystallized from ethyl acetate/hexane.
mp = 118-119 °C

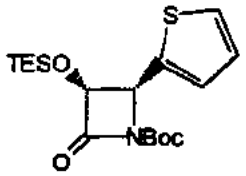
(c) The compound obtained in part (b) above (3.78 g, 19.4 mmol) in 60 mL of methanol was stirred with K_2CO_3 (20 mg, 0.14 mmol) for 90 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 80 mL of anhydrous THF and stirred at 0 °C with imidazole (1.44 g, 21.2 mmol) and TESCl (3.4 mL, 20.2 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 4.47g (Y: 86%) of (±)- cis-3-triethylsilyloxy-4-(2-furyl)-azetidin-2-one as a colorless oil.

(d) The product of part (c) (2.05 g, 7.7 mmol) in 30 mL of dichloromethane was stirred at 0 °C with diisopropylethyl amine (1.5 mL, 8.6 mmol) and di-t-butylcarbonate (2.0g, 9.2 mmol) in addition to a catalytic amount of dimethylaminopyridine (DMAP). The solution was diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 8:1 hexane/ethyl acetate) to give 2.0 (Y: 70%) of the title compound as a waxy solid.

The racemic mixture obtained in part (b) may be used as substrate for enzymatic hydrolysis using a lipase such as PS-30 from Pseudomonas sp. (Amano International Co.) to give (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one. The method of enzymatic resolution using the lipase PD-30 and other enzymes is disclosed in our co-pending application U.S.S.N. 092,170, filed July 14, 1993 which is hereby incorporated by reference in its entirety.

The procedure in parts (c) and (d) was followed using (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one to provide (3R,4R)-N-(t-butoxycarbonyl)-3-triethylsilyoxy-4-(2-furyl)azetidine-2-one.

Preparation 12. (±)- cis-3-Triethylsilyloxy-4-(2-thienyl)-N-t-butoxycarbonylazetidin-2-one



(a) The procedure described in Preparation 10, step (a) was followed except that hydrothienamide [i.e. 2-thienyl-CH-(N = CH-2-thienyl)$_2$] was used instead of hydrobenzamide. Thus, hydrothienamide (30 g, 94.7 mmol), thiethylamine (15.84 mL, 114 mmol) and acetoxyacetyl chloride (11.6 mL, 108 mmol) provided (±)-cis-3-acetyloxy-1-[(2-thienyl)(2-trienylmethylenimino)methyl]-4-(2-thienyl)azetidin-2-one as viscous oil.

(b) A 70% aqueous solution of acetic acid (0.35 mL glacial acetic acid and 0.15 mL water) was added in one portion to a stirred solution of the product obtained in part (a) (.431 g, 1.03 mmol) in dichloromethane (2.93 ml) at 25 °C. The reaction mixture was brought to reflux and stirred for 2.5 h. The reaction was diluted with 50 mL dichloromethane and then washed with two 75 mL portions of saturated aqueous sodium bicarbonate and then one 50 mL portion of saturated brine. The organic extract was concentrated *in vacuo* to a brown oil, dissolved in a minimal amount of dichloromethane, and then placed on a silica gel column measuring 4" by 0.5". Elution using a gradient of 10 through 60% EtOAc in hexane provided less polar sideproducts and then (±)-cis-3-acetyloxy-4-(2-thienyl)azetidin-2-one (0.154 g, Y: 75%) as a white solid.

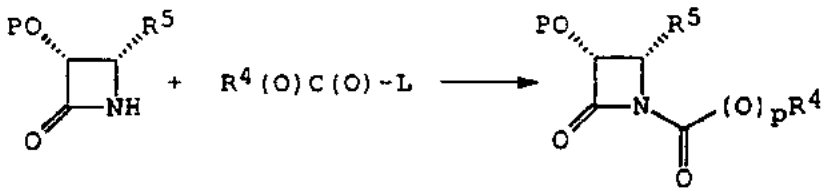
(c) A solution of the product obtained in part (b) (2.5 g, 11.8 mmol) was dissolved in methanol (10 mL) and treated with saturated aqueous sodium bicarbonate (10 mL) and the resulting slurry was allowed to stir at ambient temperature for 3 h. The reaction was then diluted with ethyl acetate (20 mL) and washed with water (15 mL). The aqueous fraction was back extracted several times with ethyl acetate and the combined organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid (Y: 1.7 g). The crude material was dissolved in dry tetrahydrofuran (20 mL) and the solution was cooled to 5 °C in an ice/water bath. Imidazole (752 mg, 1.1 eq) was then added. After stirring 5 min, triethylchlorosilane (1.85 mL, 1.1 eq) was added dropwise. The resulting suspension was allowed to stir for 3 h at that temperature; then the solids were removed by filtration. The organic fraction was washed with water (2x 20 mL) then dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (eluted with hexanes/ethyl acetate 7:3) to give (±)-cis-3-triethylsilyloxy-4-(2-thienyl)-azetidin-2-one as a colorless solid (1.5 g, Y: 45%). m.p. 70-71 °C.

Alternate Run:

The product obtained in part (b) (2.0 g, 9.37 mmol) in 40 mL of methanol was stirred with K_2CO_3 (60 mg, 0.43 mmol) for 30 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 50 mL of anhydrous THF and stirred at 0 °C with imidazole (0.85 g, 11.3 mmol) and TESCl (1.9 mL, 12.5 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 2.13g (Y: 86%) of the title product as a colorless oil.

(d) A solution of the product obtained in part (c) (425.7 mg, 1.48 mmol) was dissolved in dichloromethane (10 mL) and cooled to 5 °C in an ice/water bath. The reaction was treated with a catalytic amount of DMAP followed by diisopropylethylamine (TESCl, 0.25 mL, 1.0 eq) then by di-t-butylcarbonate (388.4 mg, 1.2 eq). After stirring 2 h at that temperature the reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and the organic fraction was washed with water (5 mL) then dried ($MgSO_4$), passed through a short plug of silica gel and concentrated to give the desired product as a colorless oil (525.3 mg, Y: 93%).

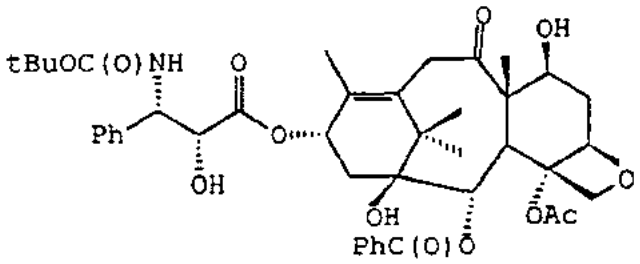
The procedure described above in Preparations 9, 11(d) and 12(d) may be adapted to the preparation of other N-substituted azetidinones useful in the preparation of compounds of the invention. Examples of such azetidinones are listed in the following table; P below is a hydroxy protecting group such as triethyl silyl, triisopropylsilyl and ethoxyethyl.



L	$R^4(O)_p$	R^5
Cl	Ph	4-CH_3O-Ph- 3,4-diCH_3O-Ph- Ph- 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- 2-furanyl-CH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$- 4-Cl-Ph 2-F-Ph 3-F-Ph 4-CH_3-Ph
Cl	4-CH_3O-Ph-	3,4-diCH_3O-Ph- 4-CF_3-Ph- 2-furanyl- PhCH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $PhCH_2CH_2$-

L	$R^4(O)_p$	R^5
$(CH_3)_3CO$-	$(CH_3)_3CO$-	4-CH_3O-Ph- 4-F-Ph- 4-CF_3-Ph- PhCH=CH- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-
Cl	CH_3-	4-CH_3O-Ph- Ph- 4-F-Ph- 2-furanyl- 2-furanyl-CH=CH- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-

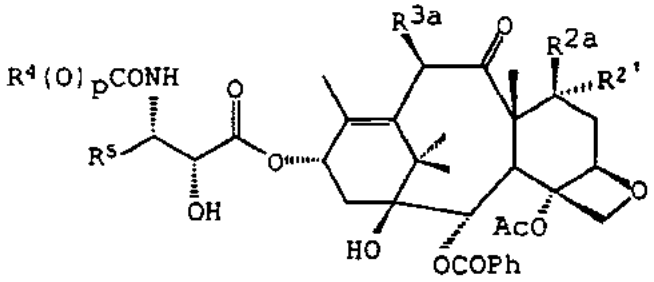
Preparation 13. 10-deoxytaxotere



10-Desacetoxy-7-O-triethylsilylbaccatin III (100 mg, 0.156 mmol) was placed in a flask under argon and dissolved in dry tetrahydrofuran (1.5 mL). Upon cooling to -40°C, n-butyllithium (1.45M in hexanes, 0.119 mL, 0.170 mmol) was added dropwise, followed by (3R,4S)-1-tert-butoxycarbonyl-4-phenyl-3-triethylsilyloxy-2-azetidinone (94.2 mg, 0.25 mmol) in tetrahydrofuran (0.5 mL) over a period of 2 min. The mixture was immediately warmed to 0°C and stirred for 45 min before being quenched with saturated ammonium chloride (3 mL). The mixture was extracted with ethyl acetate, dried, and concentrated. Silica gel chromatography (eluted with 30% ethyl acetate in hexane) afforded 10-deoxy-2',7-bis-O-(triethylsilyl)-taxotere as a foam (125 mg, Y: 76%). This compound (100 mg, 0.098 mmol) was immediately dissolved in acetonitrile (2 mL) at -5°C and treated with hydrochloric acid (0.037 mL, 36%, 12M). The mixture was stirred for 2h at -5°C, then quenched with aqueous bicarbonate, extracted with ethyl acetate, and dried. Evaporation of the solvent was followed by silica gel chromatography (eluted with 75% ethyl acetate in hexane) to afford the title compound as a foam (80.5 mg, Y: 80%).

The general procedure provided in Preparation 13 may be adapted to the preparation of other compounds of formula (Ia) by starting with the appropriate baccatin III component and the azetidinone component; examples of other compounds of formula (Ia) are listed in the following table. It will be understood that even though the compounds below are shown with free hydroxy groups, with the judicious

selection of the various hydroxy protecting groups, any one of the protecting groups at the 2'-, 7- or 10-position may be selectively removed without affecting other protecting groups present.



$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_p$	R^5
H	OH	AcO	Ph	4-CH_3O-Ph-
				3,4-diCH_3O-Ph-
				Ph-
				4-F-Ph-
				4-CF_3-Ph-
				2-furanyl-
				2-thienyl-
				PhCH=CH-
				2-furanyl-CH=CH-
				$(CH_3)_2CHCH_2$-
				C_6H_{11}-CH_2-
				$(CH_3)_2CH$-
				$PhCH_2CH_2$-
				C_6H_{11}-CH_2CH_2-
				$CH_3CH_2CH_2$-
				4-Cl-Ph
				2-F-Ph
				3-F-Ph
				4-CH_3-Ph

$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_e$	R^6
H	OH	OH	$(CH_3)_3CO$	4-CH_3O-Ph- Ph 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$-
	OH	H	Ph	4-CH_3O-Ph- 3,4-diCH_3O-Ph- 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- 2-furanyl-CH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-

$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_p$	R^5
	H	H	$(CH_3)_3CO$	4-CH_3O-Ph- 3,4-diCH_3O-Ph- Ph- 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- 2-furanyl-CH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-
H	OH	AcO	2-naphthyl 4-OH-Ph 4-CH_3O-Ph 4-F-Ph $(CH_3)_3CO$- CH_3- $(CH_3)_2CH$- $CH_2=CHCH_2$- 4-Cl-Ph	Ph
F	H	AcO	$(CH_3)_3CO$-	Ph
F	H	OH	Ph	Ph

$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_b$	R^5
H	H	AcO	Ph	4-CH_3O-Ph-
				3,4-diCH_3O-Ph-
				Ph-
				4-F-Ph-
				4-CF_3-Ph-
				2-furanyl-
				2-thienyl-
				PhCH=CH-
				2-furanyl-CH=CH-
				$(CH_3)_2CHCH_2$-
				C_6H_{11}-CH_2-
				$(CH_3)_2$CH-
				$PhCH_2CH_2$-
				C_6H_{11}-CH_2CH_2
				$CH_3CH_2CH_2$-

Preparation 14. Bis(methylthiomethyl)ether

$CH_3SCH_2OCH_2SCH_3$

Sodium iodide (8.23g, 55.23 mmol) was added to a solution of 1,1'-dichlorodimethyl ether (3.0g, 26.3 mmol) in acetone (100 ml) at 0°C and the mixture was stirred at this temperature for 20 min. Sodium thiomethoxide (1.84g, 5.23 mmol) was then added in four portions and the resulting solution was stirred for an additional 1h. The heterogeneous solution was then filtered through a pad of celite and the filtrate concentrated in vacuo. The residual oil was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was removed and further extracted with ethyl acetate. The combined organics were then treated with a 1:1 (v:v) mixture of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution. The organics were then washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (30:1, hexanes:ethyl acetate) to provide 1.9 g of a yellow oil which was subsequently distilled using a kugelrhor apparatus (120-130°C, 20mmHg) yielding 1.5 g (45%) of the title compound as colorless oil:
^{1}H NMR (300 MHz, CDCl3) δ 4.73 (4H, s), 2.15 (6H, s).

Preparation 15. Dibenzyl methylthiomethyl phosphate

$CH_3SCH_2OP(O)(OBu)_2$

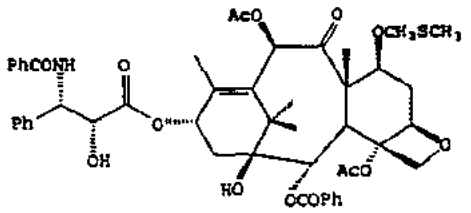
To a solution of bis(methylthiomethyl)ether (30 mg, 2.34 mmol) and molecular sieves (300 mg) in THF (100 ml) at room temperature was added dibenzyl phosphate (2.74 g, 9.85 mmol) followed by N-iodosuccinimide (608 mg, 2.71 mmol) and the solution was stirred for 4h. The reaction mixture was then diluted with ethyl acetate and filtered through a pad of celite. The filtrate was treated with a 1:1 (v:v) solution of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate. The colorless organic extract was then washed with brine, dried over sodium sulfate and concentrated in vacuo to provide 600 mg (69%) of the title compound:
^{1}H NMR (300 MHz, CDCl3) δ 7.35 (10H, s), 5.29 (2H, d, J=12.2 Hz), 5.08 (4H, dd, J=8.0, 1.0 Hz), 4.68 (2H, s), 2.10 (3H, s).

EXAMPLES

The following examples are provided to illustrate the synthesis of representative compounds of the instant invention and are not to be construed as limiting the scope of the invention in any manner. One skilled in the art will be able to adapt these methods, without undue experimentation, to the synthesis of compounds within the scope of this invention but not specifically disclosed.

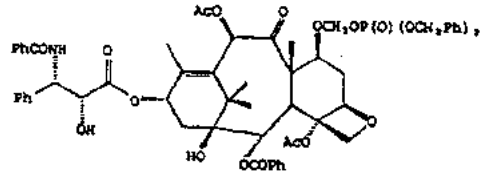
Example 1. 7-O-phosphonooxymethylpaclitaxel and its monosodium salt

(a) preparation of 7-O-methylthiomethylpaclitaxel.



Benzoyl peroxide (0.98 g, 4 mmol) was added to a vigorously stirred mixture of paclitaxel (0.85 g, 1 mmol) and dimethyl sulfide (0.72 mL, 8 mmol) in dry acetonitrile (10 ml) at 0°C. Stirring was continued for 2.5 hours at 0°C. Progress of the reaction was monitored by silica gel TLC in toluene : acetone (2 : 1, v/v) solvent system ($R_{f\ tax.}$ = 0.38, $R_{f\ prod.}$ = 0.64), and when formation of higher polarity products was observed the reaction was quenched by evaporation of solvents using Rotavapor at 30°C. A TLC analysis of the reaction mixture indicated the presence of some quantities of unreacted paclitaxel and 2',7-O-bis-(methylthiomethyl)paclitaxel. Separation of the title compound from the reaction mixture was achieved by flash column chromatography on Silica Gel 60 (40 - 63 µm) EM Science (100 mL), column diameter: 2 in. using ethyl acetate : hexane (1:1, v/v) solvent system ($R_{f\ prod.}$ = 0.34). The product (552 mg, 60% yield) was recovered from fractions 12 to 18 (each fraction ca. 20 ml).
MS (FAB/matrix NOBA, NaI, KI): $[M+H]^+$, m/z 914; $[M+Na]^+$, m/z 936; $[M+K]^+$, m/z 952
Elemental Analysis: C: 64.28 (calc. 64.39), H: 5.85 (calc. 6.07), N: 1.46 (calc. 1.53)
UV (MeOH): λmax = 226 nm , E(1%/1 cm) = 150, A = 0.2653
IR (KBr): 3432, 3066, 2940, 1726, 1668, 1602, 1582, 1514, 1484, 1452, 1372, 1242, 1178, 1142, 1108, 1068, 1026, 990, 916, 884, 852, 802, 774, 710, 608, 570, 538, 482 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.19 (3H, s), 1.73 (3H, s), 1.79 (H, s), 1.90 (3H, d), 2.09 (3H, s), 2.16 (3H, s), 2.29 (2H, d), 2.35 (3H, s), 2.77 (H, m), 3.70 (H, d), 3.83 (H, d), 4.17 (H, d), 4.26 (H, m, overlaps with H, d), 4.63 (2H, t), 4.77 (H, dd), 4.91 (H, d), 5.65 (H, d), 5.77 (H, dd), 6.16 (H, dd), 6.48 (H, s), 7.07 (H, d), 7.29 - 7.50 (10H, m), 7.57 (H, m), 7.73 (2H, d), 8.08 (2H, d).

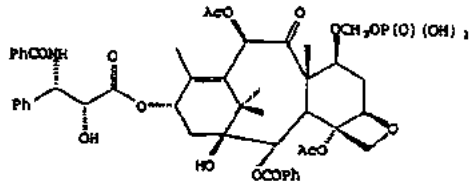
(b) preparation of 7-O-dibenzylphosphonooxymethylpaclitaxel.



A solution of N-iodosuccinimide (45 mg, 0.2 mM) and dibenzyl phosphate (55 mg, 0.2 mM) in dry tetrahydrofuran (4 mL) was added to a mixture of 7-O-methylthiomethylpaclitaxel (119 mg, 0.13 mM) and powdered molecular sieves 4Å (ca. 120 mg)in dry 1,2-dichloroethane (5 ml). The reaction mixture was stirred at room temperature for 16 hrs. Progress of the reaction was monitored by TLC in toluene : acetone (2 : 1, v/v) system ($R_{f\ prod.}$ = 0.48). Molecular sieves were removed by filtration through Celite 545 and the filtrate was extracted with methylene chloride (100 ml). The organic layer was washed with 1% solution of

sodium thiosulfate (ca. 100 ml) and 0.5 M sodium bicarbonate (100 ml) and with brine. Extract was filtered through Whatman Phase Separator and solvents were evaporated. Purification on Silica Gel 60 flash column in methylene chloride : ethyl acetate (2 : 1, v/v) yielded 7-O-dibenzylphosphonooxymethylpaclitaxel (41.5 mg).

(c) preparation of 7-O-phosphonooxymethylpaclitaxel and its monosodium salt.



7-O-Dibenzylphosphonooxymethylpaclitaxel (41.5 mg) was dissolved in ethyl acetate (5 ml) and 10% palladium on charcoal (20 mg) was added. Hydrogenation was performed at 40 PSI (275 kPa) at room temperature for 1 hour. Progress of the reaction was monitored by TLC in chloroform:methanol:water (120:45:8, v/v). Purification by preparative TLC (20x20x0.05 cm silica gel plate in the analytical system) gave 7-O-phosphonooxymethylpaclitaxel (26 mg, 75% yield).

Because decomposition of 7-O-dibenzylphosphooxymethylpaclitaxel was observed during silica gel purification, the hydrogenation procedure has been modified. Thus, a crude extract of 7-O-dibenzylphosphonooxymethylpaclitaxel was hydrogenated without any purification. Hydrogenation of the crude extract of 7-O-dibenzylphosphonooxymethylpaclitaxel was performed at 60 PSI (400 kPa) for 24 hrs.

7-O-Phosphonooxymethylpaclitaxel (70 mg) was dissolved in 5 mL of acetone - water (1 : 1) solution and diluted with water to 50 ml. Dry sodium bicarbonate (18 mg, 1.2 eq.) was added. Acetone was evaporated at room temperature using Rotavapor and the remaining water solution was lyophilized. Crude 7-O-phosphonooxymethylpaclitaxel monosodium salt was purified by C18 reverse phase column chromatography in water: acetonitrile (70 : 30, v/v) system. Eluate was monitored by analytical HPLC (15 cm, Jones C18 column, 1 mL/min., λ = 230/270 nm) in acetonitrile : 0.05 M ammonium acetate buffer (45 : 55, v/v), pH = 7, Rt = 2.09 min. Fractions containing the desired product were combined, acetonitrile evaporated and the remaining aqueous solution lyophilized to provide 7-O-phosphonooxymethylpaclitaxel monosodium salt (112 mg).

MS (FAB): $[M+H]^+$, m/z 986; $[M+Na]^+$, m/z 1008

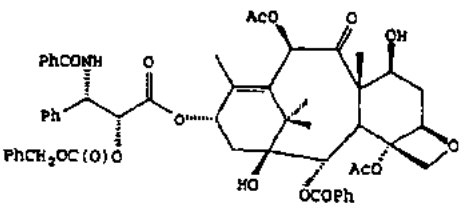
UV (MeOH): λmax = 230 nm, E(1%/1cm) = 248

IR (KBr): 3430, 3066, 2948, 1724, 1652, 1602,1580, 1518, 1486, 1452, 1372, 1316, 1246, 1178, 1154, 1108, 1070, 1000, 982, 946, 856, 802, 776, 710, 628, 538 cm^{-1}.

^{1}H-NMR (acetone-d_6/D_2O) δ: 8.05 (2H, d), 7.92 (2H, d), 7.65 (1H, dd), 7.58 - 7.35 (9H, m, overlap), 7.23 (1H, dd), 6.38 (1H, s), 6.08 (1H, t), 5.65 (1H, d), 5.60 (1H, d), 5.10 (1H, br.s), 4.99 (1H, d), 4.97 (1H, br.s), 4.80 (1H, d), 4.28 (1H, dd), 4.11 (2H, s), 3.79 (1H, d), 2.94 (1H, m), 2.35 (3H, s), 2.35 - 2.10 (1H, m), 2.13 (3H,s), 1.95 (3H, s), 1.84 (1H, m), 1.67 (3H, s), 1.13 (6H, s, overlap).

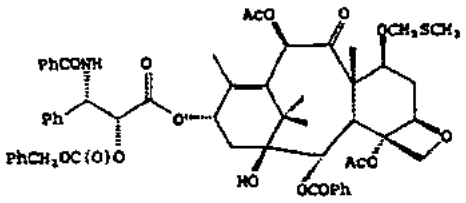
Example 2. Alternate method for the preparation of 7-O-phosphonooxymethylpaclitaxel.

(a) preparation of 2'-O-(benzyloxycarbonyl)paclitaxel



To a stirred solution of paclitaxel (150 mg, 0.176 mmol) and N,N-diisopropylethylamine (93 µL, 0.534 mmol, 3 eq.) in anhydrous methylene chloride (4 mL) at room temperature was added benzyl chloroformate (75 µL, 0.525 mmol, 3 eq.). The reaction mixture was stirred at room temperature for 3 h, concentrated to 2 mL, and purified on a silica gel column, using 1:1 of ethyl acetate/hexanes as eluant, to obtain the title compound as a white powder (150 mg, Y:86%). MP 140-150 °C (decomposition).

(b) preparation of 2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a cooled (dry ice - CCl_4; -30 °C bath temp.) solution of 2'-O-(benzyloxycarbonyl)paclitaxel (4.935 g; 5.0 mmol) in dry acetonitrile (80 ml) was added in succession dimethylsulfide (3.6 ml; 40 mmol) and benzoyl peroxide (4.9 g; 20.247 mmol). After 10 mins. at -30 °C, the cold bath was removed and the reaction mixture was stirred vigorously for 2 hr at room temperature. The reaction mixture was then diluted with ethyl acetate to a volume of 200 ml and washed with water and brine. The organic layer was dried ($MgSO_4$), and the solvent was then evaporated to give a residue which was kept under vacuum for 18 h to remove any dimethylsulfoxide that was present as a reaction side product. The residue was purified on a silica gel column using first ethyl acetate: hexane (1:2) as eluant to remove the less polar impurities, followed by ethyl acetate: hexane (1:1) to give the expected title compound as a foam. This was triturated with dry ether and filtered to give the title compound as a fluffy solid (5.0 g, 95%). MP 120-122 °C.

MS (FAB): $[MH]^+$, m/z 1048; $[M+Na]^+$, m/z 1070; $[M+K]^+$, m/z 108

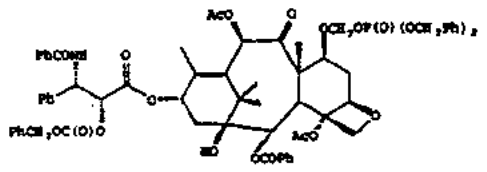
IR (KBr): 3440, 3066, 1750, 1722, 1664, 1602, 1583, 1538 cm^{-1}.

NMR ($CDCl_3$) δ: 1.177 (3H,s) 1.236 (3H, s) 1.745 (3H, s) 2.023 (3H, s) 2.121 (3H s) 2.162 (3H, s) 2.436 (3H, s) 3.887 (H, d) 4.134 (H, d) 4.197 (H, d) 4.295 (H, m) 4.964 (H, d) 5.161 (2H, d) 5.450 (H, d) 5.703 (H, d) 5.981 (H, dd) 6.257 (H, t) 6.541 (H, s) 6.920 (H, d, NH) 7.322-8.22 (15H, m).

The title compound was also prepared by the following alternative method:

To a solution of 2'-O-(benzyloxycarbonyl)paclitaxel (2.0 g; 2.0263 mmol) in dry dimethylsulfoxide (10 ml) was added dropwise acetic anhydride (10 ml). The resulting mixture was stirred at room temperature for 18 h under N_2, diluted with ethyl acetate (100 ml), and washed carefully with cold 6% sodium bicarbonate solution (6x30 ml), cold water (6x30 ml) and brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give a residue. This was purified by silica gel column and eluted with methylene chloride, methylene chloride-5% acetonitrile, and methylene chloride-10% acetonitrile to give the expected title compound (1.86 g, 87.7%). This compound is identical to that obtained via the previously described dimethyl sulfide/benzoyl peroxide method.

(c) preparation of 2'-O-(benzyloxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel



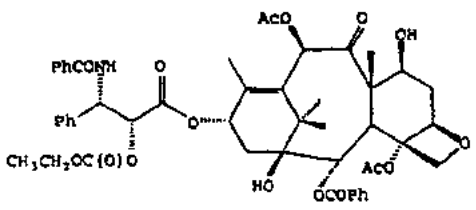
To a solution of 2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel (5.0 g; 5.5396 mmol) in dry 1,2-dichloroethane (120 ml) was added activated powdered 4Å molecular sieves (5.0 g). To this mixture was added dropwise at room temperature a solution mixture of N-iodosuccinimide (1.61 g; 7.1632 mmol) and dibenzyl phosphate (1.97 g; 7.1632 mmol) in dry tetrahydrofuran (90 ml). After stirring vigorously at room temperature for 30 min. the reaction mixture was filtered over Celite and the filtrate was evaporated to dryness to give a red residue. The residue was taken up in ethyl acetate (100 ml), washed with cold 6% $NaHSO_3$ solution (2x50 ml), cold 6% $NaHCO_3$ solution (2x50 ml) and brine (1x50 ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated to give a solid mass which was triturated with dry ether and filtered to give the title compound as an ivory colored solid (5.9 g, 97%). MP 124-127 °C.
MS (FAB): $[MH]^+$, m/z 1278; $[M+Na]^+$, m/z 1301; $[M+K]^+$, m/z 1316
IR (KBr): 3430, 3066, 3032, 1750, 1726, 1664, 1582, 1532 cm^{-1}
NMR ($CDCl_3$) δ: 1.160 (3H, s) 1.703 (3H, s) 1.985 (3H, s) 2.164 (3H, s) 2.420 (3H, s) 3.854 (H, d) 4.151 (H, d) 4.216 (H, m) 4.298 (H, d) 4.873 (H, d) 5.043 (6H, m) 5.140 (2H, d) 5.417 (H, d) 5.670 (H, d) 5.971 (H, dd) 6.241 (H, t) 6.317 (H, s) 6.912 (H, d, NH) 7.280-8.115 (25H, m).

(d) preparation of 7-O-phosphonooxymethylpaclitaxel.

To a solution of 2'-O-(benzyloxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (6.0 g; 4.7095 mmol) in ethyl acetate (120 ml) was added 10% Pd/C (6.0 g) and the mixture was hydrogenated at 60 psi (400 kPa) for 24 hr. The reaction mixture was filtered over Celite and the solvent was evaporated to give 4.07 g of a crude residue. This was purified on a short silica gel column by successive elution with chloroform:10%, 20% and 40% methanol to give the title compound as a white solid (3.2 g, 71%) MP 155-158 °C.
This product has the same Rf(TLC) and same retention time (HPLC) as an authentic sample.
MS (FAB): $[MH]^+$, m/z 964; $[M+Na]^+$, m/z 986; $[M+K]^+$, m/z 1002; $[M+K^++Na^+-H]^+$, m/z 1024; $[M+2K-H]^+$, m/z 1040
UV (MeOH): λmax = 230 nm, E(1%/1cm) = 252.5
IR (KBr): 3432, 3066, 2992, 1722, 1648, 1602, 1580, 1522, 1488, 1452, 1372, 1316, 1246, 1178, 1154., 1110, 1070, 1000, 980, 946, 854, 802, 776, 710, 628, 538 cm^{-1}.
^{1}NMR (acetone-d_6/D_2O), δ: 1.08 (3H, s), 1.10 (3H, s), 1.63 (3H, s), 1.88 (3H, s), 1.96 (H, m), 2.13 (3H, s), 2.32 (3H, s), 2.89 (H, m), 3.76 (H, d), 4.19 (H, m), 4.89 (H, dd), 5.09 (H, dd), 5.55 - 5.60 (2H, overlapping d's), 6.04 (H, t), 6.32 (H, s), 720 (H, t), 7.34 - 7.67 (10H, overlapping m's), 7.87 (2H, dd), 8.02 (2H, dd).

Example 3. 2'-O-(ethoxycarbonyl)-7-O-phosphoncoxymethylpaclitaxel

(a) preparation of 2'-O-(ethoxycarbonyl)paclitaxel



To a solution of paclitaxel (4.35 g, 5.1 mmol) in dry methylene chloride (51 ml) was added N,N-diisopropylethylamine (2.67 ml, 15.3 mmol), followed by ethyl chloroformate (1.46 ml, 15.3 mmol). The reaction mixture was stirred at 0 °C for 2 hrs, and then at room temperature for an additional 1 hr. The reaction mixture was diluted with ethyl acetate (400 ml), the organic phase was washed with saturated solution of $NaHCO_3$ (2 x 30ml), and with brine (30ml). The resulting organic phase was dried over $MgSO_4$ to provide crude title compound (93%) which was used in the next step without further purification.
MS (FAB/NOBA, NaI, KI): $[M + H]^+$, m/z 926; $[M + Na]^+$, m/z 948; $[M + K]^+$, m/z 964
HRMS (FAB/ NOBA, CsI/Gly external reference): $[M + H]^+$ m/z 926.3588 observed, $C_{50}H_{56}NO_{16}$, calculated value: 926.3599 (deviation Δ = 1.2 ppm)
^{1}HNMR ($CDCl_3$): δ 1.13 (3H, s), 1.23 (3H, s), 1.30 (3H, t), 1.67 (3H, s), 1.92 (3H, s), 2.21 (3H, s), 2.37 (H, d), 2.45 (3H, s), 2.54 (H, m), 3.80 (H, d), 4.15 - 4.32 (4H, m's overlapping), 4.43 (H, dd), 4.96 (H, d), 5.42 (H, d), 5.68 (H, d), 5.98 (H, dd), 6.28 (2H, m's, overlapping), 7.00 (H, d), 7.34 - 7.59 (11H, m's overlapping), 7.74 (2H, d), 8.12 (2H, d).

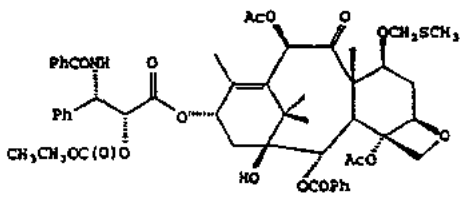
Alternate Run:

Paclitaxel (5.40 g, 6.324 mmol) in dry dichloromethane (63 mL) was cooled to 0 °C and treated with neat N,N- diisopropylethylamine (3.30 mL, 3 equiv) and then neat ethyl chloroformate (1.81 mL, 3 equiv) dropwise over a 5 min period. The reaction was monitored by TLC (50% ethyl acetate in hexane). After 2h at 0 °C and 16h at room temperature, the reaction was complete and the yellow-orange solution was diluted with ethyl acetate (300 mL) and washed with saturated sodium bicarbonate (3 x 75 mL) and brine (75 mL). Drying ($MgSO_4$) and evaporation afforded crude title compound, which was purified by precipitation: dichloromethane (ca. 100 mL) was added followed by cooling and addition of hexane (ca 60 mL) to the cloud point. After cooling in ice for several hours, the solid was collected by filtration. Yield 5.17 g (88%).

Alternate Run:

In a flame dried, single necked 3 L flask was dissolved paclitaxel (99.0 g, 115.9 mmol) in 1,350 mL of dry methylene chloride under the argon atmosphere. The solution was cooled to -10°. N,N-diisopropylethylamine (52.4 g, 405.7 mmol) was added slowly (addn. time ~3 min.), followed by $ClCO_2Et$ (31.45 g, 289.8 mmol; addn. time ~15 min.). The resulting mixture was stirred overnight (16 hrs.) at -4 °C . The reaction was judged incomplete by TLC. Another charge of N,N-diisopropylethylamine (2.62 g, 20.28 mmol) was added, followed by $ClCO_2Et$ (2.20 g, 20.28 mmol) and the stirring was continued for 3 hrs at -4 °C. No starting material was detected by TLC. The cold mixture was diluted with ethyl acetate (1.5 L) and transferred to a separatory funnel. It was then washed with 5% $KHSO_4$ (2x500 mL), water (1x500 mL), 5% $KHSO_4$ (1x500 mL), water (1x500 mL), satd. $NaHCO_3$ (2x500 mL) and brine (2x500 mL), dried ($MgSO_4$) and the solvents were removed *in vacuo* to give 147 g of the crude product. The residue was dissolved in hot methylene chloride (800 mL, bath temp. 42 °C) and hexanes were added dropwise (530 mL) with stirring, while the temperature was maintained. The crystallizing mixture was set aside for 3 hrs. at room temperature and then in the cold room (0 °C) overnight. The heavy white crystals were collected by filtration and washed with hexanes/CH_2Cl_2 1:1 (v/v) (2x200 mL). After drying on the suction filter for 1 hr. it was dried *in vacuo* (~1.0 mmHg) overnight to give 95.7 g (89% yield) of the title compound (homogeneity index as measured by HPLC = 98.5%).

(b) preparation of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of 2'-O-(ethoxycarbonyl)paclitaxel (4.38 g, 4.7 mmol) in dry dimethylsulfoxide (12.5 ml) was added acetic anhydride (12.5 ml). The reaction mixture was stirred for 24 hrs at room temperature and then diluted with ethyl acetate (500 ml), washed with saturated solution of $NaHCO_3$ (3 x 40 ml) and with water (2 x 40 ml). The resulting organic layer was dried over $MgSO_4$, and the solvents were evaporated in vacuo to dryness. The residue was purified by silica gel chromatography (40% ethyl acetate in hexanes) to afford the desired title compound (4.39 g, 94 %).
MS (FAB / NOBA, NaI, KI): $[M + H]^+$, m/z 986; $[M + Na]^+$, m/z 1008; $[M + K]^+$, m/z 1024
HRMS (FAB/NOBA, CsI/Gly external reference): $[M + H]^+$ m/z 986.3646 (calculated value: 986.3633, deviation Δ = 1.3 ppm)
^{1}HNMR (CDCl3) δ: 1.18 (3H, s), 1.20 (3H, s), 1.30 (3H, s), 1.75 (3H, s), 1.84 (H, m), 2.09 (3H, s), 2.11 (3H, s), 2.16 (3H, s), 2.24 (H, d), 2.37 (H, d), 2.45 (3H, s), 2.80 (H, m), 3.68 (H, d), 4.08 - 4.33 (5H, m, overlapping), 4.65 (2H, s), 4.96 (H, d), 5.43 (H, d), 5.69 (H, d), 5.98 (H, dd), 6.26 (H, t), 6.55 (H, s), 7.00 (H, d), 7.32 - 7.61 (11H, m, overlapping), 7.73 (2H, dd), 8.11 (2H, dd).

Alternate Run:

2'-O-(Ethoxycarbonyl)paclitaxel (2.260 g, 2.4406 mmol) was dissolved in anhydrous dimethylsulfoxide (6 mL), and acetic anhydride (6 mL) was added in one lot at room temperature. The reaction was monitored by HPLC (C18 analytical column; 60% acetonitrile - 40% 10 mM ammonium phosphate buffer, pH 6). After 30h, the solution was diluted with ethyl acetate (250 mL) and washed with saturated aqueous bicarbonate (3 times) then water and brine. After drying over magnesium sulfate and filtration, the crude product was chromatographed on silica (40% ethyl acetate in hexane) to yield the title compound as a white foam (2.030 g, 91%) that was 90% pure by HPLC. A portion was further purified by a second column (5% acetonitrile in dichloromethane) to afford material that was ca. 97% pure by HPLC.

Alternate method for the preparation of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel.

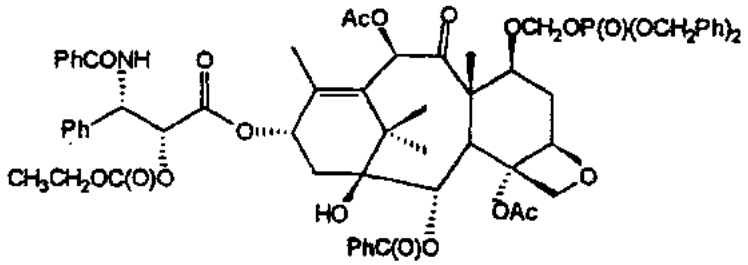
2'-O-(Ethoxycarbonyl)paclitaxel (4.170 g, 4.503 mmol) was dissolved in anhydrous acetonitrile (68 mL) at -40 °C, and dimethyl sulfide (3.2 mL, 44.10 mmol) was added, followed by benzoyl peroxide (4.400 g, 18.24 mmol). The mixture was placed in an ice bath and stirred at 0 °C, and the course of the reaction was monitored by TLC (40% ethyl acetate in hexane). After 3 h. no starting material was detected, and the solution was worked up by adding ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (100 mL). The organic phase was further washed with bicarbonate, water, and brine, then dried over magnesium sulfate and filtered. The residue was purified by silica gel flash chromatography (4% acetonitrile in dichloromethane), to yield the title compound as a white foam (2.571 g, 58% yield). The purity of this sample was judged as >97% by HPLC. The NMR spectrum was identical to the one reported above.

Alternate run for preparing 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel.

2'-O-(Ethoxycarbonyl)paclitaxel (49.3 g, 53.2 mmol) was placed in a flame dried single necked 1 L flask and dissolved in dry acetonitrile (500 mL) at room temperature. Methyl sulfide (39.1 mL, 0.532 mol) was rapidly added *via* syringe. The stirred reaction mixture was cooled to -16 °C in an ice/salt bath and solid benzoyl peroxide (51.6 g, 0.213 mol) was added to the mixture in one lot. (Full four equivalents are required for the reaction to proceed to completion.) Stirring was continued for 30 minutes, during which time the temperature rose to −10 °C. The reaction medium remained heterogeneous throughout this period (benzoyl peroxide has not dissolved completely). The cooling bath was changed to ice/water, the temperature was

raised to 0 °C and the remaining benzoyl peroxide dissolved ~5 min. after the warm-up. The reaction was judged complete by TLC after stirring at 0 °C for another 2.5 hours. The volume of the solution was reduced ~200 mL by removing the solvent on a rotovap and it was then transferred to a separatory funnel where it was washed with heptane (5x500 mL). The acetonitrile layer was diluted with ethyl acetate (1.5 L) and washed with a 3:1 mixture satd. $NaHCO_3$/5% K_2CO_3 (v/v) (2x500 mL), satd. $NaHCO_3$ (2x500 mL), half-satd. brine (1x500 mL) and brine (1x500 mL), dried ($MgSO_4$) and the solvents were removed in *vacuo* to give 67.0 g of the crude product. It was dissolved in acetone (200 mL), warmed to 40 °C in a water bath and hexanes were added dropwise with stirring until the cloudiness was observed (400 mL). The crystallizing mixture was set aside for 3 hrs. at room temperature and then transferred to a cold room (0 °C) where it was kept overnight (16 hrs.). A thick cake was formed. The solid was collected by filtration and washed with hexanes/acetone 3:1 (v/v) (2x50 mL). The resulting white crystals were dried on the suction filter for 1 hr. and then *in vacuo* (~0.5 mmHg) overnight to give 47.5 g (91% yield) of the title compound (homogeneity index as measured by HPLC = 94.8%).

(c) preparation of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel.



A solution of N-iodosuccinimide (1.953g, 8.65 mmol) and dibenzyl phosphate (2.41g, 8.65 mmol) in tetrahydrofuran was added to a mixture of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (5.677g, 5.76 mmol) and 4Å molecular sieves (5.7g) in methylene chloride (100 ml) at room temperature. The reaction mixture was stirred for 40 min. at room temperature. After this period the reaction was complete as judged by TLC. The reaction mixture was filtered through Celite and the filtrate was concenterated in vacuo to give a brownish residue which was diluted with ethyl acetate (800 ml), the organic phase was washed with 1% Na_2SO_3 (2 x 80 ml), then washed with 5% brine (2 x 50 ml). The organic phase was concentrated in vacuo and dried. Chromatography of the resulting residue (50 - 60% ethyl acetate in hexanes) gave the desired title compound (6.23g, 89%).

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1238; $[M + K]^+$, m/z 1254

HRMS (FAB/NOBA, CsI/Gly external reference): $[M + Na]^+$ m/z 1216.4291 ($C_{65}H_{71}NO_{20}P$ calculated value: 1216.4307; deviation Δ = 1.3 ppm)

^{1}HNMR ($CDCl_3$), δ: 1.18 (3H, s), 1.21 (3H, s), 1.30 (3H, t), 1.67 (6H, s), 1.80 (H, s), 1.93 (H, m), 1.99 (3H, d), 2.18 (3H, s), 2.23 (H, m), 2.38 (H, m), 2.45 (3H, s), 2.80 (H, m), 3.86 (H, d), 4.14 - 4.32 (5H, m's, overlapping), 4.88 (H, d), 5.00 - 5.07 (4H, m's, overlapping), 5.42 (H, d), 5.68 (H, d), 5.96 (H, dd), 6.26 (H, t), 6.33 (H, s), 6.95 (H, d), 7.30 - 7.61 (11H, m's overlapping), 7.75 (2H, dd), 8.12 (2H, dd).

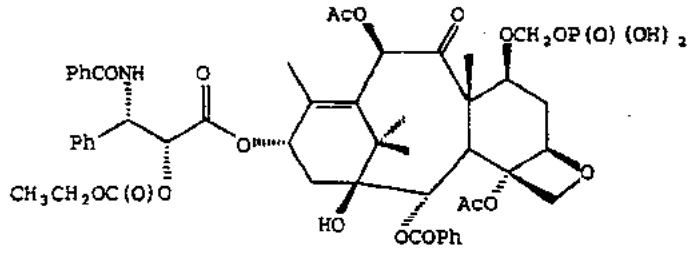
Alternate Run:

To a solution of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (350 mg, 0.355 mmol) in anhydrous tetrahydrofuran (8 mL) was added a solution of N-iodosuccinimide (120 mg, 0.532 mmol) and dibenzyl phosphate (148 mg, 0.532 mmol)in tetrahydrofuran (5 mL). The reaction was monitored by HPLC (C18 column; 70% acetonitrile, 30% 10 mM ammonium phosphate, pH 6). After 2h, less than 5% starting material was detected, and the reaction was worked-up. The solution was diluted with ethyl acetate (75 mL), and washed with 1% aqueous sodium bisulfite (2x50 mL) and brine (50 mL). After quick drying over magnesium sulfate and filtration, the solvent was evaporated. Silica gel flash chromatography (45% ethyl acetate/hexane) provided the title compound as a white foam (281 mg, 65%). HPLC analysis indicated a purity of ca. 95%.

Alternte Run:

Crushed 4 A molecular sieves were placed in a flame dried one-necked 1 L flask which was then connected to a vacuum line (~0.5 mmHg). The sieves were heated with a heatgun for ~10 min. while being shaken manually. After cooling under *vacuum* argon was introduced into the flask and 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (37.5 g, 38.03 mmol) was added, followed by dibenzyl phosphate (14.8 g, 53.24 mmol) and THF (400 mL). The heterogeneous mixture was vigorously stirred for 15 min. at room temperature with a magnetic stirrer. In a separate flame dried flask, N-iodosuccinimide (10.7 g, 47.54 mmol) was dissolved in THF (50 mL) under argon. (During the preparation of the NIS solution, liquid transfer and during the reaction course, the vessels were covered with aluminum foil for protection against light.) It was then added slowly (10 min) to the reaction mixture via a syringe. The flask containing NIS was washed with 5 mL of THF and transferred to the reaction mixture, which was then stirred for 2 hrs. at room temperature. TLC analysis showed absence of the starting material. The deeply red colored solution was filtered through a pad of Celite® directly into a vigorously stirred bi-phasic mixture containing ethyl acetate (500 mL), 10% aq. sodium thiosulfate (300 mL) and satd. sodium bicarbonate (200 mL). The red color disappeared in a few seconds giving a colorless solution. The Celite® pad was washed with EtOAc (~100 mL) and both liquid layers were transferred into a separatory funnel. The organic layer was diluted with 1L of EtOAc, the layers were separated and the organic layer was washed with a mixture of satd. $NaHCO_3$ and 5% K_2CO_3 (3:1 v/v, 2X500 mL), then satd. $NaHCO_3$ (2x500 mL), half-saturated brine (1x500 mL) and brine (1x500 mL). The extract was dried with anhydrous $MgSO_4$ and filtered. It was treated with 5.0 g of neutral Norit (charcoal) by stirring at room temperature for 15 min. It was filtered again through a Celite® pad and the solvent was removed under the reduced pressure to give 52 g of the crude product. It was dissolved in toluene/methylene chloride (280 mL/25 mL) and hexanes were added dropwise (20 mL). After being set aside for 3 hrs. at room temperature the crystallizing mixture was left at 0°C overnight. A pale yellow solid was formed on the flask walls. After decanting the mother liquor, the residue was triturated with toluene (50 mL), filtered, washed with toluene and dried on the suction filter for 30 min. It was then transferred to a desiccator with Drierite® and further dried *in vacuo* (~0.5 mmHg) for four hours to give 24.4 g (53% yield) of the title compound (homogeneity index as measured by HPLC = 95.9%). The mother liquor was evaporated to dryness, triturated with toluene (100 mL), filtered, washed with toluene and dried on the suction filter for 30 min. After drying in a desiccator as described above it gave 12.5 g (27% yield) of the same product (homogeneity index as measured by HPLC = 97.1%).

(d) preparation of 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel; its monosodium, monopotassium, triethylamine, arginine, lysine, ethanolamine, N-methylglucamine, and triethanolamine salts.



To a solution of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel(1.23 g, 1.01 mmol) in dry ethyl acetate (40 ml) was added 10% Pd on carbon (428 mg, 10%, 0.404 mmol). The reaction mixture was subjected to hydrogenation (60 PSI = 400 kPa) with continuous shaking for 24 hrs. The solid was filtered off through Celite, then the Celite was rinsed several times with ethyl acetate. The filtrate was concentrated to give free acid form of the title compound (1.01g, 80% purity as judged by HPLC). The impurities were removed at the next step by preparative C-18 column chromatography.

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1058; $[M + K]^+$, m/z 1074; $[M + 2Na - H]^+$, m/z 1080; $[M + Na + K - H]^+$, m/z 1096; $[M + 2K - H]^+$, m/z 1112

HR-MS (FAB/NOBA, CsI/Gly, external reference): $[M + Na]^+$, m/z 1058.3163 ($C_{51}H_{58}NO_{20}PNa$ calculated value: 1058.3188; deviation Δ = 2.3 ppm)

^1H NMR (acetone-d_6/D2O) δ: 1.13 (3H, s), 1.21 (3H, s), 1.66 (3H, s), 1.87 (H, m), 1.93 (3H, s), 2.14 (3H, s),

2.18 (H, m), 2.44 (3H, s), 2.95 (H, m), 3.81 (H, d), 4.12 (2H, s), 4.15 - 4.27 (3H, m's overlapping), 4.92 - 4.99 (2H, br.m's overlapping), 5.15 (H, br.s), 5.48 (H, d), 5.61 (H, d), 5.84 (H, dd), 6.07 (H, t), 6.36 (H, s), 7.25 (H, t), 7.28 - 7.69 (10H, m's overlapping), 7.89 (2H, dd), 8.08 (2H, dd), 8.86 (H, d).

Alternate Run:

2'-O-(Ethoxycarbonyl)-7-O-(dibenzylphosphonooxymethyl)paclitaxel (490 mg, 0.402 mmol) in ethyl acetate (20 mL) was hydrogenated in a Parr shaker at 60 psi (400 kPa) in the presence of palladium on charcoal (10% w/w, 150 mg). Monitoring was carried out by TLC and HPLC. When no more starting material nor an intermediate (presumably the monobenzyl phosphate) were detected (26h), the suspension was filtered through Celite and evaporated to dryness. HPLC analysis showed a purity of 88-92%.

Alternate Run:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt to be described below (5.4 g, 4.75 mmole) was partitioned vigorously between EtOAc (100 mL) and 5% $NaHSO_4$ (45 ml) with stirring at 0 °C for 30 minutes. The aqueous layer was separated and extracted with EtOAc (20 ml). The combined EtOAc layer was washed with half-brine (25 ml), brine (25 mL x 2), dried over $NaSO_4$ and filtered to give a solution of the acid (~4.75 mmole) in EtOAc (~150 mL). This EtOAc solution was then concentrated to dryness on a rotary evaporator to give 3.75 g of the title compound in free acid form in 95% yield. HPLC analysis showed homogeneity index of 96.1%.

The monosodium salt was prepared as follows:

A sample of 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel (1.6 g, 1.55 mmol) was dissolved in acetonitrile (30 ml) by sonication. This solution was diluted with water (30 ml) and 1.1 M solution of $NaHCO_3$ (2.11 ml, 2.32 mmol) was added, alternately shaking and sonicating to obtain a solution (5-20 min). The somewhat milky solution was applied onto a C-18 column, washing with two column volumes of water, then eluting the monosodium salt with 25% acetonitrile/water. The appropriate fractions were pooled, the acetonitrile evaporated, and the aqueous phase lyophilized, to yield the monosodium salt of the title compound (850 mg, ca 50%), having HPLC purity of 97%.

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1180

HR - MS (FAB/NOBA, CsI/Gly external reference): $[M + Na]^+$, m/z 1080.2968 ($C_{51}H_{57}NO_{20}PNa_2$ calculated value: 1080.3007; deviation D = 3.6 ppm)

Elemental analysis: C: 52.65 (calc. 56.72), H: 5.06 (calc. 5.23), N: 1.20 (calc. 1.30), Na: 2.74 (calc. 2.12)

IR (KBr): 3430, 3066, 2988, 1746, 1722, 1660, 1602, 1582, 1526, 1488, 1452, 1374, 1246, 1178, 1150, 1108, 1070, 1052, 1026, 1002, 966, 912, 834, 792, 776, 710, 628, 538 cm^{-1}.

^{1}H-NMR (DMSO-d_6, D_2O, acetone-d_6) δ: 1.10 (6H, s), 1.23 (3H, t), 1.64 (3H, s), 1.70 (H, m), 1.90 (3H,s), 1.99 (H, m), 2.14 (3H, s), 2.37 (3H, s), 2.98 (H, m), 3.74 (H, d), 4.07 (2H, s), 4.13 - 4.26 (3H, m, overlapping), 4.80 (H, br.dd), 4.97 (H, d), 5.09 (H, br.t), 5.44 (H, d), 5.55 (H, d), 5.99 (H, t), 6.34 (H, s), 7.22 (H,t), 7.43 - 7.69 (10H, m, overlapping), 7.92 (2H, dd), 8.06 (2H, dd).

The sodium salt can also be prepared as follows:

Crude 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel (89%; 70 mg, 0.060 mmol), in EtOAc (2 ml) was treated with a solution of sodium ethylhexanoate (87.5 mM in EtOAc, 1.0 ml, 0.0875 mmol) at room temperature with stirring. After stirring at room temperature for 1 h, hexane (1.2 ml) was added to the cloud point. After storing at -20 °C for 2h, the fine amorphous powder was filtered (with some difficulty, very slow) through fine filter paper, to yield 45 mg (70%) of the sodium salt. This was 95.2% pure by HPLC and contained a small amount of ethylhexanoic acid (NMR).

The triethanolamine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel, crude from the hydrogenation (89% by HPLC) (0.69 g, 0.593 mmol after correction for impurities) was dissolved in ethyl acetate (10 ml), and stirred slowly while a solution of triethanolamine (0.11 M in EtOAc, used 5.1 ml, 0.95 eq) was added dropwise. The milky solution obtained by this procedure was digested at 0 °C for 2h, then filtered on file filter paper, rinsing with cold EtOAc. Yield: 499 mg (80%) of an amorphous, fine, non-electrostatic powder that was dried overnight *in vacuo*. HPLC shows 96.6% purity (C-18, 45% 5mM Q_{12} + 10mM ammonium phosphate pH 6, 55% actonitrile). NMR spectrum (D_2O/acetone/DMSO) shows traces of ethyl acetate and no other clearcut impurities. It analyzes for a 2-3 x hydrate.

The triethanolamine salt of lesser priority obtained from another experiment was further purified by the following procedure. The triethanolamine salt (approx. 2 g) was dissolved in about 30% acetonitrile/water. This solution was eluted with slight nitrogen pressure through a column of C18 (Bakerbond) with a gradient

of 20% to 40% acetonitrile in water. The fractions containing the desired triethanolamine salt were collected; the acetonitrile was removed by rotary evaporation under reduced pressure. The aqueous solutions were frozen and lyophilized overnight to afford 1.4 grams of the triethanolamine salt with a purity of 97.5%.

The triethanolamine salt can also be prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt (3.0 g, 2.64 mmole) was partitioned between EtOAc (60 ml) and 5% $NaHSO_4$ (30 ml) with vigorous stirring at 0°C for 15 minutes. The aqueous layer was separated and extracted with EtOAc (10 mL). The combined EtOAc layer was washed with brine (15 ml), dried over Na_2SO_4, filtered to give a solution of the acid (~2.64 mmole) in EtOAc (~70 ml). To this EtOAc solution at room temperature was added dropwise with vigorous stirring N-$(CH_2CH_2OH)_3$ (0.35 ml, 2.64 mmole) over a period of 5 minutes. The resulting suspension was stirred for an additional 1 hr and then it was filtered, washed with EtOAc (15 ml x 2), dried *in vacuo* to give 2.8 g of the triethanolamine salt in 89% yield. HPLC analysis showed homogeneity index of 98.7%; mp.: >157°C with decomposition.

Elemental analysis calculated for $C_{56}H_{73}N_2O_{23}P \cdot 2.0\ H_2O \cdot 0.3$ EtOAc: C, 55.60; H, 6.48; N, 2.27; KF (H_2O), 2.92. Found: 55.94; H, 6.59; N, 2.43; KF (H_2O), 3.50.

The triethylamine salt was prepared as follows:

To the solution of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (10 g, 8.23 mmole), in EtOAc (350 ml), at room temperature was added 10% Pd on carbon (2 g, 20% load). The resulting suspension was degassed by evacuating air and then purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the same degassing procedure. The resulting suspension was stirred under a balloon hydrogen pressure (2-3 pound per square inch) for 16 hr at room temperature with vigorous stirring. The hydrogen was evacuated and replaced with argon three times following the degassing procedure. The resulting suspension was filtered through a pad of Celite. To this homogeneous filtrate was slowly added Et_3N (8.23 mmole, 1.14 mL) over a period of 5 min with vigorous stirring. The resulting fine white suspension was stirred for an additional 30 min. It was filtered through a fritted funnel with porous size E. The filter cake was dried *in vacuo* (1 mmHg) for 16 hr to give 8.22 g of the title triethylamine salt in 88% yield. HPLC analysis showed homogeneity index of 97.4%; mp.: >178°C with decomposition.

Elemental analysis calculated for $C_{57}H_{73}N_2O_{20}P \cdot 4.5\ H_2O$: C, 56.19; H, 6.79; N, 2.30; KF (H_2O), 6.65. Found: 56.33; H, 6.87; N, 2.32; KF (H_2O), 7.96.

Alternate run for making the triethylamine salt:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (5.67 g, 4.66 mmol) was added to a 250 mL flask and dissolved in ethyl acetate (150 mL). The flask was equipped with a three-way valve with one connection to house vacuum and one connection to an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. Palladium on activated carbon (10% Pd) (0.85 g) was added to the flask. The argon line attached to the three-way valve was replaced with a hydrogen-filled balloon. Using the valve, the flask was partially evacuated and then purged with hydrogen. This process was repeated four additional times. The resulting mixture was stirred at room temperature under the hydrogen balloon atmosphere overnight. TLC analysis 17 hours after the initial exposure to hydrogen showed the starting material to be absent. The hydrogen balloon attached to the three-way valve was replaced with an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. The contents of the flask were vacuum-filtered through a pad of Celite. The Celite was rinsed with ethyl acetate (2 x 10 mL). To the stirring filtrate was added NEt_3 (0.650 mL, 4.66 mmol). The resulting suspension was stirred at room temperature for two hours, and the volume was then reduced to ~150 mL via a rotovap. The solid was filtered, washed with ethyl acetate (2 x 10 mL) and dried under vacuum to give 4.76 g (90% yield) of the title triethylamine salt as a white powder (homogeneity index of the product was determined to be 96.6 % by HPLC analysis).

Alternate run for making the triethylamine salt:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (5.17 g, 4.25 mmol) was added to a 250 mL flask and dissolved in ethyl acetate (150 mL). The flask was equipped with a three-way valve with one connection to house vacuum and one connection to an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. Palladium on activated carbon (10% Pd) (0.86 g) was added to the flask. The argon line attached to the three-way valve was replaced with a hydrogen-filled balloon. Using the valve, the flask was partially evacuated and then purged with hydrogen. This process was repeated five additional times. The resulting mixture was stirred at room temperature under the hydrogen balloon atmosphere overnight. TLC analysis 16 hours after the initial exposure to hydrogen showed the starting material to be absent. The hydrogen balloon attached to the three-way valve was replaced with an argon line. Using the valve, the flask was partially evacuated

and then purged with argon. This process was repeated two additional times. The contents of the flask were vacuum-filtered through a pad of Celite. The Celite was rinsed with ethyl acetate (4 x 10 mL). To the stirring filtrate was added NEt_3 (0.590 mL, 4.25 mmol). The resulting suspension was stirred at room temperature for one hour, and the volume was then reduced to ~140 mL via a rotovap. The solid was filtered, washed with ethyl acetate (10 mL) and dried under vacuum to give 4.46 g (92% yield) of the title triethylamine salt as a white powder (homogeneity index as determined by HPLC analysis was 96.7%).

The lysine salt was prepared as follows:

2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (15.0 g, 12.34 mmole) was added portionwise to a suspension of 10% palladium on carbon (20% load, 3 g) in EtOH (600 ml, 200 proof) at 0 °C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the same degassing procedure with vigorous stirring. The resulting mixture was stirred at 0 °C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 4-1/2 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times. It was filtered under argon through a pad of Celite. To the resulting filtrate was slowly added a solution of lysine (1.63 g, 0.94 eq) in a 1:1 mixture of H_2O:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (110 ml) and stirred for 30 minutes. It was warmed to about 55 ° C. The resulting homogeneous solution was kept in an oil bath set at 50 °C and slowly cooled down to room temperature for 16 hrs and 4 °C for 3 hrs. It was filtered and suction dried for 16 hrs to give 11.8 g (~80% yield) of the lysine salt with homogeneity index of 99.0 % as determined by HPLC; mp.: >170 °C with decomposition.

Elemental analysis calculated for $C_{57}H_{72}N_3O_{22}P \cdot 8.0\ H_2O$: C, 51.82; H, 6.69; N, 3.17; KF (H_2O), 10.87. Found: 51.76; H, 6.57; N, 3.48; KF (H_2O), 11.42.

The ethanolamine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt (3.0 g, 2.64 mmole) was partitioned between EtOAc (60 ml) and 5% $NaHSO_4$ (30 ml) with vigorous stirring at 0 °C for 15 minutes. The aqueous layer was separated and extracted with EtOAc (15 ml). The combined EtOAc layer was washed with brine (15 ml), dried over Na_2SO_4, filtered to give a solution of the free acid (~2.64 mmole) in EtOAc (~70 ml). To this EtOAc solution at room temperature was added dropwise with vigorous stirring a solution of $H_2NCH_2CH_2OH$ (0.15 ml, 2.64 mmole) in EtOAc (5 mL) over a period of 5 minutes. The resulting suspension was stirred for an additional 1 hr and then it was filtered, washed with EtOAc (15 ml x 2), and dried in vacuo to give 2.6 g of the title ethanolamine salt in 89% yield. HPLC analysis showed homogeneity index of 97.8%; mp.: >130 °C with decomposition.

Elemental analysis calculated for $C_{53}H_{65}N_2O_{21}P \cdot 2.5\ H_2O$: C, 55.73; H, 6.18; N, 2.45; KF (H_2O), 3.94. Found: C, 55.76; H, 6.39; N, 2.45; KF (H_2O), 6.00.

The arginine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (30.0 g, 24.69 mmole) was added portionwise to a suspension of 10% palladium on carbon (20%, load, 6 g) in EtOH (900 ml, 200 proof) at 0 °C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the above degassing procedure with vigorous stirring. The resulting mixture was stirred at 0 °C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 24 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times following the above degassing procedure. It was filtered under argon through a pad of Celite. The filtrate was divided into two equal portions and EtOH (190 ml, 200 proof) was added to each portion. To one portion (~630 ml) was slowly added a solution of arginine (2.0 g, 0.94 eq) in a 2:1 mixture of H_2O:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (100 ml) and stirred for 30 minutes and then warmed to about 60 °C. It was filtered hot and the filtrate was kept in an oil bath set at 50 °C, allowed to cool down to room temperature and kept at room temperature for 2 hrs and at 4 °C for 2 hrs. It was filtered and washed with cold 3% H_2O in EtOH (100 ml) and suction dried for 16 hrs to give 12.95 g (~86% yield) of the title arginine salt with homogeneity index of 96.7 %.

This material (12.95 g) was dissolved in a mixture of 15% H_2O in EtOH (~700 ml) at 55 °C. The solution was cooled down and kept at 30 °C for 3-1/2 hrs, room temperature for 16 hrs, and 4 °C for 3 hrs. The resulting crystals were filtered, washed with cold 2% H_2O in EtOH (50 ml x 2), suction dried for 4 hrs, and then dried *in vacuo* (1 mmHg) for 16 hrs to give 10.2 gs (~80% yield) of the title arginine salt (homogeneity index was 98.5%);mp.: >176 °C with decomposition.

Elemental analysis calculated for $C_{57}H_{72}N_5O_{22}P \cdot 6.4\ H_2O$: C, 51.65; H, 6.45; N, 5.28; KF (H_2O), 8.7. Found: C, 51.86; H, 6.65; N,5.53; KF (H_2O), 8.72.

The N-methylglucamine salt was prepared as follows:

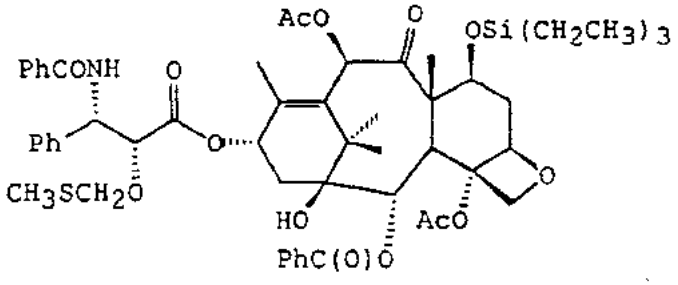
2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (30.0 g, 24.69 mmole) was added portionwise to a suspension of 10% palladium on carbon (20% load, 6 g) in EtOH (900 ml, 200 proof) at 0 °C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the above degassing procedure with vigorous stirring. The resulting mixture was stirred at 0 °C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 24 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times following the above degassing procedure. It was filtered under argon through a pad of Celite. The filtrate was divided into two equal portions and EtOH (190 ml, 200 proof) was added to each portion. To one portion (~630 ml) was slowly added a solution of N-methylglucamine (2.24 g, 0.94 eq) in a 1:1 mixture of H_2O:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (100 ml) and the suspension was stirred for 30 minutes and then warmed to about 49 °C. The clear homogeneous solution was kept in an oil bath set at 50 °C, allowed to cool down to room temperature and kept at room temperature for 2 hrs and at 4 °C for 1-1/2 hrs. It was filtered and washed with 3% H_2O in EtOH (100 ml), suction dried at room temperature for 16 hrs to give 9.65 g (~64% yield) of the title N-methylglucamine salt with homogeneity index of 96.4 %.

This material (9.65 g) was dissolved in a mixture of 15% H_2O in EtOH (~450 ml) at 52 °C. Then, the solution was cooled down and kept at 28 °C for 3-1/2 hrs, room temperature for 16 hrs, and 4 °C for 3 hrs. The resulting crystals were filtered, washed with cold 2% H_2O in EtOH (50 ml x 2), suction dried for 4 hrs, and then dried *in vacuo* (1 mmHg) for 16 hrs to give 7.5 g (~80% yield) of the title N-methylglucamine salt (homogeneity idex as determined by HPLC was 98.6%); mp.: >154 °C with decomposition.

Elemental analysis calculated for $C_{58}H_{75}N_2O_{25}P \cdot 5.0\ H_2O$: C, 52.72; H, 6.48; N, 2.12; KF (H_2O), 6.82. Found: C, 53.09; H, 6.50; N, 2.08; KF (H_2O), 7.12.

Example 4. 2'-O-(Phosphonooxymethyl)paclitaxel

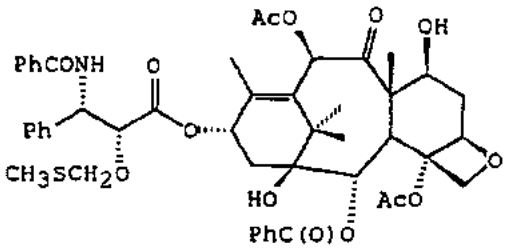
(a) Preparation of 2'-O-(methylthiomethyl)-7-O-(triethylsilyl)paclitaxel



To a cooled (0 to -5 °C) solution of 7-O-(triethylsily)paclitaxel (2.46 g; 2.5439 mmol) in dry acetonitrile (100 ml) was added dimethylsulfide (1.348 g; 1.59 ml; 21.6976 mmol) followed by benzoyl peroxide (2.628 g; 10.8488 mmol). The heterogeneous mixture was stirred at 0 °C for 1 h and kept at 5 °C for 18 h. A yellow solution was observed. This was evaporated to dryness and purified by silica gel column (eluting with ethyl acetate: hexane, 1:4; 1:3 and 1:2) to give the title compound (1.0 g, 38%). This was used as such for next step.

MS: $[M+H]^+$, 1028; $[M+Na]^+$, 1050; $[M+K]^+$, 1066

(b) Preparation of 2'-O-(methylthiomethyl)paclitaxel



To a cooled (-15 °C) solution of the product of step (a) (1.0 g; 0.9737 mmol) in dry acetonitrile (30 ml) was added dropwise 0.5 N HCl (3 ml). The resulting solution was stirred at -15 °C for 1 h and at 5 °C for 18 h. This was diluted with ethyl acetate (20 ml) and washed with cold 6% $NaHCO_3$ solution and brine. It was dried ($MgSO_4$) and evaporated to dryness. This was purified by silica gel plate (methylene chloride: 15% acetonitrile) to give pure title compound (280 mg, 31.4%).

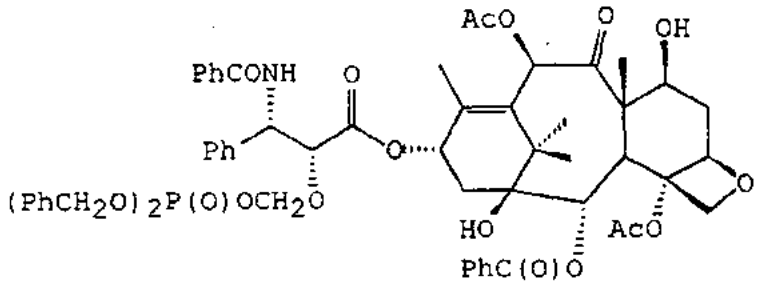
IR(KBr): 3446, 3064, 2940, 1726, 1666, 1582, 1516,1486.

NMR ($CDCl_3$): δ 1.118 (s, 3H), 1.229 (s, 3H), 1.662 (s, 3H), 1.689 (s, 3H), 1.871 (s, 3H), 2.209 (s, 3H), 2.450 (s, 3H), 3.800 (d, H), 4.119 (d, H), 4.305 (d, H), 4.413 (m, H), 4.563 (d, H), 4.703 (d, H), 4.940 (d, H), 4.958 (dd, H), 5.667 (d, H), 5.822 (dd, H), 6.263 (m, 2H), 7.019 (d, NH), 7.293-8.127 (m, 15H).

MS: $[M+H]^+$, 914; $[M+Na]^+$, 936; $[M+K]^+$, 952

HRMS: MH^+: 914.3394 (calculated = 914.3422)

(c) Preparation of 2'-O-(dibenzylphosphonooxymethyl)paclitaxel



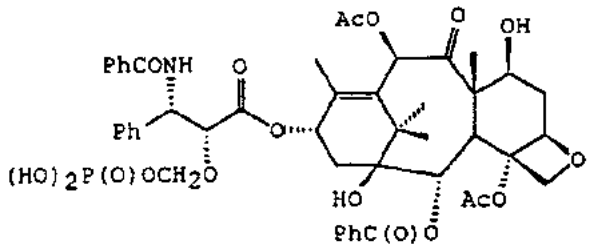
To a stirred solution of the product of step (b) (0.89 g; 0.9748 mmol) in dry 1,2-dichloroethane (12 ml) was added powdered 4Å molecular sieves (1.0 g) followed by dropwise addition of a solution mixture of N-iodosuccinimide (0.33 g; 1.4622 mmol) and dibenzyl phosphate (0.41 g; 1.4622 mmol) in dry tetrahydrofuran (8 ml). The resulting mixture was stirred at room temperature for 1 h., then filtered over Celite. The filtrate was evaporated to dryness and the red residue was taken up in ethyl acetate (50 ml) and washed with cold 6% $NaHSO_3$, cold 6% $NaHCO_3$ and brine. It was dried ($MgSO_4$) and evaporated to give a foam. This was purified by silica gel plate (methylene chloride:20% acetonitrile) to give pure product (0.77 g; 69%).

IR(KBr): 3854, 3744, 3362, 3066, 1960, 1722, 1602, 1580.

NMR ($CDCl_3$): δ 1.075 (s, 3H), 1.167 (s, 3H), 1.651 (s, 3H), 1.799 (s, 3H), 2.209 (s, 3H), 2.296 (s, 3H), 2.464 (m, H), 3.686 (d, H), 4.121 (d, H), 4.240 (d, H), 4.293 (m, H), 4.808-4.957, (m, 6H), 5.006 (m, H), 5.565-5.649 (m, 2H), 6.034 (t, H), 6.194 (3, H), 7.100-8.132, (m, 26H).

MS: $[M+H]^+$, 1144; $[M+Na]^+$, 1166; $[M+K]^+$, 1182

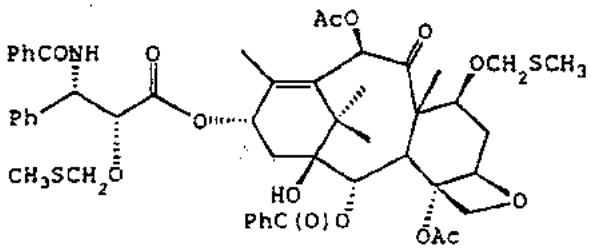
(d) Preparation of 2'-O-(phosphonooxymethyl)paclitaxel



A mixture of the product of step (c) (0.9 g; 0.7874 mmol) and 10% Pd/C (1.0 g) in ethyl acetate (20 ml) was hydrogenated at 60 psi (400 kPa) for 24 h. The reaction mixture was filtered over Celite and the filtrate evaporated to dryness. The residue was purified by silica gel plate (methylene chloride:40% methanol) to give the title product (0.254 g, 33.4%). MP 202-205 °C (d).
IR (KBr): 3438, 3066, 2942, 1722, 1652, 1602 cm^{-1}.
NMR (acetone-d_6/D_2O): δ 1.081 (s, 6H), 1.571 (s, 3H), 1.847 (s, 3H), 2.115 (s, 3H), 2.357 (s, 3H), 3.707 (d, H), 4.08 (m, 2H), 4.275 (m, H), 4.941-5.085 (m, 4H), 5.231 (t, H), 5.430 (d, H), 5.544 (d, H), 5.970 (t, H), 6.376 (s, H), 6.961-8.017 (m, 16H).
MS: $[M+Na]^+$, 986; $[M+K]^+$, 1002; $[M+2Na-H]^+$, 1008; $[M+Na+K-H]^+$, 1024; $[M+2K-H]^+$, 1040
HRMS: MNa^+, 986.2955 (Calculated = 986.2976)

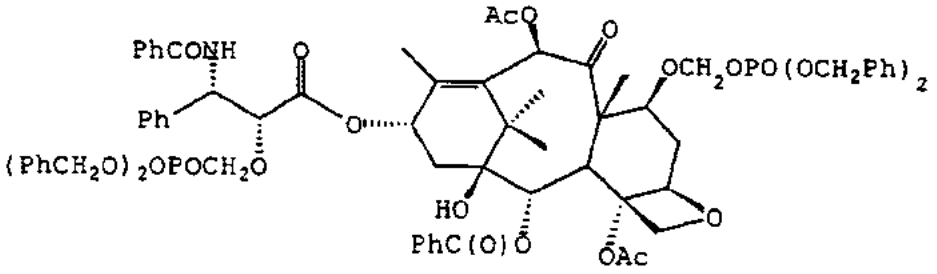
Example 5. 2',7-O-bis(phosphonooxymethyl)paclitaxel sodium salt

(a) Preparation of 2',7-O-bis(methylthiomethyl)paclitaxel



Solid benzoyl peroxide (1.995 g, 8 mmol) was added to a stirred solution of paclitaxel (0.853 g, 1 mmol) and dimethyl sulfide (1.465 g, 20 mmol) acetonitrile (20 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 3 hours. Its progress was monitored by TLC in hexane : ethyl acetate (1 : 1, v/v), R_f paclitaxel = 0.24, R_f product = 0.60. When starting material disappeared (ca. after 3 hrs) the reaction was quenched by evaporation of solvents to dryness at 25 °C using house vacuum. The dry residue was separated using silica gel column (EM Science, 40 - 63µm), 100 mL of dry silica gel, column size: Φ = 3/4 in., solvent system: hexane : ethyl acetate (3 : 2, v/v), volume of each fraction: ca. 25 mL. The title compound (0.515 g, 53% yield) was recovered from fractions 15 to 19.
MS (FAB/matrix NOBA,NaI KI): $[M + H]^+$, m/z 974; $[M + Na]^+$, m/z 996; $[M + K]^+$, m/z 1012
UV (MeOH): λmax = 204 nm, E(1%/1cm) = 243.45; λmax = 228 nm, E(1%/1cm) = 313.99
IR (KBr): 3440, 3064, 2926, 1724, 1668, 1602, 1582, 1514, 1484, 1452, 1372, 1314, 1266, 1242, 1178, 1142, 1068, 1026, 990, 916, 886, 848, 800, 774, 710, 646, 606, 570, 540, 480 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.20 (3H, s), 1.68 (3H, s), 1.74 (3H, s), 1.84 (H, dd), 2.04 (3H, d), 2.09 (3H, s), 2.15 (3H, s) overlaps with (H, m), 2.37 (H, dd), 2.51 (3H, s), 2.79 (H, ddd), 3.78 (H, d), 4.18 (H, d), 4.28 (H, m), 4.31 (H, d), 4.53 - 4.74 (4H, two overlapping AB m), 4.93 (H,d), 4.95 (H, d), 5.68 (H, d), 5.82 (H, dd), 6.24 (H, dd), 6.54 (H, s), 7.05 (H, d), 7.28 - 7.59 (10H, overlapping m), 7.57 (H, m), 7.76 (2H, d), 8.09 (2H, d).

(b) Preparation of 2',7-O-bis(dibenzylphosphonooxymethyl)paclitaxel



A solution of N-iodosuccinimide, (135 mg, 0.5 mmol) and dibenzylphosphate, (167 mg, 0.5 mmol) in dry tetrahydrofuran (8 mL) was added to a mixture of 2',7-O-bis(methylthiomethyl)paclitaxel (198 mg, 0.2 mmol) and 5 Å molecular sieves (ca. 200 mg) in methylene chloride (12 mL) at room temperature. The reaction mixture was stirred for 1.5 hours, then the molecular sieves were filtered off on celite, washed with methylene chloride (10 mL) and the solvents were evaporated to dryness at room temperature using house vacuum. The residue was dissolved in ethyl acetate (100 ml) and washed in a separation funnel with 1% sodium thiosulfate (50 mL), with 0.5 m sodium bicarbonate (50 mL), and twice with water (2x50 mL). The organic phase was dried over magnesium sulfate, evaporated to dryness and re-dissolved in ethyl acetate (1 mL). The product was precipitated with 50 mL of ethyl ether : hexane (1:1) and washed twice with the same solvent system (2x50 mL). A crude product (218 mg) was obtained in 74% yield. Purification of this product was performed by loading its methylene chloride solution (3 mL) on silica gel (Φ = 3/4 in. x L = 1 in.) and eluting the product with 50 mL of methylene chloride : ethyl acetate (3:1) solvent system. The title compound (172.7 mg) was obtained in 59.3% yield.

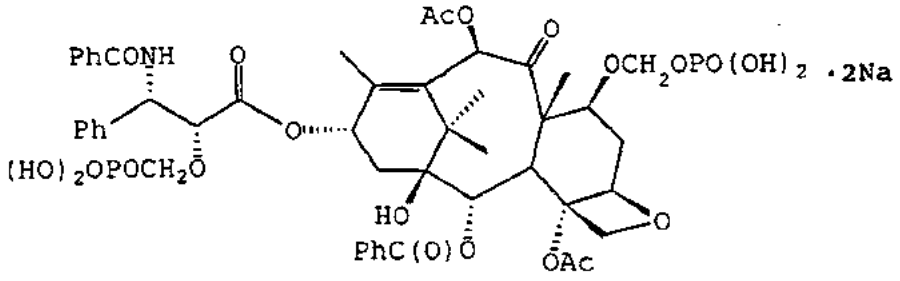
MS (FAB, matrix NOBA/NaI, KI): $[M + Na]^+$, m/z 1456; $[M + K]^+$, m/z 1472

UV (MeCN): λmax = 194 nm, E(1%/1cm) = 1078.36; λmax = 228 nm, E(1%/1cm) = 311.95

IR (KBr): 3430, 3066, 3032, 2958, 1744, 1726, 1664, 1602, 1582, 1532, 1488, 1456, 1372, 1270, 1244, 1158, 1108, 1068, 1016, 1000, 952, 886, 800, 776, 738, 698, 604, 498 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s), 1.14 (3H, s), 1.56 (H, m), 1.67 (3H, s), 1.84 (3H, d), 1.90 (H, m), 2.17 (3H, s), 2.29 (3H, s), 2.73 (H, m), 3.73 (H, d), 4.08 (H, d), 4.15 (H, m), 4.20 (H, d), 4.77 (H, m), 4.79 (H, d), 4.91 - 5.04 (10H overlapping m), 5.25 (H, dd), 5.38 (H, dd), 5.54 - 5.64 (2H, overlapping m), 5.99 (H, br. dd), 6.25 (H, s), 7.11 - 7.14 (2H, m), 7.24 - 7.64 (28H, overlapping m), 7.94 (2H, dd), 8.04 (2H, dd), 8.30 (H, d).

(c) Preparation of 2',7-O-bis(phosphonooxymethyl)paclitaxel sodium salt



A sample of 2',7-O-bis(dibenzylphosphonooxymethyl)paclitaxel (112 mg, 0.078 mmol) was dissolved in ethyl acetate (7 ml) and hydrogenated over 10% palladium on charcoal (50 mg) at room temperature, 60 PSI (400 kPa), for 2 hours. The catalyst was removed by filtration over Celite. The Celite was rinsed with ethyl acetate (10 mL). The filtrate was treated with solid sodium bicarbonate (20 mg, 3 eq.) and then the solvent was evaporated to dryness. A dry residue was re-dissolved in 5 mL of water : acetone (4:1, v/v) and purified by C-18 reverse phase column chromatography (55 - 105μ C-18, Waters, 50 mL of dry C-18, Φ = 3/4 in. in water : acetone (4 : 1, v/v). Eluant was monitored on analytical HPLC Jones C-18 column (15 cm, 1

mL/min., λ = 230mn) in acetonitrile : phosphate buffer pH 6 (50/50, v/v) with the addition of Q12 ion pair cocktail (Regis), Rt = 4.7min. Fractions containing the title product were combined, acetone was evaporated under house vacuum at 20°C, and the solution was lyophilized. The title product (44.2 mg) was obtained in 58.8% yield.

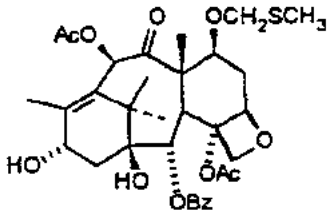
MS (FAB,matrix NOBA/NaI, KI): $[M + H]^+$, m/z 1118; $[M + Na]^+$, m/z 1140

UV (MeCN): λmax = 192 nm, E(1%/1cm) = 129.73; λmax = 230 nm, E(1%/1cm) = 26.43

IR (KBr): 3430, 3068, 2956, 1724, 1658, 1604, 1582, 1520, 1486, 1452, 1374, 1316, 1256, 1152, 1110, 1070, 1026, 966, 914, 802, 772, 710, 538 cm^{-1}.

^{1}H-NMR (acetone-d_6/D_2O) δ: 0.97 (3H, s), 1.02 (3H, s), 1.47 (H, m), 1.54 (3H, s), 1.70 (H, m), 1.75 (3H, s), 1.85 (H, m), 2.11 (3H, s), 2.30 (3H, s), 2.88 (H, m), 3.64 (H, d), 4.03 (H, m), 4.06 (H, d), 4.16 (H, d), 4.74 (H, m), 4.86 (H, m), 5.11 (H, br. t), 5.22 (H, d), 5.42 (H, d), 5.90 (H, br. t), 6.21 (H, s), 7.06 (H, br.t), 7.32 - 7.69 (10H, ovelapping m), 7.80 (2H, d), 7.93 (2H, d).

Example 6. 7-O-methylthiomethylbaccatin III



To a solution of 2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel (compound of Example 3(b), 27 g, 27.4 mmol) in 100 mL of THF and 500 mL of methanol was added freshly ground K_2CO_3 (2.7 g, 19 mmol). The solution was stirred for 30 minutes and neutralized with IR-120 (H^+) resin, filtered and concentrated. The crude filtrate was then dissolved in 200 mL of dichloromethane and stirred for 24 hours with tetrabutylammonium borohydride (10 g). The solution was diluted with dichloromethane and washed with water, saturated bicarbonate and brine. The organic fraction was then dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 9.4 g of the title compound (53%) with a melting point of 269°C.

FABMS (NOBA) M+H calcd for $C_{33}H_{43}SO_{11}$: 647. Found: 647.

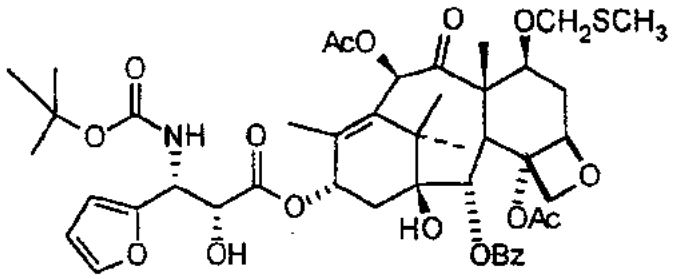
IR(KBr) 3474, 1746, 1724, 1712, 1270, 1240, 1070 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.1 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 6.55 (s, 1H), 4.94 (d, J=8.1 Hz, 1H), 4.83 (br q, J=5.1 Hz, 1H), 4.66 (ABq, J=14.7,12.3 Hz, 2H), 4.30 (m, 2H), 4.13 (d, J=8.4 Hz, 1H), 3.91 (d, J=6.6 Hz, 1H), 2.79 (m, 1H), 2.27 (s, 3H), 2.25 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 4H), 1.81 (m, 1H), 1.72 (s, 3H), 1.61 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 170.8, 169.3, 167.0, 144.2, 132.6, 132.1, 130.1, 129.4, 128.6, 83.9, 80.9, 78.7, 75.7, 74.5, 73.9, 67.9, 57.6, 47.6, 42.7, 38.3, 26.7, 22.6, 21.0, 20.1, 15.2, 15.0, 10.8.

Example 7. 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

(a) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethyl-paclitaxel



To a solution of HMDS (0.40 mL, 1.90 mmol) in 15 mL of THF was added a solution of n-BuLi (0.75 mL, 2.5 M in hexanes, 1.88 mmol) and stirred 5 minutes at -55°C. To this solution was added 7-MTM baccatin III (compound of example 6, 1.03 g, 1.59 mmol) in 10 mL of THF and stirred for 10 minutes before addition of an 10 mL solution of (3R,4R)-1-(t-butyloxycarbonyl)-4-(2-furyl)-3-(triethylsilyloxy)-2-azetidinone (883 mg, 2.40 mmol). The cold bath was removed and replaced with a 0°C bath and the reaction mixture was stirred for 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (2.5:1 hexane/ethyl acetate) to give 1.5 g of the coupling product 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (93%).

FABMS (NOBA) M+Na calcd for $C_{50}H_{71}NSSiO_{15}$: 1036. Found: 1036.

IR(film) 3446 (s), 1720, 1368, 1242, 1166, 1144, 1124, 1066 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.56 (m, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.36 (m, 1H), 6.56 (s, 1H), 6.33 (m, 1H), 6.20 (m, 2H), 5.67 (d, J=6.9 Hz, 1H), 5.29 (br s, 2H), 4.94 (d, J=7.8 Hz, 1H), 4.75 (s, 1H), 4.65 (s, 2H), 4.28 (m, 2H), 4.16 (d, J=8.1 Hz, 1H), 3.89 (d, J=6.9 Hz, 1H), 2.80 (m, 1H), 2.46 (s, 3H), 2.37 (m, 1H), 2.22 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.65 (m, 1H), 1.33 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H), 0.81 (t, J=7.8 Hz, 9H), 0.47 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 171.2, 170.3, 169.3, 167.1, 155.3, 152.0, 141.9, 141.0, 133.6, 132.9, 130.2, 129.2, 128.7, 110.7, 107.3, 84.0, 81.1, 80.2, 78.7, 76.1, 75.7, 74.7, 74.1, 72.4, 71.1, 57.4, 52.8, 47.1, 43.3, 35.2, 33.0, 28.1, 26.3, 22.9, 21.2, 21.0, 15.0, 14.5, 10.9, 6.5, 4.3.

To a solution of the 2'-triethylsilyl ether obtained above (330 mg, 0.32 mmol) in 7 mL of THF was added tetrabutylammonium fluoride (0.35 mL, 1.0M in THF, 0.35 mmol) and stirred 10 minutes. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated and the residue was chromatographed over silica gel (2:1 hexane/ethyl acetate) to give 301 mg of the title compound (95%).

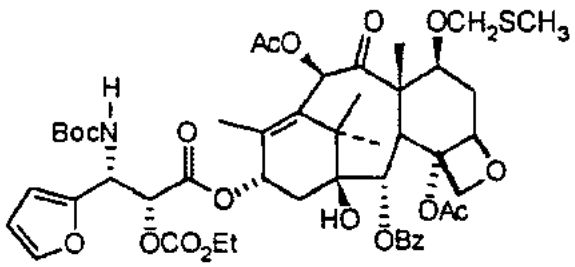
FABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{16}S$: 900. Found: 900.

IR(film) 3442, 1720, 1242, 1066, 1026 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 2H), 7.57 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.38 (s, 1H), 6.53 (s, 1H), 6.34 (d, J=3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 6.17 (t, J=8.1 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.29 (m, 2H), 4.92 (d, J=8.0 Hz, 1H), 4.70 (m, 1H), 4.64 (d, J=4.6 Hz, 2H), 4.29 (m, 2H), 4.14 (d, J=8.3 Hz, 1H), 3.86 (d, J=6.8 Hz, 1H), 3.37(d, J = 5.8 Hz, 1H), 2.77 (m, 1H), 2.38 (s, 3H), 2.32 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.77 (m, 3H), 1.73 (s, 3H), 1.33 (s, 9H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.6, 170.3, 169.2, 167.0, 155.2, 151.3, 142.4, 140.4, 133.7, 133.2, 130.2, 129.1, 128.7, 110.7, 107.4, 83.9, 81.2, 80.5, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 72.5, 71.8, 57.4, 51.7, 47.2, 43.2, 35.2, 32.8, 28.1, 26.4, 22.6, 20.9, 15.2, 14.6, 10.9, 8.3.

(b) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel



To a solution of the product of step (a) (864 mg, 0.96 mmol) in 50 mL of dichloromethane at 0°C was added diisopropylethyl amine (2.0 mL, 11.5 mmol) and ethyl chloroformate (0.50 mL, 5.25 mmol) and stirred for 4 hours. The solution was diluted with dichloromethane and washed with saturated bicarbonate and dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 884 mg of the 2' ethyl carbonate title compound (95%).

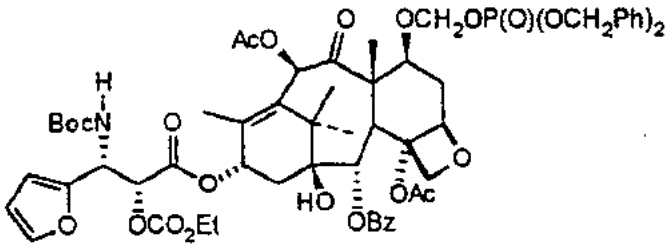
FABMS (NOBA) M + H calcd for $C_{48}H_{62}NO_{18}S$ 972.3688. Found: 972.3654.

IR(film) 1752, 1720, 1370, 1244, 1196, 1176, 1064 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.38 (s, 1H), 6.55 (s, 1H), 6.35 (m, 1H), 6.27 (m, 1H), 6.22 (t, J = 7.8 Hz, 1H), 5.67 (d, J = 7.2 Hz, 1H), 5.51 (d, J = 9.9 Hz, 1H), 5.34 (d, J = 2.4 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 4.95 (d, J = 8.1 Hz, 1H), 4.65 (s, 2H), 4.30 (m, 2H), 4.22 (m, 2H), 3.88 (d, J = 7.2 Hz, 1H), 2.81 (m, 1H), 2.41 (s, 3H), 2.36 - 2.21 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.67 (s, 1H), 1.59 (s, 1H), 1.34 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 169.9, 169.1, 167.6, 167.0, 154.0, 150.1, 142.6, 141.0, 133.6, 132.9, 130.2, 129.2, 128.7, 110.7, 107.5, 83.9, 81.1, 80.7, 78.7, 76.0, 75.7, 75.1, 74.7, 74.2, 71.8, 65.1, 57.4, 49.7, 47.1, 43.2, 35.0, 33.0, 28.1, 26.3, 22.6, 21.1, 20.9, 15.1, 14.5, 14.1, 10.9.

(c) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-dibenzylphosphonooxymethylpaclitaxel



To a solution of the product of step (b) (230 mg, 0.236 mmol) in 10 mL of anhydrous THF was added 300 mg of 4A sieves, dibenzylphosphate (270 mg, 0.98 mmol) and recrystallized NIS (62 mg, 0.28 mmol). To this solution was added silver trifluoromethanesulfonate (45 mg, 0.17 mmol) and the solution stirred for 3 hours. The solution was filtered through Celite and diluted with ethyl acetate and washed with 10% NaS_2O_8, sautruated bicarbonate, and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (15% acetonitrile/chloroform) to give 219 mg of the dibenzyl phosphate title compound (77%).

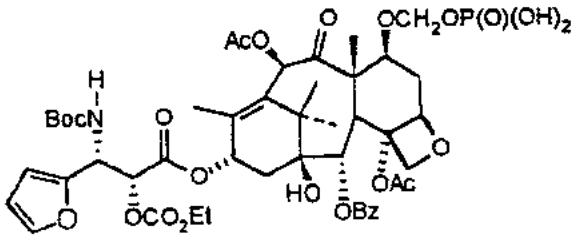
FABMS (NOBA) M + Na calcd for $C_{61}H_{72}NPO_{22}Na$ 1224. Found: 1224.

IR(film) 3422 (br), 1750, 1722, 1370, 1244, 1160, 1036, 1016, 1000, 976, 944 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 6.9 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39 (s, 1H), 7.31 (m, 10), 6.35 (m, 2H), 6.28 (s, 1H), 6.21 (t, J = 7.8 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.50 (d, J = 10.5 Hz, 1H), 5.39 (d, J = 6.6 Hz, 1H), 5.32 (d, J = 2.4 Hz, 1H), 5.25 (d, J = 9.9 Hz, 1H), 5.01 (dd, J = 8.1,

6.3 Hz, 5H), 4.86 (d, J = 8.4 Hz, 1H), 4.29-4.09 (m, 4H), 3.85 (d, J = 6.9 Hz, 1H), 2.77 (m, 1H), 2.40 (s, 3H), 2.30 (m, 2H), 2.16 (s, 3H), 1.99 (s, 3H), 1.94 (m, 1H), 1.70 (s, 3H), 1.67 (s, 1H), 1.54 (s, 1H), 1.34 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.17 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.8, 169.9, 169.2, 167.7, 167.0, 155.1, 154.0, 150.0, 142.74, 141.1, 133.7, 132.9, 130.2, 129.1, 128.7, 128.5, 128.4, 128.0, 110.7, 107.6, 93.8, 84.1, 81.6, 80.8, 80.7, 78.8, 76.3, 75.1, 74.6, 71.8, 69.3, 69.2, 65.1, 57.0, 49.7, 46.7, 43.2, 35.0, 28.1, 26.4, 22.6, 21.2, 20.8, 14.6, 14.1, 10.5.

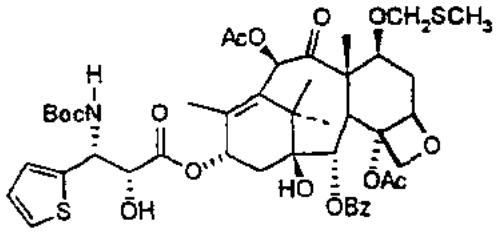
(d) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt



To a solution of the product of step (c) (311 mg, 0.259 mmol) in 25 mL of ethyl acetate was added 60 mg of Pd on carbon (10%) and the solution stirred under an atmosphere of H_2 for 30 minutes. The catalyst was removed by filtratation through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in 3 mL of ethyl acetate and triethananolamine added (2.3 mL, 0.1M in ethyl acetate, 0.23 mmol). The solution was concentrated and the residue was chromatographed over C_{18} (40% acetonitrile/water) and lyophilized to give 205 mg of the phosphate triethanolamine salt (67%).
FABMS (NOBA) M + Na calcd for $C_{47}H_{60}HPO_{22}Na$ 1044. Found: 1044.
IR(film) 3432 (br), 1752, 1722, 1372, 1246, 1158, 1108, 1096, 1070, 1002 cm^{-1}
^1H NMR (d_6 acetone/D_2O, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.62 (m, 2H), 7.52 (t, J = 7.5 Hz, 2H), 6.48 (d, J = 3.3 Hz, 1H), 6.42 (m, 2H), 6.16 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.46 (d, J = 3.6 Hz, 1H), 5.30 (d, J = 3.6 Hz, 1H), 5.17 (br s, 1H), 5.01 (br d, J = 9.0 Hz, 1H), 4.19 (br s, 1H), 4.18 (m, 5H), 3.95 (m, 6H), 3.87 (d, J = 6.9 Hz, 1H), 3.68 (s, 7H), 3.50 (br t, J = 4.8 Hz, 6H), 2.95 (m, 1H), 2.44 (s, 3H), 2.41 (m, 2H), 2.16 (s, 3H), 1.9 (s, 3H), 1.94 (m, 1H), 1.68 (s, 3H), 1.34 (s, 9H), 1.24 (t, J = 6.9 Hz, 3H), 1.17 (s, 6H).

Example 8. 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

(a) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethyl-paclitaxel



To a solution of HMDS (0.5 mL, 2.4 mmol) in 18 mL of THF at -55 °C was added n-BuLi (0.85 mL, 2.5 M in hexanes, 2.1 mmol). After 10 minutes 7-MTM baccatin III (1.15 g, 1.78 mmol) in 18 mL of THF was added dropwise and stirred in the cold for 10 minutes. (±)Cis-1-(t-butyloxycarbonyl)-4-(2-thienyl)-3-(triethylsilyloxy)-2-azetidinone (2.80 g, 7.3 mmol) in 18 mL of THF was added and the cold bath allowed to slowly warm to 0 °C over 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (5:1

hexane/ethyl acetate) to give 1.87 g of recovered lactam (3:1 hexane/ethyl acetate) to give 1.44 g of the coupling product 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (78%).

FABMS (NOBA) M + Na calcd for $C_{51}H_{71}NO_{15}S_2SiNa$ 1052. Found: 1052.

IR(film) 3442 (br), 1720, 1490, 1368, 1270, 1242, 1162, 1110, 1064, 1024, 984, 754 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.22 (m, 1H), 6.95 (m, 2H), 6.55 (s, 1H), 6.21 (t, J = 9.3 Hz, 1H), 5.68 (d, J = 6.9 Hz, 1H), 5.49 (br d, 1H), 5.39 (br d, J = 9.6 Hz, 1H), 4.94 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 4.57 (s, 1H), 4.28 (m, 2H), 4.17 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.46 (s, 3H), 2.37 (m, 1H), 2.20 (m, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.68 (s, 1H), 1.62 (s, 1H), 1.31 (s, 9H), 1.20 (s, 6H), 0.84 (t, J = 7.8 Hz, 9H), 0.50 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9, 171.1, 170.7, 170.1, 169.3, 167.0, 155.1, 142.8, 140.9, 133.6, 132.9, 130.2, 129.2, 128.7, 126.9, 124.6, 83.9, 81.2, 80.1, 78.8, 77.4, 76.0, 75.7, 75.2, 74.8, 74.1, 71.3, 57.4, 53.8, 47.0, 43.3, 35.3, 33.3, 28.1, 26.3, 23.0, 21.3, 20.9, 14.9, 14.4, 10.9, 6.6, 4.5.

To a solution of the 2'-triethylsilyl ether obtained above (1.41 g, 1.37 mmol) in 14 mL of THF was added tetrabutylammonium fluoride (1.4 mL, 1.0 M in THF, 1.40 mmol). The solution was stirred for 30 minutes, diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 1.16 g of the title compound (92%).

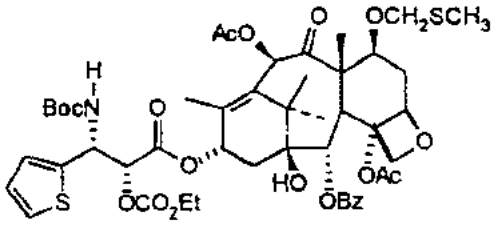
FABMS (NOBA) M + Na calcd for $C_{45}H_{57}NO_{15}S_2Na$ 938. Found: 938.

IR(film) 3440 (br), 1720, 1368, 1242, 1168, 1106, 1066, 710 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.2 Hz, 2H), 7.59 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.24 (m, 1H), 7.07 (m, 1H), 6.99 (m, 1H), 6.53 (s, 1H), 6.18 (t, J = 8.1 Hz, 1H), 5.56 (d, J = 6.9 Hz, 1H), 5.49 (d, J = 9.6 Hz, 1H), 5.32 (d, J = 9.6 Hz, 1H), 4.92 (d, J = 7.8 Hz, 1H), 4.63 (m, 3H), 4.28 (m, 2H), 4.15 (d, J = 8.4 Hz, 1H), 3.86 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 3.47 (d, J = 5.4 Hz, 1H), 2.78 (m, 1H), 2.36 (s, 3H), 2.34 (, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.72 (s, 1H), 1.61 (s, 1H), 1.33 (s, 9H), 1.21 (s, 3H), 1.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9,172.3, 170.3, 169.2, 167.0, 154.0, 141.5, 140.2, 133.7, 133.3, 130.2, 129.1, 128.7, 127.0, 125.4, 125.4, 83.9, 81.3, 80.4, 78.6, 76.1, 75.4, 74.5, 74.0, 73.4, 72.5, 57.5, 52.8, 47.2, 43.2, 35.3, 32.9, 28.2, 26.4, 22.6, 20.9, 15.1, 14.7, 10.8.

(b) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel



To a solution of the product of step (a) (621 mg, 0.677 mmol) in 35 mL of dichloromethane at 0 °C was added diisopropylethyl amine (1.20 mL, 6.89 mmol) and ethyl chloroformate (0.35 mL, 3.7 mmol) and stirred for 1 hour. The cold bath was removed and the solution stirred for 2 hours and was diluted with dichloromethane and was washed with saturated bicarbonate and dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 528 mg of the title compound (79%).

FABMS (NOBA) M + Na calcd for $C_{48}H_{61}NO_{17}S_2Na$ 1010. Found: 1010.

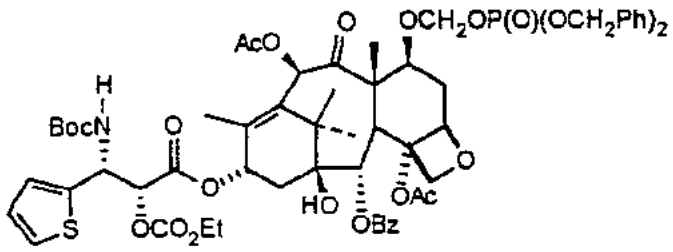
IR(film) 3510, 3440, 1752, 1720, 1370, 1244, 1198, 1170, 1026, 988, 756 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.58 (m, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.26 (m, 1H), 6.99 (, 2H), 6.55 (s, 1H), 6.23 (t, J = 9.0 Hz, 1H), 5.68 (d, J = 6.9 Hz, 2H), 5.33 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 2.4 Hz, 1H), 4.94 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 4.33-4.08 (m, 5H), 3.88 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.40 (s, 3H), 2.40 - 2.20 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.69 (s, 1H), 1.60 (s, 1H), 1.33 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 169.7, 169.1, 167.5, 167.1, 154.0, 140.9, 133.6, 132.9, 130.2, 129.2,

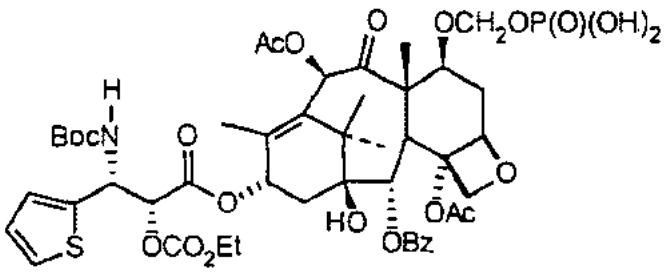
128.7, 127.2, 125.4, 125.3, 83.9, 81.2, 80.6, 78.8, 76.9, 76.0, 75.7, 74.7, 74.2, 72.8, 72.0, 65.2, 57.4, 50.9, 47.1, 43.3, 35.1, 33.0, 28.1, 26.4, 22.7, 21.2, 20.9, 15.1, 14.5, 14.1, 10.9.

(c) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-dibenzylphosphonooxymethylpaclitaxel



To a solution of the product of step (b) (516 mg, 0.522 mmol) in 15 mL of anhydrous THF was added 530 mg of 4A sieves, dibenzylphosphate (576 mg, 2.09 mmol) and recrystalized NIS (136 mg, 0.604 mmol). To this solution was added silver trifluoromethanesulfonate (50 mg, 0.194 mmol) and the solution stirred for 1 hour. The solution was filtered through Celite and diluted with ethyl acetate and washed with 10% NaS_2O_8, saturated bicarbonate and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (15% acetonitrile/chloroform) to give 535 mg of the title compound (84%).
FABMS (NOBA) M+Na calcd for $C_{61}H_{72}NO_{21}PSNa$ 1240. Found: 1240.
IR(film) 3424 (br), 1750, 1722, 1370, 1244, 1016, 1000, 944 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.0 Hz, 2H), 7.58 (m, 1H), 7.47 (t, J=7.5 Hz, 2H), 7.28 (m, 11H), 6.99 (m, 2H), 6.33 (s, 1H), 6.22 (t, J=7.8 Hz, 1H), 5.66 (m, 2H), 5.39 (t, J=6.6 Hz, 1H), 5.34 (d, J=12 Hz, 1H), 5.22 (d, J=2.4 Hz, 1H), 5.01 (dd, J=8.1, 6.0 Hz, 5H), 4.86 (d, J=7.8 Hz, 1H), 4.29-4.08 (m, 5H), 3.85 (d, J=6.6 Hz, 1H), 2.76 (m, 1H), 2.39 (s, 3H), 2.35-2.16 (m, 2H), 2.16 (s, 3H), 1.97 (s, 4H), 1.69 (s, 4H), 1.33 (s, 9H), 1.30 (t, J=7.2 Hz, 3H), 1.20 (s, 3H), 1.17 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 197.4, 165.4, 164.9, 163.3, 162.7, 150.6, 149.7, 136.7, 136.0, 129.4, 128.6, 125.9, 124.7, 124.3, 124.2, 124.1, 123.6, 122.9, 121.1, 121.0, 89.4, 79.8, 77.3, 76.5, 76.3, 74.4, 72.0, 70.7, 70.3, 67.7, 64.9, 64.9, 60.9, 52.7, 46.5, 42.3, 38.9, 30.7, 23.8, 22.0, 18.3, 17.0, 16.4, 10.3, 9.8, 6.2.

(d) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

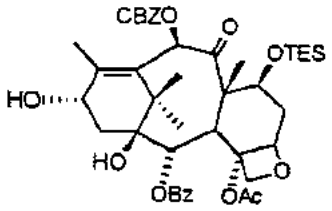


To a solution of the product of step (c) (512 mg, 0.42 mmol) in 30 mL of ethyl acetate was added 53 mg of Pd on carbon (10%) and the solution stirred under an atmosphere of H_2 for 3 hours. The catalyst was removed by filtratation through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in 2 mL of ethyl acetate and triethananolamine added (4.0 mL, 0.1M in ethyl acetate, 0.40mmol). The solution was concentrated and the residue was chromatographed over C_{18} (40% acetonitrile/water) and lyophilized to give 280 mg of the phosphate triethanolamine salt (56%). HPLC analysis showed the purity of the salt to be 96%.

FABMS (NOBA) M + Na calcd for $C_{47}H_{66}NO_{21}PS$ 1060. Found: 1060.
IR(KBr) 3422 (br), 1750, 1720, 1372, 1246, 1162, 1096, 1068, 1000 cm^{-1}
^1H NMR (d_6 acetone/D_2O, 300 MHz) δ 8.06 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.38 (d, J = 4.2 Hz, 1H), 7.16 (d, J = 3.5 Hz, 1H), 7.01 (dd, J = 5.1, 3.6 Hz, 1H), 6.37 (s, 1H), 6.11 (t, J = 8.7 Hz, 1H), 5.61 (d, J = 6.9 Hz, 1H), 5.60 (s, 1H), 5.26 (d, J = 4.5 Hz, 1H), 5.14 (d, J = 6.6 Hz, 1H), 5.00 (d, J = 8.4 Hz, 1H), 4.86 (dd, J = 12.0, 6.3 Hz, 1H), 4.17 (m, 5H), 4.00 (s, 7H), 3.92 (t, J = 4.8 Hz, 6H), 3.84 (d, J = 6.9 Hz, 1H), 3.48 (t, J = 5.4 Hz, 6H), 2.94 (m, 1H), 2.42 (s, 3H), 2.36 (m, 1H), 2.27 (m, 1H), 2.15 (s, 3H), 1.95 (s, 4H), 1.66 (s, 3H), 1.30 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.14 (s, 6H).

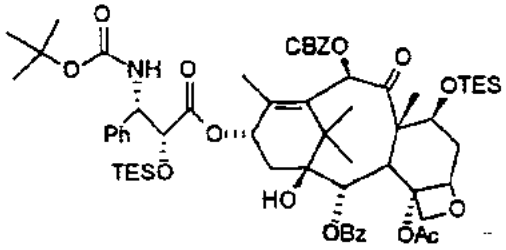
Example 9. 10-Desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel

(a) preparation of 10-desacetyl-10-O-benzyloxycarbonyl-7-O-triethylsilylbaccatin III



To a dry flask under an argon atmosphere containing 7-O-triethylsilyl-10-desacetyl baccatin III (2.093g, 3.177 mmol) was added dry THF (30 mL) and cooled to -70°C. To this was added 1.6 M n-butyllithium (2.38mL, 3.81mmol) in a dropwise fashion. After stirring for 15 min, benzyl chloroformate (0.91mL, 6.35mmol) was added dropwise. The resulting mixture was stirred for 3 h with gradual warming to ambient temperature. The reaction was quenched with 25 mL of sat. NH_4Cl, washed with brine, and dried with $MgSO_4$. Flash chromatography (silica gel, 30-45% ethyl acetate/hexane) furnished 2.24g (89%) of the title compound as a white foam.
^1H NMR (300MHz, $CDCl_3$) δ 8.10 (d, J = 8.0, 2H); 7.63-7.58 (m, 1H) 7.47 (t, J = 8.0, 2H); 7.41-7.26 (m, 5H); 6.29 (s, 1H); 5.61 (d, J = 7.0, 1H); 5.20 (q, J = 12.2, 2H); 4.96 (d, J = 9.0, 1H); 4.87-4.84 (m, 1H); 4.48 (dd, J = 6.7, J = 10.4, 1H); 4.30 (d, J = 8.5, 1H); 4.14 (d, J = 8.5, 1H); 3.84 (d, J = 7.0, 1H); 2.58-2.48 (m, 1H); 2.29 (m, 4H); 2.20 (s, 3H); 2.03 (d, J = 5.0, 1H); 1.92-1.83 (m, 1H); 1.68 (s, 3H); 1.17 (s, 3H); 1.04 (s, 3H); 0.91 (t, J = 7.5, 9H); 0.57 (q, J = 7.4, 6H).

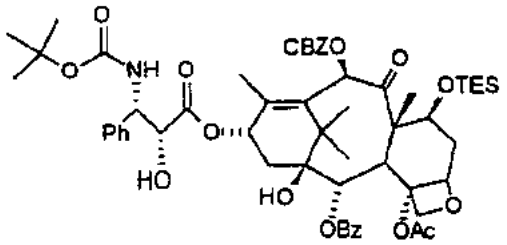
(b) preparation of 10-desacetyl-10-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-2',7-bis-O-triethylsilylpaclitaxel



To a dry flask containing the product of step (a) (3.50g, 4.42mmol) was added a small amount of toluene and the solution was then concentrated under vacuum. This flask was placed under an argon atmosphere and 100 mL of dry THF was added. The flask was cooled to -70°C and 1.0 M lithium hexamethyldisilazide (6.19mL, 6.19mmol) was added in a dropwise fashion. After stirring for 20 min, a solution of (3R,4S)-1-(t-butyloxycarbonyl)-4-phenyl-3-triethylsilyloxy-2-azetidinone (2.58g, 7.07mmol) in 10 mL dry THF was added dropwise. The reaction mixture was stirred for 3.5 h, gradually warming to ambient temperature. It was then

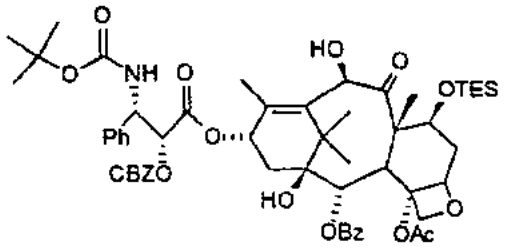
quenched with 70 mL of sat. NH_4Cl, washed with brine and dried with $MgSO_4$. Flash chromatography (silica gel, 5-15% ethyl acetate/hexanes) provided 5.12g (99%,) of the title compound as a white foam.
^1H NMR (300MHz, $CDCl_3$) δ 8.11 (d, J=8.0, 2H); 7.60-7.58 (m, 1H); 7.48 (t, J=8.0, 2H); 7.24 -7.26 (m, 10H); 6.32-6.26 (m, 2H); 5.69 (d, J=7.0, 1H); 5.47 (bd, J=9.7, 1H); 5.31-5.10 (m, 3H); 4.94 (d, J=8.5, 1H); 4.56 (s, 1H); 4.46 (dd, J=6.9, J=10.6, 1H); 4.31 (d, J=8.3, 1H); 4.17 (d, J=8.3, 1H); 3.81 (d, J=7.0, 1H); 2.53 (s, 3H); 2.48-2.33 (m, 1H); 2.22-2.17 (m, 1H); 2.09 (s, 3H); 1.95-1.86 (m, 1H); 1.70 (s, 3H); 1.65 (s, 1H); 1.52 (s, 1H); 1.30 (s, 9H); 1.26-1.19 (m, 6H); 0.94-0.87 (m, 9H); 0.80-0.75 (m, 9H); 0.61-0.53 (m, 6H); 0.48-0.30 (m, 6H).

(c) preparation of 10-desacetyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-triethylsilylpaclitaxel



The product of step (b) (5.12 g, 4.40 mmol) was dissolved into 100 mL of ethyl acetate, transferred to a Parr bottle and placed under a blanket of argon. To this was added 10% palladium on carbon (2.4g) and the reaction mixtre was placed on a Parr hydrogenation apparatus (55psi) for a period of 8 h. The reaction mixture was filtered through a plug of Celite and concentrated. Flash chromatography (silica gel, 15-20% ethyl acetate/hexane) provided 3.24g (79%) of the title compound as a white foam. Hydrolysis of the 2'-triethylsilyl group of the product of step (b) was a result of trace acidic residues in the Parr equipment.
^1H NMR (300MHz, $CDCl_3$) δ 8.10 (d,J=8.0, 2H); 7.63-7.58 (m, 1H); 7.49 (d, J=8.0, 2H); 7.39-7.26 (m, 5H); 6.27-6.17(m, 1H); 5.64 (d, J=7.2); 5.42(d, J=9.4, 1H); 5.28-5.25 (m, 1H); 5.12 (s, 1H); 4.92 (d, J=8.6, 1H); 4.62 (bs, 1H); 4.38-4.28 (m, 3H); 4.17 (d, J=8.5, 1H); 3.85 (d, J=6.7, 1H); 3.36 (d, J=5.3, 1H); 2.49-2.40 (m, 1H); 2.36 (s, 3H);
2.25 (bd, J=8.7, 2H); 1.99-1.91 (m, 1H); 1.85 (s, 3H); 1.74 (s, 3H); 1.69 (s, 1H), 1.67 (s, 1H); 1.35 (s, 9H); 1.22 (s, 3H); 1.11 (s, 3H); 0.93 (t, J=7.5 9H); 0.61-0.49 (m, 6H).

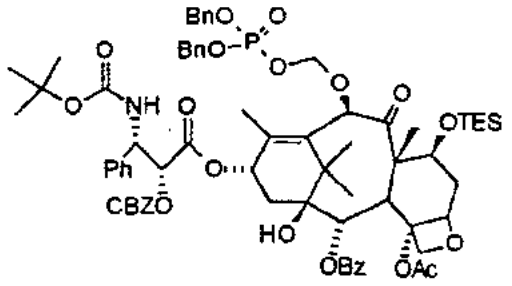
(d) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-triethylsilylpaclitaxel



To a flask containing the product of step (c) (3.24g, 3.51mmol) was added 30 mL of dry dichloromethane. The flask was placed under argon and cooled to 0°C. N,N-diisopropylethylamine (1.22 mL, 7.02 mmol) was added to the reaction mixture, followed by addition of benzyl chloroformate (1.00mL, 7.02 mmol) in a dropwise manner. After 15 min, the cooling bath was removed and the reaction allowed to stir at ambient temperature for 7 h. The mixture was quenched with 30 mL sat. NH_4Cl, washed with brine and dried with $MgSO_4$. Flash chromatography (silica gel, 7-20% ethyl acetate/hexane) provided 3.24g (89%) of the title compound as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ 8.10 (d, J=8.0, 2H); 7.62-7.57 (m, 1H); 7.48 (t, J=8.0, 2H); 7.40-7.26 (m, 10H); 6.33-6.27 (m, 1H); 5.66 (d, J=7.0, 1H); 5.49-5.42 (m, 2H); 5.31 (s, 1H); 5.22-5.13 (m , 3H); 4.93 (d, J-9.4, 1H); 4.38 (dd, J=6.5, J=10.7, 1H); 4.34-4.28 (m, 2H); 4.18 (d J=8.3, 1H); 3.90 (d, J=6.7, 1H); 2.52-2.30 (m, 4H); 2.24-2.20 (m, 1H); 1.97-1.87 (m, 3H); 1.74 (s, 3H); 1.59 (s, 3H); 1.32 (s, 9H); 1.26, (s, 3H); 1.11 (s, 3H); 0.96-0.88 (m, 9H); 0.61-0.48 (m, 6H).

(e) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)-7-O-triethylsilylpaclitaxel



The product of step (d) was dissolved into 13.5 mL (54%) of DMSO, 8.75 mL (35%) acetic anhydride and 2.75 mL (11%) glacial acetic acid and placed under an atmosphere of argon. The reaction mixture stirred for 56 h, after which it was diluted with ethyl acetate to a volumn of 60 mL. The solution was washed with sat. $NaHCO_3$ until neutral by pH paper and then washed with brine. The organic fraction was dried with $MgSO_4$ and concentrated. Flash chromatography with 15-20% EtOAc/hexane provided 3.12g of crude white foam with the desired thiomethyl acetal product (i.e. 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(methylthiomethyl)-7-O-triethylsilylpaclitaxel accounting for 70% of the material by NMR.

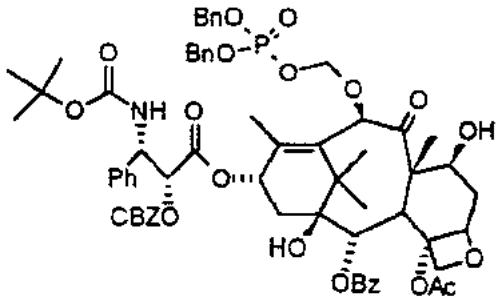
The above crude mixture (3.12g) was then dissolved in 1,2-dichloroethane (61 mL) and placed under a blanket of argon. 4Å powdered molecular sieves (3.12 g) were added and the resulting heterogeneous mixture was stirred vigorously. To this was added a solution of recrystallized N-iodosuccinimide (0.830 g, 3.69 mmol) and dibenzyl phosphate (1.027 g, 3.69 mmol) in dry THF (46 mL) via cannula. The resulting mixture was stirred for 5 h, filtered through a plug of Celite, and diluted to a volume of 250 mL with ethyl acetate . It was washed with (2 x 125mL) of cold 2% $NaHSO_3$, cold 6% $NaHCO_3$ (2 x 125 mL) and brine. The organic phase was dried with $MgSO_4$ and concentrated. Flash chromatography (silica gel, 25-35% ethyl acetate/hexane) provided 1.52g (40%) of title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.0, 2H); 7.59-7.55 (m, 1H); 7.46 (t, J=7.2, 2H); 7.38-7.25 (m, 20H); 6.30 (t, J=8.5, 1H); 5.65 (d, J=6.8, 1H); 5.49-5.39 (m, 4H); 5.32 (s, 1H); 5.18-4.19 (m, 4H); 4.93 (d, J=9.2, 1H); 4.44 (dd, J=6.6, J=10.2, 1H); 4.31 (d, J=8.4, 1H); 4.16 (d, J=8.5, 1H); 3.80 (d, J=6.9, 1H); 2.69-2.39, (m, 4H), 2.33-2.23 (m, 3H); 2.03 (s, 3H); 1.90 (t, J=12.6, 1H); 1.68-1.63 (m, 6H); 1.28 (s, 9H); 1.16-1.10 (m, 6H); 0.93 (t, J=7.4, 9H); 0.55 (q, J=7.8, 6H).

^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 204.1, 169.7, 167.9, 167.1, 151.1, 140.7, 135.7, 133.6, 130.2, 129.2, 128.9, 128.8, 128. 7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 126.4, 90.4, 84.2, 81.1, 80.4, 79.3, 78.8, 74.9, 72.8, 72.0, 70.5, 69.2, 69.1, 69.0, 58.1, 46.8, 43.2, 37.1, 35.0, 28.1, 26.5, 22.8, 21.0, 14.1, 10.0, 6.9, 5.5.

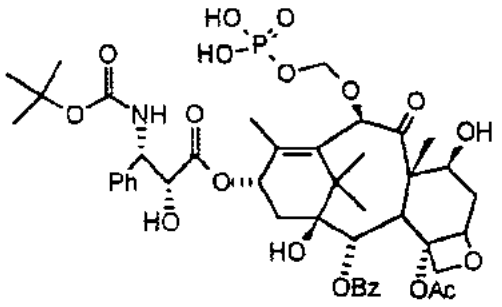
M. S. (FAB) m/z+: 1345

(f) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)paclitaxel



A solution of the product of step (e) (50.8 mg, 0.038 mmol) in dry THF (2.5 mL), under argon was cooled to -40°C. To this solution was added tetrabutylammonium fluoride (0.057 mL, 0.057 mmol) in THF (1.0 M) in a dropwise manner. The reaction mixture stirred for 1.5 h with gradual warming to -20°C. The mixture was quenched with 15 mL sat. NH_4Cl and diluted with 30 mL EtOAc. The organic phase was washed with 2 x 15mL $NaHCO_3$, and brine. It was dried with $MgSO_4$ and concentrated. Preparative layer chromatography (silica gel, 50% ethyl acetate/hexane) provided 36 mg (77%) of title compound as a white powder.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J=8.5, 2H); 7.60-7.55 (m, 1H); 7.49-7.44 (m, 2H); 7.36-7.18 (m, 20H); 6.27-6.22 (m, 1H); 5.78 (s, 1H); 5.67 (d, J=7.0, 1H); 5.44-5.34 (m, 3H); 5.27 (d, J=2.2, 1H); 5.24-5.05 (m, 4H); 5.01-4.91 (m, 4H); 4.39-4.28 (m, 2H); 4.17 (d, J=8.2, 1H); 3.87 (d, J=7.0, 1H); 2.58-2.51 (m, 1H); 2.41 (s, 3H); 2.40-2.18 (m, 2H), 2.00-1.87 (m, 5H); 1.73-1.69 (m, 4H); 1.30 (s, 9H); 1.22-1.15 (m, 6H).
M.S. (FAB) m/z+: 1231

(g) preparation of 10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)-paclitaxel triethanolamine salt



A 500 mL Parr bottle was charged with 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)paclitaxel (264.9mg, 0.215mmol) and ethyl acetate (20 mL). The flask was then flushed with argon and 10% Pd/C (318mg) was added. The resulting mixture was placed on a Parr apparatus with a 55 pounds per square inch (psi) hydrogen atmosphere. The reaction was monitored by HPLC (70:30 CH_3CN/Q8 buffer pH 6.0, 1.00 mL/min., Zorbax C-18 column, 25.0 cm, λ=230 nm) until no starting material was evident (12.5 hours). The mixture was filtered through a plug of Celite, which was washed with ethyl acetate and a small amount of dichloromethane. The resulting filtrate was concentrated and the residue was taken up in dichloromethane (5 mL). Addition of hexane caused a white precipitate to form, of which 140.3mg of the free acid (80% purity by HPLC) was isolated as a white solid. This material was passed directly on to the next step.
To a flask containing the above free acid (140mg, 0.153mmol) was added dichloromethane (10 mL). The resulting solution was then treated with 0.100 M triethanolamine solution in ethyl acetate (1.16 mL, 0.116mmol) which caused the solution to become turbid. Approximately 2 mL of hexane was added and the

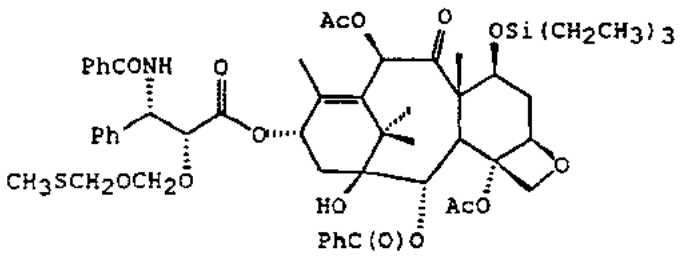
mixture was placed at -20 °C overnight. The resulting precipitate was filtered through a 4.0-5.5 μm fritted glass funnel. The solid was removed and placed under vacuum for 4 h to yield 69.9mg (42%) the title triethanolamine salt as a gray powder, which was determined to be 95-96% pure by HPLC analysis. (T_R = 2.05 min, 70:30 CH_3CN/QB Buffer pH 6.0, 1.00 mL/min, Zorbax C-18 25.0 cm, λ = 230 nm).

^{1}H-NMR (d_6-acetone/D_2O, 300 MHz): δ 8.03 (d, J = 7.4, 2H); 7.65 (t, J = 7.3, 1H); 7.54 (t, J = 7.6, 2H); 7.42-7.33 (m, 5H); 7.21 (t, J = 7.0, 1H); 6.09 (t, J = 9.0, 1H); 5.81 (s, 1H); 5.59 (d, J = 7.0, 1H); 5.12 (bs, 2H); 4.93 (d, J = 8.4, 2H), 4.56 (d, J = 4.9, 1H); 4.31-4.26 (m, 1H); 4.11 (s, 2H); 3.41-3.37 (m, 6H); 2.42-2.32 (m, 5H); 2.15 (bs, 1H); 1.97 (s, 3H); 1.77-1.64 (m, 2H); 1.58 (s, 3H); 1.13 (s, 9H); 1.15-1.07 (m, 6H). ^{13}C NMR (d_6-acetone, D_2O, 75.6 MHz): δ 171.6, 166.9, 156.6, 141.8, 135.1, 134.2, 131.0, 130.7,129.4, 129.3, 128.4, 128.1, 88.3, 85.4, 81.9, 79.7, 78.6, 78.1, 76.8, 76.0, 74.8, 71.9, 71.2, 47.4, 44.0, 37.1, 36.3, 28.5, 27.0, 23.1, 22.0, 14.7, 10.4.

HRMS: MNa^+, 940.3142 (Calculated for $C_{44}H_{55}NO_{18}PNa$ = 940.3133)

Example 10. 2'-O-Phosphonooxymethoxymethylpaclitaxel

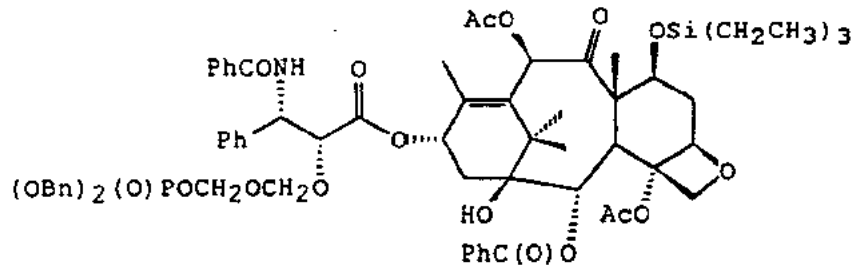
(a) preparation of 2'-O-(methylthiomethoxymethyl)-7-O-triethysilylpaclitaxel



To a solution of 7-O-triethylsilylpaclitaxel (70.0 mg, 72.2 mmol), bis(methylthiomethyl)ether (90 mg, 72.2 mmol), molecular selves (70 mg), and N-iodosuccinimide (160 mg, 72.2 mmol) in THF (2.0 ml) at room temperature was added silver triflate (5.0 mg, 19.5 mmol) and the resulting solution was stirred for 2 h. The reaction mixture was then diluted with ethyl acetate and filtered through a pad of celite. The filtrate was washed with saturated aqueous sodium bicarbonate solution, followed by a 1:1 (v:v) mixture of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution and finally brine. The organics were then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (3:1, hexanes:ethyl acetate) to provide 22.0 mg (29%) of the title compound as a white solid:

^{1}H NMR (300MHz, CDCl3) δ 8.12-7.20 (15H, m), 7.04 (1H, d, J = 8.9 Hz), 6.41 (1H, s), 6.25 (1H, m), 5.81 (1H, dd, J = 8.9, 2.4 Hz), 5.68 (1H, d, J = 7.0 Hz), 4.93 (1H, d, 8.0 Hz), 4.79 (2H, m), 4.71 (1H, d, 2.4 Hz), 4.45 (1H, dd, J = 10.5, 6.6 Hz), 4.30 (1H, d, J = 8.3 Hz), 4.28 (1H, d, J = 11.7 Hz), 4.17 (1H, d, J = 8.3 Hz), 4.04 (1H, d, J = 11.7 Hz), 3.80 (1H, d, J = 6.9 Hz), 2.48-1.13 (25H, m, incl. singlets at 2.51, 2.13, 2.05, 2.01, 1.69, 1.19, 1.16), 0.98-0.85 (9H, m), 0.65-0.50 (6H, m).

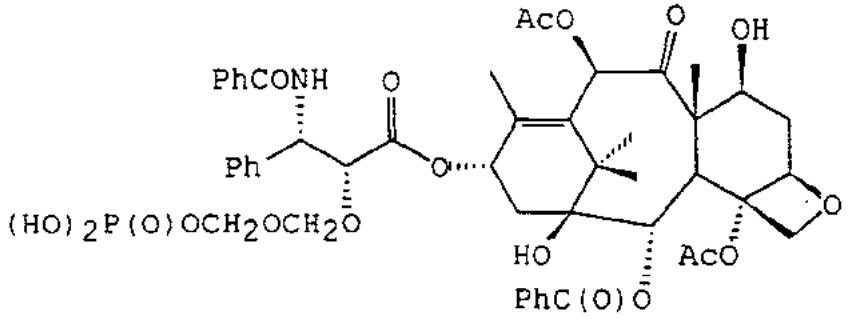
(b) preparation of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-triethylsilylpaclitaxel



To a solution of the product obtained in step (a) (15 mg, 0.0141 mmol) and molecular sieves (15 mg) in THF (0.5 ml) at room temperature was added dibenzyl phosphate (20.0 mg, 0.089 mmol) followed by N-iodosuccinimide (4.2 mg, 0.0187 mmol) and the solution was stirred for 1h. A TLC analysis of the reaction mixture at this time indicated the presence of starting material only. Silver triflate (5.0 mg, 0.019 mmol) was then added in three portions over 2h and the reaction was stirred for an additional 1h. The reaction mixture was then diluted with ethyl acetate and the resulting solution filtered through a pad of celite. The filtrate was treated with a 1:1 (v:v) solution of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution. The organic extract was then washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (1:1, hexanes:ethyl acetate) to provide 5.0 mg (33%) of the title compound:

^{1}H NMR (300 MHz, CDCl3) δ 8.08-7.16 (25H, m), 7.18 (1H, d, J = 8.8 Hz), 6.41 (1H, s), 6.21(1H, m), 5.82 (1H, dd, J = 9.0, 3.1 Hz), 5.66 (1H, d, 7.0 Hz), 5.01-4.65 (10H, m), 4.56 (1H, dd, J = 14.7, 5.6 Hz), 4.43(1H, dd, J = 10.4, 6.7 Hz), 4.29 (1H, d, J = 8.3 Hz), 4.16 (1H, d, J = 8.3 Hz), 3.78 (1H, d, J = 7.0 Hz), 2.60-1.13 (22H, m, incl. singlets at 2.49, 2.15, 1.93, 1.66, 1.15, 1.13, 3H each), 0.95-0.84 (9H, m), 0.63-0.45 (6H,m).

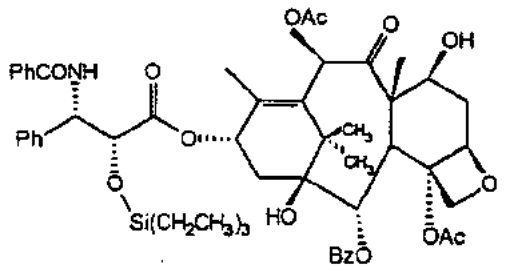
(c) preparation of 2'-O-phosphonooxymethoxymethylpaclitaxel



The product of step (b) is treated with tetrabutylammonium fluoride according to the procedure given in Example 9(f) to remove the 7-O-triethylsilyl protecting group. The compound thus obtained is subject to catalytic hydrogenation according to the procedure described in previous examples to provide the title compound.

Example 11. 2'-O-Phosphonooxymethoxymethylpaclitaxel (Alternate route)

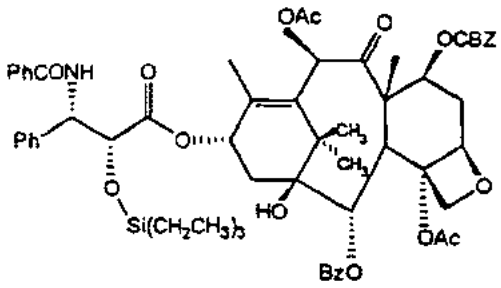
(a) preparation of 2'-O-triethylsilylpaclitaxel



To a solution of paclitaxel (20.0 g, 0.0234 mol) and imidazole (3.59 g, 0,052 mol) in 150 mL of DMF (dimethylformamide) at 0° C was added triethylsilyl chloride (6.0 mL, 0.053 mol) in 2.0 mL quantities over 20 min. The reaction mixture was then stirred at 0° C for 1h. The mixture was then diluted with ethyl acetate and saturated aqueous ammonium chloride. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo to provide a yellow oil. Purification of the crude product via flash chromatography (hexanes: ethyl acetate: 1:3 then 1:1) provided 21.07 g (98% yield) of the desired title compound as a colorless white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (2H, m), 7.70 (2H, m), 7.65-7.30 (11H, m) 7.15 (1H, d, J = 8.9 Hz), 6.30 (1H, s), 6.25 (1H, m), 6.70-6.10 (2H, m), 4.94 (1H, d, J = 7.9 Hz), 4.67 (1H, d, 2.0 Hz), 4.40 (1H, m), 4.29 (1H, d, J = 8.4 Hz), 4.18 (1H, d, J = 8.4 Hz), 3.81 (1H, d, J = 7.1 Hz), 2.65-1.10 (22H, including singlets at 2.55, 2.20, 1.88, 1.69, 1.22, 1.13, 3H each).

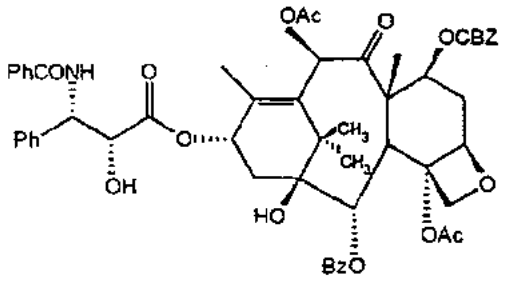
(b) preparation of 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel



Butyllithium (1.6 M in hexanes, 12.9 mL, 8.06 mmol) was added dropwise over 10 min to a solution of 2'-O-triethylsilylpaclitaxel (22.3 g, 24.1 mmol) in THF (250 mL) cooled to -50° C. The resulting solution was stirred for 20 min and the temperature maintained between -50° C and -35° C. The reaction mixture was then cooled to -50° C and benzyl chloroformate (5.08 mL, 29.8 mmol) was added dropwise over 5 min. The reaction mixture was maintained at -40° C for 30 min then equilibrated to 0° C over approximately 30 min. The mixture was then diluted with ethyl acetate and saturated aqueous ammonium chloride and the resulting organic layer washed with brine, dried over sodium sulfate and concentrated in vacuo. A ^{1}H-NMR analysis of the crude reaction mixture showed the presence of desired 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel as well as 2'-O-triethylsilyl-7-epihydroxypaclitaxel (3 :1 ratio, respectively). This product mixture was used in the next step without further purification and the isomers subsequently separated. An analytical sample of the major product 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel was purified via flash chromatography; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (2H, m), 7.72 (1H, m), 7.65-7.27 (1H, d, J = 8.8 Hz), 6.41 (1H, m), 6.20 (1H, m), 5.72-5.65 (2H, m), 5.52 (1H, m), 5.24 (1H, d, J = 12.3 Hz), 5.16 (1H, d, J = 12.3 Hz), 4.95 (1H, d, J = 8.7 Hz), 4.69 (1H, s), 4.35 (1H, d, J = 8.3 Hz), 4.25 (1H, d, J = 8.3 Hz), 3.94 (1H,

d, J = 6.8 Hz), 2.70-1.12 (22H, including singlets at 2.54, 2.14, 2.01, 1.80, 1.20, 1.15, 3H each), 0.81-0.73 (9H, m), 0.55-0.31 (6H, m).

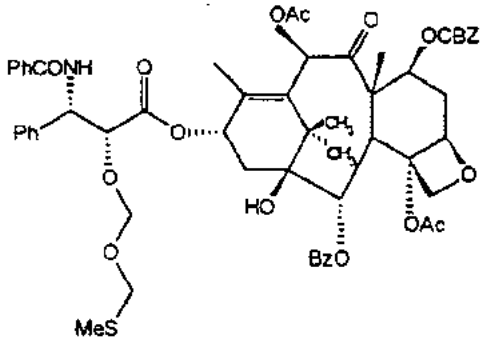
(c) preparation of 7-O-benzyloxycarbonylpaclitaxel



Hydrochloric acid (6N, 1.0 mL, 6.0 mmol) was added to a solution the product from Step (b) (24.0 g, 22.6 mmol) in acetonitrile (250 mL) cooled to 0° C. After 10 min a TLC analysis (hexanes : ethyl acetate, 1 : 1) indicated the reaction was complete. The reaction mixture was diluted with saturated aqueous sodium bicarbonate followed by ethyl acetate and the organic layer was removed, washed with brine, dried using sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (hexanes : ethyl acetate, 1:3, then 1:1) to provide 11.4 g (48% over 2 steps) of the title compound and 4.8 g (20%) of 7-epihydroxypaclitaxel.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (2H, m), 7.71 (2H, m), 7.65-7.27 (16H, m), 7.10 (1H, d, 8.9 Hz), 6.39 (1H, s), 6.16 (1H, m), 5.81 (1H, d, J = 8.9, 2.4 Hz), 5.65 (1 H, d, J = 6.9 Hz), 5.49 (1H, dd, J = 10.6, 7.2 Hz), 5.20 (1H, d, J = 11.9 Hz), 5.12 (1H, d, J = 11.9), 4.91 (1H, d, J = 8.4 Hz), 4.78 (1H, m), 4.30 (1H, d, J = 8.4 Hz), 4.15 (1H, d, J = 8.4 Hz), 3.91 (1H, d, J = 6.8 Hz), 3.69 (1H, d, J = 4.9 Hz), 2.65-1.10 (22H, including singlets at 2.39, 2.18, 1.81, 1.75, 1.21, 1.15, 3H each).

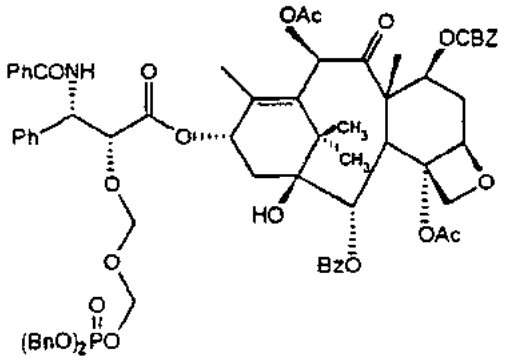
(d) preparation of 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel



Silver triflate (300 mg, 1.17 mmol) was added to a solution 7-O-benzyloxycarbonylpaclitaxel (5.53 g, 5.71 mmol), 1, 1'-dithiomethyldimethyl ether (7.8 g, 57.1 mmol), N-iodosuccinimide (6.35 g, 28.3 mmol) and oven dried, powdered molecular sieves (5.0 g) in THF (110 mL) at room temperature. A TLC analysis (hexanes : ethyl acetate, 1:1) of the reaction mixture after 20 min indicated the conversion of approxiately 40% of the starting material to a higher running product. Silver triflate (150 mg, 0.585 mmol) was then added and the reaction was monitored by TLC which indicated after 30 min the reaction was appoximately 65% complete. The mixture was diluted with ethyl acetate (100 mL), filtered using a pad of celite and the filtrate was poured into a separatory funnel containing 200 mL of a saturated aqueous solution of sodium bicarbonate and 50 mL of a 5% aqueous sodium thiosulfate solution. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash

chromatography (hexanes : ethyl acetate, gradient elution 4:1 to 3:2) to provide 3.0 g (54% yield) of the title product as a light yellow solid.
^{1}H-NMR (300 MHz, CDCL3) δ 8.10 (2H, m), 7.74 (2H, m), 7.66-7.25 (18H, m), 7.05 (1H, d, J = 8.9 Hz), 6.40 (1H, s), 6.26 (1H, m), 5.77 (1H, dd, J = 8.8, 2.5 Hz), 5.71 (1H, d, J = 6.9 Hz), 5.51 (1H, dd, J = 10.6, 7.1 Hz), 5.21 (1H, d, J = 11.9 Hz), 5.14 (1 H, d, J = 11.9 Hz), 4.92 (1H, m), 4.79 (2H, m), 4.68 (1H, d, J = 2.5 Hz), 4.31 (1H, d, J = 11.8 Hz), 4.30 (1H, d, J = 8.5 Hz), 4.16 (1H, d, J = 8.5 Hz), 4.10 (1H, d, J = 11.8 Hz), 3.93 (1H, d, J = 6.9 Hz), 2.65-1.10 (25H including singlets at 2.50, 2.15, 2.05, 1.74, 1.72, 1.20, 1.15, 3H each).

(e) preparation of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel



To a solution of 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel (1.06 g, 1.07 mmol) and oven dried, powdered molecular sieves (1.0 g) in THF (20 mL) at room temperature was added dibenzyl phosphate (1.49 g, 5.30 mmol) followed immediately by N-iodosuccinimide (2.65 g, 1.18 mmol). A TLC analysis (hexanes : ethyl acetate 1:1) of the reaction mixture after 2.5 h indicated the reaction was approximately 60% complete. N-iodosuccinimide (175 mg, 0.78 mmol) was then added and the reaction stirred for an additional 30 min, after which time a TLC analysis indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate (50 mL) and filtered using a pad of celite. The filtrate was poured into a separatory funnel containing 100 mL of a saturated aqueous solution of sodium bicarbonate and 20 mL of a 5% aqueous solution of sodium thiosulfate. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (hexanes: ethyl acetate, gradient elution, 3:1 to 1:1) to provide 750 mg (62% yield) of the desired title compound as a white solid.
^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.10 (2H, m), 7.79 (2H, m), 7.65-7.24 (26H, m), 7.10 (1H,m), 6.41 (1H, s), 6.20 (1H,m), 5.79 (1H, dd, J = 8.8, 3.6 Hz), 5.65 (1H, d, J = 7.0 Hz), 5.52 (1H,m), 5.20 (1H, d, J = 11.8 Hz), 5.11 (1H, d, J = 11.8 Hz), 5.04-4.85 (6H, m), 4.75-4.60 (4H, m), 4.30 (1H, d, 8.4 Hz), 4.15 (1H, d,J = 8.4 Hz), 3.92 (1H, d, J = 7.0 Hz) 2.65-1.10 (22 H including singlets at 2.48, 2.19, 1.95, 1.80, 1.20, 1.10, 3H each).

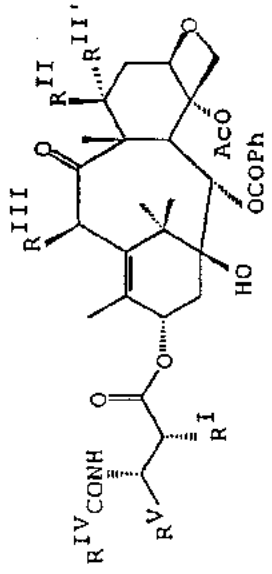
(f) preparation of 2'-O-phosphonooxymethoxymethylpaclitaxel triethanolamine salt

Palladium (10%) on carbon was added to a solution of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel (500 mg, 0.382 mmol) in ethly acetate (40 mL) housed in a Parr bottle. The vessel was affixed to a Parr apparatus and the reaction mixture subjected to hydrogen at 50 psi. The reaction mixture was shaken for 6.5 h, then filtered using a sintered glass funnel. Triethanolamine (0.1 N in ethyl acetate, 4.0 mL) was added to this filtrate and the resulting solution was concentrated in vacuo. The crude solid was suspended in approximately 5.0 mL of ethyl acetate and the solvent decanted. This process was repeated three times and the resulting title triethanolamine salt (300 mg) was obtained with purity of 87% as determined by HPLC analysis. Further purification of this compound via C18 chromatography (water : acetonitrile, 3:1) provided the desired title compound (120 mg, 34%) at 95% purity by HPLC.
^{1}H-NMR (300MHz, CD_3COCD_3, D_2O) δ 9.05 (1H, d, J = 8.7 Hz), 8.15-7.12 (21H, m), 6.40 (1H,m), 6.05 (1H, m), 5.69-5.55 (2H, m), 5.01-4.85 (6H, m), 4.35 (1H, m), 4.14 (2H, m), 3.96-3.85 (6H, m), 3.25 (1H, d, J = 7.1

Hz), 3.30-3.15 (6H, m) 2.50-1.04 (22H, including singlets at 2.49, 2.15, 2.05, 1.81, 1.60, 3H each).

Additional Examples

The general procedures provided in the foregoing examples and descriptions are followed in the preparation of the following compounds within the scope of formula (A) of the present invention.



R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	Ph	4- F-Ph- 4-CH_3-Ph 2-furanyl 2-thienyl $(CH_3)_2CH$- isobutanyl (2-methyl-1-propenyl) • c-C_3H_5- 3-furanyl 3-thienyl 2-propenyl

• "c" indicates cyclo

R^{I}	R^{II}	R^{II}	R^{III}	R^{IV}	R^{V}
$-OCH_2OP(O)(OH)_2$	H	OH	AcO	Ph	4-CF_3-Ph- 2-furanyl $(CH_3)_2CH$- 2-thienyl isobutenyl cyclopropyl 3-thienyl 3-furanyl 2-propenyl isopropyl
$CH_3CH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	Ph	4-F-Ph- 2-thienyl isopropyl 2-propenyl isobutenyl cyclopropyl 2-furanyl 3-furanyl 3-thienyl
$-OCH_2OP(O)(OH)_2$	H	OH H $CH_3CH_2OC(O)O$-	OH	$(CH_3)_3CO$-	Ph

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R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
OH $CH_3CH_2OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO$-	Ph
-$OCH_2OP(O)(OH)_2$	H	H $CH_3CH_2OC(O)O$-	AcO	Ph	Ph
OH $CH_3OC(O)O$- $CH_3CH_2OC(O)O$- $CH_3(CH_2)_2OC(O)O$- $CH_3(CH_2)_3OC(O)O$- $CCl_3CH_2OC(O)O$- $CH_3C(O)O$- $CH_3CH_2(O)O$- $CH_3(CH_2)_2C(O)O$- $CH_3(CH_2)_3C(O)O$- PhC(O)O- PhOC(O)O- $CH_2=CHCH_2OC(O)O$- $PhCH_2OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	Ph	Ph
OH	H	OH	-$OCH_2OP(O)(OH)_2$	Ph	Ph
OH	H	H	-$OCH_2OP(O)(OH)_2$	Ph	Ph
-$OCH_2OP(O)(OH)_2$	H	H	H	$(CH_3)_3CO$-	4-CH_3O-Ph

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R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3OC(O)O-$	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$CH_3CH_2OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3(CH_2)_2OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$CH_3(CH_2)_3OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CCl_3CH_2OC(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	R^{II}	R^{II}	R^{III}	R^{IV}	R^V
$CH_3C(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3CH_2(O)O$-	H	-$OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$CH_3(CH_2)_2C(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3(CH_2)_3C(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
PhC(O)O-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
PhOC(O)O-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$CH_2=CHCH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$PhCH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	R^{II}	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl 3-furanyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl 2-thienyl isopropyl
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl 3-furanyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl 2-thienyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	AcO	isopropyloxy	2-furanyl 3-furanyl 2-thienyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl isopropyl
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	isopropyloxy	2-furanyl 3-furanyl 2-thienyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
OH $CH_3OC(O)O$- $CH_3CH_2OC(O)O$- $CH_3(CH_2)_2OC(O)O$- $CH_3(CH_2)_3OC(O)O$- $CCl_3CH_2OC(O)O$- $CH_3C(O)O$- $CH_3CH_2(O)O$- $CH_3(CH_2)_2C(O)O$- $CH_3(CH_2)_3C(O)O$- $PhC(O)O$- $PhOC(O)O$- $CH_2=CHCH_2OC(O)O$- $PhCH_2OC(O)O$-	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	3-furanyl isobutenyl 2-propenyl 2-thienyl 3-thienyl cyclopropyl isopropyl

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R^{I}	R^{II}	R^{III}	R^{IV}	R^{V}
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	2-furanyl isobutenyl 2-thienyl 2-propenyl isopropyl cyclopropyl 3-thienyl 3-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

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R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
OH	H	$-OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph $CH_3CH_2CH_2CH_2O-$ isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph $CH_3CH_2CH_2CH_2O-$ isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	OMe	Ph $CH_3CH_2CH_2CH_2O-$ isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	OMe	Ph $CH_3CH_2CH_2CH_2O-$ isopropyloxy	2-furanyl

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R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph $CH_3CH_2CH_2CH_2O$- isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph $CH_3CH_2CH_2CH_2O$- isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO$- isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO$- isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO$- isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO$- isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO$- isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl

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R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$ isopropyloxy $CH_3CH_2CH_2CH_2O-$	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	isobutenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	isobutenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	isobutenyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	Ph	2-furanyll
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-propenyl

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R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	AcO	$(CH_3)_3CO-$	2-furanyl 2-thienyl 3-furanyl 3-thienyl isobutenyl 2-propenyl cyclopropyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	AcO	$CH_3CH_2CH_2CH_2O-$ isopropyloxy $(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	$-OCO_2CH_3$	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	OMe	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	-OC(O)Ph	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	Ph	Ph

R^I	R^{II}	R^{II}	R^{III}	R^{IV}	R^V
OH	F	H	$-OCH_2OP(O)(OH)_2$	$(CH_3)_3CO$-Ph	Ph
$-OCO_2CH_2CH_3$	F	H	$-OCH_2OP(O)(OH)_2$	$(CH_3)_3CO$-Ph	Ph
$-OCH_2OP(O)(OH)_2$	F	H	AcO	Ph	2-furanyl isobutenyl 3-furanyl 2-thienyl 2-propenyl cyclopropyl 3-thienyl isopropyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	AcO	Ph	2-furanyl isobutenyl 3-furanyl 2-thienyl 2-propenyl cyclopropyl 3-thienyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$-OCH_2OP(O)(OH)_2$	F	H	AcO	$(CH_3)_3CO-$	2-furanyl 3-thienyl isobutenyl 3-furanyl cyclopropyl 2-thienyl Ph 2-propenyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	AcO	$(CH_3)_3CO-$	2-furanyl 3-thienyl isobutenyl 3-furanyl cyclopropy 2-thienyl Ph 2-propenyl
$-OCH_2OP(O)(OH)_2$	F	H	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OP(O)(OH)_2$	F	H	OMe	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OP(O)(OH)_2$	F	H	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	OMe	$(CH_3)_3CO-$	2-furanyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	-OC(O)Ph	$(CH_3)_3CO$-	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	OH	$(CH_3)_3CO$-	Ph
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO$-	Ph
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO$-	Ph
OH	H	OH	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO$-	Ph
$-OCO_2CH_2CH_3$	H	OH	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO$-	Ph
OH	F	H	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO$-	Ph 2-furanyl 3-furanyl 2-thienyl 3-thienyl isobutenyl cyclopropyl 2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	F	H	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$	Ph 2-furanyl 3-furanyl 2-thienyl 3-thienyl isobutenyl cyclopropyl 2-propenyl

Claims

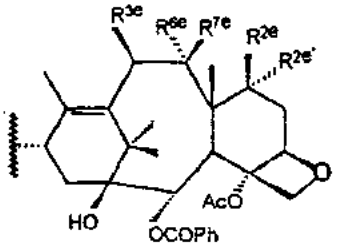
1. A compound having the formula

$$T\text{---}\left[OCH_2(OCH_2)_mOP(O)(OH)_2\right]_n \quad (A)$$

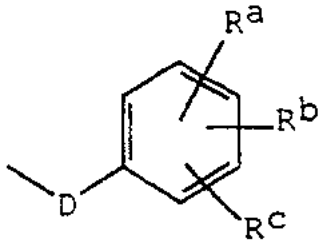
wherein
T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group;
m is 0 or an integer from 1 to 6 inclusive;
n is 1, 2 or 3;
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein said taxane moiety is further characterized as containing at least a C11-C12 double bond, C1 hydroxy, C2 benzoyloxy, C4 acetyloxy, C9 oxy, and C5-C20 oxetane.

3. A compound of claim 1 wherein said taxane moiety is derived from a residue having the formula

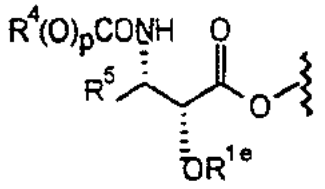


wherein $R^{2e'}$ is hydrogen and R^{2e} is hydrogen, hydroxy, - $OC(O)R^x$, or $-OC(O)OR^x$; or R^{2e} is hydrogen and $R^{2e'}$ is fluoro; R^{3e} is hydrogen, hydroxy, $-OC(O)R^x$, C_{1-6} alkyloxy, or $-OC(O)OR^x$; one of R^{6e} or R^{7e} is hydrogen and the other is hydroxy or $-C(O)OR^x$; or R^{6e} and R^{7e} together form an oxo group; R^x is C_{1-6} alkyl optionally substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or a radical of the formula



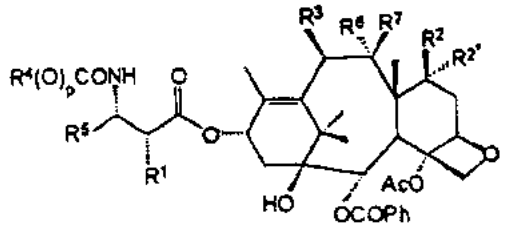
wherein D is a bond or C_{1-6} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-6} alkylamino, di-C_{1-6}alkylamino, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy.

4. A compound of any one of the preceding claims wherein said substituted 3-amino-2-hydroxypropanoyloxy group is derived from a residue having the formula



wherein
R^{1a} is hydrogen or $-C(O)R^x$, $-C(O)OR^x$;
R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-Z-R^6$;
Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl;
R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl, or heteroaryl;
p is 0 or 1; and
R^x is as defined previously.

5. A compound of claim 1 having the formula



wherein
R^1 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$;
$R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; or $R^{2'}$ is fluoro, and R^2 is hydrogen;
R^3 is hydrogen, hydroxy, acetoxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$;
one of R^6 or R^7 is hydrogen and the other is hydroxy, C_{1-6} alkenoyloxy, or $-OCH_2(OCH_2)_mOP(O)-(OH_2)$; or R^5 and R^7 together form an oxo group; with the proviso that at least one of R^1, R^2, R^3, R^6 or R^7 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$;
m is 0, 1 or 2;
R^4, R^5, R^x and p are as previously defined;
or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5 wherein $R^{2'}$ is hydrogen, and R^2 is $-OCH_2OP(O)(OH)_2$; or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6 wherein R^1 is hydroxy or $-OC(O)OR^x$; and R^x is as previously defined, in particular C_{1-6} alkyl.

8. A compound of claim 7 wherein R^3 is hydrogen, hydroxy or acetoxy.

9. A compound of claim 7 or 8 wherein $R^4(O)_p$ is phenyl or t-butoxy.

10. A compound of any one of claims 7 to 9 wherein R^5 is phenyl, 2-furyl or 2-thienyl.

11. A compound of claim 1 which is 2'-O-(ethoxycarbonyl)-7-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the sodium salt, triethanolamine salt, triethylamine salt, arginine salt, lysine salt, ethanolamine salt and N-methylglucamine salt;
7-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the sodium salt;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt;
or 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt.

12. A compound of claim 5 wherein R^1 is $-OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

13. A compound of claim 12 wherein $R^{2'}$ is hydrogen, R^2 is hydrogen, hydroxy or -OC(O)OR^x, and R^x is as defined in claim 5.

14. A compound of claim 13 wherein R^3 is hydrogen, hydroxy or acetoxy.

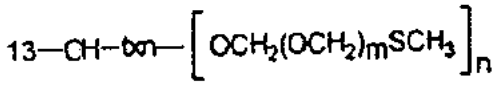
15. A compound of claim 13 or 14 wherein $R^4(O)_p$ is phenyl or t-butoxy.

16. A compound of any one of claims 13 to 15 wherein R^5 is phenyl.

17. A compound of claim 1 which is 2'-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof;
2',7-O-bis(phosphonooxymethyl)paclitaxel or a pharmaceutically acceptable salt thereof, in particular the sodium salt;
2'-O-phosphonooxymethoxymethylpaclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt; or
10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt.

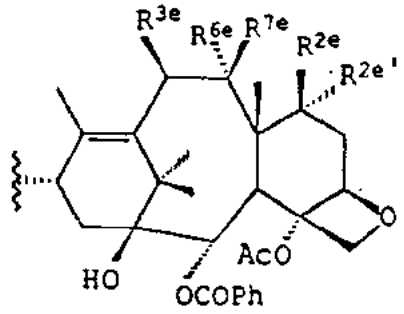
18. A compound of claim 5 wherein R^1 and R^2 are both -$OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof;
or
wherein R^1 is -$OCH_2OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof;
or
wherein R^3 is -$OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

19. A compound having the formula



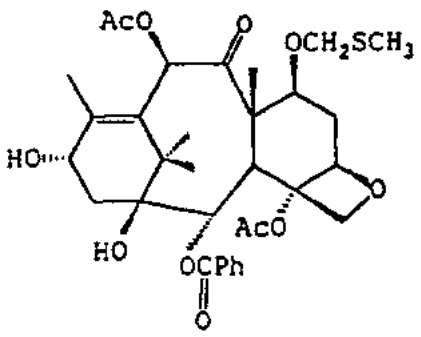
wherein txn is a taxane moiety, m and n are as previously defined, or a C13 metal alkoxide thereof.

20. A compound of claim 19 wherein said taxane moiety is derived from a residue having the formula



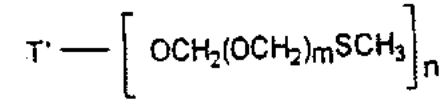
wherein R^{2e}, $R^{2e'}$, R^{3e}, R^{6e} amd R^{7e} are as previously defined.

21. A compound of claim 19 having the formula



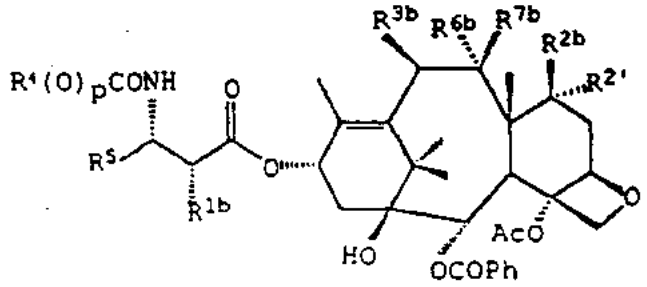
or a C13 metal alkoxide thereof.

22. A compound having the formula



wherein T' is T in which non-reacting hydroxy groups have been blocked, m and n are as defined above.

23. A compound of claim 22 having the formula

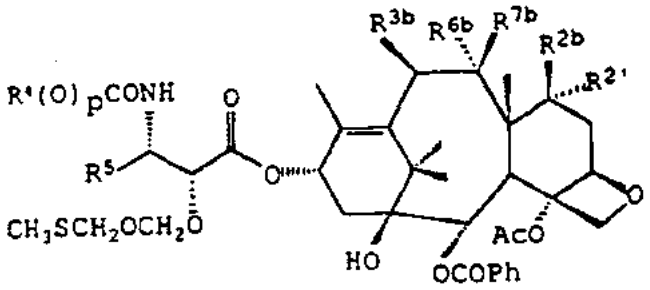


wherein R^{1b} is hydroxy, protected hydroxy, $-OCH_2SCH_3$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2b} is hydrogen, hydroxy, protected hydroxy, $-OCH_2SCH_3$ or $-OC(O)OR^x$; or $R^{2'}$ is fluoro, and R^{2b} is hydrogen; R^{3b} is hydrogen, hydroxy, protected hydroxy, acetoxy, $-OCH_2SCH_3$ or $-OC(O)OR^x$; one of R^{6b} or R^{7b} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2SCH_3$; or R^{6b} and R^{7b} together form an oxo group; with the proviso that at least one of R^{1b}, R^{2b}, R^{3b}, R^{6b}, R^{7b} is $-OCH_2SCH_3$; p, R^4, R^5 and R^x are as previously defined.

24. A compound of claim 23 that is
7-O-methylthiomethylpaclitaxel;
2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
2'O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel;
2'-O-(methylthiomethyl)-7-O-(triethylsilyl)paclitaxel;
2'-O-(methylthiomethyl)paclitaxel;
2',7-O-bis(methylthiomethyl)paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethylpaclitaxel; or

3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel.

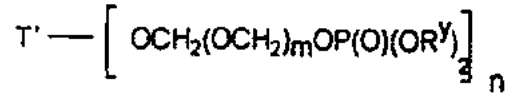
25. A compound of claim 22 having the formula



wherein $R^{2'}$, R^{2b}, R^{3b}, R^4, R^5, R^{6b}, R^{7b} and p are as previously defined.

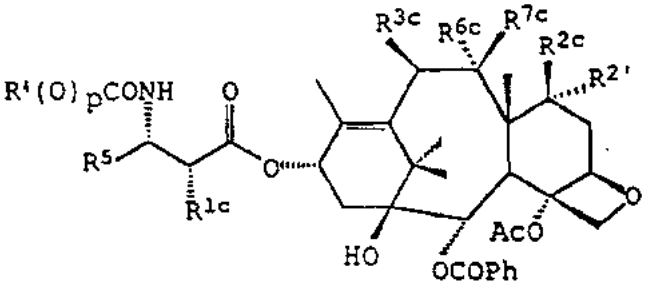
26. A compound of claim 25 that is 2'-O-(methylthiomethoxymethyl)-7-O-triethylsilylpaclitaxel, or 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel.

27. A compound having the formula



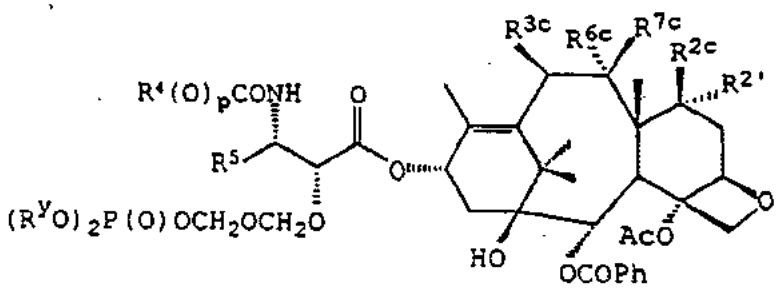
wherein T', m and n are as defined above, and R^y is a phosphono protecting group.

28. A compound of claim 27 having the formula



wherein R^{1c} is hydroxy, protected hydroxy, $-OCH_2OP(O)(OCH_2R^y)_2$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, R^{2c} is hydrogen, hydroxy, protected hydroxy, $-OCH_2OP(O)(OCH_2R^y)_2$ or $-OC(O)OR^x$; or $R^{2'}$ is fluoro, R^{2c} is hydrogen; R^{3c} is hydrogen, hydroxy, protected hydroxy, acetoxy, $-OCH_2OP(O)(OCH_2R^y)_2$ or $-OC(O)OR^x$; one of R^{6c} or R^{7c} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2OP(O)(OR^y)_2$; or R^{6c} and R^{7c} together form an oxo group; with the proviso that at least one of R^{1b}, R^{2b}, R^{3b}, R^{6c} or R^{7c} is $-OCH_2OP(O)(OCH_2R^y)_2$; p, R^4, R^5, R^x and R^y are as previously defined.

29. A compound of claim 27 or 28 having the formula



wherein $R^{2'}$, R^{2c}, R^{3c}, R^4, R^5, R^{6c}, R^{7c}, R^y and p are as previously defined.

30. A pharmaceutical composition which comprises an antitumor effective amount of a compound of any one of claims 1 to 18 and a pharmaceutically acceptable carrier.

31. The use of a compound of any one of claims 1 to 18 for preparing a pharmaceutical composition, in particular a composition for oral administration, for inhibiting tumor growth.

32. A process for preparing a compound of any one of claims 1 to 18 comprising:
removing hydroxy and phosphono protecting group(s) from a compound of formula (C)

$$T'\text{-}[OCH_2(OCH_2)_mOP(O)(OR^y)_2]_n \quad (C)$$

in which R^y is phosphono protecting group and T' is a taxane derivative in which non-reacting hydroxy groups have been blocked.

33. A process for preparing a compound of any one of claims 22 to 26 comprising:
reacting a compound of formula (Aa)

$$T'\text{-}[OH]_n \quad (Aa)$$

with dimethylsulfoxide and acetic anhydride, or with dimethylsulfide and an organic peroxide, or comprising:
reacting a compound of formula (Aa)

$$T'\text{-}[OH]_n \quad (Aa)$$

with $CH_3SCH_2OCH_2SCH_3$ and N-iodosuccinimide.

34. A process of claim 33 in which the organic peroxide is benzoyl peroxide.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 12 0801

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Y	US-A-5 059 699 (DAVID G. I. KINGSTON) * the whole document * ---	1-18,30, 31	C07F9/655 A61K31/675 C07F9/6558 C07D305/14
P,Y	EP-A-0 558 959 (BRISTOL-MYERS SQUIBB COMPANY) * the whole document * ------	1-18,30, 31	C07D407/12 C07F7/18

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07F
A61K
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16 March 1994	Beslier, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0C03)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 694 539 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
31.01.1996 Bulletin 1996/05

(51) Int. Cl.[6]: C07D 305/14, C07D 407/12, A61K 31/335

(21) Application number: 95111843.9

(22) Date of filing: 27.07.1995

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: 28.07.1994 US 282129

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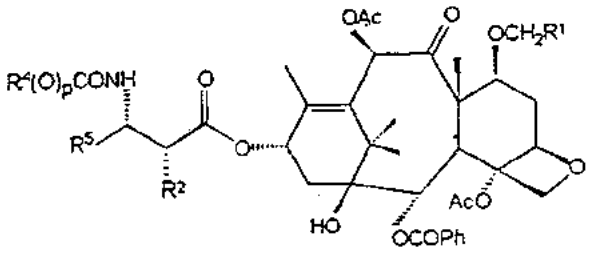
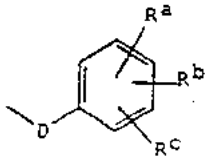
(54) 7-o-Ethers of taxane derivatives

(57) The present invention concerns taxane derivatives of formula I,



(I)

wherein R^1 is hydrogen, C_{1-8} alkyloxy, C_{2-8} alkenyloxy, or C_{2-8} alkynyloxy, each can be optionally substituted with hydroxy; R is hydroxy, $-OC(O)R^X$ or $-OC(O)OR^X$; R^4 and R^5 are independently C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, or $-Z-R^6$; p is zero or one; Z is a direct bond, C_{1-8} alkylene or C_{2-8} alkenediyl; R^6 is aryl, substituted aryl, C_{3-8} cycloalkyl or heteroaryl; and R^X is C_{1-8} alkyl optionally, substituted with one to six same or different halogen atoms, C_{3-8} cycloalkyl or C_{2-8} alkenyl; or R^X is a radical of the formula



wherein D is a bond or C_{1-8} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-8} alkylamino, di-C_{1-8}alkylamino, halogen, C_{1-8} alkyl, or C_{1-8} alkyloxy, their use as antitumor agents and pharmaceutical compositions containing the novel compounds.

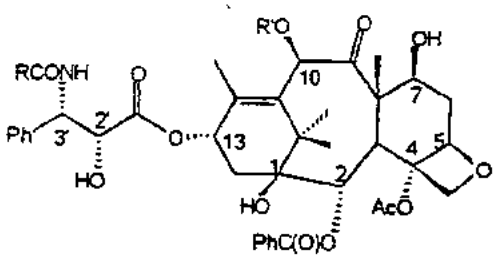
EP 0 694 539 A1

Description

The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

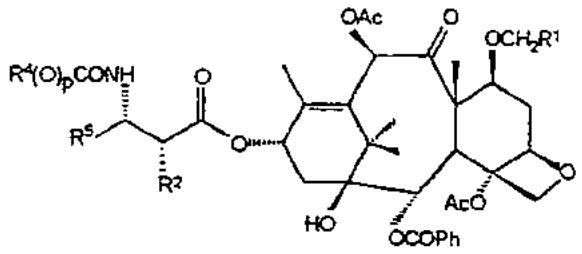
Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It has been recently approved for the treatment of ovarian cancer; and studies involving breast, colon, and lung cancers have shown promising results. The results of paclitaxel clinical studies are reviewed in Rowinsky and Donehower, "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics" Pharmac. Ther., 52:35-84, 1991.

Recently, a semi-synthetic analog of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models. Taxotere® is also currently undergoing clinical trials in Europe and the United States. The structures of paclitaxel and Taxotere® are shown below along with the conventional numbering system of taxane molecules; such numbering system is also employed in this application.



Taxol®: R = Ph; R' = acetyl
Taxotere®: R = t-butoxy; R' = hydrogen

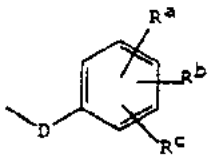
The instant invention relates to a novel class of taxanes. More particularly they are 7-O ethers of taxane derivatives. The present invention relates to taxane derivatives having the formula (I):



(I)

wherein R^1 is hydrogen, C_{1-8} alkyloxy, C_{2-8} alkenyloxy, or C_{2-8} alkynyloxy, each can be optionally substituted with hydroxy; R^2 is hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; R^4 and R^5 are independently C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, or $-Z-R^6$; p is zero or one; Z is a direct bond, C_{1-8} alkylene or C_{2-8} alkenediyl; R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl or heteroaryl; and R^x is C_{1-8} alkyl optionally, substituted with one to six same or different halogen atoms, C_{3-8} cycloalkyl

or C_{2-8} alkenyl; or R^x is a radical of the formula



wherein D is a bond or C_{1-8} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-8} alkylamino, di-C_{1-8}alkylamino, halogen, C_{1-8} alkyl, or C_{1-8} alkyloxy.

Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of the formula (I).

Yet another aspect of the present invention provides a pharmaceutical composition (formulation) which comprises an antitumor effective amount of a compound of the formula (I) and a pharmaceutically acceptable carrier.

Detailed Description Of The Invention

In the application, unless otherwise specified explicitly or in context, the following definitions apply. "Alkyl" means a straight or branched saturated carbon chain having from one to eight carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, n-hexyl, n-heptyl, and n-octyl. "Alkylene" means alkyl with two points of attachment; examples include methylene, ethylene, and propylene. "Alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to eight carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. "Alkenediyl" refers to alkenyl with two points of attachment; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-dinyl, 2-hexene-1,6-diyl, and the like groups. "Alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to eight carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyt.

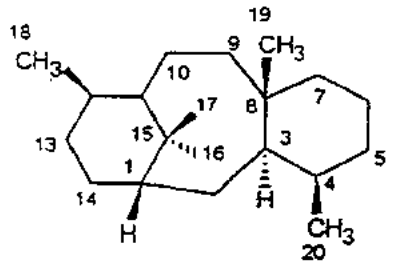
"Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl substituted with at least one group selected from C_{1-8} alkanoyloxy, hydroxy, halogen, C_{1-8} alkyl, trifluoromethyl, C_{1-8} alkoxy (alkyloxy), aryl, C_{2-8} alkenyl, C_{1-8} alkanoyl, nitro, amino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

"Methylthiomethyl" (also abbreviated as MTM) refers to the group $-CH_2SCH_3$.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Hydroxy protecting groups" include, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl. Additional examples of hydroxy protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., 1991, John Wiley & Sons, and McOmie, Protective Groups in Organic Chemistry, 1975, Plenum Press. Methods for introducing and removing protecting groups are also found in such textbooks.

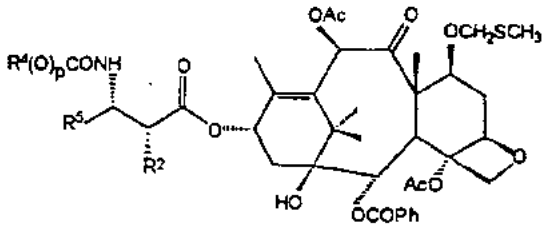
"Taxane" denotes moieties containing the twenty carbon taxane core framework represented by the structural formula shown below with the absolute configuration.



The numbering system shown above is one used in conventional taxane nomenclature, and is followed throughout the application. For example, the notation C1 refers to the carbon atom labelled as "1"; C5-C20 oxetane refers to an oxetane ring formed by the carbon atoms labelled as 4, 5 and 20 with an oxygen atom.

A compound of formula (I) can be prepared by a process of Scheme I. In Scheme I, 7-O-methylthiomethyl is either (1) reduced to 7-O-methyl with Raney Nickel; or (2) reacted with R^3OH, in which R^3 is C_{1-8} alkyloxy, C_{2-8} alkenyloxy or C_{2-8} alkynyloxy, each can optionally be substituted with hydroxy, in the presence of NIS with triflate as a catalyst. Preferred triflate is silver triflate or trialkylsilyltriflate. An analogous reaction of an alcohol with methylthiomethyloxy group in the presence of NIS was reported by Veeneman et al. in Tetrahedron, 1991, v47, pp. 1547-1562, the relevant portions thereof are hereby incorporated by reference.

SCHEME I

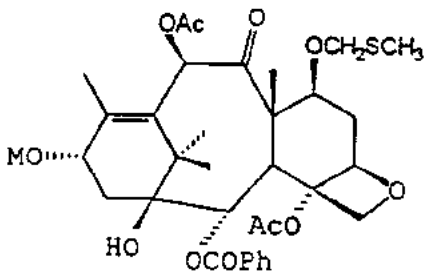


(II)

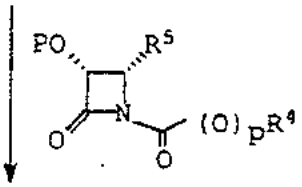
Raney Nickel
or
NIS/R3OH

(I)

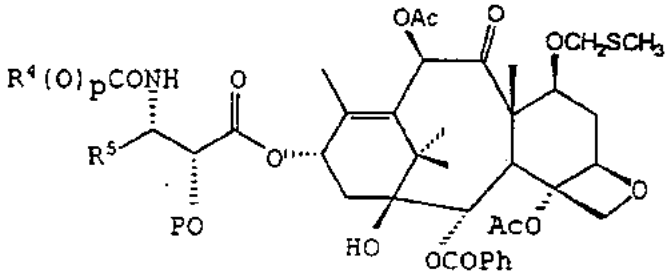
SCHEME IIa



(III)



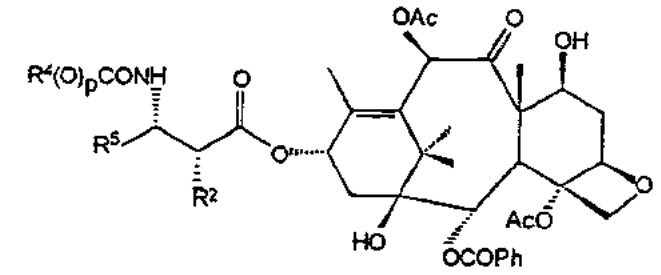
(IV)



(V)

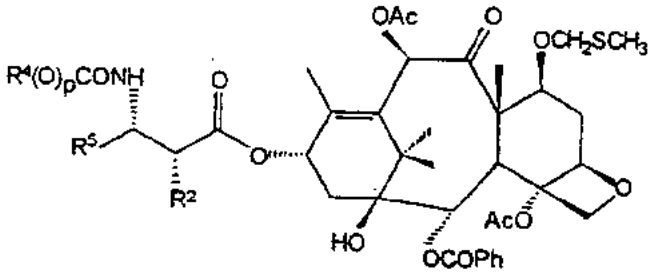
(II)

SCHEME IIb



(VI)

(1a) SMe_2 / $(PhCOO)_2$
or
(1b) Ac_2O / DMSO



(II)

A starting compound of formula (II) can be readily availabe by either process of Scheme IIa or IIb.

Scheme IIa depicts essentially a coupling as described in EP Application 400,971 published December 5, 1990 (now U.S. Patent 5,175,315) and U.S. Patent 5,229,526. To summerize, the process as disclosed in EP 400,971 (the Holton process) involves reacting 1-benzoyl-3-(1-ethoxy)ethoxy-4-phenyl-2-azetidinone with 7-O-triethylsilylbaccatin III in the presence of N,N-dimethylaminopyridine and pyridine at 25°C for 12 hours; paclitaxel is obtained after the various hydroxy protecting groups are removed. An improvement of the Holton process is reported by Ojima et al in "New and Efficient Approaches to the Semisynthesis of Taxol and its C-13 Side Chain Analogs by Means of β-Lactam Synthon Method" Tetrahedron, 1992, 48(34):6985-7012. Ojima's process involves first generating the sodium salt of 7-O-triethylsilylbaccatin III with sodium hydride; this salt is then reacted with chiral 1-benzoyl-3-(1-ethyoxy)ethoxy-4-phenyl-2-azetidinone to provide paclitaxel after removal of the hydroxy protecting groups. In U.S. 5,229,526, Holton discloses the coupling of a metal alkoxide of baccatin III or a derivative thereof with a 2-azetidinone to provide taxanes with C13 sidechain. This process is said to be highly diastereoselective; therefore racemic mixtures of the sidechain precursor 2-azetidinone may be used. Recently, Ojima et al reported in "A Highly Efficient Route to Taxotere by the β-Lactam Synthon Method," Tetrahedron Letters, 1993, 34(26):4149-4152, the coupling of metal alkoxides of 7,10-bis-O-(trichloroethoxycarbonyl)-10-deacetylbaccatin III with chiral 1-(t-butoxycarbonyl)-4-phenyl-3-(protected hydroxy)-2-azetidinone to give Taxotere® after deprotection. The relevant portions of all references cited above are hereby incorporated by reference.

More specifically, in Scheme IIa, P is a hydroxy protecting group; M is hydrogen or a Group IA metal such as lithium, sodium or potassium. The reaction may be conducted according to the procedure disclosed in EP 400,971 wherein the baccatin III derivative of formula (III) wherein M is hydrogen is reacted with an azetidinone of formula (IV) in the presence of an organic base such as N,N-dimethylaminopyridine. Preferably, however, the baccatin III derivative is first converted to a 13-alkoxide by treating the former with a strong base such as hydrides, alkylamides, and bis(trialkylsilyl)amides of Group IA metals as disclosed in U.S. Patent 5,229,526 and the Ojima references, supra. More preferably, the 13-alkoxide is a lithium alkoxide. The formation of a lithium salt may be achieved by reacting a compound of formula (III) wherein M is hydrogen with a strong metal base, such as lithium diisopropylamide, C_{1-6} alkyllithium, lithium bis(trimethylsilyl)amide, phenyllithium, lithium hydride, or the like base.

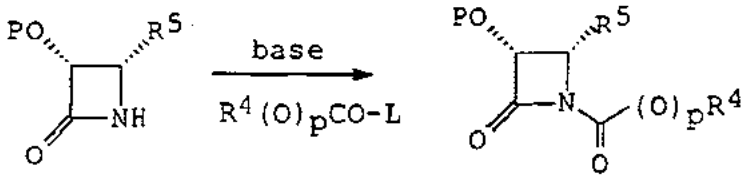
The coupling reaction between a taxane of formula (III) and an azetidinone of formula (IV) is conducted in an inert organic solvent such as tetrahydrofuran at reduced temperature in the range of about 0°C to about -78°C. The azetidinones of formula (IV) may be used as a racemic mixture; in such case, the azetidinone reactant is preferably used in at least 2 equivalents relative to the taxane reactant, and more preferably from about 3 to about 6 equivalents. Chiral azetidinones may also be used, and in such case one equivalent of the azetidinone relative to the taxane may be sufficient, but preferably the azetidinone is used in slight excess, for example up to 1.5 equivalents.

After the coupling reaction with a taxane, the hydroxy protecting group P is removed, and if desired, the free hydroxy group on the sidechain may be derivatized to an ester or a carbonate as herein described.

The 2'-hydroxy group of paclitaxel derivatives may be converted by conventional methods to the corresponding ester or carbonate; for example 2'-hydroxy may be reacted with a compound of the formula L-C(O)OR^x (L being a leaving group) such as a chloroformate in the presence of a base such as tertiary amine to give the corresponding carbonate; for example, 2'-hydroxy reacts with ethyl chloroformate in the presence of diisopropylethylamine to provide 2'-O-ethyloxycarbonyl derivative. The 2'-hydroxy may also react with a carboxylic acid R^xCO_2H or an acylating equivalent thereof (e.g. an anhydride, active ester or an acyl halide) to provide the corresponding ester.

It is to be understood that in Scheme IIa, as well as elsewhere in the specification, hydroxy protecting group may encompass suitable carbonates (e.g. -OC(O)OR^x); thus, when a carbonate is used as a hydroxy protecting group, it is intended to be removed in a later step to generate the free hydroxy group; otherwise, the carbonate moiety remains as part of the final product.

Compounds of formula (IV) can be prepared from a compound of (IVa) according to the general method described in EP 400,971 and Ojima et al, Tetrahedron, 48:6985-7012, 1992.

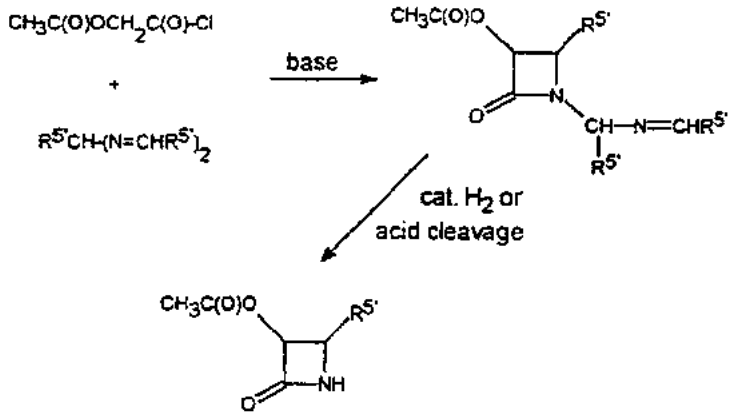


(IVa) (IV)

Thus a compound of formula (IVa) is first treated with a base such as n-butyllithium or triethylamine, and then followed by a compound of the formula $R^4(O)_pCO$-L where L is a leaving group to provide a compound of formula (IV).

Compounds of (IVa) may be prepared according to the general method disclosed in EP 400,971 by going through an intermediate compound 3-acetoxy-4-substituted-2-azetidinone (IVb); or by the method disclosed in U.S. 5,229,526 by going through an intermediate compound 3-triethylsilyloxy-4-substituted-2-azetidinone. In an improved process a compound (IVb) may be obtained by condensing acetoxyacetyl chloride with a bis-imine followed by hydrogenolysis or acid cleavage to remove the N-imine group; this process is shown in the following scheme in which $R^{5'}$ is an optionally substituted aryl or a heteroaryl group such as furyl or thienyl. This process is disclosed in co-pending application U.S.S.N

08/165,610 filed December 13, 1993 which is hereby incorporated by reference.



The products (IVb) obtained from these cycloaddition reactions are usually a racemic mixture of the two cis-azetidinones. The racemic mixture may be resolved by conventional methods such as conversion to diastereomers, differential absorption on column packed with chiral adsorbents, or enzymatically. For example, a racemic mixture of compounds of formula (IVb) may be contacted with an enzyme that catalyzes the hydrolysis of an ester, for example an esterase or a lipase, to selectively cleave the 3-acyl group of one enantiomer without affecting the other. (See e.g., Brieva et al, J. Org. Chem., 1993, 58:1068-1075; co-pending application U.S.S.N. 092,170 filed July 14, 1993; and European Patent Application Number 552041, published July 21, 1993. These are incorporated herein by reference.). Alternatively, the racemic mixture may be first subjected to base-catalyzed hydrolysis to remove the 3-acyl group and to generate a racemic mixture of the corresponding 3-hydroxy β-lactam; the racemic mixture of 3-hydroxy β-lactam is then contacted with an enzyme capable of catalyzing acylation of an hydroxy group to selectively acylate the hydroxy group of one enantiomer without affecting the other. Or the racemic mixture of 3-hydroxy β-lactam may be acylated with a chiral carboxylic acid, and the resulting diastereomeric mixture may then be separated using methods known in the art, and the chiral auxiliary removed to provide the desired enantiomer.

Ojima et al, in J. Org. Chem., 56:1681-1683, 1991; Tet. Lett., 33:5737-5740, 1992; and Tetrahedron, 48:6985-7012, 1992 reported the synthesis of a number of chiral azetidinones of formula (IVa) and/or the corresponing N-(p-methoxyphenyl) congener; wherein P is the hydroxy protecting group triisopropylsilyl; and R^5 is 4-methoxyphenyl, 3,4-dimethyoxyphenyl, phenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-furyl, 2-phenylethenyl, 2-(2-furyl)ethenyl, 2-methylpropyl, cyclohexylmethyl, isopropyl, phenethyl, 2-cyclohexylethyl, or n-propyl. Other references for making azetidinones to formula (IVa) and/or (IV) can be found in European Patent Applications 0,534,709 A1, 0,534,708 A1, and 0,534,707 A1, all three published on March 31, 1993; in PCT application WO 93/06079 published on April 1, 1993; in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2475-2478 (1993); also in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2479-2482 (1993); in *J. Org. Chem.*, 58, pp 1068-1075; in *Tetrahedron Letters*, 31, No. 44, pp 6429-6432 (1990); in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2467-2470 (1993); European Application 552,041 published on July 21, 1993; and in our copending U.S. Application Serial No. 092,170 filed on July 14, 1993. The relevant portions of all aforementioned references are hereby incorporated by reference. Other azetidinones within the definition of formula (IV) but are not specifically disclosed in these references may be prepared by a person skilled in the art following the methodologies generally known in the art.

The compounds of formula (II) can also be obtained by a process of Scheme IIb in which one of the two procedures (1a - the dimethylsulfide method) and (1b - the dimethylsulfoxide method) is used. The dimethylsulfide method for converting alcohols to methylthiomethyl ethers is reported in Medina et al, Tet. Lett., 1988, pp. 3773-3776, the relevant portions thereof are hereby incorporated by reference. The dimethylsulfoxide method is the well-known reaction commonly known as the Pummerer reaction.

It should be noted that the reactivity of a hydroxy group differs depending on its location on the taxane derivative starting material of formula (VI). Although in general the 2'-hydroxy group is more reactive in acylation reactions than the 7-hydroxy group, it has been found that, surprisingly with the dimethylsulfide method, the 7-hydroxy is more readily converted into the methylthiomethyl ether than the 2'-hydroxy group. The tertiary hydroxy group at C-1 is usually the least reactive. The difference in hydroxy reactivity may be exploited in controlling the site and degree of methylthiomethylation.

Thus with a compound of formula (VI) wherein R^2 is hydroxy, the predominant methylthiomethylation product is the corresponding 7-O-methylthiomethyl ether with the dimethylsulfide method. Even though the 7-hydroxy is the preferential methylthiomethylation site in the dimethylsulfide method, it is still preferable to protect the 2'-hydroxy group; in such case $-OC(O)R^X$ or $-OC(O)R^X$ can serve as protecting group and left as such when R^2 in the final desired compound is $-OC(O)R^X$ or $-OC(O)R^X$. Otherwise 2'-hydroxy protecting group is removed from the product.

Returning now to Scheme IIb, in procedure (1a), a compound of formula (VI) is treated with dimethylsulfide and an organic peroxide such as benzoyl peroxide. The reaction is carried out in an inert organic solvent such as acetonitrile, methylene chloride and the like at a temperature conducive to product formation; typically the reaction is carried at a temperature range of from about -40°C to about ambient temperature. Dimethylsulfide and benzoyl peroxide are used in excess relative to the taxane derivative starting material (VI), and dimethylsulfide is used in excess relative to benzoyl peroxide. Normally, up to 10 fold excess of dimethylsulfide and benzoyl peroxide relative to taxane derivative (VI) is used; and preferably, dimethylsulfide is used in about two to three fold excess relative to benzoyl peroxide.

Alternatively, a compound of formula (II) may be prepared by reacting a compound of formula (VI) with dimethylsulfoxide and acetic anhydride (procedure 1b). In this procedure 2'-hydroxy is preferably protected regardless whether such protecting group is ultimately removed or retained as $-OC(O)R^X$ or $-OC(O)R^X$. In this procedure, a compound of formula (VI) is dissolved in dimethylsulfoxide and acetic anhydride is added to the solution. The reaction is usually carried out at room temperature, and for 18-24 hours to produce the monomethylthiomethyl ether.

The compounds of formula (VI) are well known is the art. For example, they are normally made by reacting appropriately protected baccatin III with azetidinones of formula (IV) as taught in the above discussed U.S. Patents 5,175,315 and 5,229,526; Tetrahedron, 1992, 48(34):6985-7012; EP Applications 0,534,709, 0,534,708, and 0,534,707.

Representative In vivo antitumor activity

Balb/c x DBA/2 F_1 hybrid mice were implanted intraperitoneally, as described by William Rose in *Evaluation of Madison 109 Lung Carcinoma as a Model for Screening Antitumor Drugs*, Cancer Treatment Reports, 65, No. 3-4 (1981), with 0.5 mL of a 2% (w/v) brei of M109 lung carcinoma.

Mice were treated with compound under study by receiving intraperitoneal injections of various doses on days 5 and 8 post-tumor implant. Mice were followed daily for survival until approximately 75 - 90 days post-tumor implant. One group of mice per experiment remained untreated and served as the control group.

Median survival times of compound-treated (T) mice were compared to the median survial time of the control (C) mice. The ratio of the two values for each compound-treated group of mice was multiplied by 100 and expressed as a percentage (i.e. % T/C) in Table I for representative compounds of formula (I).

Table I

Example Number	% T/C (mg/kg/inj.)
2	179(8)
3	118(5)
5	121(2)
6	118(0.32)
7	158(2)
8	208(8)
9	129(16)
10	172(2)
20	118(16)
21	177 (4 or 8)

Compounds of formula (I) of the instant invention are effective tumor inhibiting agents, and thus are useful in human and/or veterinary medicine. Thus, another aspect of the instant invention concerns a method for inhibiting human and/or other mammalian tumors which comprises administering to a tumor bearing host an antitumor effective amount of a compound of formula (I).

Compounds of formula (I) of the present invention may be used in a manner similar to that of paclitaxel; therefore, an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering a compound of the present invention. The dosage, mode and schedule of admin-

istration for compounds of this invention are not particularly restricted, and will vary with the particular compound employed. Thus a compound of the present invention may be administered via any suitable route of administration, preferably parenterally; the dosage may be, for example, in the range of about 1 to about 100 mg/kg of body weight, or about 20 to about 500 mg/m^2. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient.

The present invention also provides pharmaceutical compositions (formulations) containing an antitumor effective amount of a compound of formula (I) in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. Examples of formulating paclitaxel or derivatives thereof may be found in, for example, United States Patents Nos. 4,960,790 and 4,814,470, and such examples may be followed to formulate the compounds of this invention. For example, compounds of the present invention may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. They may also be manufactured in the form of sterile solid compositions, for example, freeze dried and, if desired, combined with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use for parenteral administration.

Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

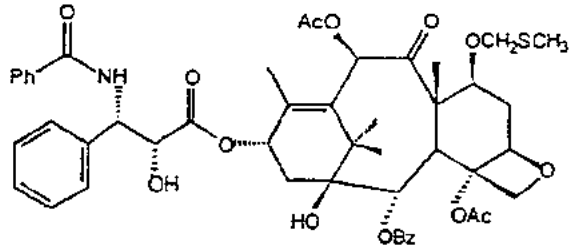
In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs or br s), broad doublet (bd or br d), broad triplet (bt or br t), broad quartet (bq or br q), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d_6 (deuterated acetone). DMSO-d_6 (perdeuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuterochloroform) and other conventional deuterated solvents. The infrared (IR) spectral description include only absorption wave numbers (cm^{-1}) having functional group identification value.

Celite is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); v/v (volume/volume); FAB (fast atom bombardment); NOBA (m-nitrobenzyl alcohol); min (minute(s)); h or hr(s) (hour(s)); NIS (N-iodosuccinimide); BOC (t-butoxycarbonyl); CBZ or Cbz (benzyloxycarbonyl); Bn (benzyl); Bz (benzoyl); TES (triethylsilyl); DMSO (dimethylsulfoxide); THF (tetrahydrofuran); HMDS (hexamethyldisilazane).

Preparation I.

7-O-methylthiomethylpaclitaxel

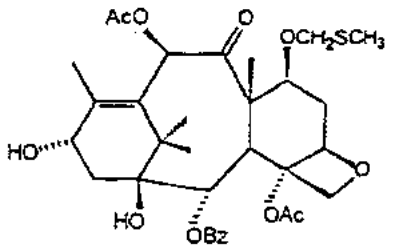


Benzoyl peroxide (0.98 g, 4 mmol) was added to a vigorously stirred mixture of paclitaxel (0.85 g, 1 mmol) and dimethyl sulfide (0.72 mL, 8 mmol) in dry acetonitrile (10 ml) at 0°C. Stirring was continued for 2.5 hours at 0°C. Progress of the

reaction was monitored by silica gel TLC in toluene:acetone (2:1, v/v) solvent system ($R_{f\ paclitaxel}$ = 0.38, $R_{f\ prod.}$ = 0.64), and when formation of higher polarity products was observed the reaction was quenched by evaporation of solvents using Rotavapor at 30°C. A TLC analysis of the reaction mixture indicated the presence of some quantities of unreacted paclitaxel and 2',7-O-bis(methylthiomethyl)paclitaxel. Separation of the title compound from the reaction mixture was achieved by flash column chromatography on Silica Gel 60 (40 - 63 µm) EM Science (100 mL), column diameter: 2 in. using ethyl acetate:hexane (1:1, v/v) solvent system ($R_{f\ prod.}$ = 0.34). The product (552 mg, 60% yield) was recovered from fractions 12 to 18 (each fraction ca. 20 ml).

Preparation II.

7-O-methylthiomethylbaccatin III (7-O-MTM baccatin III)



(a) 2'-O-(ethoxycarbonyl)paclitaxel

Paclitaxel (5.40 g, 6.324 mmol) in dry dichloromethane (63 mL) was cooled to 0°C and treated with neat N,N-diisopropylethylamine (3.30 mL, 3 equiv) and then neat ethyl chloroformate (1.81 mL, 3 equiv) dropwise over a 5 min period. The reaction was monitored by TLC (50% ethyl acetate in hexane). After 2h at 0°C and 16h at room temperature, the reaction was complete and the yellow-orange solution was diluted with ethyl acetate (300 mL) and washed with saturated sodium bicarbonate (3 x 75 mL) and brine (75 mL). Drying ($MgSO_4$) and evaporation afforded crude title compound, which was purified by precipitation: dichloromethane (ca. 100 mL) was added followed by cooling and addition of hexane (ca 60 mL) to the cloud point. After cooling in ice for several hours, the solid was collected by filtration. Yield 5.17 g (88%).

(b) 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel

2'-O-(Ethoxycarbonyl)paclitaxel (2.260 g, 2.4406 mmol) was dissolved in anhydrous dimethylsulfoxide (6 mL), and acetic anhydride (6 mL) was added in one lot at room temperature. The reaction was monitored by HPLC (C18 analytical column; 60% acetonitrile - 40% 10 mM ammonium phosphate buffer, pH 6). After 30h, the solution was diluted with ethyl acetate (250 mL) and washed with saturated aqueous bicarbonate (3 times) then water and brine. After drying over magnesium sulfate and filtration, the crude product was chromatographed on silica (40% ethyl acetate in hexane) to yield the title compound as a white foam (2.030 g, 91%) that was 90% pure by HPLC. A portion was further purified by a second column (5% acetonitrile in dichloromethane) to afford material that was ca. 97% pure by HPLC.

(c) alternate method for the preparation of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel

2'-O-(Ethoxycarbonyl)paclitaxel (4.170 g, 4.503 mmol) was dissolved in anhydrous acetonitrile (68 mL) at -40°C, and dimethyl sulfide (3.2 mL, 44.10 mmol) was added, followed by benzoyl peroxide (4.400 g, 18.24 mmol). The mixture was placed in an ice bath and stirred at 0°C, and the course of the reaction was monitored by TLC (40% ethyl acetate in hexane). After 3 h no starting material was detected, and the solution was worked up by adding ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (100 mL). The organic phase was further washed with bicarbonate, water, and brine, then dried over magnesium sulfate and filtered. The residue was purified by silica gel flash chromatography (4% acetonitrile in dichloromethane), to yield the title compound as a white foam (2.571 g, 58% yield). The purity of this sample was judged as >97% by HPLC.

(d) preparation of 7-O-MTM baccatin III

To a solution of 2'-O-(ethyloxycarbonyl)-7-O-methylthiomethylpaclitaxel (27 g, 27.4 mmol) in 100 mL of THF and 500 mL of methanol was added freshly ground K_2CO_3 (2.7 g, 19 mmol). The solution was stirred for 30 minutes and neutralized with IR-120 (H^+) resin, filtered and concentrated. The crude filtrate was then dissolved in 200 mL of dichloromethane and stirred for 24 hours with tetrabutylammonium borohydride (10 g). The solution was diluted with dichloromethane and washed with water, saturated bicarbonate and brine. The organic fraction was then dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 9.4 g of 7-O-MTM baccatin III (53%) with a melting point of 269°C.

HRFABMS (NOBA) M+H calcd for $C_{33}H_{43}SO_{11}$ 647.2526 Found: 647.2551.

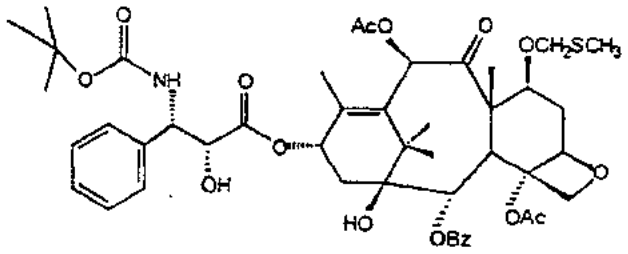
IR(KBr) 3474, 1746, 1724, 1712, 1270, 1240, 1070 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.1 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 6.55 (s, 1H), 4.94 (d, J=8.1 Hz, 1H), 4.83 (br q, J=5.1 Hz, 1H), 4.66 (ABq, J=14.7,12.3 Hz, 2H), 4.30 (m, 2H), 4.13 (d, J=8.4 Hz, 1H), 3.91 (d, J=6.6 Hz, 1H), 2.79 (m, 1H), 2.27 (s, 3H), 2.25 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 4H), 1.81 (m, 1H), 1.72 (s, 3H), 1.61 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 170.8, 169.3, 167.0, 144.2, 132.6, 132.1, 130.1, 129.4, 128.6, 83.9, 80.9, 78.7, 75.7, 74.5, 73.9, 67.9, 57.6, 47.6, 42.7, 38.3, 26.7, 22.6, 21.0, 20.1, 15.2, 15.0, 10.8.

Preparation III.

3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of hexamethyldisilazane (HMDS) (0.275 mL, 1.30 mmol) in 8 mL of THF was added a solution of n-BuLi (0.48 mL, 2.5 M in hexanes, 1.20 mmol) and stirred 5 minutes at -55°C. To this solution was added 7-O-MTM baccatin III (639 mg, 0.99 mmol) in 8 mL of THF and stirred for 10 minutes before addition of an 8 mL solution of (3R,4S)-1-(t-butyloxycarbonyl)-4-phenyl-3-(triethylsilyloxy)-2-azetidinone (575 mg, 1.52 mmol) in THF. The cold bath was removed and replaced with a 0°C bath and the reaction stirred for 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (3:1 hexane/ethyl acetate) to give 1.0 g of the coupling product 3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (98%).

FABMS (NOBA) M+Na calcd for $C_{52}H_{73}NSSiO_{15}$: 1046. Found: 1046.

IR(film) 3448 (s), 1720, 1242, 1120, 1056 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=6.9 Hz, 2H), 7.57 (m, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.35 (m, 2H), 7.26 (m, 3H), 6.55 (s, 1H), 6.25 (t, J=9.6 Hz, 1H), 5.68 (d, J=6.9 Hz, 1H), 5.45 (br d, J=9.3 Hz, 1H), 5.27 (br d, 1H), 4.95 (d, J=7.8 Hz, 1H), 4.65 (s, 2H), 4.53 (s, 1H), 4.29 (m, 2H), 4.17 (d, J=8.4 Hz, 1H), 3.89 (d, J=6.9 Hz, 1H), 2.81 (m, 1H), 2.51 (s, 3H), 2.37 (dd, J=15.3, 9.6 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.74 (s, 3H), 1.63 (d, J=14.1 Hz, 1H), 1.29 (s, 9H), 1.21 (s, 6H), 0.76 (t, J=7.8 Hz, 9H), 0.36 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 171.6, 170.1, 169.3, 167.1, 155.2, 141.0, 139.0, 133.6, 132.8, 130.2, 129.2, 128.7, 128.5, 127.7, 126.4, 83.9, 81.2, 79.9, 78.9, 76.0, 75.7, 75.2, 74.8, 74.2, 71.3, 57.3, 56.7, 47.0, 43.3, 35.3, 33.0, 28.2, 26.4, 23.0, 21.5, 21.0, 15.0, 14.4, 10.9, 6.5, 4.3.

To a solution of the silyl ether obtained above (269 mg, 0.26 mmol) in 6 mL of THF was added tetrabutylammonium fluoride (0.3 mL, 1.0M in THF, 0.3 mmol) and stirred 10 minutes. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated and the residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 240 mg of the title compound (95%).

FABMS (NOBA) M+Na calcd for $C_{47}H_{59}NO_{15}SNa$: 932. Found: 932.

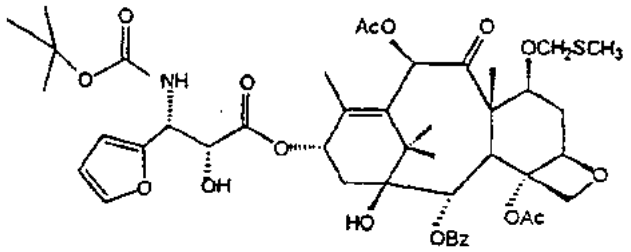
IR(film) 3440, 1720, 1370, 1242, 1170, 1108, 1066, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J=7.2 Hz, 2H), 7.57 (t, J=7.2 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.35 (m, 5H), 6.52 (s, 1H), 6.16 (t, J=8.7 Hz,1H), 5.64 (d, J=6.9 Hz, 1H), 5.43 (br d, J=9.3 Hz, 1H), 5.24 (br d, J=8.1 Hz, 1H), 4.91 (d, J=8.1 Hz, 1H), 4.63 (m, 3H), 4.26 (m, 2H), 4.14 (d, J=8.4 Hz, 1H), 3.83 (d, J=6.9 Hz, 1H), 3.46 (d, J=5.4 Hz, 1H), 2.77 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.79 (m, 2H), 1.72 (s, 3H), 1.32 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.7, 170.3, 169.2, 167.0, 155.3, 140.3, 138.4, 133.7, 133.2, 130.2, 129.1, 128.8, 128.7, 128.0, 126.7, 83.9, 81.3, 80.2, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 73.6, 72.3, 57.4, 56.1, 47.1, 43.2, 35.3, 32.8, 28.2, 26.5, 22.6, 21.0, 15.1, 14.6, 10.9.

Preparation IV.

3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel



To a solution of HMDS (0.40 mL, 1.90 mmol) in 15 mL of THF was added a solution of n-BuLi (0.75 mL, 2.5 M in hexanes, 1.88 mmol) and stirred 5 minutes at -55°C. To this solution was added 7-O-MTM baccatin III (1.03 g, 1.59 mmol) in 10 mL of THF and stirred for 10 minutes before addition of an 10 mL solution of (2R,3R)-1-(t-butyloxycarbonyl)-4-(2-furyl)-3-(triethylsilyloxy)-2-azetidinone (883 mg, 2.40 mmol) in THF. The cold bath was removed and replaced with a 0°C bath and the reaction stirred for 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (2.5:1 hexane/ethyl acetate) to give 1.5 g of the coupling product 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (93%).

FABMS (NOBA) M+Na calcd for $C_{50}H_{71}NSSiO_{16}$: 1036. Found: 1036.

IR(film) 3446 (s), 1720, 1368, 1242, 1166, 1144, 1124, 1066 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.56 (m, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.36 (m, 1H), 6.56 (s, 1H), 6.33 (m, 1H), 6.20 (m, 2H), 5.67 (d, J=6.9 Hz, 1H), 5.29 (br s, 2H), 4.94 (d, J=7.8 Hz, 1H), 4.75 (s, 1H), 4.65 (s, 2H), 4.28 (m, 2H), 4.16 (d, J=8.1 Hz, 1H), 3.89 (d, J=6.9 Hz, 1H), 2.80 (m, 1H), 2.46 (s, 3H), 2.37 (m, 1H), 2.22 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.65 (m, 1H), 1.33 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H), 0.81 (t, J=7.8 Hz, 9H), 0.47 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 171.2, 170.3, 169.3, 167.1, 155.3, 152.0, 141.9, 141.0, 133.6, 132.9, 130.2, 129.2, 128.7, 110.7, 107.3, 84.0, 81.1, 80.2, 78.7, 76.1, 75.7, 74.7, 74.1, 72.4, 71.1, 57.4, 52.8, 47.1, 43.3, 35.2, 33.0, 28.1, 26.3, 22.9, 21.2, 21.0, 15.0, 14.5, 10.9, 6.5, 4.3.

To a solution of the silyl ether obtained above (330 mg, 0.32 mmol) in 7 mL of THF was added tetrabutylammonium fluoride (0.35 mL, 1.0M in THF, 0.35 mmol) and stirred 10 minutes. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated and the residue was chromatographed over silica gel (2:1 hexane/ethyl acetate) to give 301 mg of the title compound (95%).

FABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{16}S$: 900. Found: 900.

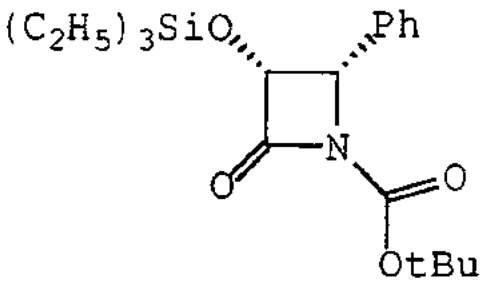
IR(film) 3442, 1720, 1242, 1066, 1026 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 2H), 7.57 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.38 (s, 1H), 6.53 (s, 1H), 6.34 (d, J=3.2 Hz, 1H), 6.29 (d, J= 3.2 Hz, 1H), 6.17 (t, J=8.1 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.29 (m, 2H), 4.92 (d, J=8.0 Hz, 1H), 4.70 (m, 1H), 4.64 (d, J=4.6 Hz, 2H), 4.29 (m, 2H), 4.14 (d, J=8.3 Hz, 1H), 3.86 (d, J=6.8 Hz, 1H), 3.37(d, J = 5.8 Hz, 1H), 2.77 (m, 1H), 2.38 (s, 3H), 2.32 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.75 (m, 6H), 1.33 (s, 9H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.6, 170.3, 169.2, 167.0, 155.2, 151.3, 142.4, 140.4, 133.7, 133.2, 130.2, 129.1, 128.7, 110.7, 107.4, 83.9, 81.2, 80.5, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 72.5, 71.8, 57.4, 51.7, 47.2, 43.2, 35.2, 32.8, 28.1, 26.4, 22.6, 20.9, 15.2, 14.6, 10.9, 8.3.

Preparation V.

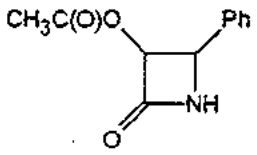
(3R, 4S)-1-t-Butoxycarbonyl-4-phenyl-3-triethylsilyloxy-2-azetidinone



To a stirred solution of (3R,4S)-4-phenyl-3-triethylsilyloxy-2-azetidinone (2.200 g, 7.92 mmol) in dry tetrahydrofuran (25 mL) was added N,N-diisopropylethylamine (1.65 mL, 9.510 mmol, 1.2 equiv) at 0°C under an argon atmosphere. The solution was stirred for 5 min followed by the addition of di-t-butyl dicarbonate (2.080 g, 9.510 mmol, 1.2 equiv) and 4-dimethylaminopyridine (193.6 mg, 1.581 mmol, 0.20 equiv). The reaction mixture was stirred at 0°C for 60 min., then diluted with ethyl acetate (25 mL). The resulting solution was washed with brine, 10% $NaHCO_3$, 10% HCl solution, dried ($MgSO_4$), and concentrated to give a crude compound (oil). The compound was further purified by silica gel flash chromatography (being eluted with 15% ethyl acetate in hexanes) to afford the title compound as a white solid (2.4 g, Y: 83%).

Preparation VI.

(±)-cis-3-Acetyloxy-4-phenylazetidin-2-one



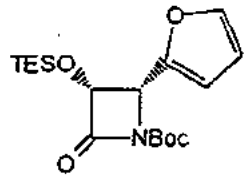
(a) To a 1 L, 3-necked round bottom flask equipped with a thermometer, magnetic stirrer and dropping funnel was added hydrobenzamide (30.00 g, 100.5 mmol) and ethyl acetate (150 mL). With stirring and under a blanket of argon, the reaction mixture was cooled to 5°C and triethylamine (16.8 mL, 121 mmol) was added. A solution of acetoxyacetyl chloride (12.4 mL, 116 mmol) in ethyl acetate (300 mL) was then added dropwise over a 90 min period. After 16 h at this temperature, the reaction mixture was allowed to warm to 20°C (1.5 h) and transferred to a separatory funnel. The organic layer was washed successively with aqueous NH_4Cl (sat) (150 mL, 100 mL), aqueous $NaHCO_3$ (saturated) (120 mL) and brine (120 mL). For purposes of characterization, the title compound can be isolated at this stage by drying the organic phase over $MgSO_4$, filtering, and removing the solvent in vacuo. This provided (±)-cis-3-acetyloxy-1-[(phenyl)(benzylidenimino)methyl]-4-phenylazetidin-2-one in quantitative crude yield as a red glass.

(b) A solution of the compound obtained in part (a) in ethyl acetate (500 mL) was carefully transferred, under a stream of argon, to a 2.0 L Parr flask containing 10% palladium on activated charcoal (6.00 g). This mixture was treated with hydrogen (4 atm) for 20 h whereupon the catalyst was removed by filtration through a pad of Celite. The filter cake was slurried in ethyl acetate (200 mL), stirred (10 min) and filtered. The filter cake was rinsed with ethyl acetate (100 mL) and the filtrates combined. The organic layer was washed with 10% HCl (300 mL) and both layers filtered through a sintered glass funnel to remove the white precipitate (dibenzylamine·HCl) which was rinsed

with ethyl acetate (100 mL). The phases were separated and the organic layer was washed with another portion of 10% HCl (200 mL). The combined 10% HCl washes were re-extracted with ethyl acetate (200 mL) and the combined organic layers were washed with aqueous $NaHCO_3$ (saturated) (300 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a final volume of 75 mL. This mixture was cooled to 4°C and the precipitated product isolated by filtration. The filter cake was washed with hexane (200 mL) to provide 16.12 g (78.1% overall yield from hydrobenzamide) of the title compound as white needles.
mp = 150-151°C

Preparation VII.

(±)- cis-3-Triethylsilyloxy-4-(2-furyl)-N-t-butoxycarbonylazetidin-2-one



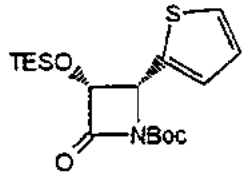
(a) The procedure described in Preparation VI, part (a), was followed except that hydrofuramide [i.e. 2-furyl-CH-(N=CH-2-furyl)$_2$] was used instead of hydrobenzamide and the reaction was performed on 18.6 mmol (vs 100 mmol) scale. Thus, hydrofuramide (5.00 g, 18.6 mmol), triethylamine (3.11 mL, 22.3 mmol) and acetoxyacetyl chloride (2.30 mL, 21.4 mmol) gave 6.192 g (Y: 90.4%) of (±)-cis-3-acetyloxy-1-[(2-furyl)(2-furylmethylenimino)methyl]-4-(2-furyl)azetidin-2-one as a pale red syrup.
(b) The procedure described in Preparation VI, part (b), was followed except that the product was isolated by preparative TLC and the reaction was performed on the 2.7 mmol scale based on the original amount of hydrofuramide. Thus, the crude product obtained in part (a) above was re-dissolved in ethyl acetate (50 mL) and added to 10% palladium on activated charcoal (150 mg). Purification of the crude solid by preparative TLC (2 mm silica gel, eluted with 1:1 ethyl acetate/hexane) gave 386 mg (65.8% corrected overall yield from hydrofuramide) (±)-cis-3-(acetyloxy)-4-(2-furyl)azetidin-2-one as a yellow solid. This was recrystallized from ethyl acetate/hexane.
mp=118-119°C
(c) The compound obtained in part (b) above (3.78 g, 19.4 mmol) in 60 mL of methanol was stirred with K_2CO_3 (20 mg, 0.14 mmol) for 90 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 80 mL of anhydrous THF and stirred at 0°C with imidazole (1.44 g, 21.2 mmol) and TESCl (3.4 mL, 20.2 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 4.47g (Y: 86%) of (±)- cis-3-triethylsilyloxy-4-(2-furyl)-azetidin-2-one as a colorless oil.
(d) The product of part (c) (2.05 g, 7.7 mmol) in 30 mL of dichloromethane was stirred at 0°C with diisopropylethyl amine (1.5 mL, 8.6 mmol) and di-t-butyl dicarbonate (2.0g, 9.2 mmol) in addition to a catalytic amount of dimethylaminopyridine (DMAP). The solution was diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 8:1 hexane/ethyl acetate) to give 2.0 (Y: 70%) of the title compound as a waxy solid.

The racemic mixture obtained in part (b) may be used as substrate for enzymatic hydrolysis using a lipase such as PS-30 from Pseudomonas sp. (Amano International Co.) to give (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one. The method of enzymatic resolution using the lipase PD-30 and other enzymes is disclosed in our co-pending application U.S.S.N. 092,170, filed July 14, 1993 which is hereby incorporated by reference in its entirety.

The general procedure in parts (c) and (d) was followed using (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one to provide (3R,4R)-N-(t-butoxycarbonyl)-3-triethylsilyoxy-4-(2-furyl)azetidine-2-one.

Preparation VIII.

(±)- cis-3-Triethylsilyloxy-4-(2-thienyl)-N-t-butoxycarbonylazetidin-2-one



(a) The procedure described in Preparation VI, step (a) was followed except that hydrothienamide [i.e. 2-thienyl-CH-(N=CH-2-thienyl)$_2$] was used instead of hydrobenzamide. Thus, hydrothienamide (30 g, 94.7 mmol), thiethylamine (15.84 mL, 114 mmol) and acetoxyacetyl chloride (11.6 mL, 108 mmol) provided (±)-cis-3-acetyloxy-1-[(2-thienyl)(2-trienylmethylenimino)methyl]-4-(2-thienyl)azetidin-2- one as viscous oil.

(b) A 70% aqueous solution of acetic acid (0.35 mL glacial acetic acid and 0.15 mL water) was added in one portion to a stirred solution of the product obtained in part (a) (.431 g, 1.03 mmol) in dichloromethane (2.93 ml) at 25°C. The reaction mixture was brought to reflux and stirred for 2.5 h. The reaction was diluted with 50 mL dichloromethane and then washed with two 75 mL portions of saturated aqueous sodium bicarbonate and then one 50 mL portion of saturated brine. The organic extract was concentrated *in vacuo* to a brown oil, dissolved in a minimal amount of dichloromethane, and then placed on a silica gel column measuring 4" by 0.5". Elution using a gradient of 10 through 60% EtOAc in hexane provided less polar sideproducts and then (±)-cis-3-acetyloxy-4-(2-thienyl)azetidin-2-one (0.154 g, Y: 75%) as a white solid.

(c) A solution of the product obtained in part (b) (2.5 g, 11.8 mmol) was dissolved in methanol (10 mL) and treated with saturated aqueous sodium bicarbonate (10 mL) and the resulting slurry was allowed to stir at ambient temperature for 3 h. The reaction was then diluted with ethyl acetate (20 mL) and washed with water (15 mL). The aqueous fraction was back extracted several times with ethyl acetate and the combined organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid (Y: 1.7 g). The crude material was dissolved in dry tetrahydrofuran (20 mL) and the solution was cooled to 5°C in an ice/water bath. Imidazole (752 mg, 1.1 eq) was then added. After stirring 5 min, triethylchlorosilane (1.85 mL, 1.1 eq) was added dropwise. The resulting suspension was allowed to stir for 3 h at that temperature; then the solids were removed by filtration. The organic fraction was washed with water (2x 20 mL) then dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (eluted with hexanes/ethyl acetate 7:3) to give (±)-cis-3-triethylsilyloxy-4-(2-thienyl)-azetidin-2-one as a colorless solid (1.5 g, Y: 45%). m.p. 70-71°C.

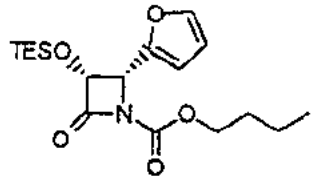
Alternate Run:

The product obtained in part (b) (2.0 g, 9.37 mmol) in 40 mL of methanol was stirred with K_2CO_3 (60 mg, 0.43 mmol) for 30 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 50 mL of anhydrous THF and stirred at 0°C with imidazole (0.85 g, 11.3 mmol) and TESCl (1.9 mL, 12.5 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 2.13g (Y: 86%) of the title product as a colorless oil.

(d) A solution of the product obtained in part (c) (425.7 mg, 1.48 mmol) was dissolved in dichloromethane (10 mL) and cooled to 5°C in an ice/water bath. The reaction was treated with a catalytic amount of DMAP followed by diisopropylethylamine (TESCl, 0.25 mL, 1.0 eq) then by di-t-butyl dicarbonate (388.4 mg, 1.2 eq). After stirring 2 h at that temperature the reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and the organic fraction was washed with water (5 mL) then dried ($MgSO_4$), passed through a short plug of silica gel and concentrated to give the desired product as a colorless oil (525.3 mg, Y: 93%).

Prepartion IX.

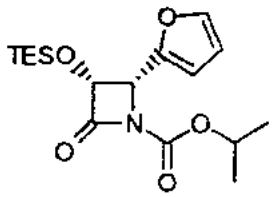
(3R, 4R)-3-Triethylsilyloxy-4-(2-furyl)-N-n-butyloxycarbonylazetidin-2-one



(3R,4R)-3-Triethylsilyloxy-4-(2-furyl)azetidin-2-one (0.58 g, 2.17 mmol) in 30 mL of dichloromethane was stirred with diisopropylethyl amine (0.4 mL, 2.30 mmol) and butylchloroformate (0.3 mL, 2.36 mmol) in addition to a catalytic amount of DMAP. The solution was stirred for 1 h and diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 523 mg of product (Y: 65%); IR(KBr) 1820, 1734, 1318, 1018, 734 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 1H), 6.35 (m, 2H), 5.09 (ABq, J=15.5, 5.6 Hz, 2H), 4.14 (m, 2H), 1.56 (m, 2H), 1.28 (s, 2H), 0.87 (t, J=8.7 Hz, 3H), 0.82 (t, J=7.9, 9H), 0.50 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 165.4, 149.1, 147.6, 142.9, 110.5, 109.9, 77.7, 66.6, 55.9, 30.5, 18.8, 13.6, 6.3, 4.3; DCIMS M+H calcd for $C_{18}H_{29}NO_5Si$: 368, Found: 368.

Preparation X.

(3R,4R)-3-Triethylsilyloxy-4-(2-furyl)-N-isopropyloxycarbonylazetidin-2-one

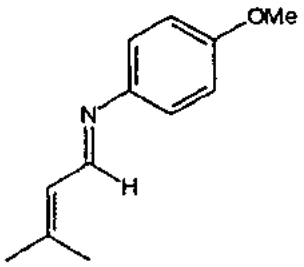


(3R, 4R)-3-Triethylsilyloxy-4-(2-furyl)azetidin-2-one (0.51 g, 1.91 mmol) in 25 mL of dichloromethane was stirred with diisopropylethyl amine (0.78 mL, 4.4 mmol) and i-propylchloroformate (4.0 mL, 1.0M in toluene, 4.0 mmol) in addition to a catalytic amount of DMAP. The solution was stirred for 1 h and diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 5:1 hexane/ethyl acetate) to give 649 mg of the title product (Y: 96%); IR(KBr) 1822, 1812, 1716, 1374, 1314, 1186, 1018, 1004, 746 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 1H), 6.35 (m, 2H), 5.08 (ABq, J=15.6, 5.6 Hz, 2H), 4.96 (d, J=10.0 Hz, 1H), 1.25 (d, J=6.3 Hz, 3H), 1.17 (d, J=6.3 Hz, 3H)), 0.83 (t, J=7.8, 9H), 0.50 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 165.5, 148.6, 147.8, 142.9, 110.5, 109.9, 77.6, 71.1, 55.9, 21.7, 21.6, 6.3, 4.4; DCIMS M+H calcd for $C_{17}H_{26}NO_5Si$: 354, Found: 354.

Preparation XI.

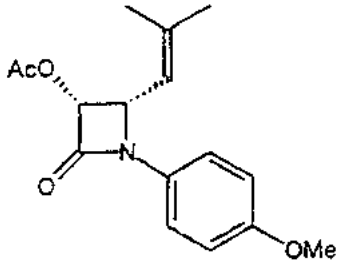
(±)-cis-3-Triethylsilyloxy-4-isobutenyl-N-t-butoxycarbonylazetidin-2-one

(a) preparation of N-4-methoxy-N-(3-methyl-2-butenyl)benzenamine



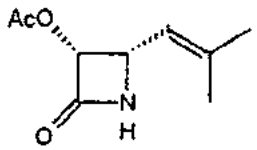
A solution of p-anisidine (5.7 g, 46.3 mmol) was dissolved in diethylether (100 mL) and was treated with a catalytic amount of p-toluensulfonic acid (10 mg). To this was added 3-methyl-2-butenal (2.67 mL, 50.9 mmol) in one portion and the reaction was allowed to stir at ambient temperature for 16 h. The solvent was then evaporated on a rotary evaporator at 0.5 torr to furnish the desired imine (8.7 g, 100%) as a brown oil; ^{1}H NMR 300 MHz, $CDCl_3$): δ 8.38 (d, 1H, J= 9.5 Hz), 7.11 (dd, 2H, J= 2.2, 6.7 Hz), 6.88 (dd, 2H, J= 2.2, 6.7 Hz), 6.22-6.18 (m, 1H), 3.81 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H).

(b) preparation of (±)-cis-N-(4-methoxyphenyl)-3-acetyloxy-4-isobutenylazetidin-2-one



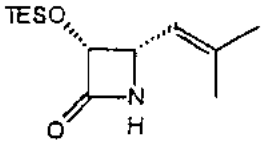
A solution of acetoxyacetyl chloride (6.9 g, 50.5 mmol) was dissolved in ethyl acetate (100 mL) and cooled to -30°C under an inert atmosphere. To this solution was added triethylamine (7.0 mL, 50.5 mmol) over a 5 min period. The resulting white slurry was then treated with an ethyl acetate solution of N-4-methoxy-N-(3-methyl-2-butenyl)benzenamine (8.7g, 40 mL) dropwise over a 20 min period. The resulting green-brown slurry was then gradually allowed to warm to ambient temperature over a 4 h period. The slurry was then filtered through a pad of celite and the filtrate was washed with water then brine. The organic fraction was dried ($MgSO_4$) and concentrated to give a brown oil. The crude product was purified by careful silica gel chromatography (eluted with hexanes/ethyl acetate 8:2) to furnish an orange oil which solidified on standing. This was recrystallized from dichloromethane/hexanes to furnish the desired product as a pale yellow solid (4.4 g, 32%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, J= 9.1 Hz), 6.86 (d, 2H, J= 9.1 Hz), 5.59 (dd, 1H, J= 3.0, 7.8 Hz), 5.14-5.10 (m, 1H), 4.96 (dd, 1H, J= 4.8, 9.3 Hz), 3.77 (s, 3H), 2.11 (s, 3H,), 1.81 (s, 3H), 1.78 (s, 3H).

(c) preparationn of (±)-cis-3-Acetyloxy-4-isobutenylazetidin-2-one



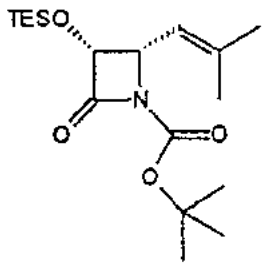
A solution of the (±)-cis-N-(4-methoxyphenyl)-3-acetyloxy-4-isobutenylazetidin-2-one (4.88g, 16.2 mmol) was dissolved in acetonitrile (50 mL) and cooled to 0-5°C in an ice bath. To this was added a cold solution of ceric ammonium nitrate (26.6 g, 48.6 mmol, 50 mL) in one portion. The deep red reaction was allowed to stir for 10 min and during that time the color gradually lightened to orange. The cold solution was transferred to a separatory funnel, diluted with water, and extracted with ethyl acetate. The organic fraction was washed with several portions of 10% aqueous sodium sulfite, followed by saturated aqueous sodium bicarbonate. The organic fraction was dried ($MgSO_4$) and concentrated to give the desired product (2.71g, 91%) as a yellow-orange solid that was used directly in the next step; ^1H NMR (300 MHz, $CDCl_3$): δ 6.11 (bs, 1H), 5.73 (dd, 1H, J= 2.2, 4.7 Hz), 5.12-5.08 (m, 1H), 4.63 (dd, 1H, 4.7, 9.1 Hz), 2.09 (s, 3H), 1.75 (s, 3H), 1.67 (s, 3H).

(d) preparation of (±)-cis-3-Triethylsilyloxy-4-isobutenylazetidin-2-one



(±)-cis-3-Acetyloxy-4-isobutenylazetidin-2-one (1.47 g, 8.0 mmol) was dissolved in methanol (15 mL) and was stirred with K_2CO_3 (110.5 mg,0.8 mmol) for 3h at ambient temperature. The solution was then neutralized with Dowex 50W-X8 resin and then filtered. The filtrate was concentrated and the crude solid was dissolved in THF (25 mL) and cooled to 5°C in an ice bath. Imidazole (544.0 mg, 8.0 mmol) was added and once dissolved, triethylsilyl chloride (1.34 mL, 8.0 mmol) was added dropwise via syringe. The resulting slurry was allowed to warm to ambient temperature and stir overnight. The solution was filtered and the filtrate was washed with water, then brine. The organic fraction was dried ($MgSO_4$) and concentrated. The crude solid was purified by silica gel chromatography (eluted with hexanes/ethyl acetate 3:1) to furnish the desired product (612 mg, 30%) as a pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87 (bs, 1H), 5.31-5.26 (m, 1H), 4.90 (dd, 1H, J= 2.2, 4.7 Hz), 4.42 (dd, 1H, J= 4.7, 9.3 Hz), 1.74 (s, 3H), 1.28 (s, 3H), 0.98-0.91 (m, 9H), 0.71-0.55 (m, 6H).

(e) preparation of (±)-cis-3-Triethylsilyloxy-4-isobutenyl-N-t-butoxycarbonylazetidin-2-one

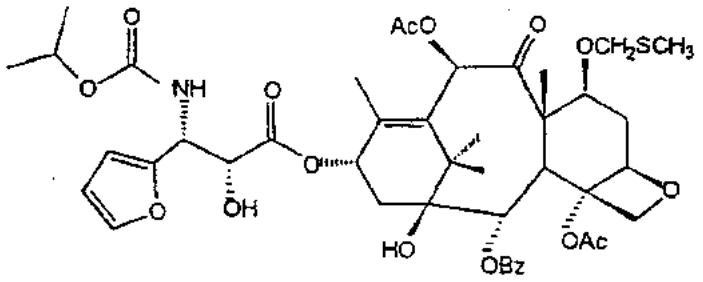


(±)-cis-3-Triethylsilyloxy-4-isobutenylazetidin-2-one (1.01 g, 3.95 mmol) was dissolved in dichloromethane (20 mL) and was treated with diisopropylethylamine (0.68 mL, 3.95 mmol) and a catalytic amount of dimethylaminopyridine. To this solution was added di-t-butyl dicarbonate (1.02 g, 4.68 mmol) and the solution was allowed to stir for 24 h at ambient temperature. The solution was then diluted with additional dichloromethane and washed with water then brine. The organic fraction was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (eluted with hexanes/ethyl acetate 8:2) to give the desired product (1.26 g, 90%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.24 (d, 1H, J= 9.6 Hz), 4.86 (d, 1H, J= 5.7 Hz), 4.72 (dd, 1H, J= 6.0, 9.9 Hz), 1.78 (d, 3H, J= 1.1 Hz), 1.75 (d, 3H, J= 1.1 Hz), 1.47 (s, 9H), 0.96-0.91 (m, 9H), 0.64-0.55 (m, 6H).

Other N-subsituted azetidinones useful in the preparation of compounds of the instant invention may be made by following the teachings of Preparations V to XI.

Preparation XII.

3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel



To a solution of the 7-MTM baccatin III (2.0 g, 3.1 mmol) in 40 mL of THF at -50 °C was added LiHMDS (3.7 mL, 1.0M, 3.7 mmol) followed by (3R,4R)-1-(isopropyloxycarbonyl)-4-(2-furyl)-3-(triethylsilyloxy)-2-azetidinone (883 mg, 2.40 mmol) in 25 mL of THF after stirring 10 min. (4.05g, 11.5 mmol). The solution was brought to 0 °C and stirred for 30 min. The solution was quenched with saturated NH_4Cl and extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (2.5:1 hexane/ethyl acetate) to give 2.8 g of silyl ether.

The silyl ether was dissolved in 30 mL of THF as stirred 10 min with Bu_4NF (3.0 mL, 1.0M, 3 mmol) diluted with ethyl acetate and washed with brine. The organic fraction was dried ($MgSO_4$), concentrated and the residue purified over silica gel (1:1 hexane/ethyl acetate) to give 2.0 g of the title product (72%).

HRFABMS (NOBA) M+H calcd for $C_{44}H_{56}NO_{16}S$ 886.3320. Found: 886.3345.

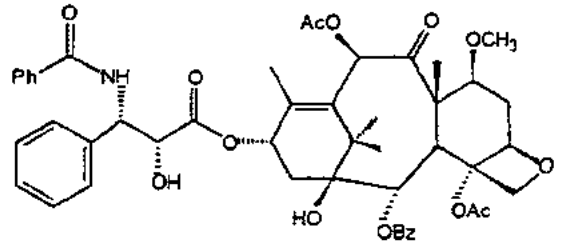
IR(film) 3448 (br), 1718, 1372, 1240, 1108, 1066 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (m, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.39 (s, 1H), 6.53 (s, 1H), 6.36 (m, 1H), 6.31 (m, 1H), 6.20 (t, J=8.1 Hz, 1H), 5.66 (d, J=6.9 Hz, 1H), 5.34 (s, 2H), 4.92 (d, J=7.8 Hz, 1H), 4.79 (m, 1H), 4.70 (m, 1H), 4.65 (ABq, J=12, 3.6 Hz, 2H), 4.29 (m, 2H), 4.15 (d, J=8.4 Hz, 1H), 3.86 (d, J=6.9 Hz, 1H), 3.39 (br s, 1H), 2.77 (m, 1H), 2.38 (s, 3H), 2.30 (m, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.72

(s, 1H), 1.20-1.10 (m, 12H)
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.8, 170.4, 169.2, 167.0, 142.5, 140.2, 133.7, 133.4, 130.2, 129.1, 128.6, 110.7, 107.6, 83.9, 81.3, 78.7, 77.2, 76.1, 75.5, 74.6, 74.0, 72.3, 71.8, 69.1, 57.5, 51.9, 47.2, 43.2, 35.3, 32.9, 26.5 22.5, 22.0, 21.9, 20.9, 15.1, 14.6, 10.9.

Example 1.

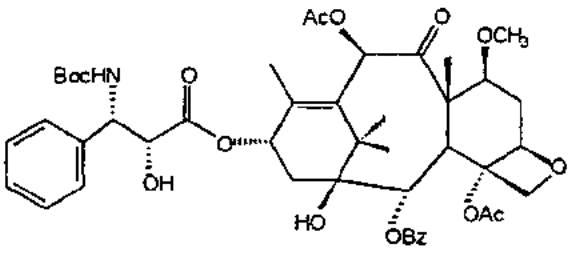
7-O-methylpaclitaxel



Raney nickel (~0.5 g) was added to a solution of 7-O-methylthiomethylpaclitaxel (73 mg, 0.0799 mmol) in 20 mL of ethyl acetate. This solution was hydrogenated on a Parr apparatus at 50 PSI (pounds per square inch) and ambient temperature for 6 h. Filtration through celite, concentration in vacuo, and purification by flash chromatography over silica gel using 1:2 ethyl acetate:hexane as eluent provided 45 mg (65%) of the title compound as a white foam.
IR (KBr) 3424, 3064, 2928, 1724, 1652, 1602, 1580, 1486, 1316, 1270, 1244, 1178 cm^{-1}
^1H NMR ($CLCl_3$) δ 1.203 (s, 6H), 1.203-2.353 (obscured multiplets, 4H), 1749 (s, 3H), 1794 (s, 3H), 2.190 (s, 3H), 2.353 (s, 3H), 2.667 (m, 3H), 3.336 (s, 3H), 3.796 (d, 1H), 4.134 (d, 1H, 4.276 (d, 1H), 4.765 d, 1H), 4.875 (d, 1H), 5.630 (d, 1H), 5.768 (d, 1H), 6.155 (t, 1H), 6.333 (s, 1H), 7.096 (d, 1H), 7.348-8.150 (m, 15H).
MS: $[M+Na]^+$ = 890; $[M+K]^+$ = 906
HRMS MH+ = $C_{48}H_{53}NO_{14}$ calcd. = 868.3544. Found = 868.3511.

Example 2.

3'-N-Debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylpaclitaxel



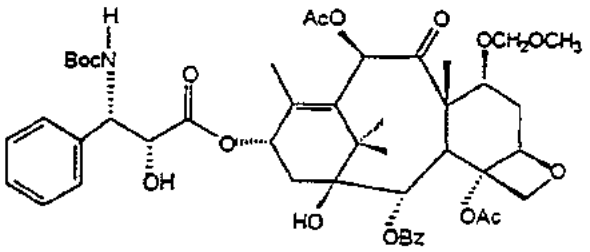
To a solution of 3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel (570 mg, 0.63 mmol) in 40 mL of ethanol was added 1-2 g of wet Raney Nickel. The suspension was refluxed for 20 min and filtered through Celite and washed with ethyl acetate. The filtrate was concentrated and the residue chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 424 mg of the title compound (78%).
HRFABMS (NOBA) M+H calcd for $C_{46}H_{58}NO_{15}$: 864.3807 Found: 864.3797.
IR(film) 3442, 1726, 1370, 1244, 1170, 1106, 1070 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (t, J=7.2 Hz, 2H), 7.58 (m, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.34 (m, 5H), 6.40 (s, 1H), 6.16 (d, J=9.0 Hz, 1H), 5.63 (d, J=6.9 Hz, 1H), 5.40 (d, J=9.4 Hz, 1H), 5.25 (m, 1H), 4.94 (d, J=7.8 Hz, 1H), 4.59 (m,

1H), 4.27 (d, J=8.3 Hz, 1H), 4.14 (d, J=8.3 Hz, 1H), 3.84 (m, 2H), 3.41 (d, J=5.3 Hz, 1H), 3.32 (s, 3H), 2.70 (m, 1H), 2.41 (s, 3H), 2.27 (d, J=8.3 Hz, 2H), 2.20 (s, 3H), 1.87 (s, 3H), 1.76 (m, 1H), 1.70 (s, 3H), 1.33 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 170.4, 169.4, 167.0, 155.3, 140.0, 133.7, 130.1, 129.1, 128.8, 128.7, 128.1, 126.7, 84.1, 81.6, 80.4, 80.2, 78.6, 74.7, 74.5, 73.6, 72.4, 57.6, 57.2, 47.2, 43.3, 35.3, 32.3, 28.2, 26.6, 22.7, 21.1, 21.0, 14.6, 10.4.

Example 3.

3'-N-Debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methoxymethylpaclitaxel



To a solution of the 3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (48 mg, 0.047 mmol) in 1 mL of dichloromethane was added methanol (20 mg, 0.6 mmol) and the solution cooled to 0°C. Then NIS (13 mg, 0.058 mmol) and triethylsilyltriflate (1μL, 0.004 mmol) were added and the dark red solution stirred 30 minutes and then warmed to 25°C for 30 minutes. The solution was diluted with ethyl acetate and washed with 10% $Na_2S_2O_3$ and bicarbonate, dried ($MgSO_4$) and concentrated. (Note: Under this reaction condition, triethylsilyl group is cleaved from 2'-O-position.) The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 32 mg of the title compound (76%).

FABMS (NOBA) M+H calcd for $C_{47}H_{60}NO_{17}$: 894. Found: 894.

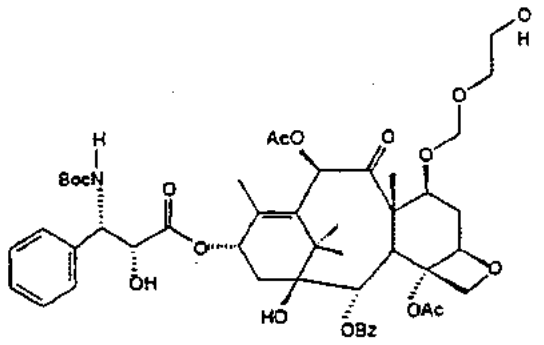
IR(film) 3440, 1722, 1370, 1242, 1106, 1068, 1026 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 2H), 7.59 (t, J=7.3 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.36 (m, 5H), 6.33 (s, 1H), 6.16 (t, J=8.8 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.40 (d, J=9.5 Hz, 1H), 5.24 (br d, J=8.1 Hz, 1H), 4.90 (d, J=7.9 Hz, 1H), 4.68 (d, J=7.6 Hz, 1H), 4.62 (d, J=7.6 Hz, 1H), 4.28 (d, J=8.4 Hz, 1H), 4.14 (d, J= 8.2 Hz, 1H), 4.08 (m, 1H), 3.82 (d, J=6.8 Hz, 1H), 3.40 (d, J=5.2 Hz, 1H), 3.27 (s, 3H), 2.77(m, 1H), 2.33 (s, 3H), 2.27 (d, J=8.9 Hz, 2H), 2.19 (s, 3H), 1.94 (m, 1H), 1.86 (s, 3H), 1.73 (s, 3H), 1.72 (m, 1H), 1.63 (br s, 1H), 1.32 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 172.7, 170.2, 169.4, 167.0, 155.3, 140.2, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.7, 128.1, 126.8, 98.2, 84.3, 81.2, 80.2, 79.9, 78.6, 75.3, 74.5, 73.6, 72.3, 57.3, 56.1, 55.8, 46.9, 43.2, 35.4, 35.3, 28.2, 26.5, 22.6, 20.9, 14.7, 10.7.

Example 4.

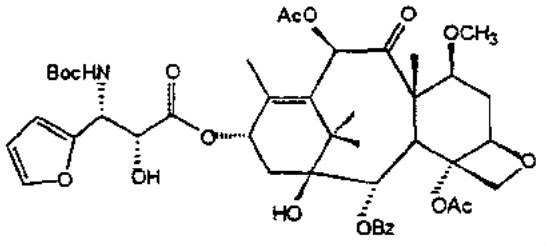
3'-N-Debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel



To a solution of 3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel (47 mg, 0.052 mmol) and ethylene glycol (20 mg, 0.32 mmol) in 1 mL of dichloromethane was added NIS (14 mg, 0.062 mmol) and triethylsilyltriflate (1 µL, 0.004 mmol). The solution was stirred for 15 minutes. The solution was diluted with ethyl acetate and washed with 10% $Na_2S_2O_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate with 5% methanol) to give 37 mg of the title compound (77%).
FABMS (NOBA) M+Na calcd for $C_{48}H_{61}NO_{17}Na$ 946. Found: 946.
IR(film) 3440, 1720, 1242, 1070, 1026, 756 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J=7.5 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.31 (m, 5H), 6.35 (s, 1H), 6.15 (t, J=8.7 Hz, 1H) 5.63 (d, J=6.9 Hz, 1H), 5.44 (br d, J=9.2, 1H), 5.24 (br s, 1H), 4.90 (d, J =8.4 Hz, 1H), 4.74 (s, 2H), 4.59 (br s, 1H), 4.27 (d, J=8.4 Hz, 1H), 4.11 (m, 2H), 3.81 (d, J=6.8 Hz, 1H), 3.66 (m, 3H), 3.48 (m, 2H), 2.75 (m, 1H), 2.33 (s, 3H), 2.26 (m, 2H), 2.18 (s, 3H), 1.90 (m, 2H), 1.87 (s, 3H), 1.78 (m, 1H), 1.72 (s, 3H), 1.32 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.8, 170.3, 169.6, 167.0, 155.3, 140.2, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.7, 128.0, 126.8, 96.8, 84.1, 81.2, 80.2, 79.4, 78.6, 76.5, 75.2, 74.5, 73.6, 72.3, 70.0, 61.8, 57.3, 56.2, 46.9, 43.2, 35.3, 35.0, 28.2, 26.5, 22.6, 21.0, 20.9, 14.6, 10.6.

Example 5.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylpaclitaxel

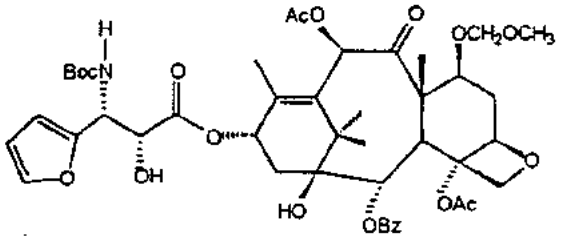


To a solution of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel (360 mg, 0.4 mmol) in 40 mL of ethanol was added 0.5-1.5 g of wet Raney Nickel. The suspension was refluxed for 90 min. and filtered through Celite and washed with ethyl acetate. The filtrate was concentrated and the residue chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 106 mg of recovered 7-MTM ether and 68 mg (28%) of 7-O-methylbaccatin III and 57 mg (16%) of the title compound.
HRFABMS (NOBA) M+H calcd for $C_{44}H_{56}NO_{18}$: 854.3599 Found: 854.3608.

IR(film) 3440, 1722, 1268, 1244, 1106, 756 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (t, J=7.2 Hz, 2H), 7.58 (t, J=7.3, 1H), 7.46 (t, J=7.7 Hz, 2H), 7.39 (m, 1H), 6.42 (s, 1H), 6.35 (m, 1H), 6.30 (m, 1H), 6.18 (t, J=7.6 Hz, 1H), 5.64 (d, J=7.0 Hz, 1H), 5.28 (m, 2H), 4.95 (d, J=7.8 Hz, 1H), 4.69 (dd, J=5.8, 2.1 Hz, 1H), 4.28 (d, J=8.3 Hz, 1H), 4.13 (d, J=8.3 Hz, 1H), 3.86 (m, 2H), 3.36 (d, J=5.6 Hz, 1H), 3.32 (s, 3H), 2.70 (m, 1H), 2.38 (s, 3H), 2.32 (d, J=8.9 Hz, 2H), 2.20 (s, 3H), 1.94 (s, 3H), 1.76 (m, 2H), 1.69 (m, 3H), 1.34 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 172.6, 170.4, 169.4, 167.1, 155.2, 151.3, 142.4, 140.0, 133.7, 130.2, 129.1, 128.7, 110.7, 107.5, 84.1, 81.5, 80.4, 78.6, 76.5, 74.7, 74.5, 72.5, 71.8, 57.6, 57.2, 51.7, 47.2, 43.3, 35.2, 32.3, 28.1, 26.5, 22.6, 21.1, 20.9, 14.6, 10.3.

Example 6.

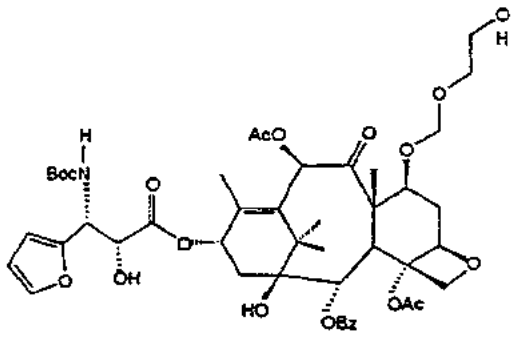
3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methoxymethylpaclitaxel



To a solution of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (65 mg, 0.064 mmol) and methanol (20 mg, 0.6 mmol) in 1 mL of dichloromethane at 0°C was added NIS (16 mg, 0.071 mmol) and triethylsilyltriflate (1 µL, 0.004 mmol). The solution was stirred at 0°C for 30 minutes and then brought to 25°C for 45 minutes. The solution was diluted with ethyl acetate and washed with saturated $NaHSO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 26 mg of the title compound (46%).
FABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{17}$: 884. Found: 884.
IR(film) 3442, 1720, 1268, 1242, 1040, 1026, 756 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (d, J=3.2 Hz, 1H), 6.17 (t, J=8.2 Hz, 1H) 5.65 (d, J=6.9 Hz, 1H), 5.32 (d, J=9.6, 1H), 5.24 (d, J=9.8 Hz, 1H), 4.91 (d, J =8.0 Hz, 1H), 4.69 (m, 2H), 4.62 (d, J=7.5 Hz, 1H), 4.29 (d, J=8.4 Hz, 1H), 4.10 (m, 2H), 3.84 (d, J=6.9Hz, 1H), 3.33 (d, J=5.7 Hz, 1H), 3.27 (s, 3H), 2.77 (m, 1H), 2.37 (s, 3H), 2.31 (d, J=9.0 Hz, 2H), 2.18 (s, 3H), 1.93 (m, 4H), 1.73 (m, 5H), 1.34 (s, 9H), 1.19 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 172.6, 170.2, 169.4, 167.0, 155.2, 151.3, 142.5, 140.2, 133.7, 133.3, 130.2, 129.1, 128.7, 110.7, 107.5, 98.2, 84.3, 81.1, 80.5, 79.8, 78.6, 75.3, 74.6, 72.5, 71.7, 57.4, 55.8, 51.7, 46.9, 43.2, 35.4, 35.2, 28.1, 26.4, 22.6, 21.0, 20.9, 14.6, 10.7.

Example 7.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel



To a solution of the 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel (59 mg, 0.065 mmol) and ethylene glycol (20 mg, 0.32 mmol) in 1 mL of dichloromethane was added NIS (17 mg, 0.076 mmol) and triethylsilyltriflate (1 µL, 0.004 mmol). The solution was stirred for 15 minutes. The solution was diluted with ethyl acetate and washed with 10% $Na_2S_2O_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate 2% methanol) to give 39.4 mg of the title compound (66%).

FABMS (NOBA) M+Na calcd for $C_{45}H_{59}NO_{18}$: 936. Found: 936.

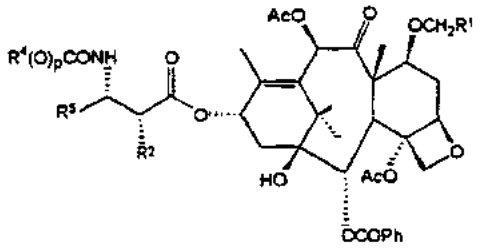
IR(film) 3440, 1722, 1370, 1244, 1166, 1108, 1070, 1050, 1026 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (d, J=1.7 Hz, 1H), 6.37 (s, 1H), 6.35 (m, 1H), 6.30 (d, J=3.2 Hz, 1H), 6.16 (t, J=8.3 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.27 (m, 2H), 4.91 (d, J =8.0 Hz, 1H), 4.73 (m, 3H), 4.28 (d, J=8.3 Hz, 1H), 4.16 (m, 2H), 3.84 (d, J=6.9 Hz, 1H), 3.65 (m, 3H), 3.46 (m, 2H), 2.77 (m, 1H), 2.37 (s, 3H), 2.32 (m, 3H), 2.18 (s, 3H), 1.93 (m, 4H), 1.72 (m, 4H), 1.33 (s, 9H), 1.19 (s, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.6, 170.4, 169.6, 167.0, 155.2, 151.3, 142.4, 140.2, 133.7, 133.4, 130.2, 129.1, 128.7, 110.7, 107.5, 96.7, 84.2, 81.1, 80.5, 79.4, 78.6, 76.5, 75.3, 74.5, 72.4, 71.7, 70.0, 61.8, 57.3, 51.7, 47.0, 43.3, 35.2, 35.0, 28.1, 26.4, 22.6, 21.1, 20.9, 14.6, 10.7.

Examples 8-22

Following the teachings contained herein, the following compounds in Examples 8-22 were prepared.



(I)

Example No.	$R^4(O)_p$	R^5	R^2	R^1
8	tBuO	Ph	OCO_2Et	OCH_3
9	tBuO	Ph	OCO_2Et	OCH_2CH_2OH
10	tBuO	2-furyl	OCO_2Et	H
11	tBuO	Ph	OCO_2Et	H
12	tBuO	2-furyl	OH	$O(CH_2)_4OH$
13	tBuO	2-furyl	OH	$O(CH_2)_5OH$
14	tBuO	2-furyl	OH	$O(CH_2)_3OH$
15	tBuO	2-furyl	OCO_2Et	OCH_2CH_2OH
16	$(CH_3)_2CHO$	2-furyl	OCO_2Et	OCH_2CH_2OH
17	$(CH_3)_2CHO$	2-furyl	OH	OCH_2CH_2OH
18	$(CH_3)_2CHO$	2-furyl	OH	$O(CH_2)_5OH$
19	$(CH_3)_2CHO$	2-furyl	OH	$O(CH_2)_6OH$
20	$(CH_3)_2CHO$	2-furyl	OH	$O(CH_2)_7OH$
21	tBuO	$(CH_3)_2CHCH_2$	OH	H
22	Ph	2-furyl	OH	H

Example 8.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methoxymethylpaclitaxel

HRFABMS (NOBA) M+H calcd for $C_{50}H_{64}NO_{18}$ 966.4123. Found: 966.4102.
IR(film) 1750, 1722, 1370, 1244, 1040 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.48 (t, J=7.3 Hz, 2H), 7.35 (m, 5H), 6.37 (s, 1H), 6.23 (t, J=8.7 Hz, 1H), 5.68 (d, J=6.9 Hz, 1H), 5.40 (br s, 2H), 5.23 (s, 1H), 4.93 (d, J=8.1 Hz, 1H), 4.69 (d, J=7.5 Hz, 1H), 4.63 (d, J= 7.5 Hz, 1H), 4.30 (d, J=8.4 Hz, 1H), 4.17 (m, 4H), 3.87 (d, J=6.6 Hz, 1H), 3.28 (s, 3H), 2.79 (m, 1H), 2.42 (s, 3H), 2.32 (m, 1H), 2.18 (s, 3H), 1.99 (s, 3H), 1.96 (m, 1H), 1.74 (s, 3H), 1.68 (s, 1H), 1.61 (s, 1H), 1.33 (s, 9H), 1.27 (t, J=7.2 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 169.5, 169.3, 168.2, 167.0, 155.1, 154.1, 140.9, 137.2, 133.6, 132.9 130.2, 129.2, 128.9, 128.7, 128.2, 126.4, 98.3, 84.4, 81.1, 80.4, 79.8, 78.8, 76.4, 75.2, 74.8, 72.0, 65.1, 57.3, 55.8, 54.2, 46.9, 43.3, 35.4, 35.1, 28.1, 26.4, 22.7, 21.4, 20.9, 14.5, 14.1, 10.7

Example 9.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{51}H_{66}NO_{19}$ 996.4229. Found: 996.4198.
IR(film) 3502, 1750, 1722, 1372, 1244, 1026 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.48 (t, J=7.3 Hz, 2H), 7.35 (m, 5H), 6.39 (s, 1H), 6.23 (t, J=8.7 Hz, 1H), 5.67 (d, J=6.9 Hz, 1H), 5.40 (br s, 2H), 5.23 (s, 1H), 4.93 (d, J=8.1 Hz, 1H), 4.77 (d, J=7.5 Hz, 1H), 4.74 (d, J = 7.5 Hz, 1H), 4.30 (d, J=8.4 Hz, 1H), 4.17 (m, 4H), 3.86 (d, J=6.6 Hz, 1H), 2.79 (m, 1H), 2.42 (s, 3H), 2.32 (m, 1H), 2.18 (s, 3H), 1.99 (s, 3H), 1.93 (m, 1H), 1.73 (s, 3H), 1.69 (s, 1H), 1.62 (s, 1H), 1.33 (s, 9H), 1.27 (t, J=7.2 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 169.7, 169.5, 168.2, 167.0, 155.1, 154.1, 140.9, 137.2, 135.0, 133.7,133.0, 130.2, 129.2, 128.9, 128.7, 128.2, 126.4, 96.9, 84.2, 81.1, 80.4, 79.5, 78.8, 76.4, 75.2, 74.7, 72.0, 70.0, 65.1, 61.8, 57.2, 54.2, 46.9, 43.3, 35.1, 28.1, 26.4, 22.7, 21.4, 20.9, 14.5, 14.1, 10.7, 9.8.

Example 10.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylpaclitaxel

HRFABMS (NOBA) M+H calcd for $C_{47}H_{60}NO_{18}$ 926.3810. Found: 926.3823.
IR(film) 3380, 1752, 1722, 1242 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.44 (s, 1H), 6.35 (m, 1H), 6.28 (m, 1H), 6.20 (t, J=9.0 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.51 (br d, J=9.9 Hz, 1H), 5.33 (s, 1H), 5.25 (br d, J=10.2 Hz, 1H), 4.97 (d, J= 8.1 Hz, 1H), 4.29 (d, J= 8.1 Hz, 1H), 4.17 (m, 3H), 3.88 (m, 2H), 3.33 (s, 3H), 2.72 (m, 1H), 2.41 (s, 3H), 2.31 (m, 1H), 2.18 (s, 3H), 2.01 (s, 3H), 1.76 (m, 1H), 1.70 (s, 3H), 1.67 (s, 1H), 1.60 (s, 1H), 1.34 (s, 9H), 1.29 (t, J=7.2 Hz, 1H), 1.19 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.4, 169.9, 169.3, 167.7, 167.0, 155.0, 154.0, 150.0, 142.6, 140.8, 133.6, 133.2, 130.2, 129.2, 128.7, 110.7, 107.6, 84.1, 81.4, 80.7, 80.4, 78.7, 76.4, 75.1, 74.8, 74.6, 71.9, 65.1, 57.6, 57.1, 49.7, 47.2, 43.3, 35.0, 32.3, 28.1, 26.4, 22.6, 21.3, 20.9, 14.6, 14.1, 10.4.

Example 11.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylpaclitaxel

HRFABMS (NOBA) M+H calcd for $C_{49}H_{62}NO_{17}$ 936.4018. Found: 936.4058.
IR(film) 3448, 1750, 1724, 1370, 1244, 1172 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.48 (t, J=7.3 Hz, 2H), 7.35 (m, 5H), 6.43 (s, 1H), 6.23 (t, J=8.7 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.40 (br s, 2H), 5.20 (s, 1H), 4.96 (d, J=8.1 Hz, 1H), 4.30 (d, J=8.4 Hz, 2H), 4.16 (m, 3H), 3.88 (m, 2H), 3.33 (s, 3H), 2.70 (m, 1H), 2.42 (s, 3H), 2.31 (m, 1H), 2.19 (s, 3H), 1.76 (m, 1H), 1.70 (s, 3H), 1.67 (s, 1H), 1.60 (s, 1H), 1.33 (s, 9H), 1.27 (t, J=7.2 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 169.7, 169.3, 168.2, 167.0, 155.1, 154.1, 140.8, 137.2, 133.7, 133.2, 130.2, 129.2, 128.9, 128.7, 128.2, 126.4, 84.2, 81.4, 80.4, 78.9, 76.4, 74.7, 74.7, 72.1, 65.1, 57.6, 57.0, 54.1, 47.2, 43.3, 35.0, 32.2, 28.1, 26.5, 22.7, 21.5, 20.9, 14.5, 14.1, 10.4.

Example 12.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(4-hydroxybutyloxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{48}H_{64}NO_{18}$ 942.4123. Found: 942.4112.
IR(film) 3450, 1718, 1242 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (s, 1H), 6.17 (t, J=9.6 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.27 (br m, 2H), 4.92 (d, J= 7.8 Hz, 1H), 4.71 (m, 2H), 4.29 (d, J= 8.4 Hz, 1H), 4.14 (m, 2H), 3.84 (d, J=6.8 Hz, 1H), 3.61 (m, 3H), 3.39 (s, 1H), 2.79 (m, 1H), 2.37 (s, 3H), 2.32 (d, J=9.0 Hz, 2H), 2.19 (s, 3H), 1.96 (m, 1H), 1.93 (s, 3H), 1.72 (s, 3H), 1.62 (m, 8H), 1.34 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.6, 170.3, 169.4, 167.0, 151.3, 142.4, 140.2, 133.7, 133.4, 130.2, 129.1, 128.7, 110.7, 108.3, 107.4, 96.8, 84.3, 81.2, 80.5, 79.7, 78.6, 77.2, 75.2, 74.6, 72.4, 72.4, 71.8, 68.2, 62.6, 57.4, 53.0, 51.4, 46.9, 43.3, 42.0, 35.2, 33.1, 29.7, 28.1, 26.4, 26.1, 22.6, 21.0, 20.9, 14.7, 12.6, 10.6.

Example 13.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(5-hydroxypentyloxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{49}H_{68}NO_{18}$ 956.4290. Found: 956.4290.
IR(film) 3441, 1721, 1169 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.38 (s, 1H), 6.34 (m, 2H), 6.30 (s, 1H), 6.17 (t, J=9.6 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.32 (s, 2H), 4.92 (d, J= 7.8 Hz, 1H), 4.69 (s, 3H), 4.29 (d, J= 8.4 Hz, 1H), 4.16 (m, 2H), 3.84 (d, J=6.8 Hz, 1H), 3.56 (m, 4H), 3.38 (m, 1H), 2.79 (m, 1H), 2.37 (s, 3H), 2.30 (d, J=8.7 Hz, 2H), 2.18 (s, 3H), 1.93 (s, 4H), 1.75 (m, 3H), 1.72 (s, 3H), 1.54 (m, 5H), 1.42 (m, 2H), 1.35 (s, 9H), 1.19 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.4, 170.7, 169.4, 166.9, 151.4, 142.4, 140.2, 133.7, 133.4, 130.1, 130.1, 129.2, 128.6, 110.6, 107.4, 96.2, 84.3, 81.3, 80.4, 78.9, 78.6, 75.3, 74.6, 72.2, 71.9, 68.2, 62.8, 57.3, 51.8, 46.9, 43.2, 35.3, 34.9, 32.5, 29.3, 28.2, 26.5, 22.6, 21.0, 20.9, 14.8, 10.6.

Example 14.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(3-hydroxypropyloxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{47}H_{62}NO_{18}$ 928.3967. Found: 928.3987.
IR(film) 3441, 1718, 1242, 1108, 1049 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.57 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (s, 1H), 6.16 (t, J=9.6 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.30 (s, 2H), 4.90 (d, J= 7.8 Hz, 1H), 4.70 (s, 3H), 4.28 (d, J= 8.4 Hz, 1H), 4.12 (m, 2H), 3.84 (d, J=6.8 Hz, 1H), 3.73 (m, 3H), 3.49 (m, 2H), 2.76 (m, 1H), 2.37 (s, 3H), 2.32 (d, J=9.0 Hz, 2H), 2.18 (s, 3H), 1.97 (s, 2H), 1.92 (s, 3H), 1.76 (m, 6H), 1.33 (s, 9H), 1.19 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.6, 170.3, 169.5, 167.0, 155.2, 151.3, 142.4, 140.2, 133.7, 133.4, 130.2, 129.1, 128.7, 110.7, 107.5, 96.8, 84.3, 81.1, 80.5, 79.6, 78.6, 77.2, 76.4, 75.2, 74.6, 72.4, 71.8, 66.7, 61.0, 57.3, 51.7, 46.9, 43.3, 35.2, 32.1, 29.5, 28.1, 26.4, 22.6, 21.1, 20.9, 14.7, 10.6.

Example 15.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{49}H_{64}NO_{20}$ 986.4022. Found: 986.4067.
IR(film) 3449, 1753, 1722, 1372, 1242, 1039, 1026 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.39 (s, 1H), 6.35 (m, 1H), 6.28 (m, 1H), 6.21 (t, J=9.6 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.51 (br d, J=10.5 Hz, 1H), 5.32 (s, 1H), 5.26 (br d, J=9.9 Hz, 1H), 4.93 (d, J= 7.8 Hz, 1H), 4.73 (ABq, J=7.5, 3.9 Hz, 2H), 4.30 (d, J= 8.4 Hz, 1H), 4.17 (m, 4H), 3.87 (d, J=6.8 Hz, 1H), 3.69 (m, 3H), 3.51 (m, 1H), 2.78 (m, 1H), 2.41 (s, 3H), 2.30 (m, 2H), 2.17 (s, 4H), 2.00 (s, 3H), 1.93 (m, 1H), 1.73 (s, 3H), 1.69 (s, 1H), 1.34 (s, 9H), 1.29 (t, J=7.2 Hz, 3H), 1.19 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 169.9, 169.5, 167.7, 167.0, 155.1, 154.0, 150.1, 142.6, 140.9, 133.7, 132.9, 130.2, 128.7, 110.7, 107.6, 97.0, 84.2, 81.0, 80.7, 79.6, 78.7, 77.2, 76.4, 75.3, 75.1, 74.7, 71.9, 70.0, 65.1, 61.8, 57.2, 49.7, 47.0, 43.3, 35.1, 35.0, 28.1, 26.3, 22.6, 21.2, 20.9, 14.8, 14.6, 14.1, 10.6.

Example 16.

2'-O-Ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{48}H_{62}NO_{20}$ 972.3865. Found: 972.3895.
IR(film) 3510, 1752, 1722, 1244 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.38 (s, 1H), 6.35 (m, 1H), 6.28 (m, 1H), 6.22 (t, J=9.6 Hz, 1H), 5.66 (d, J=6.9 Hz, 1H), 5.52 (br d, J=10.5 Hz, 1H), 5.33 (s, 1H), 5.31 (br d, J=10.0 Hz, 1H), 4.93 (d, J= 7.8 Hz, 1H), 4.75 (m, 3H), 4.30 (d, J= 8.4 Hz, 1H), 4.19 (m, 4H), 3.86 (d, J=6.8 Hz, 1H), 3.67 (m, 3H), 3.50 (m, 1H), 2.78 (m, 1H), 2.40 (s, 3H), 2.28 (m, 2H), 2.17 (s, 3H), 2.00 (s, 3H), 1.92 (m, 1H), 1.73 (s, 3H), 1.71 (s, 1H), 1.62 (s, 1H), 1.29 (t, J=6.9 Hz, 3H), 1.18 (s, 6H), 1.16 (d, J= 6.3 Hz, 3H), 1.12 (d, J= 6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 169.9, 169.5, 167.5, 167.0, 153.9, 149.9, 142.7, 140.8, 133.6, 133.1, 130.2, 129.1,

128.7, 110.7, 107.7, 97.0, 84.2, 81.0, 79.5, 78.8, 75.2, 75.0, 74.7, 71.8, 70.0, 69.3, 65.2, 61.8, 57.2, 50.0, 46.9, 43.2, 35.1, 26.4, 22.6, 21.9, 21.8, 21.3, 20.9, 14.5, 14.1, 10.7.

Example 17.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{45}H_{58}NO_{19}$ 900.3654. Found: 900.3640.
IR(film) 3440, 1722, 1242 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.37 (s, 1H), 6.35 (m, 1H), 6.31 (m, 1H), 6.18 (t, J=7.8 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.38 (m, 2H), 4.90 (d, J= 7.8 Hz, 1H), 4.75 (m, 4H), 4.28 (d, J= 8.4 Hz, 1H), 4.16 (m, 2H), 3.83 (d, J=6.8 Hz, 1H), 3.66 (m, 3H), 3.50 (m, 2H), 2.77 (m, 1H), 2.37 (s, 3H), 2.29 (m, 2H), 2.18 (s, 3H), 1.91 (s, 4H), 1.75 (m, 2H), 1.72 (s, 4H), 1.20 (s, 3H), 1.18 (s, 3H), 1.16 (d, J= 6.3 Hz, 3H), 1.11 (d, J= 6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.3, 170.5, 169.6, 166.9, 155.8, 151.2, 142.5, 140.0, 133.7, 133.5, 130.2, 129.1, 128.7, 110.7, 107.6, 96.7, 84.1, 81.2, 79.2, 78.6, 75.3, 74.6, 72.3, 71.8, 70.0, 69.2, 61.8, 57.3, 52.0, 47.0, 43.3, 35.3, 35.0, 26.5, 22.5, 22.0, 21.9, 21.1, 20.9, 14.6, 10.7.

Example 18.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(5-hydroxypentyloxy)methyl]paclitaxel

FABMS (NOBA) M+H calcd for $C_{48}H_{64}NO_{19}$ 942.4123. Found: 942.4149.
IR(film) 3442, 1716, 1242, 1110, 1044, 1026 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.57 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (m, 1H), 6.20 (t, J=8.1 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.51 (d, J=9.6 Hz, 1H), 5.35 (br d, J=9.3 Hz, 1H), 4.91 (d, J=7.8 Hz, 1H), 4.80 (m, 1H), 4.66 (m, 3H), 4.28 (d, J=8.4 Hz, 1H), 4.10 (m, 2H), 3.83 (d, J=6.8 Hz, 1H), 3.76 (br s, 1H), 3.57 (m, 3H), 3.39 (m, 1H), 2.78 (m, 1H), 2.37 (s, 3H), 2.27 (d, J=9.3 Hz, 2H), 2.18 (s, 3H), 1.92 (s, 3H), 1.88 (m, 2H), 1.82 (s, 1H), 1.65 (s, 3H), 1.56-135 (m, 6H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16 (d, J=6.3 Hz, 3H), 1.12 (d, J=6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 170.9, 169.4, 167.0, 155.7, 151.4, 142.5, 140.0, 133.7, 133.5, 130.1, 129.2, 128.6, 110.6 107.5, 96.0, 84.3, 81.4, 78.6, 75.3, 74.6, 72.0, 69.1, 68.2, 62.8, 57.3, 52.0, 47.0, 43.2, 35.3, 34.8, 32.5, 29.5, 26.6, 22.6, 22.5, 22.0, 21.9, 21.0, 20.9, 14.8, 10.7.

Example 19.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(6-hydroxyhexyloxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{49}H_{66}NO_{19}$ 956.4280. Found: 956.4309.
IR(film) 3372, 1718, 1244, 1110, 1050, 1024 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J=7.2 Hz, 2H), 7.55 (t, J=7.5 Hz, 1H), 7.44 (t, J=7.8 Hz, 2H), 7.37 (s, 1H), 6.33 (m, 2H), 6.29 (m, 1H), 6.15 (t, J=8.2 Hz, 1H), 5.62 (m, 2H), 5.31 (br d, J=9.3 Hz, 1H), 4.90 (d, J= 7.8 Hz, 1H), 4.74 (m, 1H), 4.67 (m, 3H), 4.26 (d, J= 8.4 Hz, 1H), 4.11 (m, 2H), 3.97 (m, 1H), 3.81 (d, J=6.8 Hz, 1H), 3.56 (t, J= 6.6 Hz, 4H), 3.32 (m, 1H), 2.77 (m, 1H), 2.64 (s, 1H), 2.61 (s, 1H), 2.34 (s, 3H), 2.28 (m, 2H), 2.16 (s, 3H), 1.90 (s, 3H), 1.70 (s, 3H), 1.51 (m, 4H), 1.33 (m, 4H), 1.20 (m, 12H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 177.9, 172.2, 170.5, 169.5, 166.9, 155.8, 151.3, 142.4, 140.1, 133.6, 133.5, 130.1, 129.2, 128.6, 110.6, 107.5, 96.8, 84.3, 81.2, 79.5, 78.4, 76.5, 75.2, 74.6, 72.0, 71.8, 69.1, 68.3, 62.7, 57.3, 52.1, 46.9, 43.3, 35.3, 32.5, 29.9, 26.5, 25.9, 25.5, 22.5, 22.0, 21.9, 21.1, 20.9, 14.6, 9.5.

Example 20.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(7-hydroxyheptyloxy)methyl]paclitaxel

HRFABMS (NOBA) M+H calcd for $C_{50}H_{68}NO_{19}$ 970.4436. Found: 970.4424.
IR(film) 3440, 1720, 1242, 1180, 1110, 1050, 1024 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 6.35 (m, 2H), 6.30 (m, 1H), 6.19 (t, J=8.2 Hz, 1H), 5.64 (d, J= 6.9 Hz, 1H), 5.38 (m, 2H), 4.92 (d, J= 7.8 Hz, 1H), 4.79 (m, 1H), 4.70 (m, 2H), 4.29 (d, J= 8.4 Hz, 1H), 4.12 (m, 2H), 3.84 (d, J=6.8 Hz, 1H), 3.58 (m, 4H), 3.33 (m, 1H), 2.80 (m, 1H), 2.36 (s, 3H), 2.29 (d, J= 9.3 Hz, 2H), 2.18 (s, 3H), 1.91 (s, 3H), 1.89 (m, 1H), 1.80 (s, 1H), 1.72 (s, 3H), 1.64 (m,

2H), 1.50 (m, 4H), 1.29 (m, 6H), 1.20 (s, 3H), 1.19 (s, 3H), 1.16 (d, J= 6.3 Hz, 3H), 1.12 (d, J= 6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.3, 170.4, 169.4, 167.0, 151.3, 142.5, 140.0, 133.7, 133.5, 130.2, 129.2, 128.7, 110.7, 107.6, 96.9, 84.4, 81.2, 79.6, 78.6, 75.2, 74.6, 72.2, 71.8, 69.1, 68.4, 62.9, 57.4, 52.0, 46.9, 43.3, 35.3, 32.6, 29.5, 29.4, 29.0, 26.5, 26.0, 25.6, 22.5, 22.0, 21.9, 21.0, 20.9, 14.7, 10.7.

Example 21.

3'-N-Debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-methylpropyl)-7-O-methylpaclitaxel

Anal. calcd for $C_{44}H_{61}NO_{15}$: C, 62.61; H, 7.28; N, 1.66. Found: C, 62.44; H, 7.15; N, 1.69.
HRFABMS (NOBA) M+H calcd for $C_{44}H_{62}NO_{15}$ 844. Found: 844.
IR(KBr) 3528, 1750, 1726, 1248, 1228 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 6.42 (s, 1H), 6.12 (t, J= 8.9 Hz, 1H), 5.63 (d, J= 6.9 Hz, 1H), 4.96 (d, J= 8.1 Hz, 1H), 4.60 (d, J=9.6 Hz, 1H), 4.28 (d, J= 8.4 Hz, 1H), 4.15 (m, 3H), 3.86 (m, 2H), 3.32 (s, 3H), 3.28 (m, 1H), 2.72 (m, 1H), 2.36 (m, 4H), 2.19 (s, 3H), 1.95 (s, 3H), 1.70 (m, 6H), 1.34 (s, 3H), 1.30 (s, 9H), 1.19 (s, 6H), 0.95 (m, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.2, 173.8, 170.1, 169.4, 166.9, 155.5, 140.3, 133.6, 130.2, 129.2, 128.6, 84.1, 81.6, 80.4, 79.7, 76.4, 74.7, 74.6, 73.0, 72.6, 57.5, 57.2, 51.3, 47.2, 41.1, 35.3, 32.3, 28.2, 26.4, 24.7, 23.2, 22.6, 21.9, 20.9, 18.6, 14.7, 10.4.

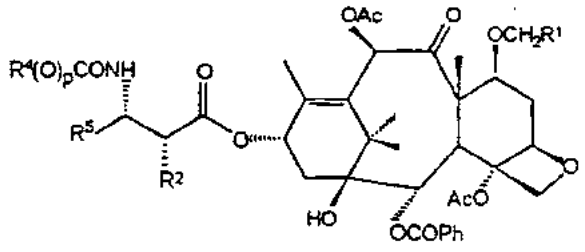
Example 22.

3'-Desphenyl-3'-(2-furyl)-7-O-methylpaclitaxel

HRFABMS (NOBA) M+H calcd for $C_{47}H_{54}NO_{16}$ 888.3443. Found: 888.3432.
IR(KBr) 3450, 1750, 1722, 1712, 1268, 1244, 1024 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.2 Hz, 2H), 7.73 (d, J= 7.2 Hz, 2H), 7.57 (m, 1H), 7.45 (m, 6H), 6.92 (d, J= 9.2 Hz, 1H), 6.38 (s, 2H), 6.33 (s, 1H), 6.18 (t, J= 8.1 Hz, 1H), 5.86 (dd, J= 9.3, 2.4 Hz, 1H), 5.65 (d, J= 6.9 Hz, 1H), 4.91 (d, J= 8.4 Hz, 1H), 4.80 (m, 1H), 4.68 (d, J= 7.5 Hz, 1H), 4.62 (d, J= 7.5 Hz, 1H), 4.29 (d, J= 8.4 Hz, 1H), 4.16 (d, J= 8.4 Hz, 1H), 4.10 (dd, J= 10.5, 3.6 Hz, 1H), 3.84 (d, J= 6.9 Hz, 1H), 3.60 (d, J= 5.4 Hz, 1H), 3.27 (s, 3H), 2.78 (m, 1H), 2.40 (s, 3H), 2.34 (d, J= 8.7 Hz, 2H), 2.18 (s, 3H), 2.00 (m, 1H), 1.89 (s, 3H), 1.80 (s, 1H), 1.75 (s, 3H), 1.18 (s, 6H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 172.2, 170.4, 169.4, 167.0, 166.9, 150.8, 142.7, 139.9, 133.7, 133.6, 133.4, 132.1, 130.2, 129.2, 128.7, 127.1, 110.8, 108.0, 98.2, 84.3, 81.2, 79.8, 78.5, 75.3, 74.5, 72.3, 71.7, 57.4, 55.8, 50.2, 46.9, 43.2, 35.4, 29.5, 26.6, 22.6, 21.0, 20.9, 14.7, 10.7.

Claims

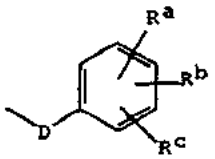
1. A compound of the formula (I):



(I)

wherein R^1 is hydrogen, C_{1-8} alkyloxy, C_{2-8} alkenyloxy, or C_{2-8} alkynyloxy, each can be optionally substituted with hydroxy; R^2 is hydroxy, -OC(O)R^x or -OC(O)OR^x; R^4 and R^5 are independently C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, or -Z-R^6; p is zero or one; Z is a direct bond, C_{1-8} alkylene or C_{2-8} alkenediyl; R^6 is aryl, substituted aryl, C_{3-8} cycloalkyl or heteroaryl; and R^x is C_{1-8} alkyl optionally, substituted with one to six same or different halogen atoms,

C_{3-8} cycloalkyl or C_{2-8} alkenyl; or R^x is a radical of the formula



wherein D is a bond or C_{1-8} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-8} alkylamino, di-C_{1-8}alkylamino, halogen, C_{1-8} alkyl, or C_{1-8} alkyloxy.

2. A compound of claim 1 in which R^1 is hydrogen or C_{1-8} alkyloxy optionally substituted with hydroxy; R^2 is hydroxy or -OC(O)OR^x; R^4 and R^5 are independently C_{1-8} alkyl, C_{2-8} alkenyl, or -Z-R^6 in which Z is a direct bond; R^6 is aryl, furyl or thienyl; and R^x is C_{1-8} alkyl.

3. The compounds of claim 2 that are 7-O-methylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methoxymethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methoxymethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methoxymethylpaclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylpaclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-methylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(4-hydroxybutyloxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(5-hydroxypentyloxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(3-hydroxypropyloxy)methyl]paclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel;
2'-O-ethoxycarbonyl-3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(2- hydroxyethoxy)methyl]paclitaxel ;
3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(2-hydroxyethoxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(5-hydroxypentyloxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(isopropyloxycarbonyl)-3'-(2-furyl)-7-O-[(6-hydroxyhexyloxy)methyl]paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-methylpropyl)-7-O-methylpaclitaxel; or
3'-desphenyl-3'-(2-furyl)-7-O-methylpaclitaxel.

4. A pharmaceutical composition which comprises an antitumor effective amount of a compound of any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

5. The use of a compound of any one of claims 1 to 3 for preparing a pharmaceutical composition for inhibiting tumor growth in a mammalian host.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 11 1843

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y,D	EP-A-0 534 708 (FLORIDA STATE UNIVERSITY) * page 1, line 49 - page 2, line 29; page 8, lines 11-25 *	1-5	C07D305/14 C07D407/12 A61K31/335
D	& US-A-5 229 526		
D	& WO-A-93 06079		
D	& EP-A-0 534 707		
D	& EP-A-0 534 709		
Y	P.J. KOCIENSKI 'Protecting Groups' 1994 , GEORGE THIEME VERLAG , STUTTGART, DE * pages 42-46, 68-71, 84 *	1-5	
A	J. AM. CHEM. SOC., vol. 116, no. 4, 1994 pages 1599-1560, R.A. HOLTON ET AL * page 1600, column 2, lines 12-13 * & DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US Accession nr. 120:134866, * abstract * & DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US * RN: 153145-55-2 *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K
A	EP-A-0 253 738 (RHONE-POULENC SANTE) * page 8, line 1 - line 16; claims 1,4 *	1,4,5	
D	& US-A-4 814 470		
A	EP-A-0 604 910 (BRISTOL-MEYERS SQUIBB CO) * examples 3A-B, 7A-B *	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	13 November 1995	Van Amsterdam, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Hervé BOUCHARD et al.	)	
	)	
Serial No.: 08/622,011	)	Group Art Unit: 1203
	)	
Filed: March 26, 1996	)	Examiner: B. Trinh
	)	
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SECOND DECLARATION UNDER 37 C.F.R. § 1.132

I, Alain Commerçon, declare and state that

1. I am the same Alain Commerçon who was the declarant in the Declaration under 37 C.F.R. § 1.132 filed October 28, 1997, but beginning in 1998, I became Director of Medicinal Chemistry at Rhône-Poulenc Rorer.

2. I am familiar with the prosecution history of this patent application, including the pending Office Action.

3. The following three pure compounds were prepared under my control and submitted for the *in vitro* and *in vivo* biological evaluations described herein: the claimed compound, the product of Example 1 of the

specification, and two comparative compounds: (1) a di-TROC (2,2,2-trichloroethoxycarbonyl) compound, Comparative A,[1] and (2) a diacetylated (-$OCOCH_3$) compound, Comparative B,[2] having the same substituents as the claimed compound except at the 7- and 10- positions as shown below in Table 1.

Antitumor activity of the three compounds prepared above was evaluated against B16 melanoma-bearing mice. The IC_{50}, the concentrations of the drugs resulting in 50% cell growth inhibition of the tumor cell lines (KB human epidermoid carcinoma; P388 murine leukemia for Comparative Compound A), was also evaluated, and the results are reported in Table 1.

---

[1] At the 7- and 10- positions, Comparative A contains TROC group, which is referenced as a hydroxy protecting group in the '601 Holton patent at column 4, lines 1-4 (2,2,2-trichloroethyl carbonate). *See also* Kingston, col. 13, lines 28-31.

[2] Comparative B, at the 7- and 10- positions, contains an acetyl group, which is referenced as a hydroxy protecting group in the '601 Holton patent at column 3, line 63. *See also* compound 6b, the substituent for Z, in column 12, line 32 of Holton '526 and *see also* column 6, lines 23-24, where in $-OR_6$, R_6 is acyl.

Table 1:

			In vivo		In vitro	
	7-position	10-position	T/C%	Cell Line	cellular IC_{50} µg/ml	Cell Line
Claimed Compound	$-OCH_3$	$-OCH_3$	0	B16	0.029	KB
Comparative A	$-OCOCH_2CCl_3$	$-OCOCH_2CCl_3$	54	B16	≥10	P388
Comparative B	$-OCOCH_3$	$-OCOCH_3$	177	B16	4.5	KB

The T/C value in percent is an indication of antitumor effectiveness:

$$T/C\ (\%) = 100 \times \frac{\text{median tumor weight of the treated groups}}{\text{median tumor weight of the control groups}}$$

According to NCI (National Cancer Institute) standards, a T/C < 42 % is the minimal level to declare activity. A T/C < 10 % is considered to indicate high anti-tumor activity and is the level used by NCI to justify further development.

The results demonstrate that the claimed compound possesses superior *in vitro* and *in vivo* anti-tumor activity compared to the comparative compounds A and B. Comparative compounds A and B demonstrate lower *in vitro* cytotoxicity ($IC_{50} \geq 4.5$ µg/ml) and are also inactive (T/C% ≥ 42%) *in vivo* on B16 melanoma. In contrast, the claimed compound is very active *in vivo* against B16 melanoma giving a full inhibition of tumor growth (T/C% = 0) and is cytotoxic *in vitro* against KB cells at a concentration of 0.029 µg/ml.

At the time this invention was made, particularly in view of the teachings of Holton '601 that methoxy at the C-7 and C-10 positions is a protective group disclosed as equivalent to the other protective groups, one skilled in the art would not have expected that having a methoxy at each of the C-7 and C-10 positions of the inventive compounds would result in superior biological results, as shown in Table 1.

4. In addition, the claimed compound possesses yet another superior biological property that is unexpected over the prior art relied on by the Examiner. The following Table 2 describes the results of a test comparing the *in vitro* biological activity of the claimed compound against docetaxel, which is a compound with the same structure as the claimed compound, except that it has an -OH at each of the 7- and 10-positions. Docetaxel has been approved by the FDA for the treatment of breast cancer. The cell line chosen was KB human epidermoid carcinoma resistant to the anticancer drug Vinblastine. The cellular IC_{50} of both the claimed compound and docetaxel were measured against this resistant cell line. As is evident from Table 2, the cellular IC_{50} of the claimed compound, i.e., 0.1600 µg/ml, was lower than that of docetaxel, which was 2 µg/ml. This means that the claimed compound was more active than docetaxel against this resistant cell line. Comparative B was also tested against the resistant KB human epidermoid carcinoma cell line. As shown in Table 2, the

cellular IC_{50} of Comparative B was higher than 10 µg/ml, which is less active than the claimed compound against the resistant cell line.

Table 2

	7-position	10-position	cellular IC_{50} µg/ml
Claimed Compound	$-OCH_3$	$-OCH_3$	0.1600
Docetaxel	-OH	-OH	2
Comparative B	$-OCOCH_3$	$-OCOCH_3$	≥10

Table 3

	7-position	10-position	cellular IC_{50} µg/ml
Docetaxel	-OH	-OH	3.3
Comparative A	$-OCOCH_2CCl_3$	$-OCOCH_2CCl_3$	≥10

Docetaxel and Comparative A were also tested against the P-388 murine leukemia cell line which is resistant to doxorubicin. As shown above in Table 3, Comparative A is less active than docetaxel against this resistant cell line. As shown in Table 1, representative compounds assumed for purposes of argument to be suggested by the prior art are less active against normal cell lines, and Comparative B, as shown in Table 2, is also less active against a

resistant cell line than is the claimed compound. As shown in Table 3, Comparative A is also less active against a resistant cell line than is docetaxel, which is consistent with the inactivity of Comparative A in Table 1. It is completely unexpected in view of the prior art that, as shown in Table 2, the claimed compound has superior activity, compared to docetaxel and a compound of the prior art, against a resistant cell line.

5. At an interview held on April 23, 1998, the Examiner asked me if I could prepare and test a compound having -OEE (ethoxyethoxy) at the 7- and 10- positions. The -OEE group is referred to as a substituent for Z in compound 6d of Holton '526. There are a number of reasons why it is unnecessary to undertake such synthesis and testing. First of all, compound 6d does not say what $-OT_1$ is at the 7-position other than it is generally a hydroxy protecting group. Further, even if there were a reason to try to make a compound like the claimed compound but having an -OEE at both the 7- and 10-positions, I do not know whether I could successfully synthesize the compound. I am aware of no literature reference that would teach how to put -OEE at both the 7- and 10-positions of a taxane molecule. Holton '526 gives no example of the synthesis of such a compound. Even if I could make the compound, I am not confident that I would be able to separate the four resulting diastereomers into a form pure enough to allow for meaningful biological

testing. I am aware that no one who has put the -OEE on the side chain of a taxane molecule has ever reported the separation of the two diastereomers from each other. If two isomers of this taxane-type couldn't be separated, it would be even more difficult to separate four such isomers. Moreover, in the Holton '526 patent, Example 1, the 2'-ethoxyethoxy group on the taxane side chain is converted to hydroxy under very mild acidic conditions, *i.e.,* 0.5% HCl (aq) in ethanol. This demonstrates that acetals of this type are not stable under acidic conditions encountered during oral administration in the human body. Therefore, in my opinion, -OEE would not be a stable group if a compound like the claimed compound but containing -OEE at both the 7- and 10-positions were orally administered. In contrast, the claimed compound has been found to be stable under mild acidic conditions, as demonstrated in detail in my October 1997 declaration. As explained to the Examiner, it can be desirable that an anticancer compound is capable of being administered either orally or intravenously. Thus, the claimed compound could be a candidate for oral and intravenous delivery as a drug for treating cancer, but the -OEE analog would not be such a candidate. The Comparative A and B compounds, referenced above, would be expected to be stable under mild acidic conditions and thus could, like the claimed compound, also be possible candidates for oral and intravenous administration. Therefore, I consider Comparative A and B to

be much more relevant to the claimed compound and also consider that I have made fair comparative tests that demonstrate that compared to the suggestions of the prior art relied on by the Examiner, the claimed compound is an unexpectedly superior breakthrough.

6. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: _____

Date: April 23, 1998 Dr. Alain Commerçon

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/622,011			

EXAMINER	
ART UNIT	PAPER NUMBER
	11

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Commercon A.C. (3) Ms Warnement TW

(2) Mr. Irving TD (4) Mr. Trinh.

Date of interview 4-23-98

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☑ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: 1-4, 17-25

Identification of prior art discussed: art of record.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: In addition to the allowed process claims, applicants will pursue only the claim 17 in this application. The novelty and the non-obviousness of claim 17 had been discussed.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Examiner's Signature

PTOL-413 (REV. 1-84)

NEPTUNE GENERICS EX. 00588

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PATENT

Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hervé BOUCHARD et al.	
Serial No.: 08/622,011	Group Art Unit: 1203
Filed: March 26, 1996	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Assistant Commissioner for Patents
Washington, D.C. 20231

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Sir:

AMENDMENT UNDER 37 C.F.R. § 1.115

In response to the Office Action dated February 25, 1998, Applicants respectfully request reconsideration of this application in view of the amendments and remarks below.

IN THE CLAIMS:

Please cancel claims 1-5, 13-15, 18-25, and 35 without prejudice or disclaimer. Please amend claims 6-9 and 27 and rewrite claims 5 and 13-15 as new claims 36-39, respectively, as follows:

Claims 6, 7, and 8, line 1 of each, delete "5" and insert therefor --36--.

Claim 9, line 1 and page 75, line 8, page 76, line 13, and page 77, line 1, delete "5" and insert therefor --36--.

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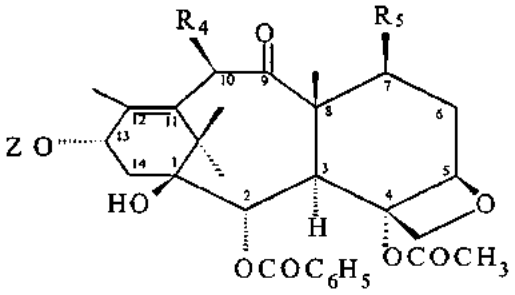
202-408-4000

Claim 27, line 6, delete "optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms,".

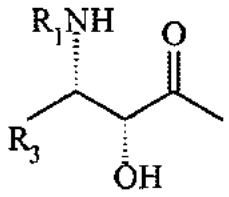
8 --36. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2-O-CO- in which R_2 represents:

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- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical, or

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- a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl

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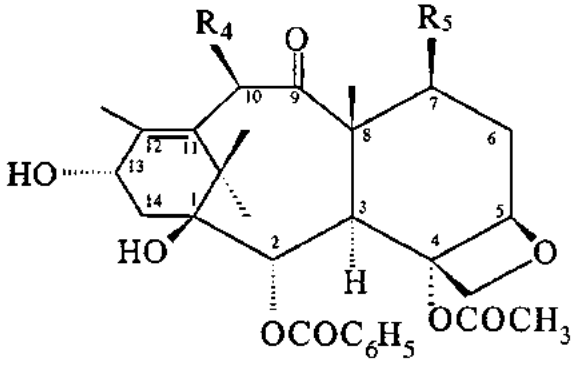
radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

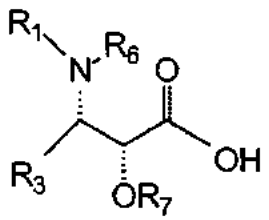
esterifying a product of formula (III):



(III)

in which R_4 and R_5 are defined as above

with an acid of formula (IV):



(IV)

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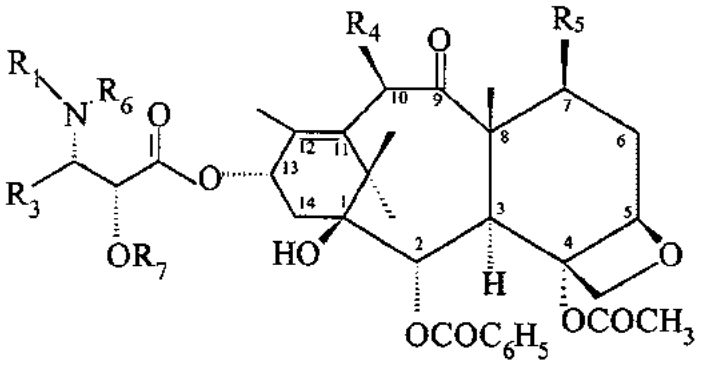
in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or

with a derivative of said acid, to obtain an ester of formula (V):



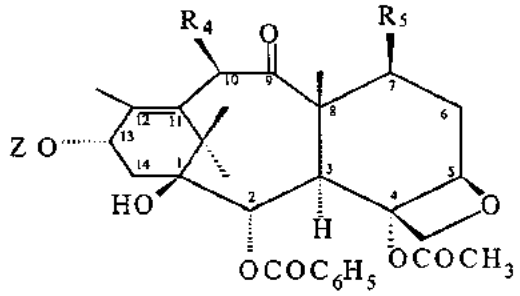
(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, and

replacing the protective group(s) of said ester of formula (V),

represented by R_7 or R_6 and R_7 together, by hydrogen atoms.

37. A process for preparing a new taxoid of the following formula (I):



(I)

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in which:

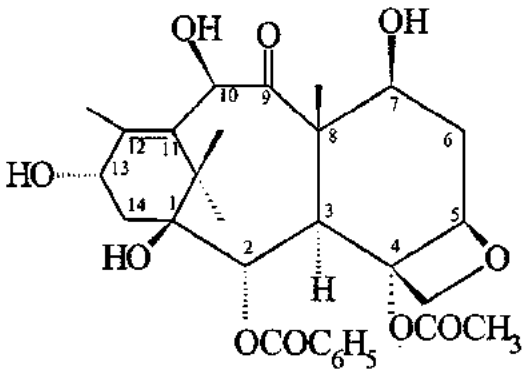
Z represents a hydrogen atom,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating 10-deacetylbaccatin III of formula (IX):



(IX)

with a silyl halide of formula:

$$(R)_3\text{-Si-Hal} \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):

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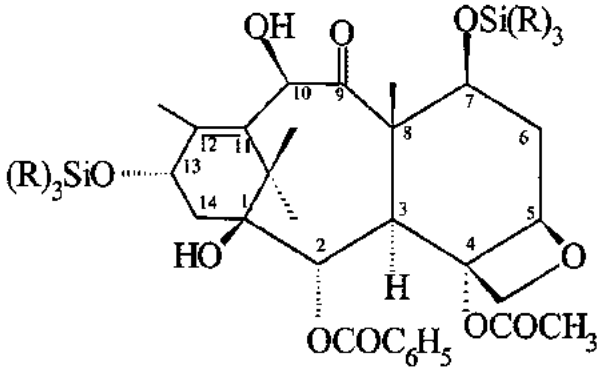


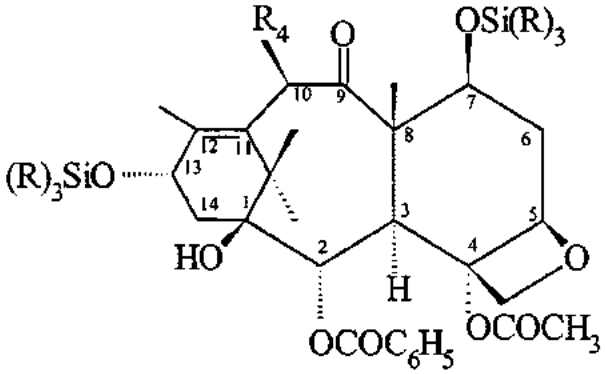
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined above and X_1 represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):



(XIII)

in which R and R_4 are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):

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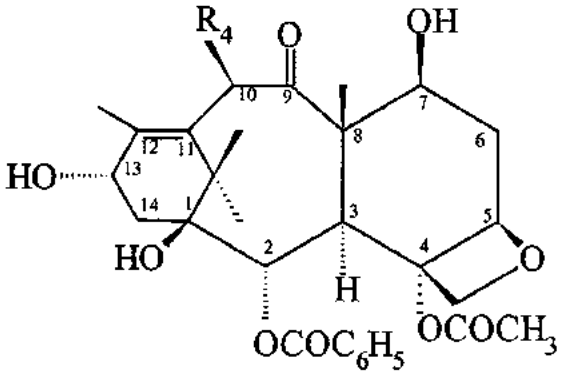


(XIV)

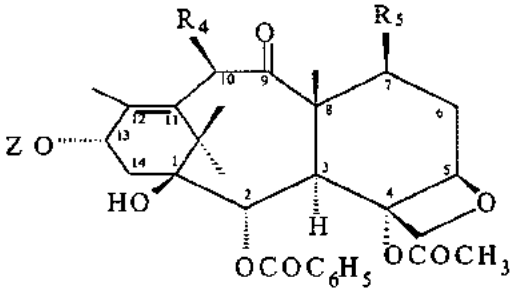
in which R_4 is defined as above, and

etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

in which R'_5 represents a radical such that R'_5-O is identical to R_5 defined as above and X_2 represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

10. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):

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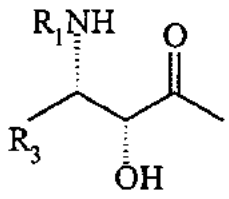

(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl

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portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical, or

- a saturated heterocyclic radical containing 4 to 6 carbon atoms,

optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino,

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dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating a product of formula (XVI):

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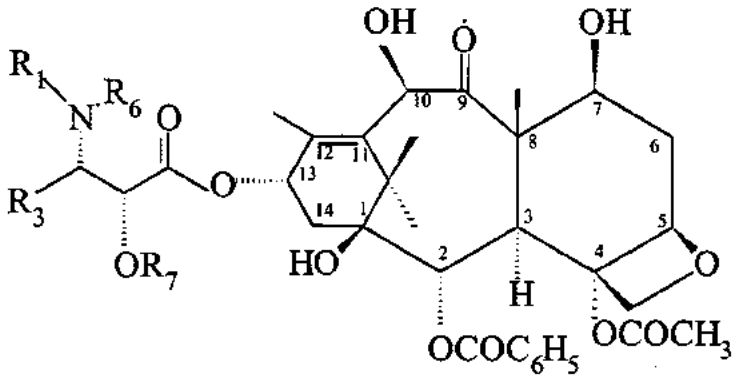
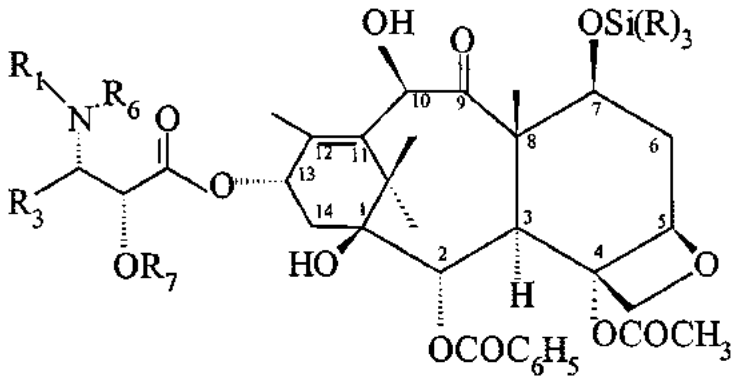


(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, with a product of formula (X):

$$(R)_3Si\text{-}Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above,

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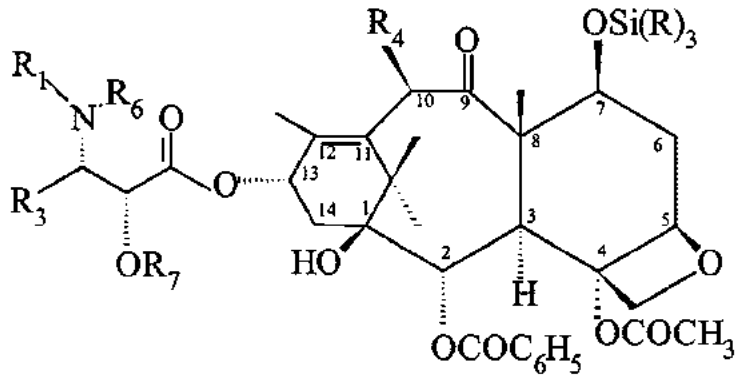
functionalizing said compound of formula (XVII) at position 10 with a product of formula:

$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined as above and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):

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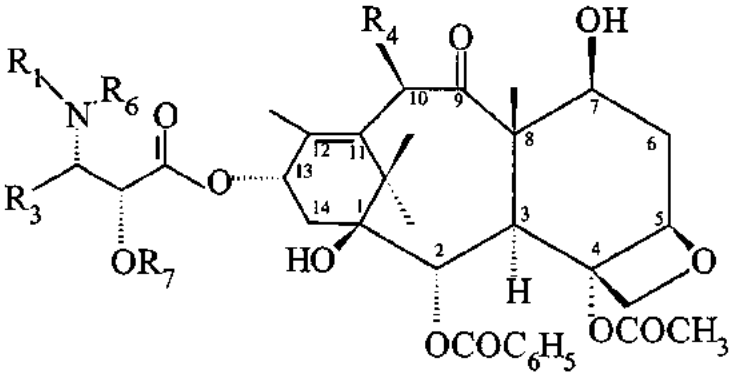


(XIX)

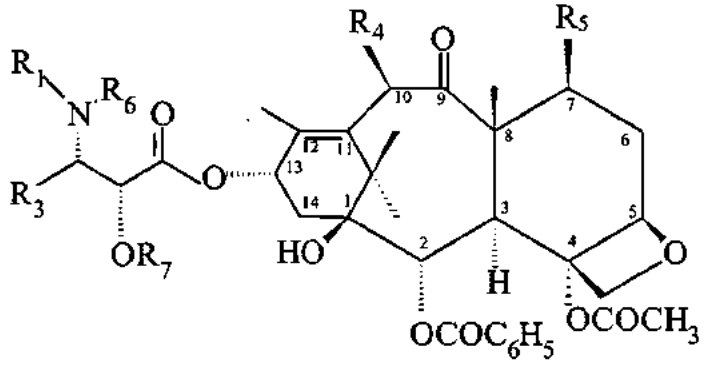
in which R_1, R_3, R_4, R_6 and R_7 are defined as above

which, when reacted with a product of formula (XV):

$$R'_5\text{-}X_2 \qquad (XV)$$

in which R'_5 represents a radical such that R'_5O is identical to R_5 defined above and X_2 represents a reactive ester residue or a halogen atom,

yields the product of formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above

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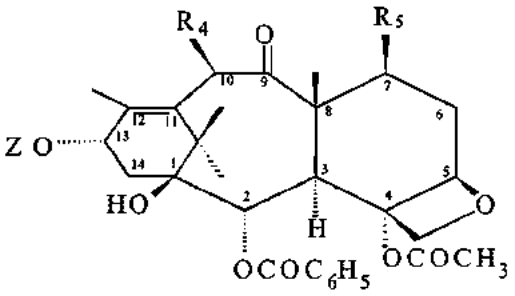
and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

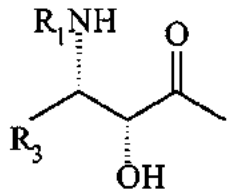
~~39~~ 11. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

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a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical, or

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- a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of R_2 and R_3, the alkyl

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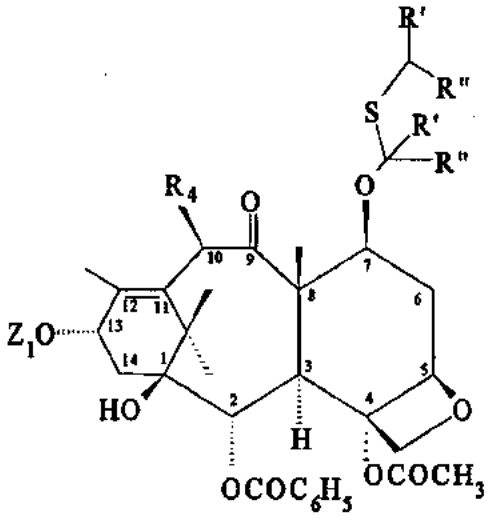
radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):



(XXI)

in which R_4 is defined as above, and R' and R", which may be identical or different,

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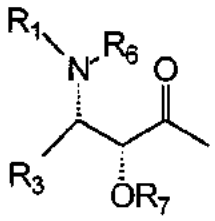
represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively

R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of formula (XXII):



(XXII)

in which R_1 and R_3 are defined as above and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to obtain a product of formula (XXIII):

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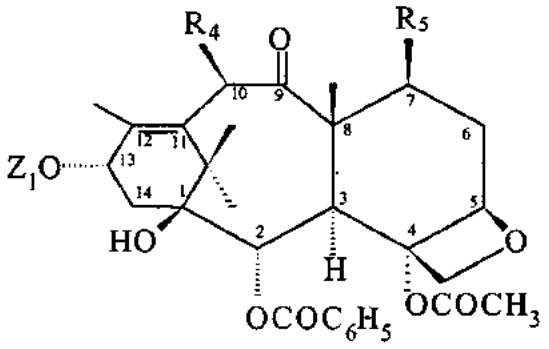

(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 together by hydrogen atoms under the following conditions :

1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitriles at a temperature from -10 to 60°C, or

with a source of fluoride ions, or

with catalytic hydrogenation, or

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):

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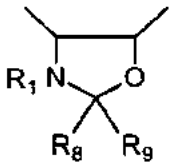

(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring,

and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

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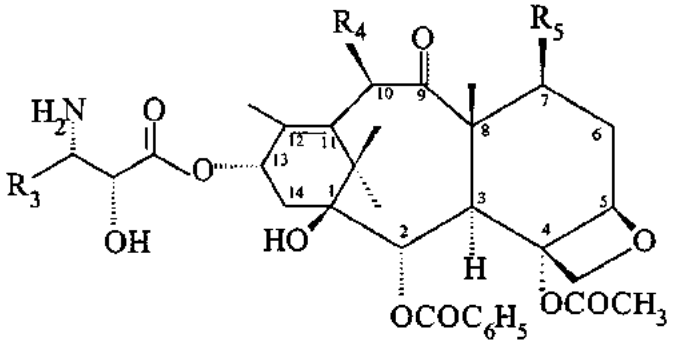
alternatively R_8 and R_9 together form a 4- to 7-membered ring,

said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



(VII)

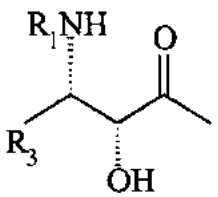
in which R_3, R_4 and R_5 are defined as in claim 1, and

acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom or a residue -O-R_2 or -O-CO-O-R_2,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

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or

b) R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

said replacing of the protective group formed by R_6 and R_7 together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from -10 to 60°C.--

REMARKS

Status of Claims

Claims 6-12, 16-17, 26-34, and 36-39 are now pending. Claims 1-5, 13-15, 18-25, and 35 have been canceled without prejudice or disclaimer. Claims 5 and 13-15 have been rewritten in independent form as new claims 36-39, respectively. Claims 6-9 have been amended to change the dependency from canceled claim 5, and claim 27 has been amended to correct a typographical

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error from the previous amendment. No new matter has been added by this amendment.

Interview

Applicants thank the Examiner for the helpful interviews conducted with Dr. Alain Commerçon, and their representatives, Thalia Warnement and Tom Irving, on April 23, 1998. The following remarks reflect the substance of the interview.

Claim 35: The Oxazolidine Moiety in Claim 35 is also Found in Claim 24, as Filed and Amended

The Examiner has refused to examine claim 35 and has withdrawn it from consideration, alleging that the oxazolidine moiety on the side chain makes the compound of claim 35 distinct from the other claims of record wherein the C-13 side chain is a phenylisoserine derivative moiety. Applicants respectfully disagree, but since this claim has been canceled without prejudice, this issue is moot.

The Rejection Under 35 U.S.C. § 102(b) over Holton '526 Fails For Claim 17

Claim 17 was again rejected as anticipated by compounds 6b to 6d of Holton, U.S. Patent No. 5,229,526.[1] According to the Examiner, the OT_1 and Z groups of Holton embrace the instant R_4 and R_5 groups as being hydroxy

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[1] The other claims rejected under § 102 have been cancelled without prejudice.

protecting groups. Applicants respectfully traverse this rejection for reasons of record.

Compounds 6b-6d have a C-13 side chain. Claim 17 also has a C-13 side chain. Claim 17 has an -OH at the 2-position of the C-13 side chain. In contrast, Holton 6b-6d display either R_1 or R_2 at that position.

As shown in attached Exhibit 1, which was discussed during the interview, Holton '526, at column 4, defines R_1 and R_2 . R_1 is $-OR_6$, $-SR_7$, or $-NR_8R_9$. Of these three possibilities, only $-OR_6$ is possibly relevant to claim 17 with respect to anticipation. R_6, however, as revealed at column 4 of Holton, cannot be H; it is rather, one of alkyl, alkenyl, alkynyl, aryl, heteroaryl, or hydroxy protecting group. Therefore, no possibility for R_1 can anticipate the species recited in claim 17.

As further shown in Exhibit 1, R_2 in Holton '526 is one of hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl. None of these is -OH. Therefore, no possibility for R_2 can anticipate the species recited in claim 17.

Accordingly, as discussed at the interview, the § 102 rejection should be withdrawn with respect to claim 17.

Rejection Under 35 U.S.C. § 103(a) over Holton '526, Greene, Holton '601

Claim 17 was rejected under § 103 over Holton '526, Greene, Holton '601. For all the reasons previously of record, Applicants disagree with this rejection. However, to advance matters, Applicants submit herewith the second

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declaration of Dr. Commerçon. As explained thoroughly therein and as explained at the interview, Dr. Commerçon prepared pure compounds and conducted tests that demonstrate that the claimed compound is patentable over the prior art of record because the biological properties thereof are unexpectedly superior. Additionally, Dr. Commerçon explains in detail why it is not necessary to prepare and test a compound like the claimed compound but having -OEE at both the 7- and 10-positions. Dr. Commerçon concludes that the Comparative A and B compounds, the structures of which are shown in Exhibit 2 (also discussed at the interview), along with the structure of the claimed compound, are much more relevant to the claimed compound. Dr. Commerçon further concludes that the comparative tests he reports demonstrate that compared to the suggestions of the prior art relied on by the Examiner, the breakthrough claimed compound is unexpectedly superior with respect to biological properties.

Rejection Under 35 U.S.C. § 103 of Claim 25

Since claim 25 has been cancelled without prejudice, this rejection is moot.

Allowable Subject Matter

Applicants thank the Examiner for his indication that claims 5-16 and 26-34 are allowable since the claimed processes are unobvious over the prior art. These claims have been amended herein to eliminate dependency from

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cancelled claims. In particular, claims 5 and 13-15 have been rewritten as claims 36-39.

CONCLUSION

In view of the foregoing, it is urged that all of the pending claims are in condition for allowance. An early and favorable action is earnestly solicited.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this amendment, such extension is hereby requested. If there are any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Thomas L. Irving
Reg. No. 28,619

Dated: April 23, 1998

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Patent and Trademark Office
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Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
[illegible]	[illegible]	BOUCHARD	3806.0367-00

EXAMINER: TRINH, B

ART UNIT: 1612 | PAPER NUMBER: 10

DATE MAILED: 02/25/98

FINNEGAN HENDERSON FARABOW GARRETT
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HM42/0225

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 10-29-97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1 – 35 is/are pending in the application.
Of the above, claim(s) 35 is/are withdrawn from consideration.
☑ Claim(s) 5-16, 26-34 is/are allowed.
☑ Claim(s) 1-4, 17-25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

PTOL-326 (Rev. 9/95) * U.S. GPO: 1996-404-486/40617

Claims 1-35 are pending.

New claim 35 is withdrawn from consideration because the claimed subject matter (the oxazolidine moiety) is distinct from the other claims of record wherein the C-13 side chain is a phenylisoserine derivative moiety. The other new claims 32-34 are entered and examined.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 17-24 are rejected under 35 U.S.C. 102(b) as being anticipated by compound 6b to 6d of Holton (US 5,229,526).

The OT, and Z groups of Holton embrace the instant R_4 and R_5 groups as being hydroxy protecting groups; note lines 23 to 35 column 6 of Holton.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 17-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holton in view of Greene et al and Holton et al (US 5,489,601).

Holton teaches a protected taxane which is analogous to the claimed compounds; note the compounds 6b to 6d in column 12 of Holton. The prior art does not specifically teach the instant R_4 and R_5 groups; note the OT, and Z groups in compounds 6b and 6d of Holton, however, Greene et al. Teaches the instant hydroxy protecting groups to be conventional; note pages 10-14 of Greene et al; and lines 23 to 35 column 6 of Holton. Holton et al further teaches an analogous taxane wherein the C-7 and C-10 positions contain an alkoxy groups; note the R_7, R_{7a}, R_{10}, R_{10a} groups of compound (3) in column 2 and lines 55 to 65 column 3 of the patent. It would have been prima facie obvious to replace the disclosed hydroxy protecting group of Holton with the hydroxy protecting groups as taught by Greene et al and Holton et al to form the claimed compounds without the loss of the same utility.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kingston et al in view of Holton et al (US 5,489,601).

Kingston et al teaches a protected taxane which is analogous to the instant compounds; note compound 24 in column 18 of Kingston et al., Holton et al teaches a similar taxane wherein the hydroxy group and the protected hydroxy groups are equivalent at the C-2', C-7 and C-10 positions of the taxane derivatives, in other word, the protection and the deprotection of the hydroxy group (s) of taxanes derivatives are obvious is the art, thus the instant taxane wherein the C-2' hydroxy is unprotected would be deemed obvious over the protected-C-2' taxane of Kingston et al.

Applicant's remarks and Declaration filed 10-29, 1997 are considered, but not found to be persuasive.

The specification would not be limited to its disclosed working examples in a narrow sense or to its prefound species. It is the inventive concept that provides the content of the disclosure and would not be interpreted as illustrative or in a limiting sense, further in view of the teachings of the secondary art. In the instant case, the hydroxy protecting technique in well known and conventional to any one of ordinary in the art and it is not a break through to show that a certain hydroxy protecting group can be or can not be deprotected by various reagents and/or condition since they are well known and documented in the art to protect or deprotect a hydroxy group using various technique on various hydroxy protecting group.

Claims 5-16, 26-34 are deemed allowable.

Any inquiry concerning this communication should be directed to Examiner Ba Trinh at telephone number (703) 308-4545.

TRINH:tcj
February 11,1998

BA K. TRINH
PRIMARY EXAMINER
GROUP 1200

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
08/622,011	1612 ~~1203~~	10

APPLICANT(S): BOUCHARD et al

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	5486011	1-96	Holton et al	514	337	—
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	
S	
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U	

EXAMINER: [signature] DATE: 2-98

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: 1203

Filed: March 26, 1996 — Examiner: B. Trinh

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT UNDER 37 C.F.R. § 1.115

In response to the Office Action dated April 29, 1997, Applicants respectfully request reconsideration of this application in view of the following amendments and remarks. The period for response has been extended three (3) months by the accompanying petition and fee.

IN THE CLAIMS:

Please amend claims 1, 2, 5, 9, 14, 15, 16, 18, 19 and 24-28, and add new claims 32-35 as follows:

1. (Amended) A taxoid of the formula (I):

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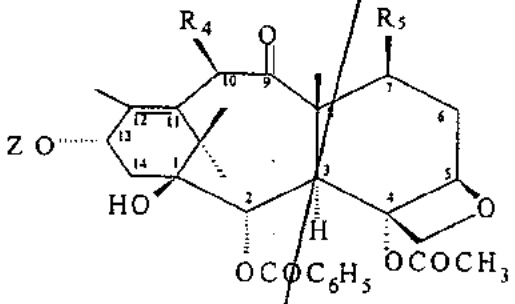
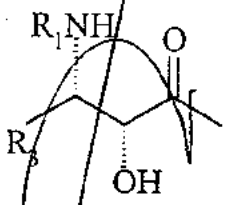


(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, **and** trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, [and] **or**

a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl

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radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- [or] a 5-membered aromatic heterocyclic radical, **or**

- [or] a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

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R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more **identical or different** atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, **or**

[or] a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals **in the definitions of R_2 and R_3**, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms,

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and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon

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atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms], and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon

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atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms].

2. (Amended) A taxoid according to claim 1, wherein Z represents a hydrogen atom or a radical of formula (II) in which

R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical,

R_3 represents an alkyl radical containing 1 to 6 carbon atoms; an alkenyl radical containing 2 to 6 carbon atoms; a cycloalkyl radical containing 3 to 6 carbon atoms; a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkoxy, dialkylamino, acylamino, alkoxycarbonylamino and trifluoromethyl radicals; or a 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl radical [, and

R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms].

Claim 5, line 8 (page 73, line 4), replace "above" by --in claim 1--;

last line (page 74, line 3), after "R_6 and R_7" insert --together--.

Claim 9, line 2 (page 74, line 18), after "R_6 and R_7" insert --together--;

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line 15 (page 75, line 8), replace "above" by --in claim 5--;

line 25 (page 75, line 18), insert --and further-- before "wherein";

line 35 (page 76, line 10), replace "where appropriate" by --optionally--;

line 38, (page 76, line12), replace "above" by -- in claim 5--;

line 43, (page 77, line 1), replace "1" by --5--.

Claim 14, line 22, (page 4, line 1 of April 18, 1996 Preliminary Amendment), after "(XV)" insert --in which R'_5 represents a radical such that R'_5O is identical to R_5 defined as in claim 1 and X_2 represents a reactive ester residue or a halogen atom--.

line 24, (page 4, line 3 of replace "April 18, 1996 Preliminary Amendment), replace "groups of formula (V) with" with --group(s) of formula (V) with one or two--.

15. (Amended) A process for preparing a product according to claim 1, comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):

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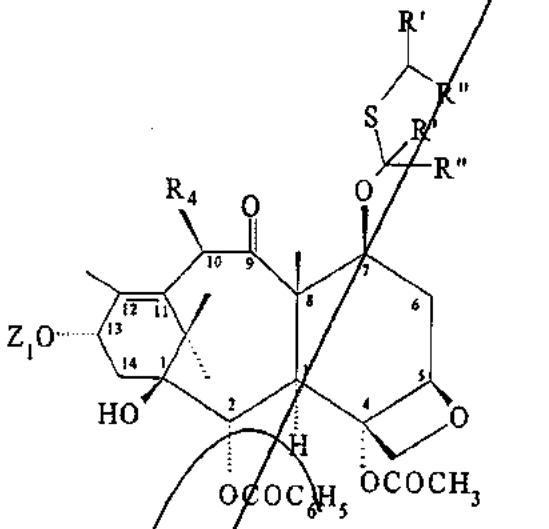

(XXI)

in which R_4 is defined as in claim 1, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing [2] **3** to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively

R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of formula (XXII):

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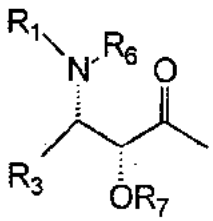
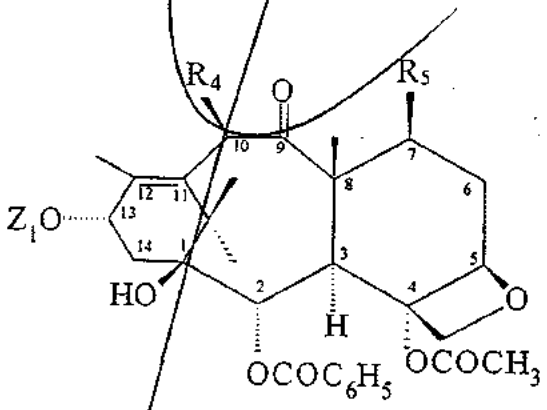


(XXII)

in which R_1 and R_3 are defined in claim 1 and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to obtain a product of formula (XXIII):



(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 **together** by hydrogen atoms under the **following** conditions [of claim 9]:

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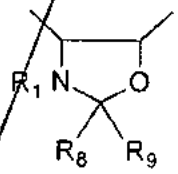
1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitriles at a temperature from -10 to 60°C, or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

---

in which R_1 is defined as in claim 1 and R_8 and R_9, which may be identical or different,

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represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring,

and further wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring,

said replacing the protective groups by hydrogen atoms is accomplished

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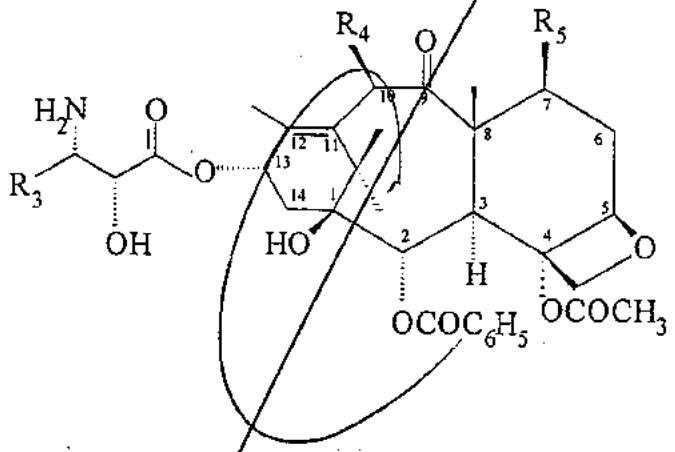
by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



(VII)

in which R_3, R_4 and R_5 are defined as in claim 1, and

acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

in which R_2 is defined in claim 1 and X represents a halogen atom or a residue -O-R_2 or -O-CO-O-R_2,

to obtain a product of formula (I) in which Z represents a radical of formula (II).

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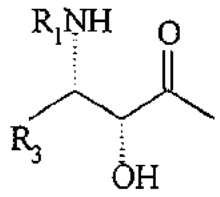

(II)

---

b) R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

said replacing of the protective group formed by R_6 and R_7 together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from -10 to 60°C.

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19 16. (Amended) A preparation process according to claim ~~15~~ 11, wherein said process **of reacting said activated Raney nickel with a product of formula (XXI)** is carried out at a temperature of from -10 to 60°C.

18. (Amended) [4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-ethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate] **4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.**

19. (Amended) [4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-(1-propyl)oxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-phenylpropionate] **4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate**.

24. (Amended) An ester of the formula (V):

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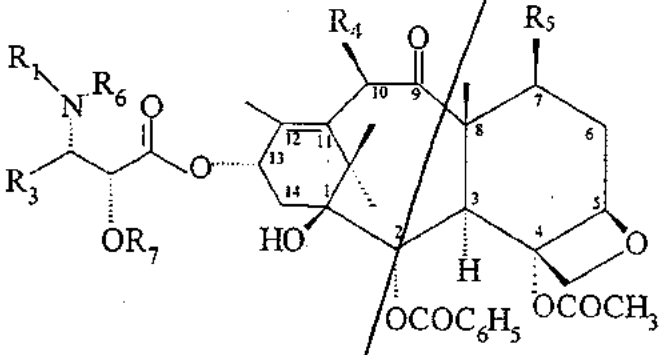

(V)

wherein

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, **and** trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, **[and]** **or**

a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl

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portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- [or] a 5-membered aromatic heterocyclic radical, **or**

- [or] a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or

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α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, **or**

[or] a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals **in the definitions of R_2 and R_3**, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon

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atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms],

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon

R5 cont'd

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atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms], and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

25. (Amended) An ester of formula (VII):

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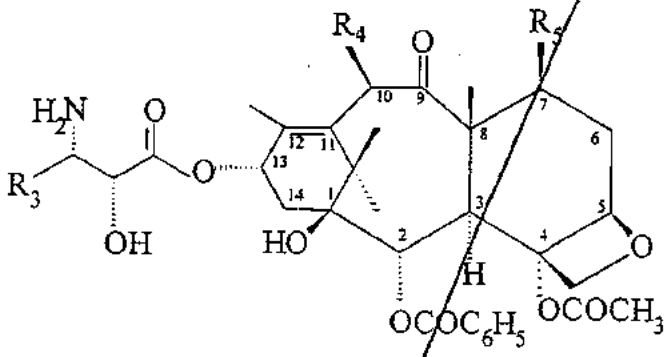

(VII)

wherein

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, **or**

[or] a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino,

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dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals **in the definitions of R_2 and R_3**, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

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or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms], and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

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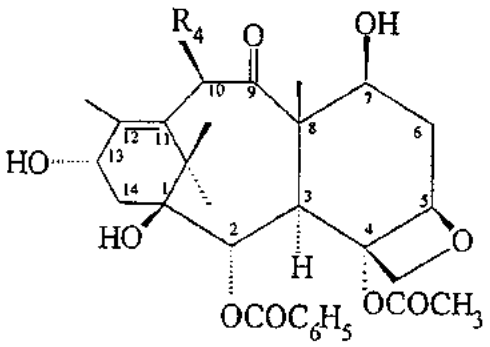
or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms].

3 28. (Amended) A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):



(XIV)

wherein R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one

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substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms],

with a compound of the formula (XV):

$$R'_5 - X_2 \qquad \text{(XV)}$$

wherein R'_5 represents a radical such that R'_5-O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon

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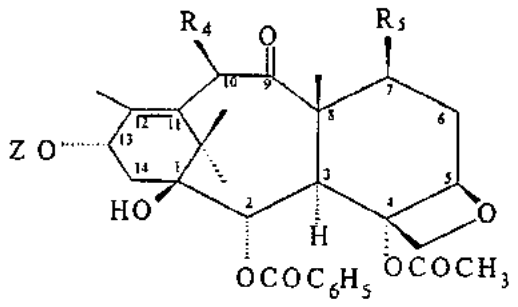
atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,] and X_2 represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

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wherein Z is hydrogen, R_4 is as defined above, and R_5 is identical to R'_5 as defined above.

4 ~~27~~. (Amended) A method comprising the step of reacting a product of the formula (XV):

$$R'_5\text{-}X_2 \qquad \underline{\text{(XV)}}$$

wherein R'_5 represents a radical such that R'_5-O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain ~~optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms~~, [an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally

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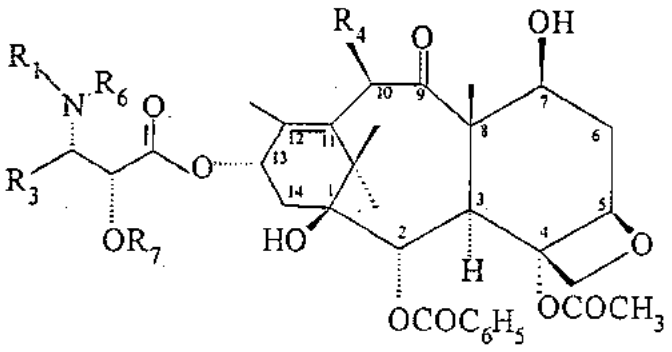
containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,] and X_2 represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, **and** trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, [and] **or**

a radical R_2-O-CO- in which R_2 represents:

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- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical, **or**

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- [or] a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, **or**

[or] a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

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with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals **in the definitions of R_2 and R_3**, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally

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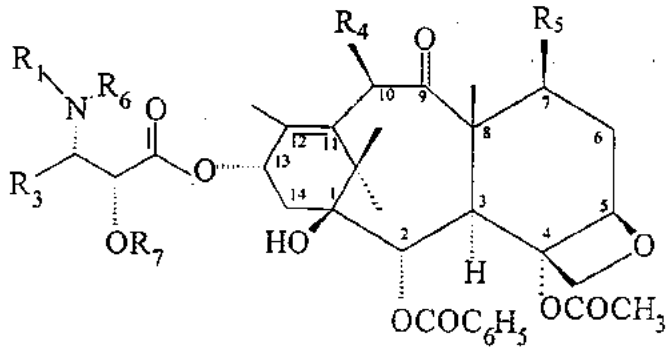
containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,] and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to form a compound of the formula (V):



(V)

wherein R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3

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to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,] and R_1, R_3, R_4, R_6, and R_7 are as defined above.

~~28~~. (Amended) A method comprising the step of replacing with hydrogen atom(s) group(s) R_6 and R_7 in a compound of the formula (V):

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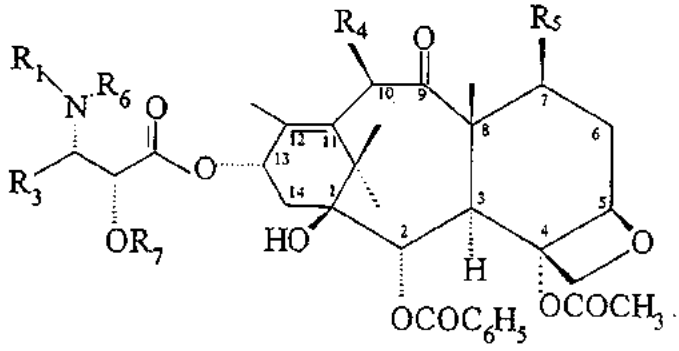

(V)

wherein:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, **and** trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, **[**and**]** **or**

a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl

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portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical, **or**

- [or] a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or

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α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, **or**

[or] a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals **in the definitions of R_2 and R_3**, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [, an alkenyloxy radical containing 3 to 6 carbon

B5 until

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atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,]

B5 contd

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain [optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon

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atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,] and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

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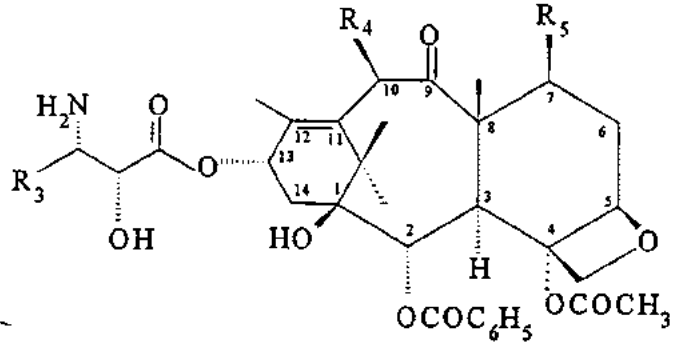
by treating the compound of formula (V) with an organic or inorganic acid, [where appropriate] **optionally** in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein R_3, R_4, and R_5 are as defined above.

32. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

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7 ~~33~~. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tertbutoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

(c) reacting the product obtained in (b) with an acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

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~~33~~ 22 ~~34~~. A process according to claim ~~33~~ 7, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

35. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate.

REMARKS

Status of Claims

Claims 1-35 are now pending. Claims 1, 2, 5, 9, 14, 15, 16, 18, 19 and 24-28 have been amended and new claims 32-35 added to more particularly point out and distinctly claim that which Applicants consider to be their invention.

Claims 1, 2, and 24-28 have been amended to more precisely define substituents R_4 and R_5 in the compounds of the invention. As will be explained in detail below, the alkoxy groups at the 7- and 10-positions of the claimed compounds and intermediates cannot be considered appropriate hydroxyl protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups taught in U.S. Patent Nos. 5,229,526 (Holton) and 5,319,112 (Kingston), the references relied upon by the Examiner. As will be explained in

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more detail below, the claimed compounds and intermediates define clearly over the hydroxy-group protected compounds of Kingston and Holton. The subject matter deleted from the present claims, however, has been deleted without prejudice or disclaimer and may be pursued in a later application.

The amendments to the definition of R_1 in claims 1, 24, 27, and 28 find support as follows: the "and" before "trifluoromethyl radicals" is supported at page 1, line 14 of the present specification and the "or" after "furoyl radical" is supported at page 2, lines 2-3.

Claim 14 has been amended to include the definition of R'_5 which was inadvertently omitted from the original claim. Support can be found in the specification, page 18, lines 3-5.

Claim 15 has been amended to specifically include the conditions of claim 9 previously referred to in the last line of claim 15. The amendment changing the number of atoms of the cycloalkyl radical from "2 to 6" to "3 to 6" was a necessary correction because a cycloalkyl radical cannot have only 2 carbons.

Claim 16 has been amended to clarify that it is the reaction with Raney nickel which is carried out at the recited temperature.

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Claims 18 and 19 have been amended to state the names of the compounds as used in the present examples, which names replace the synonyms previously used.

Overall, the amendments to claims 1, 2, 18, 19, 24, and 25, whether detailed above or not, have been made for formal clarification reasons only and to expedite allowance; the prior art of record does not require any amendment to the claims. Claims 5, 9, 14-15, and 26-28, already indicated as allowable, have been amended for clarity's sake only.

New claims 32-35 find support in Example 2 at pp. 37-42 of the present specification. In particular, new claims 32-34 are drawn to methods of producing the compound of Example 2, wherein R_4 and R_5 both represent methoxy radicals. These claims are patentable over the prior art for the same reasons that the Examiner has indicated the original process claims (claims 5-16 and 26-31) are allowable.

Claim 35 is drawn to an intermediate compound used in the process of claims 32-34. This compound, while an "intermediate" in the preparation of the product described, is not an "intermediate" at the 7 and 10 positions because, as will be explained in detail below, the methoxy groups at these positions cannot be considered appropriate hydroxy-protecting groups in taxane

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compounds under conditions for removing hydroxy-protecting groups taught in the Holton and Kingston patents of record.

No new matter has been added by this amendment, and no estoppel is effected thereby.

Interview

Applicants thank the Examiner for the helpful interviews conducted with their representatives, Thalia Warnement and Tom Irving, on August 7, 1997, and additionally with these representatives and Dr. Alain Commerçon, one of the inventors, on October 2, 1997. At the interviews, Applicants presented amended claim 1, as set forth above, limiting R_4 and R_5 to unsubstituted C_1 - C_6 alkoxy radicals. Applicants also discussed with the Examiner the rejections under 35 U.S.C. § 102(b) and §103. The second interview narrowed the issues, rendering moot much of what was discussed in the first interview.

Rejection Under 35 U.S.C. § 102

Claims 1-4 and 17-24 are rejected under 35 U.S.C. § 102 (b) as anticipated by compounds 6b-6d of Holton. See column 12, lines 20-38. According to the Examiner, the OT_1 and Z groups of Holton embrace the instant

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R_4 and R_5 groups as being hydroxy protecting groups. Applicants respectfully traverse the rejection.

As discussed above, Applicants have amended the compound claims to narrow the definitions of R_4 and R_5 to encompass only branched or unbranched C_1-C_6 alkoxy radicals. Holton, in compounds 6b-6d, does not teach such substituents. In the 7-position of the Holton compounds 6b-6d is $-OT_1$, wherein T is defined as a hydroxy-protecting group. In contrast, in the presently claimed compounds, R_5, which is at the 7-position, is branched or unbranched C_1-C_6 alkoxy. As will be now be explained in detail and as established in the Rule 132 Declaration of Dr. Commerçon submitted herewith, branched or unbranched C_1-C_6 alkoxy groups cannot be considered appropriate hydroxy-protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups taught in the Holton patent. Consequently, $-OT_1$ cannot be branched or unbranched C_1-C_6 alkoxy. For this reason alone, R_5 is different from $-OT_1$, and the claims, as amended, are therefore novel over Holton. The rejection under § 102(b) should therefore be withdrawn.

As became clear in the second interview, a key point for patentability is that the branched or unbranched C_1-C_6 alkoxy groups defined in both R_4 and R_5 of the claims cannot be considered appropriate hydroxy-protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups

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taught in the Holton patent. As explained by Dr. Commerçon at the second interview, it is basic chemical knowledge that, of the branched or unbranched C_1-C_6 alkoxy groups recited for both R_4 and R_5 of the claims, the easiest to convert to a hydroxy group would be methoxy.

Dr. Commerçon further explained in detail his belief that methoxy groups, as well as the other alkoxy groups recited in the claims, at the 7- and 10-positions of the claimed compounds cannot be considered appropriate hydroxy protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups taught in Holton and Kingston (Commerçon Declaration, ¶ 5). As explained in Greene, "Protective Groups in Organic Synthesis," First Edition, page 1 (Exhibit 1), the very nature of a protective group is to *temporarily* block a reactive site, followed by *selective removal therefrom*. According to Holton, hydroxyl protecting groups should be chosen so that they can easily be removed under conditions sufficiently mild to easily deprotect taxane compounds without disturbing the ester linkage, the basic taxane structure, or the taxane substituents. Thus, the conditions of Holton and Kingston are designed to accomplish "selective removal" of protecting groups only, as taught by Greene.

Furthermore, Greene, relied on by the Examiner, teaches rather stringent conditions for removing a methyl ether protecting group, which would

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include methoxy, from certain compounds. See pp. 15-16 of Greene (Exhibit 2), which Dr. Commerçon discussed at length at the interview. However, as further explained by Dr. Commerçon and as supported in the Chen article based on a March 1994 ACS Symposium (Exhibit 3) and Professor Kingston's 1993 work: Progress in the Chemistry of Organic Natural Products, Vol. 61, p. 77 (Exhibit 4), the rather stringent conditions established in Greene would be expected to have an adverse effect on the type of taxane compounds claimed, such as opening the oxetane ring, causing the A-ring to contract, or causing epimerization to occur.

The conditions for removing hydroxyl protecting groups in the Holton and Kingston patents are rather mild compared to the Greene conditions for removing methoxy groups. In fact, as discussed in detail by Dr. Commerçon at the interview, the Holton patent teaches at col. 4, lines 45-67 and col. 12, lines 1-37 to one skilled in the art that an alkoxy substituent on a taxane is not a hydroxy protecting group for Holton's purposes. Therefore, the conditions for removing hydroxy-protecting groups taught in the Holton and Kingston patents would not be expected to remove either or both of the 7- and 10- methoxy groups set forth in the amended claims (Commerçon Declaration, ¶ 5).

As understood at the interview, the Examiner wants to see test results demonstrating that under the conditions utilized in the Holton and Kingston

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patents to remove hydroxyl protecting groups, the 7- and 10- position methoxy groups of the claimed invention would not be removed (Commerçon Declaration, ¶5).

With respect to the conditions utilized in the Holton and Kingston patents, col. 11, lines 19-23 of Holton, relating to compounds 6b, 6c, and 6d, upon which the Examiner relies, states that the protecting groups are "hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents." (Commerçon Declaration, ¶6). The mild conditions themselves, designed to easily remove the hydroxyl protecting groups but not to disturb the ester linkage or the taxane substituents, are defined generally in Holton column 6, lines 35-40, as:

(1) 48% HF, acetonitrile, pyridine;

(2) 0.5% HCl/water/ethanol; and/or

(3) zinc, acetic acid. (Commerçon Declaration, ¶6).

Holton Example 1 demonstrates the use of conditions (1) to remove hydroxyl protecting groups. Holton Examples 2-15 demonstrate the use of conditions (2) for the same purpose. Examples 3-15 appear to disclose conditions somewhat less mild that Example 2 and of these, Dr. Commerçon considered Example 3 to be representative. The Kingston patent demonstrates the use of conditions (3) to remove hydroxyl protecting groups in the Example

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at column 20, lines 34-47. In column 18, lines 20-25, moreover, Kingston teaches the use of conditions (3) to deprotect the compounds which the Examiner relies on in his rejection. In Dr. Commerçon's view, these examples accurately reflect reasonable ways for one skilled in the art to attempt removal of hydroxyl protecting groups in taxane compounds like the Test Compound described below. (Commerçon Declaration, ¶7).

Accordingly, based on Holton Examples 1 and 3 and Kingston Example 1, Dr. Commerçon supervised the design, performance and analysis of the tests reported in his declaration (see pp. 5-9 of the declaration), to determine whether, under the type of mild acidic conditions described in these patents to remove hydroxyl protecting groups from taxane compounds, either or both methoxy groups in the 7- and 10- positions of compound 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R, 3S)-3-tert-butoxy-carbonylamino-2-hydroxy-3-phenylpropionate (referred to hereafter as the "Test Compound" and which falls within the scope of the claims) would be removed. (Commerçon Declaration, ¶8).

The test results demonstrate that when the 7,10-dimethoxy Test Compound is subjected to the mildly acidic conditions such as used in Holton and Kingston to deprotect taxane compounds without disturbing the ester linkage, the basic taxane structure, or the taxane substituents, no removal of

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the methoxy groups of the Test Compound is observed . Accordingly, one skilled in the art would conclude that the methoxy groups at the 7- and 10-positions of the Test Compound cannot be considered as appropriate hydroxy protecting groups under Holton and Kingston's art-recognized conditions for removal of hydroxyl protecting groups from taxane compounds. (Commerçon Declaration, ¶9).

In view of the amendments to the claims and the reasons set forth above, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be removed.

Rejections Under 35 U.S.C. § 103

Holton in view of Greene

Claims 1-4 and 17-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Holton in view of Greene. According to the Examiner, Holton teaches a protected taxane which is analogous to the claimed compounds (citing compounds 6b-6d of Holton). The Examiner admits that the prior art, i.e., the OT_1 and Z groups of Holton, does not specifically teach the instant R_4 and R_5 groups. However, the Examiner cites Greene as teaching the hydroxy-protecting groups to be conventional. The Examiner concludes that it would be *prima facie* obvious to replace the C-7 and C-2' protecting group of Holton by a

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hydroxy protecting group as taught by Greene without the loss of the same utility.

Applicants respectfully traverse the rejection. As explained above, in view of Dr. Commerçon's explanations offered at the interview, as well as in view of the confirming test results discussed above, one skilled in the art would certainly conclude that the alkoxy groups at the 7- and 10- positions of the claimed compounds *cannot* be considered as appropriate hydroxy protecting groups under Holton's art-recognized conditions for removal of hydroxyl protecting groups from taxane compounds. Therefore, Greene would in no way suggest replacing a protective group of Holton by an alkoxy group, as claimed.

The Federal Circuit has clearly stated that both a suggestion and a reasonable expectation of success are necessary for a successful combination of references when making a § 103 rejection:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). [Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Id.]

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In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The combination of Holton and Greene fails to meet either of the above two factors. As demonstrated above, no combination of Holton or Greene would have suggested to one of ordinary skill in the art that the presently claimed invention should be carried out and have a reasonable likelihood of success. Accordingly, a proper *prima facie* case of obviousness has not been establishd.

Thus, the rejection under 35 U.S.C. § 103 based on Holton and Greene is in error; it did not apply to the original claims, and it certainly should not be applied to the claims as amended. Applicants respectfully request that the rejection be withdrawn.

Kingston

The Examiner has also rejected claim 25 under 35 U.S.C. § 103 as unpatentable over Kingston. According to the Examiner, Kingston teaches a protected taxane which is analogous to the instant compounds (citing compound 24 in column 18 of Kingston). The Examiner alleges that since the protection and deprotection of the hydroxy groups of taxane compounds are obvious in the art, the instant taxane wherein the C2' hydroxy is unprotected would be deemed obvious over the protected C2' taxane of Kingston.

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Applicants respectfully traverse the rejection. Compound 24 of Kingston is a compound protected at both C-7 and C-2'. In particular, at C-7, R_2 of Compound 24 is defined as "troc or other protecting group." Significantly, Professor Kingston goes on to teach that his Compound 24 can be reacted with di-t-butyl dicarbonate, hydrolyzed, and de-protected to yield Taxotere, which, as the Examiner knows, has been approved by the FDA as an anticancer agent. The structure of the intermediate 24 in no way suggests the claimed compounds, which possess no protective group at C-7.

As explained above, in view of Dr. Commerçon's explanations offered at the interview, as well as in view of the confirming test results discussed above, one skilled in the art would conclude that the alkoxy groups at the 7- and 10-positions of the claimed compounds cannot be considered as appropriate hydroxy protecting groups under Kingston's art-recognized conditions for removal of hydroxyl protecting groups from taxane compounds. Therefore, there is no way Kingston would suggest the compounds recited in claim 25.

Accordingly, there is neither a teaching nor a suggestion in the art of record that would have motivated one of ordinary skill in the art to substitute the C7, C10 and C2' positions of Kingston in order to obtain formula (VII) of present claim 25. The rejection under 35 U.S.C. § 103 is therefore in error and should be withdrawn.

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Allowable Subject Matter

Applicants thank the Examiner for his indication that claims 5-16 and 26-31 are allowable since the claimed processes are unobvious over the prior art. As noted above, these claims have been clarified by some formal amendments.

CONCLUSION

In view of the foregoing amendments and remarks, it is urged that all of the pending claims are in condition for allowance. An early and favorable action is earnestly solicited.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Amendment, such extension is hereby requested. If there are any fees due under 37 C.F.R. § 1.16 or 1.17 which are not enclosed,

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including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge those fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Thalia V. Warnement, Reg No. 39,064
for Thomas L. Irving
Thomas L. Irving
Reg. No. 28,619

Dated: October 29, 1997

Attachments: Exhibits 1-4 (Greene, Greene, Chen, Kingston)

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GAU 1203

PATENT
Attorney Docket No. 3806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: 1203

Filed: March 26, 1996 — Examiner: B. Trinh

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION FOR EXTENSION OF TIME

Applicants hereby petition for three month extension of time to respond to the Office Action of April 29, 1997. A fee of $950.00 is enclosed.

If there are any other fees due in connection with the filing of this petition, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
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PATENT
Attorney Docket No. 3806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
Hervé BOUCHARD et al.	)	
Serial No.: 08/622,011	)	Group Art Unit: 1203
Filed: March 26, 1996	)	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	)	

TRANSMITTAL LETTER

NOV 7

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed is a response to the Office Action of April 29, 1997.
The items checked below are appropriate:

[XX] Applicants hereby petition for a three-month extension of time to respond to the above Office Action. The fee of $950.00 for the Extension is enclosed.

The claims are calculated below:

	Claims Remaining After Amendment		Highest Number Previously Paid	Present Extra	Rate	Additional Fee
Total	35	-	31	4	x $ 22	$ 88.00
Indep.	12	-	9	3	x $ 82	246.00
[ ] First Presentation of Multiple Dep. Claim(s)					+ $270	
					Subtotal	$
					Reduction by ½ if small entity	-
					TOTAL	$ 334.00

[XX] A fee of $334.00 to cover the cost of the additional claims added by this response is enclosed.

11/05/1997 MPEOPLES 00000028 08622011
02 FC:103 246.00 OP
04 FC:102

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[XX] A check for $1,284.00 to cover the above fees is enclosed.

To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this response, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Date: October 29, 1997

By: Thalia V. Warnement

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PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hervé BOUCHARD et al.	
Serial No.: 08/622,011	Group Art Unit: 1203
Filed: March 26, 1996	Examiner: B. Trinh
For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. ALAIN COMMERÇON

I, Alain Commerçon, declare and state that

1. I am a citizen of France, residing in Vitry-sur-Seine, France.

2. I received a degree of "Ingénieur Chimiste" from Ecole Nationale Supérieure de Chimie de Toulouse in 1973. In 1976, I received my PhD ("Docteur-ès-Sciences") in chemistry from the University of Pierre and Marie Curie (Paris VI) in Paris.

3. I have been employed since 1979 by Rhône-Poulenc Rorer, S.A. (formerly Rhône-Poulenc, S.A.) and have held the positions of Senior Research Scientist (1978-1988), Senior Research Fellow (1988-1991), Department Manager of Oncology Chemistry (1991), Rhône-Poulenc Group Senior Research Advisor (1992-present), Director of Oncology Chemistry (1995) and

since 1996, I have been the Director of the New Lead Generation Combinatorial Chemistry group. My research in the last ten years has been in the area of medicinal chemistry in oncology, including the synthesis of anti-tumor agents of natural origin, such as taxoids. Since becoming Director of New Lead Generation, my responsibilities include overseeing the development of new technologies, particularly the design and synthesis of new molecules for new biological targets in e.g., natural products chemistry.

4. I am a co-inventor of this application. I am the co-author of some 45 articles relating to taxane chemistry, as is evidenced in my curriculum vitae, which is attached as Exhibit 1.

5. I attended an interview at the USPTO on October 2, 1997 with the Examiner at which the claims as amended were discussed. At the interview, I explained in detail my belief that methoxy groups at the 7- and 10-positions of the claimed compounds cannot be considered appropriate hydroxy protecting groups in taxane compounds under conditions for removing hydroxy-protecting groups taught in U.S. Patent Nos. 5,229,526 (Holton) and 5,319,112 (Kingston). These conditions are designed to easily deprotect taxane compounds without disturbing the ester linkage, the basic taxane structure, or the taxane substituents. In particular, I discussed with the Examiner that the conditions for removing hydroxy-protecting groups taught in the Holton and

Kingston patents, upon which I understand the Examiner relies to reject the claims of this application, would not be expected to remove either or both of the 7- and 10- methoxy groups set forth in the amended claims. I also discussed with the Examiner why the Holton patent he relies on teaches one skilled in the art that an alkoxy substituent on a taxane is not a hydroxy protecting group for Holton's purposes. As I understood it, the Examiner wants to see test results demonstrating that under the conditions utilized in the Holton and Kingston patents to remove hydroxyl protecting groups, the 7- and 10- position methoxy groups of the claimed invention would not be removed. I will now explain these conditions utilized in the Holton and Kingston patents.

6. At column 11, lines 19-23 of Holton, relating to compounds 6b, 6c, and 6d, upon which I understand the Examiner relies, it is stated that the protecting groups (in this case, triethylsilyl and ethoxyethyl) are "hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents." The mild conditions themselves, designed to easily remove the hydroxyl protecting groups but not to disturb the ester linkage or the taxane substituents, are defined generally in Holton column 6, lines 35-40, as:

(1) 48% HF, acetonitrile, pyridine;

(2) 0.5% HCl/water/ethanol; and/or

(3) zinc, acetic acid.

7. Holton Example 1 demonstrates the use of conditions (1) to remove hydroxyl protecting groups. Holton Examples 2-15 demonstrate the use of conditions (2) for the same purpose. Examples 3-15 appear to disclose conditions somewhat less mild that Example 2 and of these, I consider Example 3 to be representative.[1] The Kingston patent demonstrates the use of conditions (3) to remove hydroxyl protecting groups in the Example at column 20, lines 34-47. In column 18, lines 20-25, moreover, Kingston teaches the use of conditions (3) to deprotect the compounds which I understand the Examiner relies on in his rejection. In my view, these examples accurately reflect reasonable ways for one skilled in the art to attempt removal of hydroxyl protecting groups in taxane compounds like the Test Compound described below.

8. Accordingly, based on Holton Examples 1 and 3 and Kingston Example 1, I supervised the design, performance and analysis of the following tests, to determine whether, under the type of mild acidic conditions described in these patents to remove hydroxyl protecting groups from taxane compounds, either or both methoxy groups in the 7- and 10- positions of compound 4α-

[1] In my view, it was most fair to use the *least* mild conditions (i.e., the strongest of the mild acidic conditions) disclosed in the Holton and Kingston patents to evaluate whether the 7- and 10- position methoxy groups of the Test Compound, defined below, are removed.

acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R, 3S)-3-tert-butoxy-carbonylamino-2-hydroxy-3-phenylpropionate (referred to hereafter as the "Test Compound" and which falls within the scope of the claims) would be removed.

Test 1*: *HF

This test was based on the procedure set forth in Example 3, col. 14, lines 60-68, of U.S. Patent No. 5,229,526 to Holton. The Test Compound was used instead of the 2',7,10-tris-triethylsilyl taxotere. 2.16 ml of at least 40% HF was used instead of 1.8 ml of 48% HF. Appropriate adjustments were made to account for the difference in molecular weight of the two taxoid compounds, i.e., so that the same number of mmol of Test Compound was used as was used of 2',7,10-tris-triethylsilyl taxotere.

To a solution of 0.248 mmol of the Test Compound (207.3 mg) in 12 ml acetonitrile and 0.6 ml pyridine at 0°C was added 2.16 ml of at least 40% aqueous HF. The mixture was stirred at 0°C for 3 hours, then at 25°C for 13 hours, and was checked by thin layer chromatography (TLC) throughout. The stirred mixture was then partitioned between saturated aqueous sodium bicarbonate (3 x 30 ml) and 60 ml ethyl acetate, including washing with 2 x 30 ml H_2O. The organic phase was dried over $MgSO_4$ and then the ethyl acetate

solution was evaporated to give a crude residue in an amount of 214.6 mg.[2] Based on TLC, I did not consider it necessary to purify by chromatography, as Holton did. In my opinion, this procedure constitutes a fair reproduction of the mild conditions used in Holton Example 3 to remove hydroxyl protecting groups.

The residue was analyzed with NMR and TLC, which were consistent with the Test Compound being the only taxoid present. Although there are other analytical techniques, such as HPLC, IR, and MS, which could have been used in each experiment, I considered it reasonable and sufficient to utilize TLC and NMR to evaluate the results of this and the following experiments.[3]

---

[2] The residue was slightly greater in amount than the starting Test Compound because of incomplete removal of at least pyridine from the residue.

[3] There was one other stability test run at RPR using 50 ml of a 200 µg/ml solution of the Test Compound in acetonitrile/water, 80/20 v/v, to which 5 ml of 0.1M HCL was added. The resulting solution was kept at 37°C for up to 2.5 hours. In that test, HPLC was used to analyze the results, and the results demonstrated that the 7- and 10- position methoxy groups were not converted to hydroxy groups. Even though this result is consistent with what I observed, I decided not to rely on this test because the acidic conditions used were much milder than those taught in the Holton patent for HCl, and the acidic system was not exactly the same as taught in Holton because water was used instead of pyridine.

Test 2: HCl

This test was based on the procedure set forth in Example 1, col. 13, lines 51-60, of U.S. Patent No. 5,229,526 to Holton. The Test Compound was used instead of (2'R,3'S)-2'-ethoxyethyl-7-triethylsilyl taxol. Appropriate adjustments were made to account for the difference in molecular weight, i.e., so that the same number of µmol of Test Compound was used as was used of (2'R,3'S)-2'-ethoxyethyl-7-triethylsilyl taxol.

A 4 mg sample of the Test Compound (4.81 µmol) was dissolved in 2 ml ethanol, and 0.5 ml of 0.5% aqueous HCl solution was added. The mixture was stirred at 0°C for 30 hours and was checked by TLC throughout. The mixture was diluted with 50 ml ethyl acetate, extracted with 20 ml saturated aqueous sodium bicarbonate solution dried over sodium sulfate, and concentrated, by evaporation at 40°C under 3 mbar pressure, giving a residue in an amount of 4.2 mg.[4] Based on TLC, I did not consider it necessary to purify by chromatography, as Holton did. In my opinion, this procedure constitutes a fair reproduction of the mild conditions used in Holton Example 1 to remove

---

[4] The residue was slightly greater in amount than the starting Test Compound because of incomplete removal of at least ethyl acetate from the residue.

hydroxyl protecting groups. The residue was analyzed with NMR and TLC, which were consistent with the Test Compound being the only taxoid present.

Test 3: CH_3COOH

This test was based on the procedure set forth in Example 1, col. 20, lines 34-46, of U.S. Patent No. 5,319,112 to Kingston. The Test Compound was used instead of 7-(2,2,2-trichloroethyloxycarbonyl)taxol. Appropriate adjustments were made to account for the difference in molecular weight, i.e., so that the same number of µmol of Test Compound was used as was used of 7-(2,2,2-trichloroethyloxycarbonyl)taxol.

A 20.2 mg sample of the Test Compound (24.2 µmol) was dissolved in 2 ml acetic acid, and 20 mg of zinc dust were added. The resulting heterogeneous solution was stirred at 40°C for 2 hours and was checked by TLC throughout. The solution was filtered to remove the zinc, diluted with 20 ml ethyl acetate, extracted with 3 x 20 ml saturated sodium bicarbonate solution and 2 x 10 ml water, and dried over magnesium sulfate. The solvent was removed under vacuum at 40°C under 3 mbar, giving a residue in an amount of 19.4 mg. Based on TLC, I did not consider it necessary to purify by chromatography, as Kingston did. In my opinion, this procedure constitutes a fair reproduction of the mild conditions used in Kingston Example 1 to remove

hydroxyl protecting groups. The residue was analyzed with NMR, TLC, and MS, which were consistent with the Test Compound being the only taxoid present.

DISCUSSION OF RESULTS:

9. The test results demonstrate that when the 7,10-dimethoxy Test Compound is subjected to the mildly acidic conditions such as used in Holton and Kingston to deprotect taxane compounds without disturbing the ester linkage, the basic taxane structure, or the taxane substituents, no removal of the methoxy groups of the Test Compound is observed . Accordingly, one skilled in the art would conclude that the methoxy groups at the 7- and 10-positions of the Test Compound cannot be considered as appropriate hydroxy protecting groups under Holton and Kingston's art-recognized conditions for removal of hydroxyl protecting groups from taxane compounds.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

Serial No.: 08/622,011
Attorney Docket No.: 03806.0367

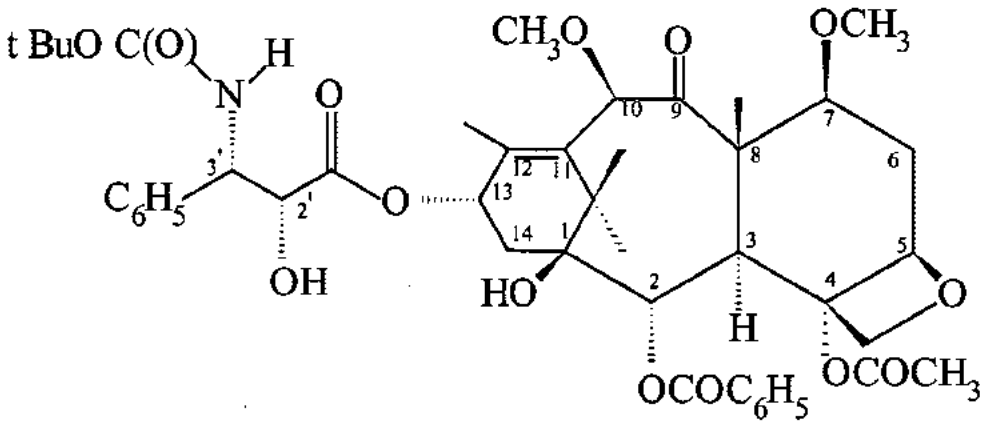
States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: _____
Dr. Alain Commerçon

Date: October 23, 1997

exhibit #12

REJECTION UNDER 35 U.S.C. § 102 OVER HOLTON '526



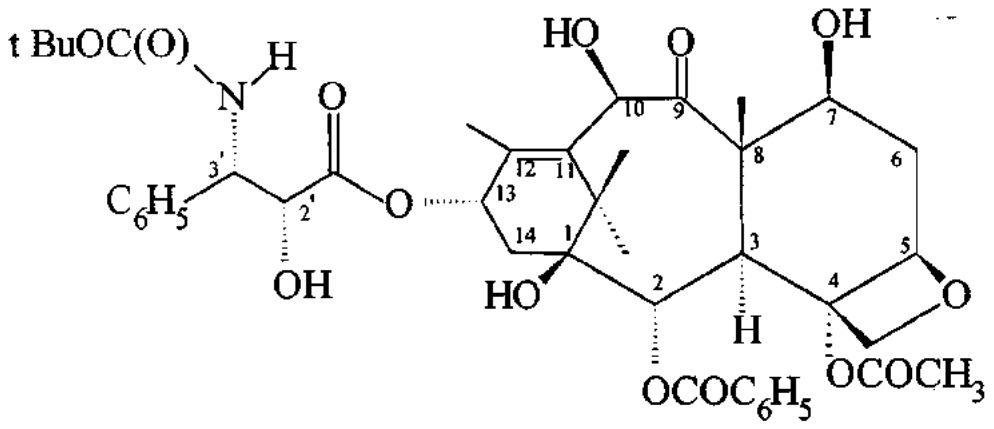
CLAIMED COMPOUND : DIMETHOXY

HOLTON '526 COMPOUNDS 6b-6d v. COMPOUND of CLAIM 17 IN THE C-13 SIDE CHAIN:

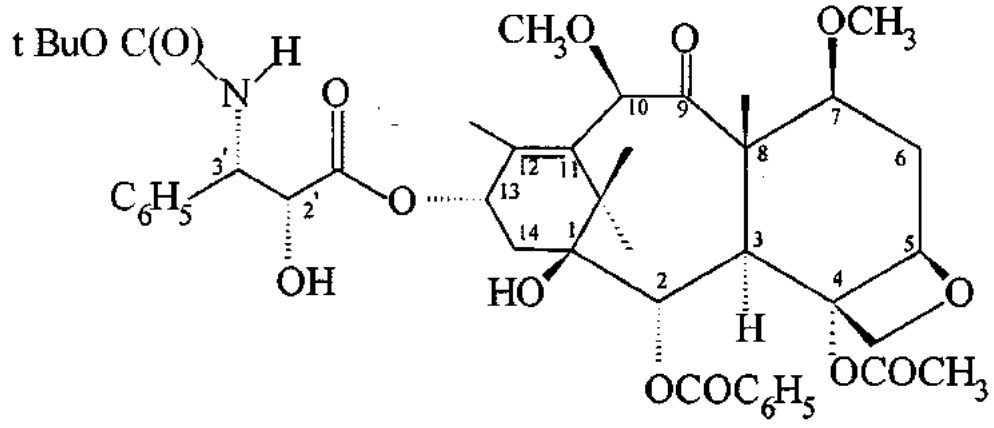
Compound of Claim 17	Holton compounds 6b-6d
-OH at 2'-position of side chain	R_1 or R_2 at 2'-position, defined at col. 4: R_1 = $-OR_6$, $-SR_7$, or $-NR_8R_9$ *only $-OR_6$ is possibly relevant to claim 17 with respect to anticipation issue, but ***R_6 cannot be H***; instead R_6 = alkyl, alkenyl, alkynyl, aryl, heteroaryl, or hydroxy protecting group. R_2 = hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl but ***R_2 cannot be -OH***

THEREFORE, NO POSSIBILITY FOR R_1 OR FOR R_2 CAN ANTICIPATE THE SPECIES RECITED IN CLAIM 17.

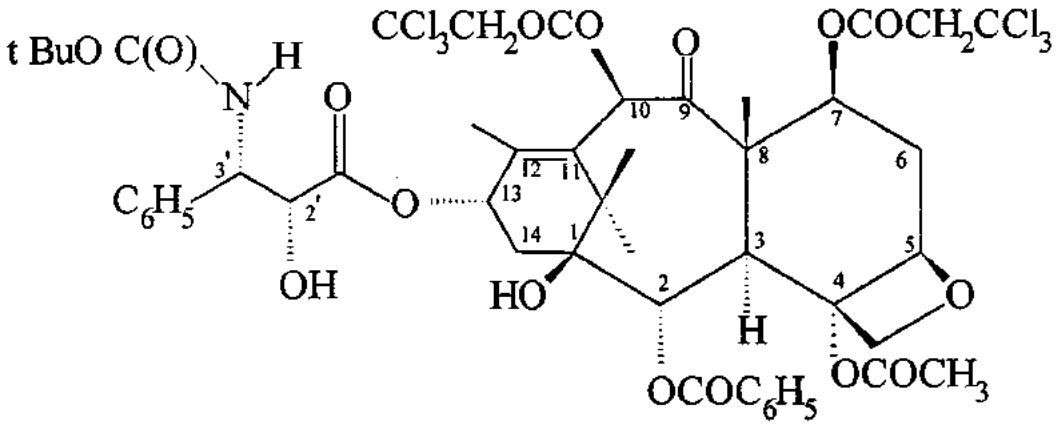
exhibit 2



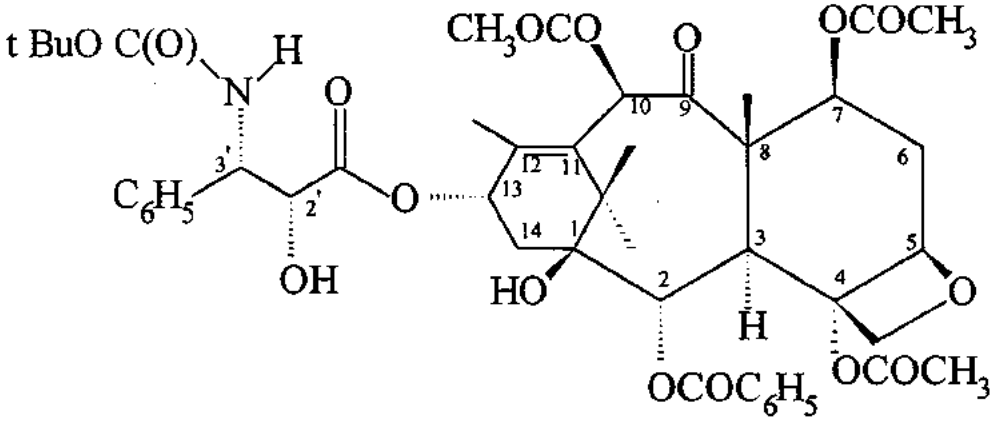
TAXOTERE



CLAIMED COMPOUND : DIMETHOXY



COMPARATIVE COMPOUND A: diTROC



COMPARATIVE COMPOUND B: diacetylated

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.

EXAMINER	
ART UNIT	PAPER NUMBER

8

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Irving [illegible] (3) Mr. Warnement TW

(2) Mr. Commercon [illegible] (4) Mr. Trinh

Date of Interview 10-2-97

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☑ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: 1-4, 17-25

Identification of prior art discussed: art of record

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: No agreement had been reached regarding to the claims and the prior art.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Examiner's Signature

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E2           23     COMMERCON A/AU
E3           71 --> COMMERCON ALAIN/AU
E4            1     COMMERCON BOURGAIN M/AU
E5            1     COMMERCON BOURGAIN MONIQUE/AU
E6            6     COMMERCON J C/AU
E7            5     COMMERCON M/AU
E8            3     COMMERCON MONIQUE/AU
E9            4     COMMERCON P/AU
E10           2     COMMERCON PASCAL/AU
E11          10     COMMERE B/AU
E12           1     COMMERE BERNARD/AU

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            71 "COMMERCON ALAIN"/AU
L1          94 ("COMMERCON A"/AU OR "COMMERCON ALAIN"/AU)

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            67 "COMMERCON ALAIN"/AU
L2          77 ("COMMERCON A"/AU OR "COMMERCON ALAIN"/AU)
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=> D L2 1-77

L2 ANSWER 1 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:511914 CAPLUS
DN 127:135637
TI Preparation of (4-methoxybenzyl)indane derivatives having antitumor and antileukemia activity
IN Bouchard, Herve; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.; Bouchard, Herve; Commercon, Alain
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
PI WO 9721657 A1 970619
DS W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, FI, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR1910 961202
PRAI FR 95-14756 951213
DT Patent
LA French
OS MARPAT 127:135637

L2 ANSWER 2 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:506642 CAPLUS
DN 127:121900
TI Preparation of novel taxoids with antitumoral and antileukemic properties
IN Bouchard, Herve; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.; Bouchard, Herve; Commercon, Alain
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
PI WO 9723472 A1 970703
DS W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR2030 961219
PRAI FR 95-15380 951222
DT Patent
LA English
OS CASREACT 127:121900; MARPAT 127:121900

L2 ANSWER 3 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:506635 CAPLUS
DN 127:121899
TI Preparation of novel taxoids and pharmaceutical compositions containing them for treatment of cancer and leukemia
IN Bouchard, Herve; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.; Bouchard, Herve; Commercon, Alain
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
PI WO 9723473 A1 970703
DS W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB,

GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR2031 961219
PRAI FR 95-15379 951222
DT Patent
LA English
OS CASREACT 127:121899; MARPAT 127:121899

L2 ANSWER 4 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:456960 CAPLUS
DN 127:95194
TI New benzisoindole derivatives as inhibitors of farnesyl transferase, their preparation, and pharmaceutical compositions containing them.
IN **Commercon, Alain**; Lebrun, Alain; Mailliet, Patrick; Peyronel, Jean Francois; Sounigo, Fabienne; Truchon, Alain; Zucco, Martine; Cheve, Michel
PA Rhone Poulenc Rorer Sa, Fr.
SO Fr. Demande, 96 pp.
CODEN: FRXXBL
PI FR 2736641 A1 970117
AI FR 95-8296 950710
DT Patent
LA French
OS MARPAT 127:95194

L2 ANSWER 5 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:318287 CAPLUS
DN 127:44434
TI Novel Conformationally Extended Naphthalene-Based Inhibitors of Farnesyltransferase
AU Burns, Christopher J.; Guitton, Jean-Dominique; Baudoin, Bernard; Lelievre, Yves; Duchesne, Marc; Parker, Fabienne; Fromage, Nadine; **Commercon, Alain**
CS Centre de Recherches de Vitry-Alfortville, Rhone-Poulenc Rorer S. A., Vitry-sur-Seine, 94403, Fr.
SO J. Med. Chem. (1997), 40(12), 1763-1767
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CJACS-IMAGE; CJACS

L2 ANSWER 6 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:293742 CAPLUS
DN 126:264351
TI Preparation of naphthoyl amino acids as antitumor agents and farnesyltransferase inhibitors
IN Baudoin, Bernard; Burns, Christopher; **Commercon, Alain**; Lebrun, Alain
PA Rhone Poulenc Rorer Sa, Fr.
SO Fr. Demande, 25 pp.
CODEN: FRXXBL
PI FR 2736638 A1 970117
AI FR 95-8423 950712
DT Patent
LA French
OS MARPAT 126:264351

L2 ANSWER 7 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:175224 CAPLUS
DN 126:261164
TI [3H](Azidophenyl)ureido Taxoid Photolabels Peptide Amino Acids 281-304 of .alpha.-Tubulin

AU Loeb, C.; Combeau, C.; Ehret-Sabatier, L.; Breton-Gilet, A.; Faucher, D.; Rousseau, B.; **Commercon, A.**; Goeldner, M.
CS Laboratoire de Chimie Bio-organique URA 1386 CNRS Faculte de Pharmacie, Universite Louis Pasteur Strasbourg, Illkirch, 67401, Fr.
SO Biochemistry (1997), 36(13), 3820-3825
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CJACS-IMAGE; CJACS

L2 ANSWER 8 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1997:162032 CAPLUS
TI Novel conformationally extended naphthalene-based inhibitors of farnesyltransferase.
AU Burns, C. J.; Guitton, J.-D.; Baudoin, B.; Lebrun, A.; LeLievre, Y.; Duchesne, M.; Parker, F.; Fromage, N.; **Commercon, A.**
CS Rhone-Poulenc Rorer S. A., Centre de Recherches de Vitry-Alfortville, Vitry-sur-Seine, 94403, Fr.
SO Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-200 Publisher: American Chemical Society, Washington, D. C.
CODEN: 64AOAA
DT Conference; Meeting Abstract
LA English

L2 ANSWER 9 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:746207 CAPLUS
DN 126:19069
TI Preparation and pharmaceutical compositions of novel antitumoral and antineoplastic taxoids
IN Bouchard, Herve; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
PI WO 9632387 A1 961017
DS W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR559 960412
PRAI FR 95-4559 950414
DT Patent
LA French
OS CASREACT 126:19069; MARPAT 126:19069

L2 ANSWER 10 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:718313 CAPLUS
DN 126:8328
TI Novel acylated taxoids as antitumor agents
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
PI WO 9631493 A1 961010
DS W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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AI WO 96-FR487 960401

PRAI FR 95-3868 950403
DT Patent
LA French
OS MARPAT 126:8328

L2 ANSWER 11 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:695853 CAPLUS
DN 126:16157
TI Constrained pseudopeptides as inhibitors of Ras-farnesyl transferase: Structure-activity relationship studies
AU Byk, G.; Burns, C.; Duchesne, M.; Parker, F.; Lelievre, Y.; Guitton, J. D.; Clerc, F. F.; **Commercon, A.**; Tocque, B.; et al.
CS UMR-133 CNRS/Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp., 14th (1996), Meeting Date 1995, 213-214. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Publisher: Mayflower Scientific, Kingswinford, UK. CODEN: 63NTAF
DT Conference
LA English

L2 ANSWER 12 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:687358 CAPLUS
DN 125:329088
TI Novel taxoids as antitumor agents
IN Bouchard, Herve; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
PI WO 9630373 A1 961003
DS W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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AI WO 96-FR442 960325
PRAI FR 95-3546 950327
DT Patent
LA French
OS MARPAT 125:329088

L2 ANSWER 13 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:687356 CAPLUS
DN 125:329087
TI Novel taxoids as antitumor agents
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
PI WO 9630355 A1 961003
DS W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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AI WO 96-FR440 960325
PRAI FR 95-3545 950327
FR 95-15381 951222
DT Patent
LA French
OS MARPAT 125:329087

L2 ANSWER 14 OF 77 CAPLUS COPYRIGHT 1997 ACS

AN 1996:687355 CAPLUS
DN 125:329086
TI Novel taxoids as antitumor agents
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
PI WO 9630356 A1 961003
DS W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR441 960325
PRAI FR 95-3545 950327
FR 95-15381 951222
DT Patent
LA French
OS MARPAT 125:329086

L2 ANSWER 15 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:560526 CAPLUS
DN 125:196377
TI Preparation of tetrahydronaphthyl amino acids as antitumors and farnesyltransferase inhibitors
IN Baudoin, Bernard; Burns, Christopher; **Commercon, Alain**; Lebrun, Alain
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
PI WO 9622278 A1 960725
DS W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 96-FR67 960116
PRAI FR 95-494 950118
DT Patent
LA French
OS MARPAT 125:196377

L2 ANSWER 16 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:539682 CAPLUS
DN 125:222241
TI Semisynthesis of RPR 121056A, a major metabolite of Irinotecan (CPT-11)
AU Bourzat, Jean-Dominique; Vuilhorgne, Marc; Rivory, Laurent P.; Robert, Jacques; **Commercon, Alain**
CS Rhone-Poulenc Rorer S. A., CRVA, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1996), 37(35), 6327-6330
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English

L2 ANSWER 17 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:506709 CAPLUS
DN 125:211705
TI Identification and properties of a major plasma metabolite of irinotecan (CPT-11) isolated from the plasma of patients
AU Rivory, Laurent P.; Riou, Jean-Francois; Haaz, Marie-Christine; Sable, Serge; Vuilhorgne, Marc; **Commercon, Alain**; Pond,

Susan M.; Robert, Jacques
CS Princess Alexandra Hosp., Univ. Queensland, Queensland, 4102, Australia
SO Cancer Res. (1996), 56(16), 3689-3694
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L2 ANSWER 18 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:394209 CAPLUS
DN 125:58788
TI Novel taxoids as neoplasm inhibitors
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Terrier, Corinne; Zucco, Martine
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
PI WO 9613494 A1 960509
DS W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR1393 951023
PRAI FR 94-12795 941026
DT Patent
LA French
OS MARPAT 125:58788

L2 ANSWER 19 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:332429 CAPLUS
DN 125:11177
TI Taxoids, preparation thereof and pharmaceutical compositions containing same
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PI WO 9603395 A1 960208
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR987 950724
PRAI FR 94-9209 940726
DT Patent
LA French
OS CASREACT 125:11177; MARPAT 125:11177

L2 ANSWER 20 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:319813 CAPLUS
DN 125:48353
TI Synthesis and biological evaluation of a new series of phenylhydroquinone derivatives as inhibitors of EGF-R-associated PTK activity
AU Million, Marie-Emmanuelle; Mailliett, Patrick; Chen, Huixiong; Bashiardes, Georges; Boiziau, Janine; Parker, Fabienne; **Commercon, Alain**; Tocque, Bruno; Roques, Bernard P.; Garbat, Christiane
CS Dep. de Pharmacochimie Moleculaire st Structurale, INSERUM-URA, Paris, F-75270, Fr.

SO Anti-Cancer Drug Des. (1996), 11(2), 129-153
CODEN: ACDDEA; ISSN: 0266-9536
DT Journal
LA English

L2 ANSWER 21 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:305532 CAPLUS
DN 125:25614
TI Preparation and biological evaluation of new docetaxel analogs modified at the 3' position of the side-chain
AU Bourzat, J. -D.; Bouchard, H.; **Commercon, A.**; Bissery, M. -C.; Combeau, C.; Vrignaud, P.; Riou, J. -F.; Lavelle, F.
CS Rhone-Poulenc Rorer S.A., Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, Fr.
SO Proc. Int. Cancer Congr., Free Pap. Posters, 16th (1994), Volume 4, 2751-2755. Editor(s): Rao, R. S. Publisher: Monduzzi Editore, Bologna, Italy.
CODEN: 62UYAO
DT Conference
LA English

L2 ANSWER 22 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:202766 CAPLUS
DN 124:261423
TI Novel taxoids, preparation thereof and pharmaceutical compositions containing same
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
PI WO 9601259 A1 960118
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR885 950703
PRAI FR 94-8198 940704
DT Patent
LA French
OS MARPAT 124:261423

L2 ANSWER 23 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:185425 CAPLUS
DN 124:306500
TI Synthesis and biological evaluation of series of hydroxybenzylphenylamine derivatives as inhibitors of EGF receptor-associated tyrosine kinase activity
AU Chen, H.; Bashiardes, G.; Mailliet, P.; **Commercon, A.**; Sounigo, F.; Boiziau, J.; Parker, F.; Tocque, B.; Roques, B. P.; Garbay, C.
CS Dep. de Pharmacochimie Moleculaire et Structurale, Univ. Rene Descartes, Paris, 75270, Fr.
SO Anti-Cancer Drug Des. (1996), 11(1), 49-71
CODEN: ACDDEA; ISSN: 0266-9536
DT Journal
LA English

L2 ANSWER 24 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:177861 CAPLUS
DN 124:233166
TI Novel farnesyl transferase inhibitors

IN Baudoin, Bernard; Burns, Christopher; **Commercon, Alain**; Guitton, Jean-Dominique
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
PI WO 9534535 A1 951221
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR739 950607
PRAI FR 94-7116 940610
FR 94-12338 941017
DT Patent
LA French
OS MARPAT 124:233166

L2 ANSWER 25 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:126646 CAPLUS
DN 124:176586
TI Taxoids, preparation and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
PI WO 9533737 A1 951214
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR736 950607
PRAI FR 94-7050 940609
DT Patent
LA French
OS CASREACT 124:176586; MARPAT 124:176586

L2 ANSWER 26 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:123751 CAPLUS
DN 124:176585
TI New taxoids, preparation thereof and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Terrier, Corinne; Zucco, Martine
PA Rhone-Poulenc Rorer S. A., Fr.
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
PI WO 9533736 A1 951214
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR735 950607
PRAI FR 94-7049 940609
DT Patent
LA French
OS CASREACT 124:176585; MARPAT 124:176585

L2 ANSWER 27 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:123750 CAPLUS

DN 124:176584
TI New taxoids, preparation thereof and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Pulicani, Jean-Pierre
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
PI WO 9533738 A1 951214
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR737 950607
PRAI FR 94-7051 940609
DT Patent
LA French
OS CASREACT 124:176584; MARPAT 124:176584

L2 ANSWER 28 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1996:123748 CAPLUS
DN 124:176582
TI New taxoids, preparation thereof and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Terrier, Corinne; Zucco, Martine
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
PI WO 9533739 A1 951214
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR738 950607
PRAI FR 94-7052 940609
DT Patent
LA French
OS CASREACT 124:176582; MARPAT 124:176582

L2 ANSWER 29 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:996309 CAPLUS
DN 124:56362
TI Process for the preparation of 7-hydroxy taxanes
IN Bastart, Jean-Pierre; Bourzat, Jean-Dominique; **Commercon, Alain**; leconte, Jean-Pierre
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
PI WO 9526961 A1 951012
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-FR420 950403
PRAI FR 94-3980 940405
DT Patent
LA French
OS CASREACT 124:56362; MARPAT 124:56362

L2 ANSWER 30 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:828467 CAPLUS
DN 123:228574
TI Novel taxicine derivatives, their preparation and pharmaceutical compositions containing them
IN **Commercon, Alain**; Terrier, Corinne
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
PI WO 9513270 A1 950518
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-FR1282 941107
PRAI FR 93-13232 931108
DT Patent
LA French
OS MARPAT 123:228574

L2 ANSWER 31 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:813018 CAPLUS
DN 123:228573
TI Novel taxoids, their preparation and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Pulicani, Jean-Pierre
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
PI WO 9513271 A1 950518
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-FR1283 941107
PRAI FR 93-13233 931108
DT Patent
LA French
OS MARPAT 123:228573

L2 ANSWER 32 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:763635 CAPLUS
DN 123:169939
TI Novel taxoids, preparation thereof and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Guenard, Daniel; Gueritte-Voegelein, Francoise
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9511247 A1 950427
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-FR1196 941017
PRAI FR 93-12345 931018

DT Patent
LA French
OS MARPAT 123:169939

L2 ANSWER 33 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:752262 CAPLUS
DN 124:30335
TI Constrained analogs of KCVFM with improved inhibitory properties against farnesyl transferase
AU Clerc, Francois-Frederic; Guitton, Jean-Dominique; Fromage, Nadine; Lelievre, Yves; Duchesne, Marc; Tocque, Bruno; James-Surcouf, Evelyne; **Commercon, Alain**; Becquart, Jerome
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Bioorg. Med. Chem. Lett. (1995), 5(16), 1779-84
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English

L2 ANSWER 34 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:750522 CAPLUS
DN 123:169607
TI Preparation of oxazolidinecarboxylates as therapeutic taxoid intermediates
IN Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone Poulenc Rorer Sa, Fr.
SO Fr. Demande, 36 pp.
CODEN: FRXXBL
PI FR 2706457 A1 941223
AI FR 93-7240 930616
DT Patent
LA French
OS MARPAT 123:169607

L2 ANSWER 35 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:731657 CAPLUS
DN 123:144320
TI Novel taxoids, their preparation and compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Publicani, Jean-Pierre; Zucco, Martine
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
PI WO 9511241 A1 950427
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-FR1210 941019
PRAI FR 93-12488 931020
DT Patent
LA French
OS MARPAT 123:144320

L2 ANSWER 36 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:701903 CAPLUS
DN 123:112461
TI Method of preparing taxoids
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Pulicani, Jean-Pierre
PA Rhone-Poulenc Rorer S.A., Fr.

SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
PI WO 9509163 A1 950406
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 94-FR1125 940927
PRAI FR 93-11564 930929
DT Patent
LA French
OS CASREACT 123:112461; MARPAT 123:112461

L2 ANSWER 37 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:545180 CAPLUS
DN 123:83772
TI Synthesis and biological activity of para-substituted 3'-phenyldocetaxel analogs
AU Bourzat, Jean-Dominique; Lavelle, Francois; **Commercon, Alain**
CS Center Recherches Vitry-Alfortville, Phone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Bioorg. Med. Chem. Lett. (1995), 5(8), 809-14
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English

L2 ANSWER 38 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:526785 CAPLUS
DN 122:291218
TI Preparation of biologically active dioxoepoxytaxoids
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
PI WO 9501969 A1 950119
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 94-FR823 940705
PRAI FR 93-8387 930708
DT Patent
LA French
OS CASREACT 122:291218; MARPAT 122:291218

L2 ANSWER 39 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:358715 CAPLUS
DN 122:133464
TI Preparation of novel antitumor taxoids by electrolytic reduction and their pharmaceutical formulations
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**; Pulicani, Jean-Pierre
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
PI WO 9420484 A1 940915
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 94-FR222 940228
PRAI FR 93-2370 930302
DT Patent
LA French
OS CASREACT 122:133464; MARPAT 122:133464

L2 ANSWER 40 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:312401 CAPLUS
DN 122:105523
TI Preparation of 3-hydroxy-2-azetidinones
IN Bourzat, Jean-dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
PI WO 9424103 A1 941027
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 94-FR416 940414
PRAI FR 93-4495 930416
DT Patent
LA French
OS CASREACT 122:105523; MARPAT 122:105523

L2 ANSWER 41 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:297000 CAPLUS
DN 122:291180
TI Direct access to 2-debenzoyl taxoids by electrochemistry, synthesis of 2-modified docetaxel analogs
AU Pulicani, Jean-Pierre; Bezard, Daniel; Bourzat, Jean-Dominque; Bouchard, Herve; Zucco, Martine; Deprez, Dominique; **Commercon, Alain**
CS Centre Recherches Vitry-Alfortville, Rhone-Poulenc Rorer S. A., Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(52), 9717-20
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 122:291180

L2 ANSWER 42 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:296999 CAPLUS
DN 122:265687
TI Improved access to 19-nor-7.beta.,8.beta.-methylene-taxoids and formation of a 7-membered C-ring analog of docetaxel by electrochemistry
AU Bouchard, Herve; Pulicani, Jean-Pierre; Vuilhorgue, Marc; Bourzat, Jean-Dominque; **Commercon, Alain**
CS Center Recherches Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(52), 9713-16
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 122:265687

L2 ANSWER 43 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:296998 CAPLUS
DN 122:265686
TI Preparation of 7-modified docetaxel analogs using electrochemistry
AU Pulicani, Jean-Pierre; Bouchard, Herve; Bourzat, Jean-Dominque; **Commercon, Alain**
CS Center Recherches Vitry-Alfortville, Rhone-Poulenc Rorer S. A., Vitry-sur-Seie, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(52), 9709-12
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English

OS CASREACT 122:265686

L2 ANSWER 44 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:280267 CAPLUS
DN 122:106131
TI Practical semisynthesis and antimitotic activity of docetaxel and side-chain analogs
AU **Commercon, A.**; Bourzat, J. D.; Didier, E.; Lavelle, Francois
CS Rhone-Poulenc Rorer, Centre de Recherches de Vitry Alfortville, Vitry sur Seine, 94403, Fr.
SO ACS Symp. Ser. (1995), 583(Taxane Anticancer Agents), 233-46
CODEN: ACSMC8; ISSN: 0097-6156
DT Journal; General Review
LA English

L2 ANSWER 45 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:213968 CAPLUS
DN 122:10301
TI New taxoids, their preparation, and pharmaceutical compositions containing them
IN Bouchard, Herve; Bourzat, Jean-Dominique; **Commercon, Alain**
PA Rhone Poulenc Rorer SA, Fr.
SO Fr. Demande, 35 pp.
CODEN: FRXXBL
PI FR 2698871 A1 940610
AI FR 92-14813 921209
DT Patent
LA French
OS CASREACT 122:10301; MARPAT 122:10301

L2 ANSWER 46 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1995:58257 CAPLUS
DN 122:106165
TI Partial synthesis of major human metabolites of docetaxel
AU **Commercon, Alain**; Bourzat, Jean-Dominique; Bezard, Daniel; Vuilhorgne, Marc
CS Centre Recherches Vitry-Alfortville, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron (1994), 50(34), 10289-98
CODEN: TETRAB; ISSN: 0040-4020
DT Journal
LA English

L2 ANSWER 47 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:701105 CAPLUS
DN 121:301105
TI Preparation of taxane derivatives as antiproliferatives
IN Bouchard, Herve; Bourzat, Jean-Dominique; **commercon, Alain**
PA Rhone Poulenc Rorer SA, Fr.
SO Fr. Demande, 44 pp.
CODEN: FRXXBL
PI FR 2698363 A1 940527
AI FR 92-14023 921123
DT Patent
LA French
OS MARPAT 121:301105

L2 ANSWER 48 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:680914 CAPLUS
DN 121:280914
TI Electrochemical reduction of taxoids: selective preparation of 9-dihydro-, 10-deoxy- and 10-deacetoxy-taxoids

AU Pulicani, Jean-Pierre; Bourzat, Jean-Dominique; Bouchard, Herve; **Commercon, Alain**
CS Rhone-Poulenc Rorer S.A., Centre Recherches Vitry-Alfortville, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(28), 4999-5002
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English

L2 ANSWER 49 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:631103 CAPLUS
DN 121:231103
TI Preparation of taxane derivatives as antiproliferatives
IN Bourzat, Jean Dominique; **Commercon, Alain**; Deprez, Dominique; Publicani, Jean Pierre
PA Rhone Poulenc Rorer SA, Fr.
SO Fr. Demande, 20 pp.
CODEN: FRXXBL
PI FR 2697841 A1 940513
AI FR 92-13586 921112
DT Patent
LA French
OS MARPAT 121:231103

L2 ANSWER 50 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:630593 CAPLUS
DN 121:230593
TI Preparation of taxane derivatives as antitumor agents
IN Bourzat, Jean Dominique; **Commercon, Alain**; Deprez, Dominique; Pulicani, Jean Pierre
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
PI WO 9408984 A1 940428
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR1013 931013
PRAI FR 92-12331 921015
DT Patent
LA French
OS MARPAT 121:230593

L2 ANSWER 51 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:605748 CAPLUS
DN 121:205748
TI Method of preparing taxane derivatives
IN **Commercon, Alain**; Didier, Eric; Fouque, Elie
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
PI WO 9407878 A1 940414
DS W: AU, BY, CA, CZ, FI, HU, JP, KR, KZ, NO, NZ, PL, RU, SK, UA, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR968 931004
PRAI FR 92-11742 921005
DT Patent
LA French
OS MARPAT 121:205748

L2 ANSWER 52 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:605723 CAPLUS
DN 121:205723

TI Expeditious semisynthesis of docetaxel using 2-trichloromethyl-1,3-oxazolidine as side-chain protection
AU Didier, Eric; Fouque, Elie; **Commercon, Alain**
CS Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(19), 3063-4
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 121:205723

L2 ANSWER 53 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:605130 CAPLUS
DN 121:205130
TI Taxoid antitumor agents
IN Bouchard, Herve; Bourzat, Jean Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
PI WO 9412485 A1 940609
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR1173 931130
PRAI FR 92-14500 921202
DT Patent
LA French
OS MARPAT 121:205130

L2 ANSWER 54 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:579921 CAPLUS
DN 121:179921
TI Preparation of taxol analogs as antiproliferatives
IN Bourzat, Jean Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
PI WO 9407880 A1 940414
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR970 931004
PRAI FR 92-11744 921005
DT Patent
LA French
OS MARPAT 121:179921

L2 ANSWER 55 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:579898 CAPLUS
DN 121:179898
TI 2-Monosubstituted-1,3-oxazolidines as improved protective groups of N-Boc-phenylisoserine in docetaxel preparation
AU Didier, Eric; Fouque, Elie; Taillepied, Isabelle; **Commercon, Alain**
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1994), 35(15), 2349-52
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 121:179898

L2 ANSWER 56 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:534801 CAPLUS
DN 121:134801

TI Method for preparing .beta.-phenylisoserine and analogs thereof, useful as intermediates for taxane derivatives
IN Bourzat, Jean Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
PI WO 9317997 A1 930916
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR224 930308
PRAI FR 92-2821 920310
DT Patent
LA French
OS CASREACT 121:134801; MARPAT 121:134801

L2 ANSWER 57 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:534499 CAPLUS
DN 121:134499
TI Preparation of taxane derivatives
IN **Commercon, Alain**; Didier, Eric; Fouque, Elie
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
PI WO 9407879 A1 940414
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR969 931004
PRAI FR 92-11743 921005
DT Patent
LA French
OS MARPAT 121:134499

L2 ANSWER 58 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:534485 CAPLUS
DN 121:134485
TI Synthesis of 19-hydroxy docetaxel from a novel baccatin
AU Margraff, Rodolphe; Bezard, Daniel; Bourzat, Jean Dominique; **Commercon, Alain**
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Bioorg. Med. Chem. Lett. (1994), 4(2), 233-6
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
OS CASREACT 121:134485

L2 ANSWER 59 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:322877 CAPLUS
DN 120:322877
TI Structure-Activity Relationships in a Series of 5-[(2,5-Dihydroxybenzyl)amino]salicylate Inhibitors of EGF-Receptor-Associated Tyrosine Kinase: Importance of Additional Hydrophobic Aromatic Interactions
AU Chen, Huixiong; Boiziau, Janine; Parker, Fabienne; Mailliet, Patrick; **Commercon, Alain**; Tocque, Bruno; Le Pecq, Jean-Bernard; Roques, Bernard-Pierre; Garbay, Christiane
CS Departement de Pharmacochimie Moleculaire et Structurale, Faculte de Pharmacie, Paris, 75270, Fr.
SO J. Med. Chem. (1994), 37(6), 845-59
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English

OS CJACS-IMAGE; CJACS

L2 ANSWER 60 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:318744 CAPLUS
DN 120:318744
TI Predominant Labeling of .beta.- over .alpha.-Tubulin from Porcine Brain by a Photoactivatable Taxoid Derivative
AU Combeau, Cecile; **Commercon, Alain**; Mioskowski, Charles; Rousseau, Bernard; Aubert, Francois; Goeldner, Maurice
CS Centre de Recherches de Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Biochemistry (1994), 33(21), 6676-83
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
OS CJACS-IMAGE; CJACS

L2 ANSWER 61 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:314463 CAPLUS
DN 120:314463
TI Platinum (IV) derivatives, method of preparation and pharmaceutical composition
IN Barreau, Michel; Chottard, Jean Claude; **Commercon, Alain**; Le Pecq, Jean Bernard; Mailliet, Patrick
PA Laboratoire Roger Bellon, Fr.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
PI WO 9323410 A1 931125
DS W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 93-FR453 930511
PRAI FR 92-5850 920514
DT Patent
LA French
OS MARPAT 120:314463

L2 ANSWER 62 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:270862 CAPLUS
DN 120:270862
TI A practical access to chiral phenylisoserinates, preparation of Taxotere analogs
AU Bourzat, Jean Dominique; **Commercon, Alain**
CS Cent. Recherches Vitry-Alfortville, Rhone-Poulenc Rorer S.A., Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1993), 34(38), 6049-52
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 120:270862

L2 ANSWER 63 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:245558 CAPLUS
DN 120:245558
TI Preparation of taxane derivatives as antitumor agents
IN Bourzat, Jean Dominique; **Commercon, Alain**; Margraff, Rodolphe
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
PI WO 9401425 A1 940120

DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR660 930630
PRAI FR 92-8194 920703
DT Patent
LA French
OS CASREACT 120:245558; MARPAT 120:245558

L2 ANSWER 64 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:245556 CAPLUS
DN 120:245556
TI Preparation of taxane derivatives as antitumor agents
IN Bourzat, Jean Dominique; **Commercon, Alain**
PA Rhone-Poulenc Rorer S. A., Fr.
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
PI WO 9316060 A1 930819
DS W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-FR112 930204
PRAI FR 92-1381 920207
DT Patent
LA French
OS MARPAT 120:245556

L2 ANSWER 65 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1994:164575 CAPLUS
DN 120:164575
TI Novel taxane derivatives, their preparation, and compositions containing them
IN Bourzat, Jean Dominique; **Commercon, Alain**
PA Rhone-Poulenc Industries S. A., Fr.
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
PI WO 9323389 A1 931125
DS W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 93-FR477 930518
PRAI FR 92-6177 920521
DT Patent
LA French
OS CASREACT 120:164575; MARPAT 120:164575

L2 ANSWER 66 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1993:539229 CAPLUS
DN 119:139229
TI Preparation of bis(N-protected)-2-aminoimidazole-4-carboxaldehyde
IN **Commercon, Alain**
PA Rhone-Poulenc Rorer S. A., Fr.
SO Fr. Demande, 12 pp.
CODEN: FRXXBL
PI FR 2681323 A1 930319
AI FR 91-11301 910913
DT Patent
LA French
OS MARPAT 119:139229

L2 ANSWER 67 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1993:496043 CAPLUS
DN 119:96043

TI Synthesis of 2'-deoxy-2'-spirocyclopropyl cytidine as potential inhibitor of ribonucleotide diphosphate reductase
AU Czernecki, Stanislas; Mulard, Laurence; Valery, Jean Marc; **Commercon, Alain**
CS Lab. Chim. Glucides, Univ. Pierre et Marie Curie, Paris, F-75005, Fr.
SO Can. J. Chem. (1993), 71(3), 413-16
CODEN: CJCHAG; ISSN: 0008-4042
DT Journal
LA English
OS CASREACT 119:96043

L2 ANSWER 68 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1993:409005 CAPLUS
DN 119:9005
TI Preparation of O-carbamoyl taxol analogs as neoplasm inhibitors
IN Bourzat, Jean Dominique; **Commercon, Alain**; Guenard, Daniel; Gueritte-Voegelein, Francoise; Potier, Pierre
PA Rhone-Poulenc Rorer SA, Fr.
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
PI EP 524093 A1 930120
DS R: PT
AI EP 92-402046 920716
PRAI FR 91-8937 910716
DT Patent
LA French
OS MARPAT 119:9005

L2 ANSWER 69 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1993:7213 CAPLUS
DN 118:7213
TI Improved protection and esterification of a precursor of the Taxotere and taxol side chains.
AU **Commercon, A.**; Bezard, D.; Bernard, F.; Bourzat, J. D.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1992), 33(36), 5185-8
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 118:7213

L2 ANSWER 70 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1992:651589 CAPLUS
DN 117:251589
TI Method for preparing taxane derivatives, novel derivatives thereby obtained and pharmaceutical compositions containing same.
IN Bourzat, Jean Dominique; **Commercon, Alain**; Paris, Jean Marc
PA Rhone-Poulenc Rorer S.A., Fr.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
PI WO 9209589 A1 920611
DS W: AU, CA, CS, FI, HU, JP, KR, NO, PL, SU, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE
AI WO 91-FR928 911122
PRAI FR 90-14635 901123
FR 91-9423 910725
DT Patent
LA French
OS CASREACT 117:251589; MARPAT 117:251589

L2 ANSWER 71 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1992:6797 CAPLUS
DN 116:6797
TI Enantioselective synthesis of girolline
AU **Commercon, A.**; Paris, J. M.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1991), 32(37), 4905-6
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 116:6797

L2 ANSWER 72 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1991:536475 CAPLUS
DN 115:136475
TI Imidazolepropanamide derivative, its preparation, and its use
IN **Commercon, Alain**; Paris, Jean Marc; Radisson, Xavier
PA Rhone-Poulenc Sante, Fr.
SO Can. Pat. Appl., 21 pp.
CODEN: CPXXEB
PI CA 2026128 AA 910327
AI CA 90-2026128 900925
PRAI FR 89-12574 890926
DT Patent
LA French
OS MARPAT 115:136475

L2 ANSWER 73 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1991:471599 CAPLUS
DN 115:71599
TI Preparation of racemic threo-3-amino-1-(2-amino-1H-imidazol-4-yl)-2-chloro-1-propanol (girolline) as an antitumor agent
IN Ahond, Alain; Almourabit, Ali; Zurita, Manuel Bedoya; **Commercon, Alain**; Potier, Pierre; Poupat, Christiane
PA Rhone-Poulenc Sante, Fr.
SO Fr. Demande, 28 pp.
CODEN: FRXXBL
PI FR 2646849 A1 901116
AI FR 89-6251 890512
DT Patent
LA French
OS MARPAT 115:71599

L2 ANSWER 74 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1991:450066 CAPLUS
DN 115:50066
TI A diasteroselective synthesis of girolline
AU **Commercon, A.**; Gueremy, C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1991), 32(11), 1419-22
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 115:50066

L2 ANSWER 75 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1991:121867 CAPLUS
DN 114:121867
TI Preparation of a girolline enantiomer as an antitumor agent

IN **Commercon, Alain**; Cousin, Jacky; Gueremy, Claude; Ponsinet, Gerard
PA Rhone-Poulenc Sante, Fr.
SO Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
PI EP 397567 A1 901114
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 90-401236 900510
PRAI FR 89-6249 890512
DT Patent
LA French
OS MARPAT 114:121867

L2 ANSWER 76 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1991:23649 CAPLUS
DN 114:23649
TI Diastereoselective chlorocyclofunctionalization of N-allylic trichloroacetamides: synthesis of an analog and potential precursor of RP49532
AU **Commercon, A.**; Ponsinet, G.
CS Cent. Rech. Vitry-Alfortville, RHONE-POULENC SANTE, Vitry-sur-Seine, 94403, Fr.
SO Tetrahedron Lett. (1990), 31(27), 3871-4
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 114:23649

L2 ANSWER 77 OF 77 CAPLUS COPYRIGHT 1997 ACS
AN 1990:135034 CAPLUS
DN 112:135034
TI Selective inhibition of tyrosine protein kinase by a synthetic multisubstrate analog
AU Baginski, Isabelle; **Commercon, Alain**; Tocque, Bruno; Colson, Genevieve; Zerial, Aurelio
CS Cent. Rech. Vitry, Rhone-Poulenc Sante, Vitry sur Seine, 94403, Fr.
SO Biochem. Biophys. Res. Commun. (1989), 165(3), 1324-30
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	63.56	63.86

STN INTERNATIONAL LOGOFF AT 09:30:12 ON 09 SEP 1997

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.
08/622,011			

EXAMINER	
ART UNIT	PAPER NUMBER
	7

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Thomas Irving TLI (3) Mr. TRINH

(2) Ms Thalia Warnement TW (4)

Date of interview 8-7-97

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: 1-4, 17-25

Identification of prior art discussed: art of record

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: applicant will amend the claims to limit R_4 and R_5 to an unsubstituted alkoxy radical containing 1-6 carbons. Examiner will consider the proposed amendment. (The issue of intermediate vs final product had been discussed.).

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Examiner's Signature

PTOL-413 (REV. 2-93)

ORIGINAL FOR INSERTION IN RIGHT HAND FLAP OF FILE WRAPPER

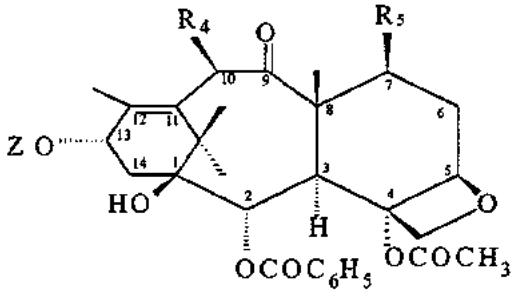
Serial No.:08/622,011
Attorney Docket No.: 03806.0367

Samples

INTERVIEW -- August 7, 1997

Proposed Amendment to Claim 1:

Claim 1 is drawn to a taxoid of the formula (I):



(I)

We will amend the claim to limit each of R_4 and R_5 to only an unsubstituted alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain or an unsubstituted cycloalkyloxy radical containing 3 to 6 carbon atoms.

Rejection Under 35 U.S.C. § 102(b)

- Claims 1-4,17-24 rejected over compounds 6b-d of Holton.
- The Office's reliance on col. 6, lines 23-35, as teaching that OT_1 and Z groups of Holton are hydroxy protecting groups encompassing instant R_4 and R_5 groups, is misplaced. Col. 6 describes hydroxy protecting groups for R_1 of the β-lactam (2), not for OT_1 and Z groups.
- Applicants have amended claim 1 to narrow the definitions of R_4 and R_5 to encompass only unsubstituted C_1-C_6 alkoxy radicals or C_3-C_6 cycloalkyloxy radicals. Holton does not teach or suggest such substituents.

Rejections Under 35 U.S.C. § 103

Holton in view of Greene

- Claims 1-4 and 17-24 rejected.
- Holton does not teach or suggest the presently claimed taxoids; Holton's compounds are intermediates to make taxoids (col. 1, lines 14-15). As amended, definitions of R_4 and R_5 in claim 1 encompass only unsubstituted C_1-C_6 alkoxy radicals or C_3-C_6 cycloalkyloxy radicals as substituents in those positions. As admitted by the Office, Holton does not teach such substituents.
- Greene does not remedy the deficiencies of Holton. Greene lists protective groups for the -OH in general. Pp. 10-14 are not tied to specific compounds (see Kingston col. 28). The claimed compounds are final pharmaceutical products (p. 25); at the 7 and 10 position, the substitutents are not protective groups because they are not removed. No motivation to look at protective group art, such as Greene.

Kingston

- Claim 25 rejected based on compound 24 of Kingston.
- Compound 24 of Kingston is an intermediate compound which can be reacted with di-t-butyl dicarbonate, hydrolyzed, and de-protected to yield 10-acetyl Taxotere.
- Nothing in the art of record would motivate modification of compound 24 to achieved the claimed invention. One would have to modify the 7, 10 and C2' positions, without any teaching in the art to do so.
- Kingston does not teach or suggest C_1-C_6 alkoxy radicals or C_3-C_6 cycloalkyloxy radicals as protecting groups in the C7 and C10 positions. Thus, one of ordinary skill in the art would have had absolutely no motivation to substitute the C7, C10 and C2' positions of Kingston in order to obtain formula (VII) of present claim 25. Also, claim 25 is a final product and thus has no protective groups. The protective groups of Kingston are not useful in the final products of the invention (see col. 18; see col 12-13; col. 13, lines 66-67; col. 16-17; col. 18).

RULE 132 Declaration: Test Results

	7-position	10-position	T/C%	KB IC_{50} µg/ml	KB/VLB IC_{50}
Product of Example 1	$-OCH_3$	$-OCH_3$	0.000	0.0034	0.1600
Product of Example 3	$-OCH_3$	$-OC_2H_5$	-	0.0060	0.0930
Product of Example 4	$-OCH_3$	$-OC_3H_7$	-	0.0150	0.0730
Holton diprotected	$-OCOCCl_3$	$-OCOCCl_3$	54.000	10.000	10.000
Holton diacetylated	$-OCOCH_3$	$-OCOCH_3$	-	4.500	10.000
Kingston cpd 28	-OH	$-OCOCH_3$	7.000	0.600	0.600

T/C determines "in vivo" activity in the mouse bearing a tumor. It represents the percentage of the average weight of the tumor of the treated group over the average weight of the tumor of the control group. If the T/C% is less than 42%, the product is considered active. The table shows that the diprotected product of Holton is clearly inactive (T/C% = 54.000).

In contrast, the presently claimed compound 1 is much more active (T/C% = 0.000; $KBIC_{50}$) than the diprotected or diacetylated compounds of Holton or compound 28 of Kingston.

These results are unexpectedly superior, as the declarant will attest.

Allowable Subject Matter

Applicants thank the Examiner for his indication that claims 5-16 and 26-31 are allowable since the claimed processes are unobvious over the prior art.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/626,011	03/26/96	BOUCHARD H	3206.0367-00

12M2/0429
FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
TRINH, B	
ART UNIT	PAPER NUMBER
1203	6

DATE MAILED: 04/29/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 4-18-96

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1 – 31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☑ Claim(s) 5-16, 26-31 is/are allowed.
☑ Claim(s) 1-4, 17-25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☑ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 6-26-96
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

PTOL-326 (Rev. 9/95)

Claims 1-31 are pending.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 17-24 are rejected under 35 U.S.C. § 102(b) as being anticipated by compounds 6b to 6d of Holton (US 5,229,526).

The OT, and Z groups of Holton embrace the instant R4 and R5 groups as being hydroxy protecting groups; note lines 23 to 35 column 6 of Holton.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 17-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Holton in view of Greene et al.

Holton teaches a protected taxane which is analogous to the claimed compounds; note the compounds 6b to 6d in column 12 of Holton. The prior art does not specifically teach the instant R4 and R5 groups; note the OT, and Z groups in compounds 6b and 6d of Holton, however, Greene et al. teaches the instant hydroxy protecting groups to be conventional; note pages 10-14 of Greene et al; and lines 23 to 35 column 6 of Holton. It would be prima facie obvious to replace the hydroxy protecting group as taught by Greene et al. without the loss of the same utility.

Claim 25 is rejected under 35 U.S.C. § 103 as being unpatentable over Kingston et al.

Kingston et al. teaches a protected taxane which is analogous to the instant compounds; note compound 24 column 18, of Kingston et al. Since the protection and the deprotection of he hydroxy group(s) of taxane compounds are obvious in the art; the instant taxane wherein the C2' hydroxy is unprotected would be deemed obvious over the protected - C2' taxane of Kingston et al.

Claims 5-16 and 26-31 are deemed allowable since the claimed processes are unobvious over the prior art.

Any inquiry concerning this communication should be directed to Examiner Ba Trinh at telephone number (703) 308-4545.

TRINH:tcj
April 17, 1997

BA K. TRINH
PRIMARY EXAMINER
GROUP 1200

OMB No. 0651-0011

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

Atty. Docket No.	Serial No.
3806.0367-00	08/622,011

Applicant

Hervé BOUCHARD et al.

Filing Date	Group
March 26, 1996	~~Unassigned~~ 1612 1203

U.S. PATENT DOCUMENTS

*Examiner Initial		Document Number	Date	Name	Class	Sub Class	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub Class	Translation Yes	Translation No
BT	O	WO 94/18164	08/18/94	PCT				
BT	O	EP 0 639 577	02/22/95	EUROPE				
BT	✓	WO 94/07878	04/14/94	PCT				
BT	✓	EP 0 336 841	10/11/89	EUROPE w/Derwent Abstr.				
BT	✓	WO 92/09589	06/11/92	PCT				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

BT	✓	M.L. Shelanski et al., "Microtubule Assembly in the Absence of Added Nucleotides", Proc. Natl. Acad. Sci. Vol. 70, No. 3,pp. 765-768 (1973).
BT	✓	G. Chauvière et al., "Analyse structurale et etude biochimique de produits isoles de l'if: Taxus baccata L. (Taxaces)", C.R. Acad. Sc. Paris, t.293, pp. 501-503 (1981).
BT	✓	J. Kant et al., "A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol Analogues", Tetrahedron Letters, Vol. 35, No. 31, pp. 5543-5546, 1994.

Examiner	Date Considered
	3-97

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
08/622,044	1203	6

APPLICANT(S): BOUCHARD et al

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	5,292,956	7.20.93	HOLTON	549	213	
	B	5,319,112	6.7.94	KINGSTON et al	549	510	
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG.	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Greene et al, "Protective Groups in Organic Synthesis" pp 70-14, 2nd edition, 1991
S	
T	
U	

EXAMINER: [signature] DATE: 3.97

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

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0880

PATENT

Attorney Docket No. 3806.0367-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011

Filed: March 26, 1996

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Group Art Unit: 1108

Examiner: ~~unassigned~~

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicants bring to the attention of the Examiner the documents listed on the attached PTO 1449. This Information Disclosure Statement is being filed within three months of the filing date of the above-referenced application.

Copies of the listed documents are attached.

Applicants respectfully request that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

The following is a concise statement of relevance of the non-English language documents.

1. The relevance of EP 0 336 841 can be found in its English language Derwent Abstract.

LAW OFFICES
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202-408-4000

Attorney Docket No.: 3806.0367-00
Serial No.: 08/628,169

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicants determine that the cited documents do not constitute "prior art" under United States law, Applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Date: June 26, 1996

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 205/08, 305/14 — A1

(11) International Publication Number: WO 94/18164

(43) International Publication Date: 18 August 1994 (18.08.94)

(21) International Application Number: PCT/US94/00669

(22) International Filing Date: 28 January 1994 (28.01.94)

(30) Priority Data:
08/011,922 1 February 1993 (01.02.93) US

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(81) Designated States: AU, CA, CZ, FI, JP, KR, NO, NZ, PL, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND β-LACTAM INTERMEDIATES THEREFOR

(57) Abstract

Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. However, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. TAXOTERE (III) seems to have antitumor activity superior to taxol with better bioavailability. Taxotère has a modified taxol structure with a modified C-13 side chain. This fact strongly indicates that modification on the C-13 side chain would provide a new series of taxol and TAXOTERE analogues which may have higher potency, better bioavailability and less unwanted toxicity. The present invention provides efficient and practical methods for the syntheses of TAXOTERE and its analogues through β-lactam intermediates and their coupling with baccatin III.

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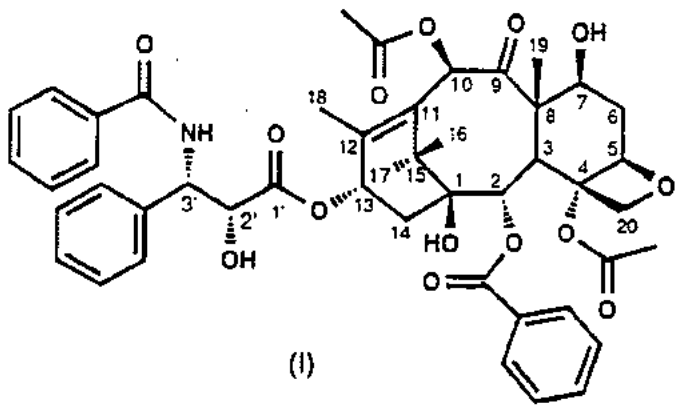
PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND ß-LACTAM INTERMEDIATES THEREFOR

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of taxoid(s) including TAXOTÈRE and its analogs and the ß-lactam intermediates useful in this process.

BACKGROUND OF THE INVENTION

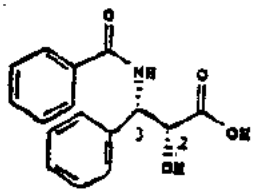
Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. For example, taxol is currently in phase III clinical trials for advanced ovarian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.



(I)

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. It is common for improved drugs to be derived from naturally occurring lead compounds. In fact, French researchers, Potier, Guéritte-Voegelein,

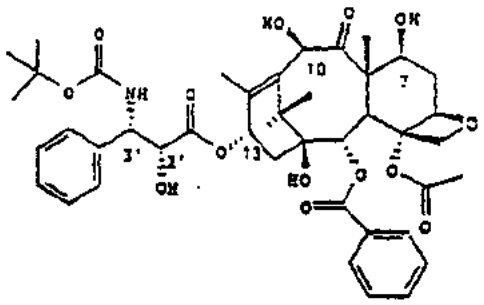
Guénard et al. have discovered that a modification of the C-13 side chain of taxol brought about a new anticancer agent which seems to have antitumor activity superior to taxol with better bioavailability. This synthetic compound was named "TAXOTÈRE (II)", which has t-butoxycarbonyl instead of benzoyl on the amino group of (2R,3S)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of an acetoxy group at C-10. [Colin, M. et al. Eur. Pat. Appl. EP253,738 (1988)]. Taxotère is currently in phase II clinical trial in both United States and Europe. TAXOTÈRE has been synthesized by a semisynthetic process, including a coupling of N-tert-butoxycarbonyl-(2R,3S)-3-phenylisoserine with 10-deacetylbaccatin III with proper protecting groups. (Denis, J.-N. recently reported (Commercon, A. et al., Tetrahedron Letters, 1992, 33 5185)).



(II)

It is known that the C-13 side chain of taxol, i.e., N-benzoyl-(2R, 3S)-3-phenylisoserine (III) moiety, is crucial for the strong antitumor activity of taxol. (Senilh et al., C.R. Séancas Acad. Sci. Ser. 2 1984, 299, 1039; Guéritte-Voegelein et al., Tetrahedron, 1986, 42, 4451, and Mangatal et al., Tetrahedron, 1989, 45, 4177; Guéritte-Voegelein et al. J. Med. Chem. 1991, 34, 992; and Swindell et al., J. Med. Chem. 1992, 35, 145; Mathew, A.E. et al., J. Med. Chem. 1992, 35, 145). Moreover, some modification of the C-13 side chain can provide a new series of taxol analogs which may have higher potency, better bioavailability and less unwanted toxicity, as

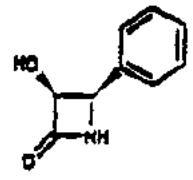
exemplified by the discovery of TAXOTÈRE (II).



(III)

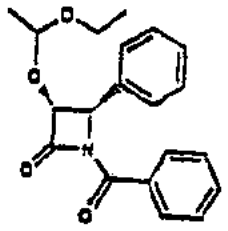
Accordingly, the development of an efficient method which can be applied to various analogs of taxol and TAXOTÈRE and analogs thereof, i.e., a method having flexibility and wide applicability, is extremely important and of current demand. It has been shown that such a new and efficient method with flexibility can be developed by using enantiomerically pure ß-lactams as key-intermediates [Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985; Holton, R.A., Eur. Patent Appl. EP 400,971 (1990)].

Lithium chiral ester enolate-imine cyclocondensation strategy has been applied to the asymmetric synthesis of the side chain of taxol via a (3*R*,4*S*)-3-hydroxy-4-phenylazotidin-2-one (IV) as the key-intermediate. (Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985)

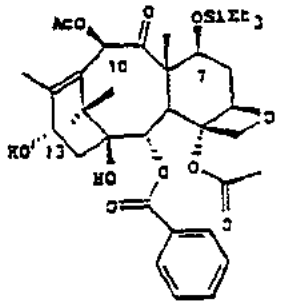


(IV)

Based on this protocol, the side chain can be obtained in 3 steps in high yield with virtually 100% e.e. (Ojima, I. et al. J. Org. Chem. 1991 56, 1681). Recently, it was found that 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one (V), readily derived from the hydroxy-ß-lactam (IV), served as the key-intermediate for the synthesis of taxol [Holton, R.A. Eur. Pat. Appl. EP 400,971 (1990)]. Therefore, this ß-lactam intermediate serves as the key-intermediate for both coupling methods.



(V)

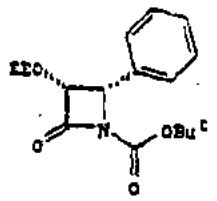


7-TES-baccatin III (VI)

In the published European application to Holton (hereinafter Holton), the ß-lactam intermediate (V) was

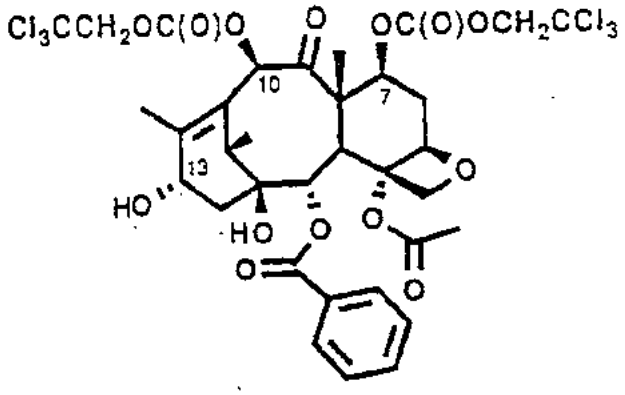
obtained through tedious optical resolution of the racemic cis-3-hydroxy-ß-lactam. According to Holton's procedure, the coupling of the ß-lactam (V) with 7-triethylsilylbaccatin III (VI) (7-TES-baccatin III) proceeds at 25°C in the presence of dimethylaminopyridine (DMAP) and pyridine for 12 hours to give protected taxol in 92% yield, which was deprotected with 0.5% hydrochloric acid in ethanol at 0°C to afford taxol in ca. 90% yield.

However, the Holton procedure did not work at all when 1-tert-butoxycarbonyl-(3*R*,4*S*)-3-(1-ethoxylethoxy)-4-phenylazetidin-2-one (VII) was used for the attempted synthesis of TAXOTÈRE (II) by the present inventors.



(VII)

It is believed that this may be due to the lack of reactivity of the 1-tert-butoxycarbonyl-ß-lactam (VII) toward the C-13 hydroxyl group of a protected baccatin III (VI or VIII) under the conditions used by Holton. The lack of reactivity may be ascribed to the substantially weaker electron-withdrawing ability of tert-butoxycarbonyl group than that of benzoyl group.



7,10-di-Troc-10-deacetylbaccatin III (VIII)

Therefore, it was an objective of the present invention to develop a new method which can achieve the coupling of the 1-tert-butoxycarbonyl-ß-lactam (VII) with the protected baccatin III (VIII) for the synthesis of TAXOTÈRE (II).

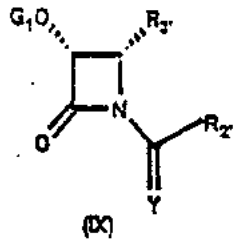
All of the references cited above and any reference which may be mentioned herein below are expressly incorporated into the present disclosure.

It is an object of the present invention to provide new ß-lactams useful in the syntheses of TAXOTÈRE (II) and analogs thereof.

It is further object of the present invention to provide a new coupling method for the syntheses of TAXOTÈRE (II) and analogs thereof.

SUMMARY OF THE INVENTION

A ß-lactam of the formula (IX)



(IX)

in which

R_2, represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl, wherein substituents bearing one or more active hydrogens such as hydroxyl, amino, marcapto and carboxyl groups are protected; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure; Examples of R_2, include methoxy, ethoxy, isopropoxy, tert-butoxy, neopentyloxy, cyclohexyloxy, allyloxy, propargyloxy, adamantyloxy, phenyoxy, 4-methoxyphenoxy, 2-fluorophenoxy, 4-methoxycarbonylphenoxy, methylthio, ethylthio, isopropylthio, tert-butylthio, neopentylthio, cyclohexylthio, phenylthio, 3,4-dimethoxyphenylthio, methylamino, ethylamino, isopropylamino, tert-butylamino, neopentylamino, cyclohexylamino, dimethylamino, pyrrolidino, piperidino and morpholino group.

R_3, represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl

radical, an unsubstituted or substituted cycloalkyl, or cycloalkenyl radical, an unsubstituted or substituted aryl radical wherein substituents bearing one or more active hydrogens such as hydroxy, amino, mercapto and carboxyl groups are protected; Examples of R_3, include phenyl, 4-methoxyphenyl, 3,4-dimethoxylphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, cyclohexyl, cyclohexylmethyl, 2-phenylethenyl, 2-phenylethyl, benzyl, neopentyl, tert-butyl, isobutyl, isopropyl, allyl and proparagyl;

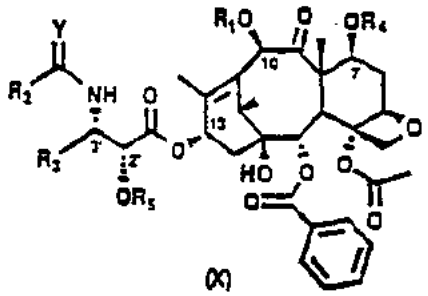
G_1 represents a hydrogen or hydroxyl protecting group such as methoxymethyl (MOM), methoxylethyl (MEM), 1-ethoxyethyl (EE) benzyloxymethyl, (ß-trimethylsilylethoxyl)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl (Troc), tert-butoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-tricholoroethoxymethyl, trimethylsilyl, triethylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl and diphenylmethylsilyl;

Y is oxygen or sulfur.

The present inventor investigated the ß-lactam coupling reaction with protected Baccatin III in detail and found that the coupling could be achieved by increasing the nucleophilicity of the 13-hydroxyl group of a protected baccatin III (VI or VIII) through transformation of the hydroxyl group to the corresponding metal alkoxide. Such a C-13 metal alkoxide of a baccatin III was readily generated by reacting the baccatin III (VI or VIII) with an alkali or alkaline earth metal base. This finding is the basis of the present invention. The method of the present invention not only enables the coupling of the ß-lactam (VII) and its derivatives and analogs with a protected baccatin III, but also requires only a stoichiometric amount of the ß-lactams. The latter makes a sharp contrast with the Holton procedure for taxol

synthesis which needs 5-6 equivalents of the more reactive ß-lactam (V). Moreover, the coupling reactions of the present invention proceeds very smoothly and complete typically within 30 minutes at -30°C - 0°C.

The present invention also relates to a process for the preparation of taxane derivatives of the formula (X)



(X)

in which

R_1 represents a hydrogen atom or an acyl or an alkyl or an alkenyl or an alkynyl or carbocyclic aryl or a heteroaryl radical or a hydroxyl protecting group (G_1 defined above);

R_2 represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure;

Y is oxygen or sulfur;

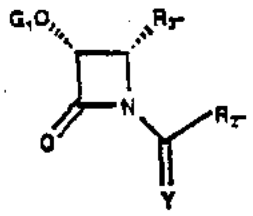
R_3 represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an

unsubstituted or substituted cycloalkyl, cycloalkenyl radical or an unsubstituted or substituted carbocyclic aryl radical;

R_4 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl group protecting group (G_1 defined above);

R_5 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical, or a hydroxyl protecting group (G_1 defined above);

which comprises condensing a β-lactam of the formula



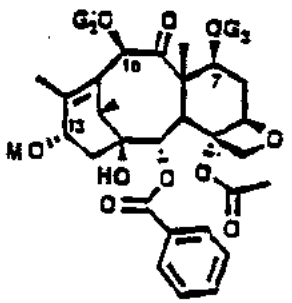
in which

Y and G_1 are defined above;

R_2, represents a radical R_2 as defined above or a protected R_2 whenever R_2 includes one or more active hydrogens such as hydroxyl, amino, mercapto and carboxyl groups;

R_3, represents a radical as R_3 defined above or a protected R_3 whenever R_3 includes one or more active

hydrogens such as hydroxyl, amino, mercapto and carboxyl groups; with a baccatin III derivative of the formula:



in which

M is an alkali metal or alkaline earth metal atom (ion);

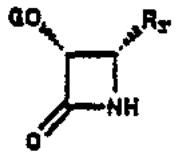
G_2 represents a hydroxyl protecting group (G_1 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heteroycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical;

G_3 represents a hydroxyl group protecting group (G_3 defined above) or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or

substituted carbocyclic aryl or heteroaryl radical.

DETAILED DESCRIPTION OF THE INVENTION

The new ß-lactams of the formula (IX) herein above are synthesized by modifying the ß-lactams of the formula (XI)

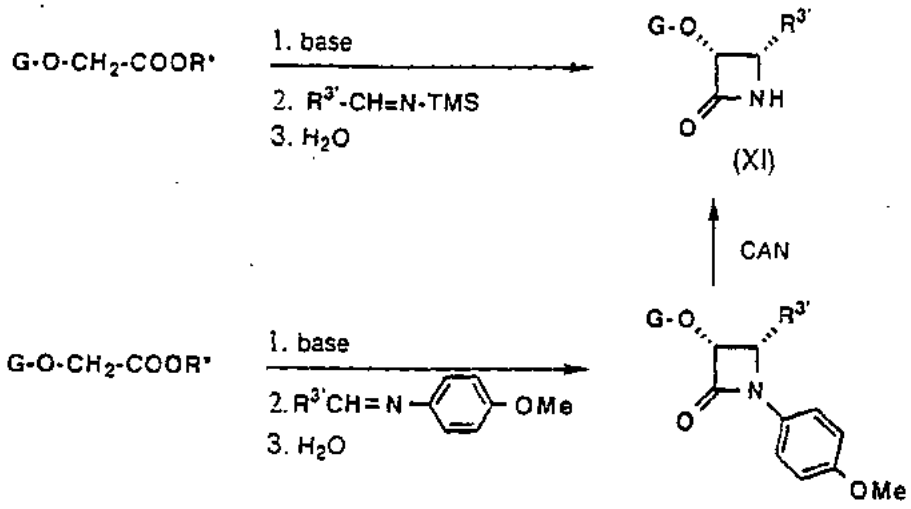


(XI)

wherein G is a hydroxyl protecting group such as triisopropylsilyl (TIPS) and dimethyl(tert-butyl) silyl (TBDMS), and R_3' has been defined hereinabove.

The ß-lactams (XI) are readily prepared by using the chiral enolate - imine cyclocondensation method which has been developed in the present inventor's laboratory as shown in Scheme 1 (Ojima, I. et al., Tetrahedron, 1992, 48, 6985; Ojima, I. et al., J. Org. Chem. 1991, 56, 1681). In this preparation the ß-lactams (XI) with extremely high enantiomeric purities are obtained in high yields. In Scheme 1, R* is a chiral auxiliary moiety which is (-)-trans-2-phenyl-1-cyclohexyl, TMS is a trimethylsilyl radical, and base is lithium diisopropylamide or lithium hexamethyldisilazide; G and R_3' have been defined hereinabove.

Scheme 1



The ß-lactams (VI) are converted to the 3-hydroxy-ß-lactams (XII), followed by protection with ethoxyethyl group (EE) to give the ß-lactams (XIII). The ß-lactams (XIII) are reacted with chloroformates or formic anhydrides or thiocholorformates or thioformic anhydrides in the presence of a base to yield the ß-lactams (XIV) (or thioanalogs thereof) which are used for the coupling with protected 10-deacetylbaccatin III to produce TAXOTÈRE and its analogs. The ß-lactams (XIV) are deprotected under weakly acidic conditions to afford the ß-lactams (XV) which can serve as very useful intermediates to the ß-lactams (XVI) bearing a variety of protecting groups (G_1) at the C-3 position of ß-lactam skeleton. The ß-lactams (XVI) can also be used for the coupling with a protected 10-deacetylbaccatin III to produce Taxotère and its analogs after deprotection.

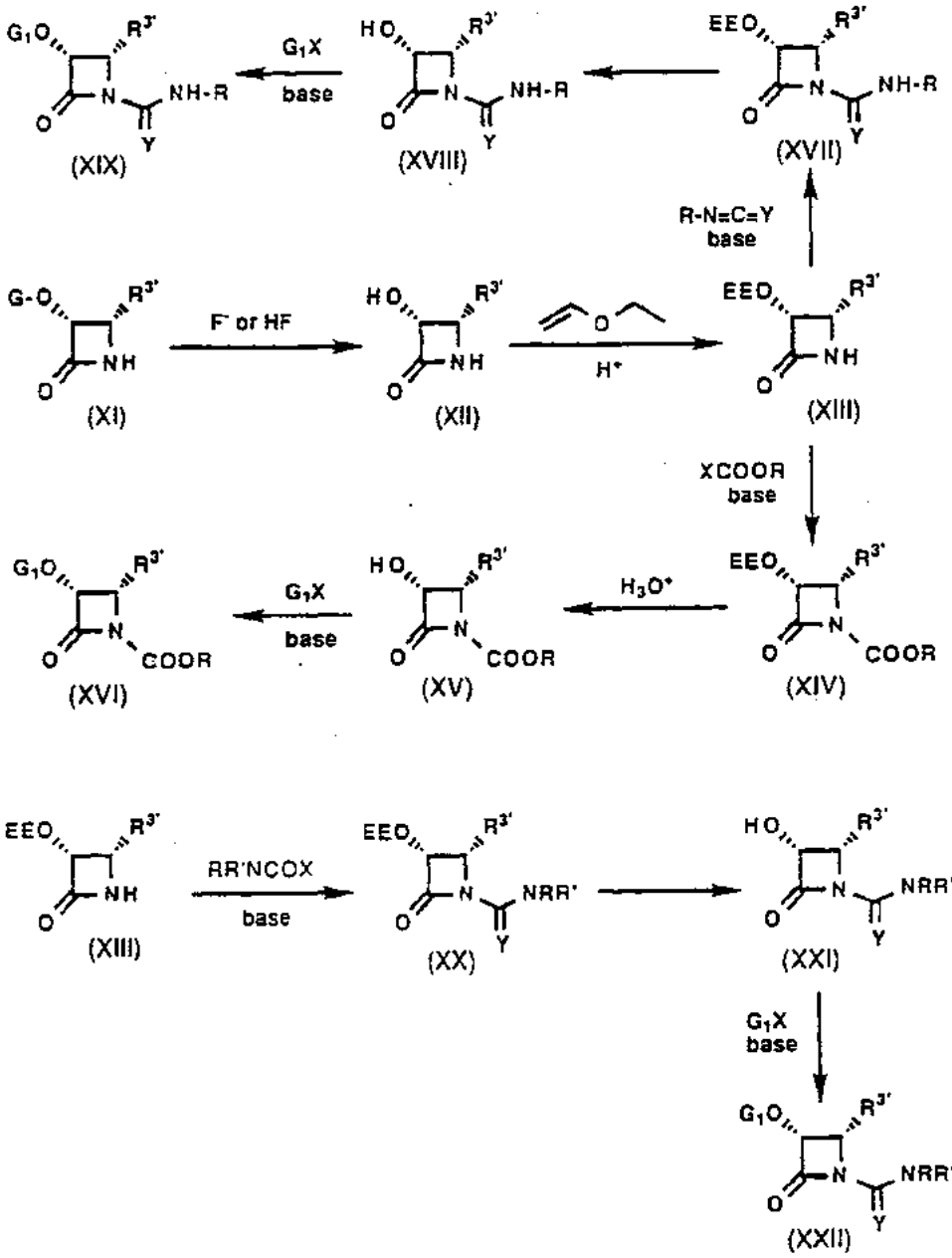
In a similar manner, the ß-lactams (XVII) are prepared by reacting the ß-lactams (XIII) with isocyanates or isothiocyanates in the presence of a base which can be used for the protection of other potent anticancer agents of formula (X) in which R_2 represents RRN-. The ß-lactams (XVII) are deprotected under weakly acidic conditions to give the ß-lactams (XVIII) which can serve as very useful intermediates to a variety of protected 3-hydroxyl-ß-

lactams (XIX). The β-lactams (XVII and XIX) can also be used for the coupling with a protected 10-deacetylbaccatin III to yield a compound of formula (X) in which R_2 represents RR'N- after deprotection.

In a manner similar to that described above, the ß-lactams (XX) are prepared by reacting the ß-lactams (XIII) with N,N-disubstituted carbamoyl halides in the presence of a base. The ß-lactams (XX) are deprotected under weakly acidic conditions to give the 3-hydroxy-ß-lactams (XXI), which can serve as very useful intermediates to various protected 3-hydroxy-ß-lactams (XXII). The ß-lactams (XX and XXII) can readily be used for the coupling with a protected baccatin III to afford a compound of formula (X) after deprotection.

The transformations described above are illustrated in Scheme 2. In Scheme 2, X represents a leaving group such as fluoride, chloride, bromide, iodide, tosylate, mesylate and trifluoromesylate. G_1 represents a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (ß-trimethylsilylethoxyl) methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (TROC), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (t-BOC), 9-fluorenyl methoxycarbonyl (FMOC) 2,2,2-trichloroethoxymethyl, trimethyl silyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethyl phenylsilyl and diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl. $R^{2'}$, $R^{3'}$, R, and R' are defined hereinabove.

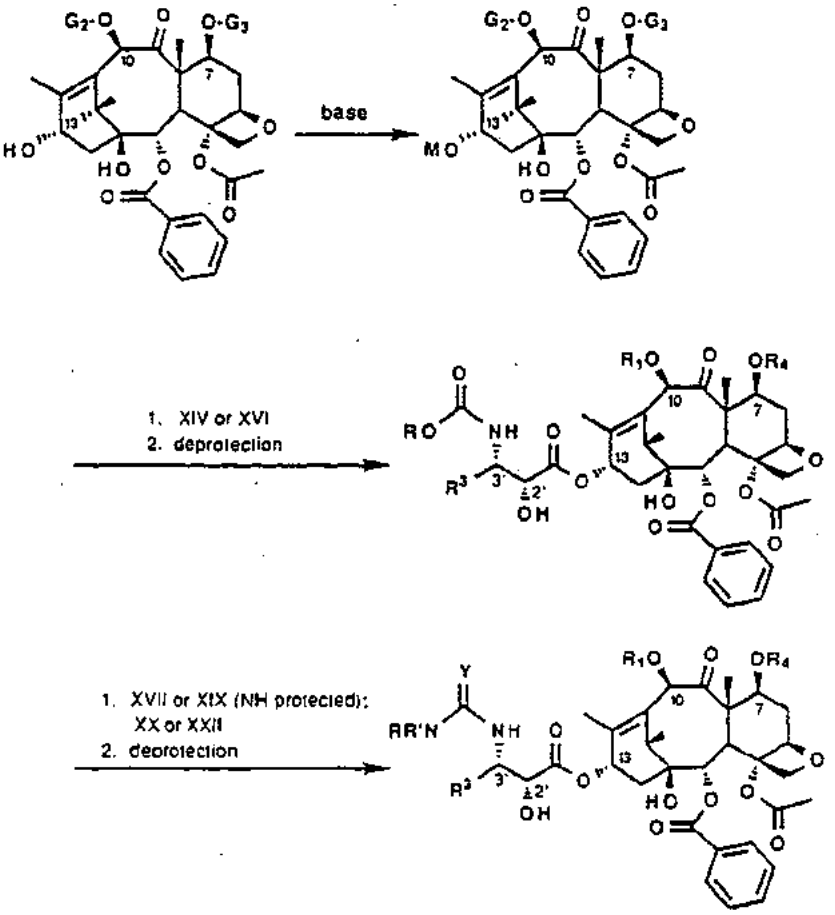
Scheme 2



The ß-lactams (XIV) and (XVI) are readily used for the coupling with protected baccatin IIIs in the presence of base, followed by deprotection to give TAXOTÈRE and its analogs in high yields (Scheme 3). In a similar manner, the ß-lactams (XVII and XIX; with

protection of -NH- moiety) and the ß-lactams (XX and XXII) can be used for the coupling with protected baccatin IIIs, followed by deprotection to give a compound of formula (X) in which R_2 represents $RR'N$- (Scheme 3).

Scheme 3



G_2 and G_3 represents an hydroxyl protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl or heteroaryl radical.

When G_2 and G_3 are hydroxyl protecting groups (G_2 defined above and 1-ethoxyethoxyl (EE)), these protecting

groups can be attached to the hydroxyl groups of 10-deacetylbaccatin III and its analogs by methods which are generally known to those skilled in the art.

The coupling reaction of the protected baccatin III and the ß-lactam is carried out via an alkali metal or alkaline earth metal alkoxide of the protected baccatin III at the C-13 hydroxyl group. The alkoxide can readily be generated by reacting the protected baccatin III with an alkali metal or alkaline earth metal base such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide, sodium hydride, potassium hydride, lithium hydride, calcium hydride, magnesium hydride, in a dry nonprotic organic solvent such as tetrahydrofuran (THF), dioxane, ether, dimethoxyethane (DME), diglyme, dimethylformamide (DMF), mixtures of these solvents with hexane, toluene, an xylene, in a preferred temperature range from about -100°C to about 50°C, more preferably at about -78°C to about 25°C. This reaction is preferably carried out under inert atmosphere such as nitrogen and argon. The amount of the base used for the reaction is preferably approximately equivalent to the amount of the protected baccatin III when soluble bases such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide, lithium diisopropylamide are used. The use of a slight excess of the base does not adversely affect the reaction. When heterogeneous bases such as sodium hydride and potassium hydride are used, 5-10 equivalents of the base (to the amount of the protected baccatin III) is preferably employed.

The coupling reaction of the metal alkoxide of the protected baccatin III thus generated with the ß-lactam is typically carried out by adding the solution of the ß-lactam in a dry organic solvent exemplified above in

a preferred temperature range from about -100°C to 50°C, more preferably at about -35°C to 25°C. The mixture of reactants is stirred for 15 minutes to 24 hours and the progress and the completion of the reaction is monitored by thin layer chromatography (TLC), for example. When the limiting reactant is completely consumed, the reaction is quenched by addition of a brine. The crude reaction mixture is worked up using the standard isolation procedures which are generally known to those skilled in the art to give the corresponding protected taxoid. The proportion of the ß-lactam and the protected baccatin III is in a range from 2:1 to 1:2, more preferably approximately 1:1 for purposes of economy and efficiency, but the ratio is not critical for the reaction.

The protecting groups, EE, G_1, G_2 and G_3, can then be removed by using the standard procedures which are generally known to those skilled in the art to give the desired taxane derivatives. For example, EE and triethylsilyl groups can be removed with 0.5 N HCl at room temperature for 36 h, and Troc group can be removed with zinc and acetic acid in methanol at 60°C for 1 hour without disturbing the other functional groups and the skeleton of the taxoid.

The following non-limiting examples are illustrative of the present invention. It should be noted that various changes would be made in the above examples and processes therein without departing from the scope of the present invention. For this reason, it is intended that the illustrative embodiments of the present application should be interpreted as being illustrative and not limiting in any sense.

Examples 1-2

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-phenyl-2-azetidinone (1a): To a solution of 645 mL (4.6 mmol) of diisopropylamine in 10 mL of THF, was added 1.85 mL (4.6

mmol, 2.5M) of n-BuLi at 0°C. The solution was stirred 1 h at 0°C followed by the addition of 1.5 g (3.8 mmol) of (-) TIPS ester in 15 mL of THF over a 1 h period (using a cannula) at -78°C. The reaction was stirred 2 h at this temperature followed by the addition of 817 mg (4.6 mmol) of N-TMS benzaldimine in 15 mL of THF over a 2 h period at -95°C. The reaction was stirred overnight at this temperature and allowed to slowly warm up at room temperature. The reaction was quenched by addition of sat. NH_4Cl. The aqueous layer was extracted with ether. The organic layer was washed with 3% HCl and brine, dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using 1:5 EtAcO/hexanes to give 1.03 g (84%) of ß-lactam as a white solid: Mp 76-77°C; $[\alpha]D^{20}$ +52.7° (C 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.93 (m, 21H), 4.81 (d, J = 4.7 Hz, 1H), 5.17 (dd, J = 4.7, 2.6 Hz, 1H), 6.18 (bs, 1H), 7.17-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 11.8, 17.4, 17.5, 59.6, 79.9, 127.9, 128.0, 128.1, 136.4, 170.0; IR (KBr) 3234, 2946-2866, 1760, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_2Si$: C 67.66%, H 9.15%, N 4.38%. Found: C 67.64%, H 9.25%, N 4.44%.

In the same manner, ß-lactam 1b was obtained in good yield.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-phenylethenyl)-2-azetidinone (1b): 72%; colorless liquid; $_1H$ NMR (300 MHz, $CDCl_3$) δ 0.98-1.02 (m, 21H), 4.36 (dd, J = 4.6, 8.3 Hz, 1H), 5.09 (dd, J = 2.3, 4.6 Hz, 1H), 6.29 (dd, J = 8.3, 16.0 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.83, (bs, 1H), 7.23-7.39 (m, 5H); NMR (75 MHz,$CDCl_3$) δ 11.79, 17.61, 17.66, 58.34, 79.86, 126.05, 126.45, 127.90, 128.56, 134.41, 136.30, 169.69; IR (neat) 3262, 3032, 2944, 2865, 1748, 1672, 1623 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04; N, 4.05. Found: C, 69.75; H, 9.02; N, 3.89.

Examples 3-4

To a solution of 2.51 mmol of diisopropylamine in 15 mL of THF was added 2.51 mL of n-butyllithium (2.5M in THF) at -10°C. After 30 min, the lithium diisopropylamide (LDA) was generated and the solution was cooled to -95°C. A solution of 2.17 mmol of chiral ester in 5 mL of THF was added. After 1 hr, a solution of 2.5 mmol of the appropriate imine in 3mL of THF was added. The mixture was stirred at -95°C overnight, and the progress of the reaction was monitored by TLC or ^{1}H NMR. The reaction was quenched with sat. NH_4Cl and THF was removed using a rotary evaporator. Ether (10 mL) was added and the aqueous layer was extracted with ether (10 mL x3). Drying and removal of the solvent gave the crude product which was purified by silica gel column chromatography (hexane/ethyl acetate=10:1) to afford the corresponding pure ß-lactam. The enantimeric excess was determined by HPLC using a CHIRALCEL OD column using n-hexane/i-PrOH (90/10) as the eluent.

(3*R*,4*S*)-4-(2-Methylpropyl)-1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinone (2a): 87%; pale yellow solid; mp 59-60°C; $[\alpha]D^{20}$ +60.46° (c 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.10-1.30 (m, 21H), 1.60-1.68 (m, 1H), 1.70-1.92 (m, 2H), 3.75 (s, 3H), 4.16-4.22 (m, 1H), 5.06 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.34, 17.82, 17.91, 22.18, 23.37, 25.34, 35.89, 55.50, 57.33, 76.34, 114.52, 118.73, 131.00, 156.29, 165.58; IR (KBr) 2946, 1742, 1513, 1458, 1249 cm^{-1}. Anal. Calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.70; N, 3.45. Found: C, 68.26; H, 9.85; N, 3.35.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-1-(4-methoxyphenyl)-3-triisophropylsilyloxy-2-azetidinone (2b): 83%; low melting point solid; $[\alpha]D^{20}$ +43.7° (c 0.92,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85-1.95 (m, 34H), 3.78 (s, 3H), 4.19-4.25 (m, 1H), 5.05 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, CDC_{13}) δ 12.15, 17.76, 17.83, 26.12, 26.22, 26.47, 32.84, 34.22, 34.51, 55.36, 56.41, 76.13, 114.30, 118.45, 130.81, 155.99, 165.55; IR (neat) 2925-2865, 1749, 1513, 1464, 1448, 1389, 1246, 1174, 1145, 1128, 939, 882, 828, 684 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO_3Si$: C, 70.06; H, 9.72; N, 3.14. Found: C, 69.91; H, 9.71; N, 3.02.

Examples 5-6

To a solution of 0.24 mmol of 1-(4-methoxyphenyl)-8-lactam in CH_3CN (20 mL) was added 0.65 mmol of CAN in 10 mL CH_3CN and 20 mL of water in 20 min at -15°C. After stirring for 1 hr, it was diluted with water (20 mL), and the mixture was then extracted with ethyl acetate (15 mL x2). The combined organic layer was washed with $NaHSO_3$ water (7 mL), 5% (10 mL x 2), 5% Na_2CO_3 (10 mL) and brine (5 mL) in sequence. Drying, removal of the solvent in vacuo followed by decolorization with activated charcoal afforded the crude product. It was further purified by silica gel column chromatography (hexanes/ethyl acetate, 3/1) to furnish N-deprotected 8-lactam.

(3*R*,4*S*)-4-(2-Methylpropyl)-3-triisopropylsilyloxy-2-azetidinone (1c): 83%; yellow oil; $[\alpha]D^{20}$+35.45° (c 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.05-1.25 (m, 22H), 1.52 (M, 1H), 1.67 (m, 1H), 3.78 (m, 1H), 4.96 (dd, J = 4.8, 2.4 Hz, 1H), 6.02 (bs, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 12.12, 17.72, 17.80, 22.29, 23.08, 25.35, 39.08, 54.45, 78.04, 170.00; IR (neat) 3238, 1759, 1465, 1184 cm^{-1}. Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.1; N, 4.68. Found: C, 64.17; H, 10.96; N, 4.47.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-

triisopropylsilyloxy-2-azetidinone (1d): 85%; yellow oil; $[\alpha]D^{20}$+12.44° (c 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.25 (m, 32H), 1.40-1.70 (m, 2H), 3.80 (dt, J = 8.4, 4.8 Hz, 1H), 4.95 (dd, J = 4.8, 2.4 Hz, 1H), 6.05 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.06, 17.77, 17.82, 26.16, 26.25, 26.46, 33.15, 33.82, 34.85, 37.72, 53.89, 77.98, 169.98; IR (neat) 3238, 1759, 1465, 1184 cm^1. Anal. Calcd for $C_{19}H_{37}NO_2Si$: C, 67.20; H, 10.98; N, 4.12. Found: C, 67.40; H, 10.79; N, 3.98.

Examples 7-11

To a solution of 2.6 mmol of 3-triisopropylsilyloxy-4-substituted-2-azetidinone in 20 mL of THF, was added at room temperature 3.1 mmol (1M in THF) of NBu_4F. After 5 h, the solvent was evaporated and the crude oil was directly purified by chromatography on silica gel using 5:1 EtAcO/hexanes to afford of 3-hydroxy-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-Hydroxy-4-phenyl-2-azetidinone (3a): 100%; white solid; mp 189-190°C; $[\alpha]D^{20}$ +181.6° (c 0.5, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.84 (d, J = 4.7 Hz, 1H), 5.04 (d, J = 4.7 Hz, 1H), 7.25-7.35 (m, 5H); IR (KBr) 3373, 3252, 1732, 1494 cm^{-1}. Anal. Calcd for $C_9H_9NO_2$: C 66.25%, H 5.56%, N 8.58%. Found: C 66.42%, H 5.74%, N 8.62%.

(3*R*,4*S*)-3-Hydroxy-4-(2-phenylethenyl)-2-azetidinone (3b): 82%; white solid; mp 143-144°C; $[\alpha]D^{20}$ +21.9° (c 1.05, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 4.35 (ddd, J = 0.8, 4.7, 7.7 Hz, 1H), 4.93 (d, J = 4.7 Hz, 1H), 6.28 (dd, J = 7.7, 16.0 Hz, 1H), 7.18-7.43 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ 58.95, 79.63, 126.83, 127.58, 128.88, 129.61, 135.28, 137.96, 172.79; IR (KBr) 3320,

3276, 1754, 1464 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.92; N, 7.24.

(3*R*,4*S*)-3-Hydroxy-4-(2-methylpropyl)-2-azetidinone (3c): 94%; white solid; mp 141-142°C; $[\alpha]D^{20}$ +26.6° (c 0.70, MeOH); ^1H NMR (300 MHz, MeOH-d4) d 0.94 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.45 (m, 2H), 1.71 (sept, J = 6.6 Hz, 1H), 3.75 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 22.62, 23.48, 26.53, 39.90, 55.47, 77.76, 173.18; IR (KBr) 3274, 3178, 1762, 1685, 1155 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 9.41; N, 9.69.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-hydroxy-2-azetidinone (3d): 92%; white solid; mp 147-148°C; $[\alpha]D^{20}$ + 8.73° (c, 0.573, CH_3OH); ^1H NMR (300 MHz, MeOH-d4) δ 0.88-1.82 (m, 13H), 3.78 (m, 1H), 4.79 (d, J = 4.7 Hz, 1H); ^1H NMR (300 MHz, DMSO-d6) δ 0.86-1.72 (m, 13H), 3.58 (m, 1H), 4.63 (m, 1H), 5.82 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 5.6, 1H); ^{13}C NMR (75 MHz, MeOH-d4) δ 27.29, 27.41, 27.48, 34.07, 35.06, 36.11, 38.52, 55.02, 77.65, 173.22; IR (KBr) 3301, 3219, 2915, 2847, 1754, 1694, 1168 cm^{-1}. Anal.Calcd for $C_{10}H_{17}NO_2$: C, 65.54, H, 9.35, N, 7.64. Found: C, 65.72, H, 9.46, N, 7.42.

(3*R*,4*S*)-4-cyclohexyl-3-hydroxy-2-azetidinone (3e): A suspension of 500 mg (3.06 mmol) of 4-phenyl-3-hydroxy-2-azetidinone 1a and 15 mg of Rh-C in 10 mL of methanol was heated at 90°C under 800 psi in an autoclave. After 5 days, the hydrogen pressure was released and the catalyst filtrated on celite. Evaporation of the solvent afforded a solid which was recrystallized in ethyl acetate to give 440 mg (85%) of 3e as a white solid: White solid; mp 140-140.5°C; $[\alpha]_D^{20}$ + 65.1° (c 0.66, CH_3OH); ^1H NMR (250

MHz, MeOH-d_4) δ 0.75-1.10 (m, 2H), 1.12-1.35 (m, 3H), 1.40-2.00 (m, 6H), 3.28 (dd, J = 9.7, 4.6 Hz, 1H), 4.81 (d, J = 4.6 Hz, 1H); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75-1.00 (m, 2H), 1.10-1.35 (m, 3H), 1.37-1.55 (m, 1H), 1.58-1.85 (m, 5H), 3.10 (dd, J = 9.6, 4.7 Hz, 1H), 4.67 (m, 1H), 5.87 (d, J = 7.8 Hz, 1H), 8.21 (bs, 1H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 25.08, 25.36, 26.07, 28.83, 29.17, 37.51, 59.04, 76.41, 170.21; IR (KBr) 3312, 3219, 2928, 1726 cm^{-1}. Anal.Calcd for $C_9H_{15}NO_2$: C, 63.88, H, 8.93, N, 8.28. Found: C, 63.70, H, 9.00, N, 8.06.

Examples 12-16

To a solution of 1.9 mmol of 3-hydroxy-4-substituted-2-azetidinone in 20 mL of THF, was added at 0°C 3.9 mmol of ethylvinylether. After 2 h, at 0°C, the reaction mixture was diluted with ether and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2CO_3, filtered and concentrated to yield of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-2-azetidinone (4a): 100%; white solid; mp 78-80°C; ^{1}H NMR ($CDCl_3$) δ [0.98 (d, J = 5.4 Hz), 1.05 (d, J = 5.4 Hz), 3H], [1.11 (t, J = 7.1 Hz), 1.12 (t, J = 7.1 Hz), 3H], [3.16-3.26 (m), 3.31-3.42 (m), 3.59-3.69 (m), 2H], [4.47 (q, J=5.4 Hz), 4.68 (q, J = 5.4 Hz), 1H], [4.82 (d, J = 4.7 Hz), 4.85 (d, J = 4.7 Hz), 1H], 5.17-5.21 (m, 1H), 6.42 (bd, 1H), 7.35 (m, 5H); IR (KBr) 3214, 2983, 2933, 1753, 1718, 1456 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.11; N, 5.88.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-phenylethenyl)-2-azetidinone (4b): 98%; white solid; mp 98-99°C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ [1.17 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.26 (d, J = 5.4 Hz), 1.35 (d, J = 5.4 Hz), 3H], [3.44-3.52 (m), 3.60-3.68 (m), 3.75-3.82 (m), 2H], 4.41 (dd, J = 4.9, 8.5 Hz, 1H), [4.81 (q, J = 5.4 Hz), 4.90 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 4.9 Hz), 5.12 (d, J = 4.9 Hz), 1H], 6.01 (bs, 1H), [6.27 (dd, J = 8.5, 15.9 Hz), 6.28 (dd, J = 8.5, 15.9 Hz), 1H], [6.61 (d, J = 15.9 Hz), 6.63 (d, J = 15.9 Hz), 1H], 7.27-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.04, 20.37, 20.42, 57.22, 57.81, 61.23, 62.22, 78.77, 79.29, 99.50, 99.82, 125.56, 125.79, 126.59, 128.12, 128.65, 134.47, 134.58, 136.15, 168.59, 168.77; IR (KBr) 3310, 3030, 2963, 1770 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.44; N, 5.16.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(2-methylpropyl)-2-azetidinone (4c): 100%; colorless oil: $[\alpha]D^{20}$ +20.93° (c 1.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), [1.29 (d, J = 5.3 Hz), 1.34 (d, J = 5.3 Hz), 3H], 1.46 (m, 2H), 1.62 (m, 1H), [3.49 (m), 3.69 (m), 2H)], 3.80 (m, 1H), [4.79 (q, J = 5.4 Hz), 4.90 (q, J = 5,4 Hz); 1H], 4.87 (m, 1H), 6.78 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.08, 20.42, (21.98, 22.06), (23.15, 23.22), 25.35, (39.01, 39.10), (53.35, 53.69), (61.24, 62.24), (77.79, 77.92), (99.75, 100.05), (169.56, 169.65); IR (neat) 3269, 2956, 2871, 1758, 1468, 1382, 1340, 1152, 1115, 1083, 1052, 936, 893 cm^{-1}.

(3*R*,4*S*)-4-(Cyclohexylmethyl)-3-(1-ethoxyethoxy)-2-azetidinone (4d): 100%; colorless oil; $[\alpha]D^{20}$ + 10.92° (c 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-1.71 (m, 13H), 1.16 (t, J = 7.0 Hz, 3H), [1.28 (d, J = 5.3 Hz), 1.33 (d, J = 5.3 Hz), 3H], 3.48 (m, 1H), [3.72 (m), 3.8 (m), 2H], [4.78 (q, J = 5.4 Hz), 4.85 (q, J=5.4 Hz), 1H],

4.82 (m, 1H), 6.76 (bs, 1H); ^{13}C NMR (75 MHz, CDC_{13}) δ 14.37, 19.72, 25.30, 25.44, 25.63, (32.02, 32.13), (33.09, 33.17), (34.03, 34.07), (36.98, 37.07), (52.15, 52.49), (60.49, 61.52), (75.97, 76.39), (99.00, 99.35), (168.98, 169.05); IR (neat) 3278, 2924, 2852, 1758, 1448, 1382, 1150, 1114, 1086, 938, 886 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_3$: C,65.85; H, 9.87; N, 5.49. Found: C, 66.03; H, 9.71; N, 5.30.

(3*R*,4*S*)-4-Cyclohexyl-3-(1-ethoxyethoxy)- 2-azetidinone (4e): 100%; white solid; mp 87-89°C; $[\alpha]_D^{20}$ + 83° (c 0.76, CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (m, 2H), 1.07-1.34 (m, 9H), 1.66 (m, 6H), 3.32 (m, 1H), [3.42 (q, J = 7.7 Hz), 3.54 (q, J = 7.7 Hz), 3.65 (q, J = 7.7 Hz), 3.74 (q, J = 7.7 Hz), 2H], 4.81 (m, 1H), [4.80 (m), 4.90 (q, J = 5.2 Hz), 1H], 6.92 (bs, 1H); IR ($CHCl_3$) 3412, 2989, 2931, 1760, 1443, 1155, 1114 cm^{-1}. Anal. Calcd for $C_{13}H_{27}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.82; H, 9.66; N, 5.64.

Examples 17-32

To a solution of 2.2 mmol of 3-(1-ethoxyethoxy)-4-substituted-2-azetidinone, 5 mg of DMAP, 4.5 mmol of triethylamine in 20 mL of dichloromethane, was added dropwise at 0°C 3.3 mmol of alkylchloroformate dissolved in 5 mL of dichloromethane. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-1-Methoxycarbonyl-3-(1-ethoxyethoxy)-

4-phenyl-2-azetidinone (5a): 62%; pale yellow oil; $[\alpha]D^{20}$ +98.2° (c 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], 1.10 (bt, J = 7.3 Hz, 3H), [3.21 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.64 (dq, J = 9.5, 7.1 Hz), 2H], [3.76 (s), 3.77 (s), 3H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.11 (d, J = 5.9 Hz), 5.14 (d, J = 5.9 Hz), 1H], 5.23 (d, J = 5.9 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.96, 15.07), (19.84, 20.69), 53.59, (60.74, 62.36), (61.14, 61.92), (76.21, 77.21), (99.16, 99.56), (127.73, 128.03, 128.31, 128.36, 128.62, 128.85), (133.41, 133.58), (149.51, 149.57), (165.21, 165.67); IR (neat) 3033, 2979, 2957, 1821, 1738, 1654, 1440, 1336, 1101 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.55; H, 6.51; N, 4.90.

(3*R*,4*S*)-1-Ethoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5b): 82%; colorless oil; $[\alpha]D^{20}$ +100.9° (c 1.08, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.95 (d, J = 5.4 Hz), 1.06 (d, J = 5.4 Hz), 3H], 1.08 (bt, J = 7.3 Hz, 3H), [1.19 (t, J = 7.1 Hz), 1.20 (t, J = 7.1 Hz), 3H], [3.20 (dq, J = 9.4, 7.1 Hz), 3.31 (q, J = 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.63 (dq, J = 9.4, 7.1 Hz), 2H], [4.18 (q, J = 7.1 Hz), 4.19 (q, J = 7.1 Hz), 2H], [4.47 (q, J = 5.4 Hz), 4.67 (q, J = 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.13 (d, J = 5.8 Hz), 1H], 5.21 (d, J = 5.8 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.14, (14.95, 15.07), (19.86, 20.05), (60.76, 62.35), 62.36, (61.14, 61.90), (76.18, 77.20), (99.17, 99.53), (127.73, 128.02, 128.25, 128.30, 128.50, 128.63), (133.59, 133.77), (148.99, 149.05), (165.33, 165.79); IR (neat) 2978, 2934, 1814, 1731, 1646, 1540, 1456, 1323, 1175, 1096 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.63; N, 4.83.

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5c): 83%; colorless oil; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), [0.94 (d, J = 5.1 Hz), 1.07 (d, J = 5.1 Hz), 3H], 1.07 (t, J = 7.4 Hz, 3H), 1.20 (m, 2H), 1.51 (quint, J = 6.7 Hz, 2H), [3.21 (m), 3.30 (q, J = 7.1 Hz), 3.61 (m), 2H], 4.09 (m, 2H), [4.46 (q, J = 5.2 Hz), 4.66 (q, J = 5.2 Hz), 1H], [5.07 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], 5.19 (d, J = 5.8 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.50, (14.95, 15.29), 18.71, (19.84, 20.05), 30.42, (60.77, 62.33), (61.25, 62.02), 66.51, (76.24, 77.26), (99.17, 99.52), (127.76, 128.03, 128.22, 128.27, 128.50, 128.60), (133.61, 133.80), (148.96, 149.02), (165.40, 165.85); IR (neat) 2961, 2933, 1817, 1732, 1653, 1456, 1394, 1250, 1099 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.44; H, 7.57; N, 4.24.

(3*R*,4*S*)-1-tert-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (5d): 83%; white solid; mp 90-91°C; $[\alpha]D^{20}$ +70.4° (c 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.4 Hz), 1.08 (d, J = 5.4 Hz), 3H], [1.09 (t, J = 7.0 Hz), 1.10 (t, J = 7.0 Hz), 3H], [1.36 (s), 1.37 (s), 9H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.32 (q, J = 7.1 Hz), 3.65 (dq, J = 9.5, 7.1 Hz), 2H], [4.48 (q, J = 5.4 Hz), 4.69 (q, J = 5.4 Hz), 1H], [5.03 (d, J = 5.8 Hz), 5.07 (d, J = 5.8 Hz), 1H], 5.18 (d, J = 5.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.98, 15.08), (19.89, 20.10), 27.84, (60.74, 62.32), (61.28, 62.08), (75.91, 76.54), 83.48 (99.10, 99.41), (127.76, 128.07, 128.20, 128.42, 128.85), (133.98, 134.16), 147.56, (165.61, 166.04); IR ($CHCl_3$) 3025, 2982, 2932, 1809, 1725, 1601, 1497, 1331, 1256, 1152 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.50; H, 7.41; N, 4.17.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenoxycarbonyl-4-phenyl-2-azetidinone (5e): 79%; white solid; mp 50-52°C; $[\alpha]D^{20}$ +64.9° (c 0.94, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.00 (d, J = 5.3 Hz), 1.11 (m), 3H], [1.14 (m), 3H], [3.27 (m), 3.35 (q, J = 7.1 Hz), 3.70 (m), 2H], [4.54 (q, J = 5.3 Hz), 4.74 (q, J = 5.3 Hz), 1H], [5.25 (d, J = 5.8 Hz), 5.29 (d, J = 5.8 Hz), 1H], 5.34 (d, J = 5.8 Hz, 1H), 7.03-7.39 (m, 10H); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1744, 1591, 1486, 1327, 1192 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.33; H, 6.06; N, 3.75.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-phenyl-1-phenylmethoxycarbonyl-2-azetidinone (5f): 44%; white solid; mp 58-60°C; $[\alpha]D^{20}$ +91.4° (c 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.97 (d, J = 5.3 Hz), 1.09 (d, J = 5.3 Hz), 3H], [1.10 (t, J = 7.0 Hz), 1.11 (t, J = 7.0 Hz), 3H], [3.23 (dq, J = 9.5, 7.1 Hz), 3.33 (q, J = 7.1 Hz), 3.66 (dq, J = 9.5, 7.1 Hz), 2H], [4.50 (q, J = 5.4 Hz), 4.70 (q, J = 5.4 Hz), 1H], [5.13 (d, J = 5.6 Hz), 5.15 (d, J = 5.6 Hz), 1H], [5.19 (s), 5.20 (s), 2H], 5.23 (d, J = 5.6 Hz, 1H), 7.21 (m, 2H), 7.26-7.37 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.99, 15.10), (19.90, 20.10), (60.83, 62.41), (61.64, 62.14), 68.01, (76.31, 77.28), (99.19, 99.53), (127.37, 127.86, 128.07, 128.16, 128.36, 128.52, 128.63, 128.85), (133.49, 133.68), 134.89, (148.72, 148.78), (165.37, 165.81); IR ($CHCl_3$) 3028, 2981, 2934, 1815, 1733, 1604, 1450, 1380, 1004 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.07; H, 6.43; N, 3.72.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl-3-(1-ethoxyethoxy)-2-azetidinone (5g): 91%; colorless oil; $[\alpha]_D^{20}$ +62.5° (c 1.12, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.10-1.28 (m, 6H), 1.15 (t, J = 7.0 Hz, 3H), [1.27 (d, J =

5.4 Hz), 1.31 (d, J = 5.4 Hz), 3H], [1.45 (s), 1.46 (s), 9H], 1.63-1.70 (m, 5H), [3.43 (dq, J = 9.2, 7.0 Hz), 3.62 (m), 3.75 (d, J = 7.0 Hz), 3.78 (d, J = 7.0 Hz), 2H], 3.85 (t, J = 6.1 Hz, 1H), [4.78 (q, J = 5.4 Hz), 4.88 (m), 1H], [4.85 (d, J = 6.1 Hz), 4.86 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.07, (20.25, 20.37), (26.05, 26.14), 26.26, (27.33, 27.95), (29.05, 29.20), (30.04, 30.23), (37.54, 37.64), (61.19, 62.53), (62.06, 62.32), (75.42, 75.85), 83.06, 100.11, 148.72, (166.70, 166.76); IR (neat) 2980, 2931, 2854, 1807, 1725, 1450, 1370, 1329, 1212, 1118 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.15; H, 8.97; N, 3.96.

(3*R*,4*S*)-1-tert-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-phenylethenyl)-2-azetidinone (5h): 86%; white solid; mp 69-73°C; ^1H NMR (300 MHz, $CDCl_3$) δ [1.16 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz), 3H], [1.25 (d, J = 5.4 Hz), 1.36 (d, J = 5.4 Hz), 3H], 1.48 (s, 9 H), [3.47 (m), 3.62 (m), 3.80 (m), 2H], 4.68 (dd, J = 5.8, 8.8 Hz, 1H), [4.82 (q, J = 5.4 Hz), 4.91 (q, 5.4 Hz), 1H], [5.09 (d, J = 5.8 Hz), 5.11 (d, J = 5.8 Hz), 1H], [6.23 (dd, J = 8.8, 15.8 Hz), 6.25 (dd, J = 8.8, 15.8 Hz), 1H], [6.72 (d, J = 15.8 Hz), 6.73 (d, J = 15.8 Hz), 1H], 7.27-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.98, 20.31, 27.98, 60.24, 60.85, 61.46, 62.36, 63.58, 83.38, 99.63, 99.87, 122.45, 122.63, 126.69, 128.20, 128.61, 136.15, 136.34, 136.38, 147.74, 147.79, 165.33, 165.53; IR (KBr) 3027, 3020, 2984, 2933, 1809, 1723 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.50; N, 3.87.

(3*R*,4*S*)-1-tert-Butoxycarbonyl-3-(1-ethoxy ethoxy)-4-(2-methylpropyl)-2-azetidinone (5i): 80%; yellow oil; $[\alpha]D^{20}$ +77.45° (c 0.216, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 5.7 Hz, 6H), 1.41 (t, J = 7.1

Hz, 3H), [1.25 (d, J = 5.3 Hz), 1.31 (d, J = 5.3 Hz), 3H], 1.45 (s, 9H), 1.51-1.67 (m, 3H), [3.48 (dq, J = 9.3, 7.1 Hz), 3.55-3.71 (m, 1H), 3.80 (dq, J = 9.3, 7.1 Hz), 2H], 4.08 (q, J = 6.1 Hz, 1H), [4.70 (q, J = 5.3 Hz), 4.90 (q, J = 5.3 Hz), 1H], 4.85 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.95, (20.11, 20.28), (22.42, 22.59), 22.70, (24.89, 25.07), 27.83, (37.03, 37.31), (56.14, 56.38), (61.07, 62.27), (75.65, 75.92), 82.98, 99.91, 148.1, (166.1, 165.9); IR (neat) 2931, 2960, 2872, (1790, 1807), (1708, 1726), (1454, 1465), 1332, 1256, 1048, 1158, 996, 955, 857, 834, 770 cm^{-1}. Anal. Calcd for $C_{16}H_{26}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 61.19; H, 9.41; N, 4.37.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl methyl-3-(1-ethoxyethoxy)-2-azetidinone (5j): 93%; yellow oil; $[\alpha]D^{20}$ +75.64° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-1.74 (m, 13H), 1.19 (t, J = 7.1 Hz, 3H), 1.48 (s, 9H), [1.30 (d, J = 5.3 Hz), 1.35 (d, J = 5.3 Hz), 3H], [3.45 (dq, J = 9.3, 7.1 Hz), 3.62-3.71 (m), 3.78 (dq, J = 9.3, 7.1Hz), 2H], 4.01 (m, 1H), [4.81 (q, J = 5.3 Hz), 4.91 (q, J = 5.3 Hz), 1H], [4.86 (d, J = 6.1 Hz), 4.87 (d, J = 6.1 Hz), 1H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.03, 20.19, 20.36, 26.10, 26.36, 27.91, (33.17, 33.31), (33.35, 33.49), (34.33, 34.58), (35.39, 35.68), (55.77, 55.99), (61.14, 62.21), (75.74, 75.90), 82.96, (99.86, 99.95), 147.96, 166.13; IR (neat) 2979, 2923, 2850, 1719, 1807, 1449, 1336, 1154 cm^{-1}. Anal. Calcd. for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N,3.94. Found: C, 64.00; H, 9.17; N, 4.02.

Examples 28-32

To a solution of 0.5 mmol of 3-(1-ethoxyethoxy)-4-phenyl-

2-azetidinone in 6 mL of tetrahydrofuran, was added dropwise at -78°C 0.6 mmol of n-BuLi. After 5 min, 1 mmol of an isocyanate or an isothiocyanate was added. The reaction mixture was stirred 30 min at -78°C and quenched by addition of 2 mL sat. NH_4Cl solution. The reaction mixture was diluted with 30 mL of ether and the organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude solid was purified by chromatography on silica gel to yield N-protected β-lactam:

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylcarbamoyl-4-phenyl-2-azetidinone (7a): 66%; pale yellow solid; mp 152-155°C; $[\alpha]D^{20}$ +87.8° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.07 (d, J = 5.4 Hz), 1.13 (d, J = 5.4 Hz), 3H], 1.16 (t, J = 7.1 Hz, 3H), [3.26 (dq, J = 9.5, 7.1 Hz), 3.37 (q, J = 7.1 Hz), 3.39 (q, J = 7.1Hz), 3.67 (dq, J = 9.5, 7.1 Hz), 2H], [4.53 (q, J = 5.4 Hz), 4.72 (q, J = 5.4 Hz), 1H], 5.28 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.10-7.55 (m, 10H), 8.68 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.16), (19.98, 20.11), (60.99, 62.53), 61.80, (76.05, 76.66), (99.34, 99.70), (119.63, 120.69, 124.37, 127.67, 127.95, 128.40, 128.45, 128.67, 128.85, 129.04, 129.12, 130.49), 133.48, (137.03, 137.28), (147.23, 147.29), (168.12, 168.52); IR ($CHCl_3$) 3342, 3017, 2982, 2932, 1773, 1719, 1602, 1548, 1445, 1312, 1224, 1210 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.92; H, 5.98; N, 8.17.

(3*R*,4*S*)-1-tert-Butylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7b): 74%; pale yellow viscous oil; $[\alpha]D^{20}$ +144.3° (c 0.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.96 (d, J = 5.3 Hz), 1.05 (d, J = 5.3 Hz), 3H], 1.10 (t, J = 7.1 Hz, 3H), [1.33 (s), 1.34 (s), 9H], [3.21 (dq, J = 9.3, 7.0 Hz), 3.30 (q, J = 7.0 Hz), 3.33

(q, J = 7.1Hz), 3.62 (dq, J = 9.1, 7.0 Hz), 2H], [4.46 (q, J = 5.4 Hz), 4.66 (q, J = 5.4 Hz), 1H], 5.10-5.19 (m, 2H), [6.59 (bs), 6.60 (bs), 1H], 7.23-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (14.86, 14.99), (19.75, 19.95), (28.81, 29.30), (60.62, 61.20), (60.80, 62.29), (75.57, 76.76), (98.91, 99.34), (127.07, 127.40, 127.70, 128.17, 128.29, 128.53), (133.71, 133.86), (148.54, 148.59), (167.67, 168.13); IR ($CHCl_3$) 3362, 3035, 2977, 2932, 1767, 1710, 1605, 1537, 1457, 1366, 1320, 1282, 1217, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.46; H, 7.75; N, 8.39.

(3*R*,4*S*)-1-Benzylcarbamoyl-3-(1-ethoxy ethoxy)-4-phenyl-2-azetidinone (7c): 50%; pale yellow viscous oil; $[\alpha]D^{20}$ +66.2° (c 0.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [0.99 (d, J = 5.5 Hz), 1.08 (d, J = 5.5 Hz), 3H], 1.12 (m, 3H), [3.16-3.40 (m), 3.63 (m), 2H], [4.35-4.55 (m), 4.69 (q, J = 5.5 Hz), 3H], 5.21 (m, 2H), [7.03 (bs), 7.05 (bs), 1H], 7.32 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.01, 15.14), (19.90, 20.11), 43.83, (60.66, 62.44), (60.75, 61.54), (75.93, 77.04), (99.16, 99.56), (127.25, 127.64, 127.69, 128.17, 127.93, 128.35, 128.55, 128.64, 128.74), (133.59, 133.76), 137.80, 150.02, (167.73, 168.19); IR ($CHCl_3$) 3379, 3090, 3033, 2980, 2930, 1773, 1707, 1604, 1536, 1455, 1319, 1270, 908 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.30; H, 6.66; N, 7.51.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-ethylcarbamoyl-4-phenyl-2-azetidinone (7d): 63%; pale yellow oil; $[\alpha]D^{20}$ +96.7° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) d [0.96 (d, J = 5.3 Hz), 1.04 (d, J = 5.3 Hz), 3H], 1.05-1.18 (m, 3H), [3.13-3.39 (m), 3.59 (m), 4H], [4.45 (q, J = 5.3 Hz), 4.65 (q, J = 5.3 Hz), 1H], 5.16 (m, 2H), [6.60 (bs), 6.62 (bs), 1H], 7.27 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.98, (19.84,

29.93), 34.79, (60.56, 61.35), (60.72, 62.35), (75.91, 77.03), (99.14, 99.54), (127.28, 127.55, 127.85, 128.27, 128.40), (133.74, 133.89), (149.87, 149.93), (167.62, 168.07); IR ($CHCl_3$) 3378, 3035, 2980, 2934, 1774, 1704, 1537, 1455, 1321, 1271, 1112, 1025 cm^{-1}.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-1-phenylthio carbamoyl-4-phenyl-2-azetidinone (7e): 82%; yellow solid; mp 108-112°C; $[\alpha]D^{20}$ +68° (c 1.14, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ [1.02 (d, J = 5.5 Hz), 1.11 (d, J = 5.5 Hz), 3H], 1.16 (t, J = 7.3 Hz, 3H), [3.20-3.44 (m), 3.66 (dq, J = 9.4, 7.3 Hz), 2H], [4.52 (q, J = 5.5 Hz), 4.72 (q, J = 5.5 Hz), 1H], [5.30 (d, J = 5.5 Hz), 5.32 (d, J = 5.5 Hz), 1H], [5.49 (d, J = 5.5 Hz), 5.52 (d, J = 5.5 Hz), 1H], 7.36 (m, 8H), 7.67 (d, J = 7.8 Hz, 2H), 10.37 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (15.04, 15.17), (19.95, 20.13), (60.96, 62.57), (63.92, 64.75), (74.75, 75.84), (99.34, 99.68), (123.43, 126.58, 127.91, 128.28, 128.49, 128.86, 128.91), (133.10, 133.25), (137.36), (166.55, 166.52), (174.812); IR ($CHCl_3$) 3288, 3024, 2983, 1760, 1497, 1385, 1222 cm^{-1}.

Examples 33-34

(3*R*,4*S*) -1-Morpholinecarbonyl-3-(-1-ethoxyethoxy)-4-phenyl-2-azetidinone (7f): To a solution of 30 mg (0.13 mmol) of 3-(1-ethoxyethoxy)-4-phenyl-2-azedinone 6 in 2 mL of CH_2Cl_2, 2 mg of DMAP and 0.05 mL of triethylamine was added at room temperature. After 5 min. 22.9 mg (0.15 mmol) of morpholinecarbonyl chloride was added. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and the organic layer was washed two times with brine, dried over Na_2CO_3 and concentrated. The crude solid product was purified by chromatography on silica gel to yield pure 7f: 87%; pale yellow oil; ^1H NMR (250 MHz,

$CDCl_3$) δ [0.90 (d, J = 5.3 Hz), 1.01 (d, J = 5.3 Hz) (3H)], [1.04 (t, J = 7.1 Hz), 1.18 (t, J = 7.1 Hz)] (3H), 3.20 (m, 4H), [3.28 (m), 3.53 (m), 3.67 (m), (2H)], 3.60 (m, 4H), [4.41 (q, J = 5.3 Hz), 4.63 (q, J = 5.3 Hz) (1H), [5.07 (d, J = 5.8 Hz), 5.08 (d, J = 5.8 Hz) (1H), [5.29 (d, J = 5.8 Hz), 5.32 (d, J = 5.8 Hz) (1H)], 7.23-7.27 (m, 5H).

Examples 35-53

To a solution of 0.37 mmol of O-EE β-lactam in 4 mL THF was added 4 mL of 0.5 N HCl. The completion of reaction was monitored by TLC. After 1-3 hr, the reaction mixture was concentrated in vacuo to remove THF. The residue was dissolved in 30 mL ether and washed with 10 mL saturated $NaHCO_3$ solution. The ether layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 3-hydroxy β-lactam:

(3*R*,4*S*)-3-Hydroxy-1-methoxycarbonyl-4-phenyl-2-azetidinone (6a): 66%; white solid; mp ; 91-92°C $[\alpha]D^{20}$ +108° (c 0.63, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.13 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.25-7.42 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 53.77, 61.44, 77.33, 127.16, 128.94, 132.65, 149.20, 166.04; IR ($CHCl_3$) 3432, 3024, 2996, 1806, 1730, 1440, 1333, 1188 cm^{-1}. MS(FAB) m/z (%) 222 (M+1, 38), 194(29), 164(100).

(3*R*,4*S*)-1-Ethoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6b): 59%; white solid; mp 112-113°C; $[\alpha]D^{20}$ +181° (c 0.97, CHCl3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 5.14 (d, J = 6.0 Hz, 1H), 5.22 (d, J = 6.0 Hz, 1H), 7.27-7.39 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.08, 61.36, 63.00, 77.26, 127.08, 128.83, 132.75, 149.08, 165.79; IR ($CHCl_3$)

3605, 3017, 2985, 1815, 1732, 1684, 1396, 1373, 1268, 1020 cm^{-1}; MS (FAB; m/z (%) 236 (M+1,98), 208(23), 178(100).

(3*R*,4*S*)-1-*n*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6c): 69%; white solid; mp 88-89°C; $[\alpha]D^{20}$ +159.1° (c 0.71, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (t, J = 7.3 Hz, 3H), 1.14 (m, 2H), 1.50 (m, 2H), [4.07 (q, J = 8.9 Hz), 4.10 (q, J = 8.9 Hz), 2H), 5.05 (d, J = 5.9 Hz, 1H), 5.11 (d, J = 5.9 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.44, 18.71, 30.44, 61.54, 66.72, 77.31, 127.21, 128.80, 132.89, 149.15, 166.06; IR ($CHCl_3$) 3562, 3018, 2962, 1813, 1730, 1456, 1395, 1324, 1222, 1099 cm^{-1}. MS (FAB) m/z (%) 264(M+1,62), 236(20), 208(40), 206(100).

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6d): 88%; white solid; mp 131.5-132°C; $[\alpha]D^{20}$ +173.5° (c 0.98, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.70 (bs, 1H), 5.08 (d, J = 5.9 Hz, 1H), 5.14 (d, J = 5.9 Hz, 1H), 7.27 (d, J = 6.1 Hz, 2H), 7.38 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.87, 61.56, 77.00, 83.85, 127.20, 128.77, 128.82, 133.13, 147.72, 169.49; IR ($CHCl_3$) 3616, 3019, 2976, 1807, 1726, 1601, 1522, 1422, 1333, 1212, 1152 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.71; H, 6.38; N, 5.12.

(3*R*,4*S*)-3-Hydroxy-1-phenoxycarbonyl-4-phenyl-2-azetidinone (6e): 72%; white solid; mp 125-126°C; $[\alpha]D^{20}$ +107° (c 1.45, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.21 (d, J = 6.1 Hz, 1H), 5.34 (d, J = 6.1 Hz, 1H), 7.07-7.45 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.83, 73.24, 121.15, 125.46, 126.80, 127.22, 128.09, 128.80, 129.11, 129.30, 132.40, 138.49, 154.05; IR ($CHCl_3$) 3615, 3020, 2976, 1821, 1740, 1506, 1487, 1332, 1219 cm^{-1}.

(3*R*,4*S*)-1-Benzyloxycarbonyl-3-hydroxy-4-phenyl-2-azetidinone (6f): 85%; white solid; mp 105-106°C; $[\alpha]D^{20}$ +177° (c 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 (d, J = 6.2 Hz, 1H), 5.22 (m, 3H), 7.24-7.40 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 61.53, 68.30, 77.43, 127.19, 128.13, 128.58, 129.06, 132.55, 134.74, 148.90, 165.92; IR ($CHCl_3$) 3557, 3018, 2924, 1814, 1731, 1383, 1273, 1162, 1004 cm^{-1}. MS (FAB) m/z (%) 298(M+1,14), 273(4).

(3*R*,4*S*)-1-tert-Butoxycarbonyl-4-cyclohexyl-3-hydroxy-2-azetidinone (6g): 96%; white solid; mp 121-122°C; $[\alpha]D^{20}$+78° (c 0.68, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.17-1.75 (m, 11H), 1.48 (s, 9H), 3.83 (t, J+6.5 Hz, 1H), 4.96 (d, J=6.5 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.87, 25.99, 26.24, 27.96, 29.69, 29.90, 37.45, 63.30, 75.24, 83.43, 148.80, 168.60; IR ($CHCl_3$) 3354, 2931, 2848, 1801, 1724, 1324, 1154 cm^{-1}.

(3*R*,4*S*)-1-tert-Butoxycarbonyl-3-hydroxy-4-(2-phenylethenyl)-2-azetidinone (6h): 96%; white solid; mp 132-133°C; $[\alpha]D^{20}$ +122.0° (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.88 (bs, 1H), 4.71 (dd, J = 4.8, 8.0 Hz, 1H), 5.07 (d, J = 4.8 Hz, 1H), 6.26 (dd, J = 8.0, 15.9 Hz, 1H), 6.72 (d, J = 15.9 Hz, 1H), 7.24-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.94, 60.78, 76.58, 83.77, 121.41, 126.75, 128.26, 128.59, 135.94, 136.62, 147.85, 166.95; IR (KBr) 3242, 3039, 2954, 1812, 1726 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.31; H, 6.71; N, 4.76.

(3*R*,4*S*)-1-tert-Butoxycarbonyl-3-hydroxy-4-(2-methylpropyl)-2-azetidinone (6i): 98%; pale yellow solid; mp 108°C; $[\alpha]D^{20}$ +76.14° (c 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.3 Hz, 6H), 1.48 (s, 9H),

1.62-1.82 (m, 3H), 4.12 (m, 1H), 4.30 (bs, 1H), 4.93 (d, J = 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.45, 22.78, 25.12, 27.96, 36.28, 57.59, 75.39, 83.46, 148.13, 168.00; IR (KBr) 3363, 2960, 2926, 1733, 1763, 1458, 1370, 1350, 1303, 1153 cm^{-1}. Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.47; H, 8.91; N, 5.51.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-cyclohexyl methyl-3-hydroxy-2-azetidinone (6j): 100%; white solid; mp 105-106°C; $[\alpha]D^{20}$ +61.89° (c 0.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-1.84 (m, 13H), 1.50 (s, 9H), 3.82 (bs, 1H), 4.14 (m, 1H), 4.93 (d, J = 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.12, 26.17, 26.42, 33.20, 33.47, 33.59, 34.71, 28.00, 57.13, 75.49, 83.47, 148.08, 167.57; IR (KBr) 3442, 2921, 2850, 1797, 1682, 1447, 1354, 1342, 1159 cm^{-1}. Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.76; H, 8.72; N, 4.68.

(3*R*,4*S*)-3-hydroxy-4-phenyl-1-phenylcarbamoyl-2-azetidinone (8a): 88%; white solid; mp 197-200°C; $[\alpha]D^{20}$ +206.4° (c 1.26, $CHCl_3$); ^1H NMR (250 MHz, CD_3COCD_3) δ 5.39-5.47 (m, 2H), 7.07-7.60 (m, 10H), 8.80 (bs, 1H); ^{13}C NMR (63 MHz, CD_3COCD_3) δ 61.98, 78.06, 119.85, 124.31, 128.11, 128.31, 128.60, 129.48, 135.31, 138.43, 148.17, 169.76; IR ($CHCl_3$) 3343, 3018, 2975, 1772, 1712, 1603, 1548, 1447, 1362, 1219, 1045 cm^{-1}; MS (FAB) m/z(%) 283(2), 263 (33) 207(22), 143(100).

(3*R*,4*S*)-1-*tert*-Butylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8b): 89%; white solid; mp 148-151°C; $[\alpha]D^{20}$ +160.9° (c 1.28, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.16 (bs, 1H), 4.97 (d, J = 5.5 Hz, 1H), 5.11 (d, J = 5.5 Hz, 1H), 6.60 (bs, 1H), 7.19-7.38 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.84, 51.53, 60.74, 76.61, 127.00, 128.61, 128.70, 133.13, 148.78, 168.30; IR

($CHCl_3$) 3362, 3018, 2975, 1767, 1710, 1533, 1422, 1318, 1216, 1045 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.10; H, 7.08; N, 10.49.

(3*R*,4*S*)-1-Benzylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8c): 63%; white solid; mp 165-168°C; $[\alpha]D^{20}$ +139° (c 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (bs, 1H), 4.43 (dd, J = 15.2, 5.8 Hz, 1H), 4.50 (dd, J = 15.2, 5.8 Hz, 1H), 5.03 (d, J = 5.6 Hz, 1H), 5.20 (d, J = 5.6 Hz, 1H), 7.06 (t, J = 5.8 Hz, 1H), 7.23-7.33 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 43.79, 61.01, 76.94, 127.13, 127.73, 128.80, 128.86, 132.94, 137.59, 150.15, 168.34; IR ($CHCl_3$) 3364, 3028, 2925, 1771, 1704, 1537, 1455, 1361, 1219, 1190, 987 cm^{-1}. Anal. Calcd for $C_7H_{16}N_2O_3$: C_1 68.91; H, 5.44; N. 9.45. Found: C_1 68.89; H. 5.66; N, 9.34.

(3*R*,4*S*)-1-Ethylcarbamoyl-3-hydroxy-4-phenyl-2-azetidinone (8d): 55%; white solid; mp 141- 42°C; $[\alpha]D^{20}$ +211.4° (c 0.44, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H), 3.34 (qd, J = 7.2, 1.6 Hz, 2H), 5.09 (d, J = 5.6 Hz, 1H), 5.27 (d, J = 5.6 Hz, 1H), 6.63 (bt, J = 1.6 Hz, 1H), 7.23-7.44 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) d 15.04, 34.94, 60.77, 76.98, 127.00, 128.92, 129.06, 132.83, 149.96, 167.98; IR ($CHCl_3$) 3381, 3018, 2990, 1770, 1732, 1651, 1589, 1422, 1298, 1210, 1045 cm^{-1}.

(3*R*,4*S*)-3-(1-Hydroxy)-1-phenylthiocarbamoyl-4-phenyl-2-azetidinone (8e): 78%; yellow solid; mp 85-88°C; $[\alpha]D^{20}$ + 156.7° (c 0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (d, J = 5.8 Hz, 1H), 5.53 (d, J = 5.8 Hz, 1H), 7.31-7.44 (m, 8H), 7.66 (d, J = 7.8 Hz, 2H), 10.33 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.97, 75.72, 123.29, 126.49, 127.27, 128.77, 132.49, 137.26, 174.87; IR ($CHCl_3$)

3553, 3295, 3048, 2949, 1760, 1601, 1384, 1313 cm^{-1}; MS (FAB) m/z (%) 299(M+1, 46), 179(100).

(3*R*,4*S*)-1-(Morpholinecarbonyl)-3-hydroxy-4-phenyl-2-azetidinone (8f): 83%; white solid; mp 55-57°C; ^1H NMR (250 MHz, $CDCl_3$) δ 3.05 (bs, 1H), 3.56-3.78 (m, 8H), 5.00 (d, J = 5.9 Hz, 1H), 5.38 (d, J = 5.9 Hz, 1H), 7.24-7.40 (m, 5H).

(3*R*,4*S*)-1-(N,N-Dimethylcarbamoyl)-3-hydroxy-4-phenyl-2-azetidinone (8g): 88%; white crystal; mp 123-125°C; $_1H$ NMR (250 MHz, $CDCl_3$) δ3.06 (bs, 6H, 4.98 (d, J=5.9 Hz, 1H), 5.35 (d, J=5.9 Hz, 1H), 7.29-7.39 (m, 5H).

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-4-phenyl-3-(1,1,1-trichloroethoxycarbonyl)-2-azetidinone (9a): To a solution of 99 mg (0.38 mmol) of 1-*tert*-butylcarbonyl-3-hydroxy-4-phenyl- 2-azetidinone, 5 mg of DMAP and 263 mL (2 mmol) of triethylamine in 5 mL of dichloromethane, was added at 0°C 105 mL (0.8 mmol) of 1,1,1-trichloroethyl-chloroformate. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over $MgSO_4$ and concentrated. The crude solid was purified by chromatography on silica gel to yield 65 mg (40%) of O-protected β-lactam: White solid; mp 122-124°C; $[\alpha]D^{20}$ +28° (c 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.39 (s, 9H), 4.43 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 5.28 (d, J = 5.5 Hz, 1H), 5.76 (d, J = 5.5 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.81, 60.80, 77.03, 78.76, 84.40, 127.73, 128.58, 129.09, 131.55, 147.71, 152.17, 160.34; IR ($CHCl_3$) 3016, 2976, 1819, 1771, 1732, 1683, 1244 cm^{-1}. Anal. Calcd for $C_{17}H_{18}Cl_3NO_6$: C, 46.54; H, 4.14; N, 3.19. Found: C, 46.33; H, 4.34; N, 3.33.

(3*R*,4*S*)-3-Acetoxy-1-tert-butoxycarbonyl-4-phenyl-2-azetidinone (9b): To a solution of 82 mg (0.3 mmol) of 1-tert-butylcarbonyl-3-hydroxy-4-phenyl-2-azetidinone, 5 mg of DMAP and 210 mL (1.5 mmol) of triethylamine in 5 mL of dichloromethane, was added at 0°C 58 mL (0.7 mmol) of acetic anhydride. The reaction mixture was stirred overnight at room temperature. The organic layer was washed several times with brine, dried over $MgSO_4$ and concentrated. The crude solid was purified by chromatography on silica gel to yield 71 mg (75%) of O-acetyl β-lactam: White solid; mp 63-64°C; $[\alpha]D^{20}$ +32.1° (c 0.81, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.65 (s, 3H), 5.22 (d, J = 5.5 Hz, 1H), 5.83 (d, J = 5.5 Hz, 1H), 7.23-7.33 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.71, 27.81, 60.84, 75.94, 84.07, 127.43, 128.31, 128.67, 132.44, 147.25, 162.39, 168.83; IR ($CHCl_3$) 3026, 2984, 1815, 1752, 1731, 1497, 1371, 1286, 1224, 1152, 1024 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.17; H, 6.14; N, 4.52.

Example 54

To a suspension of NaH (35 mg in 1.0 mL of DME), was added at -10°C, a solution of 133 mg (0.15 mmol) of 7,10-ditroc-10-deacetylbaccatin III and 100 mg (0.30 mmol) of 5d in 1.5 mL of DME. The reaction was monitored by TLC and quenched at -8°C by addition of brine. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2CO_3 and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 148 mg of the coupling product 2'-EE-7,10-ditroc-Taxotère as a white solid (81% yield; 90% conversion yield) and 12 mg of 7,10-ditroc-10-deacetylbaccatin III (10% recovery).

The EE protecting group was removed by stirring

at room temperature 90 mg of 2'-EE-7,10-ditroc-Taxotère in 3 mL of THF and 2 mL of 0.5N HCl for 1 hr. The reaction mixture was diluted with dichloromethane. The organic phase was washed with sat. $NaHCO_3$ sol., brine dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 60 mg (71%) of 2'-OH-7,10-ditroc-Taxotère as a white solid: Mp 154-155°C; $[\alpha]D^{20}$ -38° (c 0.74, CHCl3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.26 (s, 3H), 1.35 (s, 9H), 1.85 (s, 3H), 1.95 (s, 3H), 2.04 (m, 1H), 2.34 (m, 2H), 2.39 (s, 3H), 2.62 (m, 1H), 3.90 (d, J = 6.4 Hz, 1H), 4.17 (d, J = 8.4 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.64 (m, 1H), 4.78 (s, 2H), 4.91 (d, J = 11.9 Hz, 1H) , 4.95 (m, 1H), 5.26 (bd, J = 8.7 Hz, 1H), 5.46 (bd, J = 9.2 Hz, 1H), 5.54 (dd, J = 10.4, 7.1 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.21 (bt, J = 8.7 Hz, 1H), 6.24 (s, 1H), 7.32-7.35 (m, 5H), 7.50 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 8.10 (d, J = 7.5 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.69, 14.63, 20.91, 22.47, 26.25, 28.14, 33.20, 35.21, 43.07, 46.91, 56.14, 72.17, 73.50, 74.10, 76.48, 77.33, 77.51, 78.55, 79.08, 80.23, 80.67, 83.61, 94.11, 126.70, 128.06, 128.70, 128.88, 130.12, 131.91, 133.79, 138.20, 142.48, 153.12, 153.17, 155.36, 166.82, 170.33, 172.78, 200.70; IR ($CHCl_3$) 3572, 3444, 3034, 2979, 1759, 1737, 1724, 1490, 1450, 1376, 1106 cm^{-1}.

Example 55

To a solution of 90 mg (0.1 mmol) of 7,10-ditroc-10-deacetylbaccatin III and 47 mg (0.14 mmol) of **5d** in 5 mL of THF, was added at -30°C 110 mL (0.11 mmol, 1M in THF) of sodium hexamethyldisilazide. The reaction was monitored by TLC and quenched by addition of brine. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over

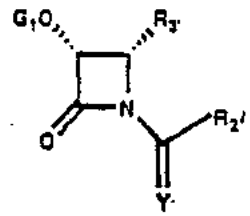
Na_2CO_3 and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/2) as the eluant to give 117 mg of the coupling product 2'-EE-7,10-ditroc-TAXOTÈRE as a white solid (94%). All physical and spectral data are identical with those of 2'-EE-7,10-ditroc-TAXOTÈRE described in Example 54.

The Troc protecting group was removed by stirring at 60°C 50 mg of 7,10-ditroc-TAXOTÈRE in 1 mL of MeOH and 1 mL of AcOH in presence of 150 mg of zinc for 1 hr. The reaction mixture was filtrated and diluted with dichloromethane. The organic phase was washed with sat. $NaHCO_3$ sol., brine dried over $MgSO_4$ and concentrated. The crude oil was purified by chromatography on silica gel using AcOEt/hexanes (1/1) as the eluant to give 28 mg (80%) of TAXOTÈRE as a white solid: $[\alpha]_D^{20}$ -34° (c 0.7, EtOH); NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.26 (s, 3H), 1.35 (s, 9H), 1.80 (s, 3H), 1.85 (m,), 1.90 (s, 3H), 2.24 (m, 2H), 2.39 (s, 3H), 2.55 (m,), 2.62 (m,), 3.53 (s,), 3.92 (d, J = 7.0 Hz,), 4.18 (d, J = 8.4 Hz,), 4.22 (m,), 4.32 (d, J = 8.4 Hz,), 4.66 (d, J = 6.9 Hz,), 6.19 (bt, J = 8.1 Hz,), 7.32-7.35 (m, 5H), 7.50 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.3 Hz,), 8.10 (d, J = 7.5 Hz, 2H). These data are consistent with those reported for TAXOTÈRE by Mangatal, L. et al. (Ref. Mangatal, L.; Adeline, M.T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177.)

Although the invention has been described in conjunction with specific embodiments, it is evident that many alternatives and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, the invention is intended to embrace all of the alternatives and variations that fall within the spirit and scope of the appended claims. The above references are hereby incorporated by reference.

We Claim:

1. A β-lactam of the formula:



in which

R_2, represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, carbocyclic aryl or heteroaryl; is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure;

R_3, represents an unsubstituted or substituted straight or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, cycloalkenyl radical, an unsubstituted or substituted carbocyclic aryl;

G_1 represents a hydrogen or a hydroxyl protecting group;

Y is oxygen or sulfur.

2. A β-lactam according to claim 1 in which

R_2, represents a radical RO-, RS- or RR'N- in which R represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a heterocycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a heterocycloalkenyl radical containing 3 to 10 carbon

atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons, a heteroaryl radical containing 3 to 15 carbon atoms; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl radicals, the alkyl portion of which contain 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which containing 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms; R' is a hydrogen or R as defined above; R and R' can be connected to form a cyclic structure which contains 2-10 carbon atoms;

R_3 represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, or an aryl radical containing 6 to 20 carbons; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl radicals, the alkyl portion of which contain 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which contain 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms.

3. A β-lactam according to claim 1 in which R_2 represents an RO-, RS-, or RR'N- in which R is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 9-fluorenylmethyl, benzyl and adamantyl, or an alkenyl radical selected from vinyl and allyl, or an aryl radical selected from phenyl and naphthyl, or a heteroaryl radical selected from furyl, pyrrolyl, and pyridyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl, or a heterocycloalkyl radical selected from an oxiranyl, tetrahydrofuryl, pyrrolidinyl, piperdinyl, tetrahydropyranyl, or a heterocycloalkenyl radical selected from dihydrofuryl, dihydropyrrolyl, dihydropyranyl, dihydropyridyl; R' is a hydrogen or R as defined above; cyclic RR'N- radical includes aziridino, azetidino, pyrrolidino, piperidino or morpholino group;

R_3, is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclohexylmethyl, cyclohexylethyl, benzyl, phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 9-fluorenylmethyl, benzyl and adamantyl, or an alkenyl radical selected from vinyl, allyl, 2-phenylethenyl, or an alkynyl radical selected from ethynyl and propargyl or an aryl radical selected from phenyl and naphthyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl;

G_1 represents a hydrogen or a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (β-trimethylsilylethoxyl), methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (Troc), benzyloxycarbonyl (CBZ), tertbutoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-

trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

4. A β-lactam according to claim 1 in which Y is oxygen and R_2, represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl, or 9-fluorenylmethyl; R_3, is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-phenylethenyl;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

5. A β-lactam according to claim 1 in which Y is oxygen and R_2, is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, neopentylamino, cyclohexylamino, phenylamino or benzylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, dicyclohexylamino, methyl(tert-butyl)amino, cyclohexyl(methyl)amino, methyl(phenyl)amino, pyrrolidino, piperidino or morpholino group;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxycarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

6. A β-lactam according to claim 1 in which Y is sulfur and R_2, represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl or 9-

fluorenylmethyl; R_3, is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-naphthyl;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

7. A β-lactam according to claim 1 in which

Y is sulfur and R_2 is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, neopentylamino, cyclohexylamino, phenylamino, or benzylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, dicyclohexylamino, methyl(tert-butyl)amino, cyclohexyl(methyl)amino, methyl(phenyl)amino, pyrrolidino, piperidino, or morpholino group;

G_1 is a hydrogen, 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc), trimethylsilyl, triethylsilyl or acetyl.

8. A β-lactam according to claim 1 in which

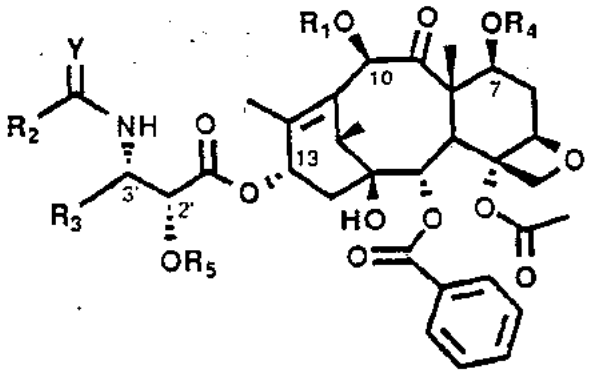
Y is oxygen, R_2, represents RO- in which R is a methyl, ethyl, butyl, tert-butyl, phenyl or benzyl and R_2 is a phenyl, 2-phenylethenyl, cyclohexylmethyl or isobutyl;

Y is oxygen, R_2, is an ethylamino, tert-butylamino, phenylamino, benzylamino, dimethylamino or morpholino group, and R_3, is a phenyl;

Y is sulfur, R_2, is a phenylamino, dimethylamino or morpholino group, R_3, is a phenyl;

G_1 is a hydrogen or 1-ethoxyethyl (EE), 2,2,2-trichloroethoxylcarbonyl (Troc) or acetyl.

9. A process for the preparation of a taxane derivative of the formula



in which

R_1 represents a hydrogen or an acyl or an alkyl or an alkenyl or an alkynyl or an aryl or a heteroaryl radical or a hydroxyl protecting group;

R_2 represents an RO-, RS- or RR'N- in which R represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or aklynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl or heteroaryl; R' is a hydrogen or R defined above; R and R' can be connected to form a cyclic structure;

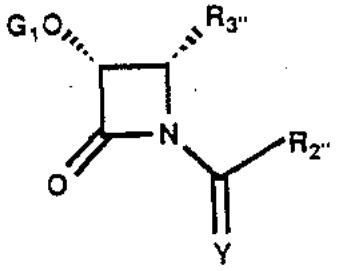
Y is oxygen or sulfur;

R_3 represents an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, cycloalkenyl or an unsubstituted or substituted carbocyclic aryl;

R_4 represents a hydrogen or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl radical, or a hydroxyl group protecting group;

R_5 represents a hydrogen or a acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl, or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl radical, or a hydroxyl

protecting group;
which comprises reacting a β-lactam of the formula

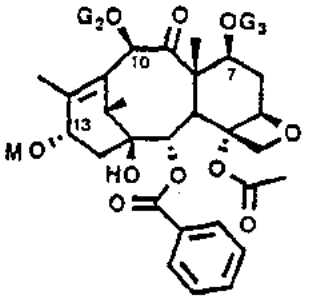


in which

Y is defined above; G_1 represents an hydroxyl protecting group;

R_2, represents a radical R_2 defined above or a protected R_2 whenever R_2 includes one or more active hydrogens,

R_3, represents a radical R_3 defined above or a protected R_3 whenever R_3 includes one or more active hydrogens;
with a baccatin III derivative of the formula:



in which M is an alkali metal or alkaline earth metal atom (ion);

G_2 represents a hydroxyl protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl radical, an

unsubstituted or substituted aryl or heteroaryl radical;

G_3 represents a hydroxyl group protecting group or an acyl radical or an unsubstituted or substituted straight chain or branched radical alkyl, alkenyl or alkynyl radical, an unsubstituted or substituted cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl radical, an unsubstituted or substituted aryl or heteroaryl.

10. The process according to claim 9, in which

R_2 represents a radical RO-, RS-, or RR'N- in which R represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a heterocycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a heterocycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons, a heteroaryl radical containing 3 to 15 carbon atoms; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl the alkyl portion of which contains 1 to 15 carbon atoms, aryloxycarbonyl the aryl portion of which containing 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms; R' is a hydrogen or R defined above; R and R' can form a cyclic structure which contains 2-10 carbon atoms;

R_3 represents a straight chain or branched alkyl radical containing 1 to 10 carbon atoms, a straight chain or branched alkenyl radical containing 2 to 10 carbon

atoms, or a straight chain or branched alkynyl radical containing 2 to 10 carbon atoms, a cycloalkyl radical containing 3 to 10 carbon atoms, a cycloalkenyl radical containing 3 to 10 carbon atoms, a polycycloalkyl radical containing 6 to 20 carbon atoms, an aryl radical containing 6 to 20 carbons; these radicals being optionally substituted with one or more halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl, the alkyl portion of which containing 1 to 15 carbon atoms, aryloxycarbonyl, the aryl portion of which contains 6 to 20 carbon atoms, or heteroaryloxycarbonyl the heteroaryl portion of which containing 3 to 15 carbon atoms;

R_2, represents a radical R_2 defined above or a protected R_2 whenever R_2 includes one or more active hydrogens;

R_3, represents a radical R_3 defined above or a protected R_3 whenever R_3 includes one or more active hydrogens.

11. The process according to claim 9, wherein R_2 represents an RO-, RS-, or RR'N- in which R is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl, or an alkenyl radical selected from vinyl and allyl, or an aryl radical selected from phenyl and naphthyl, or a heteroaryl radical selected from furyl, pyrrolyl, and pyridyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclyhexenyl and cycloheptenyl, or a heterocycloalkyl radical selected from an oxiranyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl,

tetrahydropyranyl, or a heterocycloalkenyl radical selected from dihydrofuryl, dihydropyrrolyl, dihydropyranyl, dihydropyridyl; R' is a hydrogen or R defined above; cyclic RR'N- radical includes aziridino, azetidino, pyrrolidino, piperidino or morpholino group;

R_3 is an unsubstituted or substituted alkyl radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl, isooctyl, cyclohexylmethyl, cyclohexylethyl, benzyl, phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl, or an alkenyl radical selected from vinyl, allyl or an alkynyl radical selected from ethynyl and propargyl or an aryl radical selected from phenyl and naphthyl, or a cycloalkenyl radical selected from cyclopentenyl, cyclohexenyl and cycloheptenyl.

R_{2a} represents a radical R_2 defined above or a protected R_2 wherever R_2 includes one or more active hydrogens;

R_{3a} represents a radical R_3 defined above or a protected R_3 wherever R_3 includes one or more active hydrogens;

G_1 represents a group protecting the hydroxyl function selected from methoxylmethyl (MOM), methoxyethyl (MEM), 1-ethoxyethyl (EE), benzyloxymethyl, (β-trimethylsilyl-ethoxyl)-methyl, tetrahydropyranyl, 2,2,2-trichloroethoxylcarbonyl (Troc), benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (t-BOC), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl and diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl;

G_2 represents an acetyl or a 2,2,2-trichloroethoxycarbonyl (Troc) group;

G_3 represents a 2,2,2-trichloroethoxycarbonyl (Troc) or silyl group selected from trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethylphenylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl and diphenylmethylsilyl.

12. The process according to claim 9, wherein M is an alkali metal.

13. The process according to claim 10, wherein M is an alkali metal selected from lithium, sodium and potassium.

14. The process according to claim 11, wherein M is sodium or potassium.

15. The process according to claim 11 wherein R_1 is a hydrogen, an acetyl or an trichloroethoxycarbonyl (Troc); R_4 is a hydrogen, a triethylsilyl or a trichloroethoxycarbonyl (Troc); R_5 is a hydrogen, a triethylsilyl or ethoxyethyl.

16. The process according to claim 11 wherein R_2 represents RO- in which R is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, neopentyl, cyclohexyl, phenyl, benzyl or 9-fluoroenylmethyl; R_3 is a phenyl, tolyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-naphthyl and 2-phenylethenyl; R_5 is a hydrogen.

17. The process according to claim 11 wherein R_2 is a methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-

butylamino, neopentylamino, cyclohexylamino, phenylamino or benzylamino, dimethylamino or morpholino group; R_5 is a hydrogen.

18. The process according to claim 9 wherein R_1 is a hydrogen or a acetyl; R_2 (= R_2') is tert-butoxy or tert-butylamino; R_3 (= R_3') is a phenyl; Y is oxygen; R_4 is a hydrogen; R_5 is a hydrogen; G_1 is an ethoxyethyl, triethylsilyl or trichloroethoxycarbonyl (Troc); M is sodium or potassium.

INTERNATIONAL SEARCH REPORT

Inte mal Application No
PCT/US 94/00669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D205/08 C07D305/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON, (INCL. TETRAHEDRON REPORTS) vol. 48, no. 34 , 1992 , OXFORD GB pages 6985 - 7012 I. OJIMA ET AL. 'New and efficient approaches to the semisynthesis of taxol and its C-13 side chain analogs by means of beta-lactam synthon method' cited in the application see the whole document --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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1

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1994	28.04.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

Int ional Application No
PCT/US 94/00669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF ORGANIC CHEMISTRY vol. 56, no. 5 , 1991 , EASTON US pages 1681 - 1683 I. OJIMA ET AL. 'Efficient and practical asymmetric synthesis of the taxol C-13 side chain, N-benzoyl-(2R,3S)-3-phenylisoserine, and its analogues via chiral 3-hydroxy-4-aryl-beta-lactams through chiral ester enolate-imine cyclocondensation' cited in the application see the whole document	1-18
Y	EP,A,0 400 971 (FLORIDA STATE UNIVERSITY) 5 December 1990 cited in the application see claims	1-18
P,X	WO,A,93 06093 (FLORIDA STATE UNIVERSITY) 1 April 1993 see pages 15, 28-33 and claims	1-18
P,Y	EP,A,0 525 589 (BRISTOL-MYERS SQUIBB COMPANY) 3 February 1993 see the whole document	1-18

Inte mal Application No
PCT/US 94/00669

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0400971	05-12-90	US-A-	5175315	29-12-92
		AU-B-	630696	05-11-92
		AU-A-	5515090	20-12-90
		CA-A-	2016951	30-11-90
		CN-A-	1057049	18-12-91
		JP-A-	3086860	11-04-91
WO-A-9306093	01-04-93	AU-A-	2212292	25-03-93
		AU-A-	2212392	25-03-93
		AU-A-	2212492	25-03-93
		AU-B-	643911	25-11-93
		AU-A-	2688892	27-04-93
		AU-B-	647971	31-03-94
		AU-A-	2689092	27-04-93
		AU-A-	2692692	27-04-93
		AU-A-	3983793	19-08-93
		AU-A-	3983893	19-08-93
		CA-A-	2077394	24-03-93
		CA-A-	2077598	24-03-93
		CA-A-	2077621	24-03-93
		CN-A-	1075315	18-08-93
		CN-A-	1075718	01-09-93
		EP-A-	0534707	31-03-93
		EP-A-	0534708	31-03-93
		EP-A-	0534709	31-03-93
		PT-A-	100884	30-11-93
		WO-A-	9306094	01-04-93
		WO-A-	9306079	01-04-93
		US-A-	5229526	20-07-93
		US-A-	5227400	13-07-93
		US-A-	5243045	07-09-93
		US-A-	5250683	05-10-93
		US-A-	5274124	28-12-93
		US-A-	5284864	08-02-94
		US-A-	5283253	01-02-94
		US-A-	5284865	08-02-94
EP-A-0525589	03-02-93	AU-A-	2064092	04-02-93
		CN-A-	1069028	17-02-93
		JP-A-	5201969	10-08-93

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 639 577 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 94112803.5

(22) Date of filing: 16.08.94

(51) Int. Cl.[6]: C07F 9/655, A61K 31/66, A61K 31/335, C07D 305/14, C07D 407/12, C07F 9/6558

(30) Priority: 17.08.93 US 108015
24.11.93 US 154840
17.05.94 US 245119

(43) Date of publication of application:
22.02.95 Bulletin 95/08

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

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(54) Phosphonooxymethyl or methylthiomethyl ethers of taxane derivatives as antitumor agents.

(57) The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

EP 0 639 577 A1

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our co-pending application U.S.S.N. 08/154,840, filed November 24, 1993, which is a continuation-in-part of U.S.S.N. 08/108,015 filed August 17, 1993, which in turn is a continuation-in-part of U.S.S.N. 07/996,455 filed December 24, 1992, now abandoned. U.S.S.N. 08/154,840 is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

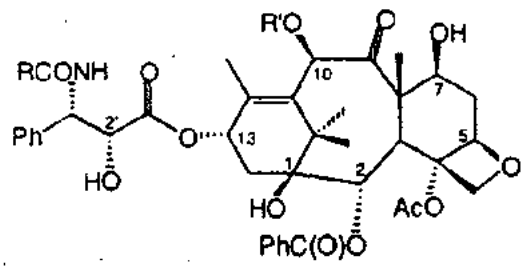
1. Field of the Invention

The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

2. Background Art

Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It was recently approved for the treatment of ovarian cancer; and studies involving breast, colon, and lung cancers have shown promising results. The results of paclitaxel clinical studies are reviewed in Rowinsky and Donehower, "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics" Pharmac. Ther., 52:35-84, 1991.

Recently, a semi-synthetic analog of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models. Taxotere® is also currently undergoing clinical trials in Europe and the United States. The structures of paclitaxel and Taxotere® are shown below; the conventional numbering system of the paclitaxel molecule is provided.



Taxol®: R = Ph; R' = acetyl
Taxotere®: R = t-butoxy; R' = hydrogen

One drawback of paclitaxel is its very limited water solubility requiring it to be formulated in nonaqueous pharmaceutical vehicles. One commonly used carrier is Cremophor EL which may itself have undesirable side effects in man. Accordingly, a number of research teams have prepared water-soluble derivatives of paclitaxel which are disclosed in the following references:

(a) Haugwitz et al, U.S. Patent No. 4,942,184;
(b) Kingston et al, U.S. Patent No. 5,059,699;
(c) Stella et al, U.S. Patent No. 4,960,790;
(d) European Patent Application 0,558,959 A1 published September 8, 1993;
(e) Vyas et al, Bioorganic & Medicinal Chemistry Letters, 1993, 3:1357-1360; and
(f) Nicolaou et al, Nature, 1993, 364:464-466

Compounds of the present invention are phosphonooxymethyl ethers of taxane derivatives and pharmaceutically acceptable salts thereof. The water solubility of the salts facilitates preparation of pharmaceutical formulations.

SUMMARY OF THE INVENTION

The present invention relates to taxane derivatives having the formula (A):

$$T—[OCH_2(OCH_2)_mOP(O)(OH)_2]_n \quad (A)$$

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is 1, 2 or 3; m is 0 or an integer from 1 to 6 inclusive; or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides taxane derivatives having the formula (B):

$$T'—[OCH_2(OCH_2)_mSCH_3]_n \quad (B)$$

wherein T' is T in which non-reacting hydroxy groups have been blocked, m and n are as defined under formula (A).

Yet another aspect of the present invention provides intermediates having the formula (C):

$$T'—[OCH_2(OCH_2)_mOP(O)(OR^y)_2]_n \quad (C)$$

wherein T', m and n are as defined under formula (A), and R^y is a phosphono protecting group.

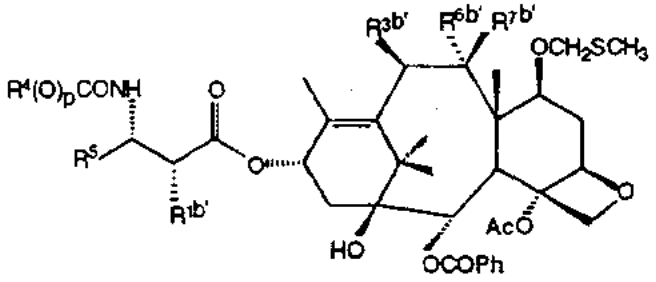
Another aspect of the present invention provides compounds of the formula (D):

$$13—OH—txn—[OCH_2(OCH_2)_mSCH_3]_n \quad (D)$$

wherein m and n are as defined above; and txn is a taxane moiety; or a C13 metal alkoxide thereof.

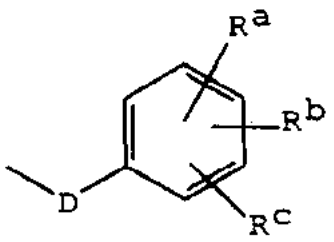
Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula (A).

Further aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of the formula (B'):



(B')

wherein $R^{1b'}$ is hydroxy, -OC(O)R^x or -OC(O)OR^x; $R^{3b'}$ is hydrogen, hydroxy, -OC(O)OR^x, C_{1-6}alkyloxy or -OC(O)R^x; one of $R^{6b'}$ or $R^{7b'}$ is hydrogen and the other is hydroxy or C_{1-6} alkanoyloxy; or $R^{6b'}$ and $R^{7b'}$ together form an oxo group; R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or -Z-R^6; Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl; R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl or heteroaryl; p is 0 or 1; R^x is C_{1-6} alkyl optionally, substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl or hydroxy; or R^x is a radical of the formula



wherein D is a bond or C_{1-6} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-6} alkylamino, di-C_{1-6} alkylamino, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy.

Thus, another aspect of the present invention provides a pharmaceutical composition which comprises an antitumor effective amount of a compound of formula (B') or (A) and a pharmaceutically acceptable carrier.

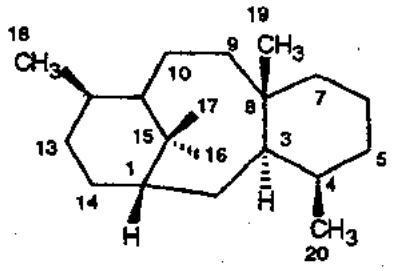
DETAILED DESCRIPTION OF THE INVENTION

In the application, unless otherwise specified explicitly or in context, the following definitions apply. "Alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. "Alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. "Alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

"Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl substituted with at least one group selected from C_{1-6} alkanoyloxy, hydroxy, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, aryl, C_{2-6} alkenyl, C_{1-6} alkanoyl, nitro, amino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

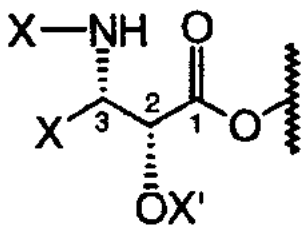
"Phosphono-" means the group $-P(O)(OH)_2$ and "phosphonooxymethoxy" or "phosphonooxymethyl ether" means generically the group $-OCH_2(OCH_2)_mOP(O)(OH)_2$. "(Methylthio)thiocarbonyl" means the group $-C(S)SCH_3$. "Methylthiomethyl" (also abbreviated as MTM) generically refers to the group $-CH_2SCH_3$.

"Taxane moiety" (also abbreviated as txn) denotes moieties containing the twenty carbon taxane core framework represented by the structural formula shown below with the absolute configuration.



The numbering system shown above is one used in conventional taxane nomenclature, and is followed throughout the application. For example, the notation C1 refers to the carbon atom labelled as "1"; C5-C20 oxetane refers to an oxetane ring formed by the carbon atoms labelled as 4, 5 and 20 with an oxygen atom; and C9 oxy refers to an oxygen atom attached to the carbon atom labelled as "9", said oxygen atom may be an oxo group, α- or β-hydroxy, or α- or β-acyloxy.

"Substituted 3-amino-2-hydroxypropanoyloxy" denotes a residue represented by the formula



(X is a nonhydrogen group and X' is hydrogen or a non-hydrogen group.) The stereochemistry of this residue is the same as the paclitaxel sidechain. This group is sometimes referred to in the application as the "C13 sidechain."

"Taxane derivative" (abbreviated as T) refers to a compound having a taxane moiety bearing a C13 sidechain.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Phosphono protecting groups" means moieties which can be employed to block or protect the phosphono functional group; preferably such protecting groups are those that can be removed by methods that do not appreciably affect the rest of the molecule. Suitable phosphonooxy protecting groups are well known to those skilled in the art and include for example benzyl and allyl groups.

"Hydroxy protecting groups" include, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl.

Additional examples of hydroxy and phosphono protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., 1991, John Wiley & Sons, and McOmie, Protective Groups in Organic Chemistry, 1975, Plenum Press. Methods for introducing and removing protecting groups are also found in such textbooks.

"Pharmaceutically acceptable salt" means a metal or an amine salt of the acidic phosphono group in which the cation does not contribute significantly to the toxicity or biological activity of the active compound. Suitable metal salts include lithium, sodium, potassium, calcium, barium, magnesium, zinc, and aluminum salts. Preferred metal salts are sodium and potassium salts. Suitable amine salts are for example, ammonia, tromethamine (TRIS), triethylamine, procaine, benzathine, dibenzylamine, chloroprocaine, choline, diethanolamine, triethanolamine, ethylenediamine, glucamine, N-methylglucamine, lysine, arginine, ethanolamine, to name but a few. Preferred amine salts are lysine, arginine, triethanolamine, and N-methylglucamine salts. Even more preferred salt is N-methylglucamine or triethanolamine.

As used herein, the term $-OCH_2(OCH_2)_mOP(O)(OH)_2$ is intended to emcompass both the free acid and its pharmaceutically acceptable salts, unless the context indicates specifically that the free acid is meant.

One aspect of the present invention provides taxane derivatives of the formula (A)

$$T-[OCH_2(OCH_2)_mOP(O)(OH)_2]_n \quad (A)$$

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is an 1, 2 or 3; m is 0, or an integer from 1 to 6 inclusive, or a pharmaceutically acceptable salt thereof.

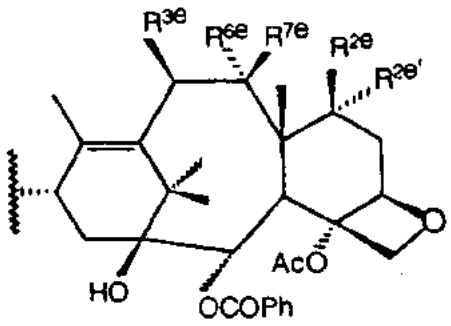
Another aspect of the present invention provides taxane derivatives having the formula (B)

$$T'-[OCH_2(OCH_2)_mSCH_3]_n \quad (B)$$

which are useful in making taxane derivatives of the formula (A).

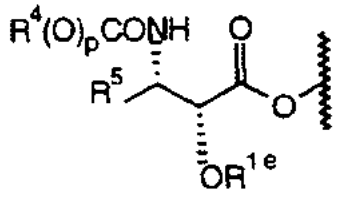
In one embodiment the taxane moiety contains at least the following functionalities: C1-hydroxy, C2-benzoyloxy, C4-acetyloxy, C5-C20 oxetane, C9-oxy, and C11-C12 double bond.

In a preferred embodiment the taxane moiety is derived from a residue having the formula

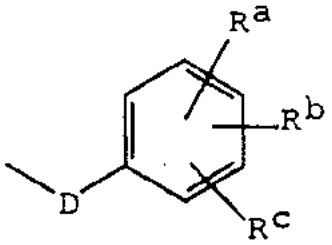


wherein $R^{2e'}$ is hydrogen and R^{2e} is hydrogen, hydroxy, -OC(O)R^x, or -OC(O)OR^x; R^{3e} is hydrogen, hydroxy, -OC(O)R^x, -OC(O)OR^x or C_{1-6} alkyloxy; one of R^{6e} or R^{7e} is hydrogen and the other is hydroxy or -OC(O)R^x; or R^{6e} and R^{7e} together form an oxo group; R^x is as defined below.

In another embodiment, the C13 sidechain is derived from a residue having the formula



wherein R^{1e} is hydrogen or -C(O)R^x, -C(O)OR^x; R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or -Z-R^6; Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl; R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl, or heteroaryl; and R^x is C_{1-6} alkyl optionally substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, c_{2-6} alkenyl or hydroxy; or R^x is a radical of the formula

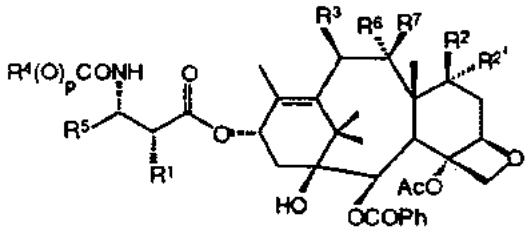


wherein D is a bond or C_{1-6} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-6} alkylamino, di-C_{1-6}alkylamino, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy; p is 0 or 1.

In a preferred embodiment, R^4 is C_{1-6} alkyl and p is 1, or R^4 is -Z-R^6 and p is 0. More preferably, R^4-$(O)_p$ is t-butoxy, phenyl, isopropyloxy, n-propyloxy, or n-butoxy.

In another preferred embodiment R^5 is C_{2-6}alkenyl or -Z-R^6 and Z and R^5 are as previously defined. More preferably, R^5 is phenyl, 2-furyl, 2-thienyl, isobutenyl, 2-propenyl, or C_{3-6}cycloalkyl.

In another embodiment, compound of formula (A) may be more specifically represented by the formula (I)



(I)

wherein R^1 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; R^3 is hydrogen, hydroxy, C_{1-6} alkyloxy, $-OC(O)R^x$,$-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; one of R^6 or R^7 is hydrogen and the other is hydroxy, C_{1-6} alkanoyloxy, or $-OCH_2(OCH_2)_mOP(O)(OH)_2$; or R^6 and R^7 together form an oxo group; with the proviso that at least one of R^1, R^2, R^3, R^6 or R^7 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^4, R^5, R^x, m and p are as previously defined; or a pharmaceutically acceptable salt thereof.

In compounds of formula (I), examples of R^x include methyl, hydroxymethyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, chloromethyl, 2,2,2-trichloroethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, 2-propenyl, phenyl, benzyl, bromophenyl, 4-aminophenyl, 4-methylaminophenyl, 4-methylphenyl, 4-methoxyphenyl and the like. Examples of R^4 and R^5 include 2-propenyl, isobutenyl, 3-furanyl (3-furyl), 3-thienyl, phenyl, naphthyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, ethenyl, 2-propenyl, 2-propynyl, benzyl, phenethyl, phenylethenyl, 3,4-dimethoxyphenyl, 2-furanyl (2-furyl), 2-thienyl, 2-(2-furanyl)ethenyl, 2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl and the like.

In one embodiment, the present invention provides a preferred group of compounds of formula (I) in which R^5 is C_{2-6} alkenyl or -Z-R^6 and Z and R^6 are as previously defined. More preferably, R^5 is phenyl, 3-furyl, 3-thienyl, 2-propenyl, isobutenyl, 2-furyl, 2-thienyl, or C_{3-6} cycloalkyl.

In another preferred embodiment R^4 of compounds of formula (I) is C_{1-6} alkyl in which case p is 1; or R^4 is -Z-R^6 and Z and R^6 are as previously defined, and in which case p is 0. More preferably $R^4(O)_p$- is t-butoxy, phenyl, isopropyloxy, n-propyloxy, n-butoxy.

In another preferred embodiment, the present invention provides compounds of formula (I) in which R^1 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$. In a more preferred embodiment, R^2 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)OR^x$ or $-OC(O)R^x$, and R^x is preferably C_{1-6} alkyl. In another more preferred embodiment, R^3 is hydroxy or acetoxy.

In another preferred embodiment, the present invention provides compound of formula (I) in which R^2 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^1 is hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; and R^3 is hydrogen, hydroxy, acetoxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$; and R^x is as previously defined. In a more preferred embodiment R^1 is hydroxy or $-OC(O)OR^x$ and R^x is preferably C_{1-6} alkyl; and R^3 is hydroxy or acetoxy.

In another preferred embodiment, the present invention provides compound of formula (I) in which R^3 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$; R^1 is hydroxy or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy or $-OC(O)OR^x$; and R^x is as previously defined. In a more preferred embodiment, R^1 is hydroxy or $-OC(O)OR^x$, and R^x is preferably C_{1-6} alkyl. In another more preferred embodiment, R^2 is hydroxy.

In another preferred embodiment, m is 0, 1 or 2 when the phosphonooxymethoxy group is present on the C7 of the taxane moiety.

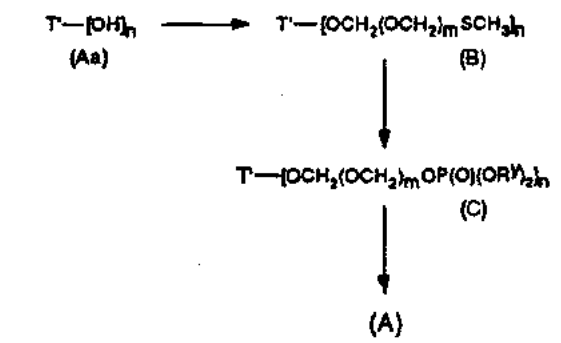
The preferred pharmaceutically acceptable salts of a compound of formula (A) are alkali metal salts including lithium, sodium and potassium salts; and amine salts including triethylamine, triethanolamine, ethanolamine, arginine, lysine and N-methylglucamine salts. Even more preferred salts are sodium, triethanolamine, and N-methylglucamine salts.

The most preferred embodiments of taxane derivatives of formula (A) include the following compounds: (1) 7-O-phosphonooxymethylpaclitaxel, (2) 2'-O-(ethyloxycarbonyl)-7-O-phosphonooxymethylpaclitaxel; (3) 2'-O-phosphonooxymethylpaclitaxel; (4) 2',7-bis-O-(phosphonooxymethyl)paclitaxel; (5) 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel; (6) 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel; (7) 10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel; (8) 2'-O-phosphonooxymethoxymethylpaclitaxel; (9) 2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel; (10) 2'-O-methylcarbonyl-7-O-phosphonooxymethylpaclitaxel; (11) 2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxel; (12) 2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel; and their respective pharmaceutically acceptable salts, particularly the

sodium, potassium, arginine, lysine, N-methylglucamine, ethanolamine, triethylamine and triethanolamine salts.

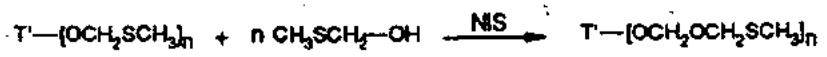
Compounds of formula (A) may be prepared from a taxane derivative starting material T-$[OH]_n$ wherein T and n are as previously defined. The identity of T-$[OH]_n$ is not particularly limited so long as there is at least one reactive hydroxy group present on either the taxane moiety or the C13 side chain to allow the formation of phosphonooxymethyl ether linkage. It is to be understood that the reactive hydroxy group may be directly attached to the C13 propanoyloxy backbone (e.g. the 2'-hydroxy group of paclitaxel) or to the taxane core framework (e.g. the 7-hydroxy group of paclitaxel); or it may be present on a substituent on the C13 sidechain, or on a substituent on the taxane core. The reaction sequence shown in Scheme I may be used to prepare compounds of formula (A)

Scheme I



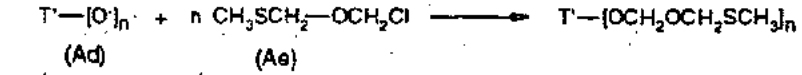
In Scheme I T' is a taxane derivative in which non-reacting hydroxy groups have been blocked; R^Y is a phosphono protecting group; n and m are as previously defined. Thus an appropriately protected T' having one or more reactive hydroxy groups is first converted to a corresponding methylthiomethyl ether of formula (B). Using paclitaxel as an example, T' may be paclitaxel itself (to effect 2',7-bismethylthiomethylation), 7-O-triethylsilylpaclitaxel, 7-O-benzyloxycarbonylpaclitaxel, or 2'-O-ethoxycarbonylpaclitaxel. A compound of formula (B) where m is 0 may be prepared by treating T'-$[OH]_n$ with dimethylsulfoxide/acetic anhydride, or with dimethylsulfide and an organic peroxide. These reactions are discussed more fully in a subsequent section.

The MTM ether having one intervening methyleneoxy unit (i.e. compounds of formula (B) where m = 1) may be prepared by several possible routes. In one a compound of formula (B) where m = 0 is reacted with N-iodosuccinimide (NIS) and methylthiomethanol to extend the chain by one methyleneoxy unit.



An analogous reaction of an alcohol with methylthiomethyloxy group in the presence of NIS was reported by Veeneman et al, in Tetrahedron, 1991, v47, pp. 1547-1562, the relevant portions thereof are hereby incorporated by reference. Silver triflate is preferably used as a catalyst. The compound of methylthiomethanol and its preparation is reported in Syn. Comm., 1986, 16 (13): 1607-1610.

In an alternative method, the T-alkoxide (Ad) generated by treating a compound of formula (Aa) with a base such as n-butyl lithium, lithium diisopropylamide or lithium hexamethyldisilazide, is reacted with chloromethyl methylthiomethyl ether to provide a compound of formula (B) in which m = 1.



Compound (Ae) is prepared by reacting methylthiomethoxide (obtained from methythiomethanol by treatment with a base such as n-butyl lithium, lithium diisopropylamide or lithium hexamethyldisilazide) with chloroiodomethane. Compound (Ae) may also be prepared by treating 1,1'-dichlorodimethylether ($ClCH_2OCH_2Cl$) with a stoichiometric amount or less (e.g. about 0.8 equivalent) of sodium iodide followed by sodium thiomethoxide. 1,1'-Dichlorodimethyl ether is reported in Ind. J. Chem., 1989, 28B, pp. 454-456.

In another method, a compound of formula (Aa) is reacted with bis(MTM)ether, $CH_3SCH_2OCH_2SCH_3$, and NIS to give a compound of formula (B) in which m = 1.

$$T'—[OH]_n + n\ CH_3SCH_2OCH_2SCH_3 \rightarrow T'—[OCH_2OCH_2SCH_3]_n$$

Bis(MTM)ether is prepared by reacting 1,1'-dichlorodimethyl ether with sodium iodide followed by sodium thiomethoxide.

The procedure described above using methylthiomethanol and NIS may be applied to any reagent having an MTM group to extend the chain by one methyleneoxy unit at a time. For example, a compound of formula (B) wherein m = 1 can be reacted with methythiomethanol and NIS to provide a compound of formula (B) wherein m = 2. The process may be repeated to provide compounds of formula (B) in which m is 3, 4, 5 or 6.

In the second step shown in Scheme I, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether. This is accomplished by treating the MTM ether with NIS and protected phosphate $HOP(O)(OR^Y)_2$. In the third step, the phosphono protecting group and any hydroxy protecting group(s) are removed to provide a compound of formula (A). For example, a suitable phosphono protecting group is benzyl which may be removed by catalytic hydrogenolysis; hydroxy protecting groups such as trialkysilyl may be removed by fluoride ion, trichloroethoxycarbonyl may be removed by zinc. Removal of protecting groups are taught in textbooks such as Green and Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991; and McOmie, Protective in Organic Chemistry, Plenum Press, 1973. Both steps are discussed in detail in a later section in the specification.

A variation of the reaction sequence shown in Scheme I is provided in Scheme II.

Scheme II

$$T'—[OH]_n + n\ CH_3SCH_2(OCH_2)_mOP(O)(OR^Y)_2$$

(Aa) (Ca)

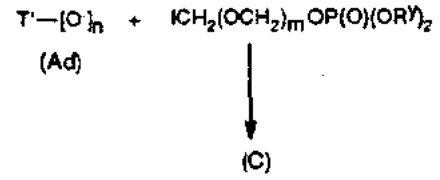
$$\downarrow$$

(C)

In Scheme II, a compound of formula (Aa) is reacted with a compound of formula (Ca) and NIS to give a compound of formula (C), which is then deblocked to give a compound of formula (A). Compounds of formula (Ca) in which m is 0 may be prepared by first treating methylthiomethanol with a base such as Na, Li or K hexamethyldisilazide to give methylthiomethoxide; the methoxide is then reacted with a protected chlorophosphate such as dibenzyl chlorophosphate to provide the desired compound. Compounds of formula (Ca) in which m is 1 may be prepared by treating $CH_3SCH_2OCH_2Cl$ with a diprotected phosphate salt, e.g. sodium, potassium, tetra(n-butyl)ammonium salts of dibenzyl phosphate; or $CH_3SCH_2OCH_2Cl$ may be first converted to the corresponding iodo compound using sodium iodide prior to reacting with the phosphate salt. Alternatively, compounds of formula (Ca) in which m is 1 may be prepared by treating $ClCH_2OCH_2Cl$ with sodium iodide followed by sodium thiomethoxide to provide $CH_3SCH_2OCH_2SCH_3$; this compound is then treated with NIS and a diprotected phosphate such as dibenzyl phosphate to give the desired product. Any of the previously mentioned reagents having a MTM group may be extended one methyleneoxy unit at a time by reacting said reagent with methylthiomethanol and NIS.

In another method for preparing a compound of formula (A), T-alkoxide (Ad) is reacted with an iodophosphate as shown in Scheme III.

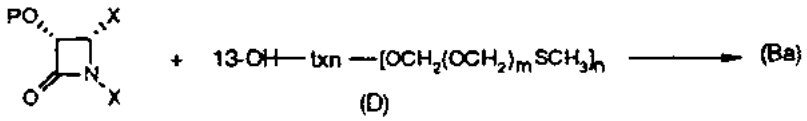
Scheme III



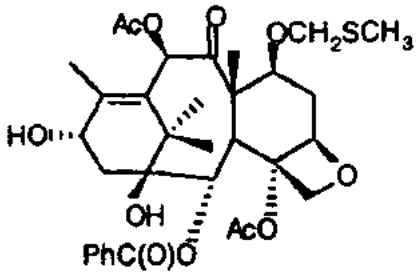
In Scheme III, the iodophosphate compound is obtained by reacting $ClCH_2(OCH_2)_mCl$ with a diprotected phosphate salt to give $ClCH_2(OCH_2)_mOP(O)(OR^Y)_2$ which is then treated with sodium iodide to give the desired product.

Yet another method suitable for preparing a subset of compounds of formula (A) in which at least one of the phosphonooxymethoxy groups is linked to the taxane moiety is shown in Scheme IV.

Scheme IV



In Scheme IV, m and n are as previously defined; X is a non-hydrogen group, P is a hydroxy protecting group; txn is a taxane moiety. Compounds of formula (D) are taxanes having a 13α-hydroxy group and one or more methylthiomethyl ether linked directly or indirectly to the taxane core; also included are C13 metal alkoxides of formula (D). An example of a compound of formula (D) is 7-O-methylthiomethylbaccatin III:



The coupling of the taxane (D) with the azetidinone is analogous to the one shown in Scheme VI, infra; thus the procedure described there for the preparation of a compound of formula (Id) is also applicable to the preparation of a compound of formula (Ba) [i.e. a compound of formula (B) in which at least one of the MTM group is linked directly or indirectly to the taxane moiety], if a compound of formula (D) is used in place of a compound of formula (II) in Scheme VI. The taxane (D) is preferably first converted to a C13 metal alkoxide such as sodium, potassium or lithium alkoxide; lithium alkoxide is preferred. The azetidinone serves as the precursor of the C13 sidechain. After the coupling reaction with a taxane, the hydroxy protecting group P is removed, and if desired, the free hydroxy group on the sidechain may be converted to the MTM ether or derivatized to an ester or a carbonate as herein described.

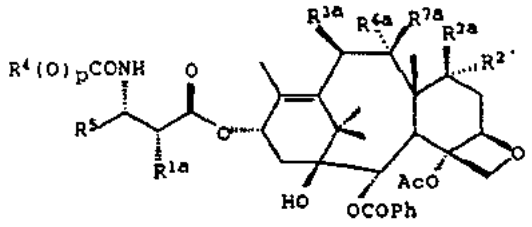
The azetidinone may be prepared by methods described later which are also methods generally known in the art. Compounds of formula (D) may be prepared by the general procedure described above for the preparation of compounds of formula (B) using a suitably protected taxane. However, more conveniently, they can be obtained from a compound of formula (Ba) by cleaving the 13-sidechain using a borohydride such as sodium or tetrabutylammonium borohydride; for example, 7-O-MTM of paclitaxel is treated with

tetrabutylammonium borohydride to give 7-O-MTM baccatin III.

The general process of Scheme I for the preparation of a compound of formula (A) is more particularly exemplified in Scheme V which illustrates the preparation of a compound of formula (I') (i.e. a compound of formula (I) in which m is 0). The procedure employed in this synthetic sequence is generally applicable to other taxane derivatives not specifically encompassed by formula (I). Furthermore, the procedure in Scheme (V) may be modified in accordance with teachings contained herein by one skilled in the art to arrive at taxane derivatives of formula (A) in which m is 1, 2 or 3.

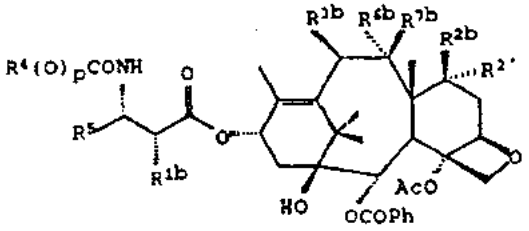
It is to be understood that in Scheme V as well as elsewhere in the specification, the term "hydroxy protecting group" may encompass suitable carbonates (e.g. -OC(O)OR^x in which R^x does not contain hydroxy); thus, when a carbonate is used as a hydroxy protecting group, it is intended to be removed in a later step to generate the free hydroxy group, otherwise, the carbonate moiety remains as part of the final product.

Scheme V



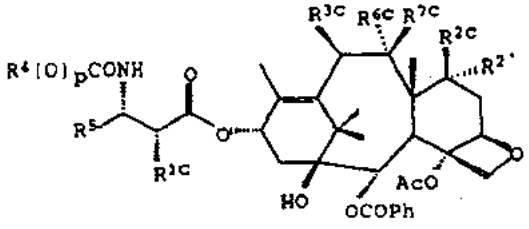
(Ia)

(1a) $SMe_2/(PhCOO)_2$
or (1b) $Ac_2O/DMSO$



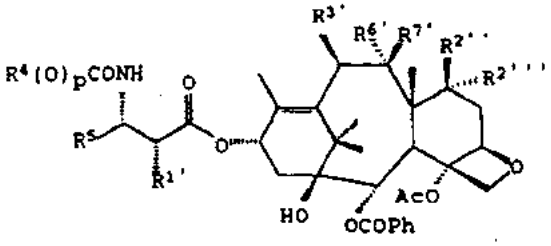
(Ib)

(2) $NIS/HOP(O)(OR^y)_2$



(Ic)

(3) removal of phosphono protecting group and, if present, hydroxy protecting group



(I')

In Scheme V, R^{1a} is hydroxy, protected hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2a} ishydrogen, hydroxy, protected hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; R^{3a} is hydrogen, hydroxy, protected hydroxy, C_{1-6}alkyloxy, $-OC(O)R^x$ or $-OC(O)OR^x$; one of R^{6a} or R^{7a} is hydrogen and the other is hydroxy, protected hydroxy or C_{1-6} alkanoyloxy; or R^{6a} and R^{7a} together form an oxo group; with the proviso that at least one of R^{1a}, R^{2a} or R^{3a}, R^{6a} or R^{7a} is hydroxy. R^{1b} is hydroxy, protected hydroxy, $-OCH_2SCH_3$, $-OC(O)-R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2b} is hydrogen, hydroxy, protected hydroxy, $-OCH_2SCH_3$, $-OC(O)-R^x$ or $-OC(O)OR^x$; R^{3b} is hydrogen, hydroxy, protected hydroxy, C_{1-6}alkyloxy, $-OC(O)R^x$, $-OCH_2SCH_3$ or

$-OC(O)OR^x$; one of R^{6b} or R^{7b} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2SCH_3$; or R^{6b} and R^{7b} together form an oxo group; with the proviso that at least one of R^{1b}, R^{2b}, R^{3b}, R^{6b} or R^{7b} is $-OCH_2SCH_3$. R^{1c} is hydroxy, protected hydroxy, $-OCH_2OP(O)(OR^y)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2c} is hydrogen, hydroxy, protected hydroxy, $-OCH_2OP(O)(OR^y)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; R^{3c} is hydrogen, hydroxy, protected hydroxy, C_{1-6} alkyloxy, $-OC(O)R^x$, $-OCH_2OP(O)(OR^y)_2$ or $-OC(O)OR^x$; one of R^{6c} or R^{7c} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2OP(O)(OR^y)_2$; with the proviso that at least one of R^{1c}, R^{2c}, R^{3c}, R^{6c} or R^{7c} is $-OCH_2OP(O)(OR^y)_2$. $R^{1'}$ is hydroxy, $-OCH_2OP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2''}$ is hydrogen, and $R^{2'''}$ is hydrogen, hydroxy, $-OCH_2OP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{3'}$ is hydrogen, hydroxy, C_{1-6} alkyloxy, $-OC(O)R^x$, $-OCH_2OP(O)(OH)_2$ or $-OC(O)OR^x$; one of $R^{6'}$ or $R^{7'}$ is hydrogen and the other is hydroxy, C_{1-6} alkanoyloxy or $-OCH_2OP(O)(OH)_2$; with the proviso that at least one of $R^{1'}$, $R^{2'''}$, $R^{3'}$, $R^{6'}$ or $R^{7'}$ is $-OCH_2OP(O)(OH)_2$. R^4, R^5, R^x, and p are as defined previously, and R^y is a phosphono protecting group.

In the first step, the free hydroxy group of a compound of formula (Ia) is converted to the corresponding methylthiomethyl ether ($-OCH_2SCH_3$) group. This conversion may be accomplished by either one of the two procedures (1a - the dimethylsulfide method) and (1b - the dimethylsulfoxide method). The dimethylsulfide method for converting alcohols to methylthiomethyl ethers is reported in Medina et al, Tet. Lett., 1988, pp. 3773-3776, the relevant portions thereof are hereby incorporated by reference. The dimethylsulfoxide method is the well-known reaction commonly known as the Pummerer reaction.

It should be noted that the reactivity of a hydroxy group differs depending on its location on the taxane derivative starting material of formula (Ia). Although in general the 2'-hydroxy group is more reactive in acylation reactions than the 7-hydroxy group which in turn is more reactive than the 10-hydroxy group, it has been found that, surprisingly with the dimethylsulfide method, the 7-hydroxy is more readily converted into the methylthiomethyl ether than the 2'-hydroxy group. The tertiary hydroxy group at C-1 is usually the least reactive. The difference in hydroxy reactivity may be exploited in controlling the site and degree of methylthiomethylation.

Thus with a compound of formula (Ia) wherein R^{1a} and R^{2a} are both hydroxy, the predominant methylthiomethylation product is the corresponding 7-O-methylthiomethyl ether with the dimethylsulfide method. In order to obtain a compound of formula (Ib) wherein R^{1b} is methylthiomethoxy, without also converting the 7-hydroxy group, if present, into a methylthiomethyl ether, the 7-hydroxy group is blocked with a conventional hydroxy protecting group such as triethylsilyl or benzyloxycarbonyl. Similarly, 10-methylthiomethyl ether may be obtained without also converting the 7- and/or 2'-hydroxy groups, if present, when the latter groups are blocked by the same of different hydroxy protecting groups. Even though the 7-hydroxy is the preferential methylthiomethylation site in the dimethylsulfide method, it is still preferable to protect the 2'-hydroxy group if the 7-monomethylthiomethyl ether is the desired product.

Moreover, the reaction conditions may be manipulated to favor the formation of bis- or trismethylthiomethyl ether taxane derivatives. For example, in the case of paclitaxel, increasing reaction time or using a larger excess of the methylthiomethylating reagents can result in a higher ratio of 2',7-bis-(methylthiomethyl) ether paclitaxel in the product mixture.

Returning now to Scheme V, in procedure (1a) a compound of formula (Ia) is treated with dimethylsulfide and an organic peroxide such as benzoyl peroxide. The reaction is carried out in an inert organic solvent such as acetonitrile, methylene chloride and the like at a temperature conducive to product formation; typically the reaction is carried at a temperature range of from about -40 °C to about ambient temperature. Dimethylsulfide and benzoyl peroxide are used in excess relative to the taxane derivative starting material (Ia), and dimethylsulfide is used in excess relative to benzoyl peroxide.

The relative amounts of starting materials used will depend on the degree of methylthiomethylation to be achieved. Thus when one free hydroxy group of the taxane derivative starting material (Ia) is to be converted to the methylthiomethyl ether, dimethylsulfide and benzoyl peroxide may be used in up to 10 fold excess relative to taxane derivative (Ia); and preferably, dimethylsulfide is used in about two to three fold excess relative to benzoyl peroxide. In the case where the starting material (Ia) has both 2'- and 7-hydroxy groups, the amount of 2',7-bis(methylthiomethyl)ether obtained increases with the relative amounts of dimethylsulfide and benzoyl peroxide. When 2',7-bis(methylthiomethyl) ether is the desired product, dimethylsulfide is preferably used in about 15 to about 20 fold excess of the taxane derivative starting material; and benzoyl peroxide is used in about 5 to about 10 fold excess relative to the taxane derivative starting material.

Alternatively, a compound of formula (Ib) may be prepared by reacting a compound of formula (Ia) with dimethylsulfoxide and acetic anhydride (procedure 1b). This procedure is suitable for derivatizing a non-2'-hydroxy group into its methylthiomethyl ether. In procedure (1b), a compound of formula (Ia) is dissolved in dimethylsulfoxide and acetic anhydride is added to the solution. The reaction is usually carried out at room

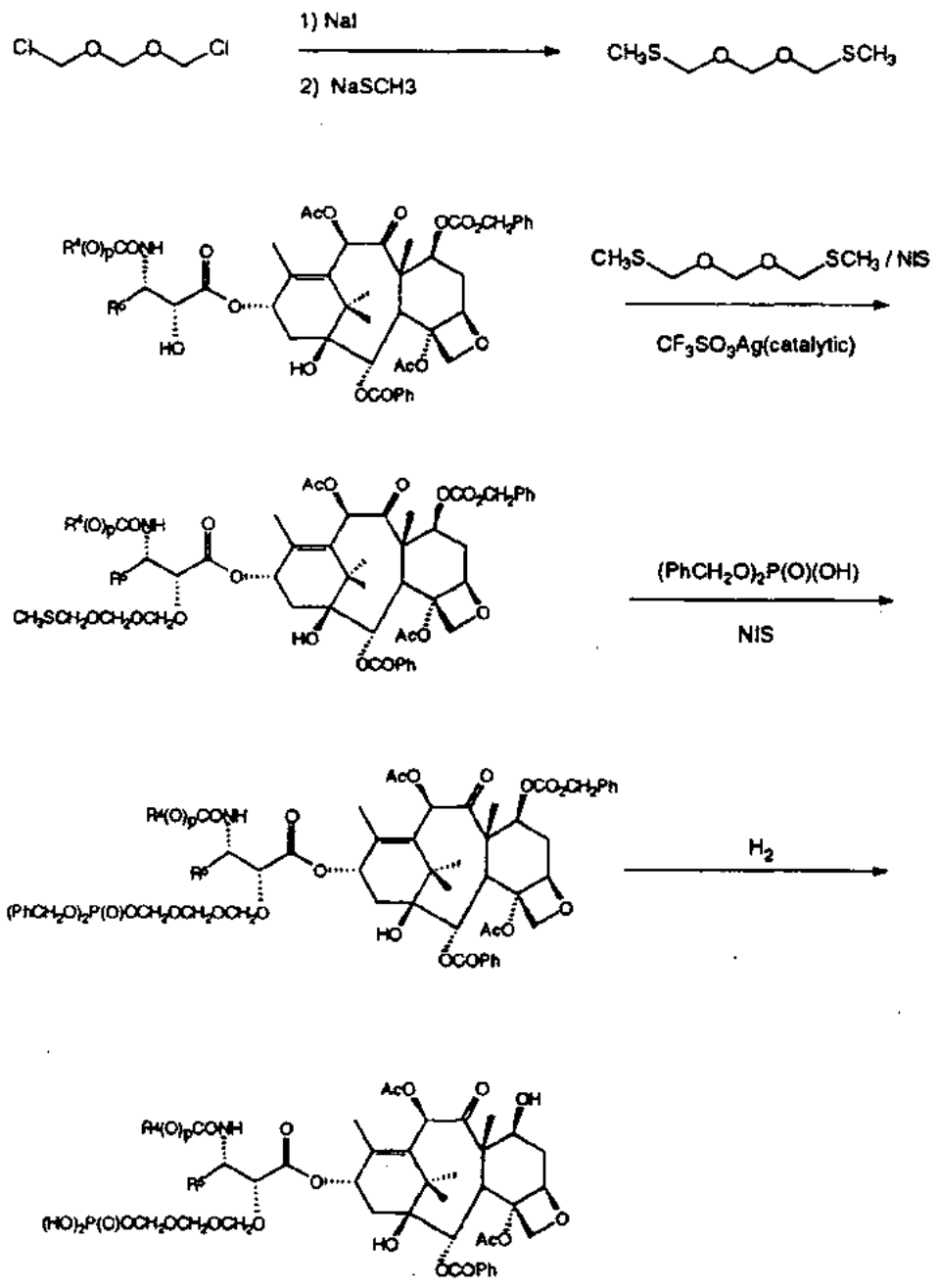
temperature, and for 18-24 hours to produce the monomethylthiomethyl ether.

In the second step of the reaction sequence, the methylthiomethyl ether is converted to the corresponding protected phosphonooxymethyl ether. The methylthiomethyl to protected phosphonooxymethyl conversion may be accomplished by the general method reported in Veeneman et al, Tetrahedron, 1991, v47, pp. 1547-1562, the relevant portions thereof are hereby incorporated by reference. Thus, a compound of formula (Ib) with at least one methylthiomethyl ether group is treated with N-iodosuccinimide and a protected phosphoric acid such as dibenzyl phosphate. The reaction is carried out in an inert organic solvent such as tetrahydrofuran or a halogenated hydrocarbon such as 1,2-dichloroethane or methylene chloride, and optionally in the presence of a dehydrating agent such as molecular sieves. A catalyst such as silver trifluoromethanesulfonate may also be added to accelerate the reaction. The reaction is carried out at a temperature ranging from about 0°C to about room temperature, preferably at room temperature. N-Iodosuccinimide and the protected phosphoric acid are used in about the same molar equivalent as the methylthiomethylether (Ib), but preferably they are used in slight excess, for example about 1.3 to about 1.5 equivalents relative to compound of formula (Ib).

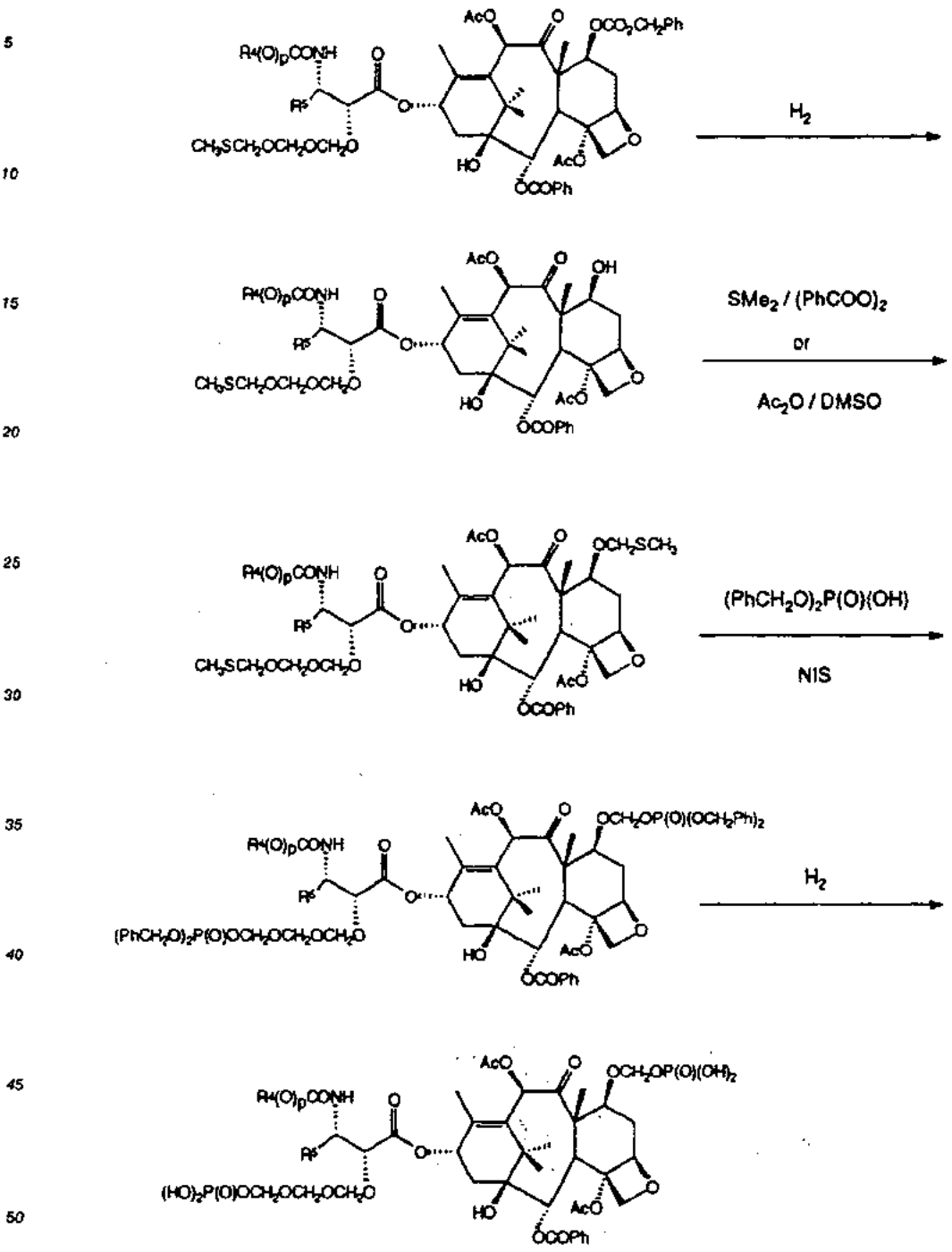
In the third step of the reaction sequence, the phosphono protecting group and hydroxy protecting group, if present, are removed. The deblocking is accomplished by conventional methods well known in the art such as acid- or base-catalyzed hydrolysis, hydrogenolysis, reduction, and the like. For example, catalytic hydrogenolysis can be used to remove the benzyl phosphono protecting group as well as the benzyloxycarbonyl hydroxy protecting group. Deprotecting methodologies may be found in standard texts such as Greene and Wutz, or McOmie, supra. Needless to say if a compound of formula (Ia) contains hydroxy groups in radical R^x, said hydroxy groups are preferably protected with suitable hydroxy protecting groups until deprotected in this last step.

As indicated earlier the procedure in Scheme V may be modified in accordance with the teaching contained herein by one skilled in the art to arrive at taxane derivatives of formula A in which m is 1, 2 or 3. As examples, Schemes Va and Vb specifically illustrate how one skilled in the art can modify the teaching contained herein to arrive at certain compounds of formula A wherein at least one substitutent is $-OCH_2-(OCH_2)_2OP(O)(OH)_2$. Similarly other compounds of formula A in which m is 3 can be readily obtained.

SCHEME Va



SCHEME Vb

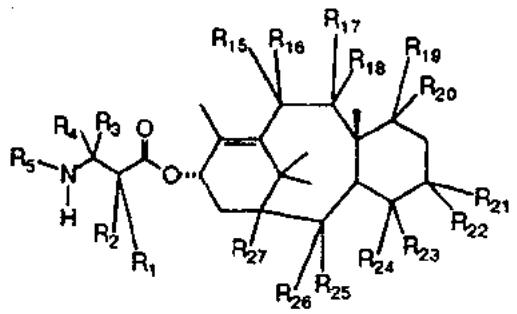


The base salts of a compound of formula (I) may be formed by conventional techniques involving contacting a compound of formula (I) free acid with a metal base or with an amine. Suitable metal bases include hydroxides, carbonates and bicarbonates of sodium, potassium, lithium, calcium, barium, magnesium, zinc, and aluminum; and suitable amines include triethylamine, ammonia, lysine, arginine, N-methylglucamine, ethanolamine, procaine, benzathine, dibenzylamine, tromethamine (TRIS), chloroprocaine, choline, diethanolamine, triethanolamine and the like. The base salts may be further purified by chromatog-

raphy followed by lyophilization or crystallization.

TAXANE DERIVATIVES STARTING MATERIALS

The processes described above may be applied to any taxane derivatives of the formula T-[OH]$_n$ to form compounds of formula (A). Many examples of T-[OH]$_n$ have been reported in the literature and some of which are listed below. (a) paclitaxel; (b) Taxotere®; (c) 10-desacetylpaclitaxel; (d) taxane derivatives disclosed in PCT application 93/06079 (published April 1, 1993) having the formula



wherein R_1 is -OR_6, -SR_7, or -NR_8R_9; R_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; R_3 and R_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or acyl, provided, however, that R_3 and R_4 are not both acyl; R_5 is -COR_{10}, -$COOR_{10}$, -$COSR_{10}$, -$CONR_8R_{10}$, -SO_2R_{11}, or -$POR_{12}R_{13}$;R_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative; R_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group; R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_9 is an amino protecting group; R_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, -OR_{10}, or -NR_8R_{14}; R_{12} and R_{13} are independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, -OR_{10}, or -NR_8R_{14}; R_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl; R_{15} and R_{16} are independently hydrogen, hydroxy, lower alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy or R_{15} and R_{16} together form an oxo; R_{17} and R_{18} are independently hydrogen, hydroxy, lower alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy or R_{17} and R_{18} together form an oxo; R_{19} and R_{20} are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; R_{21} and R_{22} are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or R_{21} and R_{22} together form an oxo; R_{24} is hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{23} and R_{24} together form an oxo or methylene or R_{23} and R_{24} together with the carbon atom to which they are attached form an oxirane ring or R_{23} and R_{22} together with the carbon atom to which they are attached form an oxetane ring; R_{25} is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{26} is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or R_{26} and R_{25} taken together form an oxo; and R_{27} is hydrogen, hydroxy or lower alkoxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; (e) taxane derivatives disclosed in U.S. Patent 5,227,400 3'-desphenyl-3'-(2-furyl) or 3'-(2-thienyl) derivatives of paclitaxel, Taxotere®; (f) taxane derivatives disclosed in EP 534,709 published March 31, 1993 (paclitaxel derivatives in which the sidechain phenyl groups are independently replaced with naphthyl, styryl or substituted phenyl). See also PCT 92/09589 published June 11, 1992; (g) taxane derivatives disclosed in EP 534,707 published March 31, 1993 (paclitaxel derivatives in which the 3'-N-benzoyl group is replaced with ethoxycarbonyl or methoxycarbonyl); (h) PCT Application 93/06093 published April 1, 1993 (10-desacetoxy derivatives of paclitaxel and Taxotere®); (i) EP 524,093 published January 20, 1993 (10-, 7-, or 7,10-bis-O-(N-substituted carbamoyl taxane derivatives); (j) 9-α-hydroxy analog of paclitaxel is disclosed in Klein, "Synthesis of 9-Dihydrotaxol: A New Bioactive Taxane," Tetrahedron Letters, 1993, 34(13):2047-2050; (k) 14-β-hydroxy analog of paclitaxel and Taxotere® prepared from 14β-hydroxy-10-deacetylbaccatin III are disclosed at the 205th ACS National Meeting in Colorado, 1993. (Med. Chem. Division, Abstract No. 28); and (l) other taxanes, such as C7-fluorotaxanes and various C10-substituted taxanes, as disclosed in European Patent Application 577,082A1 published January 5, 1994, which is herein incorporated by reference in its entirety.

The free hydroxy group or groups of taxane derivatives may be converted by conventional methods to the corresponding ester or carbonate; for example in compounds of formula (Ia) one of R^{1a}, R^{2a} or R^{3a} is

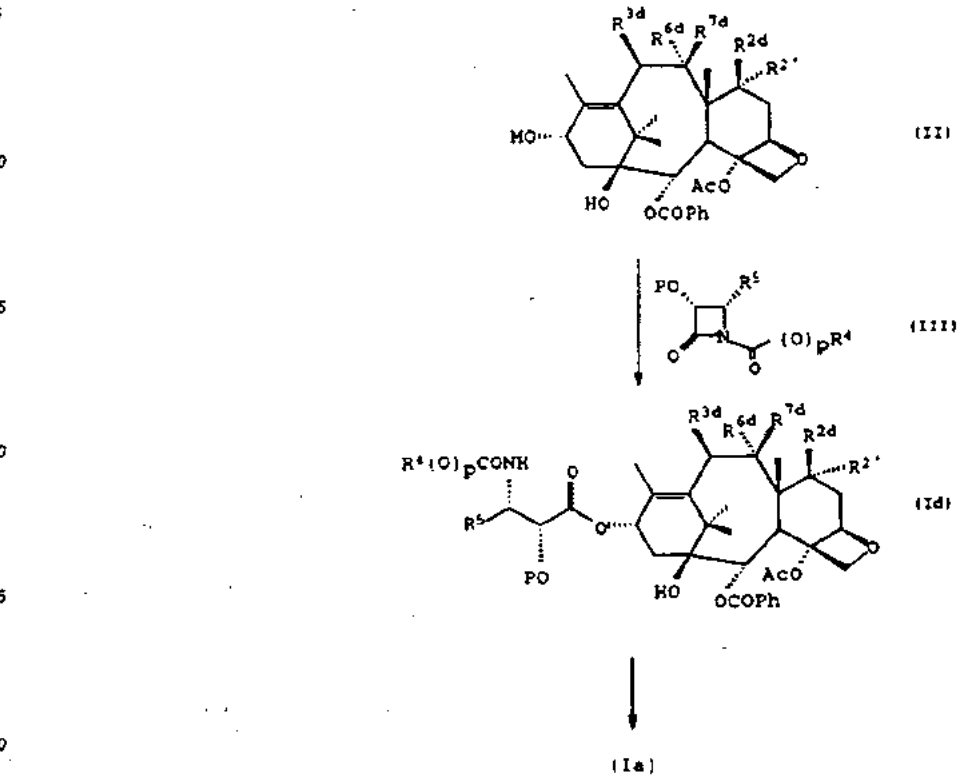
$-OC(O)R^x$ or $-OC(O)OR^x$ and R^x is as previously defined. Thus, a taxane derivative T-OH may be reacted with a compound of the formula $L-C(O)OR^x$ (L being a leaving group) such as a chloroformate in the presence of a base such as tertiary amine to give the corresponding carbonate; for example, paclitaxel reacts with ethyl chloroformate in the presence of diisopropylethylamine to provide 2'-O-ethyloxycarbonyl-paclitaxel. T-OH may also react with a carboxylic acid R^xCO_2H or an acylating equivalent thereof (e.g. an anhydride, active ester or an acyl halide) to provide the corresponding ester. Needless to point out when R^x in $L-C(O)OR^x$, or R^xCO_2H or an acylating equivalent thereof contains hydroxy groups, they are preferably protected with suitable hydroxy protecting groups.

Additionally, taxane derivatives $T-[OH]_n$ may be prepared by acylating a taxane moiety having a C13-hydroxy group with an appropriately substituted 3-amino-2-hydroxypropanoic acid, an acylating equivalent thereof, or a precursor thereof. Suitable precursors of substitutd 3-amino-2-hydroxypropanoic acid are for example azetidinones of formula (III). This acylation reaction is exemplified in the coupling of hydroxy protected baccatin III or hydroxy protected 10-deacetylbaccatin III and a phenylisoserine derivative to give paclitaxel derivatives as disclosed in e.g. Denis et al, U.S. Patents 4,924,011 and 4,924,012; and in the coupling of a protected baccatin III and an azetidinone to give paclitaxel and derivatives thereof as disclosed in EP Published Application 400,971 published December 5, 1990 (now U.S. Patent 5,175,315) and U.S. Patent 5,229,526.

The process as disclosed in EP 400,971 (the Holton process) involves reacting 1-benzoyl-3-(1-ethoxy)-ethoxy-4-phenyl-2-azetidinone with 7-O-triethylsilylbaccatin III in the presence of N,N-dimethylaminopyridine and pyridine at 25°C for 12 hours; paclitaxel is obtained after the various hydroxy protecting groups are removed. An improvement of the Holton process is reported by Ojima et al in "New and Efficient Approaches to the Semisynthesis of Taxol and its C-13 Side Chain Analogs by Means of β-Lactam Synthon Method" Tetrahedron, 1992, 48(34):6985-7012. Ojima's process involves first generating the sodium salt of 7-triethylsilylbaccatin III with sodium hydride; this salt is then reacted with chiral 1-benzoyl-3-(1-ethyoxy)-ethoxy-4-phenyl-2-azetidinone to provide paclitaxel after removal of the hydroxy protecting groups. In U.S. 5,229,526 Holton discloses the coupling of a metal alkoxide of baccatin III or a derivative thereof with a 2-azetidinone to provide taxanes with C13 sidechain. This process is said to be highly diastereoselective; therefore racemic mixtures of the sidechain precursor 2-azetidinone may be used. Recently, Ojima et al reported in "A Highly Efficient Route to Taxotere by the β-Lactam Synthon Method," Tetrahedron Letters, 1993, 34(26):4149-4152, the coupling of metal alkoxides of 7,10-bis-O-(trichloroethoxycarbonyl)-10-deacetyl-baccatin III with chiral 1-(t-butoxycarbonyl)-4-phenyl-3-(protected hydroxy)-2-azetidinone to give Taxotere® after deprotection. The relevant portions of all references cited above are hereby incorporated by reference.

The baccatin/azetidinone process generalized to the preparation of compounds of formula (Ia) is illustrated in Scheme VI. Again, other taxane derivatives not specifically encompassed within the formula (Ia) may also be prepared by this process by employing appropriate starting materials.

Scheme VI



In Scheme VI, $R^{2'}$ is hydrogen, and R^{2d} is hydrogen, protected hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; R^{3d} is hydrogen, $-OC(O)R^x$, C_{1-6}alkyloxy, protected hydroxy or $-OC(O)OR^x$; one of R^{6d} or R^{7d} is hydrogen and the other is hydroxy, protected hydroxy or C_{1-6} alkanoyloxy; or R^{6d} and R^{7d} together form an oxo group; P is a hydroxy protecting group; M is hydrogen or a Group IA metal such as lithium, sodium or potassium; and p, R^4, R^5 and R^x are as previously defined. The reaction may be conducted according to the procedure disclosed in EP 400,971 wherein the baccatin III derivative of formula (II) wherein M is hydrogen is reacted with an azetidinone of formula (III) in the presence of an organic base such as N,N-dimethylaminopyridine. Preferably, however, the baccatin III derivative is first converted to a 13-alkoxide by treating the former with a strong base such as hydrides, alkylamides, and bis(trialkylsilyl)amides of Group IA metals as disclosed in U.S. Patent 5,229,526 and the Ojima references, supra. More preferably, the 13-alkoxide is a lithium alkoxide. The formation of a lithium salt may be achieved by reacting a compound of formula (II) wherein M is hydrogen with a strong metal base, such as lithium diisopropylamide, C_{1-6} alkyllithium, lithium bis-(trimethylsilyl)amide, phenyllithium, lithium hydride, or the like base. Needless to point out that if a compound of formula (II) contains hydroxy groups in radical R^x, said hydroxy groups are preferably protected with suitable hydroxy protecting groups.

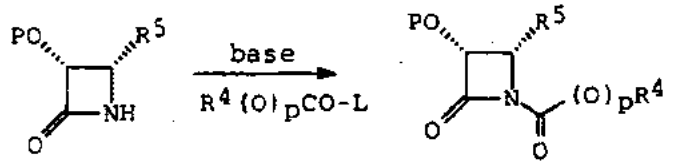
The coupling reaction between a taxane of formula (II) and an azetidinone of formula (III) is conducted in an inert organic solvent such as tetrahydrofuran at reduced temperature in the range of about 0°C to about -78°C. The azetidinones of formula (III) may be used as a racemic mixture to couple with taxane metal alkoxides of formula (II) in which M is a group 1A metal; in such case, the azetidinone reactant is preferably used in at least 2 equivalents relative to the taxane reactant, and more preferably from about 3 to about 6 equivalents. Chiral azetidinones may also be used, and in such case one equivalent of the azetidinone relative to the taxane may be sufficient, but preferably the azetidinone is used in slight excess, for example up to 1.5 equivalents.

The hydroxy protecting groups may be the same or they may be chosen in a manner to allow the selective removal of one or more protecting groups without substantially affecting the others; for example, in a compound of formula (Id), R^{2d} and PO may be both triethylsilyloxy, and R^{3d} may be benzyloxycarbonyl;

catalytic hydrogenolysis in the presence of palladium on carbon removes the benzyloxycarbonyl protecting group without removing the triethylsilyl group. Thus, the hydroxy protecting groups of a compound of formula (Id) may be selectively removed to provide a compound of formula (Ia).

Compounds of formula (Ii) are either known in the literature, e.g baccatin III, 10-deacetylbaccatin III and their hydroxy protected derivatives, or can be prepared from the known compounds by conventional conventional methods, e.g converting a hydroxy group to a carbonate. Additional compounds of formula (II) may be prepared according to procedures described hereinbelow in the section PREPARATION OF STARTING MATERIALS.

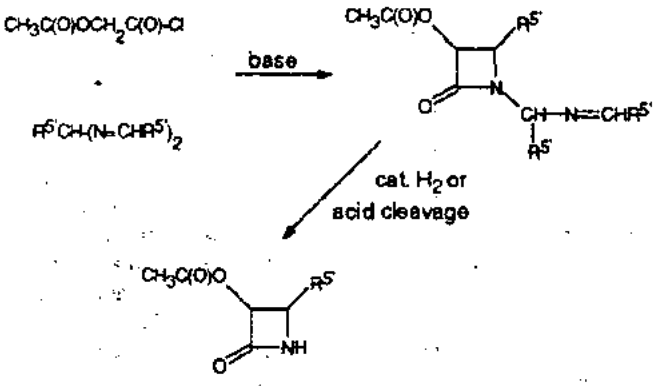
Compounds of formula (III) can be prepared from a compound of (IIIa) according to the general method described in EP 400,971 and Ojima et al, Tetrahedron, 48:6985-7012, 1992.



(IIIa) (III)

Thus a compound of formula (IIIa) is first treated with a base such as n-butyllithium or triethylamine, and then followed by a compound of the formula $R^4(O)_pCO$-L where L is a leaving group to provide a compound of formula (III).

Compounds of (IIIa) may be prepared according to the general method disclosed in EP 400,971 by going through an intermediate compound 3-acetoxy-4-substituted-2-azetidinone (IIIb); or by the method disclosed in US5,229,526 by going through an intermediate compound 3-triethylsilyloxy-4-substituted-2-azetidinone. In an improved process a compound (IIIb) may be obtained by condensing acetoxyacetyl chloride with a bis-imine followed by hydrogenolysis or acid cleavage to remove the N-imine group; this process is shown in the following scheme in which $R^{5'}$ is an optionally substituted aryl or a heteroaryl group such as furyl or thienyl. This process is disclosed in co-pending application U.S.S.N 08/165,610 filed December 13, 1993 which is hereby incorporated by reference.



The products (IIIb) obtained from these cycloaddition reactions are usually a racemic mixture of the two cis-azetidinones. The racemic mixture may be resolved by conventional methods such as conversion to diastereomers, differential absorption on column packed with chiral adsorbents, or enzymatically. For example, a racemic mixture of compounds of formula (IIIb) may be contacted with an enzyme that catalyzes the hydrolysis of an ester, for example an esterase or a lipase, to selectively cleave the 3-acyl group of one enantiomer without affecting the other. (See e.g. Brieva et al, J. Org. Chem., 1993, 58:1068-1075; also co-pending application U.S.S.N. 092,170 filed July 14, 1993, European Patent Application Number 552041, published July 21, 1993). Alternatively, the racemic mixture may be first subjected to base-catalyzed hydrolysis to remove the 3-acyl group and to generate a racemic mixture of the corresponding 3-hydroxy β-lactam; the racemic mixture of 3-hydroxy β-lactam is then contacted with an enzyme capable of catalyzing

acylation of an hydroxy group to selectively acylate the hydroxy group of one enantiomer without affecting the other. Or the racemic mixture of 3-hydroxy β-lactam may be acylated with a chiral carboxylic acid, and the resulting diastereomeric mixture may then be separated using methods known in the art, and the chiral auxiliary removed to provide the desired enantiomer.

Ojima et al, in J. Org. Chem., 56:1681-1683, 1991; Tet. Lett., 33:5737-5740, 1992; and Tetrahedron, 48:6985-7012, 1992 reported the synthesis of a number of chiral azetidinones of formula (IIIa) and/or the corresponing N-(p-methoxyphenyl) congener; wherein P is the hydroxy protecting group triisopropylsilyl; and R^5 is 4-methoxyphenyl, 3,4-dimethyoxyphenyl, phenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-furyl, 2-phenylethenyl, 2-(2-furyl)ethenyl, 2-methylpropyl, cyclohexylmethyl, isopropyl, phenethyl, 2-cyclohexylethyl, or n-propyl. Other references for making azetidinones fo formula (IIIa) and/or (III) can be found in European Patent Applications 0,534,709 A1, 0,534,708 A1, and 0,534,707 A1, all three published on March 31, 1993; in PCT application WO 93/06079 published on April 1, 1993; in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2475-2478 (1993); also in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2479-2482 (1993); in *J. Org. Chem.*, 58, pp 1068-1075; in *Tetrahedron Letters*, 31, No. 44, pp 6429-6432 (1990); in *Bioorganic and Medicinal Chemistry Letters*, 3, No. 11, pp 2467-2470 (1993); European Application 552,041 published on July 21, 1993; and in our copending U.S. Application Serial No. 092,170 filed on July 14, 1993. The relevant portions of all aforementioned references are hereby incorporated by reference. Other azetidinones within the definition of formula (III) but are not specifically disclosed in these references may be prepared by a person skilled in the art following the methodologies generally known in the art.

BIOLOGICAL EVALUATION

Compounds of formula (B) of the present invention are useful intermediates for novel antitumor agents of formula (A). In addition, some compounds within the scope of formula (B), namely compounds of formula (B'), were themselves found to be antitumor agents. Biological Section I below demonstrates the antitumor activity of the compounds of formula (A). On the other hand, Biological Section II below demonstrates the antitumor activity of the compounds of formula (B').

Biological Section I

In vitro cytotoxicity data

The compounds of formula (A) showed in vitro cytoxicity activity against human colon carcinoma cells HCT-116 and HCT-116/VM46. The HCT-116/VM46 cells are cells that have been previously selected for teniposide resistance and express the multi-drug resistance phenotype, including resistance to paclitaxel. Cytotoxicity was assessed in HCT-116 human colon carcinoma cells by XTT (2,3-bis(2-methoxy-4-nitro-5-sulfphenyl)-5-[(phenylamino)carbonyl]2H-tetrazolium hydroxide) assay as reported in D.A. Scudiero, et al., "Evaluation of soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines," Cancer Res. 48:4827-4833, 1988. Cells were plated at 4000 cells/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37°C for 72 hours at which time the tetrazolium dye, XTT, was added. A dehydrogenase enzyme in live cells reduces the XTT to a form that absorbs light at 450 nm which can be quantitated spectrophotometrically. The greater the absorbance, the greater the number of live cells. The results are expressed as an IC_{50}, which is the drug concentration required to inhibit cell proliferation (i.e., absorbance at 450 nm) to 50% of that of untreated control cells. The IC_{50} values for representative compounds evaluated in this assay are given in Table I.

Table I

In vitro cytotoxicity data against human colon carcinoma cells.		
Compound[1]	IC_{50} (μM)	
	HCT-116	HCT-116/VM46
Taxotere®	0.004	0.213
paclitaxel	0.004	0.44
Example 1	0.0158	1.24
Example 3	0.312	6.25
Example 4	0.0457	>6.3

[1]Examples 1 and 4 as free acid; example 3 as sodium salt.

The compound 7-O-methylthiomethylpaclitaxel (Example 1 (a) was also tested in the cytotoxicity assay and it showed IC_{50} of 0.003 μM against HCT-116 and 0.025 μM against HCT-116/VM46.)

In vivo antitumor activity

Balb/c x DBA_2 F_1 (CDF_1) hybrid mice were implanted subcutaneously (sc) with 0.1 ml of a 2% (w/v) brei of M109 lung carcinoma (as described in W. Rose "Evaluation of Madison 109 Lung Carcinoma as a Model for Screening Antitumor Drugs," Cancer Treatment Reports, 65, No. 3-4 pp. 299-312 (1981). The test compounds and reference drug, paclitaxel, were administered intravenously to groups of mice; each group received a compound at a different dose level, and three or four different dose levels were evaluated per compound. Mice were followed daily for survival until their death or about day 75 post-tumor implant, whichever occurred first. One group of mice per experiment remained untreated and served as the control. Tumors were also measured once or twice weekly and the size in mm was used to estimate tumor weight according to the published procedure (ibid).

Median survival times of compound-treated (T) mice were compared to the median survival time of parallel control (C) mice. The ratio of the two values for each compound-treated group of mice was multiplied by 100 and expressed as a percentage (i.e., % T/C) in Table II for representative compounds. Additionally, the difference between the median time for treated groups and that for the control group to grow tumor to 1 gm, expressed as T-C values in days, is also shown in Table II. The greater the T-C value, the greater the delay in primary tumor growth. Compounds showing % T/C ≥ 125% and/or T-C ≥ 4.0 days are considered to be active in the M109 SC model.

Table II

Compound	Maximum Effect		Opt. Dose
	% T/C	T-C (days)	(mg/kg/inj;)
Example 1[d]	131	14.0	45[a]
paclitaxel	134	14	48/24[a,c]
Example 3[d]	160	18.8	24[b]
paclitaxel	151	15	18[b]

[a]Compound was administered i.v. once daily, on days 4, 5, 6, 7 and 8 post-tumor implant.
[b]Compound was administered i.v. once daily, on days 5, 6, 7, 8 and 9 post-tumor implant.
[c]Higher dose achieved maximum increase in lifespan; lower dose associated with causing maximum delay in tumor growth.
[d]sodium salt.

Compound of Example 3 (as the triethanolamine salt) was further evaluated in murine and human xenograft tumor models (M109, A2780/cDDP - human ovarian carcinoma resistant to cisplatin, and HCT-116

- human colon carcinoma) against paclitaxel as positive control. The A2780/cDDP model is described in Rose and Basler, In Vivo, 1990, 4:391-396; the HCT-116 model is described in Rose and Basler, In Vivo, 1989, 3:249-254. M109 was passaged sc biweekly in Balb/C mice and implanted sc into CDF1 mice for antitumor evaluation. A2780/cDDP and HCT-116 were grown in athymic mice for both passage (every two to three weeks) and therapy experiments. Compound of Example 3 was administered iv in water, or orally in water with a few drops of Tween 80, while paclitaxel was either suspended in water plus Tween 80, or dissolved in cremophore/ethanol (50%/50%) and diluted with saline. The treatment regimen for the sc M109 tumor tests was once daily for 5 consecutive days beginning on Day 4 post tumor implant. For the human tumor xenograft tests, compounds were given once daily every other day for five administrations beginning when the tumors were staged to between 50 to 100 mg.

In one M109 experiment, compound of Example 3 administered iv achieved max. %T/C of 155 (T-C of 19 days) at 36 mg/kg/inj. (cf. paclitaxel max. %T/C of 132 (T-C of 13 days) at 36 or 18 mg/kg/inj.). In the same experiment, compound of Example 3 administered orally achieved a max. %T/C of 158 (T-C of 22.8 days) at a dose of 160 mg/kg/adm. while paclitaxel at the same dose (highest tested) suspended in water and Tween 80 did not show activity. In another M109 experiment, iv administered compound of Example 3 produced max. %T/C of 170 (T-C of 17 days) at 48 mg/kg/inj. (cf. paclitaxel max.%T/C of 167 (T-C of 14 days) at 48 or 36 mg/kg/inj.). In the same experiment, orally administered compound of Example 3 produced max. %T/C of 172 (T-C of 17 days) at a dose of 200 mg/kg/adm. while paclitaxel dissolved in cremophore/ethanol/saline did not show activity at 60/mg/kg/inj. In this experiment, paclitaxel dissolved in cremophore/ethanol/saline could not be administered at greater than 60/mg/kg/inj. due to solubility and toxicity constraints.

In the A2780/cDDP experiment, iv administered compounds of Example 3 showed max. T-C value of 29.8 days at 36 mg/kg/inj (cf. paclitaxel max. T-C of 26.3 days at 36 mg/kg/inj.). Orally administered compound of Example 3 produced max. T-C of 20 days at a dose of 160 mg/kg/adm. In the HCT-116 experiment, iv treatment with 24 or 36 mg/kg/inj. of paclitaxel produced 6 cures of 7 or 6 cures of 8 treated mice, respectively, and 160 or 240 mg/kg/adm. of oral compound of Example 3 cured 6 or 7 of 8 treated mice, respectively. Cure means tumor-free on Day 80 post tumor implant.

The triethanolamine salt of compound of example 1 was also found to have oral activity in the M109 and HCT-116 models.

It is well appreciated in the art that there will be some, usually slight, variations in the anti-tumor activity depending on what particular salt form is employed.

The pharmaceutically acceptable salt of phosphonooxymethyl ethers of taxane derivatives of formula (A) exhibit improved water solubility over paclitaxel thereby allowing more convenient pharmaceutical formulations. Without being bound by theory, it is believed that the phosphonooxymethyl ethers of the present invention are prodrugs of paclitaxel or derivative thereof; the phosphonooxymethyl moiety being cleaved upon contact with phosphatase in vivo to generate subsequently the parent compound.

Biological Section II

Mice M109 Model

Balb/c x DBA/2 F_1 hybrid mice were implanted intraperitoneally, as described by William Rose in *Evaluation of Madison 109 Lung Carcinoma as a Model for Screening Antitumor Drugs*, Cancer Treatment Reports, 65, No. 3-4 (1981), with 0.5 mL of a 2% (w/v) brei of M109 lung carcinoma.

Mice were treated with compound under study by receiving intraperitoneal injections of various doses on either days 1, 5 and 9 post-tumor implant or days 5 and 8 post-implant. Mice were followed daily for survival until approximately 75 - 90 days post-tumor implant. One group of mice per experiment remained untreated and served as the control group. Median survival times of compound-treated (T) mice were compared to the median survial time of the control (C) mice. The ratio of the two values for each compound-treated group of mice was multiplied by 100 and expressed as a percentage (i.e. % T/C) in Table III for representative compounds of formula (B').

Table III

EXAMPLE NUMBER	T/C (mg/kg/inj.; schedule in days)
14 (b)	143 (12; d. 5 + 9)
15	192 (8; d. 5 + 9)

As shown above, compounds of formula (A) and (B') of the instant invention are effective tumor inhibiting agents, and thus are useful in human and/or veterinary medicine. Thus, another aspect of the instant invention concerns a method for inhibiting human and/or other mammalian tumors which comprises administering to a tumor bearing host an antitumor effective amount of a compound of formula (A) or (B').

Compounds of formulas (A) and (B') of the present invention may be used in a manner similar to that of paclitaxel; therefore, an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering a compound of the present invention. The dosage, mode and schedule of administration for compounds of this invention are not particularly restricted, and will vary with the particular compound employed. Thus a compound of the present invention may be administered via any suitable route of administration, preferably parenterally; the dosage may be, for example, in the range of about 1 to about 100 mg/kg of body weight, or about 20 to about 500 mg/m^2. Compounds of formula (A) and (B') may also be administered orally; oral dosage may be in the range of about 5 to about 500 mg/kg of body weight. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient.

The present invention also provides pharmaceutical compositions (formulations) containing an antitumor effective amount of a compound of formula (A) or (B') in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. Examples of formulating paclitaxel or derivatives thereof may be found in, for example, United States Patents Nos. 4,960,790 and 4,814,470, and such examples may be followed to formulate the compounds of this invention. For example, compounds of the present invention may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. They may also be manufactured in the form of sterile solid compositions, for example, freeze dried and, if desired, combined with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use for parenteral administration.

Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly-(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), broad doublet (bd), broad triplet (bt), broad quartet (bq), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d_6 (deuterated acetone), DMSO-d_6 (per-deuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuterochloroform) and other conventional deuterated solvents. The infrared (IR) spectral description include only absorption wave numbers (cm^{-1}) having functional group identification value.

Celite is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

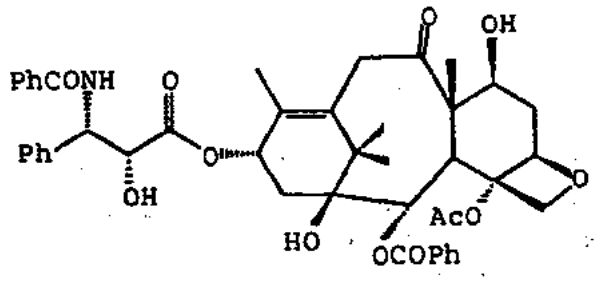
The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); v/v (volume/volume); FAB (fast atom bombardment); NOBA (m-nitrobenzyl alcohol); min (minute(s)); h or hr (s) (hour(s)); NIS (N-iodosuccinimide); BOC (t-butoxycarbonyl); CBZ or Cbz (benzyloxycarbonyl); Bn

(benzyl); Bz (benzoyl); TES (triethylsilyl); DMSO (dimethylsulfoxide); THF (tetrahydrofuran); HMDS (hexamethyldisilazane).

PREPARATION OF STARTING MATERIALS

The preparations of several specific starting materials useful in the preparation of compounds of formula (A) are exemplified below.

Preparation 1. 10-Desacetoxypaclitaxel



(a) 2',7-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetyl paclitaxel

10-Deacetyl paclitaxel (140 mg, 0.173 mmol) in dry dichloromethane (3.5 mL) was treated at 0 °C with pyridine (0.028 mL, 0.346 mmol) and trichloroethyl chloroformate (0.0724 mL, 0.260 mmol). After 1h at this temperature, the cold bath was removed and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue chromatographed on silica gel (30-50% ethyl acetate in hexane) to afford the title compound as a foam (92.3 mg, 46%). Further elution afforded unreacted starting material (35 mg, 25%), and 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetylpaclitaxel in 16% yield.

(b) 2',7-O-bis(2,2,2-trichloroethoxycarbonyl)-10-desacetoxy-11,12-dihydropaclitaxel-10,12(18)-diene

The product obtained in step (a) (92.3 mg, 0.079 mmol) in dry dichloromethane (2 mL) was treated at room temperature with 1,1,2-trifluoro-2-chlorotriethylamine (0.0384 mL, 0.238 mmol). The solution was stirred overnight. The solvent was evaporated and the residue purified by column chromatography (25% ethyl acetate in hexane) to afford the title compound as a white powder (42.8 mg, 47.3%).

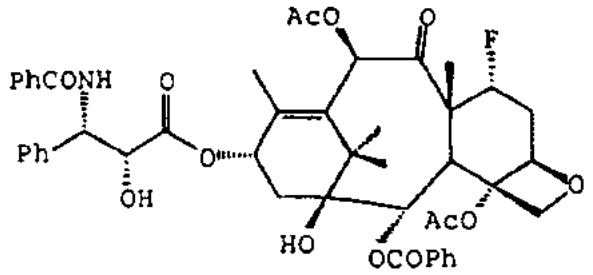
(c) 10-Desacetoxy-11,12-dihydropaclitaxel-10,12(18)-diene

The product of step (b) (39 mg, 0.034 mmol) was dissolved in methanol (0.5 mL) and acetic acid (0.5 mL), and treated with acid-washed zinc dust (66.4 mg, 1.020 mmol). The slurry was heated at 40 °C for 1h, filtered and the filtrate evaporated. Chromatography of the residue with 60% ethyl acetate/hexane gave the title compound as a foam (22 mg, 81%).

(c) 10-Desacetoxypaclitaxel

The product of step (c) (22 mg, 0.028 mmol) in ethyl acetate (0.7 mL) was hydrogenated at atmospheric pressure in the presence of palladium on charcoal (10%, 14.7 mg, 0.014 mmol Pd) After 5.5 h at RT, filtration (rinsing with ethyl acetate), evaporation and chromatography (60% ethyl acetate in hexane) gave the title product (15.0 mg, 68%) as a white foam.

Preparation 2. 7-Deoxy-7α-fluoropaclitaxel



(a) 2'-O-Benzyloxycarbonyl-7-deoxy-7α-fluoropaclitaxel

Diethylaminosulfur trifluoride (DAST, 18.7 µL, 0.141 mmol) was dissolved in dry dichloromethane (0.5 mL), and this solution was cooled to 0°C. A solution of 2'-O-(benzyloxycarbonyl)paclitaxel (71 mg, 0.072 mmol) in dichloromethane (1 mL) was added and the resulting solution was kept at 0°C for 30 min and at room temperature for 4 h. Then, water (0.15 mL) was added to the reaction mixture in order to quench the reaction and the resultant mixture was concentrated to leave a residue. The residue was chromatographed on a silica gel column (being eluted with 40% ethyl acetate in hexane) to yield 61 mg (Y: 85.7%) of a 1:1 mixture of the title compound and 2'-O-benzyloxycarbonyl-8-desmethyl-7,8-cyclopropapaclitaxel.

(b) 7-Deoxy-7α-fluoropaclitaxel

The product mixture obtained in Step (a) (89 mg) was dissolved in ethyl acetate (3 mL) and the mixture was stirred under slightly over one atmospheric pressure of hydrogen in the presence of palladium on charcoal (10% Pd, 29mg, 0.027 mmol). After 12 h, the solvent was removed, and the residue was purified by silica gel chromatography (being eluted with 40% ethyl acetate in hexane) to afford 67.7 mg of the title compound, along with 8-desmethyl-7,8-cyclopropapaclitaxel.

The following HPLC method was used to separate the 7-deoxy-7α-fluoropaclitaxel and 8-desmethyl-7,8-cyclopropapaclitaxel.

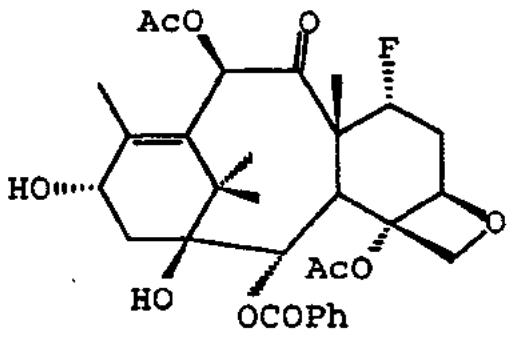
Equipment

Pump:	PE Series 4
Column:	Shandon Hypercarb (graphitized carbon), 7µ, 100 x 4.6 mm, #59864750 (information on preparative size columns may be obtained from Keystone Scientific, Bellefonte, PA)
Injector:	PE ISS-100
Detector:	HP-1040M

Conditions

Mobile Phase:	85:15 methylene chloride: hexane Separation not lost at 80:19:1 methylene chloride: hexane: isopropyl alcohol
Flow Rate:	2.5 mL/min
Detector:	254nm
Diluent:	Sample dissolved in methylene chloride

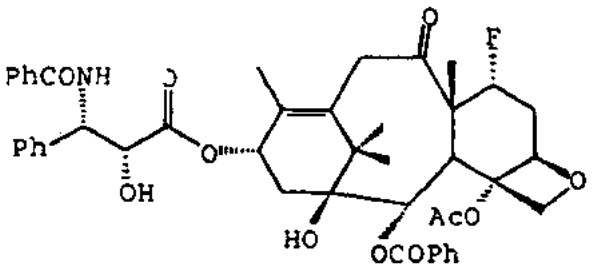
Preparation 3. 7-Deoxy-7α-fluorobaccatin III



To a dry flask under an inert atmosphere was added 2'-O-(benzyloxycarbonyl)paclitaxel (4 g, 4 mmol) and dry toluene (80 mL). The resulting slurry was stirred at ambient temperature while dry tetrahydrofuran (16 mL) was added dropwise until a colorless solution resulted. The above solution was cooled to -78 °C in a dry ice/acetone bath then treated with diethylaminosulfur trifluoride (DAST, 1.2 mL, 2.5 eq.). The reaction mixture was allowed to stir for 16h as it gradually warmed to ambient temperature. The resulting suspension was filtered and the filtrate (diluted with ethyl acetate (30 mL)) was washed with saturated aqueous sodium bicarbonate followed by brine. The organic fraction was dried ($MgSO_4$) and concentrated to give a crude product as a white foam. The crude material was partially purified by silica gel column chromatography (eluted with 10% CH_3CN in CH_2Cl_2) to afford 1.45 g of a mixture of 2'-O-(benzyloxycarbonyl)-7-deoxy-7α-fluoropaclitaxeland 2'-O-(benzyloxycarbonyl)-8-desmethyl-7,8-cyclopropapaclitaxel (82:18 mixture by ^{1}H-NMR).

The above mixture (1.45 g) was taken up in ethyl acetate (60 mL) and treated with palladium on carbon (300 mg). After shaking for 4 h under 50 pounds per square inch (psi) of hydrogen, the reaction was vented and filtered through a short plug of silica gel and concentrated. This furnished the desired product mixture, 7-deoxy-7α-fluoropaclitaxel and 8-desmethyl-7,8-cyclopropapaclitaxel, as a white foam (1.24 g, Y: 99%, 90:10 mixture by ^{1}H-NMR). This mixture was taken up in dry methylene chloride (30 mL) and treated with tetrabutylammonium borohydride (745 mg, 2.9 mmol, 2 eq) and allowed to stir for 6 h. The reaction was then quenched with acetic acid (1 mL), diluted with additional methylene chloride (30 mL) and washed with saturated aqueous sodium bicarbonate solution. The organic fraction was dried ($MgSO_4$) and concentrated. The crude, substituted taxane core mixture was partially purified by silica gel column chromatography (eluted with 10% CH_3CN in CH_2Cl_2) to give a 90:10 mixture (as determined by ^{1}H-NMR) of 7-deoxy-7-α-fluorobaccatin III and 8-desmethyl-7,8-cyclopropabaccatin III (510 mg, 60%) as a white foam. The resulting foam was crystallized from hot isopropanol to give 7-deoxy-7α-fluorobaccatin III (as small white needles (Y: 410 mg); m.p. 234-236 °C (decomposition).

Preparation 4. 10-Desacetoxy-7-deoxy-7α-fluoropaclitaxel



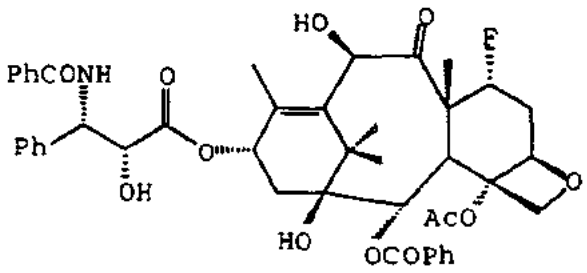
(a) 2'-O-Benzyloxycarbonyl-10-desacetoxypaclitaxel

10-Desacetoxypaclitaxel (27 mg, 0.034 mmol) in dichloromethane (1 mL) was treated with benzyl chloroformate (0.0146 mL, 0.102 mmol), followed by diisopropylethylamine (0.0177 mL, 0.102 mmol). The reaction mixture was stirred at 0 °C for 45 min, and at rt for 12 h. Evaporation of the solvent and silica gel chromatography (being eluted with 40% ethyl acetate in hexane) gave 25.5 mg (Y: 81%) of the title compound as a foam.

(b) 10-Desacetoxy-7-deoxy-7α-fluoropaclitaxel

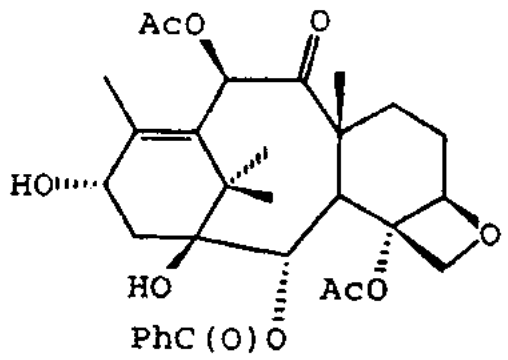
The product obtained in Step (a) (25.5 mg, 0.028 mmol) in dichloromethane (0.8 mL) at 0 °C was treated with DAST (0.0071 mL, 0.055 mmol). After 45 min at 0 °C, the reaction was allowed to proceed for 5 h at rt. Evaporation of the solvent and chromatography gave 2'-O-benzyloxycarbonyl-7-deoxy-7α-fluoropaclitaxel as a crude foam. This compound was dissolved in ethyl acetate (1 mL) and was stirred under slightly over one atmosphere of hydrogen in the presence of palladium on charcoal (10%, 8.9 mg) for 12 h at rt. The catalyst was removed by filtration and silica gel chromatography of the product gave 10 mg (Y: 40% over two steps) of the title product as a foam.

Preparation 5. 10-Deacetyl-7-deoxy-7α-fluoropaclitaxel



A solution of 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-10-deacetylpaclitaxel (120 mg, 0.103 mmol) in dichloromethane (2 mL) was cooled at 0 °C and treated with DAST (0.0266 mL, 0.207 mmol). The solution was stirred at 0 °C for 30 min and at rt for 4 h. The reaction was quenched by adding water (0.05 mL). The reaction mixture was concentrated and the residue was purified by silica gel chromatography (being eluted with 30% ethyl acetate in hexane) to afford 81 mg (Y: 68%) of 2',10-O-bis(2,2,2-trichloroethoxycarbonyl)-7-deoxy-7α-fluoropaclitaxel as a foam. This compound (63 mg, 0.054 mmol) was dissolved in methanol (0.5 mL) and acetic acid (0.5 mL) and treated with zinc dust (104 mg, 1.62 mmol) for 90 min at 45 °C. The reaction mixture was filtered and the filtrate was concentrated. Silica gel chromatography (being eluted with 40% hexane in 60% ethyl acetate) of the residue afforded 38 mg (Y: 86%) of the title compound as a white solid.

Preparation 6. 7-Deoxybaccatin III



(a) 7-O-[(Methylthio)thiocarbonyl]baccatin III

Baccatin III (750 mg, 1.278 mmol) was dissolved in dry tetrahydrofuran (20 mL) and imidazole (8.7 mg, 0.128 mmol) was added in one lot. Sodium hydride (50% in mineral oil, 77 mg, 1.597 mmol) was added at room temperature. When gas evolution had ceased (10 min), carbon disulfide (4.6 mL) was added at once. After 3 h at room temperature, the yellow solution was treated with methyl iodide (0.238 mL, 3.835 mmol) and stirred overnight. Work-up with ethyl acetate and water gave the title compound as a crude oil.

Alternate Run:

Baccatin III (394 mg, 0.672 mmol) was dissolved in tetrahydrofuran (5 mL) and carbon disulfide (1 mL). To this solution was added sodium hydride (40.3 mg, 60%, 1.009 mmol). A catalytic amount of imidazole was also added. The reaction mixture was stirred at room temperature for 1.5 h. and then methyl iodide (122.8 µL, 2.016 mmol) was added. After 40 min, the solvent was removed in vacuo, and the residue was chromatographed on silica gel (eluted with 20%-50%-60% ethyl acetate in hexanes) to afford the title product (260 mg, Y: 57.2%) together with 7-epi baccatin (98.5 mg, 25%).

(b) 7-O-[(Methylthio)thiocarbonyl]-13-O-triethylsilylbaccatin III

The product of step (a) as a crude oil was dissolved in dry dimethylformamide (5 mL) and treated with imidazole (870 mg, 12.78 mmol) and triethylsilyl chloride (2.10 mL, 12.78 mmol) at room temperature for 15 h. Addition of water was followed by extraction into ethyl acetate. The organic layer was washed extensively with water, and then dried. Silica gel flash chromatography (being eluted with 20% ethyl acetate in hexanes) gave the title compound as a glassy solid (Y: 209 mg, 20% yield over two steps).

Alternate Run:

The product of step (a) (193.4 mg, 0.286 mmol) was dissolved in dry dimethylformamide (2.86 mL). To this solution was added imidazole (77.9 mg, 1.14 mmol), followed by triethylsilyl chloride (192 µL, 1.14 mmol). The reaction mixture was stirred overnight at room temperature. After 12 h, the reaction mixture was diluted with ethyl acetate (150 mL). The organic layer was washed with water (3 X 10 mL) and brine (1 X 10 mL), dried, and concentrated in vacuo. The residue was chromatographed on silica gel (eluted with 20% Ethyl acetate in hexanes) to afford the title product (163 mg,Y: 72.0%).

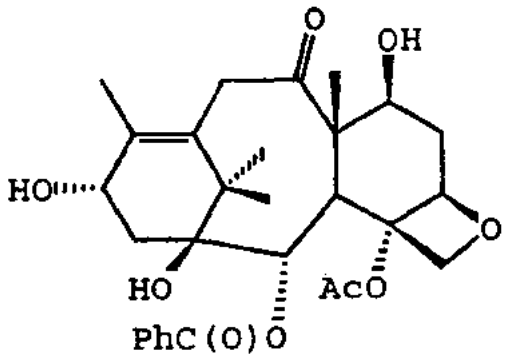
(c) 7-Deoxy-13-O-triethylsilylbaccatin III

The product of step (b) (182 mg, 0.230 mmol) in dry benzene (5 mL) was heated to 80°C in the presence of tributyltin hydride (0.310 mL, 1.150 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 10 mg). After 3h the solution was allowed to cool, and the solvent evaporated in vacuo. Silica gel chromatography of the residue (being eluted with 20% ethyl acetate in hexane) gave the title compound as an oil.

(d) 7-Deoxybaccatin III

The product of step (c) was dissolved in tetrahydrofuran (5 mL) and treated with tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.50 mL, 0.50 mmol) for 2h at room temperature. Dilution with ethyl acetate and washing with water and brine, followed by silica gel chromatography (being eluted with 1:1 ethyl acetate/hexane) gave the title compound as a white glassy solid (63 mg, Y: 58% over two steps).

Preparation 7. 10-Desacetoxybaccatin III



(a) 10-Deacetyl-10-O-(pentafluorophenoxy)thiocarbonyl-7-O-triethylsilylbaccatin III

7-O-Triethylsilyl-10-deacetylbaccatin III (see Greene et al, J. Am. Chem. Soc., 110, p. 5917, 1988) (319 mg, 0.485 mmol) was dissolved in dry tetrahydrofuran (5 mL), cooled to -40 °C, and treated with n-butyllithium (1.58M in hexanes, 0.384 mL, 0.606 mmol). After 40 min at this temperature, pentafluorophenyl chlorothionoformate (0.086 mL, 0.536 mmol) was added neat by syringe. The reaction mixture was stirred at -20 °C for 90 min, quenched with saturated ammonium chloride solution, and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated. The residue was purified by silica gel chromatography (being eluted with 40% ethyl acetate in hexane) to afford the title compound as a foam (320 mg, Y: 74%).

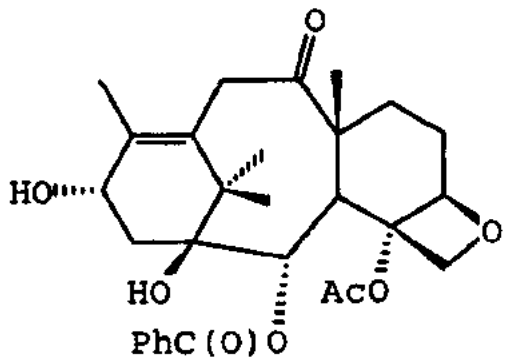
(b) 10-Desacetoxy-7-O-triethylsilylbacctain III

The product of step (a) (119 mg, 0.135 mmol) was dissolved in dry toluene (3 mL) and treated with AIBN (2 mg). The solution was degassed with dry nitrogen, then tributyltin hydride (0.055 mL, 0.202 mmol) was added. Subsequently, the solution was heated at 90 °C for 1 h. The solvent was then evaporated and silica gel chromatography of the residue (being eluted with 40% ethyl acetate in hexane) gave the title compound (87 mg, Y: 99%) as a colorless foam.

(c) 10-Desacetoxybaccatin III

The product of step (b) (120 mg, 0.187 mmol) was dissolved in acetonitrile (3.5 mL) and the solution was cooled to -10 °C. Concentrated HCl (36%, 0.060 mL) was added, and the solution was stirred for 30 min. The mixture was diluted with ethyl acetate (75 mL), and washed with saturated aqueous sodium bicarbonate and brine, then dried and concentrated. The residue was purified by flash silica chromatography (being eluted with 70% ethyl acetate in hexane) to afford 10-deacetyloxybaccatin III as a foam (75 mg, Y: 76%).

Preparation 8. 10-Desacetoxy-7-deoxybaccatin III



(a) 7-O-[(Methylthio)thiocarbonyl]-10-desacetoxybaccatin III

10-Desacetoxybaccatin III (75 mg, 0.142 mmol) was dissolved in dry tetrahydrofuran (2 mL) and carbon disulfide (0.5 mL). Sodium hydride (60% in mineral oil, 8.5 mg, 0.213 mmol) was then added, and the mixture was stirred at room temperature for 2 h. Iodomethane (0.026 mL, 0.426 mmol) was added, and the reaction was allowed to proceed overnight. The solvent was then removed and the residue was purified by silica gel chromatography (being eluted with 50-70% ethyl acetate in hexane) to give the title compound as a foam (46.4 mg, Y: 53%).

(b) 10-desacetoxy-7-deoxy-baccatin III

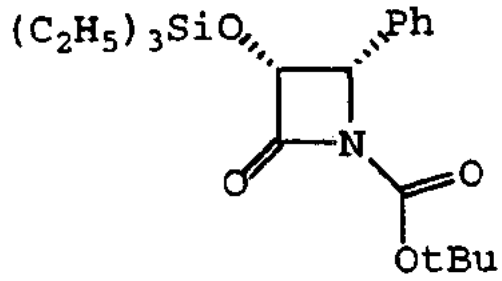
The product of step (a) (36 mg, 0.058 mmol) was refluxed in benzene (1 mL) in the presence of AIBN (2 mg) and tributyltin hydride (0.079 mL, 0.290 mmol) under an argon atmosphere for 3h. Concentration of the reaction mixture and flash silica gel chromatography of the residue (being eluted with 40% ethyl acetate in hexanes) followed by HPLC (high pressure liquid chromatography) separation from other components afforded the title compound as a foam (16.8 mg, Y: 56%).

Alternate Run:

To a solution of 7-O-[(methylthio)carbonothioyl]-13-O-triethylsilylbaccatin III (product of preparation I, step (b), 416.3 mg, 0.527 mmol) in dry toluene (10.5 mL) was added catalytic amount of AIBN, and the resulting solution was degassed with dry N_2 for 5 min. Tributyltin hydride (708.7 uL, 2.63 mmol) was the added and the reaction mixture was heated at 100°C for 2 h., after which another portion of tributyltin hydride (425.3 uL, 1.581 mmol) was added. The reaction mixture was heated for 5.5 h at 100°C, and then allowed to cool to room temperature. Silica gel chromatography (eluted with 20% ethyl acetate in hexanes) afforded 7-deoxy-10-desacetoxy-13-O-(triethysilyl)baccatin III (320 mg, Y: 97%).

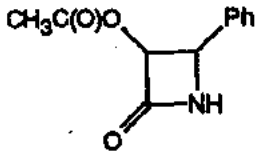
To a solution of the product of the above step (160 mg, 0.255 mmol) in dry tetrahydrofuran (2 mL) at room temperature was added tetrabutylammonium fluoride (766 uL, 1 M, 0.766 mmol). The reaction mixture was stirred for 1 h at room temperature. The solvent was removed and the residue was chromatographed on silica gel (eluted with 50-70% ethyl acetate in hexanes) to afford the desired title product (115 mg, Y: 87.9%).

Preparation 9. (3R, 4S)-1-t-Butoxycarbonyl-4-phenyl-3-triethylsilyloxy-2-azetidinone



To a stirred solution of (3R,4S)-4-phenyl-3-triethylsilyloxy-2-azetidinone (2.200 g, 7.92 mmol) in dry tetrahydrofuran (25 mL) was added N,N-diisopropylethylamine (1.65 mL, 9.510 mmol, 1.2 equiv) at 0°C under an argon atmosphere. The solution was stirred for 5 min followed by the addition of di-t-butyl dicarbonate (2.080 g, 9.510 mmol, 1.2 equiv) and 4-dimethylaminopyridine (193.6 mg, 1.581 mmol, 0.20 equiv). The reaction mixture was stirred at 0°C for 60 min., then diluted with ethyl acetate (25 mL). The resulting solution was washed with brine, 10% $NaHCO_3$, 10% HCl solution, dried ($MgSO_4$), and concentrated to give a crude compound (oil). The compound was further purified by silica gel flash chromatography (being eluted with 15% ethyl acetate in hexanes) to afford the title compound as a white solid (2.4 g, Y: 83%).

Preparation 10. (±)-cis-3-Acetyloxy-4-phenylazetidin-2-one

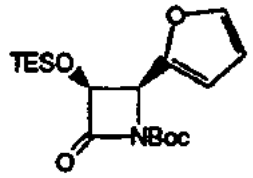


(a) To a 1 L, 3-necked round bottom flask equipped with a thermometer, magnetic stirrer and dropping funnel was added hydrobenzamide (30.00 g, 100.5 mmol) and ethyl acetate (150 mL). With stirring and under a blanket of argon, the reaction mixture was cooled to 5°C and triethylamine (16.8 mL, 121 mmol) was added. A solution of acetoxyacetyl chloride (12.4 mL, 116 mmol) in ethyl acetate (300 mL) was then added dropwise over a 90 min period. After 16 h at this temperature, the reaction mixture was allowed to warm to 20°C (1.5 h) and transferred to a separatory funnel. The organic layer was washed successively with aqueous NH_4Cl (sat) (150 mL, 100 mL), aqueous $NaHCO_3$ (saturated) (120 mL) and brine (120 mL). For purposes of characterization, the title compound can be isolated at this stage by drying the organic phase over $MgSO_4$, filtering, and removing the solvent in vacuo. This provided (±)-cis-3-acetyloxy-1-[-(phenyl)(benzylidenimino)methyl]-4-phenylazetidin-2-one in quantitative crude yield as a red glass.

(b) A solution of the compound obtained in part (a) in ethyl acetate (500 mL) was carefully transferred, under a stream of argon, to a 2.0 L Parr flask containing 10% palladium on activated charcoal (6.00 g). This mixture was treated with hydrogen (4 atm) for 20 h whereupon the catalyst was removed by filtration through a pad of Celite. The filter cake was slurried in ethyl acetate (200 mL), stirred (10 min) and filtered. The filter cake was rinsed with ethyl acetate (100 mL) and the filtrates combined. The organic layer was washed with 10% HCl (300 mL) and both layers filtered through a sintered glass funnel to remove the white precipitate (dibenzylamine-HCl) which was rinsed with ethyl acetate (100 mL). The phases were separated and the organic layer was washed with another portion of 10% HCl (200 mL). The combined 10% HCl washes were re-extracted with ethyl acetate (200 mL) and the combined organic layers were washed with aqueous $NaHCO_3$ (saturated) (300 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a final volume of 75 mL. This mixture was cooled to 4°C and the precipitated product isolated by filtration. The filter cake was washed with hexane (200 mL) to provide 16.12 g (78.1% overall yield from hydrobenzamide) of the title compound as white

needles.
mp = 150-151 °C

Preparation 11. (±)- cis-3-Triethylsilyloxy-4-(2-furyl)-N-t-butoxycarbonylazetidin-2-one



(a) The procedure described in Preparation 10, part (a), was followed except that hydrofuramide [i.e. 2-furyl-CH-(N = CH-2-furyl)$_2$] was used instead of hydrobenzamide and the reaction was performed on 18.6 mmol (vs 100 mmol) scale. Thus, hydrofuramide (5.00 g, 18.6 mmol), triethylamine (3.11 mL, 22.3 mmol) and acetoxyacetyl chloride (2.30 mL, 21.4 mmol) gave 6.192 g (Y: 90.4%) of (±)-cis-3-acetyloxy-1-[(2-furyl)(2-furylmethylenimino)methyl]-4-(2-furyl)azetidin-2-one as a pale red syrup.

(b) The procedure described in Preparation 10, part (b), was followed except that the product was isolated by preparative TLC and the reaction was performed on the 2.7 mmol scale based on the original amount of hydrofuramide. Thus, the crude product obtained in part (a) above was re-dissolved in ethyl acetate (50 mL) and added to 10% palladium on activated charcoal (150 mg). Purification of the crude solid by preparative TLC (2 mm silica gel, eluted with 1:1 ethyl acetate/hexane) gave 386 mg (65.8% corrected overall yield from hydrofuramide) (±)-cis-3-(acetyloxy)-4-(2-furyl)azetidin-2-one as a yellow solid. This was recrystallized from ethyl acetate/hexane.
mp = 118-119 °C

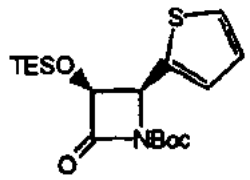
(c) The compound obtained in part (b) above (3.78 g, 19.4 mmol) in 60 mL of methanol was stirred with K_2CO_3 (20 mg, 0.14 mmol) for 90 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 80 mL of anhydrous THF and stirred at 0 °C with imidazole (1.44 g, 21.2 mmol) and TESCl (3.4 mL, 20.2 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 4.47g (Y: 86%) of (±)- cis-3-triethylsilyloxy-4-(2-furyl)-azetidin-2-one as a colorless oil.

(d) The product of part (c) (2.05 g, 7.7 mmol) in 30 mL of dichloromethane was stirred at 0 °C with diisopropylethyl amine (1.5 mL, 8.6 mmol) and di-t-butyl dicarbonate (2.0g, 9.2 mmol) in addition to a catalytic amount of dimethylaminopyridine (DMAP). The solution was diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 8:1 hexane/ethyl acetate) to give 2.0 (Y: 70%) of the title compound as a waxy solid.

The racemic mixture obtained in part (b) may be used as substrate for enzymatic hydrolysis using a lipase such as PS-30 from Pseudomonas sp. (Amano International Co.) to give (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one. The method of enzymatic resolution using the lipase PD-30 and other enzymes is disclosed in our co-pending application U.S.S.N. 092,170, filed July 14, 1993 which is hereby incorporated by reference in its entirety.

The procedure in parts (c) and (d) was followed using (3R,4R)-3-hydroxy-4-(2-furyl)-azetidin-2-one to provide (3R,4R)-N-(t-butoxycarbonyl)-3-triethylsilyoxy-4-(2-furyl)azetidine-2-one.

Preparation 12. (±)- cis-3-Triethylsilyloxy-4-(2-thienyl)-N-t-butoxycarbonylazetidin-2-one



(a) The procedure described in Preparation 10, step (a) was followed except that hydrothienamide [i.e. 2-thienyl-CH-(N = CH-2-thienyl)$_2$] was used instead of hydrobenzamide. Thus, hydrothienamide (30 g, 94.7 mmol), thiethylamine (15.84 mL, 114 mmol) and acetoxyacetyl chloride (11.6 mL, 108 mmol) provided (±)-cis-3-acetyloxy-1-[(2-thienyl)(2-trienylmethylenimino)methyl]-4-(2-thienyl)azetidin-2-one as viscous oil.

(b) A 70% aqueous solution of acetic acid (0.35 mL glacial acetic acid and 0.15 mL water) was added in one portion to a stirred solution of the product obtained in part (a) (.431 g, 1.03 mmol) in dichloromethane (2.93 ml) at 25 °C. The reaction mixture was brought to reflux and stirred for 2.5 h. The reaction was diluted with 50 mL dichloromethane and then washed with two 75 mL portions of saturated aqueous sodium bicarbonate and then one 50 mL portion of saturated brine. The organic extract was concentrated *in vacuo* to a brown oil, dissolved in a minimal amount of dichloromethane, and then placed on a silica gel column measuring 4" by 0.5". Elution using a gradient of 10 through 60% EtOAc in hexane provided less polar sideproducts and then (±)-cis-3-acetyloxy-4-(2-thienyl)azetidin-2-one (0.154 g, Y: 75%) as a white solid.

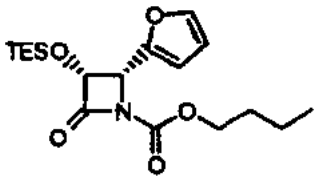
(c) A solution of the product obtained in part (b) (2.5 g, 11.8 mmol) was dissolved in methanol (10 mL) and treated with saturated aqueous sodium bicarbonate (10 mL) and the resulting slurry was allowed to stir at ambient temperature for 3 h. The reaction was then diluted with ethyl acetate (20 mL) and washed with water (15 mL). The aqueous fraction was back extracted several times with ethyl acetate and the combined organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid (Y: 1.7 g). The crude material was dissolved in dry tetrahydrofuran (20 mL) and the solution was cooled to 5 °C in an ice/water bath. Imidazole (752 mg, 1.1 eq) was then added. After stirring 5 min, triethylchlorosilane (1.85 mL, 1.1 eq) was added dropwise. The resulting suspension was allowed to stir for 3 h at that temperature; then the solids were removed by filtration. The organic fraction was washed with water (2x 20 mL) then dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (eluted with hexanes/ethyl acetate 7:3) to give (±)-cis-3-triethylsilyloxy-4-(2-thienyl)-azetidin-2-one as a colorless solid (1.5 g, Y: 45%), m.p. 70-71 °C.

Alternate Run:

The product obtained in part (b) (2.0 g, 9.37 mmol) in 40 mL of methanol was stirred with K_2CO_3 (60 mg, 0.43 mmol) for 30 min and the solution neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue dissolved in 50 mL of anhydrous THF and stirred at 0 °C with imidazole (0.85 g, 11.3 mmol) and TESCl (1.9 mL, 12.5 mmol) for 30 min. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 2.13g (Y: 86%) of the title product as a colorless oil.

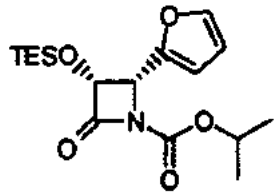
(d) A solution of the product obtained in part (c) (425.7 mg, 1.48 mmol) was dissolved in dichloromethane (10 mL) and cooled to 5 °C in an ice/water bath. The reaction was treated with a catalytic amount of DMAP followed by diisopropylethylamine (TESCl, 0.25 mL, 1.0 eq) then by di-t-butyl dicarbonate (388.4 mg, 1.2 eq). After stirring 2 h at that temperature the reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and the organic fraction was washed with water (5 mL) then dried ($MgSO_4$), passed through a short plug of silica gel and concentrated to give the desired product as a colorless oil (525.3 mg, Y: 93%).

Prepartion 13. (3R, 4R)-3-Triethylsilyloxy-4-(2-furyl)-N-n-butyloxycarbonylazetidin-2-one



(3R,4R)-3-Triethylsilyloxy-4-(2-furyl)azetidin-2-one (0.58 g, 2.17 mmol) in 30 mL of dichloromethane was stirred with diisopropylethyl amine (0.4 mL, 2.30 mmol) and butylchloroformate (0.3 mL, 2.36 mmol) in addition to a catalytic amount of DMAP. The solution was stirred for 1 h and diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 3:1 hexane/ethyl acetate) to give 523 mg of product (Y: 65%); IR(KBr) 1820, 1734, 1318, 1018, 734 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 1H), 6.35 (m, 2H), 5.09 (ABq, J = 15.5, 5.6 Hz, 2H), 4.14 (m, 2H), 1.56 (m, 2H), 1.28 (s, 2H), 0.87 (t, J = 8.7 Hz, 3H), 0.82 (t, J = 7.9, 9H), 0.50 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 165.4, 149.1, 147.6, 142.9, 110.5, 109.9, 77.7, 66.6, 55.9, 30.5, 18.8, 13.6, 6.3, 4.3; DCIMS M + H calcd for $C_{18}H_{29}NO_5Si$: 368, Found: 368.

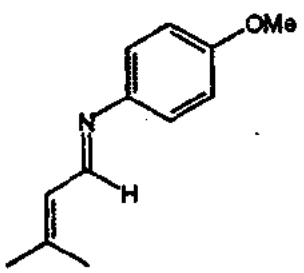
Preparation 14. (3R,4R)-3-Triethylsilyloxy-4-(2-furyl)-N-isopropyloxycarbonylazetidin-2-one



(3R, 4R)-3-Triethylsilyloxy-4-(2-furyl)azetidin-2-one (0.51 g, 1.91 mmol) in 25 mL of dichloromethane was stirred with diisopropylethyl amine (0.78 mL, 4.4 mmol) and i-propylchloroformate (4.0 mL, 1.0M in toluene, 4.0 mmol) in addition to a catalytic amount of DMAP. The solution was stirred for 1 h and diluted with dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (eluted with 5:1 hexane/ethyl acetate) to give 649 mg of the title product (Y: 96%); IR(KBr) 1822, 1812, 1716, 1374, 1314, 1186, 1018, 1004, 746 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 1H), 6.35 (m, 2H), 5.08 (ABq, J = 15.6, 5.6 Hz, 2H), 4.96 (d, J = 10.0 Hz, 1H), 1.25 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H)), 0.83 (t, J = 7.8, 9H), 0.50 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 165.5, 148.6, 147.8, 142.9, 110.5, 109.9, 77.6, 71.1, 55.9, 21.7, 21.6, 6.3, 4.4; DCIMS M + H calcd for $C_{17}H_{28}NO_5Si$: 354, Found: 354.

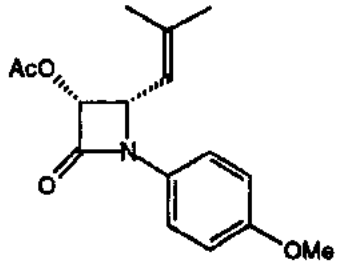
Preparation 15. (±)-cis-3-Triethylsilyloxy-4-isobutenyl-N-t-butoxycarbonylazetidin-2-one

(a) N-4-methoxy-N-(3-methyl-2-butenyl)benzenamine



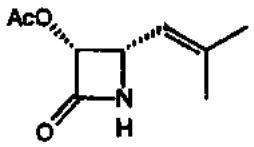
A solution of p-anisidine (5.7 g, 46.3 mmol) was dissolved in diethylether (100 mL) and was treated with a catalytic amount of p-toluensulfonic acid (10 mg). To this was added 3-methyl-2-butenal (2.67 mL, 50.9 mmol) in one portion and the reaction was allowed to stir at ambient temperature for 16 h. The solvent was then evaporated on a rotary evaporator at 0.5 torr to furnish the desired imine (8.7 g, 100%) as a brown oil; ^{1}H NMR 300 MHz, $CDCl_3$): δ 8.38 (d, 1H, J = 9.5 Hz), 7.11 (dd, 2H, J = 2.2, 6.7 Hz), 6.88 (dd, 2H, J = 2.2, 6.7 Hz), 6.22-6.18 (m, 1H), 3.81 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H).

(b) (±)-cis-N-(4-methoxyphenyl)-3-acetyloxy-4-isobutenylazetidin-2-one



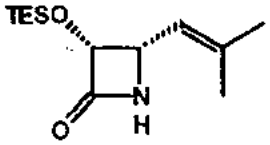
A solution of acetoxyacetyl chloride (6.9 g, 50.5 mmol) was dissolved in ethyl acetate (100 mL) and cooled to -30 °C under an inert atmosphere. To this solution was added triethylamine (7.0 mL, 50.5 mmol) over a 5 min period. The resulting white slurry was then treated with an ethyl acetate solution of N-4-methoxy-N-(3-methyl-2-butenyl)benzenamine (8.7g, 40 mL) dropwise over a 20 min period. The resulting green-brown slurry was then gradually allowed to warm to ambient temperature over a 4 h period. The slurry was then filtered through a pad of celite and the filtrate was washed with water then brine. The organic fraction was dried ($MgSO_4$) and concentrated to give a brown oil. The crude product was purified by careful silica gel chromatography (eluted with hexanes/ethyl acetate 8:2) to furnish an orange oil which solidified on standing. This was recrystallized from dichloromethane/hexanes to furnish the desired product as a pale yellow solid (4.4 g, 32%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, J = 9.1 Hz), 6.86 (d, 2H, J = 9.1 Hz), 5.59 (dd, 1H, J = 3.0, 7.8 Hz), 5.14-5.10 (m, 1H), 4.96 (dd, 1H, J = 4.8, 9.3 Hz), 3.77 (s, 3H), 2.11 (s, 3H,), 1.81 (s, 3H), 1.78 (s, 3H).

(c) (±)-cis-3-Acetyloxy-4-isobutenylazetidin-2-one



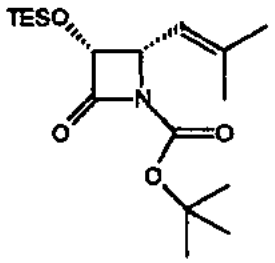
A solution of the (±)-cis-N-(4-methoxyphenyl)-3-acetyloxy-4-isobutenylazetidin-2-one (4.88g, 16.2 mmol) was dissolved in acetonitrile (50 mL) and cooled to 0-5 °C in an ice bath. To this was added a cold solution of ceric ammonium nitrate (26.6 g, 48.6 mmol, 50 mL) in one portion. The deep red reaction was allowed to stir for 10 min and during that time the color gradually lightened to orange. The cold solution was transferred to a separatory funnel, diluted with water, and extracted with ethyl acetate. The organic fraction was washed with several portions of 10% aqueous sodium sulfite, followed by saturated aqueous sodium bicarbonate. The organic fraction was dried ($MgSO_4$) and concentrated to give the desired product (2.71g, 91%) as a yellow-orange solid that was used directly in the next step; ^1H NMR (300 MHz, $CDCl_3$): δ 6.11 (bs, 1H), 5.73 (dd, 1H, J= 2.2, 4.7 Hz), 5.12-5.08 (m, 1H), 4.63 (dd, 1H, 4.7, 9.1 Hz), 2.09 (s, 3H), 1.75 (s, 3H), 1.67 (s, 3H).

(d) (±)-cis-3-Triethylsilyloxy-4-isobutenylazetidin-2-one



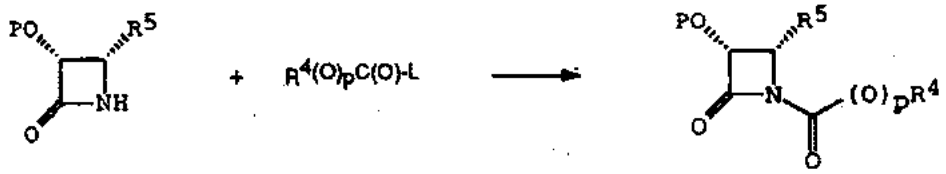
(±)-cis-3-Acetyloxy-4-isobutenylazetidin-2-one (1.47 g, 8.0 mmol) was dissolved in methanol (15 mL) and was stirred with K_2CO_3 (110.5 mg,0.8 mmol) for 3h at ambient temperature. The solution was then neutralized with Dowex 50W-X8 resin and then filtered. The filtrate was concentrated and the crude solid was dissolved in THF (25 mL) and cooled to 5 °C in an ice bath. Imidazole (544.0 mg, 8.0 mmol) was added and once dissolved, triethylsilyl chloride (1.34 mL, 8.0 mmol) was added dropwise via syringe. The resulting slurry was allowed to warm to ambient temperature and stir overnight. The solution was filtered and the filtrate was washed with water, then brine. The organic fraction was dried ($MgSO_4$) and concentrated. The crude solid was purified by silica gel chromatography (eluted with hexanes/ethyl acetate 3:1) to furnish the desired product (612 mg, 30%) as a pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87 (bs, 1H), 5.31-5.26 (m, 1H), 4.90 (dd, 1H, J= 2.2, 4.7 Hz), 4.42 (dd, 1H, J= 4.7, 9.3 Hz), 1.74 (s, 3H), 1.28 (s, 3H), 0.98-0.91 (m, 9H), 0.71-0.55 (m, 6H).

(e) (±)-cis-3-Triethylsilyloxy-4-isobutenyl-N-t-butoxycarbonylazetidin-2-one



(±)-cis-3-Triethylsilyloxy-4-isobutenylazetidin-2-one (1.01 g, 3.95 mmol) was dissolved in dichloromethane (20 mL) and was treated with diisopropylethylamine (0.68 mL, 3.95 mmol) and a catalytic amount of dimethylaminopyridine. To this solution was added di-t-butyl dicarbonate (1.02 g, 4.68 mmol) and the solution was allowed to stir for 24 h at ambient temperature. The solution was then diluted with additional dichloromethane and washed with water then brine. The organic fraction was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (eluted with hexanes/ethyl acetate 8:2) to give the desired product (1.26 g, 90%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.24 (d, 1H, J= 9.6 Hz), 4.86 (d, 1H, J= 5.7 Hz), 4.72 (dd, 1H, J= 6.0, 9.9 Hz), 1.78 (d, 3H, J= 1.1 Hz), 1.75 (d, 3H, J= 1.1 Hz), 1.47 (s, 9H), 0.96-0.91 (m, 9H), 0.64-0.55 (m, 6H).

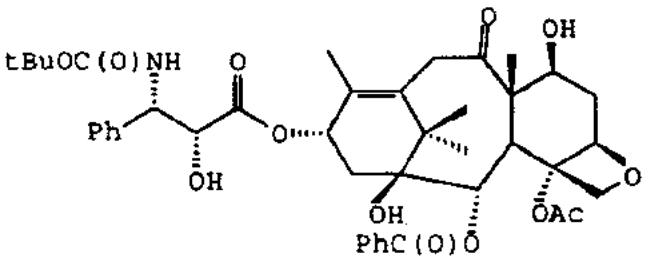
The procedure described above in Preparations 9, 11(d), 12(d), 13, 14, and 15(e) may be adapted to the preparation of other N-substituted azetidinones useful in the preparation of compounds of the invention. Examples of such azetidinones are listed in the following table; P below is a hydroxy protecting group such as triethyl silyl, triisopropylsilyl and ethoxyethyl.



L	$R^4(O)_p$	R^5
Cl	Ph	4-CH_3O-Ph-
		3,4-diCH_3O-Ph-
		Ph-
		4-F-Ph-
		4-CF_3-Ph-
		2-furanyl-
		2-thienyl-
		PhCH=CH-
		2-furanyl-CH=CH-
		$(CH_3)_2CHCH_2$-
		C_6H_{11}-CH_2-
		$(CH_3)_2CH$-
		$PhCH_2CH_2$-
		C_6H_{11}-CH_2CH_2-
		$CH_3CH_2CH_2$-
		4-Cl-Ph
		2-F-Ph
		3-F-Ph
		4-CH_3-Ph
		$(CH_3)_2C$=CH

L	$R^4(O)_p$	R^5
Cl	4-CH_3O-Ph-	3,4-diCH_3O-Ph- 4-CF_3-Ph- 2-furanyl- PhCH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $PhCH_2CH_2$-
$(CH_3)_3COCO_2$-	$(CH_3)_3CO$-	4-CH_3O-Ph- 4-F-Ph- 4-CF_3-Ph- PhCH=CH- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-
Cl	CH_3-	4-CH_3O-Ph- Ph- 4-F-Ph- 2-furanyl- 2-furanyl-CH=CH- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-

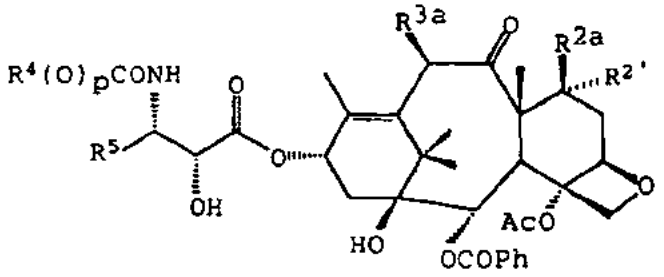
Preparation 16. 10-deoxytaxotere



10-Desacetoxy-7-O-triethylsilylbaccatin III (100 mg, 0.156 mmol) was placed in a flask under argon and dissolved in dry tetrahydrofuran (1.5 mL). Upon cooling to -40°C, n-butyllithium (1.45M in hexanes, 0.119 mL, 0.170 mmol) was added dropwise, followed by (3R,4S)-1-tert-butoxycarbonyl-4-phenyl-3-triethylsilyloxy-2-azetidinone (94.2 mg, 0.25 mmol) in tetrahydrofuran (0.5 mL) over a period of 2 min. The mixture was immediately warmed to 0°C and stirred for 45 min before being quenched with saturated ammonium chloride (3 mL). The mixture was extracted with ethyl acetate, dried, and concentrated. Silica gel

chromatography (eluted with 30% ethyl acetate in hexane) afforded 10-deoxy-2',7-bis-O-(triethylsilyl)-taxotere as a foam (125 mg, Y: 76%). This compound (100 mg, 0.098 mmol) was immediately dissolved in acetonitrile (2 mL) at -5°C and treated with hydrochloric acid (0.037 mL, 36%, 12M). The mixture was stirred for 2h at -5°C, then quenched with aqueous bicarbonate, extracted with ethyl acetate, and dried. Evaporation of the solvent was followed by silica gel chromatography (eluted with 75% ethyl acetate in hexane) to afford the title compound as a foam (80.5 mg, Y: 80%).

The general procedure provided in Preparation 16 may be adapted to the preparation of other compounds of formula (Ia) by starting with the appropriate baccatin III component and the azetidinone component; examples of other compounds of formula (Ia) are listed in the following table. It will be understood that even though the compounds below are shown with free hydroxy groups, with the judicious selection of the various hydroxy protecting groups, any one of the protecting groups at the 2'-, 7- or 10-position may be selectively removed without affecting other protecting groups present.



$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_p$	R^5
H	OH	AcO	Ph	4-CH_3O-Ph-
				3,4-diCH_3O-Ph-
				Ph-
				4-F-Ph-
				4-CF_3-Ph-
				2-furanyl-
				2-thienyl-
				PhCH=CH-
				2-furanyl-CH=CH-
				$(CH_3)_2CHCH_2$-
				C_6H_{11}-CH_2-
				$(CH_3)_2CH$-
				$PhCH_2CH_2$-
				C_6H_{11}-CH_2CH_2-
				$CH_3CH_2CH_2$-
				4-Cl-Ph
				2-F-Ph
				3-F-Ph
				4-CH_3-Ph

$R^{2'}$	R^{2a}	R^{3a}	$R^4(O)_p$	R^5
H	OH	OH	$(CH_3)_3CO$	4-CH_3O-Ph- Ph 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$-
	OH	H	Ph	4-CH_3O-Ph- 3,4-diCH_3O-Ph- 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- 2-furanyl-CH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-

$R^{2'}$	$R^{2\alpha}$	$R^{2\beta}$	$R^4(O)_p$	R^5
	H	H	$(CH_3)_3CO$	4-CH_3O-Ph- 3,4-diCH_3O-Ph- Ph- 4-F-Ph- 4-CF_3-Ph- 2-furanyl- 2-thienyl- PhCH=CH- 2-furanyl-CH=CH- $(CH_3)_2CHCH_2$- C_6H_{11}-CH_2- $(CH_3)_2CH$- $PhCH_2CH_2$- C_6H_{11}-CH_2CH_2- $CH_3CH_2CH_2$-
H	OH	AcO	2-naphthyl 4-OH-Ph 4-CH_3O-Ph 4-F-Ph $(CH_3)_3CO$- CH_3- $(CH_3)_2CH$- CH_2=$CHCH_2$- 4-Cl-Ph	Ph
F	H	AcO	$(CH_3)_3CO$-	Ph
F	H	OH	Ph	Ph

R^2	R^{2a}	R^{2a}	$R^4(O)_p$	R^6
H	H	AcO	Ph	4-CH_3O-Ph-
				3,4-diCH_3O-Ph-
				Ph-
				4-F-Ph-
				4-CF_3-Ph-
				2-furanyl-
				2-thienyl-
				PhCH=CH-
				2-furanyl-CH=CH-
				$(CH_3)_2CHCH_2$-
				C_6H_{11}-CH_2-
				$(CH_3)_2CH$-
				$PhCH_2CH_2$-
				C_6H_{11}-CH_2CH_2
				$CH_3CH_2CH_2$-

Preparation 17. Bis(methylthiomethyl)ether

$CH_3SCH_2OCH_2SCH_3$

Sodium iodide (8.23g, 55.23 mmol) was added to a solution of 1,1'-dichlorodimethyl ether (3.0g, 26.3 mmol) in acetone (100 ml) at 0°C and the mixture was stirred at this temperature for 20 min. Sodium thiomethoxide (1.84g, 5.23 mmol) was then added in four portions and the resulting solution was stirred for an additional 1h. The heterogeneous solution was then filtered through a pad of celite and the filtrate concentrated in vacuo. The residual oil was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was removed and further extracted with ethyl acetate. The combined organics were then treated with a 1:1 (v:v) mixture of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution. The organics were then washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (30:1, hexanes:ethyl acetate) to provide 1.9 g of a yellow oil which was subsequently distilled using a kugelrhor apparatus (120-130°C, 20mmHg) yielding 1.5 g (45%) of the title compound as colorless oil:
^{1}H NMR (300 MHz, CDCl3) δ 4.73 (4H, s), 2.15 (6H, s).

Preparation 18. Dibenzyl methylthiomethyl phosphate

$CH_3SCH_2OP(O)(OBu)_2$

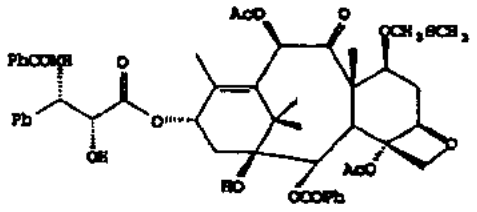
To a solution of bis(methylthiomethyl)ether (30 mg, 2.34 mmol) and molecular sieves (300 mg) in THF (100 ml) at room temperature was added dibenzyl phosphate (2.74 g, 9.85 mmol) followed by N-iodosuccinimide (608 mg, 2.71 mmol) and the solution was stirred for 4h. The reaction mixture was then diluted with ethyl acetate and filtered through a pad of celite. The filtrate was treated with a 1:1 (v:v) solution of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate. The colorless organic extract was then washed with brine, dried over sodium sulfate and concentrated in vacuo to provide 600 mg (69%) of the title compound:
^{1}H NMR (300 MHz, CDCl3) δ 7.35 (10H, s), 5.29 (2H, d, J = 12.2 Hz), 5.08 (4H, dd, J = 8.0, 1.0 Hz), 4.68 (2H, s), 2.10 (3H, s).

EXAMPLES

The following examples are provided to illustrate the synthesis of representative compounds of the instant invention and are not to be construed as limiting the scope of the invention in any manner. One skilled in the art will be able to adapt these methods, without undue experimentation, to the synthesis of compounds within the scope of this invention but not specifically disclosed.

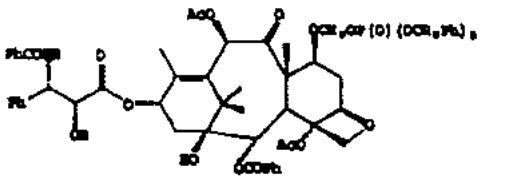
Example 1. 7-O-phosphonooxymethylpaclitaxel and its monosodium salt

(a) preparation of 7-O-methylthiomethylpaclitaxel.



Benzoyl peroxide (0.98 g, 4 mmol) was added to a vigorously stirred mixture of paclitaxel (0.85 g, 1 mmol) and dimethyl sulfide (0.72 mL, 8 mmol) in dry acetonitrile (10 ml) at 0°C. Stirring was continued for 2.5 hours at 0°C. Progress of the reaction was monitored by silica gel TLC in toluene : acetone (2 : 1, v/v) solvent system ($R_{f\ tax.}$ = 0.38, $R_{f\ prod.}$ = 0.64), and when formation of higher mobility products was observed the reaction was quenched by evaporation of solvents using Rotavapor at 30°C. A TLC analysis of the reaction mixture indicated the presence of some quantities of unreacted paclitaxel and 2',7-O-bis-(methylthiomethyl)paclitaxel. Separation of the title compound from the reaction mixture was achieved by flash column chromatography on Silica Gel 60 (40 - 63 µm) EM Science (100 mL), column diameter: 2 in. using ethyl acetate : hexane (1:1, v/v) solvent system ($R_{f\ prod.}$ = 0.34). The product (552 mg, 60% yield) was recovered from fractions 12 to 18 (each fraction ca. 20 ml).
MS (FAB/matrix NOBA, NaI, KI): $[M+H]^+$, m/z 914; $[M+Na]^+$, m/z 936; $[M+K]^+$, m/z 952
Elemental Analysis: C: 64.28 (calc. 64.39), H: 5.85 (calc. 6.07), N: 1.46 (calc. 1.53)
UV (MeOH): λmax = 226 nm , E(1%/1 cm) = 150, A = 0.2653
IR (KBr): 3432, 3066, 2940, 1726, 1668, 1602, 1582, 1514, 1484, 1452, 1372, 1242, 1178, 1142, 1108, 1068, 1026, 990, 916, 884, 852, 802, 774, 710, 608, 570, 538, 482 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.19 (3H, s), 1.73 (3H, s), 1.79 (H, s), 1.90 (3H, d), 2.09 (3H, s), 2.16 (3H, s), 2.29 (2H, d), 2.35 (3H, s), 2.77 (H, m), 3.70 (H, d), 3.83 (H, d), 4.17 (H, d), 4.26 (H, m, overlaps with H, d), 4.63 (2H, t), 4.77 (H, dd), 4.91 (H, d), 5.65 (H, d), 5.77 (H, dd), 6.16 (H, dd), 6.48 (H, s), 7.07 (H, d), 7.29 - 7.50 (10H, m), 7.57 (H, m), 7.73 (2H, d), 8.08 (2H, d).

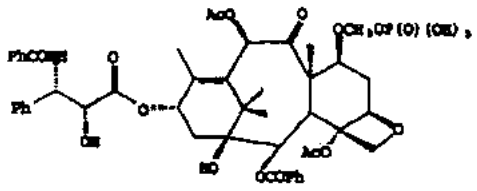
(b) preparation of 7-O-dibenzylphosphonooxymethylpaclitaxel.



A solution of N-iodosuccinimide (45 mg, 0.2 mM) and dibenzyl phosphate (55 mg, 0.2 mM) in dry tetrahydrofuran (4 mL) was added to a mixture of 7-O-methylthiomethylpaclitaxel (119 mg, 0.13 mM) and powdered molecular sieves 4Å (ca. 120 mg)in dry 1,2-dichloroethane (5 ml). The reaction mixture was stirred at room temperature for 16 hrs. Progress of the reaction was monitored by TLC in toluene : acetone (2 : 1, v/v) system ($R_{f\ prod.}$ = 0.48). Molecular sieves were removed by filtration through Celite 545 and the

filtrate was extracted with methylene chloride (100 ml). The organic layer was washed with 1% solution of sodium thiosulfate (ca. 100 ml) and 0.5 M sodium bicarbonate (100 ml) and with brine. Extract was filtered through Whatman Phase Separator and solvents were evaporated. Purification on Silica Gel 60 flash column in methylene chloride : ethyl acetate (2 : 1, v/v) yielded 7-O-dibenzylphosphonooxymethylpaclitaxel (41.5 mg).

(c) preparation of 7-O-phosphonooxymethylpaclitaxel and its monosodium salt.



7-O-Dibenzylphosphonooxymethylpaclitaxel (41.5 mg) was dissolved in ethyl acetate (5 ml) and 10% palladium on charcoal (20 mg) was added. Hydrogenation was performed at 40 PSI (275 kPa) at room temperature for 1 hour. Progress of the reaction was monitored by TLC in chloroform:methanol:water (120:45:8, v/v). Purification by preparative TLC (20x20x0.05 cm silica gel plate in the analytical system) gave 7-O-phosphonooxymethylpaclitaxel (26 mg, 75% yield).

Because decomposition of 7-O-dibenzylphosphooxymethylpaclitaxel was observed during silica gel purification, the hydrogenation procedure has been modified. Thus, a crude extract of 7-O-dibenzylphosphonooxymethylpaclitaxel was hydrogenated without any purification. Hydrogenation of the crude extract of 7-O-dibenzylphosphonooxymethylpaclitaxel was performed at 60 PSI (400 kPa) for 24 hrs.

7-O-Phosphonooxymethylpaclitaxel (70 mg) was dissolved in 5 mL of acetone - water (1 : 1) solution and diluted with water to 50 ml. Dry sodium bicarbonate (18 mg, 1.2 eq.) was added. Acetone was evaporated at room temperature using Rotavapor and the remaining water solution was lyophilized. Crude 7-O-phosphonooxymethylpaclitaxel monosodium salt was purified by C18 reverse phase column chromatography in water: acetonitrile (70 : 30, v/v) system. Eluate was monitored by analytical HPLC (15 cm, Jones C18 column, 1 mL/min., l = 230/270 nm) in acetonitrile : 0.05 M ammonium acetate buffer (45 : 55, v/v), pH = 7, Rt = 2.09 min. Fractions containing the desired product were combined, acetonitrile evaporated and the remaining aqueous solution lyophilized to provide 7-O-phosphonooxymethylpaclitaxel monosodium salt (112 mg).

MS (FAB): $[M+H]^+$, m/z 986; $[M+Na]^+$, m/z 1008

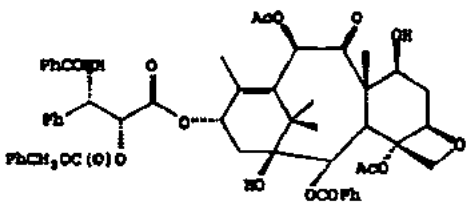
UV (MeOH): λmax = 230 nm, E(1%/1cm) = 248

IR (KBr): 3430, 3066, 2948, 1724, 1652, 1602,1580, 1518, 1486, 1452, 1372, 1316, 1246, 1178, 1154, 1108, 1070, 1000, 982, 946, 856, 802, 776, 710, 628, 538 cm^{-1}.

^{1}H-NMR (acetone-d_6/D_2O) δ: 8.05 (2H, d), 7.92 (2H, d), 7.65 (1H, dd), 7.58 - 7.35 (9H, m, overlap), 7.23 (1H, dd), 6.38 (1H, s), 6.08 (1H, t), 5.65 (1H, d), 5.60 (1H, d), 5.10 (1H, br.s), 4.99 (1H, d), 4.97 (1H, br.s), 4.80 (1H, d), 4.28 (1H, dd), 4.11 (2H, s), 3.79 (1H, d), 2.94 (1H, m), 2.35 (3H, s), 2.35 - 2.10 (1H, m), 2.13 (3H,s), 1.95 (3H, s), 1.84 (1H, m), 1.67 (3H, s), 1.13 (6H, s, overlap).

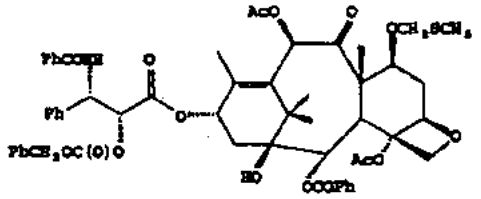
Example 2. Alternate method for the preparation of 7-O-phosphonooxymethylpaclitaxel.

(a) preparation of 2'-O-(benzyloxycarbonyl)paclitaxel



To a stirred solution of paclitaxel (150 mg, 0.176 mmol) and N,N-diisopropylethylamine (93 µL, 0.534 mmol, 3 eq.) in anhydrous methylene chloride (4 mL) at room temperature was added benzyl chloroformate (75 µL, 0.525 mmol, 3 eq.). The reaction mixture was stirred at room temperature for 3 h, concentrated to 2 mL, and purified on a silica gel column, using 1:1 of ethyl acetate/hexanes as eluant, to obtain the title compound as a white powder (150 mg, Y:86%). MP 140-150 °C (decomposition).

(b) preparation of 2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel

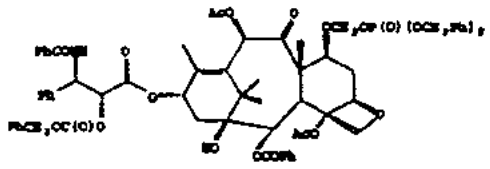


To a cooled (dry ice - CCl_4; -30 °C bath temp.) solution of 2'-O-(benzyloxycarbonyl)paclitaxel (4.935 g; 5.0 mmol) in dry acetonitrile (80 ml) was added in succession dimethylsulfide (3.6 ml; 40 mmol) and benzyol peroxide (4.9 g; 20.247 mmol). After 10 mins. at -30 °C, the cold bath was removed and the reaction mixture was stirred vigorously for 2 hr at room temperature. The reaction mixture was then diluted with ethyl acetate to a volume of 200 ml and washed with water and brine. The organic layer was dried ($MgSO_4$), and the solvent was then evaporated to give a residue which was kept under vacuum for 18 h to remove any dimethylsulfoxide that was present as a reaction side product. The residue was purified on a silica gel column using first ethyl acetate: hexane (1:2) as eluant to remove the less polar impurities, followed by ethyl acetate: hexane (1:1) to give the expected title compound as a foam. This was triturated with dry ether and filtered to give the title compound as a fluffy solid (5.0 g, 95%). MP 120-122 °C.
MS (FAB): $[MH]^+$, m/z 1048; $[M+Na]^+$, m/z 1070; $[M+K]^+$, m/z 108
IR (KBr): 3440, 3066, 1750, 1722, 1664, 1602, 1583, 1538 cm^{-1}.
NMR ($CDCl_3$) δ: 1.177 (3H,s) 1.236 (3H, s) 1.745 (3H, s) 2.023 (3H, s) 2.121 (3H s) 2.162 (3H, s) 2.436 (3H, s) 3.887 (H, d) 4.134 (H, d) 4.197 (H, d) 4.295 (H, m) 4.964 (H, d) 5.161 (2H, d) 5.450 (H, d) 5.703 (H, d) 5.981 (H, dd) 6.257 (H, t) 6.541 (H, s) 6.920 (H, d, NH) 7.322-8.22 (15H, m).

The title compound was also prepared by the following alternative method:

To a solution of 2'-O-(benzyloxycarbonyl)paclitaxel (2.0 g; 2.0263 mmol) in dry dimethylsulfoxide (10 ml) was added dropwise acetic anhydride (10 ml). The resulting mixture was stirred at room temperature for 18 h under N_2, diluted with ethyl acetate (100 ml), and washed carefully with cold 6% sodium bicarbonate solution (6x30 ml), cold water (6x30 ml) and brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to give a residue. This was purified by silica gel column and eluted with methylene chloride, methylene chloride-5% acetonitrile, and methylene chloride-10% acetonitrile to give the expected title compound (1.86 g, 87.7%). This compound is identical to that obtained via the previously described dimethyl sulfide/benzoyl peroxide method.

(c) preparation of 2'-O-(benzyloxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel



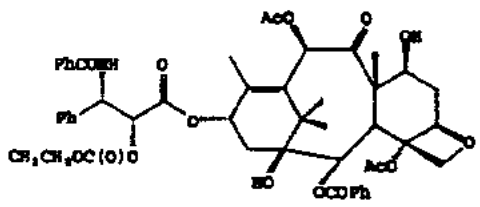
To a solution of 2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel (5.0 g; 5.5396 mmol) in dry 1,2-dichloroethane (120 ml) was added activated powdered 4Å molecular sieves (5.0 g). To this mixture was added dropwise at room temperature a solution mixture of N-iodosuccinimide (1.61 g; 7.1632 mmol) and dibenzyl phosphate (1.97 g; 7.1632 mmol) in dry tetrahydrofuran (90 ml). After stirring vigorously at room temperature for 30 min. the reaction mixture was filtered over Celite and the filtrate was evaporated to dryness to give a red residue. The residue was taken up in ethyl acetate (100 ml), washed with cold 6% $NaHSO_3$ solution (2x50 ml), cold 6% $NaHCO_3$ solution (2x50 ml) and brine (1x50 ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated to give a solid mass which was triturated with dry ether and filtered to give the title compound as an ivory colored solid (5.9 g, 97%). MP 124-127 °C.
MS (FAB): $[MH]^+$, m/z 1278; $[M+Na]^+$, m/z 1301; $[M+K]^+$, m/z 1316
IR (KBr): 3430, 3066, 3032, 1750, 1726, 1664, 1582, 1532 cm^{-1}.
NMR ($CDCl_3$) δ: 1.160 (3H, s) 1.703 (3H, s) 1.985 (3H, s) 2.164 (3H, s) 2.420 (3H, s) 3.854 (H, d) 4.151 (H, d) 4.216 (H, m) 4.298 (H, d) 4.873 (H, d) 5.043 (6H, m) 5.140 (2H, d) 5.417 (H, d) 5.670 (H, d) 5.971 (H, dd) 6.241 (H, t) 6.317 (H, s) 6.912 (H, d, NH) 7.280-8.115 (25H, m).

(d) preparation of 7-O-phosphonooxymethylpaclitaxel.

To a solution of 2'-O-(benzyloxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (6.0 g; 4.7095 mmol) in ethyl acetate (120 ml) was added 10% Pd/C (6.0 g) and the mixture was hydrogenated at 60 psi (400 kPa) for 24 hr. The reaction mixture was filtered over Celite and the solvent was evaporated to give 4.07 g of a crude residue. This was purified on a short silica gel column by successive elution with chloroform:10%, 20% and 40% methanol to give the title compound as a white solid (3.2 g, 71%) MP 155-158 °C.
This product has the same Rf(TLC) and same retention time (HPLC) as an authentic sample.
MS (FAB): $[MH]^+$, m/z 964; $[M+Na]^+$, m/z 986; $[M+K]^+$, m/z 1002; $[M+K^++Na^+-H]^+$, m/z 1024; $[M+2K-H]^+$, m/z 1040
UV (MeOH): λmax = 230 nm, E(1%/1cm) = 252.5
IR (KBr): 3432, 3066, 2992, 1722, 1648, 1602, 1580, 1522, 1488, 1452, 1372, 1316, 1246, 1178, 1154,, 1110, 1070, 1000, 980, 946, 854, 802, 776, 710, 628, 538 cm^{-1}.
^{1}NMR (acetone-d_6/D_2O), δ: 1.08 (3H, s), 1.10 (3H, s), 1.63 (3H, s), 1.88 (3H, s), 1.96 (H, m), 2.13 (3H, s), 2.32 (3H, s), 2.89 (H, m), 3.76 (H, d), 4.19 (H, m), 4.89 (H, dd), 5.09 (H, dd), 5.55 - 5.60 (2H, overlapping d's), 6.04 (H, t), 6.32 (H, s), 720 (H, t), 7.34 - 7.67 (10H, overlapping m's), 7.87 (2H, dd), 8.02 (2H, dd).

Example 3. 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel

(a) preparation of 2'-O-(ethoxycarbonyl)paclitaxel



To a solution of paclitaxel (4.35 g, 5.1 mmol) in dry methylene chloride (51 ml) was added N,N-diisopropylethylamine (2.67 ml, 15.3 mmol), followed by ethyl chloroformate (1.46 ml, 15.3 mmol). The reaction mixture was stirred at 0°C for 2 hrs, and then at room temperature for an additional 1 hr. The reaction mixture was diluted with ethyl acetate (400 ml), the organic phase was washed with saturated solution of $NaHCO_3$ (2 x 30ml), and with brine (30ml). The resulting organic phase was dried over $MgSO_4$ to provide crude title compound (93%) which was used in the next step without further purification.
MS (FAB/NOBA, NaI, KI): $[M + H]^+$, m/z 926; $[M + Na]^+$, m/z 948; $[M + K]^+$, m/z 964
HRMS (FAB/ NOBA, CsI/Gly external reference): $[M + H]^+$ m/z 926.3588 observed, $C_{50}H_{56}NO_{16}$, calculated value: 926.3599 (deviation Δ = 1.2 ppm)
^{1}HNMR ($CDCl_3$): δ 1.13 (3H, s), 1.23 (3H, s), 1.30 (3H, t), 1.67 (3H, s), 1.92 (3H, s), 2.21 (3H, s), 2.37 (H, d), 2.45 (3H, s), 2.54 (H, m), 3.80 (H, d), 4.15 - 4.32 (4H, m's overlapping), 4.43 (H, dd), 4.96 (H, d), 5.42 (H, d), 5.68 (H, d), 5.98 (H, dd), 6.28 (2H, m's, overlapping), 7.00 (H, d), 7.34 - 7.59 (11H, m's overlapping), 7.74 (2H, d), 8.12 (2H, d).

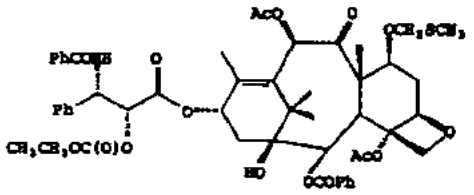
Alternate Run:

Paclitaxel (5.40 g, 6.324 mmol) in dry dichloromethane (63 mL) was cooled to 0°C and treated with neat N,N- diisopropylethylamine (3.30 mL, 3 equiv) and then neat ethyl chloroformate (1.81 mL, 3 equiv) dropwise over a 5 min period. The reaction was monitored by TLC (50% ethyl acetate in hexane). After 2h at 0°C and 16h at room temperature, the reaction was complete and the yellow-orange solution was diluted with ethyl acetate (300 mL) and washed with saturated sodium bicarbonate (3 x 75 mL) and brine (75 mL). Drying ($MgSO_4$) and evaporation afforded crude title compound, which was purified by precipitation: dichloromethane (ca. 100 mL) was added followed by cooling and addition of hexane (ca 60 mL) to the cloud point. After cooling in ice for several hours, the solid was collected by filtration. Yield 5.17 g (88%).

Alternate Run:

In a flame dried, single necked 3 L flask was dissolved paclitaxel (99.0 g, 115.9 mmol) in 1,350 mL of dry methylene chloride under the argon atmosphere. The solution was cooled to -10°. N,N-diisopropylethylamine (52.4 g, 405.7 mmol) was added slowly (addn. time ~3 min.), followed by $ClCO_2Et$ (31.45 g, 289.8 mmol; addn. time ~15 min.). The resulting mixture was stirred overnight (16 hrs.) at -4°C. The reaction was judged incomplete by TLC. Another charge of N,N-diisopropylethylamine (2.62 g, 20.28 mmol) was added, followed by $ClCO_2Et$ (2.20 g, 20.28 mmol) and the stirring was continued for 3 hrs at -4°C. No starting material was detected by TLC. The cold mixture was diluted with ethyl acetate (1.5 L) and transferred to a separatory funnel. It was then washed with 5% $KHSO_4$ (2x500 mL), water (1x500 mL), 5% $KHSO_4$ (1x500 mL), water (1x500 mL), satd. $NaHCO_3$ (2x500 mL) and brine (2x500 mL), dried ($MgSO_4$) and the solvents were removed *in vacuo* to give 147 g of the crude product. The residue was dissolved in hot methylene chloride (800 mL, bath temp. 42°C) and hexanes were added dropwise (530 mL) with stirring, while the temperature was maintained. The crystallizing mixture was set aside for 3 hrs. at room temperature and then in the cold room (0°C) overnight. The heavy white crystals were collected by filtration and washed with hexanes/CH_2Cl_2 1:1 (v/v) (2x200 mL). After drying on the suction filter for 1 hr. it was dried *in vacuo* (~1.0 mmHg) overnight to give 95.7 g (89% yield) of the title compound (homogeneity index as measured by HPLC = 98.5%).

(b) preparation of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of 2'-O-(ethoxycarbonyl)paclitaxel (4.38 g, 4.7 mmol) in dry dimethylsulfoxide (12.5 ml) was added acetic anhydride (12.5 ml). The reaction mixture was stirred for 24 hrs at room temperature and then diluted with ethyl acetate (500 ml), washed with saturated solution of $NaHCO_3$ (3 x 40 ml) and with water (2 x 40 ml). The resulting organic layer was dried over $MgSO_4$, and the solvents were evaporated in vacuo to dryness. The residue was purified by silica gel chromatography (40% ethyl acetate in hexanes) to afford the desired title compound (4.39 g, 94 %).

MS (FAB / NOBA, NaI, KI): $[M + H]^+$, m/z 986; $[M + Na]^+$, m/z 1008; $[M + K]^+$, m/z 1024

HRMS (FAB/NOBA, CsI/Gly external reference): $[M + H]^+$ m/z 986.3646 (calculated value: 986.3633, deviation Δ = 1.3 ppm)

^{1}HNMR ($CDCl_3$) δ: 1.18 (3H, s), 1.20 (3H, s), 1.30 (3H, s), 1.75 (3H, s), 1.84 (H, m), 2.09 (3H, s), 2.11 (3H, s), 2.16 (3H, s), 2.24 (H, d), 2.37 (H, d), 2.45 (3H, s), 2.80 (H, m), 3.68 (H, d), 4.08 - 4.33 (5H, m, overlapping), 4.65 (2H, s), 4.96 (H, d), 5.43 (H, d), 5.69 (H, d), 5.98 (H, dd), 6.26 (H, t), 6.55 (H, s), 7.00 (H, d), 7.32 - 7.61 (11H, m, overlapping), 7.73 (2H, dd), 8.11 (2H, dd).

Alternate Run:

2'-O-(Ethoxycarbonyl)paclitaxel (2.260 g, 2.4406 mmol) was dissolved in anhydrous dimethylsulfoxide (6 mL), and acetic anhydride (6 mL) was added in one lot at room temperature. The reaction was monitored by HPLC (C18 analytical column; 60% acetonitrile - 40% 10 mM ammonium phosphate buffer, pH 6). After 30h, the solution was diluted with ethyl acetate (250 mL) and washed with saturated aqueous bicarbonate (3 times) then water and brine. After drying over magnesium sulfate and filtration, the crude product was chromatographed on silica (40% ethyl acetate in hexane) to yield the title compound as a white foam (2.030 g, 91%) that was 90% pure by HPLC. A portion was further purified by a second column (5% acetonitrile in dichloromethane) to afford material that was ca. 97% pure by HPLC.

Alternate method for the preparation of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel.

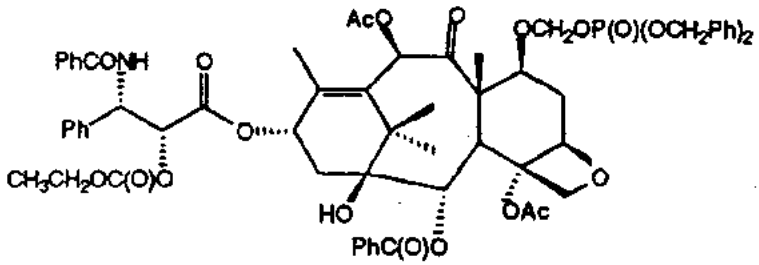
2'-O-(Ethoxycarbonyl)paclitaxel (4.170 g, 4.503 mmol) was dissolved in anhydrous acetonitrile (68 mL) at -40 °C, and dimethyl sulfide (3.2 mL, 44.10 mmol) was added, followed by benzoyl peroxide (4.400 g, 18.24 mmol). The mixture was placed in an ice bath and stirred at 0 °C, and the course of the reaction was monitored by TLC (40% ethyl acetate in hexane). After 3 h. no starting material was detected, and the solution was worked up by adding ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (100 mL). The organic phase was further washed with bicarbonate, water, and brine, then dried over magnesium sulfate and filtered. The residue was purified by silica gel flash chromatography (4% acetonitrile in dichloromethane), to yield the title compound as a white foam (2.571 g, 58% yield). The purity of this sample was judged as >97% by HPLC. The NMR spectrum was identical to the one reported above.

Alternate run for preparing 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel.

2'-O-(Ethoxycarbonyl)paclitaxel (49.3 g, 53.2 mmol) was placed in a flame dried single necked 1 L flask and dissolved in dry acetonitrile (500 mL) at room temperature. Methyl sulfide (39.1 mL, 0.532 mol) was rapidly added *via* syringe. The stirred reaction mixture was cooled to -16 °C in an ice/salt bath and solid benzoyl peroxide (51.6 g, 0.213 mol) was added to the mixture in one lot. (Full four equivalents are required for the reaction to proceed to completion.) Stirring was continued for 30 minutes, during which time the temperature rose to ~-10 °C. The reaction medium remained heterogeneous throughout this period (benzoyl

peroxide has not dissolved completely). The cooling bath was changed to ice/water, the temperature was raised to 0 °C and the remaining benzoyl peroxide dissolved ~5 min. after the warm-up. The reaction was judged complete by TLC after stirring at 0 °C for another 2.5 hours. The volume of the solution was reduced ~200 mL by removing the solvent on a rotovap and it was then transferred to a separatory funnel where it was washed with heptane (5x500 mL). The acetonitrile layer was diluted with ethyl acetate (1.5 L) and washed with a 3:1 mixture satd. $NaHCO_3$/5% K_2CO_3 (v/v) (2x500 mL), satd. $NaHCO_3$ (2x500 mL), half-satd. brine (1x500 mL) and brine (1x500 mL), dried ($MgSO_4$) and the solvents were removed in *vacuo* to give 67.0 g of the crude product. It was dissolved in acetone (200 mL), warmed to 40 °C in a water bath and hexanes were added dropwise with stirring until the cloudiness was observed (400 mL). The crystallizing mixture was set aside for 3 hrs. at room temperature and then transferred to a cold room (0 °C) where it was kept overnight (16 hrs.). A thick cake was formed. The solid was collected by filtration and washed with hexanes/acetone 3:1 (v/v) (2x50 mL). The resulting white crystals were dried on the suction filter for 1 hr. and then *in vacuo* (~0.5 mmHg) overnight to give 47.5 g (91% yield) of the title compound (homogeneity index as measured by HPLC = 94.6%).

(c) preparation of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel.



A solution of N-iodosuccinimide (1.953g, 8.65 mmol) and dibenzyl phosphate (2.41g, 8.65 mmol) in tetrahydrofuran was added to a mixture of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (5.677g, 5.76 mmol) and 4Å molecular sieves (5.7g) in methylene chloride (100 ml) at room temperature. The reaction mixture was stirred for 40 min. at room temperature. After this period the reaction was complete as judged by TLC. The reaction mixture was filtered through Celite and the filtrate was concenterated in vacuo to give a brownish residue which was diluted with ethyl acetate (800 ml), the organic phase was washed with 1% Na_2SO_3 (2 x 80 ml), then washed with 5% brine (2 x 50 ml). The organic phase was concentrated in vacuo and dried. Chromatography of the resulting residue (50 - 60% ethyl acetate in hexanes) gave the desired title compound (6.23g, 89%).

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1238; $[M + K]^+$, m/z 1254

HRMS (FAB/NOBA, CsI/Gly external reference): $[M + Na]^+$ m/z 1216.4291($C_{65}H_{71}NO_{20}P$ calculated value: 1216.4307; deviation Δ = 1.3 ppm)

^{1}HNMR ($CDCl_3$), δ: 1.18 (3H, s), 1.21 (3H, s), 1.30 (3H, t), 1.67 (6H, s), 1.80 (H, s), 1.93 (H, m), 1.99 (3H, d), 2.18 (3H, s), 2.23 (H, m), 2.38 (H, m), 2.45 (3H, s), 2.80 (H, m), 3.86 (H, d), 4.14 - 4.32 (5H, m's, overlapping), 4.88 (H, d), 5.00 - 5.07 (4H, m's, overlapping), 5.42 (H, d), 5.68 (H, d), 5.96 (H, dd), 6.26 (H, t), 6.33 (H, s), 6.95 (H, d), 7.30 - 7.61 (11H, m's overlapping), 7.75 (2H, dd), 8.12 (2H, dd).

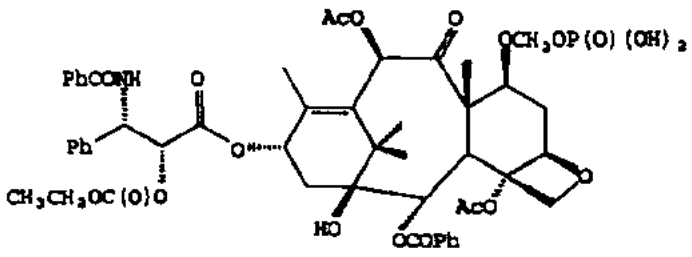
Alternate Run:

To a solution of 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (350 mg, 0.355 mmol) in anhydrous tetrahydrofuran (8 mL) was added a solution of N-iodosuccinimide (120 mg, 0.532 mmol) and dibenzyl phosphate (148 mg, 0.532 mmol)in tetrahydrofuran (5 mL). The reaction was monitored by HPLC (C18 column; 70% acetonitrile, 30% 10 mM ammonium phosphate, pH 6). After 2h, less than 5% starting material was detected, and the reaction was worked-up. The solution was diluted with ethyl acetate (75 mL), and washed with 1% aqueous sodium bisulfite (2x50 mL) and brine (50 mL). After quick drying over magnesium sulfate and filtration, the solvent was evaporated. Silica gel flash chromatography (45% ethyl acetate/hexane) provided the title compound as a white foam (281 mg, 65%). HPLC analysis indicated a purity of ca. 95%.

Alternte Run:

Crushed 4 A molecular sieves were placed in a flame dried one-necked 1 L flask which was then connected to a vacuum line (~0.5 mmHg). The sieves were heated with a heatgun for ~10 min. while being shaken manually. After cooling under *vacuum* argon was introduced into the flask and 2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel (37.5 g, 38.03 mmol) was added, followed by dibenzyl phosphate (14.8 g, 53.24 mmol) and THF (400 mL). The heterogeneous mixture was vigorously stirred for 15 min. at room temperature with a magnetic stirrer. In a separate flame dried flask, N-iodosuccinimide (10.7 g, 47.54 mmol) was dissolved in THF (50 mL) under argon. (During the preparation of the NIS solution, liquid transfer and during the reaction course, the vessels were covered with aluminum foil for protection against light.) It was then added slowly (10 min) to the reaction mixture via a syringe. The flask containing NIS was washed with 5 mL of THF and transferred to the reaction mixture, which was then stirred for 2 hrs. at room temperature. TLC analysis showed absence of the starting material. The deeply red colored solution was filtered through a pad of Celite® directly into a vigorously stirred bi-phasic mixture containing ethyl acetate (500 mL), 10% aq. sodium thiosulfate (300 mL) and satd. sodium bicarbonate (200 mL). The red color disappeared in a few seconds giving a colorless solution. The Celite® pad was washed with EtOAc (~100 mL) and both liquid layers were transferred into a separatory funnel. The organic layer was diluted with 1L of EtOAc, the layers were separated and the organic layer was washed with a mixture of satd. $NaHCO_3$ and 5% K_2CO_3 (3:1 v/v, 2X500 mL), then satd. $NaHCO_3$ (2x500 mL), half-saturated brine (1x500 mL) and brine (1x500 mL). The extract was dried with anhydrous $MgSO_4$ and filtered. It was treated with 5.0 g of neutral Norit (charcoal) by stirring at room temperature for 15 min. It was filtered again through a Celite® pad and the solvent was removed under the reduced pressure to give 52 g of the crude product. It was dissolved in toluene/methylene chloride (280 mL/25 mL) and hexanes were added dropwise (20 mL). After being set aside for 3 hrs. at room temperature the crystallizing mixture was left at 0°C overnight. A pale yellow solid was formed on the flask walls. After decanting the mother liquor, the residue was triturated with toluene (50 mL), filtered, washed with toluene and dried on the suction filter for 30 min. It was then transferred to a desiccator with Drierite® and further dried *in vacuo* (~0.5 mmHg) for four hours to give 24.4 g (53% yield) of the title compound (homogeneity index as measured by HPLC = 95.9%). The mother liquor was evaporated to dryness, triturated with toluene (100 mL), filtered, washed with toluene and dried on the suction filter for 30 min. After drying in a desiccator as described above it gave 12.5 g (27% yield) of the same product (homogeneity index as measured by HPLC = 97.1%).

(d) preparation of 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel; its monosodium, monopotassium, triethylamine, arginine, lysine, ethanolamine, N-methylglucamine, and triethanolamine salts.



To a solution of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel(1.23 g, 1.01 mmol) in dry ethyl acetate (40 ml) was added 10% Pd on carbon (428 mg, 10%, 0.404 mmol). The reaction mixture was subjected to hydrogenation (60 PSI = 400 kPa) with continuous shaking for 24 hrs. The solid was filtered off through Celite, then the Celite was rinsed several times with ethyl acetate. The filtrate was concentrated to give free acid form of the title compound (1.01g, 80% purity as judged by HPLC). The impurities were removed at the next step by preparative C-18 column chromatography.

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1058; $[M + K]^+$, m/z 1074; $[M + 2Na - H]^+$, m/z 1080; $[M + Na + K - H]^+$, m/z 1096; $[M + 2K - H]^+$, m/z 1112

HR-MS (FAB/NOBA, CsI/Gly, external reference): $[M + Na]^+$, m/z 1058.3163 ($C_{51}H_{58}NO_{20}PNa$ calculated value: 1058.3188; deviation Δ = 2.3 ppm)

^1H NMR (acetone-d_6/D2O) δ: 1.13 (3H, s), 1.21 (3H, s), 1.66 (3H, s), 1.87 (H, m), 1.93 (3H, s), 2.14 (3H, s), 2.18 (H, m), 2.44 (3H, s), 2.95 (H, m), 3.81 (H, d), 4.12 (2H, s), 4.15 - 4.27 (3H, m's overlapping), 4.92 - 4.99

(2H, br.m's overlapping), 5.15 (H, br.s), 5.48 (H, d), 5.61 (H, d), 5.84 (H, dd), 6.07 (H, t), 6.36 (H, s), 7.25 (H, t), 7.28 - 7.69 (10H, m's overlapping), 7.89 (2H, dd), 8.08 (2H, dd), 8.86 (H, d).

Alternate Run:

2'-O-(Ethoxycarbonyl)-7-O-(dibenzylphosphonooxymethyl)paclitaxel (490 mg, 0.402 mmol) in ethyl acetate (20 mL) was hydrogenated in a Parr shaker at 60 psi (400 kPa) in the presence of palladium on charcoal (10% w/w, 150 mg). Monitoring was carried out by TLC and HPLC. When no more starting material nor an intermediate (presumably the monobenzyl phosphate) were detected (26h), the suspension was filtered through Celite and evaporated to dryness. HPLC analysis showed a purity of 88-92%.

Alternate Run:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt to be described below (5.4 g, 4.75 mmole) was partitioned vigorously between EtOAc (100 mL) and 5% $NaHSO_4$ (45 ml) with stirring at 0°C for 30 minutes. The aqueous layer was separated and extracted with EtOAc (20 ml). The combined EtOAc layer was washed with half-brine (25 ml), brine (25 mL x 2), dried over $NaSO_4$ and filtered to give a solution of the acid (~4.75 mmole) in EtOAc (~150 mL). This EtOAc solution was then concentrated to dryness on a rotary evaporator to give 3.75 g of the title compound in free acid form in 95% yield. HPLC analysis showed homogeneity index of 96.1%.

The monosodium salt was prepared as follows:

A sample of 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel (1.6 g, 1.55 mmol) was dissolved in acetonitrile (30 ml) by sonication. This solution was diluted with water (30 ml) and 1.1 M solution of $NaHCO_3$ (2.11 ml, 2.32 mmol) was added, alternately shaking and sonicating to obtain a solution (5-20 min). The somewhat milky solution was applied onto a C-18 column, washing with two column volumes of water, then eluting the monosodium salt with 25% acetonitrile/water. The appropriate fractions were pooled, the acetonitrile evaporated, and the aqueous phase lyophilized, to yield the monosodium salt of the title compound (850 mg, ca 50%), having HPLC purity of 97%.

MS (FAB/NOBA, NaI, KI): $[M + Na]^+$, m/z 1180

HR - MS (FAB/NOBA, CsI/Gly external reference): $[M + Na]^+$, m/z 1080.2968 ($C_{51}H_{57}NO_{20}PNa_2$ calculated value: 1080.3007; deviation D = 3.6 ppm)

Elemental analysis: C: 52.65 (calc. 56.72), H: 5.06 (calc. 5.23), N: 1.20 (calc. 1.30), Na: 2.74 (calc. 2.12)

IR (KBr): 3430, 3066, 2988, 1746, 1722, 1660, 1602, 1582, 1526, 1488, 1452, 1374, 1246, 1178, 1150, 1108, 1070, 1052, 1026, 1002, 966, 912, 834, 792, 776, 710, 628, 538 cm^{-1}.

^1H-NMR (DMSO-d_6, D_2O, acetone-d_6) δ: 1.10 (6H, s), 1.23 (3H, t), 1.64 (3H, s), 1.70 (H, m), 1.90 (3H,s), 1.99 (H, m), 2.14 (3H, s), 2.37 (3H, s), 2.98 (H, m), 3.74 (H, d), 4.07 (2H, s), 4.13 - 4.26 (3H, m, overlapping), 4.80 (H, br.dd), 4.97 (H, d), 5.09 (H, br.t), 5.44 (H, d), 5.55 (H, d), 5.99 (H, t), 6.34 (H, s), 7.22 (H,t), 7.43 - 7.69 (10H, m, overlapping), 7.92 (2H, dd), 8.06 (2H, dd).

The sodium salt can also be prepared as follows:

Crude 2'-O-(ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel (89%; 70 mg, 0.060 mmol), in EtOAc (2 ml) was treated with a solution of sodium ethylhexanoate (87.5 mM in EtOAc, 1.0 ml, 0.0875 mmol) at room temperature with stirring. After stirring at room temperature for 1 h, hexane (1.2 ml) was added to the cloud point. After storing at -20°C for 2h, the fine amorphous powder was filtered (with some difficulty, very slow) through fine filter paper, to yield 45 mg (70%) of the sodium salt. This was 95.2% pure by HPLC and contained a small amount of ethylhexanoic acid (NMR).

The triethanolamine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel, crude from the hydrogenation (89% by HPLC) (0.69 g, 0.593 mmol after correction for impurities) was dissolved in ethyl acetate (10 ml), and stirred slowly while a solution of triethanolamine (0.11 M in EtOAc, used 5.1 ml, 0.95 eq) was added dropwise. The milky solution obtained by this procedure was digested at 0°C for 2h, then filtered on file filter paper, rinsing with cold EtOAc. Yield: 499 mg (80%) of an amorphous, fine, non-electrostatic powder that was dried overnight *in vacuo*. HPLC shows 96.6% purity (C18, 45% 5mM Q_{12} + 10mM ammonium phosphate pH 6, 55% actonitrile). NMR spectrum (D_2O/acetone/DMSO) shows traces of ethyl acetate and no other clearcut impurities. It analyzes for a 2-3 x hydrate.

The triethanolamine salt of lesser priority obtained from another experiment was further purified by the following procedure. The triethanolamine salt (approx. 2 g) was dissolved in about 30% acetonitrile/water. This solution was eluted with slight nitrogen pressure through a column of C18 (Bakerbond) with a gradient of 20% to 40% acetonitrile in water. The fractions containing the desired triethanolamine salt were collected;

the acetonitrile was removed by rotary evaporation under reduced pressure. The aqueous solutions were frozen and lyophilized overnight to afford 1.4 grams of the triethanolamine salt with a purity of 97.5%.

The triethanolamine salt can also be prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt (3.0 g, 2.64 mmole) was partitioned between EtOAc (60 ml) and 5% $NaHSO_4$ (30 ml) with vigorous stirring at 0 °C for 15 minutes. The aqueous layer was separated and extracted with EtOAc (10 mL). The combined EtOAc layer was washed with brine (15 ml), dried over Na_2SO_4, filtered to give a solution of the acid (~2.64 mmole) in EtOAc (~70 ml). To this EtOAc solution at room temperature was added dropwise with vigorous stirring $N(CH_2CH_2OH)_3$ (0.35 ml, 2.64 mmole) over a period of 5 minutes. The resulting suspension was stirred for an additional 1 hr and then it was filtered, washed with EtOAc (15 ml x 2), dried *in vacuo* to give 2.8 g of the triethanolamine salt in 89% yield. HPLC analysis showed homogeneity index of 98.7%; mp.: >157 °C with decomposition.

Elemental analysis calculated for $C_{56}H_{73}N_2O_{23}P \cdot 2.0\ H_2O \cdot 0.3$ EtOAc: C, 55.60; H, 6.48; N, 2.27; KF (H_2O), 2.92. Found: 55.94; H, 6.59; N, 2.43; KF (H_2O), 3.50.

The triethylamine salt was prepared as follows:

To the solution of 2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (10 g, 8.23 mmole), in EtOAc (350 ml), at room temperature was added 10% Pd on carbon (2 g, 20% load). The resulting suspension was degassed by evacuating air and then purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the same degassing procedure. The resulting suspension was stirred under a balloon hydrogen pressure (2-3 pound per square inch) for 16 hr at room temperature with vigorous stirring. The hydrogen was evacuated and replaced with argon three times following the degassing procedure. The resulting suspension was filtered through a pad of Celite. To this homogeneous filtrate was slowly added Et_3N (8.23 mmole, 1.14 mL) over a period of 5 min with vigorous stirring. The resulting fine white suspension was stirred for an additional 30 min. It was filtered through a fritted funnel. The filter cake was dried *in vacuo* (1 mmHg) for 16 hr to give 8.22 g of the title triethylamine salt in 88% yield. HPLC analysis showed homogeneity index of 97.4%; mp.: >178 °C with decomposition.

Elemental analysis calculated for $C_{57}H_{73}N_2O_{20}P \cdot 4.5\ H_2O$: C, 56.19; H, 6.79; N, 2.30; KF (H_2O), 6.65. Found: 56.33; H, 6.87; N, 2.32; KF (H_2O), 7.96.

Alternate run for making the triethylamine salt:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (5.67 g, 4.66 mmol) was added to a 250 mL flask and dissolved in ethyl acetate (150 mL). The flask was equipped with a three-way valve with one connection to house vacuum and one connection to an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. Palladium on activated carbon (10% Pd) (0.85 g) was added to the flask. The argon line attached to the three-way valve was replaced with a hydrogen-filled balloon. Using the valve, the flask was partially evacuated and then purged with hydrogen. This process was repeated four additional times. The resulting mixture was stirred at room temperature under the hydrogen balloon atmosphere overnight. TLC analysis 17 hours after the initial exposure to hydrogen showed the starting material to be absent. The hydrogen balloon attached to the three-way valve was replaced with an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. The contents of the flask were vacuum-filtered through a pad of Celite. The Celite was rinsed with ethyl acetate (2 x 10 mL). To the stirring filtrate was added NEt_3 (0.650 mL, 4.66 mmol). The resulting suspension was stirred at room temperature for two hours, and the volume was then reduced to ~150 mL via a rotovap. The solid was filtered, washed with ethyl acetate (2 x 10 mL) and dried under vacuum to give 4.76 g (90% yield) of the title triethylamine salt as a white powder (homogeneity index of the product was determined to be 96.6 % by HPLC analysis).

Alternate run for making the triethylamine salt:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (5.17 g, 4.25 mmol) was added to a 250 mL flask and dissolved in ethyl acetate (150 mL). The flask was equipped with a three-way valve with one connection to house vacuum and one connection to an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. Palladium on activated carbon (10% Pd) (0.86 g) was added to the flask. The argon line attached to the three-way valve was replaced with a hydrogen-filled balloon. Using the valve, the flask was partially evacuated and then purged with hydrogen. This process was repeated five additional times. The resulting mixture was

stirred at room temperature under the hydrogen balloon atmosphere overnight. TLC analysis 16 hours after the initial exposure to hydrogen showed the starting material to be absent. The hydrogen balloon attached to the three-way valve was replaced with an argon line. Using the valve, the flask was partially evacuated and then purged with argon. This process was repeated two additional times. The contents of the flask were vacuum-filtered through a pad of Celite. The Celite was rinsed with ethyl acetate (4 x 10 mL). To the stirring filtrate was added NEt_3 (0.590 mL, 4.25 mmol). The resulting suspension was stirred at room temperature for one hour, and the volume was then reduced to ~140 mL via a rotovap. The solid was filtered, washed with ethyl acetate (10 mL) and dried under vacuum to give 4.46 g (92% yield) of the title triethylamine salt as a white powder (homogeneity index as determined by HPLC analysis was 96.7%).

The lysine salt was prepared as follows:

2'-O-(ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (15.0 g, 12.34 mmole) was added portionwise to a suspension of 10% palladium on carbon (20% load, 3 g) in EtOH (600 ml, 200 proof) at 0°C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the same degassing procedure with vigorous stirring. The resulting mixture was stirred at 0°C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 4-1/2 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times. It was filtered under argon through a pad of Celite. To the resulting filtrate was slowly added a solution of lysine (1.63 g, 0.94 eq) in a 1:1 mixture of H_20:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (110 ml) and stirred for 30 minutes. It was warmed to about 55° C. The resulting homogeneous solution was kept in an oil bath set at 50°C and slowly cooled down to room temperature for 16 hrs and 4°C for 3 hrs. It was filtered and suction dried for 16 hrs to give 11.8 g (~80% yield) of the lysine salt with homogeneity index of 99.0 % as determined by HPLC; mp.: >170°C with decomposition.

Elemental analysis calculated for $C_{57}H_{72}N_3O_{22}P \cdot 8.0\ H_2O$: C, 51.62; H, 6.69; N, 3.17; KF (H_20), 10.87. Found: 51.76; H, 6.57; N, 3.48; KF (H_2O), 11.42.

The ethanolamine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-phosphonooxymethylpaclitaxel triethylamine salt (3.0 g, 2.64 mmole) was partitioned between EtOAc (60 ml) and 5% $NaHSO_4$ (30 ml) with vigorous stirring at 0°C for 15 minutes. The aqueous layer was separated and extracted with EtOAc (15 ml). The combined EtOAc layer was washed with brine (15 ml), dried over Na_2SO_4, filtered to give a solution of the free acid (~2.64 mmole) in EtOAc (~70 ml). To this EtOAc solution at room temperature was added dropwise with vigorous stirring a solution of $H_2NCH_2CH_2OH$ (0.15 ml, 2.64 mmole) in EtOAc (5 mL) over a period of 5 minutes. The resulting suspension was stirred for an additional 1 hr and then it was filtered, washed with EtOAc (15 ml x 2), and dried in vacuo to give 2.6 g of the title ethanolamine salt in 89% yield. HPLC analysis showed homogeneity index of 97.8%; mp.: >130°C with decomposition.

Elemental analysis calculated for $C_{53}H_{65}N_2O_{21}P \cdot 2.5\ H_2O$: C, 55.73; H, 6.18; N, 2.45; KF (H_20), 3.94. Found: C, 55.76; H, 6.39; N, 2.45; KF (H_2O), 6.00.

The arginine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (30.0 g, 24.69 mmole) was added portionwise to a suspension of 10% palladium on carbon (20%, load, 6 g) in EtOH (900 ml, 200 proof) at 0°C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the above degassing procedure with vigorous stirring. The resulting mixture was stirred at 0°C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 24 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times following the above degassing procedure. It was filtered under argon through a pad of Celite. The filtrate was divided into two equal portions and EtOH (190 ml, 200 proof) was added to each portion. To one portion (~630 ml) was slowly added a solution of arginine (2.0 g, 0.94 eq) in a 2:1 mixture of H_2O:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (100 ml) and stirred for 30 minutes and then warmed to about 60°C. It was filtered hot and the filtrate was kept in an oil bath set at 50°C, allowed to cool down to room temperature and kept at room temperature for 2 hrs and at 4°C for 2 hrs. It was filtered and washed with cold 3% H_2O in EtOH (100 ml) and suction dried for 16 hrs to give 12.95 g (~86% yield) of the title arginine salt with homogeneity index of 96.7 %.

This material (12.95 g) was dissolved in a mixture of 15% H_2O in EtOH (~700 ml) at 55°C. The solution was cooled down and kept at 30°C for 3-1/2 hrs, room temperature for 16 hrs, and 4°C for 3 hrs. The resulting crystals were filtered, washed with cold 2% H_2O in EtOH (50 ml x 2), suction dried for 4 hrs, and then dried *in vacuo* (1 mmHg) for 16 hrs to give 10.2 gs (~80% yield) of the title arginine salt (homogeneity

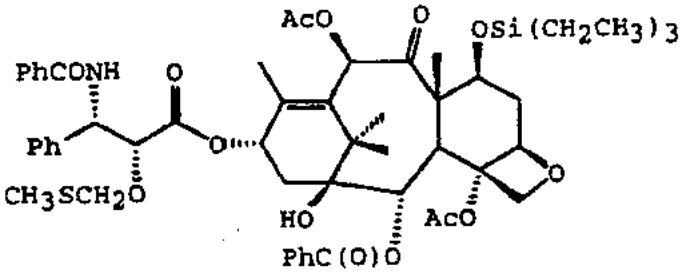
index was 98.5%);mp.: >176 °C with decomposition.
Elemental analysis calculated for $C_{57}H_{72}NsO_{22}P \cdot 6.4\ H_2O$: C, 51.65; H, 6.45; N, 5.28; KF (H_2O), 8.7. Found: C, 51.86; H, 6.65; N,5.53; KF (H_2O), 8.72.
The N-methylglucamine salt was prepared as follows:

2'-O-(Ethoxycarbonyl)-7-O-dibenzylphosphonooxymethylpaclitaxel (30.0 g, 24.69 mmole) was added portionwise to a suspension of 10% palladium on carbon (20% load, 6 g) in EtOH (900 ml, 200 proof) at 0 °C. The resulting suspension was degassed by evacuating air and purging with argon. This process was repeated two additional times. The argon then was replaced with hydrogen following the above degassing procedure with vigorous stirring. The resulting mixture was stirred at 0 °C for 2 hrs. The cooling bath was removed and the reaction solution was stirred at ambient temperature for additional 24 hrs. The reaction mixture was degassed by evacuating hydrogen and purging with argon three times following the above degassing procedure. It was filtered under argon through a pad of Celite. The filtrate was divided into two equal portions and EtOH (190 ml, 200 proof) was added to each portion. To one portion (~630 ml) was slowly added a solution of N-methylglucamine (2.24 g, 0.94 eq) in a 1:1 mixture of H_2O:EtOH (200 proof) (20 ml) over a period of 5 minutes with vigorous stirring. To the resulting white suspension was added distilled water (100 ml) and the suspension was stirred for 30 minutes and then warmed to about 49 °C. The clear homogeneous solution was kept in an oil bath set at 50 °C, allowed to cool down to room temperature and kept at room temperature for 2 hrs and at 4 °C for 1-1/2 hrs. It was filtered and washed with 3% H_2O in EtOH (100 ml), suction dried at room temperature for 16 hrs to give 9.65 g (~64% yield) of the title N-methylglucamine salt with homogeneity index of 96.4 %.

This material (9.65 g) was dissolved in a mixture of 15% H_2O in EtOH (~450 ml) at 52 °C. Then, the solution was cooled down and kept at 28 °C for 3-1/2 hrs, room temperature for 16 hrs, and 4 °C for 3 hrs. The resulting crystals were filtered, washed with cold 2% H_2O in EtOH (50 ml x 2), suction dried for 4 hrs, and then dried *in vacuo* (1 mmHg) for 16 hrs to give 7.5 g (~80% yield) of the title N-methylglucamine salt (homogeneity idex as determined by HPLC was 98.6%); mp.: >154 °C with decomposition.
Elemental analysis calculated for $C_{58}H_{75}N_2O_{25}P \cdot 5.0\ H_2O$: C, 52.72; H, 6.48; N, 2.12; KF (H_2O), 6.82. Found: C, 53.09; H, 6.50; N, 2.08; KF (H_2O), 7.12.

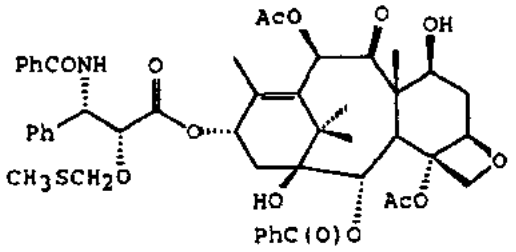
Example 4. 2'-O-(Phosphonooxymethyl)paclitaxel

(a) Preparation of 2'-O-(methylthiomethyl)-7-O-(triethylsilyl)paclitaxel



To a cooled (0 to -5 °C) solution of 7-O-(triethylsily)paclitaxel (2.46 g; 2.5439 mmol) in dry acetonitrile (100 ml) was added dimethylsulfide (1.348 g; 1.59 ml; 21.6976 mmol) followed by benzoyl peroxide (2.628 g; 10.8488 mmol). The heterogeneous mixture was stirred at 0 °C for 1 h and kept at 5 °C for 18 h. A yellow solution was observed. This was evaporated to dryness and purified by silica gel column (eluting with ethyl acetate: hexane, 1:4; 1:3 and 1:2) to give the title compound (1.0 g, 38%). This was used as such for next step.
MS: $[M+H]^+$, 1028; $[M+Na]^+$, 1050; $[M+K]^+$, 1066

(b) Preparation of 2'-O-(methylthiomethyl)paclitaxel



To a cooled (-15°C) solution of the product of step (a) (1.0 g; 0.9737 mmol) in dry acetonitrile (30 ml) was added dropwise 0.5 N HCl (3 ml). The resulting solution was stirred at -15°C for 1 h and at 5°C for 18 h. This was diluted with ethyl acetate (20 ml) and washed with cold 6% $NaHCO_3$ solution and brine. It was dried ($MgSO_4$) and evaporated to dryness. This was purified by silica gel plate (methylene chloride: 15% acetonitrile) to give pure title compound (280 mg, 31.4%).

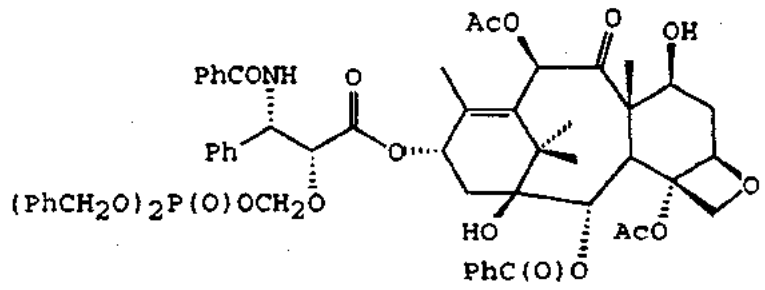
IR(KBr): 3446, 3064, 2940, 1726, 1666, 1582, 1516,1486.

NMR ($CDCl_3$): δ 1.118 (s, 3H), 1.229 (s, 3H), 1.662 (s, 3H), 1.689 (s, 3H), 1.871 (s, 3H), 2.209 (s, 3H), 2.450 (s, 3H), 3.800 (d, H), 4.119 (d, H), 4.305 (d, H), 4.413 (m, H), 4.563 (d, H), 4.703 (d, H), 4.940 (d H), 4.958 (dd, H), 5.667 (d, H), 5.822 (dd, H), 6.263 (m, 2H), 7.019 (d, NH), 7.293-8.127 (m, 15H).

MS: $[M+H]^+$, 914; $[M+Na]^+$, 936; $[M+K]^+$, 952

HRMS: MH^+: 914.3394 (calculated = 914.3422)

(c) Preparation of 2'-O-(dibenzylphosphonooxymethyl)paclitaxel



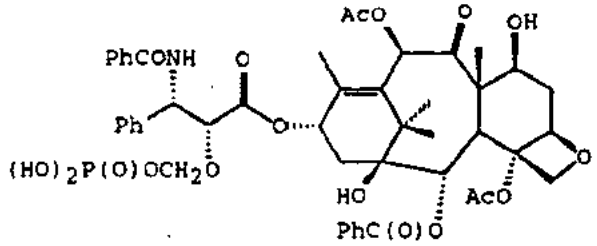
To a stirred solution of the product of step (b) (0.89 g; 0.9748 mmol) in dry 1,2-dichloroethane (12 ml) was added powdered 4Å molecular sieves (1.0 g) followed by dropwise addition of a solution mixture of N-iodosuccinimide (0.33 g; 1.4622 mmol) and dibenzyl phosphate (0.41 g; 1.4622 mmol) in dry tetrahydrofuran (8 ml). The resulting mixture was stirred at room temperature for 1 h., then filtered over Celite. The filtrate was evaporated to dryness and the red residue was taken up in ethyl acetate (50 ml) and washed with cold 6% $HaHSO_3$, cold 6% $NaHCO_3$ and brine. It was dried ($MgSO_4$) and evaporated to give a foam. This was purified by silica gel plate (methylene chloride:20% acetonitrile) to give pure product (0.77 g, 69%).

IR(KBr): 3854, 3744, 3362, 3066, 1960, 1722, 1602, 1580.

NMR ($CDCl_3$): δ 1.075 (s, 3H), 1.167 (s, 3H), 1.651 (s, 3H), 1.799 (s, 3H), 2.209 (s, 3H), 2.296 (s, 3H), 2.464 (m, H), 3.686 (d, H), 4.121 (d, H), 4.240 (d, H), 4.293 (m, H), 4.808-4.957, (m, 6H), 5.006 (m, H), 5.565-5.649 (m, 2H), 6.034 (t, H), 6.194 (3, H), 7.100-8.132, (m, 26H).

MS: $[M+H]^+$, 1144; $[M+Na]^+$, 1166; $(M+K]^+$, 1182

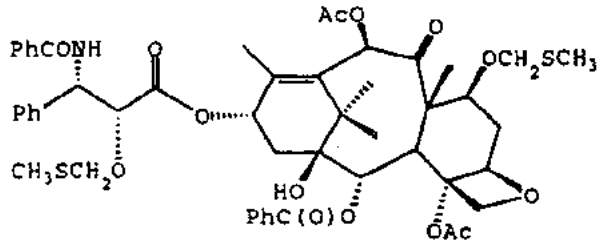
(d) Preparation of 2'-O-(phosphonooxymethyl)paclitaxel



A mixture of the product of step (c) (0.9 g; 0.7874 mmol) and 10% Pd/C (1.0 g) in ethyl acetate (20 ml) was hydrogenated at 60 psi (400 kPa) for 24 h. The reaction mixture was filtered over Celite and the filtrate evaporated to dryness. The residue was purified by silica gel plate (methylene chloride:40% methanol) to give the title product (0.254 g, 33.4%). MP 202-205 °C (d).
IR (KBr): 3438, 3066, 2942, 1722, 1652, 1602 cm^{-1}.
NMR (acetone-d_6/D_2O): δ 1.081 (s, 6H), 1.571 (s, 3H), 1.847 (s, 3H), 2.115 (s, 3H), 2.357 (s, 3H), 3.707 (d, H), 4.08 (m, 2H), 4.275 (m, H), 4.941-5.085 (m, 4H), 5.231 (t, H), 5.430 (d, H), 5.544 (d, H), 5.970 (t, H), 6.376 (s, H), 6.961-8.017 (m, 16H).
MS: $[M + Na]^+$, 986; $[M + K]^+$, 1002; $(M + 2Na-H]^+$, 1008; $(M + Na + K-H]^+$, 1024; $[M + 2K-H]^+$, 1040
HRMS: MNa^+, 986.2955 (Calculated = 986.2976)

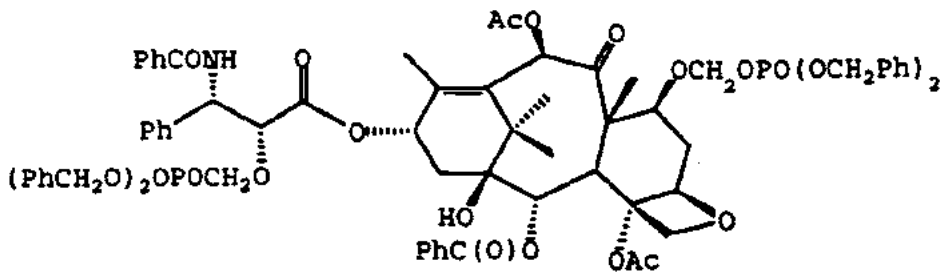
Example 5. 2',7-O-bis(phosphonooxymethyl)paclitaxel sodium salt

(a) Preparation of 2',7-O-bis(methylthiomethyl)paclitaxel



Solid benzoyl peroxide (1.995 g, 8 mmol) was added to a stirred solution of paclitaxel (0.853 g, 1 mmol) and dimethyl sulfide (1.465 g, 20 mmol) acetonitrile (20 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 3 hours. Its progress was monitored by TLC in hexane : ethyl acetate (1 : 1, v/v) R_f $_{paclitaxel}$ = 0.24, R_f $_{product}$ = 0.60. When starting material disappeared (ca. after 3 hrs) the reaction was quenched by evaporation of solvents to dryness at 25 °C using house vacuum. The dry residue was separated using silica gel column (EM Science, 40 - 63μm), 100 mL of dry silica gel, column size: Φ = 3/4 in., solvent system: hexane : ethyl acetate (3 : 2, v/v), volume of each fraction: ca. 25 mL. The title compound (0.515 g, 53% yield) was recovered from fractions 15 to 19.
MS (FAB/matrix NOBA,NaI KI): $[M + H]^+$, m/z 974; $[M + Na]^+$, m/z 996; $[M + K]^+$, m/z 1012
UV (MeOH): λmax = 204 nm, E(1%/1cm) = 243.45; λmax = 228 nm, E(1%/1cm) = 313.99
IR (KBr): 3440, 3064, 2926, 1724, 1668, 1602, 1582, 1514, 1484, 1452, 1372, 1314, 1266, 1242, 1178, 1142, 1068, 1026, 990, 916, 886, 848, 800, 774, 710, 646, 606, 570, 540, 480 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.20 (3H, s), 1.68 (3H, s), 1.74 (3H, s), 1.84 (H, dd), 2.04 (3H, d), 2.09 (3H, s), 2.15 (3H, s) overlaps with (H, m), 2.37 (H, dd), 2.51 (3H, s), 2.79 (H, ddd), 3.78 (H, d), 4.18 (H, d), 4.28 (H, m), 4.31 (H, d), 4.53 - 4.74 (4H, two overlapping AB m), 4.93 (H,d), 4.95 (H, d), 5.68 (H, d), 5.82 (H, dd), 6.24 (H, dd), 6.54 (H, s), 7.05 (H, d), 7.28 - 7.59 (10H, overlapping m), 7.57 (H, m), 7.76 (2H, d), 8.09 (2H, d).

(b) Preparation of 2',7-O-bis(dibenzylphosphonooxymethyl)paclitaxel



A solution of N-iodosuccinimide, (135 mg, 0.5 mmol) and dibenzylphosphate, (167 mg, 0.5 mmol) in dry tetrahydrofuran (8 mL) was added to a mixture of 2',7-O-bis(methylthiomethyl)paclitaxel (198 mg, 0.2 mmol) and 5 Å molecular sieves (ca. 200 mg) in methylene chloride (12 mL) at room temperature. The reaction mixture was stirred for 1.5 hours, then the molecular sieves were filtered off on celite, washed with methylene chloride (10 mL) and the solvents were evaporated to dryness at room temperature using house vacuum. The residue was dissolved in ethyl acetate (100 ml) and washed in a separation funnel with 1% sodium thiosulfate (50 mL), with 0.5 m sodium bicarbonate (50 mL), and twice with water (2x50 mL). The organic phase was dried over magnesium sulfate, evaporated to dryness and re-dissolved in ethyl acetate (1 mL). The product was precipitated with 50 mL, of ethyl ether : hexane (1:1) and washed twice with the same solvent system (2x50 mL). A crude product (218 mg) was obtained in 74% yield. Purification of this product was performed by loading its methylene chloride solution (3 mL) on silica gel (Φ = 3/4 in. x L = 1 in.) and eluting the product with 50 mL of methylene chloride : ethyl acetate (3:1) solvent system. The title compound (172.7 mg) was obtained in 59.3% yield.

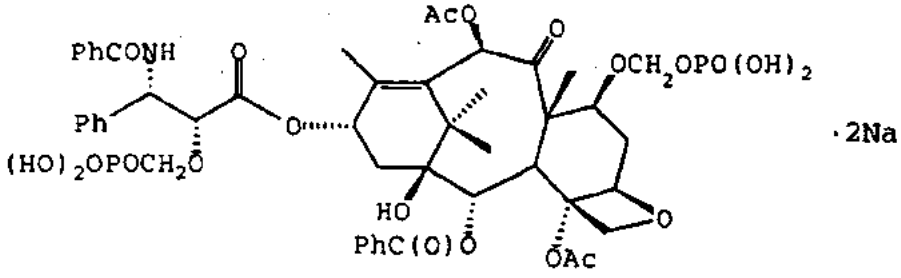
MS (FAB, matrix NOBA/NaI, KI): $[M + Na]^+$, m/z 1456; $[M + K]^+$, m/z 1472

UV (MeCN): λmax = 194 nm, E(1%/1cm) = 1078.36; λmax = 228 nm, E(1%/1cm) = 311.95

IR (KBr): 3430, 3066, 3032, 2958, 1744, 1726, 1664, 1602, 1582, 1532, 1488, 1456, 1372, 1270, 1244, 1158, 1108, 1068, 1016, 1000, 952, 886, 800, 776, 738, 698, 604, 498 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s), 1.14 (3H, s), 1.56 (H, m), 1.67 (3H, s), 1.84 (3H, d), 1.90 (H, m), 2.17 (3H, s), 2.29 (3H, s), 2.73 (H, m), 3.73 (H, d), 4.08 (H, d), 4.15 (H, m), 4.20 (H, d), 4.77 (H, m), 4.79 (H, d), 4.91 - 5.04 (10H overlapping m), 5.25 (H, dd), 5.38 (H, dd), 5.54 - 5.64 (2H, overlapping m), 5.99 (H, br. dd), 6.25 (H, s), 7.11 - 7.14 (2H, m), 7.24 - 7.64 (28H, overlapping m), 7.94 (2H, dd), 8.04 (2H, dd), 8.30 (H, d).

(c) Preparation of 2',7-O-bis(phosphonooxymethyl)paclitaxel sodium salt



A sample of 2',7-O-bis(dibenzylphosphonooxymethyl)paclitaxel (112 mg, 0.078 mmol) was dissolved in ethyl acetate (7 ml) and hydrogenated over 10% palladium on charcoal (50 mg) at room temperature, 60 PSI (400 kPa), for 2 hours. The catalyst was removed by filtration over Celite. The Celite was rinsed with ethyl acetate (10 mL). The filtrate was treated with solid sodium bicarbonate (20 mg, 3 eq.) and then the solvent was evaporated to dryness. A dry residue was re-dissolved in 5 mL of water : acetone (4:1, v/v) and purified by C-18 reverse phase column chromatography (55 - 105μ C-18, Waters, 50 mL of dry C-18, Φ = 3/4 in. in

water : acetone (4 : 1, v/v). Eluant was monitored on analytical HPLC Jones C-18 column (15 cm, 1 mL/min., λ = 230mn) in acetonitrile : phosphate buffer pH 6 (50/50, v/v) with the addition of Q12 ion pair cocktail (Regis), Rt = 4.7min. Fractions containing the title product were combined, acetone was evaporated under house vacuum at 20°C, and the solution was lyophilized. The title product (44.2 mg) was obtained in 58.8% yield.

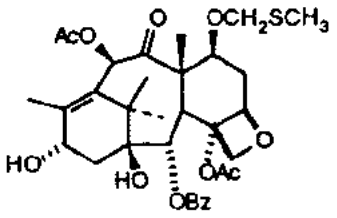
MS (FAB,matrix NOBA/NaI, KI): $[M + H]^+$, m/z 1118; $[M + Na]^+$, m/z 1140

UV (MeCN): λmax = 192 nm, E(1%/1cm) = 129.73; λmax = 230 nm, E(1%/1cm) = 26.43

IR (KBr): 3430, 3068, 2956, 1724, 1658, 1604, 1582, 1520, 1486, 1452, 1374, 1316, 1256, 1152, 1110, 1070, 1026, 966, 914, 802, 772, 710, 538 cm^{-1}.

^{1}H-NMR (acetone-d_6/D_2O) δ: 0.97 (3H, s), 1.02 (3H, s), 1.47 (H, m), 1.54 (3H, s), 1.70 (H, m), 1.75 (3H, s), 1.85 (H, m), 2.11 (3H, s), 2.30 (3H, s), 2.88 (H, m), 3.64 (H, d), 4.03 (H, m), 4.06 (H, d), 4.16 (H, d), 4.74 (H, m), 4.86 (H, m), 5.11 (H, br. t), 5.22 (H, d), 5.42 (H, d), 5.90 (H, br. t), 6.21 (H, s), 7.06 (H, br.t), 7.32 - 7.69 (10H, ovelapping m), 7.80 (2H, d), 7.93 (2H, d).

Example 6. 7-O-methylthiomethylbaccatin III (7-MTM baccatin III)



To a solution of 2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel (compound of Example 3(b), 27 g, 27.4 mmol) in 100 mL of THF and 500 mL of methanol was added freshly ground K_2CO_3 (2.7 g, 19 mmol). The solution was stirred for 30 minutes and neutralized with IR-120 (H^+) resin, filtered and concentrated. The crude filtrate was then dissolved in 200 mL of dichloromethane and stirred for 24 hours with tetrabutylammonium borohydride (10 g). The solution was diluted with dichloromethane and washed with water, saturated bicarbonate and brine. The organic fraction was then dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 9.4 g of the title compound (53%) with a melting point of 269°C.

FABMS (NOBA) M + H calcd for $C_{33}H_{43}SO_{11}$: 647. Found: 647.

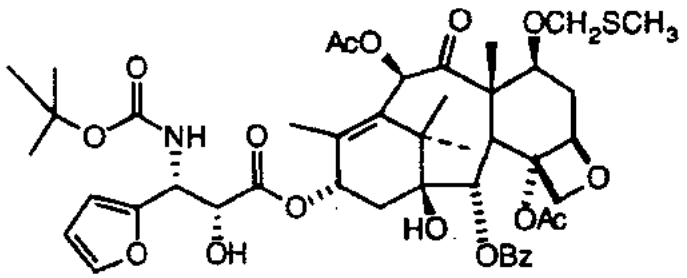
IR(KBr) 3474, 1746, 1724, 1712, 1270, 1240, 1070 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.1 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.55 (s, 1H), 4.94 (d, J = 8.1 Hz, 1H), 4.83 (bq, J = 5.1 Hz, 1H), 4.66 (ABq, J = 14.7,12.3 Hz, 2H), 4.30 (m, 2H), 4.13 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 2.79 (m, 1H), 2.27 (s, 3H), 2.25 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 4H), 1.81 (m, 1H), 1.72 (s, 3H), 1.61 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.3, 170.8, 169.3, 167.0, 144.2, 132.6, 132.1, 130.1, 129.4, 128.6, 83.9, 80.9, 78.7, 75.7, 74.5, 73.9, 67.9, 57.6, 47.6, 42.7, 38.3, 26.7, 22.6, 21.0, 20.1, 15.2, 15.0, 10.8.

Example 7. 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

(a) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethyl-paclitaxel



To a solution of HMDS (0.40 mL, 1.90 mmol) in 15 mL of THF was added a solution of n-BuLi (0.75 mL, 2.5 M in hexanes, 1.88 mmol) and stirred 5 minutes at -55°C. To this solution was added 7-MTM baccatin III (compound of example 6, 1.03 g, 1.59 mmol) in 10 mL, of THF and stirred for 10 minutes before addition of an 10 mL solution of (3R,4R)-1-(t-butyloxycarbonyl)-4-(2-furyl)-3-(triethylsilyloxy)-2-azetidinone (883 mg, 2.40 mmol). The cold bath was removed and replaced with a 0°C bath and the reaction mixture was stirred for 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (2.5:1 hexane/ethyl acetate) to give 1.5 g of the coupling product 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl) -3'-(2-furyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (93%).

FABMS (NOBA) M + Na calcd for $C_{50}H_{71}NSSiO_{16}$: 1036. Found: 1036.

IR(film) 3446 (s), 1720, 1368, 1242, 1166, 1144, 1124, 1066 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.56 (m, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.38 (m, 1H), 6.56 (s, 1H), 6.33 (m, 1H), 6.20 (m, 2H), 5.67 (d, J=6.9 Hz, 1H), 5.29 (bs, 2H), 4.94 (d, J=7.8 Hz, 1H), 4.75 (s, 1H), 4.65 (s, 2H), 4.28 (m, 2H), 4.16 (d, J=8.1 Hz, 1H), 3.89 (d, J=6.9 Hz, 1H), 2.80 (m, 1H), 2.46 (s, 3H), 2.37 (m, 1H), 2.22 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.65 (m, 1H), 1.33 (s, 9H), 1.20 (s, 3H), 1.19 (s, 3H), 0.81 (t, J=7.8 Hz, 9H), 0.47 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 171.2, 170.3, 169.3, 167.1, 155.3, 152.0, 141.9, 141.0, 133.6, 132.9, 130.2, 129.2, 128.7, 110.7, 107.3, 84.0, 81.1, 80.2, 78.7, 76.1, 75.7, 74.7, 74.1, 72.4, 71.1, 57.4, 52.8, 47.1, 43.3, 35.2, 33.0, 28.1, 26.3, 22.9, 21.2, 21.0, 15.0, 14.5, 10.9, 6.5, 4.3.

To a solution of the 2'-triethylsilyl ether obtained above (330 mg, 0.32 mmol) in 7 mL, of THF was added tetrabutylammonium fluoride (0.35 mL,, 1.0M in THF, 0.35 mmol) and stirred 10 minutes. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated and the residue was chromatographed over silica gel (2:1 hexane/ethyl acetate) to give 301 mg of the title compound (95%).

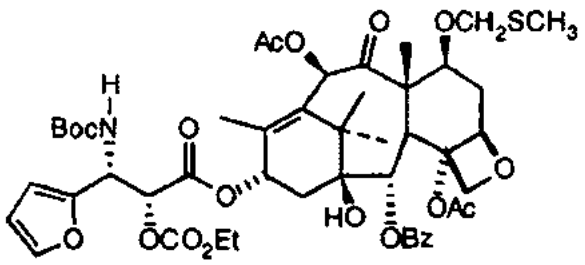
FABMS (NOBA) M + H calcd for $C_{45}H_{58}NO_{16}S$: 900. Found: 900.

IR(film) 3442, 1720, 1242, 1066, 1026 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 2H), 7.57 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.38 (s, 1H), 6.53 (s, 1H), 6.34 (d, J=3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 6.17 (t, J=8.1 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.29 (m, 2H), 4.92 (d, J=8.0 Hz, 1H), 4.70 (m, 1H), 4.64 (d, J=4.6 Hz, 2H), 4.29 (m, 2H), 4.14 (d, J=8.3 Hz, 1H), 3.66 (d, J=6.8 Hz, 1H), 3.37(d, J = 5.8 Hz, 1H), 2.77 (m, 1H), 2.38 (s, 3H), 2.32 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.77 (m, 3H), 1.73 (s, 3H), 1.33 (s, 9H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.6, 170.3, 169.2, 167.0, 155.2, 151.3, 142.4, 140.4, 133.7, 133.2, 130.2, 129.1, 128.7, 110.7, 107.4, 83.9, 81.2, 80.5, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 72.5, 71.8, 57.4, 51.7, 47.2, 43.2, 35.2, 32.8, 28.1, 26.4, 22.6, 20.9, 15.2, 14.6, 10.9, 8.3.

(b) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel



To a solution of the product of step (a) (864 mg, 0.96 mmol) in 50 mL of dichloromethane at 0°C was added diisopropylethyl amine (2.0 mL, 11.5 mmol) and ethyl chloroformate (0.50 mL, 5.25 mmol) and stirred for 4 hours. The solution was diluted with dichloromethane and washed with saturated bicarbonate and dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 884 mg of the 2' ethyl carbonate title compound (95%).

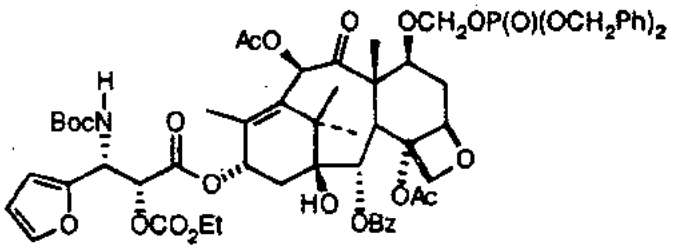
FABMS (NOBA) M+H calcd for $C_{48}H_{62}NO_{18}S$ 972.3688. Found: 972.3654.

IR(film) 1752, 1720, 1370, 1244, 1196, 1176, 1064 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.8 Hz, 2H), 7.57 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.38 (s, 1H), 6.55 (s, 1H), 6.35 (m, 1H), 6.27 (m, 1H), 6.22 (t, J=7.8 Hz, 1H), 5.67 (d, J=7.2 Hz, 1H), 5.51 (d, J=9.9 Hz, 1H), 5.34 (d, J=2.4 Hz, 1H), 5.25 (d, J=10.2 Hz, 1H), 4.95 (d, J=8.1 Hz, 1H), 4.65 (s, 2H), 4.30 (m, 2H), 4.22 (m, 2H), 3.88 (d, J=7.2 Hz, 1H), 2.81 (m, 1H), 2.41 (s, 3H), 2.36 - 2.21 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.67 (s, 1H), 1.59 (s, 1H), 1.34 (s, 9H), 1.29 (t, J=7.2 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.1, 169.9, 169.1, 167.6, 167.0, 154.0, 150.1, 142.6, 141.0, 133.6, 132.9, 130.2, 129.2, 128.7, 110.7, 107.5, 83.9, 81.1, 80.7, 78.7, 76.0, 75.7, 75.1, 74.7, 74.2, 71.8, 65.1, 57.4, 49.7, 47.1, 43.2, 35.0, 33.0, 28.1, 26.3, 22.6, 21.1, 20.9, 15.1, 14.5, 14.1, 10.9.

(c) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-dibenzylphosphonooxymethylpaclitaxel



To a solution of the product of step (b) (230 mg, 0.236 mmol) in 10 mL of anhydrous THF was added 300 mg of 4A sieves, dibenzylphosphate (270 mg, 0.98 mmol) and recrystallized NIS (62 mg, 0.28 mmol). To this solution was added silver trifluoromethanesulfonate (45 mg, 0.17 mmol) and the solution stirred for 3 hours. The solution was filtered through Celite and diluted with ethyl acetate and washed with 10% NaS_2O_8, sautruated bicarbonate, and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (15% acetonitrile/chloroform) to give 219 mg of the dibenzyl phosphate title compound (77%).

FABMS (NOBA) M+Na calcd for $C_{61}H_{72}NPO_{22}Na$ 1224. Found: 1224.

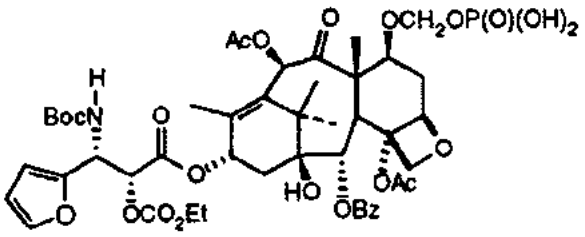
IR(film) 3422 (br), 1750, 1722, 1370, 1244, 1160, 1036, 1016, 1000, 976, 944 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=6.9 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.39 (s, 1H), 7.31 (m, 10), 6.35 (m, 2H), 6.28 (s, 1H), 6.21 (t, J=7.8 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.50 (d, J=10.5 Hz, 1H), 5.39 (d, J=6.6 Hz, 1H), 5.32 (d, J=2.4 Hz, 1H), 5.25 (d, J=9.9 Hz, 1H), 5.01 (dd, J=8.1,

6.3 Hz, 5H), 4.86 (d, J = 8.4 Hz, 1H), 4.29-4.09 (m, 4H), 3.85 (d, J = 6.9 Hz, 1H), 2.77 (m, 1H), 2.40 (s, 3H), 2.30 (m, 2H), 2.16 (s, 3H), 1.99 (s, 3H), 1.94 (m, 1H), 1.70 (s, 3H), 1.67 (s, 1H), 1.54 (s, 1H), 1.34 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.17 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.8, 169.9, 169.2, 167.7, 167.0, 155.1, 154.0, 150.0, 142.74, 141.1, 133.7, 132.9, 130.2, 129.1, 128.7, 128.5, 128.4, 128.0, 110.7, 107.6, 93.8, 84.1, 81.6, 80.8, 80.7, 78.8, 76.3, 75.1, 74.6, 71.8, 69.3, 69.2, 65.1, 57.0, 49.7, 46.7, 43.2, 35.0, 28.1, 26.4, 22.6, 21.2, 20.8, 14.6, 14.1, 10.5.

(d) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt



To a solution of the product of step (c) (311 mg, 0.259 mmol) in 25 mL of ethyl acetate was added 60 mg of Pd on carbon (10%) and the solution stirred under an atmosphere of H_2 for 30 minutes. The catalyst was removed by filtratation through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in 3 mL of ethyl acetate and triethananolamine added (2.3 mL, 0.1M in ethyl acetate, 0.23 mmol). The solution was concentrated and the residue was chromatographed over C_{18} (40% acetonitrile/water) and lyophilized to give 205 mg of the phosphate triethanolamine salt (67%).

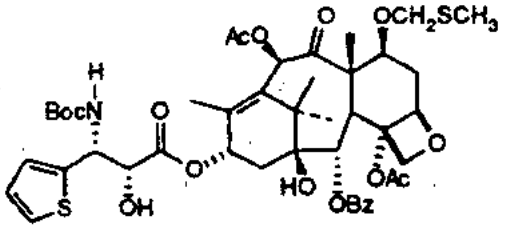
FABMS (NOBA) M + Na calcd for $C_{47}H_{60}HPO_{22}Na$ 1044. Found: 1044.

IR(film) 3432 (br), 1752, 1722, 1372, 1246, 1158, 1108, 1096, 1070, 1002 cm^{-1}

^1H NMR (d_6 acetone/D_2O, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.62 (m, 2H), 7.52 (t, J = 7.5 Hz, 2H), 6.48 (d, J = 3.3 Hz, 1H), 6.42 (m, 2H), 6.16 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.46 (d, J = 3.6 Hz, 1H), 5.30 (d, J = 3.6 Hz, 1H), 5.17 (bs, 1H), 5.01 (bd, J = 9.0 Hz, 1H), 4.19 (bs, 1H), 4.18 (m, 5H), 3.95 (m, 4H), 3.87 (d, J = 6.9 Hz, 1H), 3.68 (s, 10H), 3.50 (bt, J = 4.8 Hz, 4H), 2.95 (m, 1H), 2.44 (s, 3H), 2.41 (m, 2H), 2.16 (s, 3H), 1.99 (s, 3H), 1.94 (m, 1H), 1.68 (s, 3H), 1.34 (s, 9H), 1.24 (t, J = 6.9 Hz, 3H), 1.17 (s, 6H).

Example 8. 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

(a) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethyl-paclitaxel



To a solution of HMDS (0.5 mL, 2.4 mmol) in 18 mL of THF at -55°C was added n-BuLi (0.85 mL, 2.5 M in hexanes, 2.1 mmol). After 10 minutes 7-MTM baccatin III (1.15 g, 1.78 mmol) in 18 mL of THF was added dropwise and stirred in the cold for 10 minutes. (±)cis-1-(t-Butyloxycarbonyl)-4-(2-thienyl)-3-(triethylsilyloxy)-2-azetidinone (2.80 g, 7.3 mmol) in 18 mL of THF was added and the cold bath allowed to slowly warm to 0°C over 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl

solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (5:1 hexane/ethyl acetate) to give 1.87 g of recovered lactam (3:1 hexane/ethyl acetate) to give 1.44 g of the coupling product 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethyl-2'-O-triethylsilylpaclitaxel (78%).

FABMS (NOBA) M + Na calcd for $C_{51}H_{71}NO_{15}S_2SiNa$ 1052. Found: 1052.

IR(film) 3442 (br), 1720, 1490, 1368, 1270, 1242, 1162, 1110, 1064, 1024, 984, 754 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.22 (m, 1H), 6.95 (m, 2H), 6.55 (s, 1H), 6.21 (t, J = 9.3 Hz, 1H), 5.68 (d, J = 6.9 Hz, 1H), 5.49 (bd, 1H), 5.39 (bd, J = 9.6 Hz, 1H), 4.94 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 4.57 (s, 1H), 4.28 (m, 2H), 4.17 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.46 (s, 3H), 2.37 (m, 1H), 2.20 (m, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.68 (s, 1H), 1.62 (s, 1H), 1.31 (s, 9H), 1.20 (s, 6H), 0.84 (t, J = 7.8 Hz, 9H), 0.50 (m, 6H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9, 171.1, 170.7, 170.1, 169.3, 167.0, 155.1, 142.8, 140.9, 133.6, 132.9, 130.2, 129.2, 128.7, 126.9, 124.6, 83.9, 81.2, 80.1, 78.8, 77.4, 76.0, 75.7, 75.2, 74.8, 74.1, 71.3, 57.4, 53.8, 47.0, 43.3, 35.3, 33.3, 28.1, 26.3, 23.0, 21.3, 20.9, 14.9, 14.4, 10.9, 6.6, 4.5.

To a solution of the 2'-triethylsilyl ether obtained above (1.41 g, 1.37 mmol) in 14 mL of THF was added tetrabutylammonium fluoride (1.4 mL, 1.0 M in THF, 1.40 mmol). The solution was stirred for 30 minutes, diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 1.16 g of the title compound (92%).

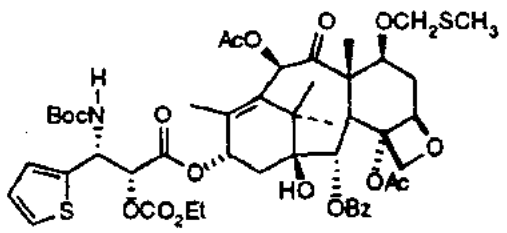
FABMS (NOBA) M + Na calcd for $C_{45}H_{57}NO_{15}S_2Na$ 938. Found: 938.

IR(film) 3440 (br), 1720, 1368, 1242, 1168, 1106, 1066, 710 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.2 Hz, 2H), 7.59 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.24 (m, 1H), 7.07 (m, 1H), 6.99 (m, 1H), 6.53 (s, 1H), 6.18 (t, J = 8.1 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 5.49 (d, J = 9.6 Hz, 1H), 5.32 (d, J = 9.6 Hz, 1H), 4.92 (d, J = 7.8 Hz, 1H), 4.63 (m, 3H), 4.28 (m, 2H), 4.15 (d, J = 8.4 Hz, 1H), 3.86 (d, J = 6.9 Hz, 1H), 3.47 (d, J = 5.4 Hz, 1H), 2.78 (m, 1H), 2.36 (s, 3H), 2.34 (, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.72 (s, 1H), 1.61 (s, 1H), 1.33 (s, 9H), 1.21 (s, 3H), 1.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9,172.3, 170.3, 169.2, 167.0, 154.0, 141.5, 140.2, 133.7, 133.3, 130.2, 129.1, 128.7, 127.0, 125.4, 125.4, 83.9, 81.3, 80.4, 78.6, 76.1, 75.4, 74.5, 74.0, 73.4, 72.5, 57.5, 52.8, 47.2, 43.2, 35.3, 32.9, 28.2, 26.4, 22.6, 20.9, 15.1, 14.7, 10.8.

(b) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel



To a solution of the product of step (a) (621 mg, 0.677 mmol) in 35 mL of dichloromethane at 0 °C was added diisopropylethyl amine (1.20 mL, 6.89 mmol) and ethyl chloroformate (0.35 mL, 3.7 mmol) and stirred for 1 hour. The cold bath was removed and the solution stirred for 2 hours and was diluted with dichloromethane and was washed with saturated bicarbonate and dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 528 mg of the title compound (79%).

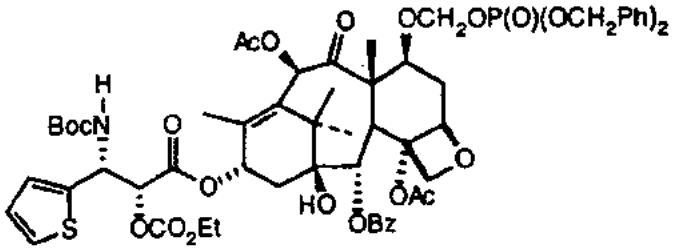
FABMS (NOBA) M + Na calcd for $C_{48}H_{61}NO_{17}S_2Na$ 1010. Found: 1010.

IR(film) 3510, 3440, 1752, 1720, 1370, 1244, 1198, 1170, 1026, 988, 756 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.2 Hz, 2H), 7.58 (m, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.26 (m, 1H), 6.99 (, 2H), 6.55 (s, 1H), 6.23 (t, J = 9.0 Hz, 1H), 5.68 (d, J = 6.9 Hz, 2H), 5.33 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 2.4 Hz, 1H), 4.94 (d, J = 7.8 Hz, 1H), 4.65 (s, 2H), 4.33-4.08 (m, 5H), 3.88 (d, J = 6.9 Hz, 1H), 2.80 (m, 1H), 2.40 (s, 3H), 2.40 - 2.20 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.69 (s, 1H), 1.60 (s, 1H), 1.33 (s, 9H), 1.31 (t, J = 7.2 Hz, 9H), 1.20 (s, 3H), 1.19 (s, 3H).

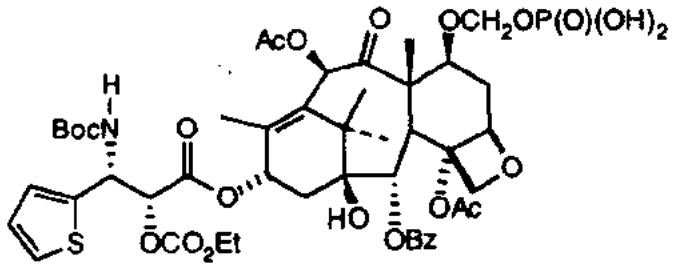
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 169.7, 169.1, 167.5, 167.1, 154.0, 140.9, 133.6, 132.9, 130.2, 129.2, 128.7, 127.2, 125.4, 125.3, 83.9, 81.2, 80.6, 78.8, 76.9, 76.0, 75.7, 74.7, 74.2, 72.8, 72.0, 65.2, 57.4, 50.9, 47.1, 43.3, 35.1, 33.0, 28.1, 26.4, 22.7, 21.2, 20.9, 15.1, 14.5, 14.1, 10.9.

(c) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-dibenzylphosphonooxymethylpaclitaxel



To a solution of the product of step (b) (516 mg, 0.522 mmol) in 15 mL of anhydrous THF was added 530 mg of 4A sieves, dibenzylphosphate (576 mg, 2.09 mmol) and recrystalized NIS (136 mg, 0.604 mmol). To this solution was added silver trifluoromethanesulfonate (50 mg, 0.194 mmol) and the solution stirred for 1 hour. The solution was filtered through Celite and diluted with ethyl acetate and washed with 10% NaS_2O_3, saturated bicarbonate and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (15% acetonitrile/chloroform) to give 535 mg of the title compound (84%).
FABMS (NOBA) M + Na calcd for $C_{61}H_{72}NO_{21}PSNa$ 1240. Found: 1240.
IR(film) 3424 (br), 1750, 1722, 1370, 1244, 1016, 1000, 944 cm^{-1}
^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.0 Hz, 2H), 7.58 (m, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.28 (m, 11H), 6.99 (m, 2H) 6.33 (s, 1H), 6.22 (t, J = 7.8 Hz, 1H), 5.66 (m, 2H), 5.39 (t, J = 6.6 Hz, 1H), 5.34 (d, J = 12 Hz, 1H), 5.22 (d, J = 2.4 Hz, 1H), 5.01 (dd, J = 8.1, 6.0 Hz, 5H), 4.86 (d, J = 7.8 Hz, 1H), 4.29-4.08 (m, 5H), 3.85 (d, J = 6.6 Hz, 1H), 2.76 (m, 1H), 2.39 (s, 3H), 2.35-2.18 (m, 2H), 2.16 (s, 3H), 1.97 (s, 4H), 1.69 (s, 4H), 1.33 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H), 1.20 (s, 3H), 1.17 (s, 3H).
^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 197.4, 165.4, 164.9, 163.3, 162.7, 150.6, 149.7, 136.7, 136.0, 129.4, 128.6, 125.9, 124.7, 124.3, 124.2, 124.1, 123.6, 122.9, 121.1, 121.0, 89.4, 79.8, 77.3, 76.5, 76.3, 74.4, 72.0, 70.7, 70.3, 67.7, 64.9, 64.9, 60.9, 52.7, 46.5, 42.3, 38.9, 30.7, 23.8, 22.0, 18.3, 17.0, 16.4, 10.3, 9.8, 6.2.

(d) preparation of 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt

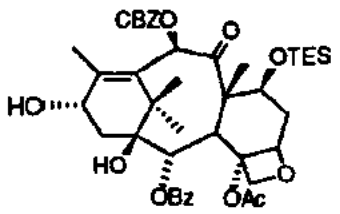


To a solution of the product of step (c) (512 mg, 0.42 mmol) in 30 mL of ethyl acetate was added 53 mg of Pd on carbon (10%) and the solution stirred under an atmosphere of H_2 for 3 hours. The catalyst was removed by filtratation through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in 2 mL of ethyl acetate and triethananolamine added (4.0 mL, 0.1M in ethyl acetate, 0.40mmol). The solution was concentrated and the residue was chromatographed over C_{18} (40% acetonitrile/water) and lyophilized to give 280 mg of the phosphate triethanolamine salt (56%). HPLC analysis showed the purity of the salt to

be 98%.
FABMS (NOBA) M + Na calcd for $C_{47}H_{50}NO_{21}PS$ 1060. Found: 1060.
IR(KBr) 3422 (br), 1750, 1720, 1372, 1246, 1162, 1096, 1068, 1000 cm^{-1}
^1H NMR (d_6 acetone/D_2O, 300 MHz) δ 8.06 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.38 (d, J = 4.2 Hz, 1H), 7.16 (d, J = 3.5 Hz, 1H), 7.01 (dd, J = 5.1, 3.6 Hz, 1H), 6.37 (s, 1H), 6.11 (t, J = 8.7 Hz, 1H), 5.61 (d, J = 6.9 Hz, 1H), 5.60 (s, 1H), 5.26 (d, J = 4.5 Hz, 1H), 5.14 (t, J = 6.6 Hz, 1H), 5.00 (d, J = 8.4 Hz, 1H), 4.86 (dd, J = 12.0, 6.3 Hz, 1H), 4.17 (m, 5H), 4.00 (s, 7H), 3.92 (t, J = 4.8 Hz, 6H), 3.84 (d, J = 6.9 Hz, 1H), 3.48 (t, J = 5.4 Hz, 6H), 2.94 (m, 1H), 2.42 (s, 3H), 2.36 (m, 1H), 2.27 (m, 1H), 2.15 (s, 3H), 1.95 (s, 4H), 1.66 (s, 3H), 1.30 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.14 (s, 6H).

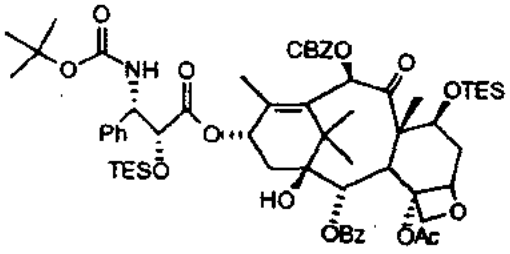
EXample 9. 10-Desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel

(a) preparation of 10-desacetyl-10-O-benzyloxycarbonyl-7-O-triethylsilylbaccatin III



To a dry flask under an argon atmosphere containing 7-O-triethylsilyl-10-desacetyl baccatin III (2.093g, 3.177 mmol) was added dry THF (30 mL) and cooled to -70 °C. To this was added 1.6 M n-butyllithium (2.38mL, 3.81mmol) in a dropwise fashion. After stirring for 15 min, benzyl chloroformate (0.91mL, 6.35mmol) was added dropwise. The resulting mixture was stirred for 3 h with gradual warming to ambient temperature. The reaction was quenched with 25 mL of sat. NH_4Cl, washed with brine, and dried with $MgSO_4$. Flash chromatography (silica gel, 30-45% ethyl acetate/hexane) furnished 2.24g (89%) of the title compound as a white foam.
^1H NMR (300MHz, $CDCl_3$) δ 8.10 (d, J = 8.0, 2H); 7.63-7.58 (m, 1H) 7.47 (t, J = 8.0, 2H); 7.41-7.26 (m, 5H); 6.29 (s, 1H); 5.61 (d, J = 7.0, 1H); 5.20 (q, J = 12.2, 2H); 4.96 (d, J = 9.0, 1H); 4.87-4.84 (m, 1H); 4.48 (dd, J = 6.7, J = 10.4, 1H); 4.30 (d, J = 8.5, 1H); 4.14 (d, J = 8.5, 1H); 3.84 (d, J = 7.0, 1H); 2.58-2.48 (m, 1H); 2.29 (m, 4H); 2.20 (s, 3H); 2.03 (d, J = 5.0, 1H); 1.92-1.83 (m, 1H); 1.68 (s, 3H); 1.17 (s, 3H); 1.04 (s, 3H); 0.91 (t, J = 7.5, 9H); 0.57 (q, J = 7.4, 6H).

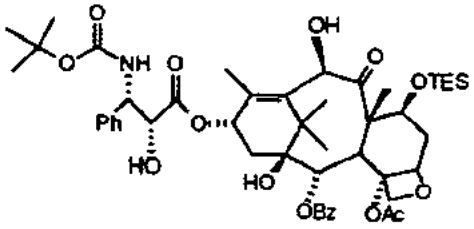
(b) preparation of 10-desacetyl-10-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-2',7-bis-O-triethylsilylpaclitaxel



To a dry flask containing the product of step (a) (3.50g, 4.42mmol) was added a small amount of toluene and the solution was then concentrated under vacuum. This flask was placed under an argon atmosphere and 100 mL of dry THF was added. The flask was cooled to -70 °C and 1.0 M lithium hexamethyldisilazide (6.19mL, 6.19mmol) was added in a dropwise fashion. After stirring for 20 min, a solution of (3R,4S)-1-(t-butyloxycarbonyl)-4-phenyl-3-triethylsilyloxy-2-azetidinone (2.58g, 7.07mmol) in 10 mL dry THF was added

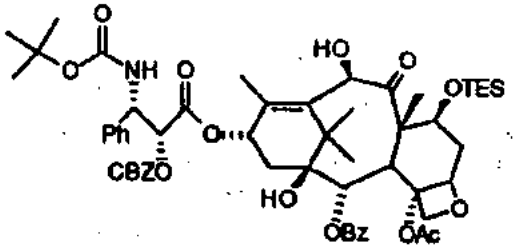
dropwise. The reaction mixture was stirred for 3.5 h, gradually warming to ambient temperature. It was then quenched with 70 mL of sat. NH_4Cl, washed with brine and dried with $MgSO_4$. Flash chromatography (silica gel, 5-15% ethyl acetate/hexanes) provided 5.12g (99%,) of the title compound as a white foam.
^1H NMR (300MHz, $CDCl_3$) δ 8.11 (d, J=8.0, 2H); 7.60-7.58 (m, 1H); 7.48 (t, J=8.0, 2H); 7.24 -7.26 (m, 10H); 6.32-6.26 (m, 2H); 5.69 (d, J=7.0, 1H); 5.47 (bd, J=9.7, 1H); 5.31-5.10 (m, 3H); 4.94 (d, J=8.5, 1H); 4.56 (s, 1H); 4.46 (dd, J=6.9, J=10.6, 1H); 4.31 (d, J=8.3, 1H); 4.17 (d, J=8.3, 1H); 3.81 (d, J=7.0, 1H); 2.53 (s, 3H); 2.48-2.33 (m, 1H); 2.22-2.17 (m, 1H); 2.09 (s, 3H); 1.95-1.86 (m, 1H); 1.70 (s, 3H); 1.65 (s, 1H); 1.52 (s, 1H); 1.30 (s, 9H); 1.26-1.19 (m, 6H); 0.94-0.87 (m, 9H); 0.80-0.75 (m, 9H); 0.61-0.53 (m, 6H); 0.48-0.30 (m, 6H).

(c) preparation of 10-desacetyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-triethylsilylpaclitaxel



The product of step (b) (5.12 g, 4.40 mmol) was dissolved into 100 mL of ethyl acetate, transferred to a Parr bottle and placed under a blanket of argon. To this was added 10% palladium on carbon (2.4g) and the reaction mixtre was placed on a Parr hydrogenation apparatus (55psi) for a period of 8 h. The reaction mixture was filtered through a plug of Celite and concentrated. Flash chromatography (silica gel, 15-20% ethyl acetate/hexane) provided 3.24g (79%) of the title compound as a white foam. Hydrolysis of the 2'-triethylsilyl group of the product of step (b) was a result of trace acidic residues in the Parr equipment.
^1H NMR (300MHz, $CDCl_3$) δ 8.10 (d,J=8.0, 2H); 7.63-7.58 (m, 1H); 7.49 (d, J=8.0, 2H); 7.39-7.26 (m, 5H); 6.27-6.17(m, 1H); 5.64 (d, J=7.2); 5.42(d, J=9.4, 1H); 5.28-5.25 (m, 1H); 5.12 (s, 1H); 4.92 (d, J=8.6, 1H); 4.62 (bs, 1H); 4.38-4.28 (m, 3H); 4.17 (d, J=8.5, 1H); 3.85 (d, J=6.7, 1H); 3.36 (d, J=5.3, 1H); 2.49-2.40 (m, 1H); 2.36 (s, 3H); 2.25 (bd, J=8.7, 2H); 1.99-1.91 (m, 1H); 1.85 (s, 3H); 1.74 (s, 3H); 1.69 (s, 1H), 1.67 (s, 1H); 1.35 (s, 9H); 1.22 (s, 3H); 1.11 (s, 3H); 0.93 (t, J=7.5 9H); 0.61-0.49 (m, 6H).

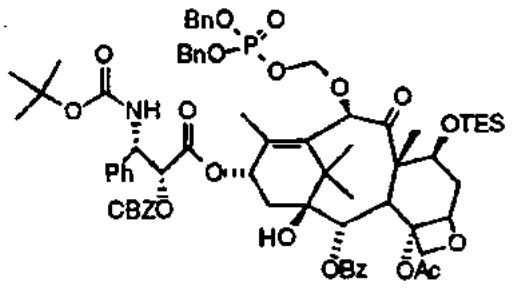
(d) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-7-O-triethylsilylpaclitaxel



To a flask containing the product of step (c) (3.24g, 3.51mmol) was added 30 mL of dry dichloromethane. The flask was placed under argon and cooled to 0°C. N,N-diisopropylethylamine (1.22 mL, 7.02 mmol) was added to the reaction mixture, followed by addition of benzyl chloroformate (1.00mL, 7.02 mmol) in a dropwise manner. After 15 min, the cooling bath was removed and the reaction allowed to stir at ambient temperature for 7 h. The mixture was quenched with 30 mL, sat. NH_4Cl, washed with brine and dried with $MgSO_4$. Flash chromatography (silica gel, 7-20% ethyl acetate/hexane) provided 3.24g (89%) of the title compound as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ 8.10 (d, J=8.0, 2H); 7.62-7.57 (m, 1H); 7.48 (t, J=8.0, 2H); 7.40-7.26 (m, 10H); 6.33-6.27 (m, 1H); 5.66 (d, J=7.0, 1H); 5.49-5.42 (m, 2H); 5.31 (s, 1H); 5.22-5.13 (m , 3H); 4.93 (d, J-9.4, 1H); 4.38 (dd, J=6.5, J=10.7, 1H); 4.34-4.28 (m, 2H); 4.18 (d J=8.3, 1H); 3.90 (d, J=6.7, 1H); 2.52-2.30 (m, 4H); 2.24-2.20 (m, 1H); 1.97-1.87 (m, 3H); 1.74 (s, 3H); 1.59 (s, 3H); 1.32 (s, 9H); 1.26, (s, 3H); 1.11 (s, 3H); 0.96-0.88 (m, 9H); 0.61-0.48 (m, 6H).

(e) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)-7-O-triethylsilylpaclitaxel



The product of step (d) was dissolved into 13.5 mL (54%) of DMSO, 8.75 mL (35%) acetic anhydride and 2.75 mL (11%) glacial acetic acid and placed under an atmosphere of argon. The reaction mixture stirred for 56 h, after which it was diluted with ethyl acetate to a volumn of 60 mL. The solution was washed with sat. $NaHCO_3$ until neutral by pH paper and then washed with brine. The organic fraction was dried with $MgSO_4$ and concentrated. Flash chromatography with 15-20% EtOAc/hexane provided 3.12g of crude white foam with the desired thiomethyl acetal product (i.e. 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(methylthiomethyl)-7-O-triethylsilylpaclitaxel accounting for 70% of the material by NMR.

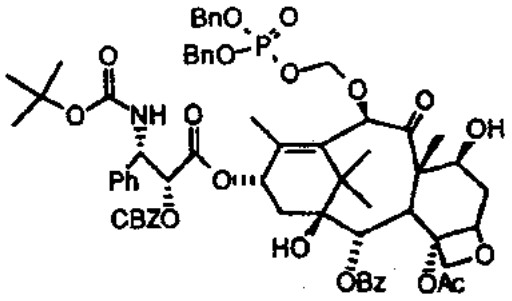
The above crude mixture (3.12g) was then dissolved in 1,2-dichloroethane (61 mL) and placed under a blanket of argon. 4Å powdered molecular sieves (3.12 g) were added and the resulting heterogeneous mixture was stirred vigorously. To this was added a solution of recrystallized N-iodosuccinimide (0.830 g, 3.69 mmol) and dibenzyl phosphate (1.027 g, 3.69 mmol) in dry THF (46 mL) via cannula. The resulting mixture was stirred for 5 h, filtered through a plug of Celite, and diluted to a volume of 250 mL with ethyl acetate . It was washed with (2 x 125mL) of cold 2% $NaHSO_3$, cold 6% $NaHCO_3$ (2 x 125 mL) and brine. The organic phase was dried with $MgSO_4$ and concentrated. Flash chromatography (silica gel, 25-35% ethyl acetate/hexane) provided 1.52g (40%) of title compound as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.0, 2H); 7.59-7.55 (m, 1H); 7.46 (t, J=7.2, 2H); 7.38-7.25 (m, 20H); 6.30 (t, J=8.5, 1H); 5.65 (d, J=6.8, 1H); 5.49-5.39 (m, 4H); 5.32 (s, 1H); 5.18-4.19 (m, 4H); 4.93 (d, J=9.2, 1H); 4.44 (dd, J=6.6, J=10.2, 1H); 4.31 (d, J=8.4, 1H); 4.16 (d, J=8.5, 1H); 3.80 (d, J=6.9, 1H); 2.69-2.39, (m, 4H), 2.33-2.23 (m, 3H); 2.03 (s, 3H); 1.90 (t, J=12.6, 1H); 1.68-1.63 (m, 6H); 1.28 (s, 9H); 1.16-1.10 (m, 6H); 0.93 (t, J=7.4, 9H); 0.55 (q, J=7.8, 6H).

^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 204.1, 169.7, 167.9, 167.1, 151.1, 140.7, 135.7, 133.6, 130.2, 129.2, 128.9, 128.8, 128. 7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 126.4, 90.4, 84.2, 81.1, 80.4, 79.3, 78.8, 74.9, 72.8, 72.0, 70.5, 69.2, 69.1, 69.0, 58.1, 46.8, 43.2, 37.1, 35.0, 28.1, 26.5, 22.8, 21.0, 14.1, 10.0, 6.9, 5.5.

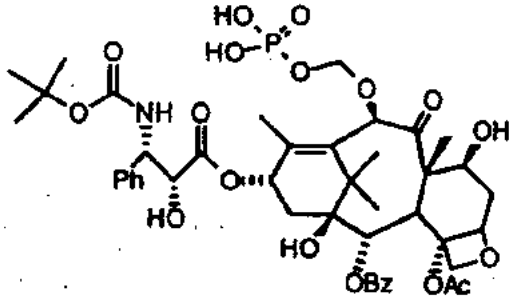
M. S. (FAB) m/z +: 1345

(f) preparation of 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)paclitaxel



A solution of the product of step (e) (50.8 mg, 0.038 mmol) in dry THF (2.5 mL), under argon was cooled to -40°C. To this solution was added tetrabutylammonium fluoride (0.057 mL, 0.057 mmol) in THF (1.0 M) in a dropwise manner. The reaction mixture stirred for 1.5 h with gradual warming to -20°C. The mixture was quenched with 15 mL sat. NH_4Cl and diluted with 30 mL EtOAc. The organic phase was washed with 2 x 15mL $NaHCO_3$, and brine. It was dried with $MgSO_4$ and concentrated. Preparative layer chromatography (silica gel, 50% ethyl acetate/hexane) provided 36 mg (77%) of title compound as a white powder.
^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J=8.5, 2H); 7.60-7.55 (m, 1H); 7.49-7.44 (m, 2H); 7.36-7.18 (m, 20H); 6.27-6.22 (m, 1H); 5.78 (s, 1H); 5.67 (d, J=7.0, 1H); 5.44-5.34 (m, 3H); 5.27 (d, J=2.2, 1H); 5.24-5.05 (m, 4H); 5.01-4.91 (m, 4H); 4.39-4.28 (m, 2H); 4.17 (d, J=8.2, 1H); 3.87 (d, J=7.0, 1H); 2.58-2.51 (m, 1H); 2.41 (s, 3H); 2.40-2.18 (m, 2H), 2.00-1.87 (m, 5H); 1.73-1.69 (m, 4H); 1.30 (s, 9H); 1.22-1.15 (m, 6H).
M.S. (FAB) m/z+: 1231

(g) preparation of 10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)-paclitaxel triethanolamine salt



A 500 mL Parr bottle was charged with 10-desacetyl-2'-O-benzyloxycarbonyl-3'-N-debenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(dibenzylphosphonooxymethyl)paclitaxel (264.9mg, 0.215mmol) and ethyl acetate (20 mL). The flask was then flushed with argon and 10% Pd/C (318mg) was added. The resulting mixture was placed on a Parr apparatus with a 55 pounds per square inch (psi) hydrogen atmosphere. The reaction was monitored by HPLC (70:30 CH_3CN/Q8 buffer pH 6.0, 1.00 mL/min., Zorbax C-18 column, 25.0 cm, λ=230 nm) until no starting material was evident (12.5 hours). The mixture was filtered through a plug of Celite, which was washed with ethyl acetate and a small amount of dichloromethane. The resulting filtrate was concentrated and the residue was taken up in dichloromethane (5 mL). Addition of hexane caused a white precipitate to form, of which 140.3mg of the free acid (80% purity by HPLC) was isolated as a white solid. This material was passed directly on to the next step.
To a flask containing the above free acid (140mg, 0.153mmol) was added dichloromethane (10 mL). The resulting solution was then treated with 0.100 M triethanolamine solution in ethyl acetate (1.16 mL,

0.116mmol) which caused the solution to become turbid. Approximately 2 mL of hexane was added and the mixture was placed at -20°C overnight. The resulting precipitate was filtered through a 4.0-5.5 µm fritted glass funnel. The solid was removed and placed under vacuum for 4 h to yield 69.9mg (42%) the title triethanolamine salt as a gray powder, which was determined to he 95-96% pure by HPLC analysis. (T_R = 2.05 min, 70:30 CH_3CN/Q8 Buffer pH 6.0, 1.00 mL/min, Zorbax C-18 25.0 cm, λ = 230 nm).

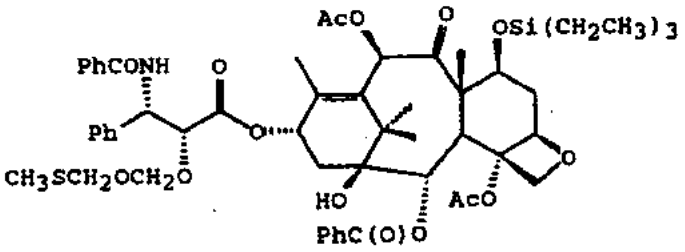
^{1}H-NMR (d_6-acetone/D_2O, 300 MHz): δ 8.03 (d, J = 7.4, 2H); 7.65 (t, J = 7.3, 1H); 7.54 (t, J = 7.6, 2H); 7.42-7.33 (m, 5H); 7.21 (t, J = 7.0, 1H); 6.09 (t, J = 9.0, 1H); 5.61 (s, 1H); 5.59 (d, J = 7.0, 1H); 5.12 (bs, 2H); 4.93 (d, J = 8.4, 2H), 4.56 (d, J = 4.9, 1H); 4.31-4.26 (m, 1H); 4.11 (s, 2H); 3.41-3.37 (m, 6H); 2.42-2.32 (m, 5H); 2.15 (bs, 1H); 1.97 (s, 3H); 1.77-1.64 (m, 2H); 1.58 (s, 3H); 1.13 (s, 9H); 1.15-1.07 (m, 6H).

^{13}C NMR (d_6-acetone, D_2O, 75.6 MHz): δ 171.6, 166.9, 156.6, 141.8, 135.1, 134.2, 131.0, 130.7,129.4, 129.3, 128.4, 128.1, 88.3, 85.4, 81.9, 79.7, 78.6, 78.1, 76.8, 76.0, 74.8, 71.9, 71.2, 47.4, 44.0, 37.1, 36.3, 28.5, 27.0, 23.1, 22.0, 14.7, 10.4.

HRMS: MNa^+, 940.3142 (Calculated for $C_{44}H_{56}NO_{18}PNa$ = 940.3133)

Example 10. 2'-O-Phosphonooxymethoxymethylpaclitaxel

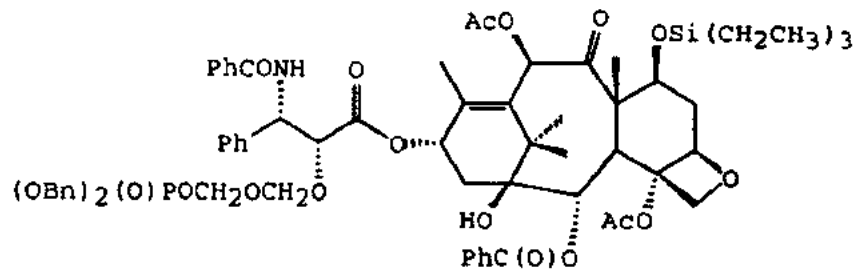
(a) preparation of 2'-O-(methylthiomethoxymethyl)-7-O-triethysilylpaclitaxel



To a solution of 7-O-triethylsilylpaclitaxel (70.0 mg, 72.2 mmol), bis(methylthiomethyl)ether (90 mg, 72.2 mmol), molecular seives (70 mg), and N-iodosuccinimide (160 mg, 72.2 mmol) in THF (2.0 ml) at room temperature was added silver triflate (5.0 mg, 19.5 mmol) and the resulting solution was stirred for 2 h. The reaction mixture was then diluted with ethyl acetate and filtered through a pad of celite. The filtrate was washed with saturated aqueous sodium bicarbonate solution, followed by a 1:1 (v:v) mixture of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution and finally brine. The organics were then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (3:1, hexanes:ethyl acetate) to provide 22.0 mg (29%) of the title compound as a white solid:

^{1}H NMR (300MHz, CDCl3) δ 8.12-7.20 (15H, m), 7.04 (1H, d, J = 8.9 Hz), 6.41 (1H, s), 6.25 (1H, m), 5.81 (1H, dd, J = 8.9, 2.4 Hz), 5.68 (1H, d, J = 7.0 Hz), 4.93 (1H, d, 8.0 Hz), 4.79 (2H, m), 4.71 (1H, d, 2.4 Hz), 4.45 (1H, dd, J = 10.5, 6.6 Hz), 4.30 (1H, d, J = 8.3 Hz), 4.28 (1H, d, J = 11.7 Hz), 4.17 (1H, d, J = 8.3 Hz), 4.04 (1H, d, J = 11.7 Hz), 3.80 (1H, d, J = 6.9 Hz), 2.48-1.13 (25H, m, incl. singlets at 2.51, 2.13, 2.05, 2.01, 1.69, 1.19, 1.16), 0.98-0.85 (9H, m), 0.65-0.50 (6H, m).

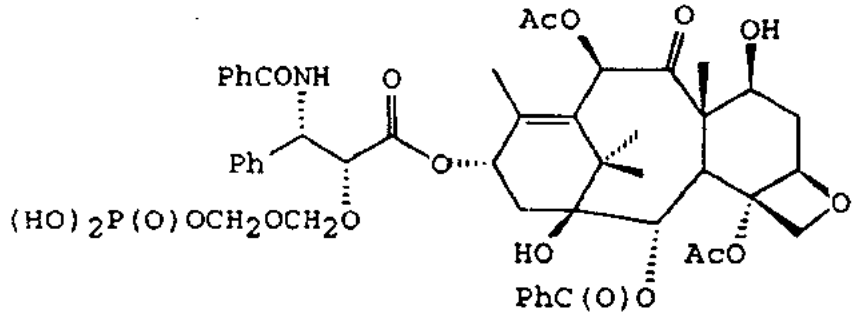
(b) preparation of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-triethylsilylpaclitaxel



To a solution of the product obtained in step (a) (15 mg, 0.0141 mmol) and molecular sieves (15 mg) in THF (0.5 ml) at room temperature was added dibenzyl phosphate (20.0 mg, 0.089 mmol) followed by N-iodosuccinimide (4.2 mg, 0.0187 mmol) and the solution was stirred for 1h. A TLC analysis of the reaction mixture at this time indicated the presence of starting material only. Silver triflate (5.0 mg, 0.019 mmol) was then added in three portions over 2h and the reaction was stirred for an additional 1h. The reaction mixture was then diluted with ethyl acetate and the resulting solution filtered through a pad of celite. The filtrate was treated with a 1:1 (v:v) solution of saturated aqueous sodium bicarbonate and 5% aqueous sodium thiosulfate solution. The organic extract was then washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (1:1, hexanes:ethyl acetate) to provide 5.0 mg (33%) of the title compound:

^{1}H NMR (300 MHz, CDCl3) δ 8.08-7.16 (25H, m), 7.18 (1H, d, J=8.8 Hz), 6.41 (1H, s), 6.21(1H, m), 5.82 (1H, dd, J=9.0, 3.1 Hz), 5.66 (1H, d, 7.0 Hz), 5.01-4.65 (10H, m), 4.56 (1H, dd, J=14.7, 5.6 Hz), 4.43(1H, dd, J=10.4, 6.7 Hz), 4.29 (1H, d, J=8.3 Hz), 4.16 (1H, d, J=8.3 Hz), 3.78 (1H, d, J=7.0 Hz), 2.60-1.13 (22H, m, incl. singlets at 2.49, 2.15, 1.93, 1.66, 1.15, 1.13, 3H each), 0.95-0.84 (9H, m), 0.63-0.45 (6H,m).

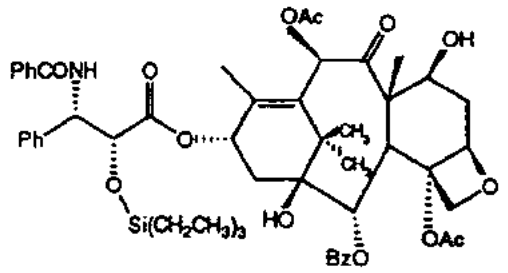
(c) preparation of 2'-O-phosphonooxymethoxymethylpaclitaxel



The product of step (b) is treated with tetrabutylammonium fluoride according to the procedure given in Example 9(f) to remove the 7-O-triethylsilyl protecting group. The compound thus obtained is subject to catalytic hydrogenation according to the procedure described in previous examples to provide the title compound.

Example 11. 2'-O-Phosphonooxymethoxymethylpaclitaxel (Alternate route)

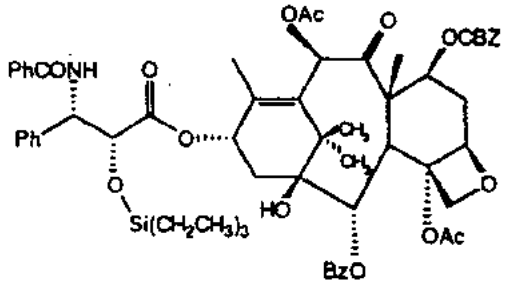
(a) preparation of 2'-O-triethylsilylpaclitaxel



To a solution of paclitaxel (20.0 g, 0.0234 mol) and imidazole (3.59 g, 0,052 mol) in 150 mL of DMF (dimethylformamide) at 0° C was added triethylsilyl chloride (6.0 mL, 0.053 mol) in 2.0 mL quantities over 20 min. The reaction mixture was then stirred at 0°C for 1h. The mixture was then diluted with ethyl acetate and saturated aqueous ammonium chloride. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo to provide a yellow oil. Purification of the crude product via flash chromatography (hexanes: ethyl acetate: 1:3 then 1:1) provided 21.07 g (98% yield) of the desired title compound as a colorless white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (2H, m), 7.70 (2H, m), 7.65-7.30 (11H, m) 7.15 (1H, d, J = 8.9 Hz), 6.30 (1H, s), 6.25 (1H, m), 6.70-6.10 (2H, m), 4.94 (1H, d, J = 7.9 Hz), 4.67 (1H, d, 2.0 Hz), 4.40 (1H, m), 4.29 (1H, d, J = 8.4 Hz), 4.18 (1H, d, J = 8.4 Hz), 3.81 (1H, d, J = 7.1 Hz), 2.65-1.10 (22H, including singlets at 2.55, 2.20, 1.88, 1.69, 1.22, 1.13, 3H each).

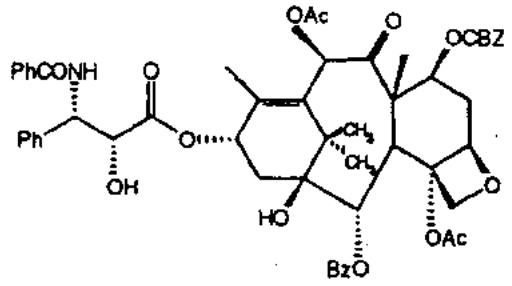
(b) preparation of 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel



Butyllithium (1.6 M in hexanes, 12.9 mL, 8.06 mmol) was added dropwise over 10 min to a solution of 2'-O-triethylsilylpaclitaxel (22.3 g, 24.1 mmol) in THF (250 mL) cooled to -50°C. The resulting solution was stirred for 20 min and the temperature maintained between -50°C and -35°C. The reaction mixture was then cooled to -50° C and benzyl chloroformate (5.08 mL, 29.8 mmol) was added dropwise over 5 min. The reaction mixture was maintained at -40° C for 30 min then equilibrated to 0° C over approximately 30 min. The mixture was then diluted with ethyl acetate and saturated aqueous ammonium chloride and the resulting organic layer washed with brine, dried over sodium sulfate and concentrated in vacuo. A ^{1}H-NMR analysis of the crude reaction mixture showed the presence of desired 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel as well as 2'-O-triethylsilyl-7-epihydroxypaclitaxel (3 :1 ratio, respectively). This product mixture was used in the next step without further purification and the isomers subsequently separated. An analytical sample of the major product 2'-O-triethylsilyl-7-O-benzyloxycarbonylpaclitaxel was purified via flash chromatography; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (2H, m), 7.72 (1H, m), 7.65-7.27 (1H, d, J = 8.8 Hz), 6.41 (1H, m), 6.20 (1H, m), 5.72-5.65 (2H, m), 5.52 (1H, m), 5.24 (1H, d, J = 12.3 Hz), 5.16 (1H, d, J = 12.3 Hz), 4.95 (1H, d, J = 8.7 Hz), 4.69 (1H, s), 4.35 (1H, d, J = 8.3 Hz), 4.25 (1H, d, J= 8.3 Hz), 3.94 (1H, d, J = 6.8 Hz), 2.70-1.12 (22H, including singlets at 2.54, 2.14, 2.01, 1.80, 1.20, 1.15, 3H each), 0.81-0.73

(9H, m), 0.55-0.31 (6H, m).

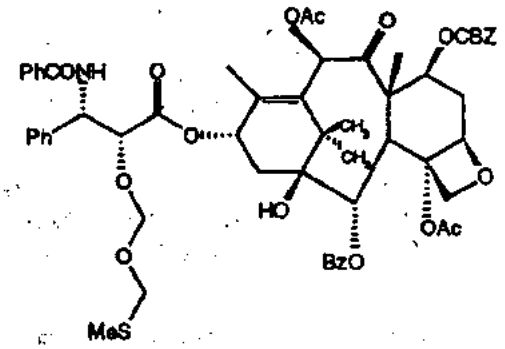
(c) preparation of 7-O-benzyloxycarbonylpaclitaxel



Hydrochloric acid (6N, 1.0 mL, 6.0 mmol) was added to a solution the product from Step (b) (24.0 g, 22.6 mmol) in acetonitrile (250 mL) cooled to 0° C. After 10 min a TLC analysis (hexanes : ethyl acetate, 1 : 1) indicated the reaction was complete. The reaction mixture was diluted with saturated aqueous sodium bicarbonate followed by ethyl acetate and the organic layer was removed, washed with brine, dried using sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (hexanes : ethyl acetate, 1:3, then 1:1) to provide 11.4 g (48% over 2 steps) of the title compound and 4.8 g (20%) of 7-epihydroxypaclitaxel.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (2H, m), 7.71 (2H, m), 7.65-7.27 (16H, m), 7.10 (1H, d, 8.9 Hz), 6.39 (1H, s), 6.16 (1H, m), 5.81 (1H, d, J = 8.9, 2.4 Hz), 5.65 (1 H, d, J = 6.9 Hz), 5.49 (1H, dd, J = 10.6, 7.2 Hz), 5.20 (1H, d, J = 11.9 Hz), 5.12 (1H, d, J = 11.9), 4.91 (1H, d, J = 8.4 Hz), 4.78 (1H, m), 4.30 (1H, d, J = 8.4 Hz), 4.15 (1H, d, J = 8.4 Hz), 3.91 (1H, d, J = 6.8 Hz), 3.69 (1H, d, J = 4.9 Hz), 2.65-1.10 (22H, including singlets at 2.39, 2.18, 1.81, 1.75, 1.21, 1.15, 3H each).

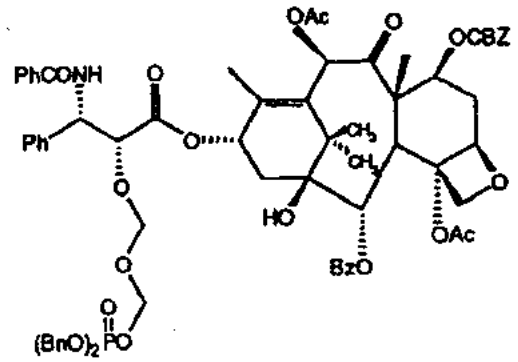
(d) preparation of 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel



Silver triflate (300 mg, 1.17 mmol) was added to a solution 7-O-benzyloxycarbonylpaclitaxel (5.53 g, 5.71 mmol), 1, 1'-dithiomethyldimethyl ether (7.8 g, 57.1 mmol), N-iodosuccinimide (6.35 g, 28.3 mmol) and oven dried, powdered molecular sieves (5.0 g) in THF (110 mL) at room temperature. A TLC analysis (hexanes : ethyl acetate, 1:1) of the reaction mixture after 20 min indicated the conversion of approxiately 40% of the starting material to a higher running product. Silver triflate (150 mg, 0.585 mmol) was then added and the reaction was monitored by TLC which indicated after 30 min the reaction was appoximately 65% complete. The mixture was diluted with ethyl acetate (100 mL), filtered using a pad of celite and the filtrate was poured into a separatory funnel containing 200 mL of a saturated aqueous solution of sodium bicarbonate and 50 mL of a 5% aqueous sodium thiosulfate solution. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (hexanes : ethyl acetate, gradient elution 4:1 to 3:2) to provide 3.0 g (54% yield) of the title

product as a light yellow solid.
^{1}H-NMR (300 MHz, CDCL3) δ 8.10 (2H, m), 7.74 (2H, m), 7.66-7.25 (18H, m), 7.05 (1H, d, J = 8.9 Hz), 6.40 (1H, s), 6.26 (1H, m), 5.77 (1H, dd, J = 8.8, 2.5 Hz), 5.71 (1H, d, J = 6.9 Hz), 5.51 (1H, dd, J = 10.6, 7.1 Hz), 5.21 (1H, d, J = 11.9 Hz), 5.14 (1 H, d, J = 11.9 Hz), 4.92 (1H, m), 4.79 (2H, m), 4.68 (1H, d, J = 2.5 Hz), 4.31 (1H, d, J = 11.8 Hz), 4.30 (1H, d, J = 8.5 Hz), 4.16 (1H, d, J = 8.5 Hz), 4.10 (1H, d, J = 11.8 Hz), 3.93 (1H, d, J = 6.9 Hz), 2.65-1.10 (25H including singlets at 2.50, 2.15, 2.05, 1.74, 1.72, 1.20, 1.15, 3H each).

(e) preparation of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel

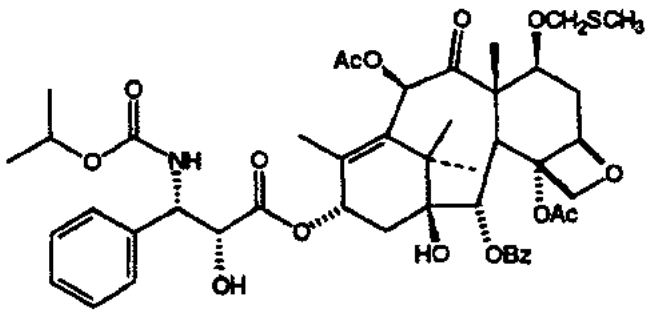


To a solution of 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel (1.06 g, 1.07 mmol) and oven dried, powdered molecular sieves (1.0 g) in THF (20 mL) at room temperature was added dibenzyl phosphate (1.49 g, 5.30 mmol) followed immediately by N-iodosuccinimide (2.65 g, 1.18 mmol). A TLC analysis (hexanes : ethyl acetate 1:1) of the reaction mixture after 2.5 h indicated the reaction was approximately 60% complete. N-iodosuccinimide (175 mg, 0.78 mmol) was then added and the reaction stirred for an additional 30 min, after which time a TLC analysis indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate (50 mL) and filtered using a pad of celite. The filtrate was poured into a separatory funnel containing 100 mL of a saturated aqueous solution of sodium bicarbonate and 20 mL of a 5% aqueous solution of sodium thiosulfate. The organic layer was removed, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (hexanes: ethyl acetate, gradient elution, 3:1 to 1:1) to provide 750 mg (62% yield) of the desired title compound as a white solid.
^{1}H-NMR (360 MHz, $CDCl_3$) δ 8.10 (2H, m), 7.79 (2H, m), 7.65-7.24 (26H, m), 7.10 (1H,m), 6.41 (1H, s), 6.20 (1H,m), 5.79 (1H, dd, J = 8.8, 3.6 Hz), 5.65 (1H, d, J = 7.0 Hz), 5.52 (1H,m), 5.20 (1H, d, J = 11.8 Hz), 5.11 (1H, d, J = 11.8 Hz), 5.04-4.85 (6H, m), 4.75-4.60 (4H, m), 4.30 (1H, d, 8.4 Hz), 4.15 (1H, d,J = 8.4 Hz), 3.92 (1H, d, J = 7.0 Hz) 2.65-1.10 (22 H including singlets at 2.48, 2.19, 1.95, 1.80, 1.20, 1.10, 3H each).

(f) preparation of 2'-O-phosphonooxymethoxymethylpaclitaxel triethanolamine salt

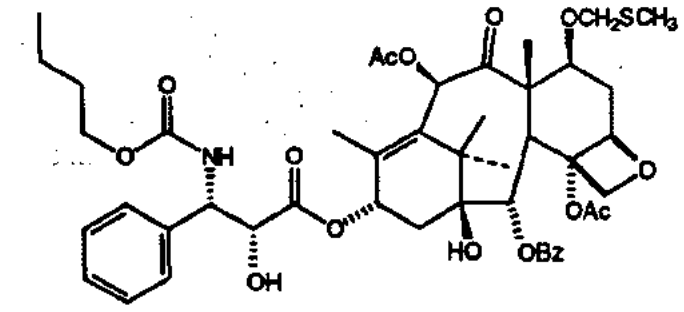
Palladium (10%) on carbon was added to a solution of 2'-O-(dibenzylphosphonooxymethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel (500 mg, 0.382 mmol) in ethly acetate (40 mL) housed in a Parr bottle. The vessel was affixed to a Parr apparatus and the reaction mixture subjected to hydrogen at 50 psi. The reaction mixture was shaken for 6.5 h, then filtered using a sintered glass funnel. Triethanolamine (0.1 N in ethyl acetate, 4.0 mL) was added to this filtrate and the resulting solution was concentrated in vacuo. The crude solid was suspended in approximately 5.0 mL of ethyl acetate and the solvent decanted. This process was repeated three times and the resulting title triethanolamine salt (300 mg) was obtained with purity of 87% as determined by HPLC analysis. Further purification of this compound via C18 chromatography (water : acetonitrile, 3:1) provided the desired title compound (120 mg, 34%) at 95% purity by HPLC.
^{1}H-NMR (300MHz, CD_3COCD_3, D_2O) δ 9.05 (1H, d, J = 8.7 Hz), 8.15-7.12 (21H, m), 6.40 (1H,m), 6.05 (1H, m), 5.69-5.55 (2H, m), 5.01-4.85 (6H, m), 4.35 (1H, m), 4.14 (2H, m), 3.96-3.85 (6H, m), 3.25 (1H, d, J = 7.1 Hz), 3.30-3.15 (6H, m) 2.50-1.04 (22H, including singlets at 2.49, 2.15, 2.05, 1.81, 1.60, 3H each).

Example 12. 3'-N-debenzoyl-3'-N-(isopropyloxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of 7-O-methylthiomethylbaccatin III (408 mg, 0.630 mmol) in 10 mL of THF at -60 °C was added nBuLi (0.30 mL, 2.5 M, 0.75 mmol) and stirred for 10 min. (3R, 4S)-3-Triethylsilyloxy-4-phenyl-N-isopropyloxycarbonylazetidin-2-one (320 mg, 0.88 mmol) in 6 mL of THF was added dropwise and then the reaction brought to 0 °C for 30 min. The solution was quenched with saturated NH_4Cl and extracted with ethyl acetate, shaken with Bu_4NF (1.0 mL, 1.0 M, 1.0 mmol) and then washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1.5:1 hexane/ethyl acetate) to give 545 mg of a product which was crystalized from acetone/hexane to give 476 mg of the title product as a white solid (84%); IR(KBr) 3460, 1720, 1266, 1244, 1230 cm^{-1} ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.47 (t, J=7.5 Hz, 2H), 7.32 (m, 5H), 6.51 (s, 1H), 6.18 (t, J=8.7 Hz, 1H), 5.65 (d, J=6.6 Hz, 1H), 5.50 (d, J=9.3 Hz, 1H), 5.28 (d J=8.4 Hz, 1H), 4.91 (d, J= 8.1 Hz, 1H), 4.77 (m, 1H), 4.64 (bs, 3H), 4.26 (m, 2H), 4.15 (d, J= 8.4 Hz, 1H), 3.83 (d, J=6.9 Hz, 1H), 3.44 (d, J=5.1 Hz, 1H), 2.78 (m, 1H), 2.34 (s, 3H), 2.25 (d, J=9.0 Hz, 2H), 2.17 (s, 3H), 2.14 (s, 1H), 2.10 (s, 3H), 1.96 (s, 3H), 1.83 (m, 1H), 1.73 (s, 3H), 1.15 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.8, 170.4, 169.2, 167.0, 156.3, 140.1, 138.3, 133.7, 133.3, 130.2, 129.1, 128.8, 128.6, 128.1, 126.8, 83.8, 81.4, 78.7, 76.0, 75.5, 74.5, 74.0, 73.6, 72.2, 68.9, 57.5, 56.4, 47.1, 43.2, 35.3, 32.9, 26.6, 22.6, 22.0, 21.9, 20.9, 15.1, 14.6, 10.9
FABMS (NOBA) M + Na calcd for $C_{46}H_{57}NSO_{15}$: 918. Found: 918.
Anal. calcd for C_{46} $H_{57}NSO_{15}$: C, 61.66; H, 6.41; N, 1.56. Found: C, 61.63; H, 6.36; N, 1.68.

Example 13. 3'-N-Debenzoyl-3'-N-(n-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of 7-O-methylthiomethylbaccatin III (425 mg, 0.66 mmol) in 10 mL of THF at -60 °C was added nBuLi (0.30 mL, 2.5 M, 0.75 mmol) and stirred for 10 min. (3R,4S)-3-Triethylsilyloxy-4-phenyl-N-(n-butyloxycarbonyl)azetidin-2-one (350 mg, 0.93 mmol) in 6 mL of THF was added dropwise and then the reaction brought to 0 °C for 30 min. The solution was quenched with saturated NH_4Cl and extracted with ethyl acetate, shaken with Bu_4NF (1.0 mL, 1.0 M, 1.0 mmol) and then washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (1.5:1 hexane/ethyl acetate) to give 581 mg of the title product which was crystalized from toluene/hexane to give 464 mg of a white solid (77%); IR-(KBr) 3444, 1722, 1372, 1242, 1108, 1066, 1026, 988 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz,

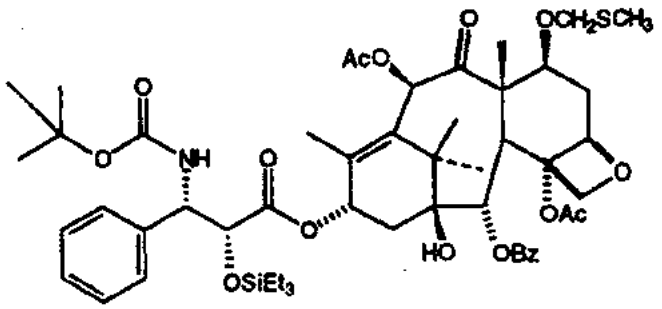
2H), 7.59 (t, J=7.5 Hz, 1H), 7.47 (t, J=7.2 Hz, 2H), 7.39 - 7.11 (m, 5H), 6.51 (s, 1H), 6.20 (t, J=8.7 Hz, 1H), 5.65 (d, J=6.9 Hz, 1H), 5.56 (d, J=9.3 Hz, 1H), 5.29 (d J=8.4 Hz, 1H), 4.91 (d, J= 8.1 Hz, 1H), 4.65 (bs, 3H), 4.27 (m, 2H), 4.15 (d, J= 8.4 Hz, 1H), 3.97 (m, 2H), 3.84 (d, J=6.9 Hz, 1H), 3.45 (d, J=4.8 Hz, 1H), 2.78 (m, 1H), 2.33 (s, 6H), 2.25 (d, J=8.7 Hz, 2H), 2.17 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H), 1.83 (m, 1H), 1.74 (s, 3H), 1.62 (s, 1H), 1.48 (m, 2H), 1.19 (m, 5H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 201.9, 172.3, 170.5, 169.2, 167.0, 156.3, 140.1, 138.4, 133.8, 133.4, 130.2, 129.2, 129.0, 128.9, 128.7, 128.2, 126.8, 125.3, 83.9, 81.4, 78.8, 77.3, 76.0, 75.6, 74.6, 74.1, 73.7, 72.2, 65.4, 57.5, 56.5, 47.2, 43.2, 35.4, 26.6, 22.6, 21.5, 21.0, 18.9, 15.1, 14.7, 13.7, 10.9.

FABMS (NOBA) M+H calcd for $C_{47}H_{60}NSO_{15}$: 910. Found: 910.

Anal. calcd for C_{47} $H_{59}NSO_{15}$: C, 62.03; H, 6.53; N, 1.54. Found: C, 62.16; H, 6.45; N, 1.57.

Example 14. 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethylpaclitaxel

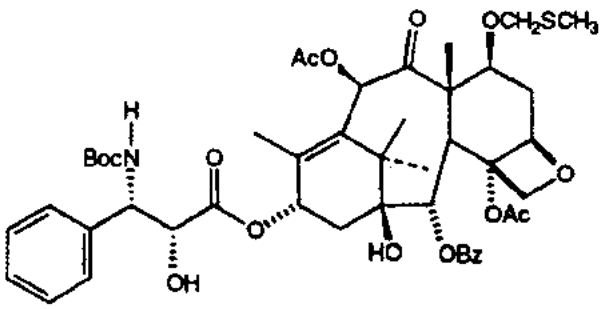
(a) preparation of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2-O-triethylsilyl-7-O-methylthiomethylpaclitaxel



To a solution of HMDS (0.275 mL, 1.30 mmol) in 8 mL of THF was added a solution of n-BuLi (0.48 mL, 2.5 M in hexanes, 1.20 mmol) and stirred 5 minutes at -55°C. To this solution was added 7-O-methylthiomethylbaccatin III (639 mg, 0.99 mmol) in 8 mL of THF and stirred for 10 minutes before addition of an 8 mL solution of (3R,4S)-3-triethylsilyloxy-4-phenyl-N-(t-butoxycarbonyl)azetidin-2-one (575 mg, 1.52 mmol). The cold bath was removed and replaced with a 0°C bath and the reaction stirred for 30 minutes. The solution was diluted with ethyl acetate and washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (3:1 hexane/ethyl acetate) to give 1.0 g of the title product (98%); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=6.9 Hz, 2H), 7.57 (m, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.35 (m, 2H), 7.26 (m, 3H), 6.55 (s, 1H), 6.25 (t, J=9.6 Hz, 1H), 5.68 (d, J=6.9 Hz, 1H), 5.45 (bd, J=9.3 Hz, 1H), 5.27 (bd, 1H), 4.95 (d, J=7.8 Hz, 1H), 4.65 (s, 2H), 4.53 (s, 1H), 4.29 (m, 2H), 4.17 (d, J=8.4 Hz, 1H), 3.89 (d, J=6.9 Hz, 1H), 2.81 (m, 1H), 2.51 (s, 3H), 2.37 (dd, J=15.3, 9.6 Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.74 (s, 3H), 1.63 (d, J=14.1 Hz, 1H), 1.29 (s, 9H), 1.21 (s, 6H), 0.76 (t, J=7.8 Hz, 9H), 0.36 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 171.6, 170.1, 169.3, 167.1, 155.2, 141.0, 139.0, 133.6, 132.8, 130.2, 129.2, 128.7, 128.5, 127.7, 126.4, 83.9, 81.2, 79.9, 78.9, 76.0, 75.7, 75.2, 74.8, 74.2, 71.3, 57.3, 56.7, 47.0, 43.3, 35.3, 33.0, 28.2, 26.4, 23.0, 21.5, 21.0, 15.0, 14.4, 10.9, 6.5, 4.3; IR-(film) 3448 (s), 1720, 1242, 1120, 1056 cm^{-1}.

FABMS (NOBA) M+H calcd for $C_{53}H_{74}NSSiO_{15}$: 1024.4549. Found: 1024.4583.

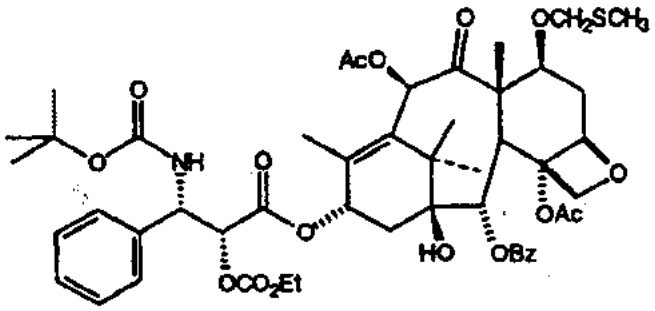
(b) preparation of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethylpaclitaxel



To a solution of the 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2-O-triethylsilyl-7-O-methylthiomethylpaclitaxel (269 mg, 0.26 mmol) in 6 mL, of THF was added tetrabutylammonium fluoride (0.3 mL, 1.0M in THF, 0.3 mmol) and stirred 10 minutes. The solution was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated and the residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 240 mg of the title product (95%); IR(film) 3440, 1720, 1370, 1242, 1170, 1108, 1066, 756 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J=7.2 Hz, 2H), 7.57 (t, J=7.2 Hz, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.35 (m, 5H), 6.52 (s, 1H), 6.16 (t, J=8.7 Hz,1H), 5.64 (d, J=6.9 Hz, 1H), 5.43 (bd, J=9.3 Hz, 1H), 5.24 (bd, J=8.1 Hz, 1H), 4.91 (d, J=8.1 Hz, 1H), 4.63 (m, 3H), 4.26 (m, 2H), 4.14 (d, J=8.4 Hz, 1H), 3.83 (d, J=6.9 Hz, 1H), 3.46 (d, J=5.4 Hz, 1H), 2.77 (m, 1H), 2.34 (s, 3H), 2.27 (d, J = 8.7 Hz, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.79 (m, 2H), 1.72 (s, 3H), 1.32 (s, 9H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 172.7, 170.3, 169.2, 167.0, 155.3, 140.3, 138.4, 133.7, 133.2, 130.2, 129.1, 128.8, 128.7, 128.0, 126.7, 83.9, 81.3, 80.2, 78.6, 76.5, 76.1, 75.4, 74.6, 74.0, 73.6, 72.3, 57.4, 56.1, 47.1, 43.2, 35.3, 32.8, 28.2, 26.5, 22.6, 21.0, 15.1, 14.6, 10.9.

FABMS (NOBA) M+H calcd for $C_{47}H_{60}NO_{15}S$: 910.3684. Found: 910.3706.

Example 15. 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel

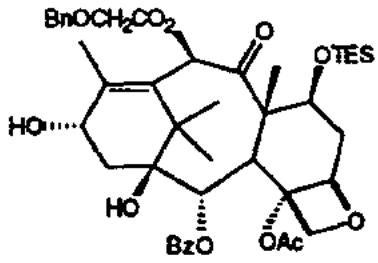


To a solution of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethylpaclitaxel (428 mg, 0.47 mmol) in 10 mL of dichloromethane was added diisopropylethyl amine (0.85 mL, 4.8 mmol) and DMAP (20 mg) and cooled to 0 °C. The ethyl chloroformate (0.25 mL, 2.6 mmol) was then added and stirred for 1 hr. The solution was diluted with ethyl acetate and washed with bicarbonate and brine, dried ($MgSO_4$) and concentrated. The residue so obtained was chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 428 mg of the title ethyl carbonate (92%); IR(film) 3448 (w), 1750, 1720, 1370, 1244, 1064 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.48 (t, J=7.8 Hz, 2H), 7.39 (m, 2H), 7.31 (m, 3H), 6.55 (s, 1H), 6.25 (t, J=9.0 Hz, 1H), 5.68 (d, J=7.2 Hz, 1H), 5.40 (bm, 2H), 5.25 (s, 1H), 4.95 (d, J = 8.1 Hz, 1H), 4.65 (s, 2H), 4.29 (m, 2H), 4.15 (m, 3H), 3.88 (d, J=6.9 Hz, 1H), 2.81 (m, 1H), 2.43 (s, 3H), 2.32 (m, 1H), 2.21 (m, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.84 (m, 1H), 1.74 (s, 3H), 1.62 (s, 1H), 1.32 (s, 9H), 1.28 (t, J=7.2 Hz, 3H), 1.20 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75.5 Hz) δ 202.0, 169.7, 169.1,

168.1, 167.0, 155.1, 154.1, 141.0, 137.2, 133.6, 132.9, 130.2., 129.2, 128.9, 128.7, 128.2, 126.4, 83.9, 81.2, 80.4, 78.9, 76.5, 76.0, 75.8, 74.8, 74.2, 72.0, 65.1, 57.4, 47.1, 43.3, 35.1, 33.0, 28.1, 26.4, 22.7, 21.3, 20.9, 15.0, 14.5, 14.1, 10.9..
FABMS (NOBA) M+H calcd for $C_{50}H_{64}NSO_{17}$: 982.3895. Found: 982.3874.

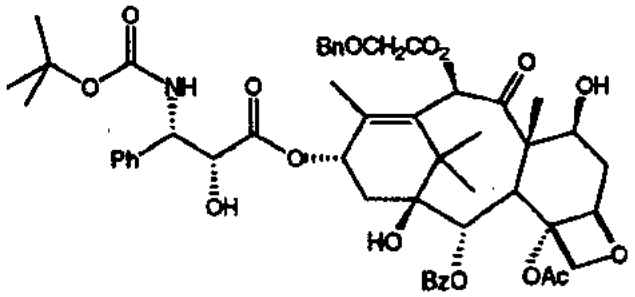
Example 16. 3'-N-Debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-10-deacetyl-10-hydroxymethylcarbonyl(paclitaxel)

(a) preparation of 7-O-Triethylsilyl-10-deacetyl-10-benzyloxymethylcarbonyl baccatin III



To a solution of 7-O-triethylsilyl-10-deacetylbaccatin III (3.85g, 5.85 mmol) in 40 mL of THF at -60 °C was added n-BuLi (2.6 mL, 2.5M in hexanes, 6.5 mmol) and stirred for 5 min before addition of benzyloxyacetyl chloride (1.0 mL, 6.5 mmol). After stirring for 30 min at -60 °C and then warming to ambient temperature the solution was diluted with ethyl acetate and washed with bicarbonate. The solution was dried over $MgSO_4$ and concentrated and the residue chromatographed over silica gel (2:1 then 1:1 hexane/ethyl acetate) to give 4.36 g of product (92%); IR(film) 3478 (br), 1724, 1270, 1244, 1136, 1110, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J=7.2 Hz, 2H), 7.60-7.23 (m, 8H), 6.54 (s, 1H), 5.60 (d, J=6.9 Hz, 1H), 4.94 (d, J=7.8 Hz, 1H), 4.79 (bq, 1H), 4.69 (s, 2H), 4.49 (dd, J=10.5, 6.6 Hz, 1H), 4.26 (m, 2H), 4.12 (m, 1H), 3.85 (d, J=6.9 Hz, 1H), 2.52 (m, 1H), 2.26 (s, 3H), 2.23 (m, 2H), 2.18 (s, 3H), 2.10 (m, 1H), 1.86 (m, 1H), 1.66 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.91 (t, J=7.5 Hz, 9H), 0.56 (m, 6H).
Anal. Calcd. for $C_{44}H_{58}SiO_{12}$: C, 65.49; H, 7.24. Found: C, 65.33; H, 7.27.
FABMS (NOBA) M+H calcd for $C_{44}H_{59}SiO_{12}$ 807. Found: 807.

(b) 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-10-deacetyl-10-benzyloxymethylcarbonyl(paclitaxel)



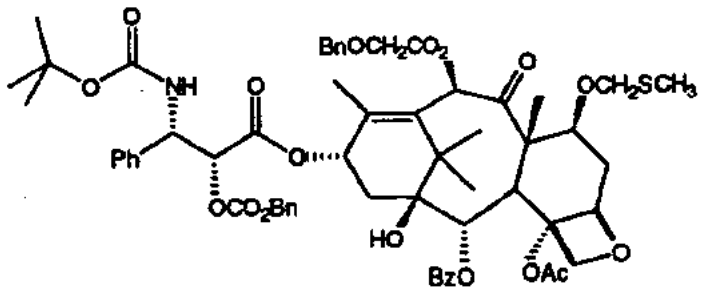
To a solution of 7-O-triethylsilyl-10-deacetyl-10-benzyloxymethylcarbonyl baccatin III (1.21g, 1.66 mmol) in 50 mL of THF at -60 °C was added n-BuLi (0.7 mL, 2.5M in hexanes, 1.75 mmol) and stirred for 5 min before addition of (3R,4S)-3-triethylsilyloxy-4-phenyl-N-(t-butoxycarbonyl)azetidin-2-one (1.2 g, 3.2 mmol). After stirring for 5 min at -60 °C and then 30 min at 0 °C the solution was diluted with ethyl acetate and washed with saturated NH_4Cl. The solution was dried over $MgSO_4$ and concentrated and the residue chromatographed over silica gel (3:1 then 1:1 hexane/ethyl acetate) to give 980 mg of product (53%). This product was dissolved in 6 mL of acetonitrile and cooled to 0 °C and stirred with 0.60 mL, of 6N HCl for 19

hrs. The solution was diluted with ethyl acetate and washed with saturated bicarbonate, dried over $MgSO_4$ and chromatographed over silica gel (1:1 hexane/ethyl acetate) to give 570 mg of product (35%); IR(film) 3448 (br), 1716, 1496, 1368, 1316, 1270, 1246, 1176, 1108, 1070, 1026 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.36 (m, 10H), 6.38 (s, 1H), 6.20 (t, J = 9.0 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.39 (bd, J = 9.3 Hz, 1H), 4.93 (d, J = 7.8 Hz, 1H), 4.69 (s, 2H), 4.60 (bs, 1H), 4.39 (m, 1H), 4.28 (m, 3H), 4.15 (d, J = 8.4 Hz, 1H), 3.78 (d, J = 6.9 Hz, 1H), 3.40 (bs, 1H), 2.54 (m, 1H), 2.43 (m, 1H), 2.36 (s, 3H), 2.28 (m, 2H), 1.84 (s, 4H), 1.72 (m, 1H), 1.67 (s, 3H), 1.31 (s, 9H), 1.23 (m, 1H), 1.21 (s, 3H), 1.10 (s, 3H).

Anal. Calcd. for $C_{52}H_{61}NO_{16}$: C, 65.33; H, 6.43; N, 1.46. Found: C, 64.97; H, 6.44; N, 1.43.

FABMS (NOBA) M + Na calcd for $C_{52}H_{61}NO_{16}Na$ 978. Found: 978.

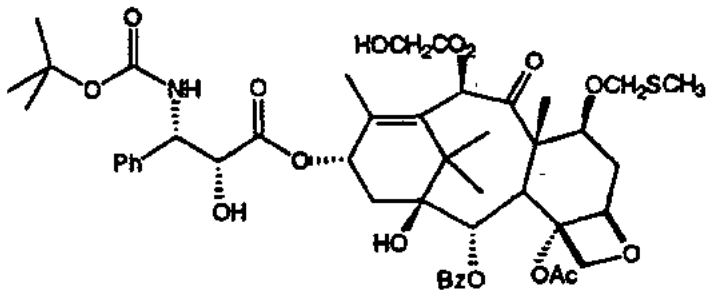
(c) preparation of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2-O-benzyloxycarbonyl-7-O-methylthiomethyl-10-deacetyl-10-benzyloxymethylcarbonyl(paclitaxel)



To a solution of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-10-deacetyl-10-benzyloxymethylcarbonyl-(paclitaxel) (570 mg, 0.59 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added diisopropylethyl amine (0.15 mL, 0.86 mmol) and CbzCl (0.10 mL, 0.70 mmol). The solution was stirred for 1 hr slowly warming to ambient temperature. The solution was washed with bicarbonate and dried over $MgSO_4$ and concentrated. The residue in 10 mL of acetonitrile at 0 °C was stirred with benzoyl peroxide (780 mg, 3.22 mmol) and dimethylsulfide (0.50 mL, 6.8 mmol) slowly warming to ambient temperature over 75 min. The solution was diluted with ethyl acetate and washed with saturated bicarbonate, dried over $MgSO_4$ and chromatographed over silica gel (2:1 hexane/ethyl acetate) to give 412 mg of the title product (65%); IR(film) 3438, 1754, 1722, 1368, 1272, 1244, 1176, 1110, 1066, 1028 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.35 (m, 15H), 6.67 (s, 1H), 6.26 (t, J = 8.7 Hz, 1H), 5.69 (d, J = 6.6 Hz, 1H), 5.41 (bm, 2H), 5.29 (s, 1H), 5.14 (ABq, J = 12, 5.7 Hz, 2H), 4.98 (d, J = 8 Hz, 1H), 4.72 (m, 4H), 4.32 (m, 3H), 4.19 (m, 2H), 3.90 (d, J = 6.0 Hz, 1H), 2.85 (m, 1H), , 2.45 (m, 1H), 2.44 (s, 3H), 2.34 (m, 1H), 2.24 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 1.87 (m, 1H), 1.77 (s, 3H), 1.33 (s, 9H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 201.6, 169.7, 168.7, 168.0, 167.0, 155.1, 154.1, 141.6, 137.1, 134.4, 133.7, 132.5, 130.2, 129.2, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 128.0, 128.0, 126.4, 83.9, 81.2, 80.4, 76.8, 77.2, 76.2, 75.8, 74.7, 74.3, 73.4, 72.0, 70.6, 67.1, 57.4, 54.1, 47.1, 43.2, 35.2, 32.9, 28.1, 26.4, 22.7, 21.3, 15.2, 14.6, 10.9.

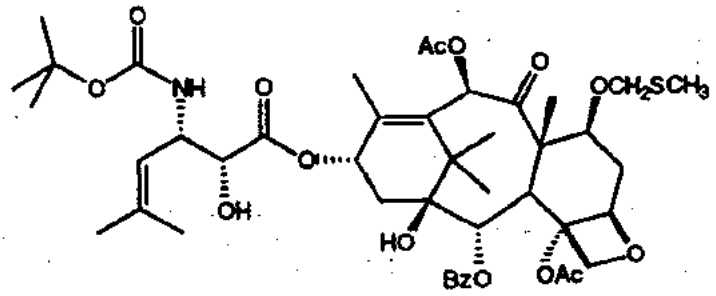
FABMS (NOBA) M + Na calcd for $C_{62}H_{71}NO_{18}SNa$ 1172. Found: 1172.

(d) preparation of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-10-deacetyl-10-hydroxymethylcarbonyl(paclitaxel)



To a solution of 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2-O-benzyloxymethylcarbonyl-7-O-methylthiomethyl-10-deacetyl-10-benzyloxycarbonyl(paclitaxel) (377 mg, 0.35 mmol) in 30 mL of ethanol was added a total of 450 mg of 10% palladium on carbon catalyst and stirred under an atmosphere of hydrogen for 120 hrs. The catalyst was removed by filtration through celite and the solution concentrated. The residue was chromatographed over silica gel (20% CH_3CN / 79% CH_2Cl_2 / 1% MeOH) to give 190 mg of the title product (65%); IR(film) 3444 (br), 1724, 1368, 1246, 1174, 1096, 1070, 1026, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.35 (m, 5H), 6.65 (s, 1H), 6.17 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 6.6 Hz, 1H), 5.39 (bd, J = 9.6 Hz, 1H), 5.26 (bd, 1H), 4.93 (d, J = 8.4 Hz, 1H), 4.67 (m, 3H), 4.28 (m, 5H), 3.83 (d, J = 6.0 Hz, 1H), 3.44 (d, J = 5.1 Hz, 1H), 2.77 (m, 1H), , 2.50 (m, 1H), 2.36 (s, 3H), 2.29 (d, J = 8.4 Hz, 2H), 2.13 (bs, 3H), 2.01 (s, 3H), 1.82 (m, 2H), 1.74 (s, 3H), 1.33 (s, 9H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 201.5, 171.7, 170.3, 167.0, 155.4, 141.3, 133.7, 132.7, 130.2, 129.0, 128.8, 128.7, 128.1, 126.8, 83.8, 81.3, 80.2, 78.6, 75.0, 74.4, 74.0, 73.6, 72.3, 60.6, 57.4, 56.2, 47.2, 43.2, 35.3, 32.6, 28.2, 26.5, 22.6, 21.0, 15.5, 14.7, 10.8.
FABMS (NOBA) M + Na calcd for $C_{47}H_{59}NO_{16}SNa$ 948. Found: 948.

Example 17. 3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel



To a solution of 7-O-methylthiomethylbaccatin III (1.5g, 2.3 mmol) in 30 mL of THF was added n-BuLi (1.0 mL, 2.5 M in hexane, 2.5 mmol) at -60 °C and stirred for 10 minutes. Then a solution of (±)-cis-3-triethylsilyloxy-4-isobutenyl-N-t-butoxycarbonylazetidin-2-one (3.3g, 9.3 mmol) in 10 mL of THF was added dropwise. The solution was then stirred at 0 °C for 30 min. and quenched with sat. NH_4Cl solution and extracted with ethyl acetate. The solution was dried over $MgSO_4$ and concentrated and the residue chromatographed over silica gel (3:1 hexane/ethyl acetate). The product was dissolved in 100 mL of THF and was shaken with Bu_4NF (2.3 mL, 1.0M in THF, 2.3 mmol) diluted with ethyl acetate and washed with brine. The solution was dried over $MgSO_4$ and concentrated and the residue chromatographed over silica gel (1.5:1 hexane/ethyl acetate) to give 1.6 g of the title product (78%); IR(film) 3452 (br), 1724, 1370, 1242,

1096, 1066 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 6.54 (s, 1H), 6.11 (t, J=9.3 Hz, 1H), 5.66 (d, J=6.0 Hz, 1H), 5.29 (d, J=6.0 Hz, 1H), 4.94 (d, J=8.1 Hz, 1H), 4.75 (m, 2H), 4.64 (ABq, J= 12.0, 2.7 Hz, 2H), 4.29 (m, 2H), 4.20 (m, 2H), 3.86 (d, J= 6.0 Hz, 1H), 3.37 (bd, 1H), 2.79 (m, 1H), 2.35 (s, 6H), 2.16 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.74 (s, 9H), 1.34 (s, 9H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 202, 170.2, 169.2, 166.9, 155.4, 140.6, 138.0, 133.7, 133.1, 130.1, 129.2, 128.6, 120.6, 83.8, 81.2, 79.9, 78.7, 77.2, 76.1, 75.5, 74.6, 74.0, 73.7, 72.2, 57.4, 51.5, 47.1, 43.2, 35.4, 32.9, 28.2, 26.4, 25.8, 22.4, 21.0, 18.6, 15.1, 14.8, 10.9.
FABMS (NOBA) M+H calcd for $C_{45}H_{62}NSO_{15}$ 888. Found: 888.

Example 18. 7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel

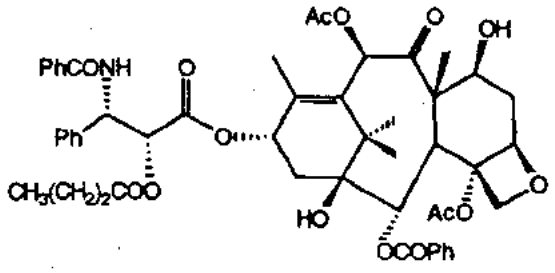
The title compound was prepared as in Example 17 from 7-O-methylthiomethylbaccatin III and (±)-cis-3-triethylsilyloxy-4-isobutenyl-N-benzoylazetidin-2-one.

Example 19. 3'-Desphenyl-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel.

The title compound can be prepared from (3R,4R)-1-benzoyl-4-(2-furyl)-3-triethylsilyloxy-2-azetidinone and 7-O-methylthiomethylbaccatin III following the procedures decribed in Example 7(a) and 7(b).

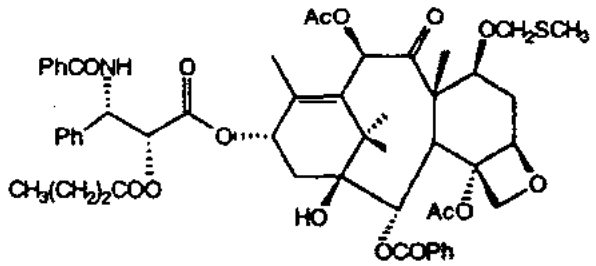
Example 20. 2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel.

(a) preparation of 2'-O-n-propylcarbonylpaclitaxel.



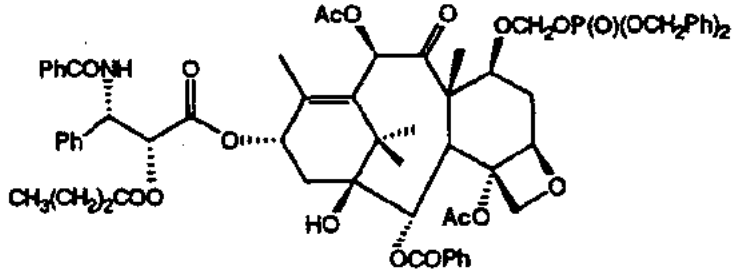
To a solution of paclitaxel (15.0 g, 17.5 mmol) and diisopropylethyl amine (18.3 mL, 105 mmol) in dichloromethane (175 mL) cooled to 0° C was added butyryl chloride (5.49 mL, 52.4 mmol) dropwise over 2 min. The reaction mixture was then warmed to room temperature and stirred for 16h. The reaction mixture was then partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic phase was then washed with a saturated sodium bicarbonate solution followed by brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (eluted with hexanes: ethyl acetate) to provide the title ester (15.9 g, 98% yield) as a white solid; ^1H-NMR ($CDCl_3$, 300MHz) δ 8.13-8.05 (2H, m), 7.75-7.65 (2H, m), 7.62-7.30 (11H, m), 6.88 (1H, d, J = 9.0 Hz), 6.26 (1H, s), 6.23 (1H, dd, J = 8.4 Hz), 5.92 (1H, dd, J = 9.3, 6.0 Hz), 5.65 (1H, d, J = 7.1 Hz), 5.48 (1H, d, J = 3.2 Hz), 4.94 (1H, d, J = 7.9 Hz), 4.21 (1H, dd, J = 10.4, 6.5 Hz), 4.28 (1H, d, J = 8.4 Hz), 4.17 (1H, d, J = 8.4 Hz), 3.78 (1H, d, J = 7.0 Hz), 2.64-1.02 (26H, m, including singlets at 2.43, 2.19, 1.91, 1.65, 1.65, 1.20, 1.10, 3H each), 0.87 (3H, dd, J = 8.2 Hz).

(b) preparation of 2'-O-n-propylcarbonyl-7-O-methylthiomethylpaclitaxel.



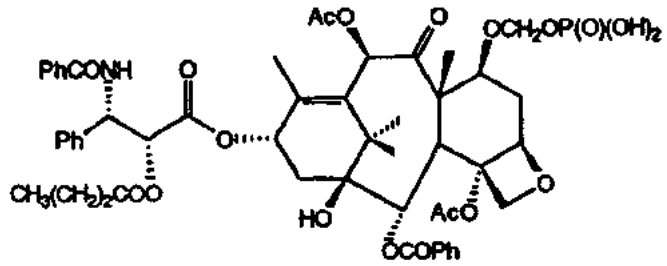
To a solution of 2'-O-n-propylcarbonylpaclitaxel (14.4 g, 15.6 mmol) and dimethyl sulfide (9.23 mL, 124.8 mmol) in acetonitrile (312 mL) cooled to -40° C was added benzoyl peroxide (15.1 g, 62.3 mmol) and the reaction mixture was warmed to room temperature over 1h. At this time a TLC (eluted with hexanes : ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate and the resulting organic solution was washed three times with a saturated sodium bicarbonate solution then brine. The organic phase was then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes: ethyl acetate) to provide the title compound (14.4 g, 93%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.21-8.19 (2H, m), 7.72-7.70 (2H, m), 7.62-7.26 (11H, m), 6.92 (3H, s), 6.20 (1H, dd, J = 8.4 Hz), 5.92 (1H, dd, J = 9.0, 3.1 Hz), 5.66 (1H, d, J = 6.9 Hz), 5.51 (1H, d, J = 3.2 Hz), 4.92 (1H, d, J = 8.2 Hz), 4.68-4.59 (2H, m), 4.32-4.26 (2H, m), 4.15 (1H, d, J = 8.3 Hz), 3.86 (1H, d, J = 6.8 Hz), 2.77 (1H, m), 2.50-1.05 (25H, m), 0.87 (3H, dd, J = 7.3 Hz).

(c) preparation of 2'-O-n-propylcarbonyl-7-O-(dibenzylphosphonooxymethyl)paclitaxel.



N-Iodosuccinimide (4.9 g, 21.8 mmol) was added in one portion to a solution of 2'-O-n-propylcarbonyl-7-O-methylthiomethylpaclitaxel (10.7 g, 11.0 mmol), dibenzylphosphate (15.3 g, 55.0 mmol) and 5 g of oven dried 3 Angstrom sieves in THF (200 mL) at room temperature and the resulting mixture was stirred for 1h. At this time a TLC analysis (eluted with hexanes:ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted to twice the initial volume with ethyl acetate and filtered through a bed of celite. The filtrate was then poured into a saturated sodium bicarbonate solution containing 1% sodium thiosulfate by weight. The organic layer was then washed four times with a saturated aqueous sodium bicarbonate solution followed by brine. The aqueous layer was then back extracted with ethyl acetate and the combined organics were dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (hexanes : ethyl acetate) to provide the title dibenzylphosphate (9.9 g, 76% yield) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.10-8.08 (2H, m), 7.74-7.71 (2H, m), 7.61-7.25 (21H, m), 6.94 (1H, d, J = 9.0 Hz), 6.31 (1H, s), 6.20 (1H, dd, J = 8.7 Hz), 5.91 (1H, dd, J = 9.0, 3.1 Hz), 5.64 (1H, d, J = 6.9 Hz), 5.49 (1H, d, J = 3.0 Hz), 5.39 (1H, dd, J = 6.6 Hz), 5.05-4.98 (5H, m), 4.86 (1H, d, J = 8.4 Hz), 4.26-4.12 (3H, m), 3.84 (1H, d, J = 6.8 Hz), 2.82-2.71 (1H, m), 2.52-1.05 (26 H, m, including singlets at 2.43, 2.18, 1.97, 1.69, 1.22, 1.20, 3H each) 0.90-0.85 (3H, dd, J = 7.3 Hz).

(d) preparation of 2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel.



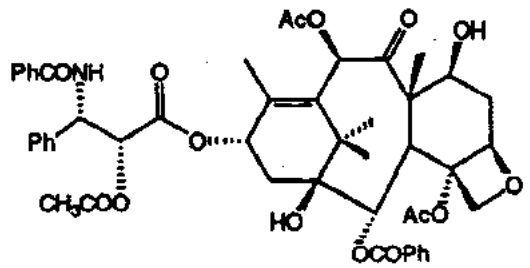
To a nitrogen purged Parr hydrogenation vessel was added 2.5 g of 10 % palladium-on-carbon followed by neat ethyl acetate (150 mL) and a solution of 2'-O-n-propylcarbonyl-7-O-(dibenzylphosphonooxymethyl)-paclitaxel (4.9 g, 4.14 mmol) in ethyl acetate (40 mL). The reaction vessel was then fixed to a Parr hydrogenator, placed under vacuum, then pressurized with a hydrogen atmosphere of 50 psi. The heterogenous mixture was then shaken for 5 h after which time a TLC analysis (eluted with hexanes : ethyl acetate) indicated the consumption of starting material. The reaction mixture was then placed under vacuum and subsequently purged with nitrogen. The mixture was then filtered using a sintered glass funnel and the filtrate concentrated in vacuo to provide the title compound (3.7 g, 91% yield) which was pure by ^{1}H-NMR analysis.

(e) preparatin of 2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt.

To a solution of 2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel (1.1 g, 1.09 mmol) in dichloromethane (50 mL,) was added a 0.1 M solution of triethanolamine (10.9 mL, 1.09 mL) in ethyl acetate and the resulting mixture was stirred for 5 min at room temperature. The reaction mixture was then concentrated in vacuo and the resulting white solid was purified by first dissolving the crude material in a minimum amount of a methylene chloride-ethyl acetate mixture. Hexanes were then added to this solution and the desired amine salt precipitated as a white solid. The mixture was then decanted to provide the amine salt as a white solid which had an observed HPLC purity greater than 95%; ^{1}H-NMR (Acetone-d_6, D_2O, 300 MHz) δ 8.09-8.07 (2H, m), 7.86-7.84 (2H), 7.69-7.24 (11H, m), 7.24 (1H, dd, J = 7.5 Hz), 6.36 (1H, s), 6.05 (1H, dd, J = 8.4 Hz), 5.85 (1H, d, J = 6.7 Hz), 5.61 (1H, d, J = 7.0 Hz), 5.49 (1H, d, J = 6.9 Hz), 5.15-5.13 (1H, m), 4.98 (1H, d, J = 8.2 Hz), 4.87 (1H, dd, J = 12.1 Hz, 6.4 Hz), 4.12 (bs, 2H), 3.89-3.80 (7H, m), 3.36-3.30 (6H, m), 2.95-2.93 (1H, m), 2.42-1.50 (25H, m, including singlets at 2.42, 2.22, 1.93, 1.66, 3H each), 1.13 (bs, 6H), 0.86-0.81 (2H, dd, J = 7.4 Hz).

Example 21. 2'-O-Methylcarbonyl-7-O-phosphonooxymethylpaclitaxel.

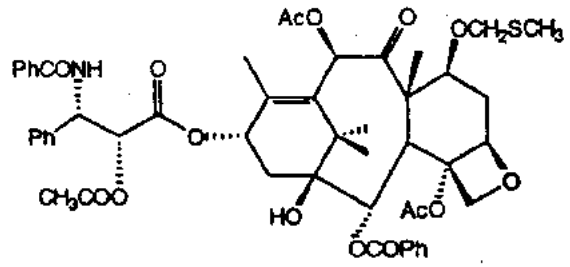
(a) preparation of 2'-O-acetylpaclitaxel.



To a solution of paclitaxel (8.0 g, 9.37 mmol) and diisopropylethyl amine (4.89mL, 28.1 mmol) in dichloromethane (140mL) cooled to 0° C was added acetyl chloride (1.0 mL, 14.1 mmol) dropwise over 2 min. The reaction mixture was then warmed to room temperature and stirred for 10h. The reaction mixture

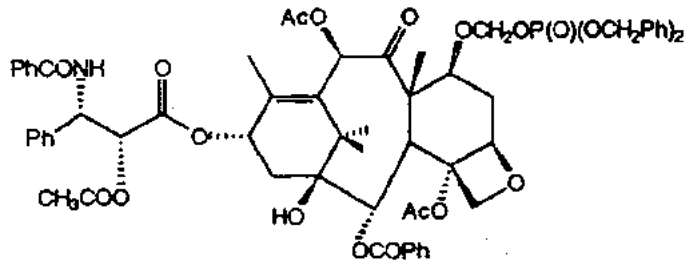
was then partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic phase was then washed with a saturated sodium bicarbonate solution followed by brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (eluted with hexanes: ethyl acetate) to provide 2'-O-acetylpaclitaxel (7.7 g, 92%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 8.10-8.08 (2H, m), 7.92-7.90 (1H, m), 7.89-7.70 (2H, m), 7.60-7.29 (11H, m), 6.94 (1H, d, J = 9.2 Hz), 6.26 (1H, s), 6.23 (1H, dd, J = 9.5 Hz), 5.93 (1H, dd, J = 9.2, 3.1 Hz), 5.65 (1H, d, J = 7.0 Hz), 5.48 (1H, d, J = 3.2 Hz), 4.94 (1H, d, J = 7.8 Hz), 4.42 (1H, dd, J = 10.8 Hz, 6.6 Hz), 4.28 (1H, d, J = 8.4 Hz), 4.16 (1H, d, J = 8.4 Hz), 3.78 (1H, d, J = 6.9 Hz), 2.60-1.02 (25H, m, including singlets at 2.42, 2.19, 2.12, 1.90, 1.65, 1.25, 1.11, 3H each).

(b) preparation of 2'-O-acetyl-7-O-methylthiomethylpaclitaxel.



To a solution of 2'-O-acetylpaclitaxel (7.7 g, 8.60 mmol) and dimethyl sulfide (5.1 mL, 68.8 mmol) in acetonitrile (200 mL) cooled to -40° C was added benzoyl peroxide (8.3 g, 34.4 mmol) and the reaction mixture was warmed to room temperature over 1h. At this time a TLC (eluted with hexanes : ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate and the resulting organic solution was washed three times with a saturated sodium bicarbonate solution then brine. The organic phase was then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (hexanes: ethyl acetate) to provide the title methylthiomethylether (7.39 g, 90%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.10-8.08 (2H, m), 7.77-7.73 (2H, m), 7.65-7.26 (11H, m), 6.53 (3H, 2), 6.20 (1H, dd, J = 8.3 Hz), 5.92 (1H, dd, J = 12.2, 3.1 Hz), 5.67 (1H, d, J = 7.0 Hz), 5.51 (1H, d, J = 3.2 Hz), 4.94 (1H, d, J = 8.2 Hz), 4.69-4.60 (3H, m), 4.33-4.28 (2H, m), 4.27 (1H, d, J = 8.4 Hz), 3.86 (1H, d, J = 6.9 Hz), 2.84-2.74 (1H, m), 2.50-1.1 (28H, m, including singlets at 2.41, 2.15, 2.13, 2.11, 2.06, 1.73, 1.18, 1.15, 3H each).

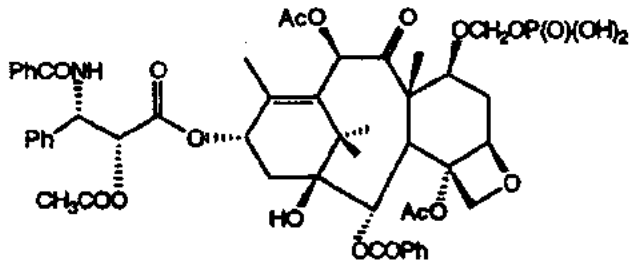
(c) preparation of 2'-O-acetyl-7-O-(dibenzylphosphonooxymethyl)paclitaxel.



N-Iodosuccinimide (1.75 g, 7.85 mmol) was added in one portion to a solution of 2'-O-acetyl-7-O-methylthiomethylpaclitaxel (5.0 g, 5.23 mmol), dibenzylphosphate (7.3 g, 26.1 mmol) and 5 g of oven dried 3 Angstrom sieves in THF (104 mL) at room temperature and the resulting mixture was stirred for 1.5 h. At this time a TLC analysis (eluted with hexanes : ethyl acetate,1: 1) indicated the reaction was complete. The reaction mixture was then diluted to twice the volume with ethyl acetate and filtered through a bed of celite.

The filtrate was then poured into a saturated sodium bicarbonate solution containing 1% sodium thiosulfate by weight. The organic layer was then washed four times with a saturated aqueous sodium bicarbonate solution followed by brine. The aqueous layers were then back extracted with ethyl acetate and the combined organics were dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes : ethyl acetate) to provide the title dibenzylphosphate (4.9 g, 80%) as a white solid.

(b) preparation of 2'-O-acetyl-7-O-phosphonooxymethylpaclitaxel.



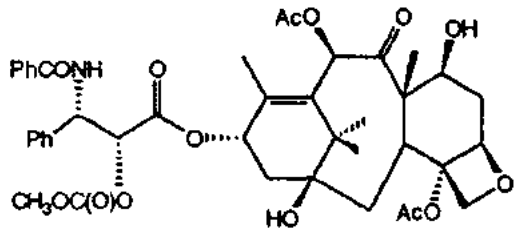
To a nitrogen purged Parr hydrogenation vessel was added 700 mg of 10 % palladium-on-carbon followed by neat ethyl acetate (130 mL) and a solution of 2'-O-acetyl-7-O-(dibenzylphosphonooxymethyl)-paclitaxel (1.0 g, 0.84 mmol) in ethyl acetate (40 mL). The reaction vessel was then fixed to a Parr hydrogenator, placed under vacuum, then pressurized with a hydrogen atmosphere of 50 psi. The reaction mixture was then shaken for 6 h after which time a TLC analysis (eluted with hexanes : ethyl acetate) indicated the consumption of the starting material. The reaction mixture was then placed under vacuum and subsequently purged with nitrogen. The heterogenous solution was then filtered using a sintered glass funnel and the filtrate concentrated in vacuo to provide a white solid (848 mg) which ^{1}H-NMR analysis showed to be a mixture of the desired title compound (50%) and 2'-O-acetylpaclitaxel.

(c) preparation of 2'-O-acetyl-7-O-phosphonooxymethylpaclitaxel triethanolamine salt.

To a solution of 2'-O-acetyl-7-O-phosphonooxymethylpaclitaxel (424 mg, 0.42 mmol) and the aforementioned side product 2'-O-acetylpaclitaxel in dichloromethane (15 mL) was added a 0.1 M solution of triethanolamine (3.7 mL, 3.8 mmol) in ethyl acetate and the resulting mixture was stirred for 10 min at room temperature. The reaction mixture was then concentrated in vacuo and the resulting white solid was purified by C18 chromatography (water : acetonitrile 2.3:1) to provide the desired amine salt (310 mg, 72%) which had an observed HPLC purity greater than 96%; ^{1}H-NMR (Acetone-d_6, D_2O, 300 MHz) δ 8.08-8.05 (2H, m), 7.86-7.83 (2H, m), 7.69-7.24 (11H, m), 7.23 (1H, dd, J = 7.4 Hz), 6.35 (1H, s), 6.02 (1H, dd, J = 8.3 Hz), 5.79 (1H, d, J = 6.9 Hz), 5.59 (1H, d, J = 7.1 Hz), 5.45 (1H, d, J = 6.9 Hz), 5.12 (1H, dd, J = 6.4 Hz), 4.95 (1H, d, J = 8.4 Hz), 4.86 (1H, dd, J = 11.5, 6.5 Hz), 4.24-4.18 (1H, m), 4.12 (2H, bs), 3.92-3.89 (6H, m), 3.80-3.77 (1H, m), 3.46-3.43 (6H, m), 3.00-2.89 (1H, m), 2.39-1.65 (21H including singlets at 2.39, 2.14, 2.12, 1.92, 1.65, 1.11 3H each) 1.11 (6H, bs).

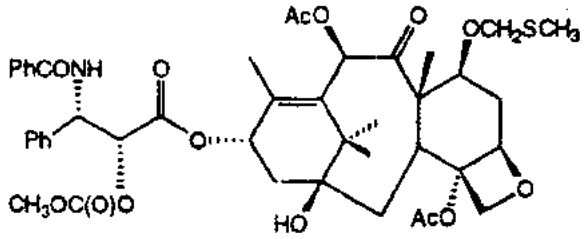
Example 22. 2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxel.

(a) preparation of 2'-O-methoxycarbonylpaclitaxel.



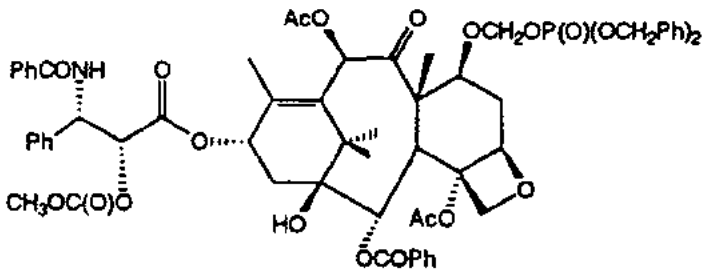
To a solution of paclitaxel (8.0 g, 9.60 mmol) and diisopropylethyl amine (5.0 mL, 28.8 mmol) in dichloromethane (96 mL) cooled to 0 ° C was added chloromethyl carbonate (1.11 mL, 14.4 mmol) dropwise over 2 min. The reaction mixture was then warmed to room temperature and stirred for 20h. The reaction mixture was then partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic phase was then washed with a saturated sodium bicarbonate solution, followed by brine, dried over sodium sulfate and concentrated in vacuo. The residual oil was purified using flash chromatography (hexanes: ethyl acetate) to provide the title compound (7.8 g, 91.3%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 8.12-8.09 (2H, m), 7.72-7.70 (2H, m), 7.62-7.30 (11H, m), 6.96 (1H, d, J = 9.3 Hz), 629-6.23 (3H, m), 5.95 (1H, dd, J = 9.3, 2.5 Hz), 5.66 (1H, d, J = 7.1 Hz), 5.38 (1H, d, J = 2.6 Hz), 4.94 (1H, d, J = 7.8 Hz), 4.41 (1H, dd, J = 10.8, 6.6 Hz), 4.28 (1H, d, J = 8.4 Hz), 4.17 (1H, d, J = 8.4 Hz), 3.79-3.78 (3H, m), 2.60-1.04 (22H, m, including singlets at 2.43, 2.19, 1.90, 1.65, 1.22, 1.10, 3H each).

(b) preparation of 2'-O-methoxycarbonyl-7-O-methylthiomethylpaclitaxel.



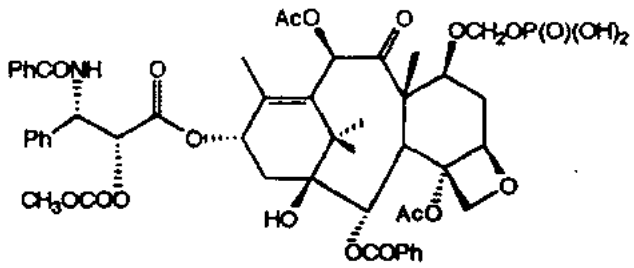
To a solution of 2'-O-methoxycarbonylpaclitaxel(7.4 g, 8.10 mmol) and dimethyl sulfide (4.8 mL, 64.8 mmol) in acetonitrile (162 mL) cooled to -40 ° C was added benzoyl peroxide (7.48 g, 32.4 mmol) and the reaction mixture was warmed to room temperature over 1h. At this time a TLC analysis (eluted with hexanes : ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate and the resulting organic solution was washed three times with a saturated sodium bicarbonate solution then brine. The organic phase was then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes: ethyl acetate) to provide the title compound (7.4 g, 95%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.25-8.23 (2H, m), 7.87-7.77 (2H, m), 7.60-7.30 (11H, m), 6.93 (1H, d, J = 9.2 Hz), 6.53 (1H, s), 6.25 (1H, dd, J = 8.2 Hz), 5.95 (1H, dd, J = 11.7, 2.4 Hz), 5.68 (1H, d, J = 6.9 Hz), 5.40 (1H, d, J = 2.6 Hz), 4.95 (1H, d, J = 8.1 Hz), 4.69-4.60 (2H, m), 4.31-4.26 (2H, m), 4.16 (1H, d, J = 8.4 Hz), 3.86 (1H, J = 6.9 Hz), 3.79 (3H, s), 2.84-2.74 (1H, m), 2.43-1.10 (25H, including singlets at 2.44, 2.15, 2.10, 2.08, 1.73, 1.19, 1.16 3H).

(c) preparation of 2'-O-methoxycarbonyl-7-O-(dibenzylphosphonooxymethyl)paclitaxel



N-Iodosuccinimide (1.74 g, 7.77 mmol) was added in one portion to a solution of 2'-O-methoxycarbonylpaclitaxel(5.04 g, 5.18 mmol), dibenzylphosphate (7.2 g, 25.8 mmol) and 5g of oven dried 3 Angstrom sieves in THF (100 mL) at room temperature and the resulting mixture was stirred for 1.5 h. At this time a TLC analysis (eluted with hexanes:ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted to twice the volume with ethyl acetate and filtered through a bed of celite. The filtrate was then poured into a saturated sodium bicarbonate solution containing 1% sodium thiosulfate by weight. The organic layer was then washed four times with a saturated aqueous sodium bicarbonate solution followed by brine. The aqueous layer was then back extracted with ethyl acetate and the combined organics were dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes : ethyl acetate) to provide the title compound (5.1 g, 96%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.12-8.08 (2H, m), 7.73-7.70 (2H, m), 7.62-7.27 (21H, m), 7.00 (1H, d, J = 9.2 Hz), 6.31 (1H, s), 6.24-6.21 (1H, m), 5.96-5.92 (1H, m), 5.66-5.64 (1H, m), 5.40-5.36 (2H, m), 5.05-4.93 (5H, m), 4.87-4.84 (1H, m), 4.29-4.05 (3H, m), 3.85-3.83 (1H, m), 3.77 (3H, s), 2.81-2.71 (1H, m), 2.62-1.05 (22H, m, including singlets at 2.43, 2.19, 2.01, 1.73, 1.22, 1.15, 3H each).

(d) preparation of 2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxel.



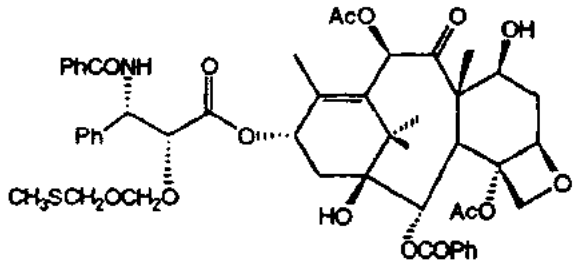
To a nitrogen purged Parr hydrogenation vessel was added 1.3 g of 10 % palladium-on-carbon followed by neat ethyl acetate (140 mL) and a solution of 2'-O-methoxycarbonyl-7-O-(dibenzylphosphonooxymethyl)-paclitaxel (3.4 g, 3.32 mmol) in ethyl acetate (40 mL). The reaction vessel was then fixed to a Parr hydrogenator, placed under vacuum, then pressurized with a hydrogen atmosphere of 50 psi. The resulting mixture was shaken for 8.5 h after which time a TLC analysis (eluted with hexanes : ethyl acetate) indicated the consumption of starting material. The reaction mixture was then placed under vacuum and subsequently purged with nitrogen. The heterogenous solution was then filtered using a sintered glass funnel and the filtrate concentrated in vacuo to provide a white solid (2.9 g) which ^{1}H-NMR analysis showed to be a mixture of the desired title product (67%) and 2'-O-methoxycarbonylpaclitaxel (33%).

(e) preparation of 2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxeltriethanolamine salt.

To a solution of 2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxel (1.91 g, 1.87 mmol) and the aforementioned side product 2'-O-methoxycarbonylpaclitaxel in dichloromethane (11 mL) was added a 0.1 M solution of triethanolamine (18.9 mL, 1.89 mmol) in ethyl acetate and the resulting mixture was stirred for 5 min at room temperature. The reaction mixture was then concentrated in vacuo and the resulting white solid was purified by C18 chromatography (eluted with water : acetonitrile 2.3:1) to provide after subsequent lyophilization the triethanolamine salt which had an observed HPLC purity greater than 97%; ^{1}H-NMR (Acetone-d_6, D_2O, 300 MHz) δ 8.08-8.06 (2H, m), 7.88-7.55 (2H, m), 7.69-7.24 (11H, m), 7.24 (1H, dd, J = 7.3 Hz), 6.36 (1H, m), 6.05 (1H, dd, J = 8.8 Hz), 5.82 (1H, d, J = 6.8 Hz), 5.60 (1H, d, J = 7.1 Hz), 5.46 (1H, d, J = 6.9 Hz), 5.13 (1H, dd, J = 6.5 Hz), 5.98 (1H, d, J = 8.1 Hz), 4.87 (1H, dd, J = 11.8 Hz, 6.3 Hz), 4.21 (1H, dd, J = 10.3, 6.9 Hz), 4.13 (bs, 6H), 3.92-3.89 (6H, m), 3.81 (1H, d, J = 7.02), 3.76 (3H, s), 3.46-3.42 (6H, m), 3.01-2.90 (1H, m), 2.42 (3H, s), 2.20-1.80 (10H, including singlets at 2.20, 1.93), 1.66 (3H, s), 1.12 (6H, bs).

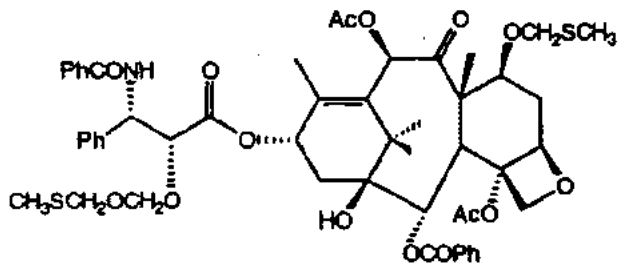
Example 23. preparation of 2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel.

(a) preparation of 2'-O-methylthiomethoxymethylpaclitaxel.



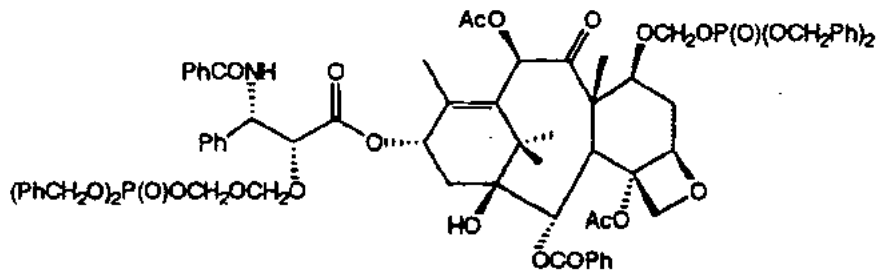
Palladium (10%) on carbon (3 g) was added to a solution of 2'-O-methylthiomethoxymethyl-7-O-benzyloxycarbonylpaclitaxel (1.2 g, 1.11 mmol) in ethyl acetate (100 mL) and ethanol (70 mL) housed in a Parr bottle. The vessel was affixed to a Parr apparatus and the reaction mixture subjected to hydrogen at 50 psi. The reaction mixture was shaken for 20.5 h, then filtered using a sintered glass funnel. The filtrate was concentrated in vacuo and the residual oil purified via flash chromatography (eluted with hexanes : ethyl acetate) to provide the desired (0.98 g, 93%) as a solid. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ 8.12-8.10 (2H, m), 7.76-7.73 (2H, m),7.61-7.27 (11H, m), 7.03 (1H, d, J = 8.9 Hz), 6.40-6.27 (1H, m), 6.25 (1H, s), 5.80 (1H, dd, J = 8.9, 2.4 Hz), 5.66 (1H, d, J = 7.1 Hz), 4.98-4.94 (1H, m), 4.86-4.79 (2H, m), 4.75-4.68 (1H, m), 4.43-4.39 (1H, m), 4.31-4.26 (2H, m), 4.05 (1H, d, J = 11.7 Hz), 3.78 (1H, d, J = 7.1 Hz), 2.60-1.06 (25H, m, including singlets at 2.45, 2.21, 2.02, 1.85, 1.66, 1.22, 1.11, 3H each).

(b) preparation of 2'-O-methylthiomethoxymethyl-7-O-methylthiomethylpaclitaxel.



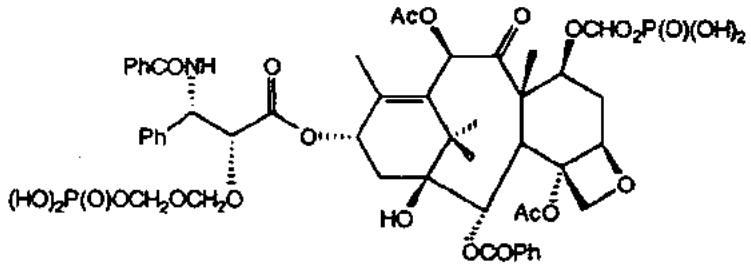
To a solution of 2'-O-methylthiomethoxymethylpaclitaxel. (0.98 g, 1.03 mmol) and dimethyl sulfide (0.6 mL, 8.11 mmol) in acetonitrile (20 mL) cooled to -40° C was added benzoyl peroxide (1.0 g, 4.13 mmol) and the reaction mixture was warmed to room temperature over 30 min. At this time a TLC analysis (eluted with hexanes : ethyl acetate, 1:1) indicated the reaction was complete. The reaction mixture was then diluted with ethyl acetate and the resulting organic solution was washed three times with a saturated sodium bicarbonate solution then brine. The organic phase was then dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes: ethyl acetate) to provide the title product (0.945 g, 91%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.13-8.11 (2H, m), 7.79-7.77 (2H m), 7.61-7.29 (11H, m), 6.54 (1H, s), 6.30-6.26 (1H, m), 5.83-5.80 (1H, m), 5.71-5.69 (1H, m), 5.01-4.66 (6H, m), 4.34-4.04 (5H, m), 3.88 (1H, d, J = 6.6 Hz), 2.90-2.80 (1H, m), 2.55-1.05 (27H, m, including singlets at 2.51, 2.18, 2.11, 1.80, 1.21, 1.20, 3H each).

(c) preparation of 2'-O-dibenzylphosphonooxymethoxymethyl-7-O-(dibenzylphosphonooxymethyl)paclitaxel.



N-Iodosuccinimide (0.615 g, 2.74 mmol) was added in one portion to a solution 2'-O-methylthiomethoxymethyl-7-O-methylthiomethylpaclitaxel (0.92 g, 0.916 mmol), dibenzylphosphate (2.03 g, 7.30 mmol) and 1 g of oven dried 3 Angstrom sieves in THF (18 mL) at room temperature and the resulting mixture was stirred for 30 min. At this time a TLC analysis (eluted with hexanes:ethyl acetate, 1: 2) indicated the reaction was complete. The reaction mixture was then diluted to twice the volume with ethyl acetate and filtered through a bed of celite. The filtrate was then poured into a saturated sodium bicarbonate solution containing 1% sodium thiosulfate by weight. The organic layer was then washed four times with a saturated aqueous sodium bicarbonate solution followed by brine. The aqueous layer was then back extracted with ethyl acetate and the combined organics were dried over sodium sulfate and concentrated in vacuo. The residual oil was purified via flash chromatography (eluted with hexanes : ethyl acetate) to provide the title product (0.768 g, 58%) as a white solid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.10-8.05 (2H, m), 7.80-7.74 (2H, m), 7.65-7.27 (11H, m), 6.30 (1H, s), 6.25-6.18 (1H, m), 5.82 (1H, dd, J = 9.1, 3.4 Hz), 5.63 (1H, dd, J = 6.9 Hz), 5.38 (1H, dd, J = 6.6 Hz), 5.10-4.60 (15H, m), 4.30-4.10 (3H, m), 3.80 (1H, d, J = 6.8 Hz), 2.85-2.65 (1H, m), 2.50-1.60 (22H, m, including singlets at 2.47, 2.16, 1.91, 1.72, 1.88, 1.15, 3H each).

(d) preparation of 2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel



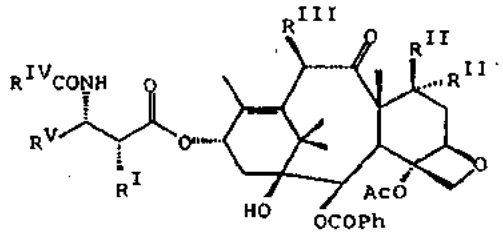
To a nitrogen purged Parr hydrogenation vessel was added 1.3 g of 10 % palladium-on-carbon followed by neat ethyl acetate (110 mL) and a solution of 2'-O-dibenzylphosphonooxymethoxymethyl-7-O-(dibenzylphosphonooxymethyl)paclitaxel (0.721 g, 0.498 mmol) in ethyl acetate (40 mL). The reaction vessel was then fixed to a Parr hydrogenator, placed under vacuum then pressurized with a hydrogen atmosphere of 50 psi. The heterogenous mixture was then shaken for 16 h after which time a TLC analysis (eluted with hexanes : ethyl acetate) indicated the consumption of starting material. The reaction mixture was then placed under vacuum and subsequently purged with nitrogen. The mixture was then filtered using a sintered glass funnel and the filtrate concentrated in vacuo to provide the title product (0.413 g) which was at 60% purity by HPLC analysis.

(e) preparation of 2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel bis-triethanolamine salt.

To a solution of crude of 2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel (413mg) in dichloromethane (10 mL) was added a 0.1 M solution of triethanolamine (7.6 mL, 0.076 mmol) in ethyl acetate and the resulting mixture was stirred for 5 min at room temperature. The reaction mixture was then concentrated in vacuo and the resulting white solid was purified by C18 chromatography (eluted with water : acetonitrile, 9:1 to 5.6:1). Fractions of eluent containing the desired salt in greater than 96% purity by HPLC were combined and the acetonitrile was removed via rotary evaporation. The resulting aqueous solution of the amine salt was lyophylized to provide the desired salt (0.210 g, 30% over 2 steps) as a white solid. ^{1}H- NMR (Acetone-d_6, D_2O, 300 MHz) δ 7.97-7.94 (2H, m), 7.79-7.76 (2H, m), 7.67-7.33 (11H, m), 7.12-7.07 (1H, m), 6.26 (1H, s), 5.89 (1H, dd, J = 8.6 Hz), 5.48 (1H, d, J = 7.9 Hz), 5.00-4.79 (8H, m), 4.70 (1H, d, J = 8.1 Hz), 4.15-4.03 (3H, m), 3.74-3.66 (7H, m), 3.14-2.86 (8H, m), 2.33-1.00 (20H, m, including singlets at 2.33, 2.10, 1.88, 1.56, 1.02, 1.00, 3H each).

Additional Examples

The general procedures provided in the foregoing examples and descriptions are followed in the preparation of the following compounds within the scope of formula (A).



R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	Ph	4- F-Ph- 4-CH_3-Ph 2-furanyl 2-thienyl $(CH_3)_2CH$- isobutenyl (2-methyl-1-propenyl) * c-C_3H_5- 3-furanyl 3-thienyl 2-propenyl

* 'c' indicates cyclo

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OP(O)(OH)_2$	H	OH	AcO	Ph	4-CF_3-Ph- 2-furanyl $(CH_3)_2CH$- 2-thienyl isobutenyl cyclopropyl 3-thienyl 3-furanyl 2-propenyl isopropyl
$CH_3CH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	Ph	4-F-Ph- 2-thienyl isopropyl 2-propenyl isobutenyl cyclopropyl 2-furanyl 3-furanyl 3-thienyl
$-OCH_2OP(O)(OH)_2$	H	OH H $CH_3CH_2OC(O)O$-	OH	$(CH_3)_3CO$-	Ph

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH $CH_3CH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO$-	Ph
$-OCH_2OP(O)(OH)_2$	H	H $CH_3CH_2OC(O)O$-	AcO	Ph	Ph
OH $CH_3OC(O)O$- $CH_3CH_2OC(O)O$- $CH_3(CH_2)_2OC(O)O$- $CH_3(CH_2)_3OC(O)O$- $CCl_3CH_2OC(O)O$- $CH_3C(O)O$- $CH_3CH_2(O)O$- $CH_3(CH_2)_2C(O)O$- $CH_3(CH_2)_3C(O)O$- PhC(O)O- PhOC(O)O- $CH_2=CHCH_2OC(O)O$- $PhCH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	Ph	Ph
OH	H	OH	$-OCH_2OP(O)(OH)_2$	Ph	Ph
OH	H	H	$-OCH_2OP(O)(OH)_2$	Ph	Ph
$-OCH_2OP(O)(OH)_2$	H	H	H	$(CH_3)_3CO$-	4-CH_3O-Ph

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3OC(O)O-$	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$CH_3CH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3(CH_2)_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$CH_3(CH_2)_3OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CCl_3CH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$CH_3C(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3CH_2(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$CH_3(CH_2)_2C(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$CH_3(CH_2)_3C(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
PhC(O)O-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
PhOC(O)O-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
CH_2=$CHCH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl
$PhCH_2OC(O)O$-	H	$-OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	isobutenyl 2-propenyl cyclopropyl 3-furanyl 3-thienyl isopropyl cyclobutyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl 3-furanyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl 2-thienyl isopropyl
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl 3-furanyl isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl 2-thienyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	AcO	isopropyloxy	2-furanyl 3-furanyl 2-thienyl Isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl Isopropyl
OH	H	$-OCH_2OP(O)(OH)_2$	AcO	Isopropyloxy	2-furanyl 3-furanyl 2-thienyl Isobutenyl 2-propenyl cyclopropyl cyclobutyl 3-thienyl Isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH $CH_3OC(O)O$- $CH_3CH_2OC(O)O$- $CH_3(CH_2)_2OC(O)O$- $CH_3(CH_2)_3OC(O)O$- $CCl_3CH_2OC(O)O$- $CH_3C(O)O$- $CH_3CH_2(O)O$- $CH_3(CH_2)_3C(O)O$- $CH_3(CH_2)_2C(O)O$- PhC(O)O- PhOC(O)O- CH_2=$CHCH_2OC(O)O$- $PhCH_2OC(O)O$-	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO$-	3-furanyl isobutenyl 2-propenyl 2-thienyl 3-thienyl cyclopropyl Isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$(CH_3)_3CO-$	2-furanyl isobutenyl 2-thienyl 2-propenyl isopropyl cyclopropyl 3-thienyl 3-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	$CH_3CH_2CH_2CH_2O-$	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	Isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl isopropyl cyclopropyl isobutenyl 2-thienyl 2-propenyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
OH	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl 3-furanyl 3-thienyl Isopropyl cyclopropyl Isobutenyl 2-thienyl 2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph $CH_3CH_2CH_2CH_2O-$ Isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph $CH_3CH_2CH_2CH_2O-$ Isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	OMe	Ph $CH_3CH_2CH_2CH_2O-$ Isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	OMe	Ph $CH_3CH_2CH_2CH_2O-$ Isopropyloxy	2-furanyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph $CH_3CH_2CH_2CH_2O$- Isopropyloxy	2-furanyl
OH	H	$-OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph $CH_3CH_2CH_2CH_2O$- Isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO$- Isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO$- Isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO$- Isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO$- Isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO$- Isopropyloxy $CH_3CH_2CH_2CH_2O$-	2-furanyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$ isopropyloxy $CH_3CH_2CH_2CH_2O-$	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	isobutenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	isobutenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	isobutenyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	Ph	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	Ph	2-furanyl
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	Ph	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OMe	$(CH_3)_3CO-$	2-propenyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	-OC(O)Ph	$(CH_3)_3CO-$	2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	AcO	$(CH_3)_3CO-$	2-furanyl 2-thienyl 3-furanyl 3-thienyl isobutenyl 2-propenyl cyclopropyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	AcO	$CH_3CH_2CH_2CH_2O-$ isopropyloxy $(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	$-OCO_2CH_3$	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	OMe	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	-OC(O)Ph	$(CH_3)_3CO-$ Ph isopropyloxy	2-furanyl
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	AcO	Ph	Ph

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
OH	F	H	$-OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$ Ph	Ph
$-OCO_2CH_2CH_3$	F	H	$-OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$ Ph	Ph
$-OCH_2OP(O)(OH)_2$	F	H	AcO	Ph	2-furanyl isobutenyl 3-furanyl 2-thienyl 2-propenyl cyclopropyl 3-thienyl isopropyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	AcO	Ph	2-furanyl isobutenyl 3-furanyl 2-thienyl 2-propenyl cyclopropyl 3-thienyl isopropyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OP(O)(OH)_2$	F	H	AcO	$(CH_3)_3CO-$	2-furanyl 3-thienyl isobutenyl 3-furanyl cyclopropyl 2-thienyl Ph 2-propenyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	AcO	$(CH_3)_3CO-$	2-furanyl 3-thienyl isobutenyl 3-furanyl cyclopropy 2-thienyl Ph 2-propenyl
$-OCH_2OP(O)(OH)_2$	F	H	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OP(O)(OH)_2$	F	H	OMe	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OP(O)(OH)_2$	F	H	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	$-OCO_2CH_3$	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	OMe	$(CH_3)_3CO-$	2-furanyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2OCH_2OP(O)(OH)_2$	F	H	-OC(O)Ph	$(CH_3)_3CO-$	2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	OH	OH	$(CH_3)_3CO-$	Ph
OH	H	$-OCH_2OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO-$	Ph
$-OCO_2CH_2CH_3$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OH	$(CH_3)_3CO-$	Ph
OH	H	OH	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$	Ph
$-OCO_2CH_2CH_3$	H	OH	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$	Ph
OH	F	H	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$	Ph 2-furanyl 3-furanyl 2-thienyl 3-thienyl isobutenyl cyclopropyl 2-propenyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCO_2CH_2CH_3$	F	H	$-OCH_2OCH_2OP(O)(OH)_2$	$(CH_3)_3CO-$	Ph 2-furanyl 3-furanyl 2-thienyl 3-thienyl isobutenyl cyclopropyl 2-propenyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OAc	Ph	Ph 2-furanyl
$-OCH_2OCH_2OP(O)(OH)_2$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OAc	tBuO	Ph 2-furanyl
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	OH $-OCH_2OCH_2OP(O)(OH)_2$ $-OCH_2OP(O)(OH)_2$ $-OCH_2(OCH_2)_2OP(O)(OH)_2$	OAc	Ph	Ph
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	OH	OAc	tBuO	Ph 2-furanyl
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	$-OCH_2OP(O)(OH)_2$	OAc	tBuO	Ph 2-furanyl

R^{I}	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^{V}
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OAc	tBuO	Ph 2-furanyl
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	$-OCH_2(OCH_2)_2OP(O)(OH)_2$	OAc	tBuO	Ph 2-furanyl
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	-OH	OAc	Ph	Ph
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	-OH	OAc	tBuO	Ph 2-furanyl
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2OP(O)(OH)_2$	OAc	Ph tBuO	Ph
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2OP(O)(OH)_2$	OAc	tBuO	2-furanyl
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OAc	Ph tBuO	Ph
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	$-OCH_2OCH_2OP(O)(OH)_2$	OAc	tBuO	2-furanyl
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2(OCH_2)_2OP(O)(OH)_2$	OAc	Ph tBuO	Ph
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2(OCH_2)_2OP(O)(OH)_2$	OAc	tBuO	2-furanyl
$-OCH_2(OCH_2)_3OP(O)(OH)_2$	H	$-OCH_2(OCH_2)_3OP(O)(OH)_2$	OAc	Ph	Ph 2-furanyl

R^I	$R^{II'}$	R^{II}	R^{III}	R^{IV}	R^V
$-OCH_2(OCH_2)_2OP(O)(OH)_2$	H	$-OCH_2(OCH_2)_2OP(O)(OH)_2$	OAc	tBuO	Ph 2-furanyl

Claims

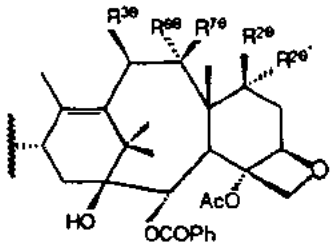
1. A compound having the formula

$T-[OCH_2(OCH_2)_mOP(O)(OH)_2]_n$ (A)

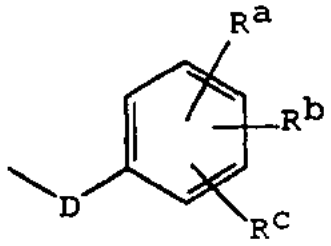
wherein
T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group;
m is 0 or an integer from 1 to 6 inclusive;
n is 1, 2 or 3;
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein said taxane moiety is further characterized as containing at least a C11-C12 double bond, C1 hydroxy, C2 benzoyloxy, C4 acetyloxy, C9 oxy, and C5-C20 oxetane.

3. A compound of claim 1 wherein said taxane moiety is derived from a residue having the formula

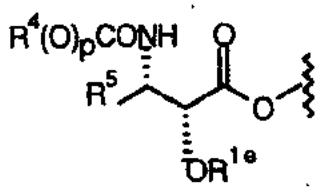


wherein $R^{2e'}$ is hydrogen and R^{2e} is hydrogen, hydroxy, $-OC(O)R^x$, or $-OC(O)OR^x$; R^{3e} is hydrogen, hydroxy, $-OC(O)R^x$, $-OC(O)OR^x$ or C_{1-6} alkyloxy; one of R^{6e} or R^{7e} is hydrogen and the other is hydroxy or $-C(O)OR^x$; or R^{6e} and R^{7e} together form an oxo group; R^x is C_{1-6} alkyl optionally substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl or hydroxy; or R^x is a radical of the formula



wherein D is a bond or C_{1-6} alkyl; and R^a, R^b and R^c are independently hydrogen, amino, C_{1-6} alkylamino, di-C_{1-6}alkylamino, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy.

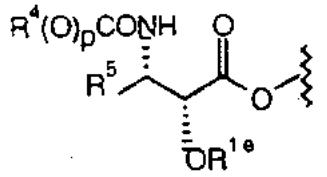
4. A compound of claim 1 wherein said substituted 3-amino-2-hydroxypropanoyloxy group is derived from a residue having the formula



wherein
R^{1e} is hydrogen or $-C(O)R^x$, $-C(O)OR^x$;
R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-Z-R^6$;

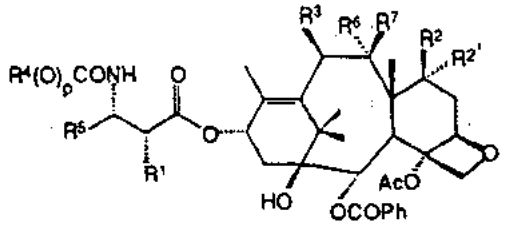
Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl;
R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl, or heteroaryl;
p is 0 or 1; and
R^x is as defined previously.

5. A compound of claim 1 wherein said taxane moiety is further characterized as containing at least a C11-C12 double bond, C1 hydroxy, C2 benzoyloxy, C4 acetyloxy, C9 oxy, and C5-C20 oxetane; and said substituted 3-amino-2-hydroxypropanoyloxy group is derived from a residue having the formula



wherein R^{1e}, R^4, R^5 and p are as previously defined.

6. A compound of claim 1 having the formula



wherein
R^1 is hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$;
$R^{2'}$ is hydrogen, and R^2 is hydrogen, hydroxy, $-OCH_2(OCH_2)_mOP(O)(OH)_2$ $-OC(O)R^x$ or $-OC(O)OR^x$;
R^3 is hydrogen, hydroxy, C_{1-6} alkyloxy, $-OC(O)R^x$,$-OCH_2(OCH_2)_mOP(O)(OH)_2$ or $-OC(O)OR^x$;
one of R^6 or R^7 is hydrogen and the other is hydroxy, C_{1-6} alkanoyloxy, or $-OCH_2(OCH_2)_mOP(O)(OH_2)$; or R^6 and R^7 together form an oxo group; with the proviso that at least one of R^1, R^2, R^3, R^6 or R^7 is $-OCH_2(OCH_2)_mOP(O)(OH)_2$:
m is 0, 1 or 2;
R^4, R^5, R^x and p are as previously defined;
or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6 wherein $R^{2'}$ is hydrogen, and R^2 is $-OCH_2OP(O)(OH)_2$; or a pharmaceutically acceptable salt thereof.

8. A compound of claim 7 wherein R^1 is hydroxy, $-OC(O)R^x$ or $-OC(O)OR^x$; and R^x is as previously defined.

9. A compound of claim 8 wherein R^x is C_{1-6} alkyl.

10. A compound of claim 8 wherein R^3 is hydrogen, hydroxy or acetoxy.

11. A compound of claim 8 wherein $R^4(O)_p$ is phenyl or t-butoxy.

12. A compound of claim 8 wherein R^5 is phenyl, 2-furyl or 2-thienyl.

13. A compound of claim 6 wherein R^1 is $-OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

14. A compound of claim 13 wherein $R^{2'}$ is hydrogen, R^2 is hydrogen, hydroxy or $-OC(O)OR^x$, and R^x is as defined in claim 6.

15. A compound of claim 14 wherein R^3 is hydrogen, hydroxy or acetoxy.

16. A compound of claim 14 wherein $R^4(O)_p$ is phenyl or t-butoxy.

17. A compound of claim 14 wherein R^5 is phenyl.

18. A compound of claim 6 wherein R^1 and R^2 are both $-OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

19. A compound of claim 6 wherein R^1 is $-OCH_2OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

20. A compound of claim 6 wherein R^3 is $-OCH_2OP(O)(OH)_2$, or a pharmaceutically acceptable salt thereof.

21. A compound of claim 6 wherein R^1 is $-OCH_2OCH_2OCH_2OP(O)(OH)_2$.

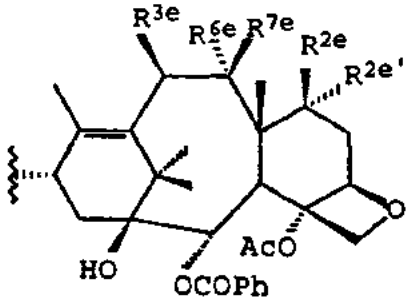
22. The compounds of claim 1 which are:
2'-O-(ethoxycarbonyl)-7-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the sodium salt;
the triethanolamine salt;
the triethylamine salt;
the arginine salt;
the lysine salt;
the ethanolamine salt; or
the N-methylglucamine salt thereof;
7-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the sodium salt thereof;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt thereof;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-phosphonooxymethylpaclitaxel or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt thereof;
2'-O-methoxycarbonyl-7-O-phosphonooxymethylpaclitaxel;
2'-O-methylcarbonyl-7-O-phosphonooxymethylpaclitaxel;
2'-O-n-propylcarbonyl-7-O-phosphonooxymethylpaclitaxel;
2'-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof;
2',7-O-bis(phosphonooxymethyl)paclitaxel or a pharmaceutically acceptable salt thereof, in particular the sodium salt thereof;
2'-O-phosphonooxymethoxymethyl-7-O-phosphonooxymethylpaclitaxel;
2'-O-phosphonooxymethoxymethylpaclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt thereof;
10-desacetyl-3'-N-desbenzoyl-3'-N-(t-butyloxycarbonyl)-10-O-(phosphonooxymethyl)paclitaxel, or a pharmaceutically acceptable salt thereof, in particular the triethanolamine salt thereof;
2'-O-[(phosphonooxymethoxy)methoxymethyl]paclitaxel; and
2'-O-[(phosphonooxymethoxy)methoxy]methyl-7-O-phosphonooxymethylpaclitaxel.

23. A compound having the formula

$$13\text{—}OH\text{—}txn\text{—}[OCH_2(OCH_2)_mSCH_3]_n$$

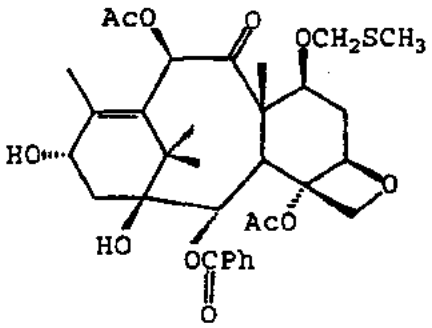
wherein txn is a taxane moiety, m and n are as previously defined, or a C13 metal alkoxide thereof.

24. A compound of claim 23 wherein said taxane moiety is derived from a residue having the formula



wherein R^{2e}, $R^{2e'}$, R^{3e}, R^{6e} and R^{7e} are as previously defined.

25. A compound of claim 23 having the formula



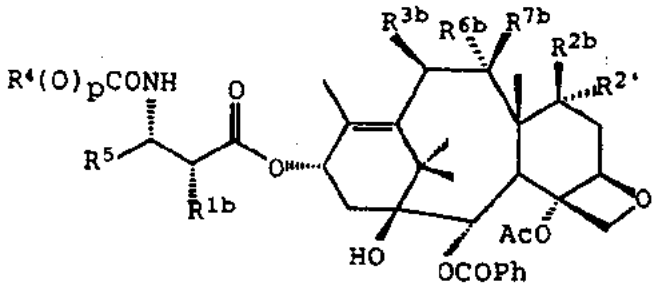
or a C13 metal alkoxide thereof.

26. A compound having the formula

$$T'—[OCH_2(OCH_2)_mSCH_3]_n$$

wherein T' is T in which non-reacting hydroxy groups have been blocked, m and n are as defined above.

27. A compound of claim 26 having the formula

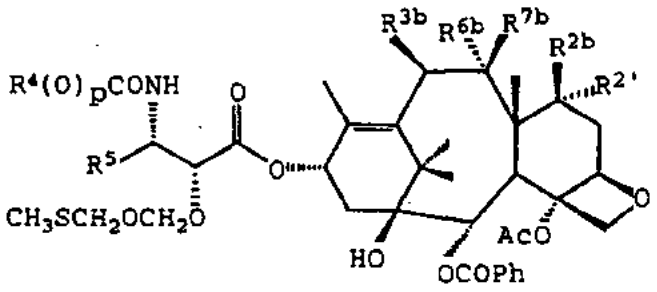


wherein R^{1b} is hydroxy, protected hydroxy, $-OCH_2SCH_3$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, and R^{2b} ishydrogen, hydroxy, protected hydroxy, $-OCH_2SCH_3$, $-OC(O)R^x$ or $-OC(O)OR^x$; R^{3b} is hydrogen, hydroxy, protected hydroxy, C_{1-6}alkyloxy, $-OC(O)R^x$, $-OCH_2SCH_3$ or $-OC(O)OR^x$; one of R^{6b} or R^{7b} is

hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2SCH_3$; or R^{6b} and R^{7b} together form an oxo group; with the proviso that at least one of R^{1b}, R^{2b}, R^{3b}, R^{6b} or R^{7b} is $-OCH_2SCH_3$; p, R^4, R^5 and R^x are as previously defined.

28. The compounds of claim 27 that are:
7-O-methylthiomethylpaclitaxel;
2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel;
2'-O-(methylthiomethyl)-7-O-(triethylsilyl)paclitaxel;
2'-O-(methylthiomethyl)paclitaxel;
2',7-O-bis(methylthiomethyl)paclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(isopropyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(n-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2-O-triethylsilyl-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-10-deacetyl-10-hydroxymethylcarbonyl-(paclitaxel);
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel; or
3'-desphenyl-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel.

29. A compound of claim 26 having the formula



wherein $R^{2'}$, R^{2b}, R^{3b}, R^4, R^5, R^{6b}, R^{7b} and p are as previously defined.

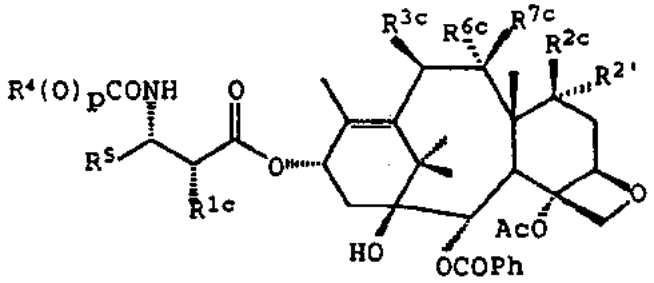
30. The compounds of claim 29 that are 2'-O-(methylthiomethoxymethyl)-7-O-triethylsilylpaclitaxel; or 2'-O-(methylthiomethoxymethyl)-7-O-benzyloxycarbonylpaclitaxel.

31. A compound having the formula

$$T'-[OCH_2(OCH_2)_mOP(O)(OR^y)_2]_n$$

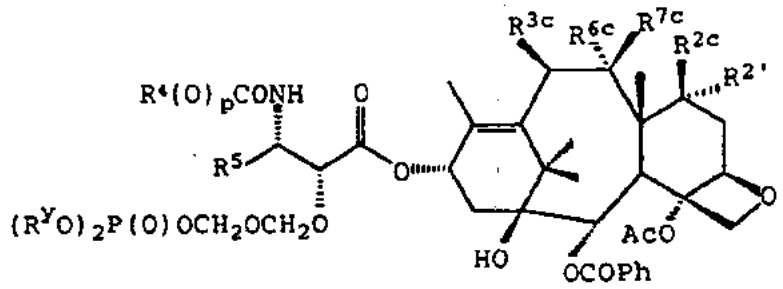
wherein T', m and n are as defined above, and R^y is a phosphono protecting group.

32. A compound of claim 31 having the formula



wherein R^{1c} is hydroxy, protected hydroxy, $-OCH_2OP(O)(OCH_2R^y)_2$, $-OC(O)R^x$ or $-OC(O)OR^x$; $R^{2'}$ is hydrogen, R^{2c} is hydrogen, hydroxy, protected hydroxy, $-OCH_2OP(O)(OCH_2R^y)_2$, $-OC(O)OR^x$ or $-OC(O)R^x$; R^{3c} is hydrogen, hydroxy, C_{1-6}alkyloxy, protected hydroxy, $-OC(O)R^x$, $-OCH_2OP(O)(OCH_2R^y)_2$ or $-OC(O)OR^x$; one of R^{6c} or R^{7c} is hydrogen and the other is hydroxy, protected hydroxy, C_{1-6} alkanoyloxy or $-OCH_2OP(O)(OR^y)_2$; or R^{6c} and R^{7c} together form an oxo group; with the proviso that at least one of R^{1c}, R^{2c}, R^{3c}, R^{6c} or R^{7c} is $-OCH_2OP(O)(OCH_2R^y)_2$; p, R^4, R^5, R^x and R^y are as previously defined.

33. A compound of claim 31 having the formula



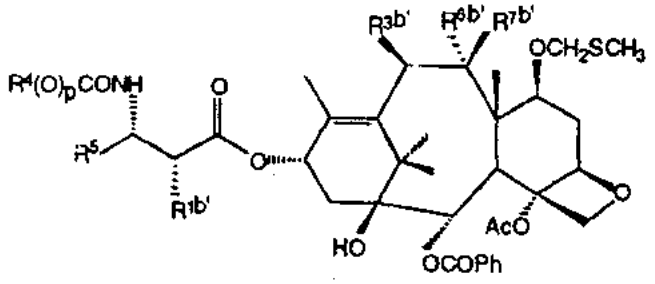
wherein $R^{2'}$, R^{2c}, R^{3c}, R^4, R^5, R^{6c}, R^{7c}, R^y and p are as previously defined.

34. A pharmaceutical composition which comprises an antitumor effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

35. The use of a compound of claim 1 for preparing a pharmaceutical composition for inhibiting tumor growth in a mammalian host.

36. The use according to claim 35, wherein the pharmaceutical composition is suitable for oral administration.

37. The use of a compound of formula (B'):



(B')

wherein $R^{1b'}$ is hydroxy, -OC(O)R^x or -OC(O)OR^x; $R^{3b'}$ is hydrogen, hydroxy, -OC(O)OR^x, C_{1-6} alkyloxy or -OC(O)R^x; one of $R^{6b'}$ or $R^{7b'}$ is hydrogen and the other is hydroxy or C_{1-6} alkanoyloxy; or $R^{6b'}$ and $R^{7b'}$ together form an oxo group; and R^4, R^5, p and R^x are as previously defined; with the proviso that a compound of formula cannot be 3,-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-7-O-methylthiomethylpaclitaxel or 3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel,
for preparing a pharmaceutical composition for inhibiting tumor in a mammalian host.

38. The use according to claim 37 of the following compounds: 7-O-methylthiomethylpaclitaxel;
2'-O-(benzyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
2'-O-(ethoxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-7-O-methylthiomethylpaclitaxel.
3'-N-debenzoyl-3'-desphenyl-3'-N-(t-butyloxycarbonyl)-3'-(2-thienyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(isopropyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(n-butyloxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-10-deacetyl-10-hydroxymethylcarbonyl-(paclitaxel);
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel;
3'-N-debenzoyl-3'-N-(t-butoxycarbonyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel;
7-O-methylthiomethyl-3'-desphenyl-3'-isobutenylpaclitaxel; or
3'-desphenyl-3'-(2-furyl)-2'-O-ethyloxycarbonyl-7-O-methylthiomethylpaclitaxel.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 2803

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	CA-A-2 088 931 (BRISTOL-MYERS SQUIBB CO.) * the whole document * ---	1-38	C07F9/655 A61K31/66 A61K31/335
P,X	EP-A-0 604 910 (BRISTOL-MYERS SQUIBB CO.) * the whole document * -----	1-36	C07D305/14 C07D407/12 C07F9/6558

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07F
C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	4 November 1994	Beslier, L

EPO FORM 1503 03.82 (P04C01)

CATEGORY OF CITED DOCUMENTS

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DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets 5 :		(11) Numéro de publication internationale:	WO 94/07878
C07D 305/14, 263/04, 413/12	A1	(43) Date de publication internationale:	14 avril 1994 (14.04.94)

(21) Numéro de la demande internationale: PCT/FR93/00968

(22) Date de dépôt international: 4 octobre 1993 (04.10.93)

(30) Données relatives à la priorité:
92/11742 5 octobre 1992 (05.10.92) FR

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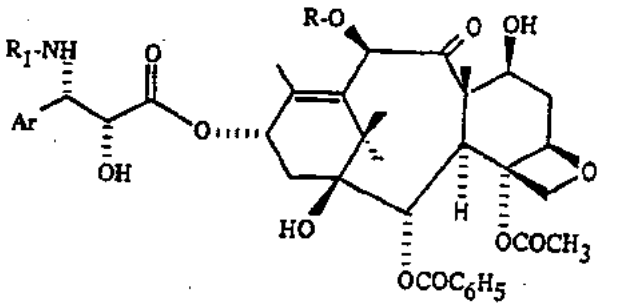
(81) Etats désignés: AU, BY, CA, CZ, FI, HU, JP, KR, KZ, NO, NZ, PL, RU, SK, UA, US, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

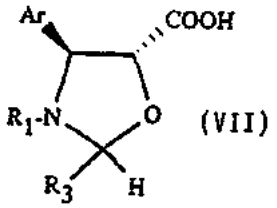
Publiée
Avec rapport de recherche internationale.

(54) Title: METHOD OF PREPARING TAXANE DERIVATIVES

(54) Titre: PROCEDE DE PREPARATION DE DERIVES DU TAXANE



(I)



(VII)

(57) Abstract

Method of preparing taxane derivatives of general formula (I) by esterification of protected baccatine III or 10-deacetyl-baccatine III by means of an acid of general formula (VII), deprotection of the side chain and elimination of the hydroxy function protection groupings. In general formulae (I) and (VII): Ar stands for aryl, R is hydrogen or acetyl, R_1 is benzoyl or R_2-O-CO- in which R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclyl, and R_3 is hydrogen, alkoxy, optionally substituted aryl.

(57) Abrégé

Procédé de préparation de dérivés du taxane de formule générale (I) par estérification de la baccatine III ou de la désacétyl-10 baccatine III protégé au moyen d'un acide de formule générale (VII), déprotection de la chaîne latérale et élimination des groupements protecteurs des fonctions hydroxy. Dans les formules générales (I) et (VII): Ar représente aryle, R représente hydrogène ou acétyle, R_1 représente benzoyle ou R_2-O-CO- dans lequel R_2 représente alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle, bicycloalkyle, phényle ou hétérocyclyle, R_3 représente hydrogène, alcoxy, aryle éventuellement substitué.

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

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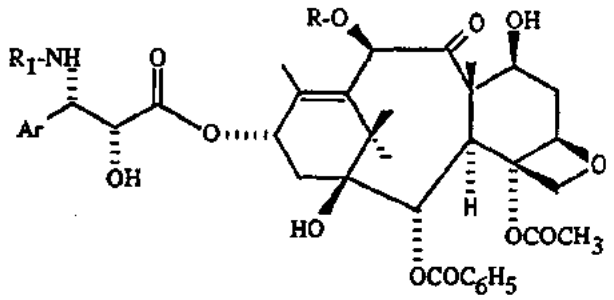
PROCEDE DE PREPARATION DE DERIVES DU TAXANE

La présente invention concerne un nouveau procédé de préparation de dérivés du taxane de formule générale :



(I)

qui présentent des propriétés antileucémiques et antitumorales remarquables.

Dans la formule générale (I) :

R représente un atome d'hydrogène ou un radical acétyle, R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle, bicycloalcoyle, phényle ou hétérocyclyle azoté, et Ar représente un radical aryle.

Plus particulièrement, R représente un atome d'hydrogène ou un radical acétyle et R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone ou bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoyloxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, phényle, cyano, carboxy ou alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,

- ou un radical phényle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoyloxy contenant 1 à 4 atomes de carbone,
- ou un radical hétérocyclyle azoté saturé ou non saturé contenant 5 ou 6 chaînons éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

étant entendu que les radicaux cycloalcoyles, cycloalcényles ou bicycloalcoyles peuvent être éventuellement substitués par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone, et

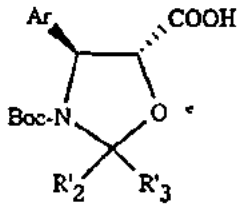
Ar représente un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles, alcényles, alcynyles, aryles, arylalcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alkylamino, dialkylamino, carboxy, alcoxycarbonyle, carbamoyle, dialcoylcarbamoyle, cyano et trifluorométhyle, étant entendu que les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone, que les radicaux alcényles et alcynyles contiennent 3 à 8 atomes de carbone et les radicaux aryles sont les radicaux phényles ou α- ou β-naphtyles.

D'un intérêt tout particulier sont les produits de formule générale (I) dans laquelle R représente un atome d'hydrogène ou un radical acétyle, R_1 représente un radical benzoyle ou t.butoxycarbonylamino et Ar représente un radical phényle.

Les produits de formule générale (I) dans laquelle R_1 représente un radical benzoyle correspondent au taxol et au désacétyl-10 taxol et les produits de formule générale (I) dans laquelle R_1 représente un radical t.butoxycarbonyle correspondent à ceux qui font l'objet du brevet européen EP 0 253 738.

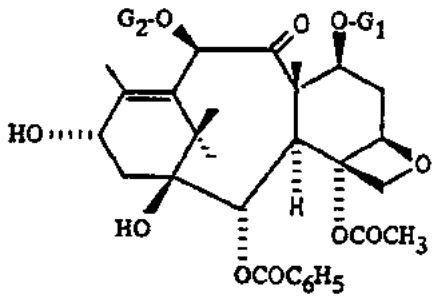
Selon le procédé qui est décrit dans la demande internationale PCT WO 92/09589, les dérivés de formule générale (I) peuvent être obtenus par :

- condensation d'un dérivé de l'oxazolidine de formule générale :



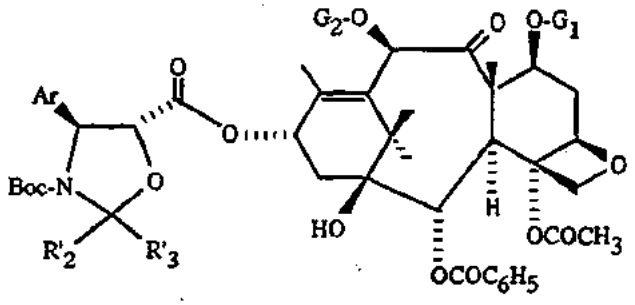
(II)

dans laquelle Ar est défini comme précédemment, Boc représente le radical t.butoxycarbonyle et R'_2 et R'_3, identiques ou différents, représentent un radical alcoyle contenant 1 à 4 atomes de carbone éventuellement substitué par un ou plusieurs radicaux aryles, ou un radical aryle, ou bien R'_2 et R'_3 forment ensemble avec l'atome de carbone auquel ils sont liés un cycle ayant de 4 à 7 chaînons, sur la baccatine III ou la désacétyl-10 baccatine III protégée de formule générale :



(III)

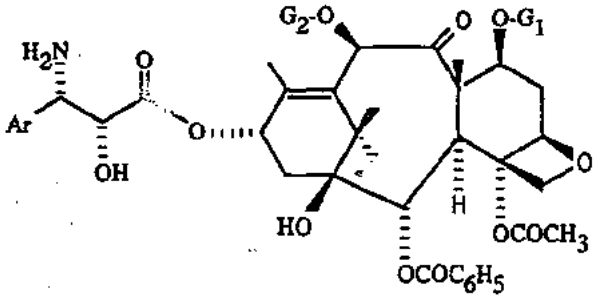
dans laquelle G_1 représente un groupement protecteur de la fonction hydroxy et G_2 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy, pour obtenir un produit de formule générale :



(IV)

dans laquelle Ar, R'_2, R'_3, G_1, G_2 et Boc sont définis comme précédemment,

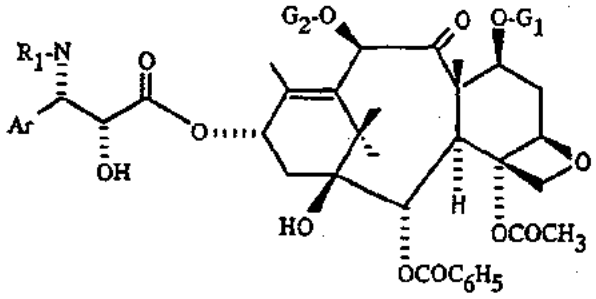
- traitement en milieu acide du produit de formule générale (IV) dans des conditions qui sont sans effet sur G_1 et G_2 pour obtenir le produit de formule générale :



(V)

dans laquelle Ar, G_1 et G_2 sont définis comme précédemment,

- traitement du produit de formule générale (V) par un réactif convenable pour introduire un radical benzoyle ou R_2-O-CO-, pour obtenir un produit de formule générale :



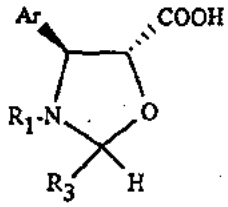
(VI)

dans laquelle Ar, R_1, G_1 et G_2 sont définis comme précédemment, et

- remplacement des groupements protecteurs G_1 et G_2 du produit de formule générale (VI) par des atomes d'hydrogène pour obtenir le produit de formule générale (I).

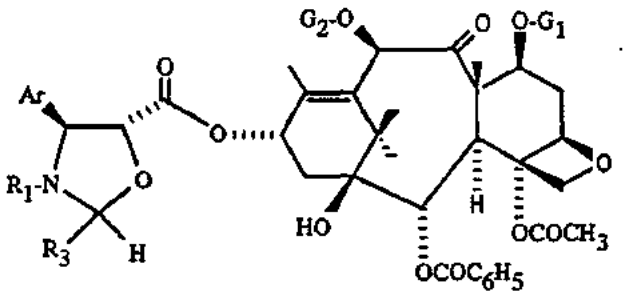
Il a maintenant été trouvé, et c'est ce qui fait l'objet de la présente invention, que les produits de formule générale (I) peuvent être obtenus par :

- condensation d'un acide de formule générale :



(VII)

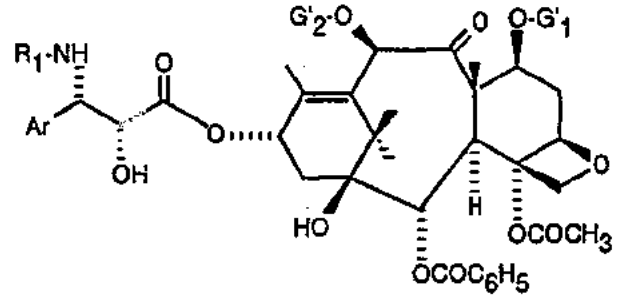
dans laquelle Ar et R_1 sont définis comme précédemment, et R_3 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical aryle éventuellement substitué ou d'un dérivé de cet acide, sur la baccatine III ou la désacétyl-10 baccatine III de formule générale (III) dans laquelle G_1 représente un groupement protecteur de la fonction hydroxy et G_2 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy, pour obtenir un produit de formule générale :



(VIII)

dans laquelle Ar, R_1, R_3, G_1 et G_2 sont définis comme précédemment,

- déprotection de la chaîne latérale et éventuellement des fonctions hydroxy protégées par G_1 et G_2 pour obtenir un produit de formule générale :



(IX)

dans laquelle Ar et R_1 sont définis comme précédemment, G'_1 représente un atome d'hydrogène ou un groupement protecteur de la fonction hydroxy et G'_2 représente un atome d'hydrogène ou un radical acétyle ou un groupement protecteur de la fonction hydroxy, puis

- éventuellement remplacement des groupements protecteurs G'_1 et éventuellement G'_2 du produit de formule générale (IX) par des atomes d'hydrogène pour obtenir un produit de formule générale (I).

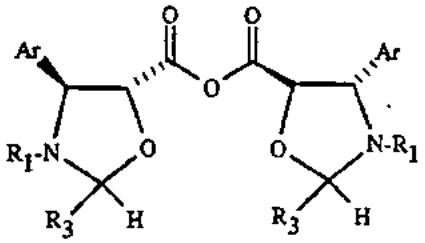
Selon l'invention, l'estérification du produit de formule générale (III) est effectuée au moyen d'un acide de formule générale (VII) éventuellement sous forme d'anhydride ou sous forme d'halogénure ou d'anhydride mixte.

De préférence, on utilise un acide de formule générale (VII), ou ses dérivés activés, dans laquelle R_3 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle éventuellement substitué par un ou plusieurs radicaux électro-donneurs choisis plus particulièrement dans le groupe des radicaux alcoxy contenant 1 à 4 atomes de carbone.

L'estérification au moyen d'un acide de formule générale (VII) peut être effectuée en présence d'un agent de condensation tel qu'un carbodiimide comme le

dicyclohexylcarbodiimide ou un carbonate réactif comme le dipyridyl-2 carbonate et d'un agent d'activation tel qu'une aminopyridine comme la diméthylamino-4 pyridine ou la pyrrolidino-4 pyridine en opérant dans un solvant organique choisi parmi les éthers tels que le tétrahydrofuranne, l'éther diisopropylique, le méthyl t.butyléther ou le dioxanne, les cétones telles que la méthylisobutylcétone, les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle, les nitriles tels que l'acétonitrile, les hydrocarbures aliphatiques tels que le pentane, l'hexane ou l'heptane, les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane ou les hydrocarbures aromatiques tels que le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène ou le chlorobenzène à une température comprise entre -10 et 90°C. Il est particulièrement avantageux d'effectuer l'estérification en opérant dans un solvant aromatique à une température voisine de 20°C.

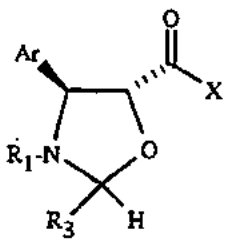
L'estérification peut aussi être réalisée en utilisant l'acide de formule générale (VII) sous forme d'anhydride de formule :



(X)

dans laquelle Ar, R_1 et R_3 sont définis comme précédemment, en présence d'un agent d'activation tel qu'une aminopyridine comme la diméthylamino-4 pyridine ou la pyrrolidino-4 pyridine en opérant dans un solvant organique choisi parmi les éthers tels que le tétrahydrofuranne, l'éther diisopropylique, le méthyl t.butyléther ou le dioxanne, les cétones telles que la méthylisobutylcétone, les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle, les nitriles tels que l'acétonitrile, les hydrocarbures aliphatiques tels que le pentane, l'hexane ou l'heptane, les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane ou les hydrocarbures aromatiques tels que le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène ou le chlorobenzène à une température comprise entre 0 et 90°C.

L'estérification peut aussi être réalisée en utilisant l'acide de formule générale (VII) sous forme d'halogénure ou sous forme d'anhydride mixte de formule générale :



(XI)

dans laquelle Ar, R_1 et R_3 sont définis comme précédemment et X représente un atome d'halogène ou un radical acyloxy ou aroyloxy, éventuellement préparé in situ, en présence d'une base qui est de préférence une base organique azotée telle qu'une amine aliphatique tertiaire comme la triéthylamine, la pyridine, une aminopyridine comme la diméthylamino-4 pyridine ou la pyrrolidino-4 pyridine en opérant dans un solvant organique inerte choisi parmi les éthers tels que le tétrahydrofuranne, l'éther diisopropylique, le méthyl t.butyléther ou le dioxanne, les cétones, les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle, les nitriles tels que l'acétonitrile, les hydrocarbures aliphatiques tels que le pentane, l'hexane ou l'heptane, les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane et les hydrocarbures aromatiques tels que le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène ou le chlorobenzène à une température comprise entre 10 et 80°C, de préférence voisine de 20°C.

De préférence, on utilise un dérivé activé de formule générale (XI) dans laquelle X représente un atome d'halogène ou un radical acyloxy contenant 1 à 5 atomes de carbone ou aroyloxy dans lequel la partie aryle est un radical phényle éventuellement substitué par 1 à 5 atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène (chlore, brome) et les radicaux nitro, méthyle ou méthoxy.

La déprotection de la chaîne latérale peut être effectuée en présence d'un acide minéral (acide chlorhydrique, acide sulfurique) ou organique (acide acétique, acide méthanesulfonique, acide trifluorométhanesulfonique, p.toluènesulfonique) utilisé seul ou en mélanges, en opérant dans un solvant organique choisi parmi les alcools (méthanol, éthanol, propanol, isopropanol), les éthers (tétrahydrofuranne, éther diisopropylique, méthyl t.butyléther), les esters (acétate d'éthyle, acétate d'isopropyle, acétate de n.butyle), les hydrocarbures aliphatiques (pentane, hexane, heptane), les hydrocarbures aliphatiques halogénés (dichlorométhane, dichloro-1,2 éthane), les hydrocarbures aromatiques (benzène, toluène, xylènes) et les nitriles (acétonitrile) à une température comprise entre -10 et 60°C, de préférence entre 15 et

30°C. L'acide minéral ou organique peut être utilisé en quantité catalytique ou stoechiométrique ou en excès.

La déprotection peut être également réalisée dans des conditions oxydantes en utilisant par exemple le nitrate d'ammonium et de cérium IV dans un mélange acétonitrile-eau ou la dichloro-2,3 dicyano-5,6 benzoquinone-1,4 dans l'eau.

La déprotection peut être également réalisée dans des conditions réductrices, par exemple par hydrogénolyse en présence d'un catalyseur.

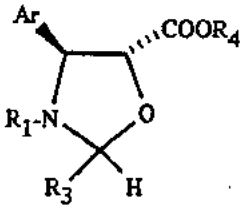
Les groupements protecteurs G_1 et G_2 sont de préférence des radicaux trichloro-2,2,2 éthoxycarbonyle, (trichlorométhyl-2 propoxy)-2 carbonyle ou des radicaux trialkylsilyle, dialkylarylsilyle, alkyldiarylsilyle ou triarylsilyle dans lesquels les parties alkyles contiennent 1 à 4 atomes de carbone et les parties aryles sont de préférence des radicaux phényles.

Le remplacement des groupements protecteurs G_1 et éventuellement G_2 représentant un radical silylé par des atomes d'hydrogène peut être effectué simultanément avec la déprotection de la chaîne latérale.

Le remplacement des groupements protecteurs G_1 et éventuellement G_2 représentant un radical trichloro-2,2,2 éthoxycarbonyle ou (trichlorométhyl-2 propoxy)-2 carbonyle, est effectué par le zinc, éventuellement associé à du cuivre, en présence d'acide acétique à une température comprise entre 20 et 60°C ou au moyen d'un acide minéral ou organique tel que l'acide chlorhydrique ou l'acide acétique en solution dans un alcool aliphatique contenant 1 à 3 atomes de carbone ou dans un ester aliphatique tel que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle en présence de zinc éventuellement associé à du cuivre.

Ce remplacement peut aussi être effectué par réduction électrolytique.

L'acide de formule générale (VII) peut être obtenu par saponification en milieu basique d'un ester de formule générale :



(XII)

dans laquelle Ar, R_1 et R_3 sont définis comme précédemment et R_4 représente un radical alcoyle contenant 1 à 4 atomes de carbone éventuellement substitué par un radical phényle.

Généralement la saponification est effectuée au moyen d'une base minérale telle qu'un hydroxyde de métal alcalin (lithium, potassium, sodium), un carbonate ou bicarbonate de métal alcalin (bicarbonate de sodium, carbonate ou bicarbonate de potassium) en milieu hydro-alcoolique tel qu'un mélange méthanol-eau à une température comprise entre 10 et 40°C, de préférence voisine de 20°C.

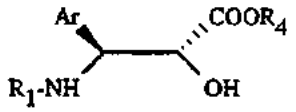
L'ester de formule générale (XII) peut être obtenu par action d'un aldéhyde de formule générale :

$$R_3\text{-CHO} \qquad \text{(XIII)}$$

dans laquelle R_3 est défini comme précédemment, éventuellement sous forme d'un dialkylacétal ou d'un alkyléther d'énol ou d'un orthoformiate de formule générale :

$$HC(OR_3)_3 \qquad \text{(XIV)}$$

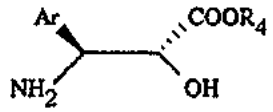
dans laquelle R_3 est défini comme précédemment, sur un dérivé de la phénylisosérine de formule générale :



(XV)

dans laquelle Ar, R_1 et R_4 sont définis comme précédemment, de préférence sous forme 2R,3S en opérant dans un solvant organique inerte en présence d'un acide fort minéral, tel que l'acide sulfurique, ou organique, tel que l'acide p.toluènesulfonique éventuellement sous forme de sel de pyridinium à une température comprise entre 0°C et la température d'ébullition du mélange réactionnel. Les solvants qui conviennent particulièrement bien sont les hydrocarbures aromatiques.

Le dérivé de la phénylisosérine de formule générale (XV) peut être obtenu par acylation d'un dérivé de la phénylisosérine de formule générale :



(XVI)

dans laquelle Ar et R_4 sont définis comme précédemment.

L'acylation est effectuée par action du chlorure de benzoyle ou d'un dérivé réactif de formule générale :

$$R_2\text{-O-CO-Y} \qquad \text{(XVII)}$$

dans laquelle R_2 est défini comme précédemment et Y représente un atome d'halogène (fluor, chlore) ou un reste -O-R_2 ou -O-CO-O-R_2 en opérant dans un

solvant organique tel qu'un ester aliphatique comme l'acétate d'éthyle ou un hydrocarbure aliphatique halogéné comme le dichlorométhane en présence d'une base minérale ou organique telle que le bicarbonate de sodium. Généralement la réaction est effectuée à une température comprise entre 0 et 50°C, de préférence voisine de 20°C.

Le produit de formule générale (XVI) peut être préparé dans les conditions décrites dans la demande internationale PCT W0 92/09589.

L'anhydride de formule générale (X) peut être obtenu en faisant réagir un agent de déshydratation tel que le dicyclohexylcarbodiimide sur l'acide de formule générale (VII) en opérant dans un solvant organique choisi parmi les éthers tels que le tétrahydrofuranne, l'éther diisopropylique, le méthyl t.butyléther ou le dioxanne, les cétones telles que la méthylisobutylcétone, les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle, les nitriles tels que l'acétonitrile, les hydrocarbures aliphatiques tels que le pentane, l'hexane ou l'heptane, les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane ou les hydrocarbures aromatiques tels que le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène ou le chlorobenzène à une température comprise entre 0 et 30°C.

L'acide activé de formule générale (XI) peut être obtenu par action d'un halogénure de sulfuryle, de préférence, le chlorure ou d'un produit de formule générale :

$$R_5\text{-CO-Z} \qquad \text{(XVIII)}$$

dans laquelle R_5 représente un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle éventuellement substitué par 1 à 5 atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux nitro, méthyle et méthoxy et Z représente un atome d'halogène, de préférence un atome de chlore sur un acide de formule générale (VII) en opérant dans un solvant organique convenable tel que le tétrahydrofuranne en présence d'une base organique telle qu'une amine tertiaire comme la triéthylamine à une température comprise entre 0 et 30°C.

Le procédé selon la présente invention est particulièrement utile pour préparer les produits de formule générale (I) dans laquelle R représente un atome d'hydrogène ou un radical acétyle, R_1 représente un radical benzoyle ou t.butoxycarbonyle et Ar représente un radical phényle éventuellement substitué.

Les exemples suivants illustrent la présente invention.

EXEMPLE 1

Une solution de 10,0 g de t.butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle et de 0,25 g de p.toluènesulfonate de pyridinium dans 200 cm3 de toluène est déshydratée par distillation de 20 cm3 de solvant. On ajoute 6,34 cm3 de diméthylacétal du p.méthoxybenzaldéhyde en 5 minutes sur le mélange réactionnel chauffé à l'ébullition. Pendant l'addition, on distille 50 cm3 de solvant puis on distille encore 100 cm3 de solvant. Après refroidissement à une température voisine de 20°C, on ajoute, en 10 minutes, 80 cm3 de cyclohexane. Le mélange est refroidi à 0-5°C. La bouillie obtenue est filtrée sur verre fritté et le gâteau de filtration est lavé avec 40 cm3 de cyclohexane puis séché sous pression réduite à une température voisine de 20°C. On obtient ainsi, avec un rendement de 74 %, 10,39 g de t.butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 méthoxycarbonyl-5 oxazolidine-1,3-(2R,4S,5R) dont les caractéristiques sont les suivantes :

- spectre infra-rouge (en comprimé avec KBr) : bandes d'absorption caractéristiques à 3100-3000, 2980, 2960, 2930, 2910, 2840, 1740, 1700, 1614, 1514, 1460, 1435, 1390, 1370, 1245, 1175, 1165, 816, 760 et 700 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; température : 323°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,11 (s, 9H) ; 3,60 (s, 3H) ; 3,82 (s, 3H) ; 4,58 (d, J = 5, 1H) ; 5,42 (d large, J = 5, 1H) ; 6,38 (s large, 1H) ; 6,92 (d, J = 7,5, 2H) ; 7,30 à 7,45 (mt, 7H).

A une solution de 3,0 g du produit obtenu précédemment dans 27 cm3 de méthanol, on ajoute 14 cm3 d'une solution aqueuse contenant 0,31 g d'hydroxyde de lithium monohydraté. On agite pendant 2 heures à une température voisine de 20°C. Le méthanol est éliminé par distillation sous pression réduite puis on ajoute 40 cm3 de dichlorométhane. Sous forte agitation, le mélange réactionnel est acidifié par addition d'acide chlorhydrique 1N jusqu'à pH = 1. Après décantation, la phase aqueuse est extraite 2 fois par 40 cm3 de dichlorométhane. Les phases organiques réunies sont séchées sur sulfate de sodium. Après filtration et évaporation du solvant, on obtient, avec un rendement de 94,5 %, 2,88 g d'acide t.butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R) dont les caractéristiques sont les suivantes :

- spectre infra-rouge (en comprimé avec KBr) : bandes d'absorption caractéristiques à 3325-2675, 2980, 2955, 2935, 2845, 1755, 1700, 1615, 1590, 1515, 1460, 1250, 1175, 1030, 835, 765 et 705 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (250 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,08 (s, 9H) ; 3,82 (s, 3H) ; 4,61 (d, J = 5, 1H) ; 5,42 (d large, J = 5, 1H) ; 6,38 (s large, 1H) ; 6,92 (d, J = 7,5, 2H) ; 7,30 à 7,45 (mt, 7H).

EXEMPLE 2

A une solution agitée de 1,0 g d'acide t.butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R), de 1,34 g d'acétoxy-4 benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 et de 0,061 g de diméthylamino-4 pyridine dans 7,6 cm3 de toluène anhydre, on ajoute, à 0°C, 0,52 g de dicyclohexylcarbodiimide. On agite pendant 2 heures à une température de 20°C. La dicyclohexylurée est séparée par filtration et lavée avec du toluène. Les phases organiques réunies sont lavées par une solution d'acide chlorhydrique 0,1N, une solution saturée d'hydrogénocarbonate de sodium et séchées sur sulfate de sodium. Après filtration et concentration à sec sous pression réduite, on obtient 2,09 g de t.butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α brut dont les caractéristiques sont les suivantes :

- spectre infra-rouge ($CHCl_3$) : bandes d'absorption caractéristiques à 3575, 1765, 1740, 1725, 1710, 1615, 1515, 1455, 1250, 1175, 980, 710 et 700 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; température : 323°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,09 (s, 9H) ; 1,18 (s, 3H) ; 1,27 (s, 3H) ; 1,67 (s, 3H) ; 1,72 (s, 1H) ; 1,82 (s, 3H) ; 1,90 (s, 3H) ; 2,02 (m, 1H) ; 2,13 (dd, J = 15 et 9, 1H) ; 2,25 (dd, J = 15 et 9, 1H) ; 2,60 (mt, 1H) ; 3,83 (d, J = 7, 1H) ; 3,83 (s, 3H) ; 4,12 (d, J = 8, 1H) ; 4,26 (d, J = 8, 1H) ; 4,60 (d, J = 5, 1H) ; 4,61 (d, J = 12, 1H) ; 4,78 (ab limite, J = 11, 2H) ; 4,90 (d large, J = 10, 1H) ; 4,90 (d, J = 12, 1H) ; 5,45 (d large, J = 5, 1H) ; 5,50 (dd, J = 11 et 7, 1H) ; 5,66 (d, J = 7, 1H) ; 6,12 (t, J = 9, 1H) ; 6,18 (s, 1H) ; 6,39 (s large) ; 6,94 (d, J = 7,5, 2H) ; 7,42 (d, J = 7,5, 2H) ; 7,35 à 7,50 (mt, 5H) ; 7,49 (t, J = 5, 2H) ; 7,63 (t, J = 7,5, 1H) ; 8,03 (d, J = 7,5, 2H).

A une solution de 0,161 g du produit obtenu précédemment dans 2,1 cm3 d'acétate d'éthyle on ajoute 9 µl d'une solution aqueuse d'acide chlorhydrique à 37 %

(p/p). On agite pendant 3 heures à une température voisine de 20°C. Un dosage par chromatographie liquide à haute performance montre que le rendement en t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α est de 95 %.

Le t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α est transformé en t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 oxo-9 trihydroxy-1,7β,10β taxène-11 yle-13α (ou Taxotère) dans les conditions décrites dans le brevet EP 0 253 738.

EXEMPLE 3

Une solution de 2,43 g de t.butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle et de 0,059 g de p.toluènesulfonate de pyridinium dans 60 cm3 de toluène est déshydratée en distillant 5 cm3 de solvant. On ajoute, en 15 minutes, une solution de 1,7 g de diméthylacétal du diméthoxy-3,4 benzaldéhyde dans 14 cm3 de toluène sur le mélange réactionnel chauffé à l'ébullition. Pendant l'addition, on disitlle 15 cm3 de toluène puis on distille encore 25 cm3. Après refroidissement à une température voisine de 20°C, on ajoute, sous agitation, 40 cm3 d'eau. Après décantation, la phase organique est séchée sur sulfate de magnésium. Après filtration et concentration à sec, le résidu est repris par 8 cm3 de diisopropyléther. Le produit qui cristallise est séparé par filtration, rincé avec du diisopropyléther puis séché sous pression réduite. On obtient ainsi, avec un rendement de 50 %, 1,7 g de t.butoxycarbonylamino-3 (diméthoxy-3,4 phényl)-2 phényl-4 méthoxycarbonyl-5 oxazolidine-1,3-(2R,4S,5R) dont les caractéristiques sont les suivantes :

- spectre infra-rouge (comprimés en mélange avec KBr) : bandes d'absorption caractéristiques à 3085, 3065, 3030, 2975, 2935, 2840, 1740, 1700, 1600, 1520, 1495, 1455, 1425, 1265, 1175, 1025, 800, 755 et 700 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (300 MHz ; DMSO d_6 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) ; 1,00 (s, 9H) ; 3,58 (s, 3H) ; 3,80 (s, 3H) ; 3,83 (s, 3H) ; 4,68 (d, J = 4, 1H) ; 5,31 (mf, 1H) ; 6,34 (mf, 1H) ; 6,95 à 7,10 (mt, 3H) ; 7,35 à 7,50 (mt, 5H).

A une solution de 1,63 g de l'ester ainsi obtenu dans 25 cm3 de méthanol et 7 cm3 d'eau distillée, on ajoute 0,24 g de potasse à 86 %. On agite pendant 40 minutes à une température voisine de 20°C. Après élimination du méthanol par distillation sous pression réduite et acidification du milieu à pH = 3-4 par addition d'acide chlorhydrique 1N, le précipité obtenu est séparé par filtration. Le gâteau de filtration est lavé à l'eau puis séché. On obtient ainsi, avec un rendement de 92 %, 1,45 g d'acide t.butoxycarbonyl-3 (diméthoxy-3,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R) dont la pureté est de 95 %, et dont les caractéristiques sont les suivantes :

- spectre infra-rouge (comprimés en mélange avec KBr) : bandes d'absorption caractéristiques à 3225, 3030, 3005, 2975, 2930, 2840, 1740, 1710, 1610, 1600, 1515, 1465, 1455, 1260, 1175, 1020, 760 et 700 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (250 MHz ; DMSO d_6 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,00 (s, 9H) ; 3,78 (s, 3H) ; 3,81 (s, 3H) ; 4,55 (d, J = 4, 1H) ; 5,23 (mf, 1H) ; 6,29 (mf, 1H) ; 6,90 à 7,10 (mt,3H) ; 7,30 à 7,50 (mt, 5H).

EXEMPLE 4

A une suspension agitée de 0,155 g d'acide t.butoxycarbonyl-3 (diméthoxy-3,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R) et de 0,24 g d'acétoxy-4 benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 dans 2,5 cm3 de toluène anhydre, on ajoute, en une seule fois, à 0°C, 0,076 g de dicyclohexylcarbodiimide et 0,0075 g de diméthylamino-4 pyridine. On agite pendant 1 heure à 0°C. La dicyclohexylurée formée est séparée par filtration. Le gâteau est lavé avec du toluène. Les phases toluéniques réunies sont lavées successivement avec une solution aqueuse saturée de bicarbonate de sodium puis avec de l'eau. Après séchage et concentration à sec sous pression réduite, on obtient, avec un rendement quantitatif, 0,435 g de t.butoxycarbonyl-3 (diméthoxy-3,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α dont les caractéristiques sont les suivantes :

- spectre infra-rouge (CCl_4) : bandes d'absorption caractéristiques à 3580, 3550-3375, 3090, 3070, 3030, 1765, 1740, 1730, 1715, 1605, 1520, 1500, 1465, 1455, 1265, 1250, 1180, 1035, 985, 710 et 695 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; température : 323°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,10 (s, 9H) ; 1,17 (s, 3H) ; 1,25 (s, 3H) ; 1,66 (s, 3H) ; 1,70 (s, 1H) ; 1,82 (s, 3H) ; 1,90 (s, 3H) ; 2,02 (mt, 1H) ; 2,13 (dd, J = 15 et 9, 1H) ; 2,24 (dd, J = 15 et 9, 1H) ; 2,60 (mt, 1H) ; 3,83 (d, J = 7, 1H) ; 3,89 (s, 3H) ; 3,93 (s, 3H) ; 4,12 (d, J = 8, 1H) ; 4,26 (d, J = 8, 1H) ; 4,60 (d, J = 4,5, 1H) ; 4,60 (d, J = 12, 1H) ; 4,78 (ab limite, 2H) ; 4,89 (d large, J = 10, 1H) ; 4,90 (d, J = 12, 1H) ; 5,46 (d large, J = 4,5, 1H) ; 5,50 (dd, J = 11 et 7, 1H) ; 5,66 (d, J = 7, 1H) ; 6,13 (t, J = 9, 1H) ; 6,15 (s, 1H) ; 6,39 (s, 1H) ; 6,90 (d, J = 7,5, 1H) ; 7,03 (d, J = 1, 1H) ; 7,07 (dd, J = 7,5 et 1, 1H) ; 7,35 à 7,50 (mt, 5H) ; 7,48 (t, J = 7,5, 2H) ; 7,62 (t, J = 7,5, 1H) ; 8,03 (d, J = 7,5, 2H).

A une solution de 0,223 g de l'ester obtenu ci-dessus dans 2,5 cm3 de méthanol, on ajoute 2 µl d'acide méthanesulfonique. On agite pendant 2 heures 30 minutes à une température voisine de 20°C. Le dosage par chromatographie liquide à haute performance montre que le rendement en t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α est de 88 %.

EXEMPLE 5

Une solution de 0,497 g de t.butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle, de 0,021 g de p.toluènesulfonate de pyridinium et de 0,295 g de diméthoxy-2,4 benzaldéhyde dans 20 cm3 de toluène anhydre est chauffée au reflux pendant 24 heures. L'eau formée pendant la réaction est éliminée au moyen d'un Dean-Stark. Après refroidissement à une température voisine de 20°C, la solution est lavée avec une solution aqueuse d'hydrogénosulfite de sodium à 37 % (p/p) puis avec une solution aqueuse saturée de bicarbonate de sodium. Après concentration de la phase organique sous pression réduite, on obtient, avec un rendement de 80 %, 0,700 g de t.butoxycarbonyl-3 (diméthoxy-2,4 phényl)-2 phényl-4 méthoxycarbonyl-5 oxazolidine-1,3-(4S,5R) sous forme d'un mélange des formes diastéréoisomériques A et B quasi équimoléculaire dont les caractéristiques sont les suivantes :

- spectre infra-rouge (CCl_4) : bandes d'absorption caractéristiques à 3095, 3070, 3035, 2980, 2955, 2935, 2840, 1760, 1745, 1710, 1615, 1590, 1510, 1465, 1455, 1435, 1210, 1160, 1040, 835 et 700 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (250 MHz ; DMSO d_6 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,00 (s, $-C(CH_3)_3$ de B) ; 1,22 (s, $-C(CH_3)_3$ de A) ; 3,55 (mf, $-COOCH_3$ ou $-OCH_3$ de B) ; 3,87 à 3,85 (mt, $-COOCH_3$ ou $-OCH_3$ de A et B) ; 4,64 (d, J = 4,5, -H5 de B) ; 5,01 (d, J = 2,5, -H5 de A) ; 5,21 (d, J = 2,5, -H4 de A) ; 5,26 (d, J = 4,5, -H4 de B) ; 6,46 [dd, J = 7,5 et 1,5, $-C_6H_5$ en 2 (-H5) de A] ; 6,52 (s, -H2 de A) ; 6,50-6,65 [mt, -H2 et $-C_6H_5$ en 2 (-H5 et -H3) de B + $-C_6H_5$ en 2 (-H3) de A] ; 7,00 [d, J = 7,5, $-C_6H_5$ en 2 (-H6) de B] ; 7,30 à 7,55 [mt, 5H, $-C_6H_5$ en 4 (-H2 à -H6) de A et B].

A une solution de 0,700 g de l'ester obtenu précédemment dans un mélange de 9 cm3 de méthanol et de 3 cm3 d'eau distillée, on ajoute 0,073 g d'hydroxyde de lithium monohydraté. On agite pendant 3 heures 30 minutes à une température voisine de 20°C. Le méthanol est éliminé par distillation sous pression réduite. La phase aqueuse est lavée avec du toluène puis est acidifiée jusqu'à pH = 3-4 par addition d'une solution aqueuse d'acide chlorhydrique 1N. Le précipité obtenu est séparé par filtration et le gâteau de filtration est lavé abondamment à l'éau jusqu'à neutralité puis séché sous pression réduite. On obtient ainsi, avec un rendement de 74 %, 0,450 g d'acide t.butoxycarbonyl-3 (diméthyl-2,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(4S,5R) sous forme d'un mélange des formes diastéréoisomériques A et B quasi équimoléculaire dont les caractéristiques sont les suivantes :

- spectre infra-rouge (en comprimé avec KBr) : bandes d'absorption caractéristiques à 3300-2700, 2700-2250, 3070, 3030, 3005, 2975, 2940, 2840, 1710, 1615, 1590, 1510, 1460, 1210, 1160, 1035, 835 et 700 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (200 MHz ; DMSO d_6 ; température : 393°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz ; mélange des 2 diastéréoisomères dans la proportion 55/45) : 1,00 (s, $-C(CH_3)_3$ de B) ; 1,25 (s, $-C(CH_3)_3$ de A) ; 3,75 à 3,85 (mt, 6H, $-OCH_3$ de A et B) ; 4,43 (d, J = 5, -H5 de B) ; 4,77 (d, J = 2, -H5 de A) ; 5,21 (d, J = 2, -H4 de A) ; 5,21 (d, J = 2, -H4 de B) ; 6,42 [dd, J = 7,5 et 1,5, $-C_6H_5$ en 2 (-H5) de A] ; 6,49 (s, -H2 de A) ; 6,45-6,60 [mt, -H2 et $-C_6H_5$ en 2 (-H5 et -H3) de B + $-C_6H_5$ en 2 (-H3) de A] ; 7,02 [d, J = 7,5, $-C_6H_5$ en 2 (-H6) de A] ; 7,15 [d, J = 7,5, $-C_6H_5$ en 2 (-H6) de B] ; 7,25 à 7,50 [mt, 5H, $-C_6H_5$ en 4 (-H2 à -H6) de A et B].

EXEMPLE 6

A une suspension agitée de 1,671 g d'acide t.butoxycarbonyl-3 (diméthoxy-2,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5-(4S,5R) et de 1,003 g d'acétoxy-4 benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 dans 8 cm3 de toluène anhydre on ajoute, en une seule fois, à 0°C, 0,656 g de dicyclohexylcarbodiimide et 0,0287 g de diméthylamino-4 pyridine. On agite pendant 10 minutes à 0°C puis pendant 5 heures à une température voisine de 20°C. La dicyclohexylurée formée est séparée par filtration et lavée avec du toluène. Les phases toluéniques réunies sont lavées avec une solution aqueuse saturée de bicarbonate de sodium, puis à l'eau. Après séchage, filtration et concentration à sec sous pression réduite, on obtient 1,623 g de t.butoxycarbonyl-3 (diméthoxy-2,4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(4S,5R) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α brut sous forme d'un mélange diastéréoisomérique dont on sépare les constituants par chromatographie liquide sur gel de silice en éluant avec un mélange acétate d'éthyle-cyclohexane (75-25 en volumes).

Un des deux diastéréoisomères présente les caractéristiques suivantes :

- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,20 (s, 3H) ; 1,25 (s, 9H) ; 1,30 (s, 3H) ; 1,76 (s, 1H) ; 1,85 (s, 3H) ; 2,00 (s, 3H) ; 2,05 (mt, 1H) ; 2,17 (s, 3H) ; 2,26 (dd, J = 15 et 9, 1H) ; 2,34 (dd, J = 15 et 9, 1H) ; 2,60 (mt, 1H) ; 3,82 (s, 3H) ; 3,92 (s, 3H) ; 3,95 (d, J = 7, 1H) ; 4,14 (d, J = 8, 1H) ; 4,30 (d, J = 8, 1H) ; 4,62 (d, J = 12, 1H) ; 4,80 (ab limite, 2H) ; 4,90 (mt, 1H) ; 4,92 (mt, 1H) ; 4,92 (d, J = 12, 1H) ; 5,36 (d, J = 2, 1H) ; 5,63 (dd, J = 11 et 7, 1H) ; 5,70 (d, J = 7, 1H) ; 6,28 (s, 1H) ; 6,34 (t, J = 9, 1H) ; 6,43 (dd, J = 7,5 et 1,5, 1H) ; 6,51 (d, J = 1,5, 1H) ; 6,69 (s, 1H) ; 7,16 (d, J = 7,5, 1H) ; 7,35 à 7,50 (mt, 3H) ; 7,48 (t, J = 7,5, 2H) ; 7,67 (d, J = 7,5, 2H) ; 7,63 (t, J = 7,5, 1H) ; 8,04 (d, J = 7,5, 2H).

L'autre diastéréoisomère présente les caractéristiques suivantes :

- spectre infra-rouge (CCl_4) : bandes d'absorption caractéristiques à 3580, 3550-3300, 3070, 3030, 1760, 1740, 1710, 1610, 1590, 1510, 1455, 1435, 1260, 1250, 1210, 1180, 1035, 985, 710 et 700 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,10 [s, 9H : $-C(C\underline{H}_3)_3$] ; 11,16 (s, 3H : $-C\underline{H}_3$ 16 ou 17) ; 1,24 (s, 3H : $-C\underline{H}_3$ 16 ou 17) ; 1,53 (s,

3H : -C$\underline{H}_3$ 19) ; 1,66 (s, 1H : -O$\underline{H}$ 1) ; 1,82 (s, 3H : -C$\underline{H}_3$ 18) ; 2,00 (s, 3H : -COC$\underline{H}_3$) ; 2,00 (mt, 1H : -(CH)-$\underline{H}$6) ; 2,12 (dd, J = 15 et 9, 1H : -(CH)-$\underline{H}$14) ; 2,24 (dd, J = 15 et 9, 1H : -(CH)-$\underline{H}$14) ; 2,60 (mt, 1H : -(CH)-$\underline{H}$6) ; 3,82 (d, J = 7, 1H : -$\underline{H}$3) ; 3,82 (s, 3H : -OC$\underline{H}_3$) ; 3,90 (s, 3H : -OC$\underline{H}_3$) ; 4,12 (d, J = 8, 1H : -(CH)-$\underline{H}$20); 4,26 (d, J = 8, 1H : -(CH)-$\underline{H}$20) ; 4,55 (d, J = 4, 1H : -$\underline{H}$5') ; 4,62 (d, J = 12, 1H : -O(CH)-$\underline{H}$ du CCl_3CH_2OCOO en -7) ; 4,78 (ab, J = 11, 2H : O-C$\underline{H}_2$ du Cl_3CH_2OCOO en -10) ; 4,89 (d large, J = 10, 1H : -$\underline{H}$5) ; 4,89 (d; J = 12, 1H : -O(CH)-$\underline{H}$ du Cl_3CCH_2OCOO en -7) ; 5,46 (d large, J = 4, 1H : -$\underline{H}$4') ; 5,50 (dd, J = 11 et 7, 1H : -$\underline{H}$7) ; 5,65 (d, J = 7, 1H : -$\underline{H}$2) ; 6,05 (t, J = 9, 1H : -$\underline{H}$13) ; 6,16 (s, 1H : -$\underline{H}$10) ; 6,50 [mt, 2H : -C_6H_5 en 2' (-$\underline{H}$3 et -$\underline{H}$5)] ; 6,72 (mf, 1H : -$\underline{H}$2') ; 7,22 [d, J = 7,5, 1H : -C_6H_5 en 2' (-$\underline{H}$6)] ; 7,30 à 7,50 [mt, 5H : -C_6H_5 en 4' (-$\underline{H}$2 à -$\underline{H}$6)] ; 7,48 [t, J = 7,5, 2H : -OCOC_6H_5 (-$\underline{H}$3 et -$\underline{H}$5)] ; 7,63 [t, J = 7,5, 1H : -OCOC_6H_5 (-$\underline{H}$4)] ; 8,03 [d, J = 7,5, 2H : -OCOC_6H_5 (-$\underline{H}$2 et -$\underline{H}$6)].

A une solution de 1,623 g de l'ester brut obtenu ci-dessus dans 20 cm3 de méthanol, on ajoute 80 µl d'acide méthanesulfonique. On agite pendant 4 heures à une température voisine de 20°C. Le dosage par chromatographie liquide à haute performance montre que le rendement en t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α est de 88 %.

EXEMPLE 7

Une solution de 10,0 g de t.butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle, de 1,0 g de p.toluènesulfonate de pyridinium et de 5,7 cm3 de diméthylacétal de benzaldéhyde dans 250 cm3 de toluène anhydre est chauffée au reflux. On distille 200 cm3 de solvant en 2 heures. La solution est refroidie à une température voisine de 20°C et est lavée avec 50 cm3 d'eau. Après décantation, séchage et concentration à sec de la phase organique, le résidu obtenu est repris dans 14 cm3 de diisopropyléther. La bouillie obtenue est filtrée, rincée et essorée. On obtient ainsi, avec un rendement de 65 %, 8,4 g de t.butoxycarbonylamino-3 diphényl-2,4 méthoxycarbonyl-5 oxazolidine-1,3-(2R,4S,5R) sous forme d'un seul diastéréoisomère dont les caractéristiques sont les suivantes :

- spectre infra-rouge (comprimé en mélange avec KBr) : bandes d'absorption caractéristiques à 3250, 3095, 3070, 3030, 2975, 1710, 1500, 1460, 1165, 760 et 700 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (300 MHz ; DMSO d_6 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 0,95 (s, 9H) ; 4,26 (mf, 1H) ; 5,10 (mf, 1H) ; 6,20 (s, 1H) ; 7,25-7,55 (mt, 5H).

A une solution de 7,07 g de l'ester obtenu précédemment dans 88 cm3 de méthanol et 22 cm3 d'eau, on ajoute 1,26 g de potasse à 86 %. On agite pendant une nuit à une température voisine de 25°C. Le méthanol est éliminé par distillation sous pression réduite. On acidifie par addition d'acide chlorhydrique 1N jusqu'à pH = 2. Le précipité obtenu est séparé par filtration, lavé abondamment à l'eau jusqu'à neutralité puis séché sous pression réduite. On obtient ainsi, avec un rendement quantitatif, 7,0 g d'acide t.butoxycarbonyl-3 diphényl-2,4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R) sous forme d'un seul diastéréoisomère dont les caractéristiques sont les suivantes :

- spectre infra-rouge (comprimé en mélange avec KBr) : principales bandes d'absorption caractéristiques à 3080, 3050, 3030, 3005, 2975, 1760, 1695, 1600, 1585, 1490, 1460, 1435, 1175, 760 et 700 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (200 MHz ; DMSO d_6 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) ; 0,98 (s, 9H) ; 3,38 (s, 3H) ; 4,71 (d, J = 4, 1H) ; 5,30 (d large, J = 4, 1H) ; 6,38 (s, 1H) ; 7,25 à 7,55 (mt, 5H).

EXEMPLE 8

A une suspension agitée de 1,25 g d'acide t.butoxycarbonyl-3 diphényl-2,4 oxazolidine-1,3 carboxylique-5-(2R,4S,5R) et de 1,08 g d'acétoxy-4 benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 dans 12 cm3 de toluène anhydre, on ajoute 0,70 g de dicyclohexylcarbodiimide et 0,030 g de diméthylamino-4 pyridine. On agite pendant 24 heures à une température voisine de 20°C. La dicyclohexylurée formée est séparée par filtration et lavée par du toluène. Les phases organiques réunies sont lavées avec une solution aqueuse saturée de bicarbonate de sodium. Après séchage et concentration à sec sous pression réduite, on obtient 2,27 g d'un produit brut qui est purifié par chromatographie liquide sur gel de silice en éluant avec un mélange hexane-acétate d'éthyle (1-1 en volumes). On obtient ainsi, avec un rendement de 75 %, 1,05 g de t.butoxycarbonyl-3 diphényl-2,4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9

bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α sous forme d'un seul diastéréoisomère dont les caractéristiques sont les suivantes :

- spectre infra-rouge (en comprimé avec KBr) : principales bandes d'absorption caractéristiques à 3250, 3095, 3070, 3030, 2975, 1710, 1500, 1460,1165, 760 et 700 cm^{-1};
- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,05 (s, 9H) ; 1,15 (s, 3H) ; 1,25 (s, 3H) ; 1,63 (s, 3H) ; 1,73 (s, 1H) ; 1,80 (s, 3H) ; 1,87 (mf, 3H) ; 2,01 (mt, 1H) ; 2,08 (dd, J = 15 et 9, 1H) ; 2,23 (dd, J = 15 et 9, 1H) ; 2,58 (mt,1H) ; 3,81 (d, J = 7, 1H) ; 4,10 (d, J = 8, 1H) ; 4,26 (d, J = 8, 1H) ; 4,60 (d, J = 12, 1H) ; 4,61 (d, J = 4, 1H) ; 4,78 (ab, J = 11, 2H) ; 4,87 (d large,J = 10, 1H) ; 4,90 (d, J = 12, 1H) ; 5,46 (mt, 1H) ; 5,50 (dd, J= 11 et 7, 1H) ; 5,63 (d, J = 7, 1H) ; 6,13 (mt, 1H) ; 6,13 (s, 1H) ; 6,43 (mf, 1H) ; 7,35 à 7,50 (mt, 10H) ; 7,48 (t, J = 7,5, 2H) ; 7,62 (t, J = 7,5, 1H) ; 8,03 (d, J = 7,5, 2H).

A une solution de 41 mg de l'ester obtenu précédemment dans 0,4 cm3 de méthanol, on ajoute 2,6 µl d'acide méthanesulfonique. On agite pendant 48 heures à une température voisine de 20°C. Le dosage par chromatographie liquide à haute performance montre que l'on obtient le t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α avec un rendement de 50 %.

EXEMPLE 9

Une solution de 10,0 g de t.butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle, de 0,334 g de p.toluènesulfonate de pyridinium et de 3,75 cm3 d'orthoformiate de triméthyle dans 70 cm3 de toluène est chauffée au reflux. On distille 4 cm3 de solvant. Après refroidissement à une température voisine de 20°C et filtration, le filtrat est concentré à sec sous pression réduite. Le résidu est repris par 50 cm3 d'hexane. La bouillie obtenue est filtrée, rincée et essorée. On obtient ainsi, avec un rendement de 40 %, 4,6 g de t.butoxycarbonyl-3 méthoxy-2 phényl-4 méthoxycarbonyl-5 oxazolidine-1,3-(4S,5R), sous forme d'un mélange des diastéréoisomères dont les caractéristiques sont les suivantes :

- spectre infra-rouge (CH_2Cl_2) : bandes d'absorption caractéristiques à 2980, 2955, 2935, 2840, 1760, 1745, 1710, 1495, 1460, 1440, 1175, 1080 et 1065 cm^{-1}

- spectre de résonance magnétique nucléaire du proton (300 MHz ; DMSO d_6 ; température : 393°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) sur le mélange 65/35 des diastéréoisomères : 1,22 (s, 3H) ; 1,32 (s, 3H) ; 3,34 (s, 3H) ; 3,43 (s, 3H) ; 3,75 (s, 3H) ; 4,55 (d, J = 3, 1H) ; 4,68 (d, J = 8, 1H) ; 4,98 (d, J = 8, 1H) ; 5,17 (d, J = 3, 1H) ; 6,10 (s, 1H) ; 6,13 (s, 1H) ; 7,20 à 7,50 (mt, 5H).

A une solution de 11,27 g du produit obtenu ci-dessus dans 85 cm3 de méthanol et 28 cm3 d'eau, on ajoute 16,1 g d'hydroxyde de lithium monohydraté. On agite pendant 30 minutes à une température voisine de 20°C. Le méthanol est éliminé par distillation sous pression réduite puis on ajoute 145 cm3 d'eau et 245 cm3 d'acétate d'éthyle. Le mélange biphasique est refroidi à 0°C sous agitation puis acidifié par de l'acide chlorhydrique 1N jusqu'à pH = 5. La phase aqueuse est séparée par décantation et extraite avec 2 fois 75 cm3 d'acétate d'éthyle. Les phases organiques sont réunies et séchées sur sulfate de sodium. Après filtration et concentration sous pression réduite à 25°C jusqu'à un volume de 50 cm3, on ajoute à cette solution résiduelle, à 0°C, 9,80 g d'acétoxy-4 benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11, 4,29 g de dicylohexylcarbodiimide et 0,25 g de diméthylamino-4 pyridine. On agite pendant 15 minutes à 0°C puis pendant 3 heures à une température voisine de 20°C. La dicyclohexylurée formée est séparée par filtration et lavée par de l'acétate d'éthyle. Les phases organiques réunies sont lavées par une solution aqueuse saturée de bicarbonate de sodium. Après séchage et concentration à sec sous pression réduite, on obtient 14,75 g de t.butoxycarbonyl-3 méthoxy-2 phényl-4 oxazolidine-1,3 carboxylate-5-(4S,5R) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α, sous la forme d'un mélange diastéréoisomérique, dont les caractéristiques sont les suivantes :

- spectre infra-rouge (CH_2Cl_2) : bandes d'absorption caractéristiques à 1760, 1725-1710, 1600, 1450, 1245, 1175, 1060, 985 et 815 cm^{-1}
- spectre de résonance magnétique nucléaire du proton (400 MHz ; $CDCl_3$; température : 323°K ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,23 (s, 3H) ; 1,32 (s, 3H) ; 1,35 (mf, 9H) ; 1,88 (s, 3H) ; 1,91 (s, 3H) ; 2,08 (s,3H) ; 2,08 (mt, 1H) ; 2,26 (ab dédoublé, J = 15 et 9, 1H) ; 2,65 (mt, H) ; 3,65 (s, 3H) ; 3,92 (d, J = 7, 1H) ; 4,18 (d, J = 8, 1H) ; 4,31 (d, J = 8, 1H) ; 4,64 (d, J = 12, 1H) ; 4,80 (d, J = 7, 1H) ; 4,83 (ab limite, 2H) ; 4,95 (d large, J = 10, 1H) ; 4,95 (d, J = 12, 1H) ; 5,04 (d large, J = 7, 1H) ; 5,58 (dd, J = 11 et 7, 1H) ; 5,72 (d, J = 7,

1H) ; 6,25 (s, 1H) ; 6,31 (s, 1H) ; 6,34 (t, J = 9, 1H) ; 7,30 à 7,55 (mt, 5H) ; 7,54 (t, J = 7,5, 2H) ; 7,68 (t, J = 7,5, 1H) ; 8,08 (d, J = 7,5, 2H).

A une solution agitée de 0,617 g d'ester obtenu précédemment dans 7,6 cm3 d'acétate d'éthyle on ajoute 47 µl d'acide chlorhydrique à 37 % (p/p). On agite pendant 20 heures à une température voisine de 20°C. L'analyse par chromatographie liquide à haute performance montre que l'on obtient le t.butoxycarbonylamino-3 phényl-3 hydroxy-2 propionate-(2R,3S) d'acétoxy-4 benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 bis-(trichloro-2,2,2 éthoxy) carbonyloxy-7β,10β taxène-11 yle-13α, avec un rendement de 53 %.

EXEMPLE 10

Une solution de 4,01 g de benzoylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de méthyle et de 0,01 g de p.toluènesulfonate de pyridinium dans 70 cm3 de toluène est déshydratée par distillation de 30 cm3 de solvant. On ajoute 30 cm3 de toluène et distille 20 cm3 de solvant. Après refroidissement, on ajoute une solution de 2,57 g de diméthylacétal de p.méthoxybenzaldéhyde dans 6 cm3 de toluène. On ajoute 20 cm3 de toluène puis on chauffe pendant 40 minutes à une température voisine de 100°C tout en distillant 60 cm3 de solvant. Après refroidissement, la solution trouble est filtrée sur coton puis concentrée à sec. On obtient ainsi 6,13 g d'une huile jaunâtre que l'on agite pendant 12 heurse avec 30 cm3 de cyclohexane. Après filtration sur verre fritté et lavage du précipité par 2 fois 10 cm3 de cyclohexane, on obtient, avec un rendement de 91%, 5,09 g de benzoyl-3 (méthoxy-4 phényl)-2 phényl-4 méthoxycarbonyl-5 oxazolidine-1,3-(2R,4S,5R).

A une solution de 4,80 g du produit obtenu précédemment dans 120 cm3 de méthanol, on ajoute 25 cm3 d'une solution aqueuse contenant 834 mg de potasse à 86%. On agite pendant 1 heure à une température voisine de 20°C. Le méthanol est éliminé par distillation sous pression réduite puis on ajoute 25 cm3 d'eau et 50 cm3 d'éther isopropylique. La phase aqueuse est séparée par décantation puis lavée par 2 fois 25 cm3 d'oxyde isopropylique. La phase aqueuse est acidifiée par addition d'acide chlorhydrique concentré jusqu'à pH = 1, puis on ajoute 50 cm3 de dichlorométhane. Après décantation, la phase aqueuse est lavée par 25 cm3 de dichlorométhane. Les phases organiques réunies sont lavées par 25 cm3 d'eau puis séchées sur sulfate de sodium. Après filtration et concentration à sec, on obtient, avec

un rendement de 97%, 4,49 g d'acide benzoyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique -5-(2R,4S,5R).

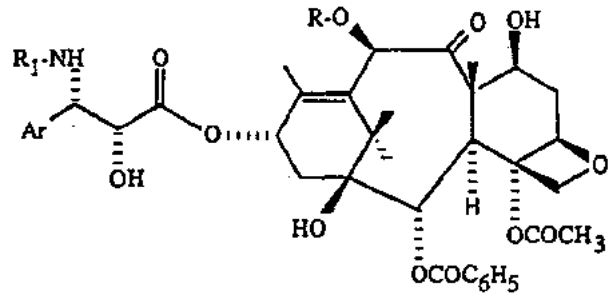
EXEMPLE 11

A une solution de 0,137 g de diacétoxy-4,10β benzoyloxy-2α époxy-5β,20 dihydroxy-1,13α oxo-9 triéthylsilyloxy-7β taxène-11 à 85% et de 0,0521 g de dicyclohexylcarbodiimide dans 1 cm3 de toluène, on ajoute une solution de 0,1023 g d'acide benzoyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique -5-(2R,4S,5R) et de 5,2 mg de diméthylamino-4 pyridine dans 3 cm3 de toluène. On agite pendant 2 heures 15 minutes à une température voisine de 20°C. La dicyclohexylurée est séparée par filtration. On ajoute au filtrat 20 cm3 d'une solution saturée de bicarbonate de sodium. Après décantation la phase aqueuse est extraite par 3 fois 30 cm3 de dichlorométhane. Les phases organiques réunies sont séchées sur sulfate de sodium. Après filtration et concentration, on obtient 0,2108 g d'un produit que l'on purifie par chromatographie sur 7 g de silice contenus dans une colonne de 30 cm de hauteur et de 1,5 cm de diamètre en éluant avec un mélange cyclohexane-acétate d'éthyle (70-30 en volumes). On obtient ainsi, avec un rendement de 70,54%, 127,4 mg de benzoyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) de diacétoxy-4,10β benzoyloxy-2α époxy-5β,20 hydroxy-1 oxo-9 triéthylsilyloxy-7β taxène-11 yle-13α dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et dont la pureté est voisine de 95%.

A une solution de 40 mg du produit obtenu précédemment dans 2 cm3 d'éthanol, on ajoute 400 µl d'une solution éthanolique d'acide chlorhydrique 0,9 N. On agite pendant 6 heures à une température voisine de 20°C. Un dosage par chromatographie liquide à haute performance montre que le rendement en benzoyl-3 phényl-3 propionate-(2R,3S) de diacétoxy-4,10β benzoyloxy-2α époxy-5β,20 dihydroxy-1,7β oxo-9 taxène-11 yle-13α (ou taxol) est de 51,4%.

REVENDICATIONS

1 - Procédé de préparation de dérivés du taxane de formule générale :



dans laquelle

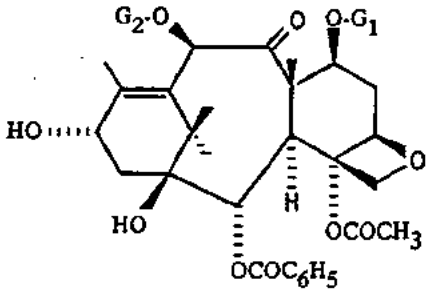
R représente un atome d'hydrogène ou un radical acétyle et R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone ou bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoyloxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, phényle, cyano, carboxy ou alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,
- ou un radical phényle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoyloxy contenant 1 à 4 atomes de carbone,
- ou un radical hétérocyclyle azoté saturé ou non saturé contenant 5 ou 6 chaînons éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

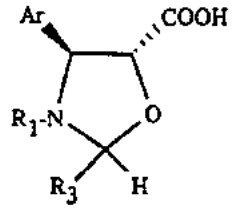
étant entendu que les radicaux cycloalcoyles, cycloalcényles ou bicycloalcoyles peuvent être éventuellement substitués par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone, et

Ar représente un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles, alcényles, alcynyles, aryles, arylalcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alkylamino, dialkylamino, carboxy, alcoxycarbonyle, carbamoyle, dialcoylcarbamoyle, cyano et trifluorométhyle, étant entendu que les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone, que les radicaux alcényles et alcynyles contiennent 3 à 8 atomes de carbone et les radicaux aryles sont les radicaux phényles ou α- ou β-naphtyles

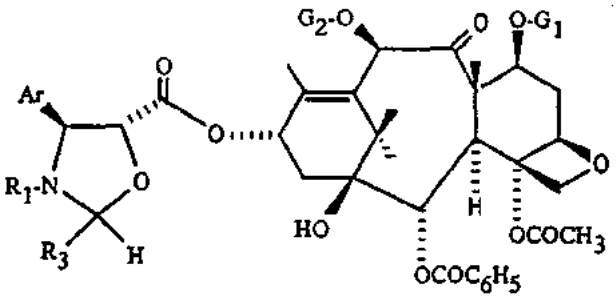
caractérisé en ce que l'on estérifie un dérivé de la baccatine III ou de la désacétyl-10 baccatine III protégée de formule générale :



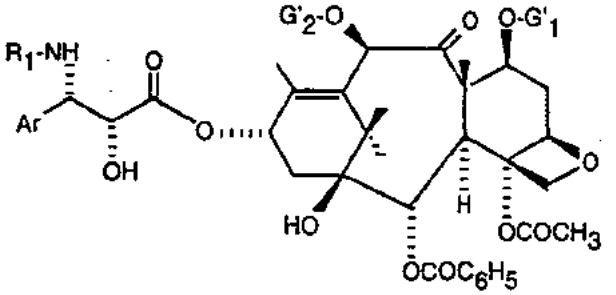
dans laquelle G_1 représente un groupement protecteur de la fonction hydroxy et G_2 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy, au moyen d'un acide de formule générale :



dans laquelle Ar et R_1 sont définis comme précédemment et R_3 représente un atome d'hydrogène ou un radical aryle éventuellement substitué, ou d'un dérivé de cet acide pour obtenir un produit de formule générale :



dans laquelle Ar, R_1, R_3, G_1 et G_2 sont définis comme précédemment, dont on déprotège la chaîne latérale et éventuellement les fonctions hydroxy protégées par G_1 et G_2 pour obtenir un produit de formule générale :



dans laquelle Ar et R_1 sont définis comme précédemment, G'_1 représente un atome d'hydrogène ou un groupement protecteur de la fonction hydroxy et G'_2 représente un atome d'hydrogène ou un radical acétyle ou un groupement protecteur de la fonction hydroxy dont on remplace éventuellement les groupements protecteurs G'_1 et éventuellement G'_2 par des atomes d'hydrogène selon des méthodes connues.

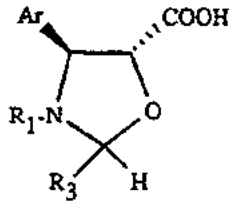
2 - Procédé selon la revendication 1 caractérisé en ce que l'on effectue l'estérification au moyen d'un acide, ou d'un de ses dérivés, pour lequel Ar et R_1 étant définis comme dans la revendication 1, R_3 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle éventuellement substitué par un ou plusieurs radicaux électro-donneurs.

3 - Procédé selon la revendication 2 caractérisé en ce que les radicaux électro-donneurs sont choisis parmi les radicaux alcoxy contenant 1 à 4 atomes de carbone.

4 - Procédé selon la revendication 1 caractérisé en ce que les groupements protecteurs de la baccatine III ou de la désacétyl-10 baccatine III représentés par G_1

et G_2 sont choisis parmi les radicaux (trichloro-2,2,2 éthoxy) carbonyle et (trichlorométhyl-2 propoxy)-2 carbonyle et les radicaux trialkylsilyle, dialkylarylsilyle, alkyldiarylsilyle ou triarylsilyle dans lesquels les parties alkyles contiennent 1 à 4 atomes de carbone et les parties aryles sont de préférence des radicaux phényles.

5 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que l'estérification au moyen d'un acide de formule générale :



dans laquelle Ar et R_1 sont définis comme dans la revendication 1 et R_3 est défini comme dans l'une des revendications 1 à 3 est effectuée en présence d'un agent de condensation et d'un agent d'activation en opérant dans un solvant organique à une température comprise entre -10 et 90°C.

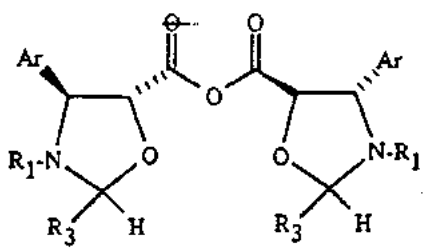
6 - Procédé selon la revendication 5 caractérisé en ce que l'agent de condensation est choisi parmi les carbodiimides et les carbonates réactifs et l'agent d'activation est choisi parmi les aminopyridines.

7 - Procédé selon la revendication 6 caractérisé en ce que l'agent de condensation est choisi parmi la dicyclohexylcarbodiimide et le dipyridyl-2 carbonate et l'agent d'activation est choisi parmi la diméthylamino-4 pyridine et le pyrrolidino-4 pyridine.

8 - Procédé selon la revendication 5 caractérisé en ce que le solvant est choisi parmi les éthers, les cétones, les esters, les nitriles, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques.

9 - Procédé selon la revendication 8 caractérisé en ce que le solvant est choisi parmi les hydrocarbures aromatiques.

10 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que l'estérification est effectuée au moyen d'un anhydride de formule générale :



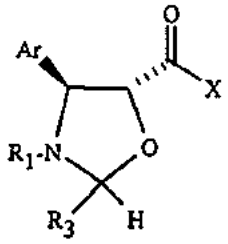
dans laquelle Ar et R_1 sont définis comme dans la revendication 1 et R_3 est défini comme dans l'une des revendications 1 à 3 en opérant en présence d'un agent d'activation dans un solvant organique à une température comprise entre 0 et 90°C.

11 - Procédé selon la revendication 10 caractérisé en ce que l'agent d'activation est choisi parmi les aminopyridines.

12 - Procédé selon la revendication 11 caractérisé en ce que l'agent d'activation est choisi parmi la diméthylamino-4 pyridine et la pyrrolidino-4 pyridine.

13 - Procédé selon la revendication 10 caractérisé en ce que le solvant est choisi parmi les éthers, les cétones, les esters, les nitriles, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques.

14 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que l'estérification est effectuée au moyen d'un acide activé de formule :



dans laquelle Ar et R_1 sont définis comme dans la revendication 1, R_3 est défini comme dans l'une des revendications 1 à 3 et X représente un atome d'halogène ou un radical acyloxy ou aroyloxy, éventuellement préparé in situ, en présence d'une base dans un solvant organique à une température comprise entre 10 et 80°C.

15 - Procédé selon la revendication 14 caractérisé en ce que la base est choisie parmi les bases organiques azotées.

16 - Procédé selon la revendication 15 caractérisé en ce que la base organique azotée est choisie parmi les amines tertiaires aliphatiques, la pyridine et les aminopyridines.

17 - Procédé selon la revendication 14 caractérisé en ce que le solvant est choisi parmi les éthers, les cétones, les esters, les nitriles, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques.

18 - Procédé selon la revendication 17 caractérisé en ce que le solvant est choisi parmi les hydrocarbures aromatiques.

19 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que la déprotection de la chaîne latérale et éventuellement des fonctions hydroxy protégées par des groupements protecteurs G_1 et G_2 silylés est effectuée en présence d'un acide minéral ou organique ou de leurs mélanges en opérant dans un solvant organique à une température comprise entre -10 et 60°C.

20 - Procédé selon la revendication 19 caractérisé en ce que l'acide minéral est choisi parmi les acides chlorhydrique et sulfurique et l'acide organique est choisi parmi les acides acétique, méthanesulfonique, trifluorométhanesulfonique et p.toluènesulfonique.

21 - Procédé selon la revendication 19 caractérisé en ce que le solvant est choisi parmi les alcools, les éthers, les esters, les nitriles, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques.

22 - Procédé selon la revendication 1 caractérisé en ce que la déprotection de la chaîne latérale est effectuée en présence d'un oxydant dans l'eau ou en milieu hydro-organique.

23 - Procédé selon la revendication 22 caractérisé en ce que l'oxydant est le nitrate d'ammonium et de cérium IV en milieu hydro-organique.

24 - Procédé selon l'une des revendications 22 ou 23 caractérisé en ce que le milieu hydro-organique est un mélange eau-acétonitrile.

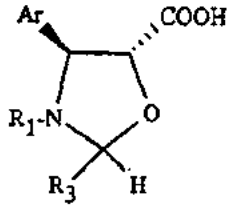
25 - Procédé selon la revendication 22 caractérisé en ce que l'oxydant est la dichloro-2,3 dicyano-5,6 benzoquinone-1,4 dans l'eau.

26 - Procédé selon la revendication 1 caractérisé en ce que la déprotection de la chaîne latérale est effectuée par hydrogénolyse.

27 - Procédé selon la revendication 26 caractérisé en ce que l'hydrogénolyse est effectuée par l'hydrogène en présence d'un catalyseur.

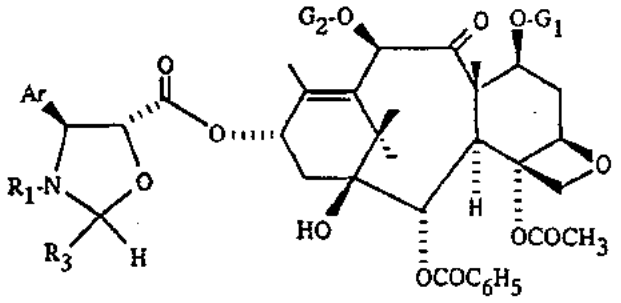
28 - Procédé selon la revendication 1 caractérisé en ce que le remplacement des groupements protecteurs G_1 et éventuellement G_2 représentant un radical trichloro-2,2,2 éthoxycarbonyle ou (trichlorométhyl-2 propoxy)-2 carbonyle par des atomes d'hydrogène est effectué par le zinc, éventuellement associé à du cuivre, en présence d'acide acétique à une température comprise entre 20 et 60°C ou au moyen d'un acide minéral ou organique en solution dans un alcool aliphatique contenant 1 à 3 atomes de carbone ou dans un ester aliphatique en présence de zinc éventuellement associé à du cuivre.

29 - Les acides de formule générale :



dans laquelle Ar et R_1 sont définis comme dans la revendication 1 et R_3 est défini comme dans l'une des revendications 1 à 3, éventuellement sous forme de sel, d'ester, d'anhydride, d'anhydride mixte ou d'halogénure.

30 - Un produit de formule générale :



dans laquelle Ar et R_1 sont définis comme dans la revendication 1, R_3 est défini comme dans l'une des revendications 1 à 3 et G_1 et G_2 sont définis comme dans l'une des revendications 1 ou 4.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/FR 93/00968

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D305/14 C07D263/04 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 09589 (RHONE-POULENC RORER) 11 June 1992 cited in the application see page 1 - page 3 ---	1,29,30
P,X	WO,A,93 16060 (RHONE-POULENC RORER) 19 August 1993 see page 4, line 20 - page 5, line 9 -----	1,29,30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 1994	19. 01. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/FR 93/00968

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9209589	11-06-92	FR-A-	2669631	29-05-92
		FR-A-	2679557	29-01-93
		AU-A-	9083891	25-06-92
		CA-A-	2096833	24-05-92
		EP-A-	0558623	08-09-93
WO-A-9316060	19-08-93	FR-A-	2687151	13-08-93
		AU-B-	3505093	03-09-93

Form PCT/ISA/210 (patent family annex) (July 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No
PCT/FR 93/00968

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 5 C07D305/14 C07D263/04 C07D413/12

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 5 C07D

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	WO,A,92 09589 (RHONE-POULENC RORER) 11 Juin 1992 cité dans la demande voir page 1 - page 3	1,29,30
P,X	WO,A,93 16060 (RHONE-POULENC RORER) 19 Août 1993 voir page 4, ligne 20 - page 5, ligne 9	1,29,30

☐ Voir la suite du cadre C pour la fin de la liste des documents

☒ Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

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"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

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"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
10 Janvier 1994	19. 01. 94

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tél. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	English, R

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 93/00968

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
WO-A-9209589	11-06-92	FR-A-	2669631	29-05-92
		FR-A-	2679557	29-01-93
		AU-A-	9083891	25-06-92
		CA-A-	2096833	24-05-92
		EP-A-	0558623	08-09-93
WO-A-9316060	19-08-93	FR-A-	2687151	13-08-93
		AU-B-	3505093	03-09-93

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Numéro de publication: **0 336 841**
A1

(12) # DEMANDE DE BREVET EUROPEEN

(21) Numéro de dépôt: 89400935.6

(22) Date de dépôt: 05.04.89

(51) Int. Cl.4: C 07 D 305/14

(30) Priorité: 06.04.88 FR 8804513

(43) Date de publication de la demande:
11.10.89 Bulletin 89/41

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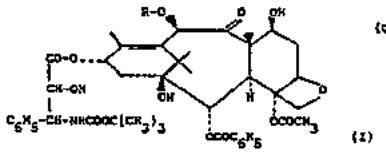
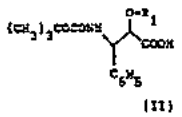
(54) **Procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III.**

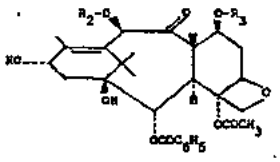
(57) Procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III de formule générale (I) dans laquelle R représente un atome d'hydrogène ou un radical acétyle, par condensation d'un acide de formule générale (II) sur un dérivé de la baccatine III ou de la désacétyl-10 baccatine III, R_1, R_2 et R_3 représentant des groupements protecteurs des fonctions hydroxy, suivie du remplacement des groupements protecteurs par un atome d'hydrogène.



(I)



(II)



(III)

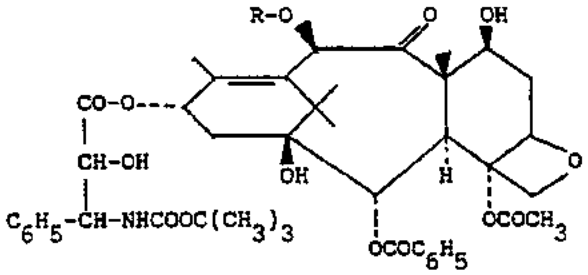
EP 0 336 841 A1

Bundesdruckerei Berlin

Description

PROCEDE DE PREPARATION DE DERIVES DE LA BACCATINE III ET DE LA DESACETYL-10 BACCATINE III

La présente invention concerne un procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III de formule générale :

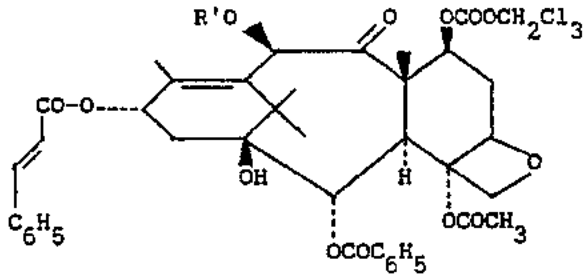


(I)

dans laquelle R représente un atome d'hydrogène ou un radical acétyle.

Dans la demande de brevet européen EP 253 738 ont été décrits les produits de formule générale (I) et leur préparation. Les produits de formule générale (I), en particulier le produit de formule générale (I) dans laquelle R représente un atome d'hydrogène, présentent des propriétés antitumorales et antileucémiques particulièrement intéressantes.

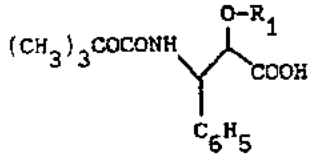
Selon la demande de brevet européen EP 253 738, les produits de formule générale (I) sont obtenus par action du sel de sodium du N-chlorocarbamate de tertiobutyle sur un produit de formule générale:



(II)

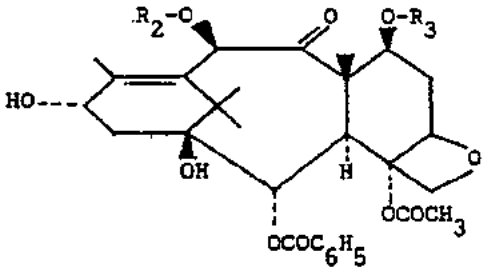
dans laquelle R' représente un radical acétyle ou trichloro-2,2,2 éthoxycarbonyle suivie du remplacement du ou des groupements trichloro-2,2,2 éthoxycarbonyle par un atome d'hydrogène. Ce procédé conduit à un mélange d'isomères qu'il est nécessaire de séparer et il en résulte que la totalité de la baccatine III ou de la désacétyl-10 baccatine III mise en oeuvre pour la préparation du produit de formule générale (II) ne peut être transformée en produit de formule générale (I).

Il a maintenant été trouvé, et c'est ce qui fait l'objet de la présente invention, que les produits de formule générale (I) peuvent être obtenus pas condensation d'un acide de formule générale :



(III)

dans laquelle R_1 représente un groupement protecteur de la fonction hydroxy, sur un dérivé du taxane de formule générale :



(IV)

dans laquelle R_2 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy et R_3 représente un groupement protecteur de la fonction hydroxy, suivie du remplacement des groupements protecteurs R_1, R_3 et éventuellement R_2 par un atome d'hydrogène.

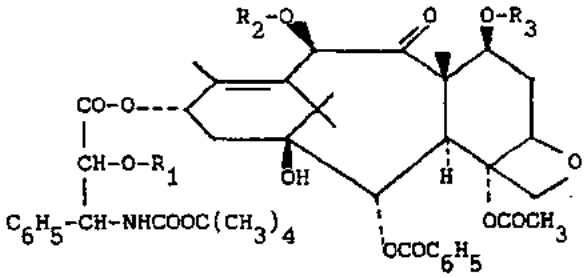
Dans la formule générale (III), le radical R_1 représente plus particulièrement un radical méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle, (β-triméthylsilyléthoxy) méthyle, tétrahydropyrannyle ou trichloro-2,2,2 éthoxycarbonyle. De préférence, le radical R_1 est le radical éthoxy-1 éthyle.

Dans la formule générale (IV), les radicaux protecteurs des fonctions hydroxy définis par R_2 et R_3 sont généralement des radicaux trichloro-2,2,2 éthoxycarbonyle, mais il est possible aussi d'utiliser des radicaux trialkylsilyles dont chaque partie alcoyle contient 1 à 3 atomes de carbone.

Généralement, l'estérification du dérivé du taxane de formule générale (IV) par l'acide de formule générale (III) est effectuée en présence d'un agent de condensation tel qu'un carbodiimide comme le dicyclohexylcarbodiimide ou un carbonate réactif comme le dipyridyl-2 carbonate et d'un agent d'activation tel qu'une dialcoylaminopyridine comme la diméthylamino-4 pyridine en opérant dans un solvant aromatique tel que le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène ou le chlorobenzène à une température comprise entre 60 et 90°C.

Il est particulièrement avantageux d'utiliser un excès molaire d'acide de formule générale (III) par rapport au dérivé du taxane de formule générale (IV), l'agent de condensation étant utilisé en quantité stoechiométrique par rapport à l'acide de formule générale (III) et la diméthylamino-4 pyridine étant utilisée en quantité stoechiométrique par rapport au dérivé du taxane de formule générale (IV). Généralement, on utilise au moins 4 moles d'acide de formule générale (III) par mole de dérivé du taxane de formule générale (IV).

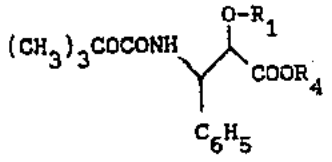
L'élimination des groupements protecteurs de l'ester obtenu de formule générale :



(V)

peut être effectuée au moyen de zinc en présence d'acide acétique à une température comprise entre 30 et 60°C ou par traitement au moyen d'un acide minéral ou organique tel que l'acide chlorhydrique ou l'acide acétique en solution dans un alcool aliphatique contenant 1 à 3 atomes de carbone en présence de zinc.

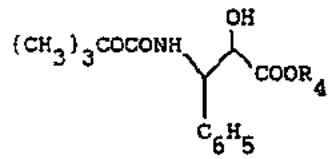
L'acide de formule générale (III) peut être obtenu par saponification d'un ester de formule générale :



(VI)

dans laquelle R_1 est défini comme précédemment et R_4 représente un radical alcoyle contenant 1 à 4 atomes de carbone et, de préférence, un radical éthyle, au moyen d'une base minérale telle qu'un hydroxyde de métal alcalin (lithine, soude), un carbonate ou bicarbonate de métal alcalin (bicarbonate de sodium, carbonate de potassium) en milieu hydro-alcoolique tel qu'un mélange méthanol-eau en opérant à une température comprise entre 10 et 40°C, de préférence voisine de 25°C.

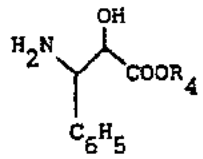
Le produit de formule générale (VI) peut être obtenu dans les conditions habituelles de préparation des éthers, et plus particulièrement selon les procédés décrits par J.N. Denis et coll., J. Org. Chem., 51, 46-50 (1986), à partir du produit de formule générale :



(VII)

dans laquelle R_4 est défini comme précédemment.

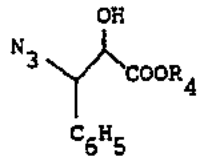
Le produit de formule générale (VII) peut être obtenu par action du dicarbonate de di-tertiobutyle sur un produit de formule générale :



(VIII)

dans laquelle R_4 est défini comme précédemment. Généralement, on opère dans un solvant organique tel que le chlorure de méthylène en présence d'une base minérale telle que le bicarbonate de sodium.

Le produit de formule générale (VIII) peut être obtenu par réduction d'un azide de formule générale :



(IX)

dans laquelle R_4 est défini comme précédemment, qui est obtenu selon les méthodes connues d'ouverture d'un époxyde de formule générale :

(X)

dans laquelle R_4 est défini comme précédemment, au moyen d'azoture de sodium dans l'éthanol à chaud.

L'époxyde de formule générale (X) peut être obtenu dans les conditions décrites par F.W. Bachelor et R.K. Bansal, J. Org. Chem., 34, 3600-04 (1969).

Pour la mise en oeuvre du procédé selon l'invention, il est particulièrement avantageux d'utiliser les produits de formules générales (VI) à (X) dans lesquelles R_4 représente un radical éthyle.

Lorsque l'on utilise un produit de formule générale (X) dans laquelle R_4 représente un radical autre que éthyle, par exemple un radical tertiobutyle, il est nécessaire, après ouverture de l'époxyde de formule générale (X), d'effecteur une réaction de transestérification pour transformer le radical R_4 en radical éthyle.

Le dérivé du taxane de formule générale (IV) dans laquelle R_2 représente un radical acétyle ou trichloro-2,2,2 éthyle peut être obtenu par action du chloroformiate de trichloro-2,2,2 éthyle sur la baccatine III ou la désacétyl-10 baccatine III en opérant dans un solvant organique basique tel que la pyridine à une température comprise entre 0 et 50°C.

Le dérivé du taxane de formule générale (IV) dans laquelle R_2 représente un radical acétyle et R_3 représente un radical trialkylsilyle peut être obtenu par action d'un halogénotrialkylsilane sur la baccatine III ou la désacétyl-10 baccatine III, suivie, dans ce dernier cas, de l'acétylation de la trialkylsilyl-7 désacétyl-10 baccatine III intermédiairement obtenue.

Généralement la réaction de l'halogénotrialkylsilane sur la baccatine III ou la désacétyl-10 baccatine III s'effectue à une température voisine de 20°C en opérant dans un solvant organique basique tel que la pyridine ou dans un solvant organique inerte tel que le chloroforme ou le dichlorométhane en présence d'une amine tertiaire telle que la triéthylamine, la pyridine ou la base de Hunig.

L'acétylation de la trialkylsilyl-7 désacétyl-10 baccatine III est généralement effectuée au moyen de chlorure d'acétyle en opérant à une température voisine de 0°C dans un solvant organique basique tel que la pyridine ou dans un solvant organique inerte tel que le chloroforme, le chlorure de méthylène ou le dichloroéthane en présence d'une amine tertiaire telle que la pyridine ou la base de Hunig.

L'exemple suivant, donné à titre non limitatif, montre comment l'invention peut être mise en pratique.

EXEMPLE

Dans un ballon tricol de 500 cm3 muni d'une agitation et d'un thermomètre, on introduit, sous atmosphère d'argon, 7,9 g d'acide (éthoxy-1, éthoxy)-2 tertiobutyloxycarbonylamino-3 phényl-3 propionique, thréo (22,4 mmoles), 150 cm3 de toluène anhydre et 4,6 g de dicyclohexylcarbodiimide (22,4 mmoles), 5 g de produit de formule générale (IV) dans laquelle R_2 et R_3 représentent chacun un radical trichloro-2,2,2 éthoxycarbonyle

(5,6 mmoles) et 0,68 g de diméthylamino-4 pyridine (5,6 mmoles). Le mélange est chauffé pendant 7 heures à 70°C sous atmosphère d'argon. Après refroidissement à 20°C, le précipité formé est séparé par filtration puis lavé par 50 cm3 de toluène froid.

Le filtrat est concentré à sec puis il est repris par 150 cm3 de chlorure de méthylène. La solution chlorométhylénique est lavée 2 fois par 50 cm3 d'eau. La phase organique est concentrée à sec.
On obtient ainsi 13,5 g d'un produit qui est chromatographié sur 270 g de silice Géduran en éluant avec un mélange chlorure de méthylène-méthanol (98-2 en volumes). Les impuretés sont éliminées en éluant avec 1 litre du mélange, puis en éluant à nouveau avec 1 litre du mélange, on obtient 8 g d'ester de formule générale (V) dans laquelle R_1 représente un radical (éthoxy-1 éthyl) et R_2 et R_3 représentent chacun un radical trichloro-2,2,2 éthoxycarbonyle. En poursuivant l'élution avec 1 litre du même mélange, on récupère 3,2 g de dérivé du taxane de départ qui peut être recristallisé dans le toluène.

On dissout 8 g d'ester obtenu ci-dessus dans 200 cm3 d'un mélange acide acétique-méthanol (1-1 en volumes), puis on ajoute 8 g de poudre de zinc fraîchement réactivé. Après 1 heure à 60°C sous atmosphère d'argon, le mélange réactionnel est refroidi à 20°C puis est filtré. Le produit solide est rincé par 50 cm3 du mélange acide acétique-méthanol. Les filtrats réunis sont concentrés à sec, puis le résidu est repris par l'acétate d'éthyle. Un insoluble est séparé par filtration et lavé 3 fois avec 60 cm3 au total d'acétate d'éthyle.

Les phases organiques réunies sont lavées avec 100 cm3 d'une solution à demi-saturée de bicarbonate de sodium, puis avec 50 cm3 d'eau. Les phases organiques sont séchées sur sulfate de sodium. Après filtration et évaporation du solvant, on obtient un résidu (5,5 g) qui est chromatographié sur 162 g de silice Géduran en éluant avec un mélange hexane-acétate d'éthyle (1-1 en volumes). On sépare 2,4 g d'impuretés, puis 0,595 g de dérivé oxy-aminé (2'R, 3'S) puis 1,794 g de produit de formule (I) (2'R, 3'S) dans laquelle R représente un atome d'hydrogène dont la pureté est de 90 %.

Le produit est identique à celui qui est décrit dans l'exemple 3 de la demande de brevet européen EP 253 738.

L'acide (éthoxy-1 éthoxy)-2 t.butoxycarbonylamino-3 phényl-3 propionique, thréo peut être préparé de la manière suivante :

On dissout 10 g d'(éthoxy-1 éthoxy)-2 t.butoxycarbonyl-amino-3 phényl-3 propionate d'éthyle, thréo dans 500 cm3 d'éthanol. On ajoute 3,3 g de lithine, $1H_2O$ en solution dans 250 cm3 d'eau. La solution trouble est agitée pendant 15 heures à une température voisine de 20°C. On évapore l'éthanol sous pression réduite. On ajoute 250 cm3 d'eau puis on lave la phase aqueuse avec au total 250 cm3 de chlorure de méthylène. La phase aqueuse est acidifiée par addition d'acide chlorhydrique 1N jusqu'à pH = 3, en extrayant au fur et à mesure par 750 cm3 au total de chlorure de méthylène. Après séchage et concentration à sec, on obtient, avec un rendement de 95 %, 8,8 g d'acide (éthoxy-1 éthoxy)-2 t.butoxycarbonylamino-3 phényl-3 propionique, thréo qui, après recristallisation dans l'acétate d'éthyle, présente les caractéristiques suivantes :
- point de fusion : 152-154°C
- spectre infra-rouge (en solution dans le chloroforme) : 3450, 2990, 2940, 1760 et 1735 cm^{-1}.

L'(éthoxy-1 éthoxy)-2 t.butoxycarbonylamino-3 phényl-3 propionate d'éthyle, thréo peut être préparé de la manière suivante :

Dans un ballon de 2 litres muni d'une agitation et d'un thermomètre, on introduit, sous atmosphère d'argon, 30 g d'hydroxy-2 t.butoxycarbonylamino-3 phényl-3 propionate d'éthyle, thréo en solution dans 1000 cm3 de chlorure de méthylène, 2,4 g de p.toluènesulfonate de pyridinium et 93 cm3 de vinyléthyléther. Après 6 heures à une température voisine de 20°C, on ajoute quelques gouttes de pyridine de façon à amener le pH à 7. La solution organique est lavée avec 200 cm3 d'eau à demi saturée de chlorure de sodium puis séchée sur sulfate de magnésium. Après filtration et élimination des solvants sous pression réduite, on obtient, avec un rendement voisin de 100 %, 38,6 g d'(éthoxy-1 éthoxy)-2 t.butoxycarbonylamino-3 phényl-3 propionate d'éthyle, thréo dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et par le spectre de mass.

L'hydroxy-2 t.butoxycarbonylamino-3 phényl-3 propionate d'éthyle, thréo peut être préparé de la manière suivante :

Dans un ballon tricol de 4 litres muni d'une agitation, d'un thermomètre et d'un réfrigérant, on introduit 136 g d'hydroxy-2 amino-3 phényl-3 propionate d'éthyle, thréo en solution dans 1500 cm3 de chlorure de méthylène puis lentement 196 g de dicarbonate de di t.butyle en solution dans 500 cm3 de chlorure de méthylène. Il y a dégagement de gaz carbonique et élévation de la température. Après 20 minutes de réaction, on ajoute 50 g de bicarbonate de sodium puis laisse la température descendre au voisinage de 20°C en 3 heures tout en agitant. Après filtration, la phase organique est lavée 2 fois à l'eau puis séchée sur sulfate de magnésium. Après filtration et évaporation des solvants, on obtient une huile qui prend en masse (305 g). Le solide est repris par 3500 cm3 d'hexane. Après 15 heures à une température de 4°C, les cristaux obtenus sont séparés par filtration et lavés à l'hexane. On obtient ainsi, avec un rendement de 73 %, 148 g d'hydroxy-2 t.butoxycarbonylamino-3 propionate d'éthyle, thréo dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et par le spectre de mass.

L'hydroxy-2 amino-3 phényl-3 propionate d'éthyle peut être préparé de la manière suivante :

Dans un ballon tricol de 4 litres, on introduit 178 g d'hydroxy-2 azido-3 phényl-3 propionate d'éthyle, thréo en solution dans 2 litres d'éthanol à 95°C, puis on ajoute 20 g de palladium sur charbon à 10 % de palladium (p/p). Après une purge à l'argon, on fait passer un courant d'hydrogène dont le débit est réglé de façon à maintenir la température inférieure à 30°C. Après 1 heure, le ballon est purgé à l'argon. Le mélange réactionnel

est filtré sur célite puis est rincé avec de l'éthanol. Après concentration à sec, on obtient une huile qui cristallise pour donner, avec un rendement de 92 %, 146 g d'hydroxy-2 amino-3 phényl-3 propionate d'éthyle, thréo dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et le spectre de masse.

L'hydroxy-2 azido-3 phényl-3 propionate d'éthyle, thréo peut être préparé de la manière suivante :

Dans un ballon tricol de 4 litres, on dissout 194 g d'hydroxy-2 azido-3 phényl-3 propionate de t.butyl thréo dans 1 litre d'éthanol absolu. On ajoute 550 cm3 d'une solution fraîchement préparée d'acide chlorhydrique dans l'éthanol à 13 % en poids. Après 3 heures à une température voisine de 20°C, l'éthanol est évaporé sous pression réduite. Le résidu est repris par 1,5 litre de chlorure de méthylène. La solution chlorométhylénique est lavée avec 200 cm3 d'une solution saturée de bicarbonate de sodium puis à l'eau. Après séchage et évaporation du solvant, on obtient, avec un rendement de 99,7 %, 180 g d'hydroxy-2 azido-3 phényl-3 propionate d'éthyle thréo dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et par le spectre de masse.

L'hydroxy-2 azido-3 phényl-3 propionate de t.butyle thréo peut être préparé de la manière suivante :

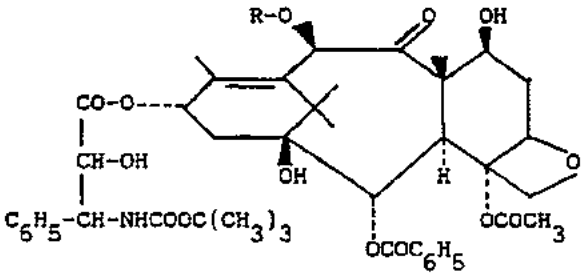
Dans un tricol de 6 litres muni d'une agitation, d'un thermomètre et d'un réfrigérant, on introduit 189 g de phényl-3 glycidate de t.butyle en solution dans 3 litres d'éthanol. On ajoute 95 g d'azoture de sodium et 75 g de chlorure d'ammonium puis chauffe à 75°C pendant 20 heurs. On distille les 2/3 de l'éthanol sous pression réduite à 50°C puis on ajoute 4 litres d'eau et enfin termine l'évaporation de l'éthanol. Après refroidissement de la suspension aqueuse, on obtient un précipité cristallin qui est séparé par filtration et lavé à l'eau. Après séchage sous pression réduite en présence d'anhydride phosphorique, on obtient, avec un rendement de 82,4 %, 186,4 g d'hydroxy-2 azido-3 phényl-3 propionate de t.butyle thréo dont la structure est confirmée par le spectre de résonance magnétique nucléaire du proton et par le spectre de mass.

Le phényl-3 glycidate de t.butyl peut être préparé selon le procédé décrit par F. W. Bachelor et R.K. Bansal, J. Org. Chem., 34, 3600 (1969). Le produit obtenu est purifié par chromatographie sur silice Merck 7734 afin d'obtenir 200 g de phényl-3 glycidate de t.butyle cis.

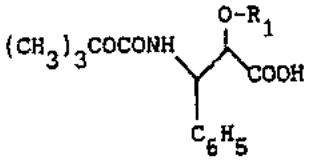
Le produit de formule générale (IV) dans laquelle R_2 et R_3 représentent chacun un radical trichloro-2,2,2 éthoxycarbonyle peut être préparé selon le procédé décrit dans la demande de brevet européen EP 253 738.

Revendications

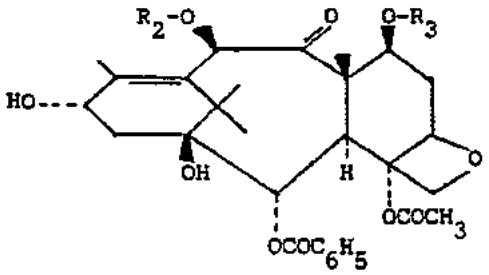
1 - Procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III de formule générale :



dans laquelle R représente un atome d'hydrogène ou un radical acétyle, caractérisé en ce que l'on condense un acide de formule générale :



dans laquelle R_1 représente un groupement protecteur de la fonction hydroxy, sur un dérivé du taxane de formule générale :



dans laquelle R_2 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy et R_3 représente un groupement protecteur de la fonction hydroxy, puis remplace les groupements protecteurs R_1, R_3 et éventuellement R_2 par un atome d'hydrogène.

2 - Procédé selon la revendication 1 caractérisé en ce que R_1 représente un radical méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle (β-triméthylsilyléthoxy) méthyle, tétrahydropyrannyle ou trichloro-2,2,2 éthoxycarbonyle.

3 - Procédé selon la revendication 2 caractérisé en ce que R_1 représente un radical éthoxy-1 éthyle.

4 - Procédé selon la revendication 1 caractérisé en ce que les radicaux protecteurs des fonctions hydroxy représentés par R_2 et R_3 sont choisis parmi les radicaux trichloro-2,2,2 éthoxycarbonyle et trialkylsilyle dont chaque partie alcoyle contient 1 à 3 atomes de carbone.

5 - Procédé selon la revendication 4 caractérisé en ce que le radical protecteur des fonctions hydroxy est le radical trichloro-2,2,2 éthoxycarbonyle.

6 - Procédé selon la revendication 1 caractérisé en ce que la condensation est effectuée en présence d'un agent de condensation et d'un agent d'activation.

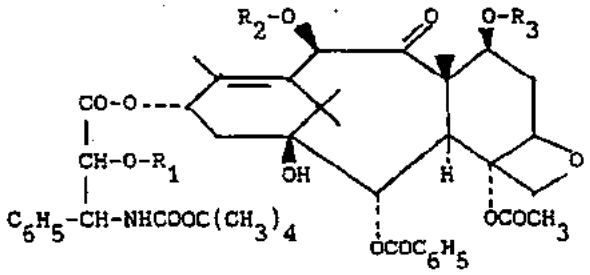
7 - Procédé selon la revendication 6 caractérisé en ce que l'agent de condensation est choisi parmi les carbodiimides et les carbonates réactifs et l'agent d'activation est choisi parmi les dialcoylaminopyridines.

8 - Procédé selon la revendication 7 caractérisé en ce que l'agent de condensation est choisi parmi le dicyclohexylcarbodiimide et le dipyridyl-2 carbonate et l'agent d'activation est la diméthylamino-4 pyridine.

9 - Procédé selon la revendication 1 caractérisé en ce que la condensation est effectuée dans un solvant aromatique choisi parmi le benzène, le toluène, les xylènes, l'éthylbenzène, l'isopropylbenzène et le chlorobenzène.

10 - Procédé selon la revendication 1 caractérisée en ce qui la condensation est effectuée à une température comprise entre 60 et 90° C.

11 - Procédé selon la revendication 1 caractérisé en ce que le remplacement des radicaux protecteurs R_1, R_3 et éventuellement R_2 du produit de formule générale :



intermédiairement obtenu par un atome d'hydrogène est effectué au moyen de zinc en présence d'acide acétique ou au moyen d'un acide minéral ou organique en solution dans un alcool aliphatique contenant 1 à 3 atomes de carbone.

Office européen des brevets

RAPPORT DE RECHERCHE EUROPEENNE

Numero de la demande

EP 89 40 0935

DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	Revendication concernée	CLASSEMENT DE LA DEMANDE (Int. Cl.4)
D,A	EP-A-0 253 738 (RHONE-POULENC) * Pages 1-4; revendications * -----	1,4,5, 10	C 07 D 305/14
			DOMAINES TECHNIQUES RECHERCHES (Int. Cl.4)
			C 07 D 305/00

Le présent rapport a été établi pour toutes les revendications

Lieu de la recherche	Date d'achèvement de la recherche	Examinateur
LA HAYE	29-06-1989	FRANCOIS J.C.L.

EPO FORM 1503 03.82 (P0402)

CATEGORIE DES DOCUMENTS CITES

X : particulièrement pertinent à lui seul
Y : particulièrement pertinent en combinaison avec un autre document de la même catégorie
A : arrière-plan technologique
O : divulgation non-écrite
P : document intercalaire

T : théorie ou principe à la base de l'invention
E : document de brevet antérieur, mais publié à la date de dépôt ou après cette date
D : cité dans la demande
L : cité pour d'autres raisons

& : membre de la même famille, document correspondant

PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
Bureau International

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets [5] : C07D 305/14, A61K 31/335 C07D 263/04 — A1

(11) Numéro de publication internationale: WO 92/09589

(43) Date de publication internationale: 11 juin 1992 (11.06.92)

(21) Numéro de la demande internationale: PCT/FR91/00928

(22) Date de dépôt international: 22 novembre 1991 (22.11.91)

(30) Données relatives à la priorité:
90/14635 23 novembre 1990 (23.11.90) FR
91/09423 25 juillet 1991 (25.07.91) FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: RHONE-POULENC RORER S.A. [FR/FR]; 20, avenue Raymond-Aron, F-92160 Antony (FR).

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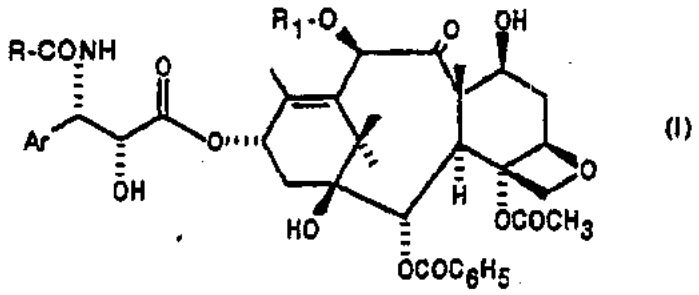
(81) Etats désignés: AT (brevet européen), AU, BE (brevet européen), CA, CH (brevet européen), CS, DE (brevet européen), DK (brevet européen), ES (brevet européen), FI, FR (brevet européen), GB (brevet européen), GR (brevet européen), HU, IT (brevet européen), JP, KR, LU (brevet européen), NL (brevet européen), NO, PL, SE (brevet européen), SU*, US.

Publiée
Avec rapport de recherche internationale.
Avant l'expiration du délai prévu pour la modification des revendications, sera republiée si de telles modifications sont reçues.

(54) Title: METHOD FOR PREPARING TAXANE DERIVATIVES, NOVEL DERIVATIVES THEREBY OBTAINED AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre: PROCEDE DE PREPARATION DE DERIVES DU TAXANE, NOUVEAUX DERIVES OBTENUS ET COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT



(I)

(57) Abstract

A method for preparing taxane derivatives having general formula (I), novel derivatives thereby obtained and compositions containing same. In general formula (I), R is t.butoxy or phenyl, R_1 is hydrogen or acetyl, and Ar is substituted phenyl or optionally substituted α or β-naphthyl. These novel taxane derivatives are useful as antileukemic and antitumoral agents.

(57) Abrégé

Procédé de préparation de dérivés du taxane de formule générale (I), nouveaux dérivés ainsi obtenus et compositions qui les contiennent. Dans la formule générale (I), R représente t.butoxy ou phényle, R_1 représente hydrogène ou acétyle et Ar représente phényle substitué ou α- ou β-naphtyle éventuellement substitué. Les nouveaux dérivés du taxane sont utiles comme antileucémiques et antitumoraux.

* Voir au verso

DIALOG(R)File 351:DERWENT WPI

008029584 WPI Acc No: 89-294696/41
XRAM Acc No: C89-130495

Prepn. of baccatine III and 10-acetyl baccatine III derivs. - used as antitumour and antileukaemia agents

Index Terms: PREPARATION DERIVATIVE ANTITUMOUR ANTILEUKAEMIA AGENT
Patent Assignee: (RHON) RHONE POULENC SANTE
Author (Inventor): COLIN M; GUENARD D; GUERITTE-VOEGELEIN F; POTIER P; GUERITTEVO F
Number of Patents: 012
Number of Countries: 020
Patent Family:

Patent No	Kind	Date	Week	Applic No	Date	LA	Pages	IPC
EP 336841	A	891011	8941	EP 89400935	890405	Fre	8	(B)
FR 2629819	A	891013	8948	FR 884513	880406			
AU 8932426	A	891012	8949					
JP 1305077	A	891208	9004	JP 8984916	890405			
ZA 8902474	A	891227	9005	ZA 892474	890404			
US 4924012	A	900508	9023	US 331758	890403			
CA 1308417	C	921006	9246	CA 595731	890405	Fre		C07D-305/14
IL 89831	A	921230	9309	IL 89831	890403			C07D-305/14
EP 336841	B1	930526	9321	EP 89400935	890405	Fre	11	C07D-305/14
DE 68906705	E	930701	9327	DE 606705	890405			C07D-305/14
				EP 89400935	890405			
ES 2055119	T3	940816	9434	EP 89400935	890405			C07D-305/14
JP 94086441	B2	941102	9442	JP 8984916	890405		8	C07D-305/14

Priority Data (CC No Date): FR 884513 (880406)
Applications (CC,No,Date): JP 8984916 (890405); EP 89400935 (890405); JP 8984916 (890405); ZA 892474 (890404); US 331758 (890403); CA 595731 (890405); IL 89831 (890403); EP 89400935 (890405); DE 606705 (890405); EP 89400935 (890405); EP 89400935 (890405)
Language: French
EP and/or WO Cited Patents: EP 253738; 1.Jnl.Ref
Designated States (Regional): AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
Filing Details: JP94086441 Based on JP 1305077; DE68906705 Based on EP 336841; ES2055119 Based on EP 336841

Abstract (Basic): EP 336841

Baccatine III and 10-desacetyl baccatine III derivatives of formula (I) are prepared by the condensation of an acid of formula (III) with a taxane of formula (IV), followed by removal of the protecting groups. R = h or acetyl, R1 = a protecting group for the hydroxy function R2 = a protecting group for the hydroxyl function.

The condensation is pref. effected in the presence of a condensation agent, such as a carbodiimide or a reactive carbonate, and an activation agent such as a dialkylamino pyridine. It is effected in an aromatic solvent at 60 - 90 deg.C.

USE/ADVANTAGE - (I) are known antitumoural and antileukaemia agents. This process does not give rise to the formation of various isomers, unlike the method described in EP253738. This method therefore gives higher yields of (I). @(8pp Dwg.No.0/0)@

Abstract (US): 9023 US 4924012

Deriv. of baccatine III or 10-deacetylbaccatine III of formula (I) is prepd. by condensing an acid of formula (II) with a taxan deriv. of formula (III) and replacing the protecting gps. R1, R3 and, where appropriate R2 by H. In the formulae, R1 and R3 are each -OH protecting gps. and R2 is acetyl or -OH protecting gp..

The condensn. is pref. effected in the presence of a condensing agent and activating agent. The condensing agent is dicyclohexylcarbodiimide or di-2-pyridyl carbonate and the activating

agent is 4-dimethylamino pyridine. The condensn. is pref. effected in an aromatic solvent e.g. benzene or toluene, etc. at 60-90 deg.C.

USE/ADVANTAGE - Cpds. (I) have antitumour and antileukaemic properties. @(6pp)@

Abstract (EP): 9321 EP 336841 B

Process for the preparation of a taxane derivative of general formula (I) in which R represents a hydrogen atom or an acetyl radical, and having the configuration 2'R,3'S, characterised in that the threo isomer of an acid of general formula (II) in which R1 represents a protective group for the alcohol functional group, chosen from methoxymethyl, 1-ethoxyethyl, bezyloxymethyl, (beta-trimethylsilylethoxy)methyl, tetrahydroxypyranyl or 2,2,2-trichloroethoxycarbonyl radicals, is subjected to a condensation reaction with a taxane derivative of general formula (III) in which R2 represents an acetyl radical or a protective group for the hydroxyl functional group and R3 represents a protective group for the hydroxyl functional group, the protective group being chosen from 2,2,2-trichloroethoxycarbonyl and trialkylsilyl radicals, each alkyl part of said trialkylsilyl radicals containing 1 to 3 carbon atoms, in the presence of a condensing agent chosen from carbodiimides and reactive carbonates and an activating agent chosen from dialkylaminopyridines, the reaction being carried out in an aromatic solvent chosen from benzene, toluene, zylenes, ethylbenzene, isopropylbenzene and chlorobenzene, at a temperature of between 60 and 90 deg.C, in order to obtain a taxane derivative of general formula (IV) in which R1, R2 and R3 are defined as above, in which the protective groups R1, R3 and, where appropriate, R2 are replaced by hydrogen atoms by means of zinc in the presence of acetic acid or by means of an inorganic or organic acid in solution in an aliphatic alcohol containing 1 to 3 carbon atoms, and the product of general formula (I) in the 2'R, 2'S form is then separated off.

Dwg.0/0

File Segment: CPI

Derwent Class: B02;

Int Pat Class: C07D-305/14; A61K-031/33; A61K-000/00; C07D-000/00

Manual Codes (CPI/A-N): B06-A03; B12-G05; B12-G07

Chemical Fragment Codes (M2):

01 D021 D024 D025 D026 D030 D220 G010 G019 G100 H4 H403 H404 H462 H463 H481 H8 J0 J013 J014 J2 J221 J231 J262 J5 J561 K0 L4 L463 M1 M123 M136 M210 M211 M214 M233 M240 M262 M272 M281 M282 M283 M312 M321 M332 M344 M371 M391 M412 M511 M520 M532 M540 M720 M903 M904 N241 N242 N262 N282 N309 N341 N362 N426 N480 N513 P632 P633 68515 8941-15301-P

Ring Index Numbers: 68515

#3

PATENT
Attorney Docket No. 3806.0367-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hervé BOUCHARD et al.

Serial No.: 08/622,011

Filed: March 26, 1996

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Group Art Unit: unassigned

Examiner: unassigned

Assistant Commissioner for Patents
Washington, D.C. 20231

ATTENTION: Application Processing Division,
Special Processing and Correspondence Branch

Sir:

RESPONSE TO NOTICE TO FILE
MISSING PARTS OF APPLICATION

In response to the communication of May 6, 1996, Applicants submit a Declaration/Power of Attorney for filing in the above-identified application, the required fee of $130.00, and a copy of the Notice of Missing Parts.

Please associate the enclosed declaration with the above identified application.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Attorney Docket No.: 3806.0367-00
Serial No.: 08/628,169

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Date: May 24, 1996

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/622,011	03/26/96	BOUCHARD	H 3806.0367-0

0262/0506
FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

DATE MAILED: 0000

NOTICE TO FILE MISSING PARTS OF APPLICATION
FILING DATE GRANTED

05/06/96

An Application Number and Filing Date have been assigned to this application. However, the items indicated below are missing. The required items and fees identified below must be timely submitted **ALONG WITH THE PAYMENT OF A SURCHARGE** for items 1 and 3-6 only of $ 130 for large entities or $ 65 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e).

If all required items on this form are filed within the period set below, the total amount owed by applicant as a ☒ large entity. ☐ small entity (verified statement filed), is $ 130.

Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

1. ☐ The statutory basic filing fee is: ☐ missing ☐ insufficient. Applicant as a ☐ large entity ☐ small entity, must submit $_____ to complete the basic filing fee.

2. ☐ Additional claim fees of $_____ as a ☐ large entity, ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

3. ☒ The oath or declaration:
   ☒ is missing.
   ☐ does not cover the newly submitted items.

   An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required.

4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

5. ☐ The signature(s) to the oath or declaration is/are: ☐ missing; ☐ by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration:

   _____ An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

7. ☐ The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of $_____ under 37 CFR 1.17(k), unless this fee has already been paid.

8. ☐ A $_____ processing fee is required since your check was returned without payment. (37 CFR 1.21(m)).

9. ☐ Your filing receipt was mailed to ~~wrong~~ because your check was returned without payment.

10. ☐ ~~This application does not comply with the Sequence Rules.~~ 320 LC 06/13/96 08622011 105 130.00 OP See attached Notice to Comply with Sequence Rules 37 CFR 1.821-1.825.

11. ☐ Other.

Direct the response to Box Missing Part and refer any questions to the Customer Service Center at (703) 308-1202.

A copy of this notice MUST be returned with the response.

FORM PTO-1535 (REV. 11-94) COPY TO BE RETURNED WITH RESPONSE

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Atty. Docket No. 03806.0367

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

the specification of which:

is attached hereto; or

was filed as United States application Serial No. 08/622,011 on March 26, 1996 and was amended on _____ (if applicable); or

was filed as PCT international application Number _____ on _____ and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office information which is material to the patentability of claims presented in this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
France	95 03545	27 March 1995	XX Yes No
France	95 15381	22 December 1995	XX Yes No
U.S. (Provisional)	60/010,144	17 January 1996	XX Yes No
			Yes No
			Yes No
			Yes No

Combined Declaration For Patent Application and Power of Attorney (Continued)
(includes Reference to PCT International Applications)

Atty. Docket No. 03806.0367

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to the patentability of claims presented in this application in accordance with Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBER ASSIGNED (if any)			

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. Reg. No. 22,540; Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014 Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; M. Paul Barker, Reg. No. 32,013; Bryan C. Diner, Reg. No. 32,409; Christopher P. Isaac, Reg. No. 32,616; Andrew C. Sonu, Reg. No. 33,457; Dirk D. Thomas, Reg. No. 32,600; and _____.

53

Send Correspondence to:	Direct Telephone Calls to: (name and telephone number)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. 1300 I Street, N.W. Washington, D.C. 20005-3315	Thomas L. Irving (202) 408-4082

Combined Declaration For Patent Application and Power of Attorney (Continued)
(includes Reference to PCT International Applications)

Atty. Docket No. 03806.0367

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF FIRST INVENTOR	100 Hervé BOUCHARD	
RESIDENCE & CITIZENSHIP	CITY AND STATE OR CITY AND FOREIGN COUNTRY 94200 Ivry-sur-Seine, France FRX	COUNTRY OF CITIZENSHIP France
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FIRST INVENTOR'S SIGNATURE X Hervé Bouchard		DATE X April, 24. 1996
FULL NAME OF SECOND INVENTOR	200 Jean-Dominique BOURZAT	
RESIDENCE & CITIZENSHIP	CITY AND STATE OR CITY AND FOREIGN COUNTRY 94300 Vincennes, France FRX	COUNTRY OF CITIZENSHIP France
POST OFFICE ADDRESS	36, boulevard de la Libération 94300 Vincennes, France	
SECOND INVENTOR'S SIGNATURE X Jean-Dominique Bourzat		DATE X May, 2, 1996
FULL NAME OF THIRD INVENTOR	300 Alain COMMERCON	
RESIDENCE & CITIZENSHIP	CITY AND STATE OR CITY AND FOREIGN COUNTRY 94400 Vitry-sur-Seine, France FRX	COUNTRY OF CITIZENSHIP France
POST OFFICE ADDRESS	1, bis rue Charles-Floquet 94400 Vitry-sur-Seine, France	
THIRD INVENTOR'S SIGNATURE X Alain Commercon		DATE X May 2, 1996

Listing of Inventors Continued on attached page(s) /__/Yes /XX/No

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/622,011	03/26/96	BOUCHARD H	3806.0367-00

#2

0262/0506

FINNEGAN HENDERSON FARABOW GARRETT
AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

DATE MAILED: 0000

NOTICE TO FILE MISSING PARTS OF APPLICATION
FILING DATE GRANTED

05/06/96

An Application Number and Filing Date have been assigned to this application. However, the items indicated below are missing. The required items and fees identified below must be timely submitted **ALONG WITH THE PAYMENT OF A SURCHARGE** for items 1 and 3-6 only of $ 130 for large entities or $ 65 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e).

If all required items on this form are filed within the period set below, the total amount owed by applicant as a ☒ large entity. ☐ small entity (verified statement filed), is $ 130.

Applicant is given **ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE** of this application, **WHICHEVER IS LATER,** within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

1. ☐ The statutory basic filing fee is: ☐ missing ☐ insufficient. Applicant as a ☐ large entity ☐ small entity, must submit $_____ to complete the basic filing fee.

2. ☐ Additional claim fees of $_____ as a ☐ large entity, ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

3. ☒ The oath or declaration:
   ☒ is missing.
   ☐ does not cover the newly submitted items.

   An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required.

4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

5. ☐ The signature(s) to the oath or declaration is/are: ☐ missing; ☐ by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration:

   _____ An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

7. ☐ The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of $_____ under 37 CFR 1.17(k), unless this fee has already been paid.

8. ☐ A $_____ processing fee is required since your check was returned without payment. (37 CFR 1.21(m)).

9. ☐ Your filing receipt was mailed in error because your check was returned without payment.

10. ☐ The application does not comply with the Sequence Rules. See attached Notice to Comply with Sequence Rules 37 CFR 1.821-1.825.

11. ☐ Other.

Direct the response to Box Missing Part and refer any questions to the Customer Service Center at (703) 308-1202.

A copy of this notice MUST be returned with the response.

OFFICE COPY

0300
5-6-96

PATENT
Attorney Docket No.: 03806.0367

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Herve BOUCHARD et al.

Serial No.: 08/622,011 — Group Art Unit: unassigned

Filed: March 26, 1996 — Examiner: unassigned

For: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

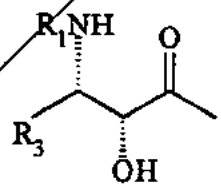
PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application as follows:

IN THE CLAIMS:

Please amend claim 14 as follows:

14. (Amended) A process for preparing a product according to claim 1, wherein Z represents a radical of formula (II)



(II)

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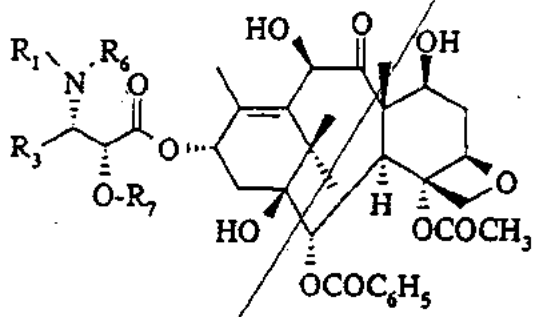
202-408-4000

and R_4 and R_5 are defined as in claim 1, said process comprising:

treating a product of formula (XVI):

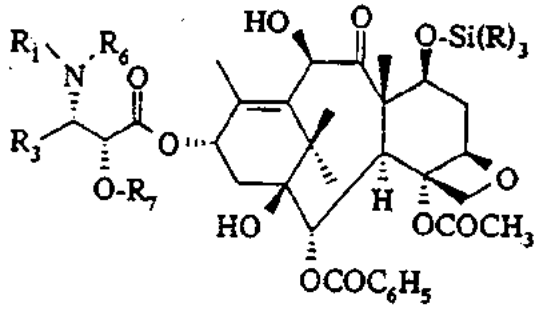


(XVI)

in which R_1, R_3, R_6 and R_7 are defined as in claim 1, with a product of formula (X):

$$(R)_3Si\text{-}Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above,

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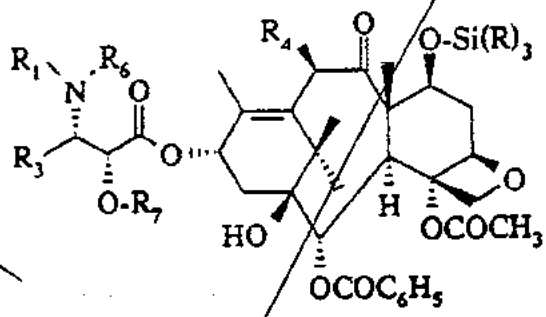
functionalizing said compound of formula (XVII) at position 10 with a product of formula (XII):

$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

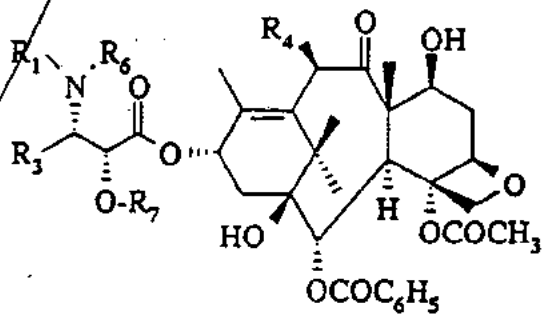
in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined as in claim 1 and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



(XIX)

which, when reacted with a product of formula (XV)

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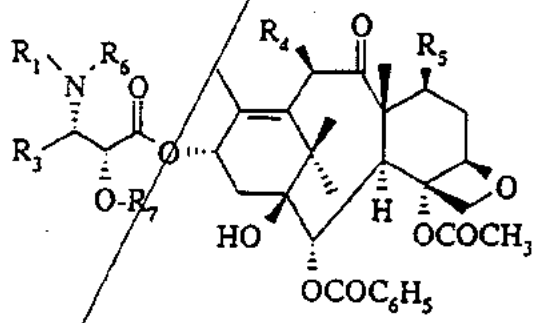
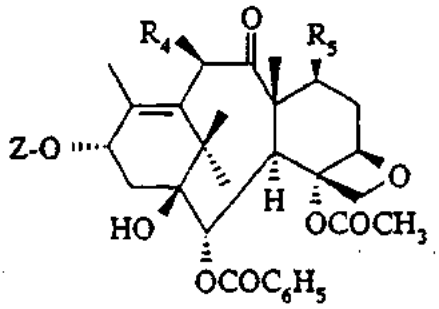
R'_5-X_2 (XV),

yields the product of formula (V),



(V)

and replacing the protective groups of formula (V) with hydrogen atoms to give a product of formula (I)



(I)

in which Z represents a radical of formula (II).

REMARKS

Claim 14 has been amended to include the structural formula of formula (V), which was inadvertently omitted, and to include the structural formulas of formulas

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(I), (II), and (XV) to make the claim excessively clear. No new matter is introduced by this amendment since all the structural formulas are disclosed in the original specification.

CONCLUSION

In view of the foregoing amendments and remarks, it is urged that the pending claims are in condition for allowance. An early and favorable action is earnestly solicited.

If there are any other fees due in connection with the filing of this preliminary amendment, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By: Thalia V Warnement
Thalia V. Warnement
Reg. No. 39,064

Dated: April 18, 1996

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FACSIMILE 011-813-3431-6945

WRITER'S DIRECT DIAL NUMBER:

(202) 408-4454

March 26, 1996

ATTORNEY DOCKET NO. 3806.0367-00

Assistant Commissioner for Patents
Washington, D.C. 20231

BOX PATENT APPLICATION

Re: New U.S. Patent Application for
Title: NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
Inventors: Herve BOUCHARD, Jean-Dominique BOURZAT, and Alain COMMERCON

Sir:

We enclose the following papers for filing in the United States Patent and Trademark Office in connection with the above patent application.

Enclosures

1. Application - 109 pages, including cover page, abstract, 9 independent claims and 31 claims total;

2. Certified copies of
French Priority Document No. 95 03545, filed March 27, 1995; and
French Priority Document No. 95 15381, filed December 22, 1995; and

3. A check (in the amount of $1,460.00 representing the filing fee).

This application is being filed under the provisions of 37 C.F.R. §1.53(d). Applicants await notification from the Patent and Trademark Office of the time set for filing the Declaration.

Applicants claim the right to priority based on 1) U.S. Provisional Application Serial No. 60/010144 filed January 17, 1996; 2) French Priority Document No. 95 03545 filed March 27, 1995; and 3) French Priority Document No. 95 15381 filed December 22, 1995.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. § 1.16 or § 1.17 during the pendency of this application to our Deposit Account No. 06-0916.

Please accord this application a serial number and filing date.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Thalia V. Warnement
Thalia V. Warnement
Reg. No. 39,064

Enclosures

by
Carol P. Edwards
Reg. No. 32,220

08/622011

Attorney Docket No.: 03806.0367

UNITED STATES PATENT APPLICATION

OF

HERVE BOUCHARD,

JEAN-DOMINIQUE BOURZAT,

AND

ALAIN COMMERCON

FOR

NEW TAXOIDS, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

1460-101 A

08/622011

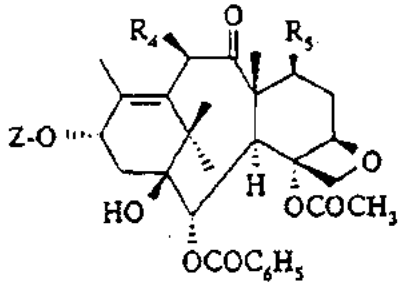
Patent
Attorney Docket No. 03806.0367

NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the priority of US provisional application 60/010,144 filed 1-17-1996.

The present invention relates to new taxoids of general formula (I)

T0020X

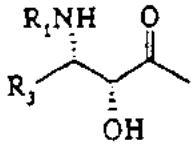


(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):

T0021X



(II)

in which:

R, represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical preferably selected from furyl and thienyl radicals,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl,

alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_6 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 4 to 6 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl

radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

Preferably, the radicals R_4 and R_5, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio,

carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

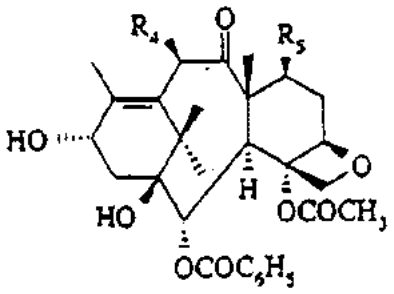
More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5- thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical

R_2-O-CO- in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and R_4 and R_5, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

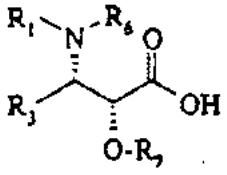
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):



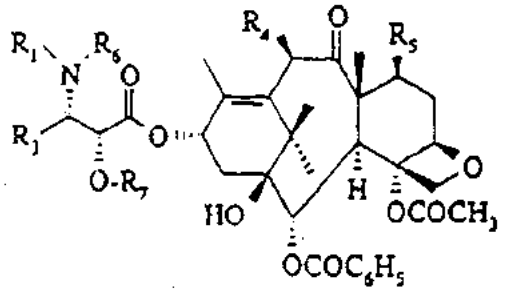
(III)

in which R_4 and R_5 are defined as above, by means of an acid of general formula (IV):



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, followed by replacement of the protective groups represented by R_7 and/or R_6 and R_7 by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from -10 to 90°C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the

presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0 to 90°C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0 to 80°C.

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

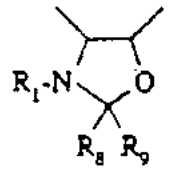
When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the

following manner:

1) when R_8 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from -10 to 60°C, or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

2) when R_8 and R_7 together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):

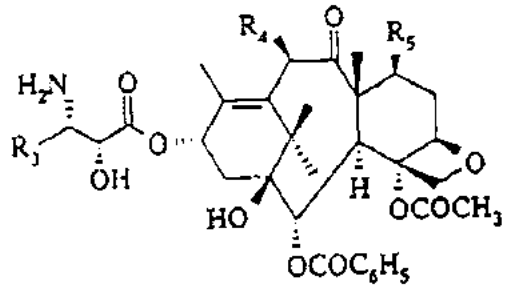


(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and R_9 represents a hydrogen atom, or alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms may be performed, depending on the meanings of R_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or alternatively R_8 and R_9 together form a 4- to 7-membered ring, treatment of the ester of general

formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII).



(VII)

in which R_3, R_4 and R_5 are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue $-O-R_2$ or $-O-CO-O-R_2$, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

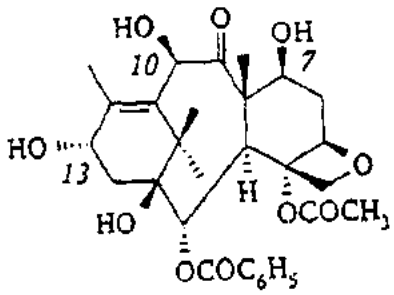
Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20°C to yield the product of general formula (VII).

Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally

substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0 to 50°C, and preferably at about 20°C.

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom, replacement of the protective group formed by R_8 and R_7 by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from -10 to 60°C, and preferably from 15 to 30°C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and R_4 and R_5 are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):



(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:

$$(R)_3\text{-Si-Hal} \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):

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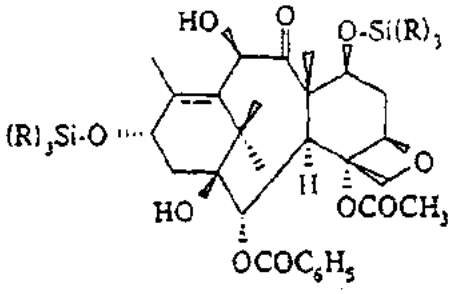

(XI)

in which R is defined as above, followed by the action of a product of general formula:

$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined as above and X_1 represents a reactive ester residue such as a sulphuric or sulphonic ester residue or a halogen atom, to obtain a product of general formula (XIII):

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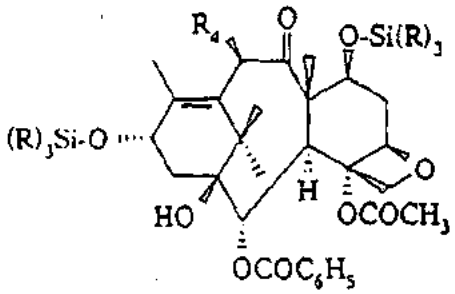

(XIII)

in which R and R_4 are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):

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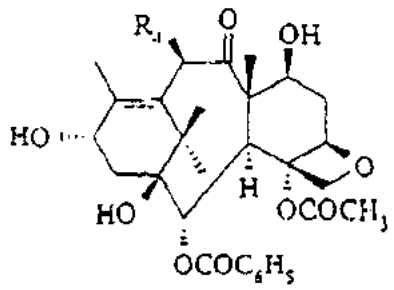


(XIV)

in which R_4 is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

in which R'_5 represents a radical such that R'_5-O is identical to R_5 defined as above and X_2 represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonic ester residue, to give the product of general formula (III).

Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0°C and the refluxing temperature of the reaction mixture.

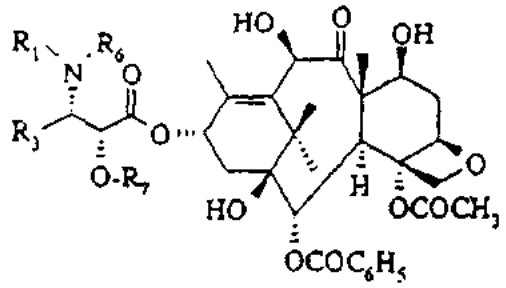
Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an

alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0 to 50°C.

Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0 to 80°C.

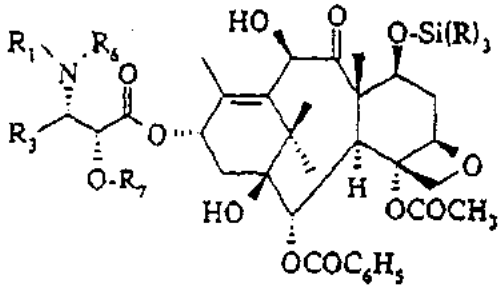
Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4 is defined as above and R_5 is defined as above may be obtained from a product of general formula (XVI):



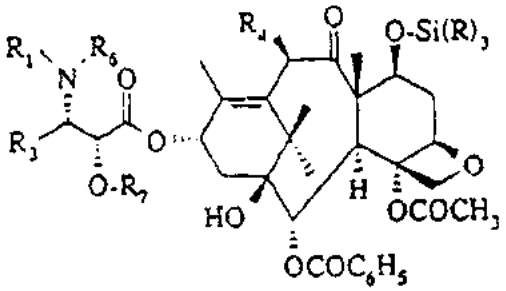
(XVI)

in which R_1, R_3, R_6 and R_7 are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):



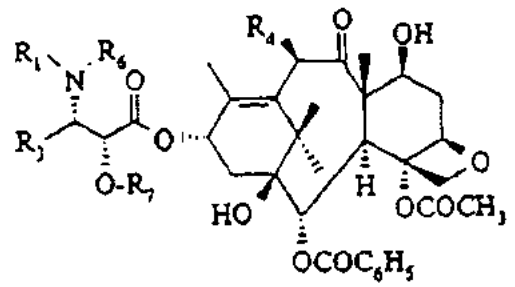
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):

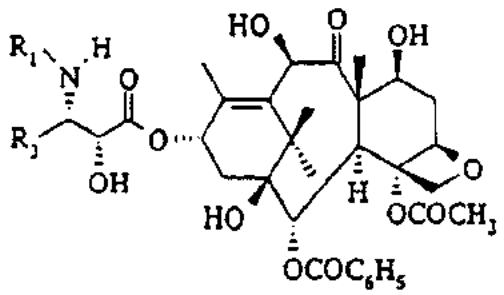


(XIX)

which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

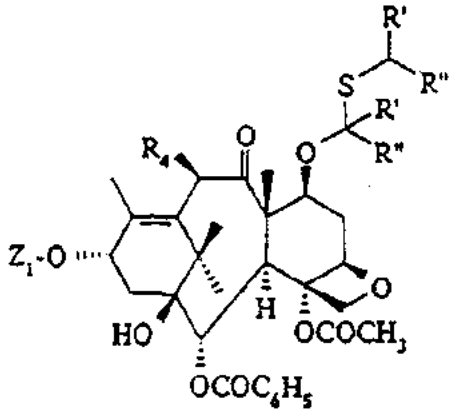
The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336,841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):



(XX)

in which R_1 and R_3 are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):



(XXI)

in which R_4 is defined as above and R' and R'', which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R'', together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of general formula (XXII):

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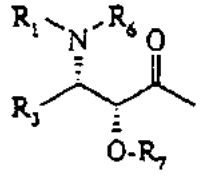
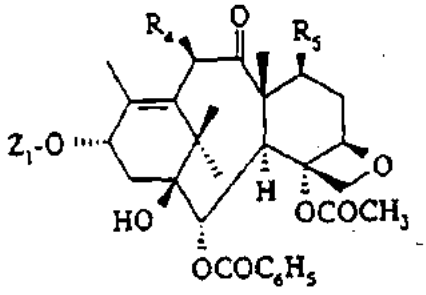


(XXII)

in which R_1, R_3, R_6 and R_7 are defined as above, and, to obtain a product of general formula (XXIII):

T0241X



(XXIII)

followed, when Z_1 represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by R_8 and/or R_9 and R_7 by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from -10 to 60°C.

According to the invention, the product of general formula (XXI) in which Z_1 and R_4 are defined as above may be obtained by the action of a sulphoxide of general formula (XXIV):

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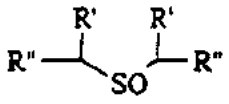

(XXIV)

in which R' and R" are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50°C, and preferably at about 25°C.

The new products of general formula (I) obtained by carrying out the

processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M.L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765-768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501-503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are

generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20°C to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4Å molecular sieve in 2 cm^3 of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20°C under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063-0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 10:90 to 40:60 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzoyloxy-

5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$ with a few drops of CD_3OD-d_4; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.63 (s, 3H: CH_3); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; CH_2 at position 6); 1.78 (unres. comp., 3H: CH_3); 2.02 and 2.15 (2 dd, J = 14 and 9, 1H each: CH_2 at position 14); 2.14 (s, 3H: CH_3); 3.22 and 3.35 (2 s, 3H each: OCH_3); 3.64 (d, J = 7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: $ArOCH_3$); 4.06 and 4.16 (2 d, J = 8.5, 1H each; CH_2 at position 20); 4.53 (d, J = 5, 1H: H at position 2'); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J = 10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J = 7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J = 8, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to OCH_3); 7.43 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.58 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 7.96 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-

butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 cm^3 of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0°C for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 cm^3 of dichloromethane and 5 cm^3 of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 cm^3 of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatography [12 Merck preparative silica gel $60F_{254}$ plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/ dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40°C, 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

- optical rotation $[\alpha]_{20}^{D}$ = -32.9 (c = 0.5; methanol)

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.39 (s, 9H: $C(CH_3)_3$); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: CH_3); 1.82 and 2.72 (2 mts, 1H each: CH_2 at position 6); 1.91 (s, 3H: CH_3); 2.31 (limiting AB, 2H: CH_2 at position 14); 2.39 (s, 3H: $COCH_3$); 3.33 and 3.48 (2 s, 3H each: OCH_3); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J = 7, 1H: H 3); 3.88 (dd, J = 11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J = 10, 1H: H at position 5); 5.30 (broad d, J = 10, 1H: H at position 3'); 5.47 (d, J = 10, 1H: CONH); 5.66 (d, J = 7, 1H: H at position 2); 6.24 (broad t, J = 9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0°C, of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-

methoxy-9-oxo-11-taxene in 5 cm^3 of iodomethane and 0.5 cm^3 of dimethylformamide. After 45 minutes at a temperature in the region of 0°C, the reaction mixture was diluted with 50 cm^3 of ethyl acetate and 8 cm^3 of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene were thereby obtained in the form of a pale yellow solid, the characteristics of which were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; with a few drops of CD_3OD-d_4; chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: CH_3); 1.11 (s, 3H: CH_3); 1.65 (s, 3H: CH_3); 1.72 and 2.67 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.21 (limiting AB, J = 14 and 9, 2H: CH_2 at

position 14); 2.25 (s, 3H: $COCH_3$); 3.26 and 3.40 (2 s, 3H each: OCH_3); 3.85 (d, J = 7, 1H: H at position 3); 3.89 (dd, J = 11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.78 (broad t, J = 9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J = 10, 1H: H at position 5); 5.53 (d, J = 7, 1H: H at position 2); 7.43 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.56 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.05 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0°C, of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyoxy)-11-taxene in 30 cm^3 of dichloromethane. After 48 hours at a temperature in the region of 20°C, the reaction mixture was poured into a suspension of 100 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0°C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 cm^3 of dichloromethane and then twice 80 cm^3 of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered

through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063-0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.10 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.48 (d, J = 8.5, 1H: OH at position 13); 1.70 (s, 3H: CH_3); 1.81 and 2.61 (2 mts, 1H each: CH_2 at position 6); 2.09 (d, J = 5, 1H: OH at position 7); 2.11 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J = 9, 2H: CH_2 at position 14); 3.48 (s, 3H: OCH_3); 3.97 (d, J = 7, 1H: H at position 3); 4.18 and 4.33 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J = 10, 1H: H at position 5); 5.66 (d, J = 7, 1H: H at position 2); 7.49 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0°C, of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 25 cm^3 of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0°C, and then for 5 hours 30 minutes at a temperature in the region of 20°C. The reaction mixture was cooled again to a temperature in the region of 0°C, and 125 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise. After 1 hour at 20°C and then 18 hours at 5°C, the reaction mixture was diluted by adding 50 cm^3 of dichloromethane and poured into 50 cm^3 of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 cm^3 of dichloroemethane, and the organic phases were then combined, washed with 10 cm^3 of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 5.15 g of a

yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063-0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

- ^1H NMR spectrum (600 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl CH_2); 0.97 and 1.04 (2 t, J = 7.5, 9H each: ethyl CH_3); 1.15 (s, 3H: CH_3); 1.18 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: CH_3); 1.89 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.04 (s, 3H: CH_3); 2.15 and 2.23 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 2.29 (s, 3H: $COCH_3$); 3.40 (s, 3H: OCH_3); 3.83 (d, J = 7, 1H: H at position 13); 4.15 and 4.30 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.43 (dd, J = 11 and 7, 1H: H at position 7); 4.91 (s, 1H: H at position 10); 4.96 (broad d, J = 10, 1H at position 5); 5.01 (broad t, J = 9, 1H: H at position 13); 5.62 (d, J = 7, 1H: H at position 2); 7.46 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the

ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 cm^3 of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20°C, of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetylbaccatin III) in 50 cm^3 of anhydrous pyridine. After 17 hours at a temperature in the region of 20°C, the reaction mixture was brought to a temperature in the region of 115°C and 10.8 cm^3 of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115°C, the reaction mixture was brought back to a temperature in the region of 20°C and diluted with 30 cm^3 of ethyl acetate and 100 cm^3 of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 cm^3 of ethyl acetate. The organic phases were combined, washed with 50 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063-0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl

acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J = 7.5, 9H each: ethyl CH_3); 1.08 (s, 3H: CH_3); 1.17 (s, 3H: CH_3); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.91 and 2.57 (2 mts, 1H each: CH_2 at position 2); 2.04 (s, 3H: CH_3); 2.12 and 2.23 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.88 (d, J = 7, 1H: H at position 3); 4.16 and 4.32 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.27 (d, J = 1, 1H: OH at position 10); 4.40 (dd, J = 11 and 7, 1H: H at position 7); 4.95 (broad d, J = 10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13); 5.16 (d, J = 1, 1H: H at position 10); 5.60 (d, J = 7, 1H: H at position 2); 7.46 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 2

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 cm^3 of a 0.1N ethanolic solution of hydrochloric acid containing 1 % of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20°C and then for 80 hours at 4°C, and 20 cm^3 of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 cm^3 of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates 20 × 20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 cm^3 of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. A white foam was obtained, which was repurified according to the same technique [3 plates: 20 × 20 × 1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)].

205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -33 (c = 0.5; methanol).

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: $-CH_3$); 1.25 (s, 3H: $-CH_3$); 1.39 [s, 9H: $-C(CH_3)_3$]; 1.70 ,(s, 1H: -OH at position 1); 1.75 (s, 3H: $-CH_3$); 1.82 and 2.72 (2 mts, 1H each: $-CH_2$ at position 6); 1.91 (s, 3H: $-CH_3$); 2.31 (limiting AB, 2H: $-CH_2$ at position 14); 2.39 (s, 3H: $-COCH_3$); 3.33 and 3.48 (2 s, 3H each: $-OCH_3$); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J = 7, 1H: -H at position 3); 3.88 (dd, J = 11 and 7, 1H: -H at position 7); 4.20 and 4.33 (2d, J = 8.5, 1H each: $-CH_2$ at position 20); 4.65 (mt, 1H: -H at position 2'); 4.83 (s, 1H: -H at position 10); 5.00 (broad d, J = 10, 1H: -H at position 5); 5.30 (broad d, J = 10, 1H: -H at position 3'); 5.47 (d, J = 10, 1H: -CONH-); 5.66 (d, J = 7, 1H: -H at position 2); 6.24 (broad t, J = 9, 1H: -H at position 13); from 7.30 to 7.50 (mt, 5H: $-C_6H_5$ at position 3'); 7.52 [t, J = 7.5, 2H: $-OCOC_6H_5$ (-H at position 3 and H at position 5)]; 7.63 [t, J = 7.5, 1H: $-OCOC_6H_5$ (-H at position 4)]; 8.12 [d, J = 7.5, 2H: $-OCOC_6H_5$ (-H at position 2 and H at position 6)].

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 cm^3 of an ethanolic suspension of activated nickel according to Raney (obtained from 80 cm^3 of the approximately 50 % commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 cm^3 of distilled water and with 5 times 100 cm^3 of ethanol) were added at a temperature in the region of 20°C to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm^3 of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20°C and then filtered through sintered glass. The sintered glass was washed with 4 times 80 cm^3 of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-cm^3 fractions. Fractions containing only the desired product are pooled and

concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 350 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxy-phenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 cm^3 of acetic acid and 7.55 cm^3 of acetic anhydride were added at a temperature in the region of 20°C to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 cm^3 of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20°C, and then poured into a mixture of 500 cm^3 of distilled water and 250 cm^3 of dichloromethane. 30 cm^3 of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with twice 250 cm^3 of dichloromethane. The organic phases were combined, washed

with 250 cm^3 of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063-0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 1.25 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 cm^3 of methanol and 100 cm^3 of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60°C, and 10 g of powdered zinc were then

added. The reaction mixture was then stirred for 15 minutes at 60°C, thereafter cooled to a temperature in the region of 20°C and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 cm^3 of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 50 cm^3 of ethyl acetate and 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 cm^3 of saturated aqueous sodium hydrogen carbonate solution and with 25 cm^3 of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy-carbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

EXAMPLE 3

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20°C to a suspension containing 135 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4Å molecular sieve in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20°C under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/ dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then

evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

- ^{1}H NMR spectrum (600 MHz; $CDCl_3$; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: $C(CH_3)_3$; 1.19 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.27 (t, J = 7, 3H: ethyl CH_3); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: CH_3); 1.68 (s, 3H: CH_3); 1.77 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.86 (s, 3H: $COCH_3$); 2.13 and 2.22 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 3.27 (s, 3H: OCH_3); 3.45 and 3.68 (2 mts, 1H each: ethyl CH_2); 3.76 (d, J = 7, 1H: H3); 3.81 (s, 3H: $ArOCH_3$); 3.85 (dd, J = 11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.58 (d, J = 4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J = 10, 1H: H at position 5); 5.46 (d, J = 4.5, 1H: H at position 3'); 5.60 (d, J = 7 Hz, 1H: H2); 6.13 (broad t, J = 9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J = 8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.50 (mt, 9H: aromatic H

at position 3' - aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ H at the meta position); 7.59 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm^3 of ethyl acetate and 0.004 cm^3 of concentrated 37 % hydrochloric acid was kept stirring at a temperature in the region of 20°C for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling

constants J in Hz): 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.32 (t, J = 7, 3H: ethyl CH_3); 1.38 (s, 9H: $C(CH_3)_3$); 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H: CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each: ethyl OCH_2); 3.84 (d, J = 7.5, 1H: H at position 3); 3.87 (dd, J = 11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J = 10, 1H: H at position 5); 5.28 (broad d, J = 10, 1H: H at position 3'); 5.42 (d, J = 10, 1H: CONH); 5.64 (d, J = 7.5, 1H: H at position 2); 6.22 (broad t, J = 9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0°C, of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 cm^3 of iodomethane and 1 cm^3 of dimethylformamide

After 30 minutes at a temperature in the region of 0°C, the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 6 cm^3 of distilled water and 8 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 cm^3 of distilled water and then 8 cm^3 of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/ dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

- ^1H NMR spectrum (300 MHz; $CDCl_3$ with the addition of a few drops of CD_3OD-d_4; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: CH_3); 1.09 (s, 3H: CH_3); 1.22 (t, J = 7, 3H: ethyl CH_3); 1.62 (s, 3H: CH_3); 1.68 and 2.66 (2 mts, 1H each: $CH_2$6); 2.03 (s, 3H: CH_3); 2.13 and

2.22 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 2.23 (s, 3H: $COCH_3$); 3.23 (s, 3H: OCH_3); from 3.40 to 3.65 (mt, 2H: ethyl CH_2); 3.84 (d, J = 7.5, 1H: H at position 3); 3.88 (dd, J = 10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J = 8.5, 1H each: CH_2 20); 4.75 (broad t, J = 9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J = 10, 1H: H at position 5); 5.51 (d, J = 7.5, 1H: H at position 2); 7.42 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.53 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20°C, of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 21 hours at a temperature in the region of 20°C, the reaction mixture was diluted with 40 cm^3 of dichloromethane and poured into a suspension of 40 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0°C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic

phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$: chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); 1.29 (t, J = 7.5, 3H: ethyl CH_3); 1.38 (d, J = 9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: CH_3); 1.82 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.02 (d, J = 5, 1H: OH at position 13); 2.08 (s, 3H: CH_3); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J = 9, 2H: CH_2 at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl OCH_2); 3.98 (d, J = 7, 1H: H at position 3); 4.18 and 4.33 (2 d, J = 8.5 Hz, 1H each: $CH_2$20); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J = 10 and 1.5, 1H: H at position 5); 5.05 (s, 1H:

H at position 10); 5.66 (d, J = 7, 1H: H at position 2); 7.49 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50 % by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20°C, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20°C, and 93 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20°C, the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 1.2 g of a yellow foam were thereby

obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063-0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl CH_2); 0.97 and 1.03 (2 t, J = 7.5, 9H each: ethyl CH_3); 1.13 (s, 3H: CH_3); 1.20 (s, 3H: CH_3); 1.29 (t, J = 7.5, 3H: CH_3 of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: CH_3); 1.89 and 2.58 (2 mts, 1H each: CH_2 at position 2); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.53 (mt, 2H: CH_2 of ethoxy at position 10); 3.84 (d, J = 7, 1H: H at position 3); 4.15 and 4.30 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.43 (dd, J = 11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5).

5.01 (s, 1H: H at position 10); 5.61 (d, J = 7, 1H: H at position 2); 7.48 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20°C to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 cm^3 of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20°C under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel

$60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 84.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

- ^1H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.97 (t, J = 7, 3H: propyl CH_3); 1.07 (s, 9H: $C(CH_3)_3$); 1.19 (s, 6H: CH_3); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central CH_2 of propyl); 1.60 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.78 and 2.63 (2 mts, 1H each: CH_2 at position 6); 1.82 (unres. comp. 3H: $COCH_3$); 2.07 and 2.19 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 3.26 (s, 3H: OCH_3); 3.30 and 3.58 (2 mts, 1H each: propyl OCH_2); 3.73 (d, J = 7.5, 1H: H at position 3); 3.81 (s, 3H: $ArOCH_3$); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.57 (d, J = 4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J = 10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J = 7.5, 1H: H at position 2); 6.13 (broad t, J = 9, 1H: H at position 13); 6.40 (spread

unres. comp. 1H: H at position 5'); 6.92 (d, J = 8.5, 2H: aromatic H at the ortho position with respect to OCH_3); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3' - aromatic H at the meta position with respect to OCH_3 and $OCOC_6H_5$ meta H); 7.63 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm^3 of ethyl acetate and 0.0071 cm^3 of concentrated 37 % hydrochloric acid was kept stirring at a temperature in the region of 20°C for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/ dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 27 mg

of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate were obtained in the form of a white foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.99 (t, J = 7, 3H: propyl CH_3); 1.22 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$); 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central CH_2 of propyl); 1.73 (s, 3H: CH_3); 1.80 and 2.70 (2 mts, 1H each: CH_2 at position 6); 1.88 (s, 3H: CH_3); 2.30 (mt, 2H: CH_2 at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: OCH_3); 3.36 and 3.64 (2 mts, 1H each: propyl OCH_2); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J = 7.5, Hz, 1H: H at position 3); 3.87 (dd, J = 11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H at position 10); 4.98 (broad d, J = 10, 1H: H at position 5); 5.28 (broad d, J = 10, 1H: H at position 3'); 5.42 (d, J = 10, 1H: CONH); 5.64 (d, J = 7.5, 1H: H at position 2); 6.22 (broad t, J = 9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-7β-methoxy-

10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0°C, of 165 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene in 1.7 cm^3 of iodomethane and 1 cm^3 of dimethylformamide. After 30 minutes at a temperature in the region of 0°C, the reaction mixture was diluted with 40 cm^3 of ethyl acetate, 5 cm^3 of distilled water and 7 cm^3 of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 cm^3 of distilled water and then 7 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 117.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were thereby

obtained in the form of a white foam, the characteristics of which were as follows:

- ^{1}H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.98 (t, J = 7, 3H: propyl CH_3); 1.05 (s, 3H: CH_3); 1.19 (s, 3H: CH_3); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: CH_2 at position 6); 1.72 (s, 3H: CH_3); 2.10 (s, 3H: CH_3); from 2.05 to 2.35 (mt, 2H: CH_2 at position 14); 2.28 (s, 3H: $COCH_3$); 3.32 (s, 3H: OCH_3); 3.45 and 3.65 (2 mts, 1H each: propyl OCH_2); 3.92 (d, J = 7.5, 1H: H3); 3.93 (dd, J = 11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J = 10, 1H: H at position 5); 5.60 (d, J = 7.5, 1H: H at position 2); 7.48 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.11 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 cm^3 of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20°C, of 585 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 cm^3 of dichloromethane. After 24 hours

at a temperature in the region of 20°C, the reaction mixture was diluted with 30 cm^3 of dichloromethane and poured into a suspension of 30 cm^3 of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0°C. After dilution with 10 cm^3 of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 cm^3 of diethyl ether. The organic phases were combined, washed with 20 cm^3 of distilled water and 20 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

- ^1H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J = 7, 3H: propyl CH_3); 1.06 (s, 3H: CH_3); 1.22

(s, 3H: CH_3); 1.45 (d, J = 7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central CH_2 of propyl); 1.67 (s, 3H: CH_3); 1.83 and 2.62 (2 mts, 1H each: CH_2 at position 6); 2.05 (s, 3H: CH_3); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: CH_2 at position 4); 2.28 (s, 3H: $COCH_3$); 3.40 and 3.57 (2 mts, 1H each: propyl OCH_2); 3.97 (d, J = 7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J = 10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J = 7.5, 1H: H at position 2); 7.50 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.00 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethyl-silyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50 % by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20°C, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 cm^3 of iodoethane and 4 cm^3 of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20°C, and 93 mg of sodium hydride at a

concentration of 50 % by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20°C, the reaction mixture was diluted with 100 cm^3 of ethyl acetate and 10 cm^3 of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 cm^3 of distilled water and then 10 cm^3 of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063-0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-cm^3 fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling

constants J in Hz): 0.57 and 0.70 (2 mts, 6H each: ethyl CH_2); 0.94 and 1.03 (2 t, J = 7.5, 9H each: ethyl CH_3); 0.94 (t, J = 7.5, 3H: propyl CH_3); 1.14 (s, 3H: CH_3); 1.21 (s, 3H: CH_3); 1.67 (s, 3H: CH_3); 1.69 (mt, 2H: central CH_2 of propyl); 1.88 and 2.48 (2 mts, 1H each: CH_2 at position 6); 2.03 (s, 3H: CH_3); 2.13 and 2.23 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); 2.30 (s, 3H: $COCH_3$); 3.40 (mt, 2H: propyl OCH_2); 3.84 (d, J = 7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J = 8.5, 1H each: CH_2 at position 20); 4.44 (dd, J = 11 and 6.5, 1H: H at position 7); 4.96 (broad d, J = 10 Hz, 1H: H5); 4.97 (s, 1H: H 10); 4.99 (broad t, J = 9Hz, 1H: H at position 13); 5.62 (d, J = 7.5, 1H: H at position 2); 7.48 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological

conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic

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solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as

dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses

will be administered until an optimum effect is obtained.

For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

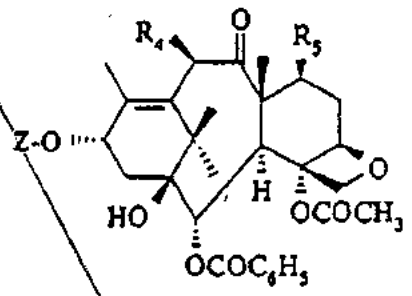
The example which follows illustrates a composition according to the invention.

EXAMPLE

40 mg of the product obtained in Example 1 are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

WE CLAIM:

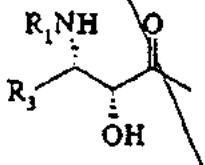
1. A taxoid of the formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, trifluoromethyl radicals, a thenoyl radical, a furoyl radical, and a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon

atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- or a 5-membered aromatic heterocyclic radical,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4

carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are

phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical

containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

2. A taxoid according to claim 1, wherein Z represents a hydrogen atom or a radical of formula (II) in which

R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical,

R_3 represents an alkyl radical containing 1 to 6 carbon atoms; an

alkenyl radical containing 2 to 6 carbon atoms; a cycloalkyl radical containing 3 to 6 carbon atoms; a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkoxy, dialkylamino, acylamino, alkoxycarbonylamino and trifluoromethyl radicals; or a 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl radical, and

R_4 and R_5, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

3. A taxoid according to claim 1, wherein Z represents a hydrogen atom or a radical of formula (II) in which

R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical,

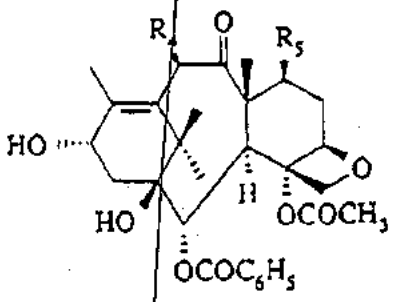
R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and

R_4 and R_5, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

4 A taxoid according to claim 1, wherein when R_2 represents a 5-membered aromatic heterocyclic radical, said radical is a furyl or thienyl radical.

5. A process for preparing the taxoid according to claim 1, wherein Z represents a radical of formula (II), said process comprising:

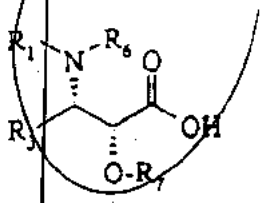
esterifying a product of formula (III):



(III)

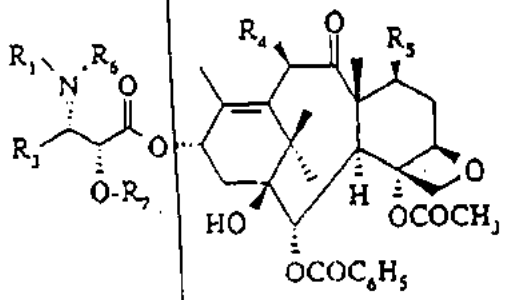
in which R_4 and R_5 are defined as in claim 1

with an acid of formula (IV):



(IV)

in which R_1 and R_3 are defined as in claim 1, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or with a derivative of said acid, to obtain an ester of formula (V):



(V)

in which R_1, R_3, R_4, R_5, R_6 and R_7 are defined as above, and

replacing the protective group(s) of said ester of formula (V), represented by R_7 or R_6 and R_7, by hydrogen atoms.

12. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from -10 to 90°C.

13. A process according to claim 8, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0 to 90°C.

14. A process according to claim 8, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0 to 80°C.

15. A process according to claim 8, further comprising replacing the protective group(s) R_7 or R_6 and R_7 by hydrogen atoms, wherein:

1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

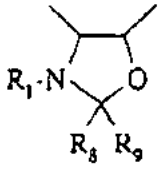
with at least one inorganic or organic acid in an organic solvent

selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitriles at a temperature from -10 to 60°C, or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

in which R_1 is defined as above and R_8 and R_9, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9, together with the carbon atom to which they are linked, form a 4- to 7-membered ring,

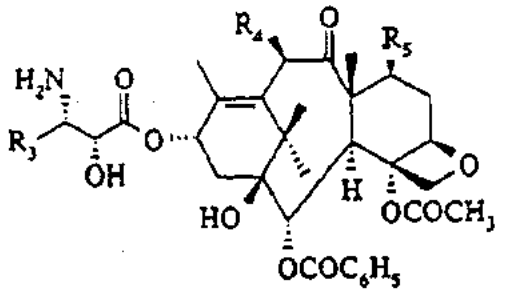
wherein when:

a) R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or

alternatively R_8 and R_9 together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, optionally and ~~where appropriate~~, in an organic solvent, to obtain the product of formula (VII):



(VII)

in which R_3, R_4 and R_5 are defined ~~as above~~ in claim 8, and

said product of formula (VII) is acylated with

benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

in which R_2 is defined in claim 8 and X represents a halogen atom or a residue -O-R_2 or -O-CO-O-R_2, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom,

the protective group formed by R_6 and R_7 is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from -10 to 60°C.

16 ~~10~~. A process according to claim 15, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9, which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon

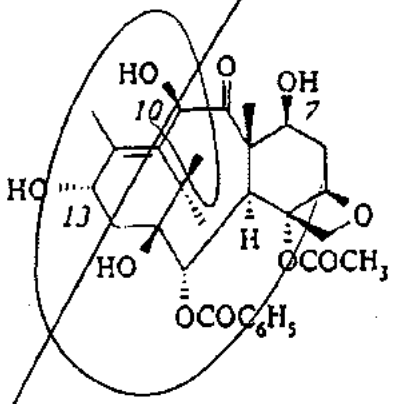
atoms.

11. A process according to claim 8, wherein when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle of formula (VI), and R_8 and R_9, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

12. A process according to claim 8, wherein said temperature ranges from 15 to 30°C.

13. A process for preparing a new taxoid according to claim 1, wherein Z represents a hydrogen atom and R_4 and R_5 are defined as in claim 1, said process comprising:

treating 10-deacetylbaccatin III of formula (IX):



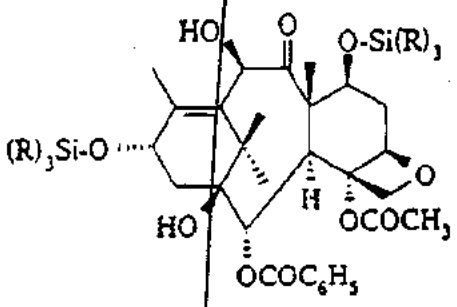
(IX)

with a silyl halide of formula:

$$(R)_3\text{-Si-Hal} \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally

substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



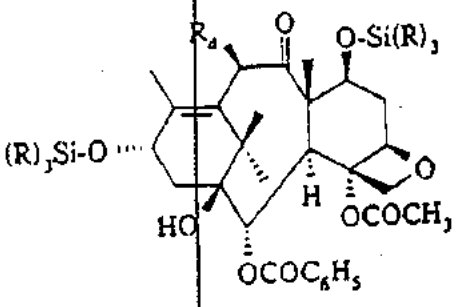
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

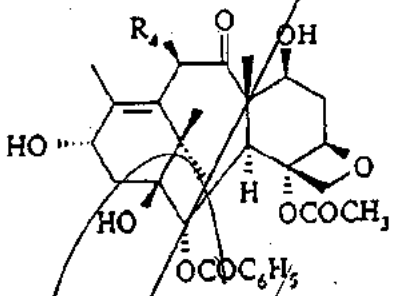
in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined as in claim 1 and X_1 represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):



(XIII)

in which R and R_4 are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):



(XIV)

in which R_4 is defined as above, and

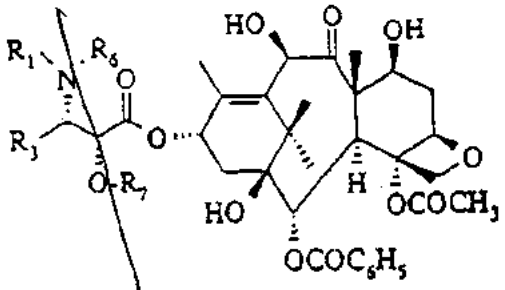
etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

in which R'_5 represents a radical such that R'_5-O is identical to R_5 defined as in claim 1 and X_2 represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

14. A process for preparing a product according to claim 1, wherein Z represents a radical of formula (II) and R_4 and R_5 are defined as in claim 1, said process comprising:

treating a product of formula (XVI):

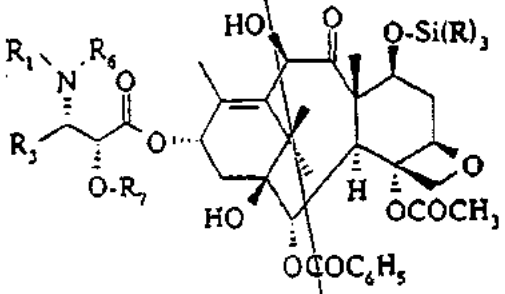


(XVI)

in which R_1, R_3, R_6 and R_7 are defined as in claim 1, with a product of formula (X):

$$(R)_3Si\text{-}Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



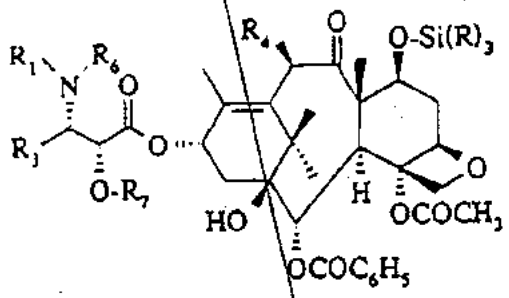
(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:

$$R'_4\text{-}X_1 \qquad (XII)$$

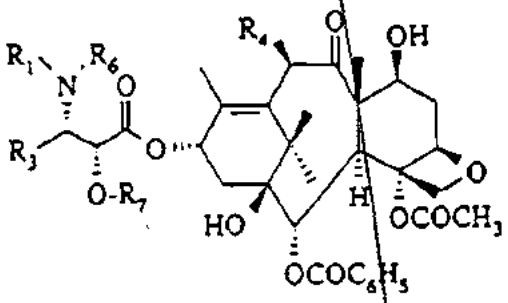
in which R'_4 represents a radical such that R'_4-O is identical to R_4 defined as in claim 1 and X_1 represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



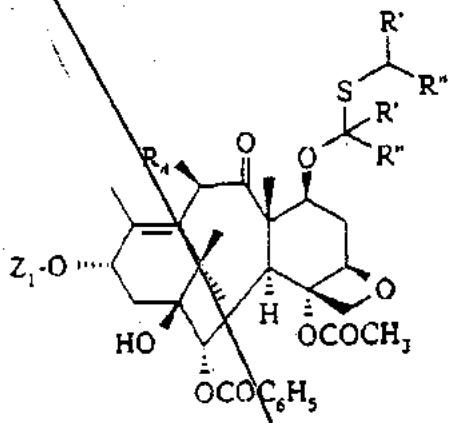
(XIX)

which, when reacted with a product of formula (XV), yields the product of formula (V),

and replacing the protective groups of formula (V) with hydrogen

atoms to give a product of formula (I) in which Z represents a radical of formula (II).

15 A process for preparing a product according to claim 1, comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):



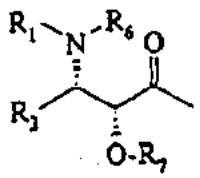
(XXI)

in which R_4 is defined as in claim 1, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 2 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively

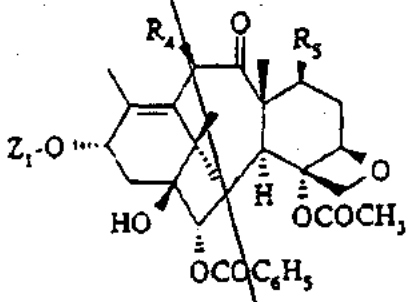
R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom

or a radical of formula (XXII):



(XXII)

in which R_1 and R_3 are defined in claim 1 and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, to obtain a product of formula (XXIII):



(XXIII)

followed, when Z_1 represents a radical of formula (XXII), by replacing the protective group(s) represented by R_6 or R_6 and R_7 by hydrogen atoms under the conditions of claim 9.

16. A preparation process according to claim 15, wherein said process is carried out at a temperature of from -10 to 60°C.

17. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

18. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-ethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

19. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-(1-propyl)oxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

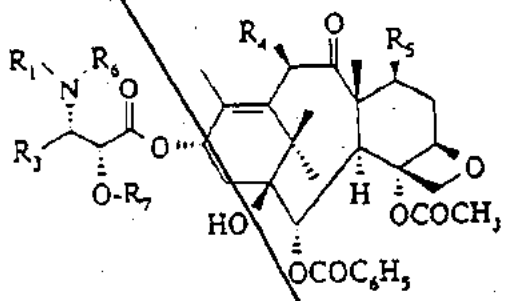
20. A pharmaceutical composition comprising at least one product according to claim 1 wherein Z represents a radical of formula (II), in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

21. A pharmaceutical composition comprising at least the product according to claim 17 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

22. A pharmaceutical composition comprising at least the product according to claim 18 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

23. A pharmaceutical composition comprising at least the product according to claim 19 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

24. An ester of the formula (V):



(V)

wherein

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, trifluoromethyl radicals, a thenoyl radical, a furoyl radical, and a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7

to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1

to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an

unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

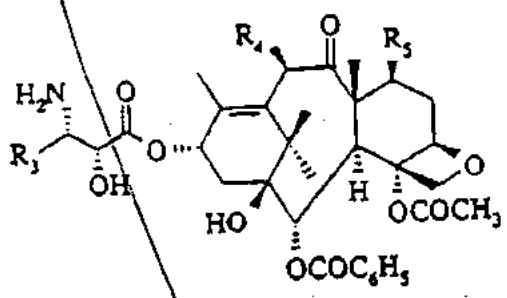
R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a

radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

25. An ester of formula (VII):



(VII)

wherein

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, arcylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1

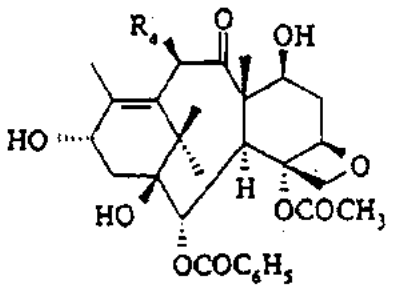
to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

26. A method comprising the step of etherifying selectively at

position 7 a compound of the formula (XIV):



(XIV)

wherein R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur

and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

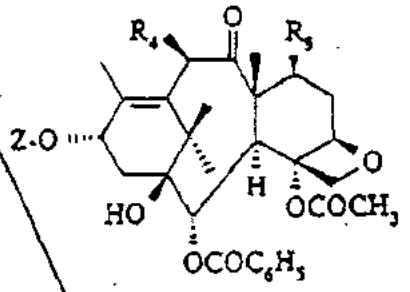
with a compound of the formula (XV):

$$R'_5 - X_2$$

wherein R'_5 represents a radical such that R'_5-O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1

to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and X_2 represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

wherein Z is hydrogen, R_4 is as defined above, and R_5 is identical to R'_5 as defined above.

27. A method comprising the step of reacting a product of the formula (XV):

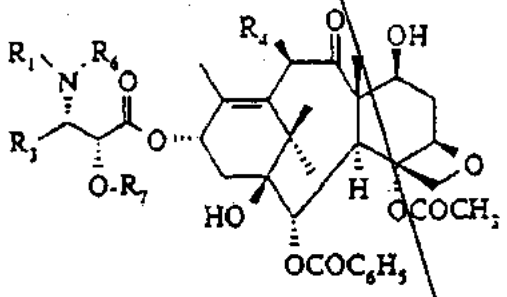
$$R'_5 - X_2$$

wherein R'_5 represents a radical such that R'_5-O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a

carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and X_2 represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, trifluoromethyl radicals, a thenoyl radical, a furoyl radical, and a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl

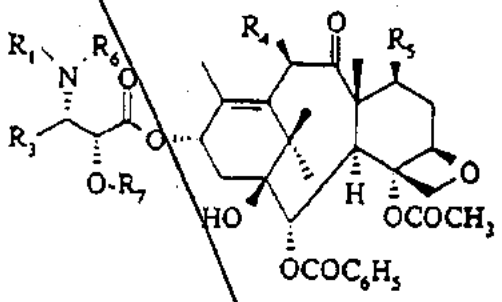
portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

to form a compound of the formula (V):

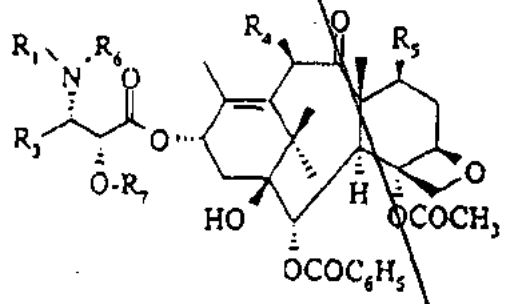


(V)

wherein R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and R_1, R_3, R_4, R_6, and R_7 are as ~~defined above.~~

28. A method comprising the step of replacing with hydrogen atom(s) group(s) R_6 and R_7 in a compound of the formula (V):



(V)

wherein:

R_1 represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, trifluoromethyl radicals, a thenoyl radical, a furoyl radical, and a radical R_2-O-CO- in which R_2 represents:

- an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical

containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

- a 5-membered aromatic heterocyclic radical,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms.

optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl

and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

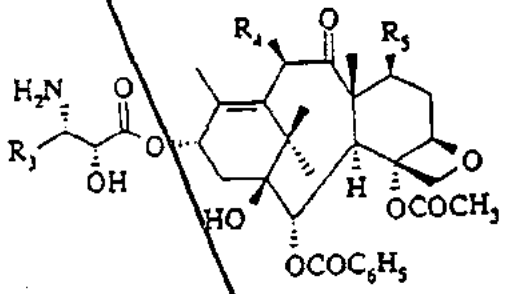
R_5 represents an alkoxy radical containing 1 to 6 carbon atoms in an

unbranched or branched chain optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and an N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms

or, both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, and

either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, where appropriate in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein R_3, R_4, and R_5 are as defined above.

19 20 29. A process according to claim 15, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

20 21 30. A process according to claim 15, wherein said trihalomethyl radical is trichloromethyl.

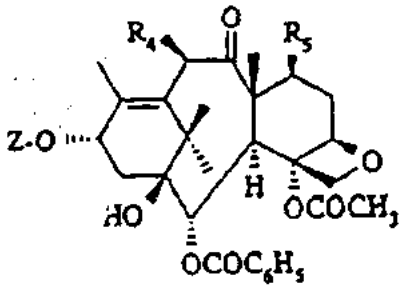
21 22 31. A process according to claim 15, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

Add B6
add
Cl

107

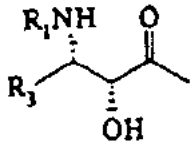
ABSTRACT

New taxoids of general formula (I):



(I)

their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):



(II)

display noteworthy antitumour and antileukaemic properties.

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/622,011	03/26/96	106	1108

APPLICANT

HERVE BOUCHARD, IVRY-SUR-SEINE, FRANCE; JEAN-DOMINIQUE BOURZAT, VINCENNES, FRANCE; ALAIN COMMERCON, VITRY-SUR-SEINE, FRANCE.

CONTINUING DATA********
VERIFIED

_____

FOREIGN/PCT APPLICATIONS********

VERIFIED	FRANCE	95 03545	03/27/95
	FRANCE	95 15381	12/22/95
_____	UNITED STATES	60/010144	01/17/96

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
FRX	0	31	9	$1,590.00	3806.0367-00

ADDRESS

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AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

TITLE

NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1995

Application or Docket Number: 6 22011

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
FOR		
BASIC FEE		
TOTAL CLAIMS	31 minus 20 =	* 11
INDEPENDENT CLAIMS	9 minus 3 =	* 6
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
	375.00	OR		750.00
x$11=		OR	x$22=	242
x39=		OR	x78=	468
+125=		OR	+250=	
TOTAL		OR	TOTAL	1460

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 35	Minus	** 31	= 4
Independent	* 12	Minus	*** 9	= 3
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	88
x39=		OR	x78=	234 6
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 21	Minus	** 35	= —
Independent	* 10	Minus	*** 12	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 29	Minus	** 31	=
Independent	* 10	Minus	*** 10	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

RÉPUBLIQUE FRANÇAISE

96/623011

INPI
INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

BREVET D'INVENTION

CERTIFICAT D'UTILITÉ - CERTIFICAT D'ADDITION

COPIE OFFICIELLE

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Fait à Paris, le 07 FEV. 1996

Pour le Directeur général de l'Institut
national de la propriété industrielle
Le Chef de Division

Yves CAMPENON

INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE
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INPI — INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

cerfa N° 55 - 1222

REQUETE

EN DÉLIVRANCE D'UN TITRE DE PROPRIÉTÉ INDUSTRIELLE *

1.

a [X] BREVET D'INVENTION
b [ ] CERTIFICAT D'UTILITÉ
c [ ] DEMANDE DIVISIONNAIRE
d [ ] TRANSFORMATION D'UNE DEMANDE DE BREVET EUROPÉEN

Pour c et d, précisez : Nature, N° et date de la demande initiale

2 OPTIONS OBLIGATOIRES au moment du dépôt (sauf pour le certificat d'utilité)

LE DEMANDEUR REQUIERT L'ÉTABLISSEMENT DIFFÉRÉ DU RAPPORT DE RECHERCHE * — [ ] OUI [X] NON

SI L'OPTION CHOISIE EST NON ET SI LE DEMANDEUR EST UNE PERSONNE PHYSIQUE IL REQUIERT LE PAIEMENT ÉCHELONNÉ DE LA REDEVANCE DE RAPPORT DE RECHERCHE — [ ] OUI [X] NON

NATURE | NUMÉRO | DATE DE LA DEMANDE INITIALE

DATE DE REMISE DES PIÈCES: 22 DEC 1995

N° D'ENREGISTREMENT NATIONAL: 95 15381

DATE DE DÉPÔT: 22 DEC. 1995

CODE POSTAL DU LIEU DE DÉPÔT:

3 NOM ET ADRESSE DU DEMANDEUR OU DU MANDATAIRE À QUI TOUTE LA CORRESPONDANCE DOIT ÊTRE ADRESSÉE

RHONE-POULENC RORER S.A.
Direction Brevets
20 avenue Raymond Aron
92165 ANTONY CEDEX

4 NUMÉRO DU POUVOIR PERMANENT: ler janvier 1994

5 RÉFÉRENCE DU CORRESPONDANT: ST 95069

6 TÉLÉPHONE DU CORRESPONDANT: (1) 40 91 70 29

7 TITRE DE L'INVENTION

PROCEDE DE PREPARATION DE TAXOIDES

8 DEMANDEUR(S) : Nom et Prénoms (souligner le nom patronymique) ou dénomination et forme juridique

N° SIREN: 3 0 4 4 6 3 2 8 4

RHONE-POULENC RORER S.A.

9 ADRESSE(S) COMPLÈTE(S)

20 avenue Raymond Aron
92160 ANTONY

PAYS: FRANCE

10 NATIONALITÉ(S): Française

REDEVANCES VERSÉES

[X] DE DÉPÔT
[X] DE RAPPORT DE RECHERCHE
[ ] DE REVENDICATION DE PRIORITÉ
[ ] DE REVENDICATION (à partir de la 11e)

11 INVENTEUR(S)

LE DEMANDEUR EST L'UNIQUE INVENTEUR * — [ ] OUI

Si la réponse est non voir notice explicative — [X] NON

12 SI LE DEMANDEUR EST UNE PERSONNE PHYSIQUE NON IMPOSABLE, IL REQUIERT* OU A REQUIS LA RÉDUCTION DES REDEVANCES* — [ ] OUI [X] NON

13 DÉCLARATION DE PRIORITÉ OU REQUÊTE DU BÉNÉFICE DE LA DATE DE DÉPÔT D'UNE DEMANDE ANTÉRIEURE

PAYS D'ORIGINE	DATE DE DÉPÔT	NUMÉRO

14 [ ] DIVISIONS ANTÉRIEURES À LA PRÉSENTE DEMANDE — N° | N° | N° | N°

15 RHONE-POULENC RORER S.A.
Fondé de Pouvoir

Jacques PILARD

SIGNATURE DU PRÉPOSÉ À LA RÉCEPTION

SIGNATURE APRÈS ENREGISTREMENT DE LA DEMANDE À L'INPI

BA 5402/200993

* Cocher la case choisie

LES ENCADRÉS GRAS SONT RÉSERVÉS À L'ADMINISTRATION

INPI
INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

BREVET D'INVENTION, CERTIFICAT D'UTILITE

DÉSIGNATION DE L'INVENTEUR
(si le demandeur n'est pas l'inventeur ou l'unique inventeur)

DIVISION ADMINISTRATIVE DES BREVETS
26bis, rue de Saint-Pétersbourg
75800 Paris Cédex 08
Tél. : (1) 42 94 52 52 - Télécopie : (1) 42 93 59 30

N° D'ENREGISTREMENT NATIONAL

9516381

ST 95069

TITRE DE L'INVENTION : PROCEDE DE PREPARATION DE TAXOIDES

LE (S) SOUSSIGNÉ (S)

RHONE-POULENC RORER S.A.
20 avenue Raymond Aron
92160 ANTONY

DÉSIGNE (NT) EN TANT QU'INVENTEUR (S) (indiquer nom, prénoms, adresse et souligner le nom patronymique) :

BOUCHARD Hervé - 7 allée de la Prévôté, 94320 THIAIS

BOURZAT Jean-Dominique - 36 boulevard de la Libération, 94300 VINCENNES

COMMERCON Alain - 1 bis rue Charles Floquet, 94400 VITRY SUR SEINE

NOTA : A titre exceptionnel, le nom de l'inventeur peut être suivi de celui de la société à laquelle il appartient (société d'appartenance) lorsque celle-ci est différente de la société déposante ou titulaire.

Date et signature (s) du (des) demandeur (s) ou du mandataire

Antony, le 21 décembre 1995

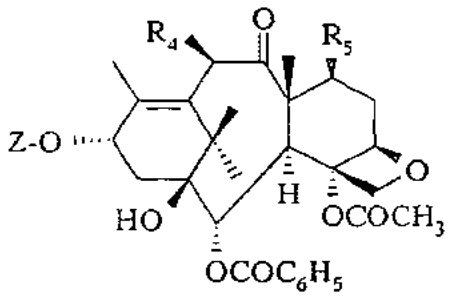
RHONE-POULENC RORER S.A.
Fondé de Pouvoir

Jacques PILARD

BA 113/270195

PRODEDE DE PREPARATION DE TAXOIDES

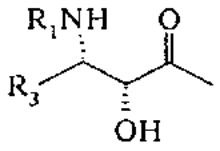
La présente invention concerne un procédé de préparation de taxoïdes de formule générale :



(I)

dans laquelle

Z représente un atome d'hydrogène ou un radical de formule générale :



(II)

dans laquelle :

R_1 représente un radical benzoyle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone ou trifluorométhyle, thénoyle ou furoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4

atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, phényle (éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone), cyano, carboxy ou alcoxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,

- un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone ou un radical hétérocyclique aromatique à 5 chaînons choisi de préférence parmi les radicaux furyle et thiényle,

- ou un radical hétérocyclyle saturé contenant 4 à 6 atomes de carbone éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

R_3 représente un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle droit ou ramifié contenant 2 à 8 atomes de carbone, alcynyle droit ou ramifié contenant 2 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles, alcényles, alcynyles, aryles, aralcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluorométhyle, ou un hétérocycle aromatique ayant 5 chaînons et contenant un ou plusieurs hétéroatomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre et éventuellement substitué par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles, aryles, amino, alcoylamino, dialcoylamino, alcoxycarbonylamino, acyle, arylcarbonyle, cyano, carboxy, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle ou alcoxycarbonyle, étant entendu que, dans les substituants des radicaux phényle, α- ou β-naphtyle et hétérocyclyles aromatiques, les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone et que les radicaux alcényles et alcynyles

contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles,

R_4 représente un atome d'hydrogène ou un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcényloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynyloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, alcanoyloxy dont la partie alcanoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcénoyloxy dont la partie alcénoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynoyloxy dont la partie alcynoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoxyacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoylthioacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoyloxycarbonyloxy dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, ou bien R_4 représente un radical benzoyloxy ou hétérocyclylcarbonyloxy dans lequel la partie hétérocyclique représente un hétérocycle aromatique à 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi les atomes d'oxygène, de soufre ou d'azote,

R_5 représente un radical alcoxy contenant 1 à 6 atomes de carbone en chaîne droite ou ramifiée.

De préférence les radicaux aryles pouvant être représentés par R_3 sont des radicaux phényles ou α- ou β-naphtyles éventuellement substitués par un ou plusieurs

atomes ou radicaux choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles, alcényles, alcynyles, aryles, arylalcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluoro-méthyle, étant entendu que les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone, que les radicaux alcényles et alcynyles contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles.

De préférence les radicaux hétérocycliques pouvant être représentés par R_3 sont des radicaux hétérocycliques aromatiques ayant 5 chaînons et contenant un ou plusieurs atomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre, éventuellement substitués par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles contenant 1 à 4 atomes de carbone, aryles contenant 6 à 10 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone, aryloxy contenant 6 à 10 atomes de carbone, amino, alcoylamino contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, acylamino dont la partie acyle contient 1 à 4 atomes de carbone, alcoxycarbonylamino contenant 1 à 4 atomes de carbone, acyle contenant 1 à 4 atomes de carbone, arylcarbonyle dont la partie aryle contient 6 à 10 atomes de carbone, cyano, carboxy, carbamoyle, alcoylcarbamoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou alcoxycarbonyle dont la partie alcoxy contient 1 à 4 atomes de carbone.

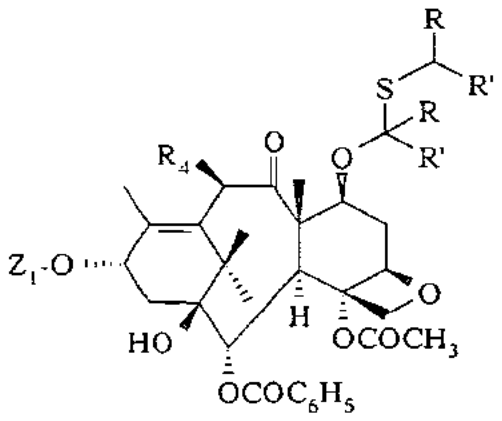
De préférence, R_4 représente un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone, alcanoyloxy contenant 1 à 6 atomes de carbone ou un radical alcoxyacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone, et R_5 représente un radical alcoxy droit ou ramifié contenant 1 à 6 atomes de carbone.

Plus particulièrement, la présente invention concerne un procédé de préparation des produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un

radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical alcoyle contenant 1 à 6 atomes de carbone, alcényle contenant 2 à 6 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents choisis parmi les atomes d'halogène (fluor, chlore) et les radicaux alcoyles (méthyle), alcoxy (méthoxy), dialcoylamino (diméthylamino), acylamino (acétylamino), alcoxycarbonylamino (tert-butoxycarbonylamino) ou trifluorométhyle ou un radical furyle-2 ou -3, thiényle-2 ou -3 ou thiazolyle-2, -4 ou -5, R_4 représente un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone ou un radical alcanoyloxy contenant 1 à 6 atomes de carbone et R_5 représente un radical alcoyloxy droit ou ramifié contenant 1 à 6 atomes de carbone.

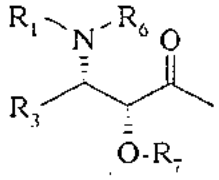
Plus particulièrement encore, la présente invention concerne un procédé de préparation des produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical isobutyle, isobutényle, butényle, cyclohexyle, phényle, furyle-2, furyle-3, thiényle-2, thiényle-3, thiazolyle-2, thiazolyle-4 ou thiazolyle-5, R_4 représente un radical hydroxy, méthoxy, acétoxy ou méthoxyacétoxy et R_5 représente un radical méthoxy.

Selon l'invention, les produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène ou un radical de formule générale (II) peuvent être obtenus par action de nickel de Raney activé en présence d'un alcool aliphatique contenant 1 à 3 atomes de carbone sur un produit de formule générale :



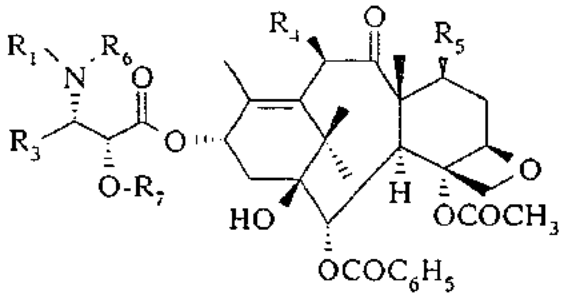
(III)

dans laquelle Z_1 représente un atome d'hydrogène ou un radical de formule générale :



(IV)

dans laquelle R_1 et R_3 sont définis comme précédemment et, ou bien, R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, et, ou bien, R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons, R_4 est défini comme précédemment, et R et R' représente un atome d'hydrogène ou un radical alcoyle contenant 1 à 6 atomes de carbone, pour obtenir un produit de formule générale :



(V)

suivi, lorsque Z_1 représente un radical de formule générale (IV), du remplacement des groupements protecteurs représentés par R_6 et/ou R_6 et R_7 par des atomes d'hydrogène.

Généralement, l'action du nickel de Raney activé en présence de l'alcool aliphatique est effectuée à une température comprise entre -10 et 20°C.

De préférence, R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy ou bien R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons.

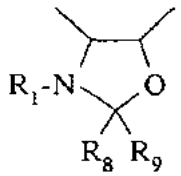
Lorsque R_6 représente un atome d'hydrogène, R_7 représente de préférence un radical méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle, triméthylsilyle, triéthylsilyle, β-triméthylsilyléthoxyméthyle, benzyloxycarbonyle ou tétrahydropyrannyle.

Lorsque R_6 et R_7 forment ensemble un hétérocycle, celui-ci est de préférence un cycle oxazolidine éventuellement mono-substitué ou gem-disubstitué en position 2.

Le remplacement des groupements protecteurs R_7 et/ou R_6 et R_7 par des atomes d'hydrogène peut être effectué, selon leur nature de la manière suivante :

1) lorsque R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, le remplacement des groupements protecteurs par des atomes d'hydrogène s'effectue au moyen d'un acide minéral (acide chlorhydrique, acide sulfurique, acide fluorhydrique) ou organique (acide acétique, acide méthanesulfonique, acide trifluorométhanesulfonique, acide p.toluènesulfonique) utilisé seul ou en mélange en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés, les hydrocarbures aromatiques ou les nitriles à une température comprise entre -10 et 60°C,

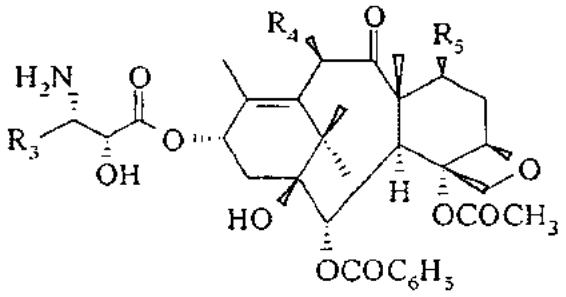
2) lorsque R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons et plus particulièrement un cycle oxazolidine de formule générale :



(VI)

dans laquelle R_1 est défini comme précédemment, R_8 et R_9, identiques ou différents, représentent un atome d'hydrogène ou un radical alcoyle contenant 1 à 4 atomes de carbone, ou un radical aralcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone et la partie aryle représente, de préférence, un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou un radical aryle représentant, de préférence un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou bien R_8 représente un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical trihalométhyle tel que trichlorométhyle ou un radical phényle substitué par un radical trihalométhyle tel que trichlorométhyle et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble avec l'atome de carbone auquel ils sont liés un cycle ayant 4 à 7 chaînons, le remplacement du groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène peut être effectué, selon les significations de R_1, R_8 et R_9, de la manière suivante :

a) lorsque R_1 représente un radical tert-butoxycarbonyle, R_8 et R_9, identiques ou différents, représentent un radical alcoyle ou un radical aralcoyle (benzyle) ou aryle (phényle), ou bien R_8 représente un radical trihalométhyle ou un radical phényle substitué par un radical trihalométhyle, et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble un cycle ayant de 4 à 7 chaînons, le traitement de l'ester de formule générale (V) par un acide minéral ou organique éventuellement dans un solvant organique tel qu'un alcool conduit au produit de formule générale :



(VII)

dans laquelle R_3, R_4 et R_5 sont définis comme précédemment, qui est acylé au moyen de chlorure de benzoyle dans lequel le noyau phényle est éventuellement substitué, de chlorure de thénoyle, de chlorure de furoyle ou d'un produit de formule générale :

R_2-O-CO-X (VIII)

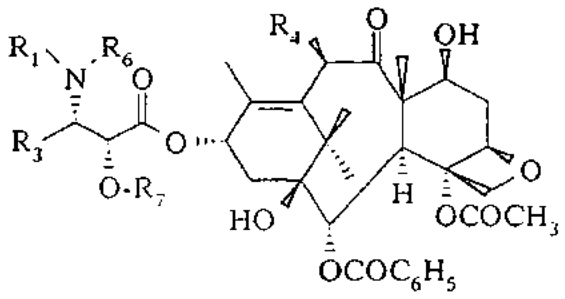
dans laquelle R_2 est défini comme précédemment et X représente un atome d'halogène (fluor, chlore) ou un reste -O-R_2 ou -O-CO-O-R_2, pour obtenir un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II).

De préférence, le produit de formule générale (V) est traité par l'acide formique à une température voisine de 20°C pour fournir le produit de formule générale (VII).

De préférence, l'acylation du produit de formule générale (VII) au moyen d'un chlorure de benzoyle dans lequel le radical phényle est éventuellement substitué, de chlorure de thénoyle ou de chlorure de furoyle ou d'un produit de formule générale (VIII) est effectuée dans un solvant organique inerte choisi parmi les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle et les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane en présence d'une base minérale telle que le bicarbonate de sodium ou organique telle que la triéthylamine. La réaction est effectuée à une température comprise entre 0 et 50°C, de préférence voisine de 20°C.

b) lorsque R_1 représente un radical benzoyle éventuellement substitué, thénoyle ou furoyle ou un radical R_2O-CO- dans lequel R_2 est défini comme précédemment, R_8 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone et R_9 représente un atome d'hydrogène, le remplacement du groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène s'effectue en présence d'un acide minéral (acide chlorhydrique, acide sulfurique) ou organique (acide acétique, acide méthanesulfonique, acide trifluoro-méthanesulfonique, acide p.toluènesulfonique) utilisé seul ou en mélange en quantité stoechiométrique ou catalytique, en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques à une température comprise entre -10 et 60°C, de préférence entre 15 et 30°C.

Selon l'invention, le produit de formule générale (III) dans laquelle Z_1 et R_4 sont définis comme précédemment peut être obtenu par action d'un dialcoylsulfoxyde dont chaque partie alcoyle contient 1 à 4 atomes de carbone sur un produit de formule générale :



(IX)

Généralement la réaction du dialcoylsulfoxyde, de préférence le diméthylsulfoxyde, sur le produit de formule générale (VIII) s'effectue en présence d'un mélange d'acide acétique et d'anhydride acétique à une température comprise entre 0 et 50°C, de préférence voisine de 25°C.

Les produits de formule générale (VIII) peuvent être obtenus dans les conditions décrites dans les demandes internationales PCT WO 94/11547, PCT WO 93/06093 ou PCT WO 95/11241.

Les produits de formule générale (I) obtenus par la mise en oeuvre du procédé selon l'invention peuvent être purifiés selon les méthodes connues telles que la cristallisation ou la chromatographie.

Les exemples suivants illustrent la présente invention.

EXEMPLE 1

800 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthoxy-7β oxo-9 taxène-11 yle-13α sont dissous dans 16 cm3 d'une solution éthanolique 0,1N d'acide chlorhydrique à 1 % d'eau. La solution ainsi obtenue est agitée pendant 5 heures à une température voisine de 20°C puis additionnée de 50 cm3 de dichlorométhane et lavée successivement par 3 fois 10 cm3 d'une solution aqueuse saturée d'hydrogénocarbonate de sodium, séchée sur

sulfate de magnésium, filtrée et concentrée à sec sous pression réduite (2,7 kPa) à 40°C. On obtient 640 mg d'une meringue blanche que l'on purifie par chromatographie sur gel de silice déposé sur plaques [(gel de 1 mm d'épaisseur ; plaques de 20 x 20 cm ; éluant : dichlorométhane-acétonitrile (80-20 en volumes)] par fractions de 80 mg (8 plaques). Après localisation aux rayons U.V. de la zone correspondant au produit cherché adsorbé, cette zone est grattée et la silice recueillie est lavée sur verre fritté par 10 fois 10 cm3 d'acétate d'éthyle. Les filtrats sont réunis et concentrés à sec sous pression réduite (0,27 kPa) à 20°C. On obtient 360 mg d'une meringue blanche que l'on purifie selon la même technique [(4 plaques : 20 x 20 x 1 mm ; éluant : dichlorométhane-méthanol (95-5 en volumes)]. On obtient ainsi 260 mg de tert-butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche dont les caractéristiques sont les suivantes :

- pouvoir rotatoire : $[\alpha]^{D}_{20}$ = - 52 (c = 0,5 ; méthanol).
- spectre de R.M.N. ^{1}H (400 MHz ; $CDCl_3$; δ en ppm ; constantes de couplage J en Hz) : 1,22 (s, 3H : -C$\underline{H}_3$) ; 1,25 (s, 3H : -C$\underline{H}_3$) ; 1,35 (s, 9H : -C(C$\underline{H}_3$)$_3$) ; 1,73 (s, 3H : -C$\underline{H}_3$) ; 1,80 et 2,75 (2 mts, 1H chacun : -C$\underline{H}_2$- 6) ; 1,92 (s, 3H : -C$\underline{H}_3$) ; 2,24 et 2,39 (s, 3H chacun : -COC$\underline{H}_3$) ; 2,30 (d, J = 9, 2H : -C$\underline{H}_2$- 14) ; 3,36 (s, 3H : -OC$\underline{H}_3$) ; 3,42 (d, J = 5, 1H : -O$\underline{H}$ 2') ; 3,85 (d, J = 7, 1H : -$\underline{H}$ 3) ; 3,88 (dd, J = 11 et 7, 1H : -$\underline{H}$ 7) ; 4,18 et 4,32 (2 d, J = 8,5, 1H chacun : -C$\underline{H}_2$- 20) ; 4,65 (mt, 1H : -$\underline{H}$ 2') ; 4,97 (d large, J = 10 Hz, 1H : $\underline{H}$ 5) ; 5,28 (d large, J = 10, 1H : -$\underline{H}$ 3') ; 5,42 (d, J = 10, 1H : -CON$\underline{H}$-) ; 5,68 (d, J = 7, 1H : -$\underline{H}$ 2) ; 6,20 (t large, J = 9, 1H : -$\underline{H}$ 13) ; 6,43 (s, 1H : -$\underline{H}$ 10) ; de 7,30 à 7,45 (mt, 5H : -C$_6\underline{H}_5$ 3') ; 7,51 [(t, J = 7,5, 2H : -OCOC$_6$H$_5$(-$\underline{H}$ 3 et $\underline{H}$ 5)] ; 7,63 [(t, J = 7,5, 1H : -OCOC$_6$H$_5$(-$\underline{H}$ 4)] ; 8,12 [(d, J = 7,5, 2H : -OCOC$_6$H$_5$(-$\underline{H}$ 2 et $\underline{H}$ 6)].

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthoxy-7β oxo-9 taxène-11 yle-13α peut être préparé de la manière suivante :

A une solution de 1,027 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-

4α,10β époxy-5β,20 hydroxy-1β méthylthiométhoxy-7β oxo-9 taxène-11 yle-13α dans 100 cm3 d'éthanol anhydre, maintenue sous atmosphère d'argon et sous agitation, on ajoute, à une température voisine de 20°C, 100 cm3 d'une suspension éthanolique de nickel activé. (cette suspension est obtenue à partir de 80 cm3 de la suspension aqueuse commerciale à environ 50 % par lavage successifs, jusqu'à un pH voisin de 7, par 15 fois 100 cm3 d'eau distillée et par 5 fois 100 cm3 d'éthanol). Le mélange réactionnel est maintenu sous agitation pendant 48 heures à une température voisine de 20°C puis filtré sur verre fritté. Le verre fritté est lavé par 5 fois 50 cm3 d'éthanol, les filtrats sont réunis et concentrés à sec sous pression réduite (2,7 kPa) à 40°C. On obtient 900 mg d'une meringue blanche que l'on purifie par chromatographie sur 50 g de silice (0,063-0,2 mm) contenus dans une colonne de 2,5 cm de diamètre [éluant : dichlorométhane-méthanol (98-2 en volumes)] en recueillant des fractions de 5 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (2,7 kPa) à 40°C. On obtient ainsi 810 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthylthiométhoxy-7β oxo-9 taxène-11 yle-13α peut être préparé de la manière suivante :

A une solution de 5 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 dihydroxy-1β,7β oxo-9 taxène-11 yle-13α dans 165 cm3 de diméthylsulfoxyde, maintenue sous atmosphère d'argon et sous agitation, on ajoute, à une température voisine de 20°C, 3,5 cm3 d'acide acétique et 12 cm3 d'anhydride acétique. Le mélange réactionnel est maintenu sous agitation pendant 8 jours à une température voisine de 20°C puis versé dans un mélange de 550 cm3 d'eau distillée et 250 cm3 de dichlorométhane. On additionne ensuite sous bonne agitation 30 cm3 d'une solution aqueuse saturée de carbonate de potassium jusqu'à un pH voisin de 7.

Après 10 minutes d'agitation, la phase organique est séparée par décantation et réextraite par 2 fois 250 cm3 de dichlorométhane. Les phases organiques sont réunies, lavées par 250 cm3 d'eau distillée, séchées sur sulfate de magnésium, filtrées et concentrées à sec sous pression réduite (2,7 kPa) à 40°C. On obtient 11,2 g d'une huile jaune pâle que l'on purifie par chromatographie sur 200 g de silice (0,063-0,4 mm) contenus dans une colonne de 3 cm de diamètre [éluant : dichlorométhane-méthanol (99-1 en volumes)] en recueillant des fractions de 50 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (2,7 kPa) à 40°C. On obtient ainsi 3,3 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 hydroxy-1β méthylthiométhoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) de benzoyloxy-2α diacétoxy-4α,10β époxy-5β,20 dihydroxy-1β,7β oxo-9 taxène-11 yle-13α peut être préparée de la manière suivante :

A une solution de 25 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidinecarboxylate-5-(2R,4S,5R) de diacétoxy-4α,10β benzoyloxy-2α époxy-5β,20 triéthylsilyloxy-7β oxo-9 hydroxy-1β taxène-11 yle-13α dans 125 cm3 d'acétonitrile et 111 cm3 de pyridine, refroidie à 5°C, on ajoute, en 45 minutes, 103,6 g d'acide trifluoroacétique. On agite pendant 15 heures à 50°C. On ajoute à nouveau 28 cm3 de pyridine et 25,9 g d'acide trifluoroacétique et agite pendant 10 heures à 50°C. On ajoute encore une fois 28 cm3 de pyridine et 25,9 g d'acide trifluoroacétique et agite pendant 15 heures à 50°C. Le mélange réactionnel est refroidi à 20°C puis est versé dans 4 litres d'eau glacée. La suspension est filtrée. Le précipité est lavé par 10 fois 200 cm3 d'eau distillée, est séché à l'air puis lavé par 140 cm3 d'oxyde d'isopropyle, essoré et enfin lavé par 2 fois 46 cm3 d'oxyde d'isopropyle. On obtient ainsi, avec un rendement de 97 %, 21,7 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidinecarboxylate-5-(2R,4S,5R) de diacétoxy-4α,10β benzoyloxy-2α époxy-5β,20 dihydroxy-1β,7β oxo-9 taxène-11 yle-13α fondant à 178°C.

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-carboxylate-5-(2R,4S,5R) de diacétoxy-4α,10β benzoyloxy-2α époxy-5β,20 triéthylsilyloxy-7β oxo-9 hydroxy-1β taxène-11 yle-13α peut être préparé de la manière suivante :

A une solution de 147 g triéthylsilyl-7 baccatine III et de 100 g d'acide tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-carboxylique-5 dans 720 cm3 d'acétate d'éthyle refroidie à une température voisine de 5°C, on ajoute successivement 64,7 g de dicyclohexyl-1,3 carbodiimide et 5,6 g de diméthylamino-4 pyridine.

La suspension ainsi obtenue est agitée pendant 4 heures à 20°C puis filtrée. Le filtrat est lavé par 2 fois 500 cm3 d'une solution aqueuse semi-saturée d'hydrogénocarbonate de sodium, 2 fois 500 cm3 d'eau distillée et 2 fois 500 cm3 d'une solution aqueuse saturée de chlorure de sodium.

La phase organique est séchée sur sulfate de magnésium. Après filtration et concentration à sec sous pression réduite, le produit obtenu est cristallisé dans 750 cm3 de méthyl tert-butyléther, on obtient 126,9 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidinecarboxylate-5-(2R,4S,5R) de diacétoxy-4α,10β benzyloxy-2α époxy-5β,20 triéthylsilyloxy-7β oxo-9 hydroxy-1β taxène-11 yle-13α fondant à 174°C.

La triéthylsilyl-7 baccatine III peut être préparée de la manière suivante :

A une solution de 293,9 g de désacétyl-10 baccatine III dans 2,7 litres de pyridine, on ajoute, en 1 heure 20 minutes, 182 g de chlorure de triéthylsilyle. La solution obtenue est agitée pendant 40 heures à 5°C. On ajoute alors 360 g d'anhydride acétique en maintenant la température à 5°C. La suspension obtenue est agitée pendant 48 heures à 20°C puis versée sur 40 litres d'eau glacée. Le précipité obtenu est séparé par filtration puis lavé par 8 fois 2 litres d'eau et enfin dissous dans 3 litres d'acétate d'éthyle. La phase organique est séchée sur sulfate de magnésium. Après filtration et concentration sous pression réduite, le produit obtenu est cristallisé dans l'oxyde d'isopropyle. On obtient ainsi, avec un rendement de 77 %, la triéthylsilyl-7 baccatine III fondant à 254°C.

EXEMPLE 2

En opérant comme dans l'exemple 1, mais à partir de 430 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α, on obtient 164 mg de de tert-butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche dont les caractéristiques sont les suivantes :

- pouvoir rotatoire : $[\alpha]^{D}_{20}$ = - 48 (c = 0,5 ; méthanol)
- spectre de R.M.N. ^{1}H (300 MHz ; $CDCl_3$; δ en ppm ; constantes de couplage J en Hz) : 1,17 (s, 3H : -C<u>H</u>$_3$) ; 1,22 (s, 3H : -C<u>H</u>$_3$) ; 1,35 (s, 9H : -C(C<u>H</u>$_3$)$_3$; 1,75 (s, 3H : -C<u>H</u>$_3$) ; 1,80 et 2,75 (2 mts, 1H chacun : -C<u>H</u>$_2$- 6) ; 1,90 (s, 3H : -C<u>H</u>$_3$) ; 2,30 (d, J = 9, 2H : -C<u>H</u>$_2$- 14) ; 2,37 (s, 3H : -COC<u>H</u>$_3$) ; 3,35 et 3,55 (2 s, 3H chacun : -OC<u>H</u>$_3$) ; 3,40 (d, J = 5, 1H : -O<u>H</u> 2') ; 3,85 (d, J = 7, 1H : -<u>H</u> 3) ; 3,88 (dd, J = 11 et 7, 1H : -<u>H</u> 7) ; 4,17 et 4,32 (2 d, J = 8,5, 1H chacun : -C<u>H</u>$_2$- 20) ; 4,19 et 4,27 (2 d, J = 15, 1H chacun : -OCOC<u>H</u>$_2$OCH$_3$) ; 4,65 (mt, 1H : -<u>H</u> 2') ; 4,97 (d large, J = 10, 1H : -<u>H</u> 5) ; 5,25 (d large, J = 10, 1H : -<u>H</u> 3') ; 5,42 (d, J = 10, 1H : -CON<u>H</u> -) ; 5,66 (d, J = 7, 1H : -<u>H</u> 2) ; 6,18 (t large, J = 9, 1H : -<u>H</u> 13) ; 6,52 (s, 1H : -<u>H</u> 10) ; de 7,30 à 7,50 (mt, 5H : -C$_6$<u>H</u>$_5$ 3') ; 7,51 [(t, J = 7,5, 2H : -OCOC$_6$H$_5$(-<u>H</u> 3 et <u>H</u> 5)] ; 7,63 [(t, J = 7,5, 1H : -OCOC$_6$H$_5$(-<u>H</u> 4)] ; 8,12 (d, J = 7,5, 2H : -OCOC$_6$H$_5$(-<u>H</u> 2 et <u>H</u> 6)].

En opérant comme dans l'exemple 1, mais à partir de 529 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxyacétoxy-10β méthylthiométhoxy-7β oxo-9 taxène-11 yle-13α, on obtient 436 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

En opérant comme dans l'exemple 1, mais à partir de 5 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α, on obtient 3,01 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4 α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxyacétoxy-10β méthylthiométhoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α peut être préparé de la manière suivante :

A une solution de 20 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 triéthylsilyloxy-7β hydroxy-1β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α dans 200 cm3 de dichlorométhane anhydre, maintenue sous atmosphère d'argon et sous agitation, on ajoute, goutte à goutte, à une température voisine de 0°C, 220 cm3 du complexe triéthylamine- acide fluorhydrique (1-3 en moles). Le mélange réactionnel est ensuite réchauffé jusqu'à une température voisine de 20°C, maintenu pendant 3 heures à cette température et versé dans 4 litres d'une solution aqueuse saturée d'hydrogénocarbonate de sodium. Le pH du milieu réactionnel étant ainsi amené aux environs de 7. Après 10 minutes d'agitation, la phase organique est séparée par décantation et réextraite par 2 fois 100 cm3 de dichlorométhane. Les phases organiques sont réunies, lavées par 100 cm3 d'eau distillée, séchées sur sulfate de magnésium, filtrées et concentrées à sec sous pression réduite (2,7 kPa) à 40°C. On obtient ainsi 17,4 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 triéthylsilyloxy-7 β hydroxy-1β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α peut être préparé dans les conditions décrites dans la demande internationale PCT WO 95/11241.

EXEMPLE 3

En opérant comme dans l'exemple 1, mais à partir de 188 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α dihydroxy-1β,10β époxy-5β,20 méthoxy-7β oxo-9 taxène-11 yle-13α, on obtient 115 mg de de tert-butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) d'acétoxy-4α benzoyloxy-2α dihydroxy-1β ,10β époxy-5β,20 méthoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche dont les caractéristiques sont les suivantes :

- pouvoir rotatoire : $[\alpha]^{D}_{20}$ = - 43 (c = 0,5 ; méthanol)
- spectre de R.M.N. ^{1}H (300 MHz ; $CDCl_3$; δ en ppm ; constantes de couplage J en Hz) : 1,14 (s, 3H : -C$\underline{H}_3$) ; 1,24 (s, 3H : -C$\underline{H}_3$) ; 1,38 [s, 9H : -C(C$\underline{H}_3$)$_3$]; 1,66 (s, 1H : -O$\underline{H}$ 1) ; 1,79 (s, 3H : -C$\underline{H}_3$) ; 1,88 et 2,72 (2 mts, 1H chacun : -C$\underline{H}_2$- en 6) ; 1,88 (s, 3H : -C$\underline{H}_3$) ; 2,29 (mt, 2H : -C$\underline{H}_2$- en 14) ; 2,38 (s, 3H : -COC$\underline{H}_3$) ; 3,27 (s, 3H : -OC$\underline{H}_3$) ; 3,40 (d, J = 5,5, 1H : -O$\underline{H}$ en 2') ; 3,84 (dd, J = 11 et 6, 1H : -$\underline{H}$ en 7) ; 3,89 (d, J = 7, 1H : -$\underline{H}$ en 3) ; 4,19 et 4,32 (2 d, J = 8,5, 1H chacun : -C$\underline{H}_2$- en 20) ; 4,30 (d, J = 1 Hz, 1H : -O$\underline{H}$ en 10) ; 4,61 (mt, 1H : -$\underline{H}$ en 2') ; 4,97 (d large, J = 10, 1H : -$\underline{H}$ en 5) ; 5,15 (d, J = 1, 1H : -$\underline{H}$ en 10) ; 5,27 (d large, J = 10, 1H : -$\underline{H}$ en 3') ; 5,45 (d, J = 10, 1H : -CON$\underline{H}$-) ; 5,64 (d, J = 7, 1H : -$\underline{H}$ en 2) ; 6,20 (t large, J = 9, 1H : -$\underline{H}$ 13) ; de 7,30 à 7,50 (mt, 5H : -C$_6\underline{H}_5$ en 3') ; 7,52 [t, J = 7,5, 2H : -OCOC$_6$H$_5$ (-$\underline{H}$ en 3 et $\underline{H}$ en 5)] ; 7,63 [t, J = 7,5, 1H : -OCOC$_6$H$_5$(-$\underline{H}$ en 4)] ; 8,11 [d, J = 7,5, 2H : -OCOC$_6$H$_5$(-$\underline{H}$ en 2 et $\underline{H}$ en 6)].

Le tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α dihydroxy-1β,10β époxy-5β,20 méthoxy-7β oxo-9 taxène-11 yle-13α peut être préparé de la manière suivante :

A une solution de 150 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-7β méthoxyacétoxy-10β oxo-9 taxène-11 yle-13α dans 4 cm3 d'éthanol anhydre, maintenue sous atmosphère d'argon et sous agitation, on ajoute, goutte à goutte et à une température voisine de 20°C, 0,263 cm3 d'hydrazine mono hydratée. Le milieu réactionnel est maintenu sous agitation pendant 1 heure à une température voisine de 20°C puis versé dans un mélange de 100 cm3 d'acétate d'éthyle et de 50 cm3 d'eau distillée. La phase organique est séparée par décantation et réextraite par 2 fois 50 cm3 d'acétate d'éthyle. Les phases organiques sont réunies lavées par 50 cm3 d'eau distillée, séchées sur sulfate de magnésium, filtrées et concentrées à sec sous pression réduite (2,7 kPa) à 40°C. On obtient 180 mg d'une meringue blanche que l'on purifie par chromatographie sur gel de silice déposé sur plaques [(gel de 1mm d'épaisseur ; plaques de 20 x 20 cm) en éluant avec un mélange dichlorométhane-méthanol (90-10 en volumes)] et en recueillant des fractions de 90 mg (2 plaques). Après localisation aux rayons U.V. de la zone correspondant au produit cherché adsorbé, cette zone est grattée et la silice recueillie est lavée sur verre fritté par 10 fois 10 cm3 d'acétate d'éthyle. Les filtrats sont réunis et concentrés à sec sous pression réduite (2,7 kPa) à 40°C. On obtient ainsi 113 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α dihydroxy-1β,10β époxy-5β,20 méthoxy-7β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

EXEMPLE 4

En opérant comme dans l'exemple 1, mais à partir de 340 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α diméthoxy-7β,10β époxy-5β,20 hydroxy-1β oxo-9 taxène-11 yle-13α, on obtient 205 mg de tert-butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) d'acétoxy-4α benzoyloxy-2α diméthoxy-7β ,10β époxy-5β,20 hydroxy-1β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche dont les caractéristiques sont les suivantes :

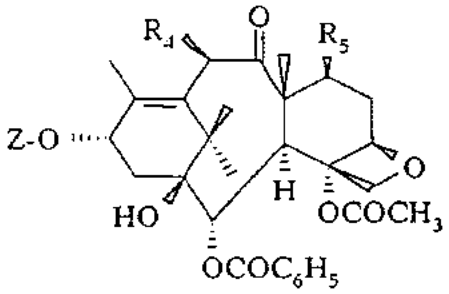
- pouvoir rotatoire : $[\alpha]^{\circ}_{20}$ = - 33 (c = 0,5 ; méthanol).

- spectre de R.M.N. ^1H (400 MHz ; $CDCl_3$; δ en ppm ; constantes de couplage J en Hz) : 1,23 (s, 3H : -C$\underline{H}_3$) ; 1,25 (s, 3H : -C$\underline{H}_3$) ; 1,39 [s, 9H : -C(C$\underline{H}_3$)$_3$] ; 1,70 (s, 1H : -O$\underline{H}$ 1) ; 1,75 (s, 3H : -C$\underline{H}_3$) ; 1,82 et 2,72 (2 mts, 1H chacun : -C$\underline{H}_2$ en 6) ; 1,91 (s, 3H : -C$\underline{H}_3$) ; 2,31 (AB limite, 2H : -C$\underline{H}_2$ en 14) ; 2,39 (s, 3H : -COC$\underline{H}_3$) ; 3,33 et 3,48 (2 s, 3H chacun : -OC$\underline{H}_3$) ; 3,48 (mt, 1H : O$\underline{H}$ en 2') ; 3,85 (d, J = 7z, 1H : -$\underline{H}$ en 3) ; ,88 (dd, J = 11 et 7, 1H : -$\underline{H}$ en 7) ; 4,20 et 4,33 (2 d, J = 8,5, 1H chacun : -C$\underline{H}_2$ en 20) ; 4,65 (mt, 1H : -$\underline{H}$ en 2') ; 4,83 (s, 1H : -$\underline{H}$ en 10) ; 5,00 (d large, J = 10, 1H : -$\underline{H}$ en 5) ; 5,30 (d large, J = 10, 1H : -$\underline{H}$ en 3') ; 5,47 (d, J = 10, 1H : -CON$\underline{H}$-) ; 5,66 (d, J = 7, 1H : -$\underline{H}$ en 2) ; 6,24 (t large, J = 9, 1H : -$\underline{H}$ en 13) ; de 7,30 à 7,50 (mt, 5H : -C$_6\underline{H}_5$ en 3') ; 7,52 [t, J = 7,5, 2H : -OCOC$_6$H$_5$(-$\underline{H}$ en 3 et $\underline{H}$ en 5)] ; 7,63 [t, J = 7,5, 1H : -OCOC$_6$H$_5$(-$\underline{H}$ en 4)] ; 8,12 [d, J = 7,5, 2H : -OCOC$_6$H$_5$(-$\underline{H}$ en 2 et $\underline{H}$ en 6)].

En opérant comme dans l'exemple 1, mais à partir de 1 g de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α bis(méthylthiométhoxy)-7β,10β époxy-5β,20 hydroxy-1β oxo-9 taxène-11 yle-13α, on obtient 350 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5-(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α diméthoxy-7β,10β époxy-5β,20 hydroxy-1β oxo-9 taxène-11 yle-13α sous forme d'une meringue blanche.

REVENDICATIONS

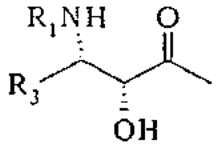
1 - Procédé de préparation de taxoïdes de formule générale :



(I)

dans laquelle

Z représente un atome d'hydrogène ou un radical de formule générale :



(II)

dans laquelle :

R_1 représente un radical benzoyle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone ou trifluorométhyle, thénoyle ou furoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle

contenant 4 à 6 atomes de carbone, phényle (éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone), cyano, carboxy ou alcoxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,

- un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone ou un radical hétérocyclique aromatique à 5 chaînons choisi de préférence parmi les radicaux furyle et thiényle,

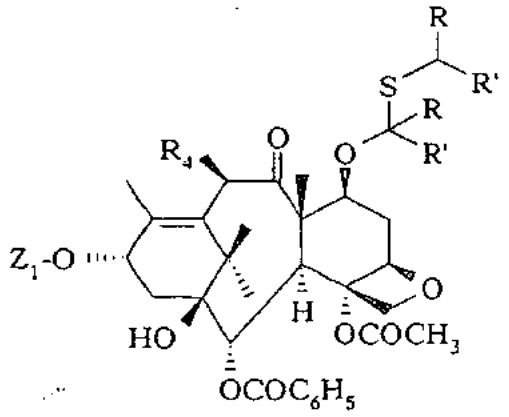
- ou un radical hétérocyclyle saturé contenant 4 à 6 atomes de carbone éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

R_3 représente un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle droit ou ramifié contenant 2 à 8 atomes de carbone, alcynyle droit ou ramifié contenant 2 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles, alcényles, alcynyles, aryles, aralcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluorométhyle, ou un hétérocycle aromatique ayant 5 chaînons et contenant un ou plusieurs hétéroatomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre et éventuellement substitué par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles, aryles, amino, alcoylamino, dialcoylamino, alcoxycarbonylamino, acyle, arylcarbonyle, cyano, carboxy, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle ou alcoxycarbonyle, étant entendu que, dans les substituants des radicaux phényle, α- ou β-naphtyle et hétérocyclyles aromatiques, les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone et que les radicaux alcényles et alcynyles

contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles,

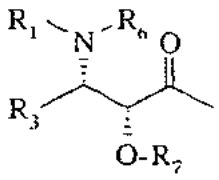
R_4 représente un atome d'hydrogène ou un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcényloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynyloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, alcanoyloxy dont la partie alcanoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcénoyloxy dont la partie alcénoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynoyloxy dont la partie alcynoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoxyacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoylthioacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoyloxycarbonyloxy dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, ou bien R_4 représente un radical benzoyloxy ou hétérocyclylcarbonyloxy dans lequel la partie hétérocyclique représente un hétérocycle aromatique à 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi les atomes d'oxygène, de soufre ou d'azote, et

R_5 représente un radical alcoxy contenant 1 à 6 atomes ce carbone en chaîne droite ou ramifiée, caractérisé en ce que l'on fait réagir du nickel Raney activé en présence d'un alcool aliphatique contenant 1 à 3 atomes de carbone sur un produit de formule générale :



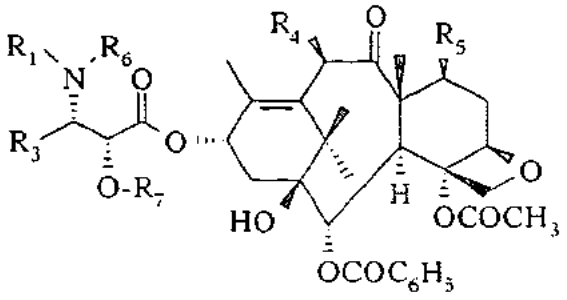
(III)

dans laquelle Z_1 représente un atome d'hydrogène ou un radical de formule générale :



(IV)

dans laquelle R_1 et R_3 sont définis comme précédemment et, ou bien, R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, et, ou bien, R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons, R_4 est défini comme précedemment, et R et R' représentent un atome d'hydrogène ou un radical alcoyle contenant 1 à 6 atomes de carbone, pour obtenir un produit de formule générale :



(V)

suivi, lorsque Z_1 représente un radical de formule générale (IV), du remplacement des groupements protecteurs représentés par R_6 et/ou R_6 et R_7 par des atomes d'hydrogène.

2 - Procédé de préparation selon la revendication 1 caractérisé en ce que l'on opére à une température comprise entre -10 et 20°C.

3 - Procédé selon la revendication 1a caractérisé en ce que lorsque Z_1 représente un radical de formule générale (IV), caractérisé en ce que l'on remplace les groupements protecteurs R_7 et/ou R_6 et R_7 par des atomes d'hydrogène en opérant, selon leur nature de la manière suivante :

1) lorsque R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, on remplace les groupements protecteurs par des atomes d'hydrogène au moyen d'un acide minéral ou organique utilisé seul ou en mélange en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés, les hydrocarbures aromatiques ou les nitriles à une température comprise entre -10 et 60°C,

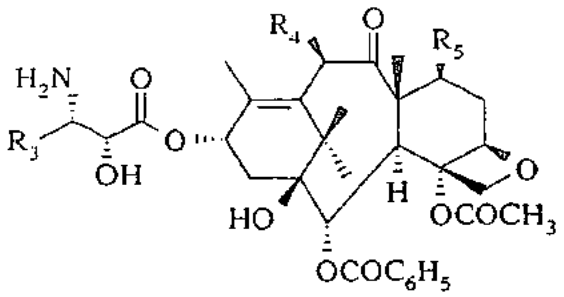
2) lorsque R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons de formule générale :

(VI)

dans laquelle R_1 est défini comme précédemment, R_8 et R_9, identiques ou différents, représentent un atome d'hydrogène ou un radical alcoyle contenant 1 à 4 atomes de carbone, ou un radical aralcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone et la partie aryle représente, de préférence, un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou un radical aryle représentant, de préférence un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou bien R_8 représente un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical trihalométhyle tel que trichlorométhyle ou un radical phényle substitué par un radical trihalométhyle tel que trichlorométhyle et R_9 représente un

atome d'hydrogène, ou bien R_8 et R_9 forment ensemble avec l'atome de carbone auquel ils sont liés un cycle ayant 4 à 7 chaînons, on remplace le groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène en opérant, selon les significations de R_1, R_8 et R_9, de la manière suivante :

a) lorsque R_1 représente un radical tert-butoxycarbonyle, R_8 et R_9, identiques ou différents, représentent un radical alcoyle ou un radical aralcoyle ou aryle, ou bien R_8 représente un radical trihalométhyle ou un radical phényle substitué par un radical trihalométhyle, et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble un cycle ayant de 4 à 7 chaînons, on traite l'ester de formule générale (V) par un acide minéral ou organique éventuellement dans un solvant organique tel qu'un alcool pour obtenir le produit de formule générale :



(VII)

dans laquelle R_3, R_4 et R_5 sont définis comme précédemment, que l'on acyle au moyen de chlorure de benzoyle dans lequel le noyau phényle est éventuellement substitué, de chlorure de thénoyle, de chlorure de furoyle ou d'un produit de formule générale :

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

dans laquelle R_2 est défini comme précédemment et X représente un atome d'halogène ou un reste $-O-R_2$ ou $-O-CO-O-R_2$, pour obtenir un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II),

b) lorsque R_1 représente un radical benzoyle éventuellement substitué, thénoyle ou furoyle ou un radical R_2O-CO- dans lequel R_2 est défini comme précédemment, R_8 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone et R_9 représente un atome d'hydrogène, on

remplace le groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène au moye d'un acide minéral ou organique utilisé seul ou en mélange en quantité stoechiométrique ou catalytique, en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques à une température comprise entre -10 et 60°C, de préférence entre 15 et 30°C.

4 - Procédé selon l'une des revendications 1, 2 ou 3 pour la préparation d'un produit de formule générale (I) pour lequel Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical alcoyle contenant 1 à 6 atomes de carbone, alcényle contenant 2 à 6 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents choisis parmi les atomes d'halogène et les radicaux alcoyles, alcoxy, dialcoylamino, acylamino, alcoxycarbonylamino ou trifluorométhyle ou un radical furyle-2 ou -3, thiényle-2 ou -3 ou thiazolyle-2, -4 ou -5, R_4 représente un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone ou un radical alcanoyloxy contenant 1 à 6 atomes de carbone et R_5 représente un radical alcoyloxy droit ou ramifié contenant 1 à 6 atomes de carbone.

5 - Procédé selon l'une des revendications 1, 2 ou 3 pour la préparation d'un produit de formule générale (I) pour lequel Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical isobutyle, isobutényle, butényle, cyclohexyle, phényle, furyle-2, furyle-3, thiényle-2, thiényle-3, thiazolyle-2, thiazolyle-4 ou thiazolyle-5, R_4 représente un radical hydroxy, méthoxy, acétoxy ou méthoxyacétoxy et R_5 représente un radical méthoxy.

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96/622011

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Fait à Paris, le 09 FEV. 1996

Pour le Directeur général de l'Institut national de la propriété industrielle
Le Chef de Division

Yves CAMPENON

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ETABLISSEMENT PUBLIC NATIONAL CREE PAR LA LOI N° 51-444 DU 19 AVRIL 1951

INPI INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

cerfa N° 55 - 1222

REQUETE

EN DÉLIVRANCE D'UN TITRE DE PROPRIÉTÉ INDUSTRIELLE *

1

a [X] BREVET D'INVENTION
b [ ] CERTIFICAT D'UTILITE
c [ ] DEMANDE DIVISIONNAIRE
d [ ] TRANSFORMATION D'UNE DEMANDE DE BREVET EUROPEEN

Pour c et d, précisez : Nature, N° et date de la demande initiale

2 OPTIONS OBLIGATOIRES au moment du dépôt (sauf pour le certificat d'utilité)

LE DEMANDEUR REQUIERT L'ÉTABLISSEMENT DIFFERE OU RAPPORT DE RECHERCHE * [ ] OUI [X] NON

SI L'OPTION CHOISIE EST NON ET SI LE DEMANDEUR EST UNE PERSONNE PHYSIQUE IL REQUIERT LE PAIEMENT ÉCHELONNE DE LA REDEVANCE DE RAPPORT DE RECHERCHE [ ] OUI [X] NON

NATURE NUMÉRO DATE DE LA DEMANDE INITIALE

DATE DE REMISE DES PIÈCES
27 MAR 1995

N° D'ENREGISTREMENT NATIONAL
95 03545

DATE DE DÉPÔT
27 MARS 1995

CODE POSTAL DU LIEU DE DÉPÔT *

3 NOM ET ADRESSE DU DEMANDEUR OU DU MANDATAIRE A QUI TOUTE LA CORRESPONDANCE DOIT ETRE ADRESSEE

RHONE-POULENC RORER S.A.
Direction Brevets
20 avenue Raymond Aron
92165 ANTONY CEDEX

4 NUMÉRO DU POUVOIR PERMANENT
15 janvier 1991

5 RÉFÉRENCE DU CORRESPONDANT
ST 95019

6 TÉLÉPHONE DU CORRESPONDANT
(1) 40 91 70 29

7 TITRE DE L'INVENTION

NOUVEAUX TAXOIDES, LEUR PREPARATION ET LES COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT

8 DEMANDEUR(S) : Nom et Prénoms (souligner le nom patronymique) ou dénomination et forme juridique

N° SIREN
3 0 4 4 6 3 2 8 4

RHONE-POULENC RORER S.A.

9 ADRESSE(S) COMPLÈTE(S)

20 avenue Raymond Aron
92160 ANTONY

PAYS
FRANCE

10 NATIONALITÉ(S)
Française

REDEVANCES VERSÉES
[X] DE DÉPÔT
[X] DE RAPPORT DE RECHERCHE
[ ] DE REVENDICATION DE PRIORITE
[X] DE REVENDICATION (à partir de la 11e)

11 INVENTEUR(S)
LE DEMANDEUR EST L'UNIQUE INVENTEUR * [ ] OUI
Si la réponse est non voir notice explicative [X] NON

12 SI LE DEMANDEUR EST UNE PERSONNE PHYSIQUE NON IMPOSABLE, IL REQUIERT * OU A REQUIS LA RÉDUCTION DES REDEVANCES * [ ] OUI [X] NON

13 DÉCLARATION DE PRIORITÉ OU REQUÊTE DU BÉNÉFICE DE LA DATE DE DÉPÔT D'UNE DEMANDE ANTÉRIEURE

PAYS D'ORIGINE	DATE DE DÉPÔT	NUMÉRO

14 [ ] DIVISIONS ANTÉRIEURES À LA PRÉSENTE DEMANDE N° N° N° N°

15 RHONE-POULENC RORER S.A.
NOM ET QUALITÉ DU SIGNATAIRE N° D'INSCRIPTION
Fondé de Pouvoir
Jacques PILARD

SIGNATURE DU PREPOSE A LA RECEPTION

SIGNATURE APRES ENREGISTREMENT DE LA DEMANDE A L'INPI

NEPTUNE GENERICS EX. 01120

RA 540/220993

* Cocher la case choisie

LES ENCADRÉS GRAS SONT RÉSERVÉS A L'ADMINISTRATION

INPI
INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE
26bis, rue de Saint-Pétersbourg 75800 Paris Cédex 08 Tél. : (1) 42 94 52 52 - Télécopie : (1) 42 93 59 30

Division Administrative des Brevets

DÉSIGNATION DE L'INVENTEUR

(si le demandeur n'est pas l'inventeur ou l'unique inventeur)

N° d'enregistrement national

95 03545

ST 95019

Titre de l'invention : NOUVEAUX TAXOIDES, LEUR PREPARATION ET LES COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT

Le (s) soussigné (s)

RHONE-POULENC RORER S.A.
20 avenue Raymond Aron
92160 ANTONY

désigne (nt) en tant qu'inventeur (s) *(indiquer nom, prénoms, adresse et souligner le nom patronymique)* :

BOUCHARD Hervé - 114 avenue Danielle Casanova, 94200 IVRY SUR SEINE

BOURZAT Jean-Dominique - 36 boulevard de la Libération, 94300 VINCENNES

COMMERÇON Alain - 1 bis rue Charles Floquet, 94400 VITRY SUR SEINE

NOTA : *A titre exceptionnel, le nom de l'inventeur peut être suivi de celui de la société à laquelle il appartient (société d'appartenance) lorsque celle-ci est différente de la société déposante ou titulaire.*

Date et signature (s) du (des) demandeur (s) ou du mandataire

RHONE-POULENC RORER S.A.
Fondé de Pouvoir

Antony, le 27 mars 1995

Jacques PILARD

BA 113/160392

DOCUMENT COMPORTANT DES MODIFICATIONS

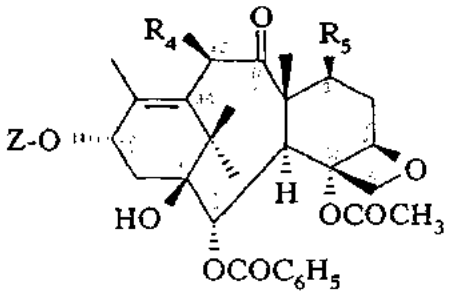
PAGE(S) DE LA DESCRIPTION OU DES REVENDICATIONS OU PLANCHE(S) DE DESSIN			R.M.*	DATE DE LA CORRESPONDANCE	TAMPON DATEUR DU CORRECTEUR
Modifiée(s)	Supprimée(s)	Ajoutée(s)			
1, 11, 12, 31-35			X	27 JUIN 1995	H 1995

Un changement apporté à la rédaction des revendications d'origine, sauf si celui-ci découle des dispositions de l'article 28 du décret du 19 septembre 1979, est signalé par la mention "R.M." (revendications modifiées).

BT 244 / 171180

NOUVEAUX TAXOIDES, LEUR PREPARATION ET LES COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT

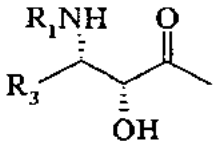
La présente invention concerne de nouveaux taxoïdes de formule générale :



(I)

dans laquelle

Z représente un atome d'hydrogène ou un radical de formule générale :



(II)

dans laquelle :

R_1 représente un radical benzoyle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone ou trifluorométhyle, thénoyle ou furoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, phényle (éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de

carbone), cyano, carboxy ou alcoxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,

- un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone ou un radical hétérocyclique aromatique à 5 chaînons choisi de préférence parmi les radicaux furyle et thiényle,

- ou un radical hétérocyclyle saturé contenant 4 à 6 atomes de carbone éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

R_3 représente un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle droit ou ramifié contenant 2 à 8 atomes de carbone, alcynyle droit ou ramifié contenant 2 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles, alcényles, alcynyles, aryles, aralcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluorométhyle, ou un hétérocycle aromatique ayant 5 chaînons et contenant un ou plusieurs hétéroatomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre et éventuellement substitué par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles, aryles, amino, alcoylamino, dialcoylamino, alcoxycarbonylamino, acyle, arylcarbonyle, cyano, carboxy, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle ou alcoxycarbonyle, étant entendu que, dans les substituants des radicaux phényle, α- ou β-naphtyle et hétérocyclyles aromatiques, les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone et que les radicaux alcényles et alcynyles contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles,

R_4 représente un atome d'hydrogène ou un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcényloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynyloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, alcanoyloxy dont la partie alcanoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée,

alcénoyloxy dont la partie alcénoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynoyloxy dont la partie alcynoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoxyacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoylthioacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoyloxycarbonyloxy dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, ou bien R_4 représente un radical benzoyloxy ou hétérocyclylcarbonyloxy dans lequel la partie hétérocyclique représente un hétérocycle aromatique 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi les atomes d'oxygène, de soufre ou d'azote,

R_5 représente un radical alcoxy contenant 1 à 6 atomes ce carbone en chaîne droite ou ramifiée éventuellement substitué par un radical alcoxy contenant 1 à 4 atomes de carbone, alcényloxy contenant 3 à 6 atomes de carbone, alcynyloxy contenant 3 à 6 atomes de carbone, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone.

De préférence les radicaux aryles pouvant être représentés R_3 sont des radicaux phényles ou α- ou β-naphtyles éventuellement substitués par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles, alcényles, alcynyles, aryles, arylalcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluoro-méthyle, étant entendu que les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone, que les radicaux alcényles et alcynyles contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles.

De préférence les radicaux hétérocycliques pouvant être représentés par R_3 sont des radicaux hétérocycliques aromatiques ayant 5 chaînons et contenant un ou plusieurs atomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre, éventuellement substitués par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène (fluor, chlore, brome, iode) et les radicaux alcoyles contenant 1 à 4 atomes de carbone, aryles contenant 6 à 10 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone, aryloxy contenant 6 à 10 atomes de carbone, amino, alcoylamino contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, acylamino dont la partie acyle contient 1 à 4 atomes de carbone, alcoxycarbonylamino contenant 1 à 4 atomes de carbone, acyle contenant 1 à 4 atomes de carbone, arylcarbonyle dont la partie aryle contient 6 à 10 atomes de carbone, cyano, carboxy, carbamoyle, alcoylcarbamoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou alcoxycarbonyle dont la partie alcoxy contient 1 à 4 atomes de carbone.

De préférence les radicaux R_4 et R_5, identiques ou différents, représentent des radicaux alcoxy droits ou ramifiés contenant 1 à 6 atomes de carbone éventuellement substitués par un radical méthoxy, éthoxy, méthyltio, éthylthio, carboxy, méthoxycarbonyle, éthoxycarbonyle, cyano, carbamoyle, N-méthyl-carbamoyle, N-éthylcarbamoyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, N-pyrrolidinocarbonyle ou N-pipéridinocarbonyle.

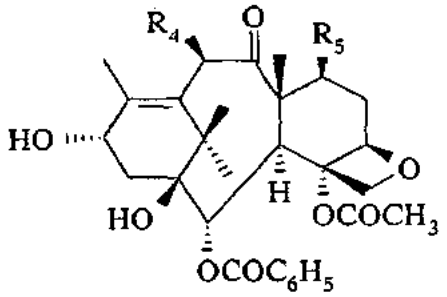
Plus particulièrement, la présente invention concerne les produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO-

dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical alcoyle contenant 1 à 6 atomes de carbone, alcényle contenant 2 à 6 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents choisis parmi les atomes d'halogène (fluor, chlore) et les radicaux alcoyles (méthyle), alcoxy (méthoxy), dialcoylamino (diméthylamino), acylamino (acétylamino), alcoxycarbonylamino (tert-butoxycarbonylamino) ou trifluorométhyle ou un radical furyle-2 ou -3, thiényle-2 ou -3 ou thiazolyle-2, -4 ou -5 et R_4 et R_5, identiques ou différents, représentent un radical alcoyloxy droit ou ramifié contenant 1 à 6 atomes de carbone.

Plus particulièrement encore, la présente invention concerne les produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical isobutyle, isobutényle, butényle, cyclohexyle, phényle, furyle-2, furyle-3, thiényle-2, thiényle-3, thiazolyle-2, thiazolyle-4 ou thiazolyle-5, R_4 et R_5 représentent chacun un radical méthoxy.

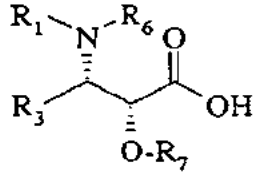
Les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) présentent des propriétés antitumorales et antileucémiques remarquables.

Selon la présente invention, les nouveaux produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) peuvent être obtenus par estérification d'un produit de formule générale :



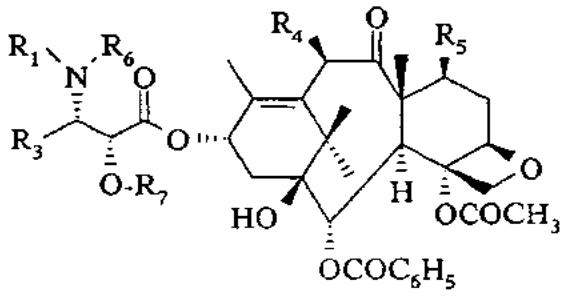
(III)

dans laquelle R_4 et R_5 sont définis comme précédemment, au moyen d'un acide de formule générale :



(IV)

dans laquelle R_1 et R_3 sont définis comme précédemment, ou bien R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, et ou bien R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons, ou d'un dérivé de cet acide pour obtenir un ester de formule générale :



(V)

dans laquelle R_1, R_3, R_4, R_5, R_6 et R_7 sont définis comme précédemment, suivi du remplacement des groupements protecteurs représentés par R_7 et/ou R_6 et R_7 par des atomes d'hydrogène.

L'estérification au moyen d'un acide de formule générale (IV) peut être effectuée en présence d'un agent de condensation (carbodiimide, carbonate réactif) et d'un agent d'activation (aminopyridines) dans un solvant organique (éther, ester, cétones, nitriles, hydrocarbures aliphatiques, hydrocarbures aliphatiques halogénés, hydrocarbures aromatiques) à une température comprise entre -10 et 90°C.

L'estérification peut aussi être réalisée en utilisant l'acide de formule générale (IV) sous forme d'anhydride symétrique en opérant en présence d'un agent d'activation (aminopyridines) dans un solvant organique (éthers, esters, cétones, nitriles, hydrocarbures aliphatiques, hydrocarbures aliphatiques halogénés, hydrocarbures aromatiques) à une température comprise entre 0 et 90°C.

L'estérification peut aussi être réalisée en utilisant l'acide de formule générale (IV) sous forme d'halogénure ou sous forme d'anhydride mixte avec un acide aliphatique ou aromatique, éventuellement préparé in situ, en présence d'une base (amine aliphatique tertiaire) en opérant dans un solvant organique (éthers, esters, cétones, nitriles, hydrocarbures aliphatiques, hydrocarbures aliphatiques halogénés, hydrocarbures aromatiques) à une température comprise entre 0 et 80°C.

De préférence, R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy ou bien R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons.

Lorsque R_6 représente un atome d'hydrogène, R_7 représente de préférence un radical méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle, triméthylsilyle,

triéthylsilyle, β-triméthylsilyléthoxyméthyle, benzyloxycarbonyle ou tétrahydropyrannyle.

Lorsque R_6 et R_7 forment ensemble un hétérocycle, celui-ci est de préférence un cycle oxazolidine éventuellement mono-substitué ou gem-disubstitué en position -2.

Le remplacement des groupements protecteurs R_7 et/ou R_6 et R_7 par des atomes d'hydrogène peut être effectué, selon leur nature de la manière suivante :

1) lorsque R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, le remplacement des groupements protecteurs par des atomes d'hydrogène s'effectue au moyen d'un acide minéral (acide chlorhydrique, acide sulfurique, acide fluorhydrique) ou organique (acide acétique, acide méthanesulfonique, acide trifluorométhanesulfonique, acide p.toluènesulfonique) utilisé seul ou en mélange en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés, les hydrocarbures aromatiques ou les nitriles à une température comprise entre -10 et 60°C,

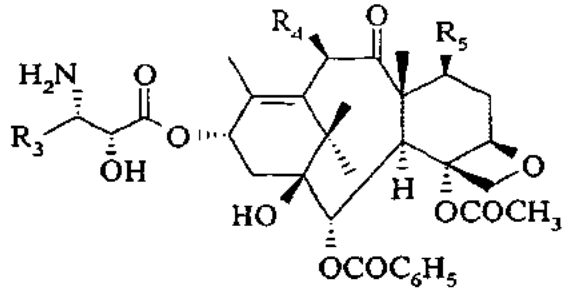
2) lorsque R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons et plus particulièrement un cycle oxazolidine de formule générale :

(VI)

dans laquelle R_1 est défini comme précédemment, R_8 et R_9, identiques ou différents, représentent un atome d'hydrogène ou un radical alcoyle contenant 1 à 4 atomes de carbone, ou un radical aralcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone et la partie aryle représente, de préférence, un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou un radical aryle représentant, de préférence un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou bien R_8 représente un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical trihalométhyle tel que trichlorométhyle ou un radical phényle substitué par un radical trihalométhyle tel que trichlorométhyle et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble avec l'atome de carbone auquel ils sont liés un cycle ayant 4 à 7 chaînons, le remplacement du groupement

protecteur formé par R_6 et R_7 par des atomes d'hydrogène peut être effectué, selon les significations de R_1, R_8 et R_9, de la manière suivante :

a) lorsque R_1 représente un radical tert-butoxycarbonyle, R_8 et R_9, identiques ou différents, représentent un radical alcoyle ou un radical aralcoyle (benzyle) ou aryle (phényle), ou bien R_8 représente un radical trihalométhyle ou un radical phényle substitué par un radical trihalométhyle, et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble un cycle ayant de 4 à 7 chaînons, le traitement de l'ester de formule générale (V) par un acide minéral ou organique éventuellement dans un solvant organique tel qu'un alcool conduit au produit de formule générale :



(VII)

dans laquelle R_3, R_4 et R_5 sont définis comme précédemment, qui est acylé au moyen de chlorure de benzoyle dans lequel le noyau phényle est éventuellemnt substitué, de chlorure de thénoyle, de chlorure de furoyle ou d'un produit de formule générale :

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

dans laquelle R_2 est défini comme précédemment et X représente un atome d'halogène (fluor, chlore) ou un reste -O-R_2 ou -O-CO-O-R_2, pour obtenir un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II).

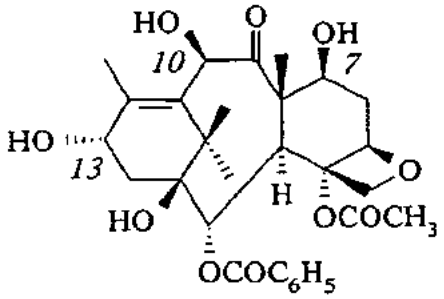
De préférence, le produit de formule générale (V) est traité par l'acide formique à une température voisine de 20°C pour fournir le produit de formule générale (VII).

De préférence, l'acylation du produit de formule générale (VII) au moyen d'un chlorure de benzoyle dans lequel le radical phényle est éventuellement substitué, de chlorure de thénoyle ou de chlorure de furoyle ou d'un produit de formule générale (VIII) est effectuée dans un solvant organique inerte choisi parmi les esters tels que l'acétate d'éthyle, l'acétate d'isopropyle ou l'acétate de n.butyle et les hydrocarbures aliphatiques halogénés tels que le dichlorométhane ou le dichloro-1,2 éthane en présence d'une base minérale telle que le bicarbonate de sodium ou organique telle

que la triéthylamine. La réaction est effectuée à une température comprise entre 0 et 50°C, de préférence voisine de 20°C.

b) lorsque R_1 représente un radical benzoyle éventuellement substitué, thénoyle ou furoyle ou un radical R_2O-CO- dans lequel R_2 est défini comme précédemment, R_8 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone et R_9 représente un atome d'hydrogène, le remplacement du groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène s'effectue en présence d'un acide minéral (acide chlorhydrique, acide sulfurique) ou organique (acide acétique, acide méthanesulfonique, acide trifluoro-méthanesulfonique, acide p.toluènesulfonique) utilisé seul ou en mélange en quantité stoechiométrique ou catalytique, en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques à une température comprise entre -10 et 60°C, de préférence entre 15 et 30°C.

Selon l'invention, les produits de formule générale (III), c'est-à-dire les produits de formule générale (I) dans laquelle Z représente un atome d'hydrogène, R_4 est défini comme précedemment mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus à partir de la 10-désacétyl-baccatine III de formule :



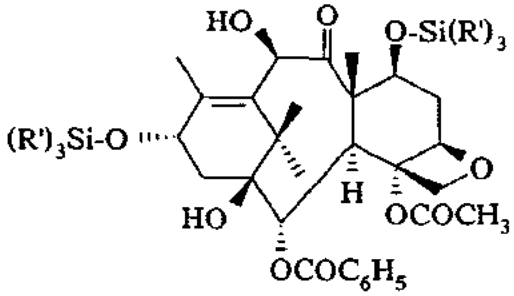
(IX)

Il peut être particulièrement avantageux de protéger sélectivement les fonctions hydroxy en positions 7 et 13, par exemple sous forme d'un di-éther silylé qui peut être obtenu par action d'un halogénure de silyle de formule générale :

$$(R')_3\text{-Si-Hal} \qquad (X)$$

dans laquelle les symboles R', identiques ou différents, représentent un radical alcoyle contenant 1 à 4 atomes de carbone éventuellement substitué par un radical phényle,

ou un radical phényle, sur la 10-désacétyl-baccatine III pour obtenir un produit de formule générale :

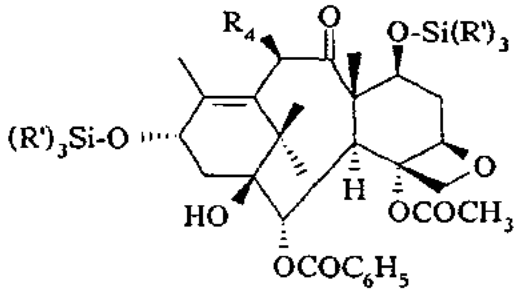


(XI)

dans laquelle R' est défini comme précédemment, puis action d'un produit de formule générale :

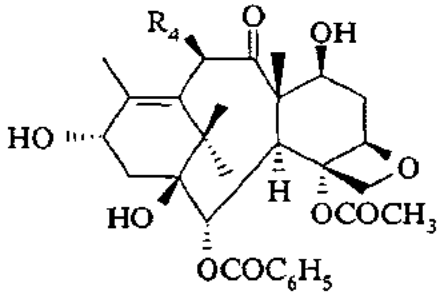
$$R_4\text{-}X_1 \qquad \text{(XII)}$$

dans laquelle R_4 est défini comme précédemment mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et X_1 représente un reste d'ester réactif ou un atome d'halogène pour obtenir un produit de formule générale :



(XIII)

dans laquelle R' et R_4 sont définis comme précédemment, R_4 ne pouvant pas représenter un atome d'hydrogène ou un radical hydroxy, dont les groupements protecteurs silylés sont remplacés par des atomes d'hydrogène pour obtenir un produit de formule générale :



(XIV)

dans laquelle R_4 est défini comme précédemment mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy, qui est éthérifié sélectivement en position 7 par action d'un produit de formule générale :

R_5-X_2 (XV)

dans laquelle R_5 est défini comme précédemment et X_2 représente atome d'halogène ou un reste d'ester réactif tel qu'un reste d'ester sulfurique ou sulfonique pour donner le produit de formule générale (III).

Généralement, l'action d'un dérivé silylé de formule générale (X) sur la 10-désacétyl-baccatine III est effectuée dans la pyridine ou la triéthylamine éventuellement en présence d'un solvant organique tel qu'un hydrocarbure aromatique comme le benzène, le toluène ou les xylènes à une température comprise entre 0°C et la température de reflux du mélange réactionnel.

Généralement, l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI), est effectuée, après métallation de la fonction hydroxy en position 10 au moyen d'un hydrure de métal alcalin tel que l'hydrure de sodium, un amidure de métal alcalin tel que l'amidure de lithium ou d'un alcoylure de métal alcalin tel que le butyllithium, en opérant dans un solvant organique tel que le diméthylformamide ou le tétrahydrofurane à une température comprise entre 0 et 50°C.

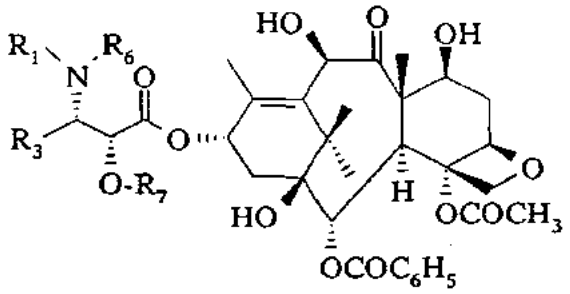
Généralement le remplacement des groupements protecteurs silylés du produit de formule générale (XIII) par des atomes d'hydrogène s'effectue au moyen d'un acide tel que l'acide fluorhydrique ou l'acide trifluoroacétique en présence d'une base telle que la triéthylamine ou la pyridine éventuellement substituée par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone, éventuellement associée à un solvant organique inerte tel qu'un nitrile comme l'acétonitrile ou un hydrocarbure aliphatique halogéné comme le dichlorométhane à une température comprise entre 0 et 80°C.

Généralement l'action d'un produit de formule générale (XV) sur un produit de formule générale (XIV) s'effectue dans les conditions indiquées précédemment pour l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI).

Les produits de formule générale (III) dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus par action d'un produit de formule générale (XV) sur un produit de formule générale (XIV) dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy dans les conditions décrites précédemment pour l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI).

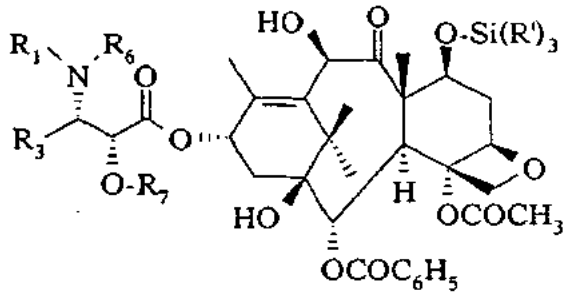
Les produits de formule générale (XIV) dans laquelle R_4 représente un atome d'hydrogène peuvent être obtenus dans les conditions décrites dans des demandes internationales PCT WO 94/11547 et PCT WO 93/06093.

Selon l'invention, les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II), R_4 est défini comme précédemment mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus à partir d'un produit de formule générale :



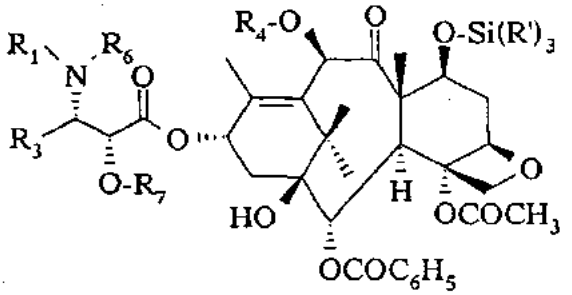
(XVI)

dans laquelle R_1, R_3, R_6 et R_7 sont définis comme précédemment par silylation en position 7 au moyen d'un produit de formule générale (X) pour obtenir un produit de formule générale :



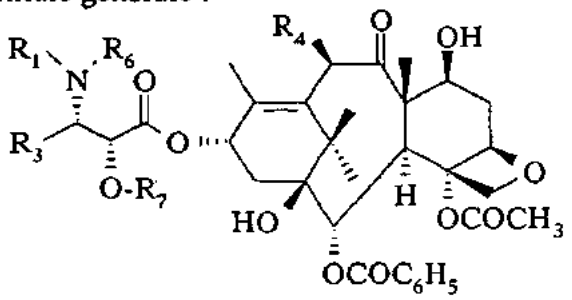
(XVII)

dans laquelle R', R_1, R_3, R_6 et R_7 sont définis comme précédemment, qui est fonctionnalisé en position 10 au moyen d'un produit de formule générale (XII) pour donner un produit de formule générale :



(XVIII)

dans laquelle R', R_1, R_3, R_4, R_6 et R_7 sont définis comme précédemment dont le groupement protecteur silylé est remplacé par un atome d'hydrogène pour donner un produit de formule générale :

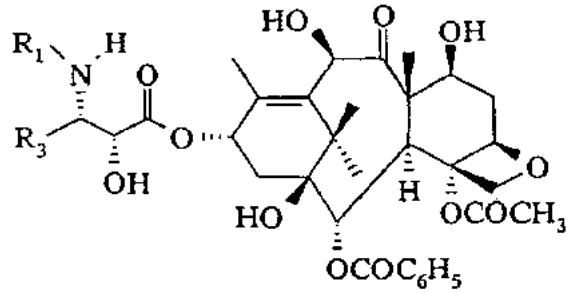


(XIX)

qui, par action d'un produit de formule générale (XV) conduit au produit de formule générale (V) dont les groupements protecteurs sont remplacés par des atomes d'hydrogène pour donner un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II).

Les réactions de silylation, de fonctinnalisation et de remplacement des groupements protecteurs par des atomes d'hydrogène sont effectuée dans des conditions analogues à celles décrites ci-dessus.

Les produits de formule générale (XVI) peuvent être obtenus dans les conditions décrites dans le brevet européen EP 0336 841 et les demandes internationales PCT WO 92/09589 et WO 94/07878 ou à partir des produits de formule générale :



(XX)

dans laquelle R_1 et R_3 sont définis comme précédemment selon les méthodes connues de protection de la fonction hydroxy de la chaîne latérale sans toucher au reste de la molécule.

Selon l'invention, les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II), R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus par action d'un produit de formule générale (XV) sur un produit de formule générale (XIX) dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy, R_1,

R_3, R_6 et R_7 sont définis comme précédemment en opérant dans les conditions décrites précédemment pour l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI) pour donner le produit de formule générale (XIII), suivie du remplacement des groupements protecteurs par des atomes d'hydrogène.

Les produits de formule générale (XIX) dans laquelle R_4 représente un atome d'hydrogène peuvent être obtenus dans les conditions décrtes dans les demandes internationales PCT WO 94/11547 et WO 93/06093.

Les nouveaux produits de formule générale (I) obtenus par la mise en oeuvre des procédés selon l'invention peuvent être purifiés selon les méthodes connues telles que la cristallisation ou la chromatographie.

Les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) présentent des propriétés biologiques remarquables.

In vitro, la mesure de l'activité biologique est effectuée sur la tubuline extraite de cerveau de porc par la méthode de M.L. Shelanski et coll., Proc. Natl. Acad. Sci. USA, 70, 765-768 (1973). L'étude de la dépolymérisation des microtubules en tubuline est effectuée selon la méthode de G. Chauvière et coll., C.R. Acad. Sci., 293, série II, 501-503 (1981). Dans cette étude les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) se sont montrés au moins aussi actifs que le taxol et le Taxotère.

In vivo, les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) se sont montrés actifs chez la souris greffée par le mélanome B16 à des doses comprises entre 1 et 10 mg/kg par voie intrapéritonéale, ainsi que sur d'autres tumeurs liquides ou solides.

Les nouveaux produits ont des propriétés anti-tumorales et plus particulièrement une activité sur les tumeurs qui sont résistantes au Taxol® ou au Taxotère®. De telles tumeurs comprennent les tumeurs du colon qui ont une expression élevée du gène mdr 1 (gène de la multi-drug resistance). La multi-drug resistance est un terme habituel se rapportant à la résistance d'une tumeur à différents produits de structures et de mécanismes d'action différents. Les taxoïdes sont généralement connus pour être fortement reconnus par des tumeurs expérimentales telles que P388/DOX, une lignée cellulaire sélectionnée pour sa résistance à la doxorubicine (DOX) qui exprime mdr 1.

Les exemples suivants illustrent la présente invention.

EXEMPLE 1

A une suspension contenant 217,8 mg d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,13α diméthoxy-7β,10β oxo-9 taxène-11, 200 mg d'acide tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylique-5 (2R,4S,5R) et 50 mg de tamis moléculaire 4Å en poudre dans 2 cm3 d'acétate d'éthyle, on ajoute successivement, à une température voisine de 20°C, 126 mg de dicyclohexylcarbodiimide, puis 14 mg de N,N'-diméthylamino-4 pyridine. La suspension obtenue est agitée à une température voisine de 20°C, sous atmosphère d'argon, pendant 16 heures puis concentrée à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. Le résidu obtenu est purifié par chromatographie à pression atmosphérique sur 50 g de silice (0,063-0,2 mm) contenus dans une colonne de 2 cm de diamètre (gradient d'élution : acétate d'éthyle-dichlorométhane de 10-90 à 40-60 en volumes) en recueillant des fractions de 10 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (0,27 kPa) à 40°C pendant 2 heures. On obtient ainsi 271,8 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5 (2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β diméthoxy-7β,10β oxo-9 taxène-11 yle-13α sous forme d'un solide blanc dont les caractéristiques sont les suivantes :

- spectre de R.M.N. ^1H (400 MHz ; $CDCl_3$ avec quelques gouttes de CD_3OD d4 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,02 (s, 9H : $C(CH_3)_3$) ; 1,10 (s, 3H : CH_3) ; 1,17 (s, 3H : CH_3) ; 1,63 (s, 3H : CH_3) ; de 1,65 à 1,85 et 2,60 (2 mts, 1H chacun : CH_2 en 6) ; 1,78 (mf, 3H : CH_3) ; 2,02 et 2,15 (2 dd, J = 14 et 9, 1H chacun : CH_2 en 14) ; 2,14 (s, 3H :CH_3) ; 3,22 et 3,35 (2 s, 3H chacun : OCH_3) ; 3,64 (d, J = 7, 1H : H en 3) ; 3,73 (mt, 1H : H en 7) ; 3,76 (s, 3H : $ArOCH_3$) ; 4,06 et 4,16 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,53 (d, J = 5, 1H : H en 2') ; 4,67 (s, 1H : H en 10) ; 4,85 (d large, J = 10, 1H : H en 5) ; 5,36 (mt, 1H : H 3') ; 5,52 (d, J = 7, 1H : H en 2) ; 6,07 (mt, 1H : H en 13) ; 6,33 (mf, 1H : H en 5') ; 6,88 (d, J = 8, 2H : H aromatiques en ortho du OCH_3) ; de 7,25 à 7,40 (mt, 7H : H aromatiques en 3' et H aromatiques en méta du OCH_3) ; 7,43 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,58 (t, J = 7,5, 1H : $OCOC_6H_5$ H en para) ; 7,96 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

Une solution de 446,3 mg de tert-butoxycarbonyl-3 (méthoxy-4 phényl)-2 phényl-4 oxazolidine-1,3 carboxylate-5(2R,4S,5R) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β diméthoxy-7β,10β oxo-9 taxène-11 yle-13α dans 11,6 cm3

d'une solution 0,1N d'éthanol chlorhydrique est maintenue sous agitation à une température voisine de 0°C pendant 16 heures sous atmosphère d'argon. Le mélange réactionnel est alors dilué avec 40 cm3 de dichlorométhane et 5 cm3 d'eau distillée. Après décantation, la phase aqueuse est extraite avec 5cm3 de dichlorométhane. Les phases organiques sont rassemblées, séchées sur sulfate de magnésium, filtrées sur verre fritté puis concentrées à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. On obtient ainsi 424,2 mg d'un solide jaune pâle que l'on purifie par chromatographie préparative sur couche mince [12 plaques préparatives Merck, Kieselgel 60F254, épaisseur 1 mm, dépôt en solution dans un mélange méthanol-dichlorométhane (5-95 en volumes), en éluant par un mélange méthanol-dichlorométhane (5-95 en volumes)]. Après élution de la zone correspondant au produit principal par un mélange méthanol-dichlorométhane (15-85 en volumes), filtration sur verre fritté, puis évaporation des solvants sous pression réduite (0,27 kPa) à une température voisine de 40°C, on obtient 126 mg de tert-butoxycarbonylamino-3 hydroxy-2 phényl-3 propionate-(2R,3S) d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β diméthoxy-7β,10β oxo-9 taxène-11 yle-13α sous forme d'une meringue couleur ivoire dont les caractéristiques sont les suivantes :

- pouvoir rotatoire $[\alpha]^{D}_{20}$ = -32,9 (c = 0,5 ; méthanol)
- spectre de R.M.N. ^{1}H (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,23 (s, 3H : CH_3) ; 1,25 (s, 3H : CH_3) ; 1,39 (s, 9H : $C(CH_3)_3$) ; 1,70 (s, 1H : OH en 1) ; 1,75 (s, 3H : CH_3) ; 1,82 et 2,72 (2 mts, 1H chacun : CH_2 en 6) ; 1,91 (s, 3H : CH_3) ; 2,31 (AB limite, 2H : CH_2 en 14) ; 2,39 (s, 3H : $COCH_3$) ; 3,33 et 3,48 (2 s, 3H chacun : OCH_3) ; 3,48 (mt, 1H : OH en 2') ; 3,85 (d, J = 7, 1H : H 3) ; 3,88 (dd, J = 11 et 7, 1H : H 7) ; 4,20 et 4,33 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,65 (mt, 1H : H en 2') ; 4,83 (s, 1H : H en 10) ; 5,00 (d large, J = 10, 1H : H en 5) ; 5,30 (d large, J = 10, 1H : H en 3') ; 5,47 (d, J = 10, 1H : CONH) ; 5,66 (d, J = 7, 1H : H en 2) ; 6,24 (t large, J = 9, 1H : H en 13) ; 6,33 (mt, 1H : H en 5') ; de 7,30 à 7,50 (mt, 5H : H aromatiques en 3') ; 7,52 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,63 (t, J = 7,5, 1H : $OCOC_6H_5$ H en para) ; 8,12 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

L'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,13α diméthoxy-7β,10β oxo-9 taxène-11 (ou 7β,10β–diméthoxy-7β,10β 10-désacétoxy-baccatine III) peut être préparé de la manière suivante :

A une solution de 500 mg d'acétoxy-4α benzoyloxy-2α époxy-5β,20 trihydroxy-1β,7β,13α méthoxy-10β oxo-9 taxène-11 dans 5 cm3 d'iodométhane et

0,5 cm3 de diméthylformamide, maintenue sous atmosphère d'argon, à une température voisine de 0°C, on ajoute par portions 86 mg d'hydrure de sodium à 50 % en poids dans l'huile de vaseline. Après 45 minutes à une température voisine de 0°C, le mélange réactionnel est dilué par 50 cm3 d'acétate d'éthyle et 8 cm3 d'eau distillée. Après décantation, la phase organique est lavée avec deux fois 8 cm3 d'eau distillée, puis 8 cm3 d'une solution aqueuse saturée en chlorure de sodium, séchée sur sulfate de magnésium, filtrée sur verre fritté, et concentrée à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. On obtient ainsi 570 mg d'un solide jaune pâle que l'on purifie par chromatographie à pression atmosphérique sur 50 g de silice (0,063-0,2 mm) contenus dans une colonne de 2,5 cm de diamètre en éluant avec un mélange méthanol-dichlorométhane (2-98 en volumes) en recueillant des fractions de 10 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (0,27 kPa) à 40°C pendant 2 heures. On obtient ainsi 380 mg d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,13α diméthoxy-7β,10β oxo-9 taxène-11 sous forme d'un solide jaune pâle dont les caractéristiques sont les suivantes :

- spectre de R.M.N. ^1H (400 MHz ; $CDCl_3$ avec quelques gouttes de CD_3OD d4 ; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,03 (s, 3H : CH_3) ; 1,11 (s, 3H : CH_3) ; 1,65 (s, 3H : CH_3) ; 1,72 et 2,67 (2 mts, 1H chacun : CH_2 en 6) ; 2,05 (s, 3H : CH_3) ; 2,21 (AB limite, J = 14 et 9, 2H : CH_2 en 14) ; 2,25 (s, 3H : $COCH_3$) ; 3,26 et 3,40 (2 s, 3H chacun : OCH_3) ; 3,85 (d, J = 7, 1H : H en 3) ; 3,89 (dd, J = 11 et 6,5, 1H : H en 7) ; 4,12 et 4,25 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,78 (t large, J = 9, 1H : H en 13) ; 4,83 (s, 1H : H en 10) ; 4.98 (d large, J = 10, 1H : H en 5) ; 5,53 (d, J = 7, 1H : H en 2) ; 7,43 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,56 (t, J = 7,5, 1H : $OCOC_6H_5$ H en para) ; 8,05 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

L'acétoxy-4α benzoyloxy-2α époxy-5β,20 trihydroxy-1β,7β,13α méthoxy-10β oxo-9 taxène-11 (ou 10β-méthoxy 10-désacétoxy-baccatine III) peut être préparé de la manière suivante :

A une solution de 3,62 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 dans 30 cm3 de dichlorométhane, maintenue sous atmosphère d'argon, à une température voisine de 0°C, on ajoute lentement 50 cm3 de complexe fluorure d'hydrogène-pyridine ($3HF.Et_3N$). Après 48 heures à une température voisine de 20°C, le mélange réactionnel est versé sur une suspension de 100 cm3 d'une solution aqueuse sursaturée en

hydrogénocarbonate de sodium maintenue à une température voisine de 0°C. Après décantation, la phase aqueuse est réextraite avec trois fois 80 cm3 de dichlorométhane, puis deux fois 80 cm3 d'acétate d'éthyle. Les phases organiques sont rassemblées, séchées sur sulfate de magnésium, filtrées sur sulfate de magnésium et concentrées à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. On obtient ainsi 3,45 g d'une meringue jaune que l'on purifie par chromatographie à pression atmosphérique sur 150 g de silice (0,063-0,2 mm) contenus dans une colonne de 3,5 cm de diamètre en éluant avec un mélange méthanol-dichlorométhane (5-95 en volumes) en recueillant des fractions de 35 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (0,27 kPa) à 40°C pendant 2 heures. On obtient ainsi 1,97 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 trihydroxy-1β,7β,13α méthoxy-10β oxo-9 taxène-11 sous forme d'un solide blanc dont les caractéristiques sont les suivantes :

- spectre de R.M.N. ^1H (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 1,10 (s, 3H : CH_3) ; 1,19 (s, 3H : CH_3) ; 1,48 (d, J = 8,5, 1H : 0H en 13) ; 1,70 (s, 3H : CH_3) ; 1,81 et 2,61 (2 mts, 1H chacun : CH_2 en 6) ; 2,09 (d, J = 5, 1H : OH en 7) ; 2,11 (s, 3H : CH_3) ; 2,30 (s, 3H : $COCH_3$) ; 2,32 (d, J = 9, 2H : CH_2 en 14) ; 3,48 (s, 3H : OCH_3) ; 3,97 (d, J = 7, 1H : H en 3) ; 4,18 et 4,33 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,31 (mt, 1H : H en 7) ; 4,93 (mt, 1H : H en 13) ; 4,99 (s, 1H : H en 10) ; 5.01 (d large, J = 10, 1H : H en 5) ; 5,66 (d, J = 7, 1H : H en 2) ; 7,49 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,63 (t, J = 7,5, 1H : $OCOC_6H_5$ Hen para) ; 8,12 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

L'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 (ou 10β-méthoxy 10-désacétoxy 7,13-bistriéthylsilyl-baccatine III) peut être préparé de la manière suivante :

A une solution de 5 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 dans 25 cm3 d'iodométhane, maintenue sous atmosphère d'argon, à une température voisine de 0°C, on ajoute par portions 375 mg d'hydrure de sodium à 50 % en poids dans l'huile de vaseline. La solution est maintenue sous agitation pendant 45 minutes à une température voisine de 0°C, puis pendant 5 heures 30 minutes à une température voisine de 20°C. Le mélange réactionnel est de nouveau refroidi à une température voisine de à 0°C, et l'on ajoute par portions 125 mg d'hydrure de sodium à 50 % en poids dans l'huile de vaseline. Après 1 heure à 20°C, puis 18 heures à 5°C, le mélange réactionnel est dilué par addition de 50 cm3 de dichlorométhane, versé sur 50 cm3 d'une solution aqueuse

saturée en chlorure d'ammonium et décanté. La phase aqueuse est extraite par 2 fois 30 cm3 de dichlorométhane, puis les phases organiques sont rassemblées, lavées avec 10 cm3 d'eau distillée, séchées sur sulfate de magnésium, filtrées sur verre fritté, et concentrées à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. On obtient ainsi 5,15 g d'une meringue jaune que l'on purifie par chromatographie à pression atmosphérique sur 300 g de silice (0,063-0,2 mm) contenus dans une colonne de 5 cm de diamètre (gradient d'élution : acétate d'éthyle-dichlorométhane de 0-100 à 10-90 en volumes) en recueillant des fractions de 30 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (0,27 kPa) à 40°C pendant 2 heures. On obtient ainsi 3,62 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 hydroxy-1β méthoxy-10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 sous forme d'une meringue jaune pâle dont les caractéristiques sont les suivantes :

- spectre de R.M.N. ^1H (600 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 0,58 et 0,69 (2 mts, 6H chacun : CH_2 éthyle) ; 0,97 et 1,04 (2 t, J = 7,5, 9H chacun : CH_3 éthyle) ; 1,15 (s, 3H : CH_3) ; 1,18 (s, 3H : CH_3) ; 1,58 (s, 1H : 0H en 1) ; 1,68 (s, 3H : CH_3) ; 1,89 et 2,48 (2 mts, 1H chacun : CH_2 en 6) ; 2,04 (s, 3H : CH_3) ; 2,15 et 2,23 (2 dd, J = 16 et 9, 1H chacun : CH_2 en 14) ; 2,29 (s, 3H : $COCH_3$) ; 3,40 (s, 3H : OCH_3) ; 3,83 (d, J = 7, 1H : H en 3) ; 4,15 et 4,30 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,43 (dd, J = 11 et 7, 1H : H en 7) ; 4,91 (s, 1H : H en 10) ; 4,96 (d large, J = 10, 1H : H en 5) ; 5,01 (t large, J = 9, 1H : H en 13) ; 5,62 (d, J = 7, 1H : H en 2) ; 7,46 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,60 (t, J = 7,5, 1H : $OCOC_6H_5$ H en para) ; 8,09 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

L'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 (ou 10-désacétyl 7,13-bistriéthylsilyl-baccatine III) peut être préparé de la manière suivante :

A une solution de 14 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 tétrahydroxy-1β,7β,10β,13α oxo-9 taxène-11 (10-désacétyl-baccatine III) dans 50 cm3 de pyridine anhydre, maintenue sous atmosphère d'argon, à une température voisine de 20°C, on ajoute 10,8 cm3 de chlorure de triéthylsilyle. Après 17 heures à une température voisine de 20°C, le mélange réactionnel est porté à une température voisine de 115°C, puis on ajoute 10,8 cm3 de chlorure de triéthylsilyle. Après 3 heures 15 minutes à une température voisine de 115°C, le mélange réactionnel est ramené jusqu'à une température voisine de 20°C, dilué avec 30 cm3 d'acétate d'éthyle

et 100 cm3 d'eau distillée. Après décantation, la phase aqueuse est extraite avec 2 fois 50 cm3 d'acétate d'éthyle. Les phases organiques sont rassemblées, lavées avec 50 cm3 d'une solution aqueuse saturée en chlorure de sodium, séchées sur sulfate de magnésium, filtrées sur verre fritté puis concentrées à sec sous pression réduite (0,27 kPa) à une température voisine de 40°C. On obtient ainsi 63,1 g d'une huile brune que l'on purifie par chromatographie à pression atmosphérique sur 800 g de silice (0,063-0,2 mm) contenus dans une colonne de 7 cm de diamètre (gradient d'élution : acétate d'éthyle-dichlorométhane de 0-100 à 5-95 en volumes) en recueillant des fractions de 60 cm3. Les fractions ne contenant que le produit cherché sont réunies et concentrées à sec sous pression réduite (0,27 kPa) à 40°C pendant 2 heures. On obtient ainsi 9,77 g d'acétoxy-4α benzoyloxy-2α époxy-5β,20 dihydroxy-1β,10β oxo-9 bistriéthylsilyloxy-7β,13α taxène-11 sous forme d'une meringue crème dont les caractéristiques sont les suivantes :

- spectre de R.M.N. ^1H (400 MHz ; $CDCl_3$; déplacements chimiques δ en ppm ; constantes de couplage J en Hz) : 0,55 et 0,68 (2 mts, 6H chacun : CH_2 éthyle) ; 0,94 et 1,03 (2 t, J = 7,5, 9H chacun : CH_3 éthyle) ; 1,08 (s, 3H : CH_3) ; 1,17 (s, 3H : CH_3) ; 1,58 (s, 1H : OH en 1) ; 1,73 (s, 3H : CH_3) ; 1,91 et 2,57 (2 mts, 1H chacun : CH_2 en 6) ; 2,04 (s, 3H : CH_3) ; 2,12 et 2,23 (2 dd, J = 16 et 9, 1H chacun : CH_2 en 14) ; 2,30 (s, 3H : $COCH_3$) ; 3,88 (d, J = 7, 1H : H en 3) ; 4,16 et 4,32 (2 d, J = 8,5, 1H chacun : CH_2 en 20) ; 4,27 (d, J = 1, 1H : OH en 10) ; 4,40 (dd, J = 11 et 7, 1H : H en 7) ; 4,95 (d large, J = 10, 1H : H en 5) ; 4,95 (mt, 1H : H en 13) ; 5,16 (d, J = 1, 1H : H en 10) ; 5,60 (d, J = 7, 1H : H en 2) ; 7,46 (t, J = 7,5, 2H : $OCOC_6H_5$ H en méta) ; 7,60 (t, J = 7,5, 1H : $OCOC_6H_5$ H en para) ; 8,09 (d, J = 7,5, 2H : $OCOC_6H_5$ H en ortho).

Les nouveaux produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) manifestent une activité inhibitrice significative de la prolifération cellulaire anormale et possèdent des propriétés thérapeutiques permettant le traitement de malades ayant des conditions pathologiques associées à une prolifération cellulaire anormale. Les conditions pathologiques incluent la prolifération cellulaire anormale de cellules malignes ou non malignes de divers tissus et/ou organes, comprenant, de manière non limitative, les tissus musculaires, osseux ou conjonctifs, la peau, le cerveau, les poumons, les organes sexuels, les systèmes lymphatiques ou rénaux, les cellules mammaires ou sanguines, le foie, l'appareil digestif, le pancréas et les glandes thyroïdes ou adrénales. Ces conditions pathologiques peuvent inclure également le psoriasis, les tumeurs solides, les cancers

de l'ovaire, du sein, du cerveau, de la prostate, du colon, de l'estomac, du rein ou des testicules, le sarcome de Kaposi, le cholangiocarcinome, le choriocarcinome, le neuroblastome, la tumeur de Wilms, la maladie de Hodgkin, les mélanomes, les myélomes multiples, les leucémies lymphocytaires chroniques, les lymphomes granulocytaires aigus ou chroniques. Les nouveaux produits selon l'invention sont particulièrement utiles pour le traitement du cancer de l'ovaire. Les produits selon l'invention peuvent être utilisés pour prévenir ou retarder l'apparition ou la réapparition des conditions pathologiques ou pour traiter ces conditions pathologiques.

Les produits selon l'invention peuvent être administrés à un malade selon différentes formes adaptées à la voie d'administration choisie qui, de préférence, est la voie parentérale. L'administration par voie parentérale comprend les administrations intraveineuse, intrapéritonéale, intramusculaire ou sous-cutanée. Plus particulièrement préférée est l'administration intrapéritonéale ou intraveineuse.

La présente invention comprend également les compositions pharmaceutiques qui contiennent au moins un produit de formule générale (I) en une quantité suffisante adaptée à l'emploi en thérapeutique humaine ou vétérinaire. Les compositions peuvent être préparées selon les méthodes habituelles en utilisant un ou plusieurs adjuvants, supports ou excipients pharmaceutiquement acceptables. Les supports convenables incluent les diluants, les milieux aqueux stériles et divers solvants non toxiques. De préférence les compositions se présentent sous forme de solutions ou de suspensions aqueuses, de solutions injectables qui peuvent contenir des agents émusifiants, des colorants, des préservatifs ou des stabilisants. Cependant, les compositions peuvent aussi se présenter sous forme de comprimés, de pilules, de poudres ou de granulés administrables par voie orale.

Le choix des adjuvants ou excipients peut être déterminé par la solubilité et les propriétés chimiques du produit, le mode particulier d'administration et les bonnes pratiques pharmaceutiques.

Pour l'administration parentérale, on utilise des solutions ou des suspensions stériles aqueuses ou non aqueuses. Pour la préparation de solutions ou de suspensions non aqueuses peuvent être utilisés des huiles végétales naturelles telle que l'huile d'olive, l'huile de sésame ou l'huile de paraffine ou les esters organiques injectables tel que l'oléate d'éthyle. Les solutions stériles aqueuses peuvent être constituées d'une solution d'un sel pharmaceutiquement acceptable en solution dans de l'eau. Les solutions aqueuses conviennent pour l'administration intraveineuse dans la mesure où

le pH est convenablement ajusté et où l'isotonicité est réalisée, par exemple, par une quantité suffisante de chlorure de sodium ou de glucose. La stérilisation peut être réalisée par chauffage ou par tout autre moyen qui n'altère pas la composition.

Il est bien entendu que tous les produits entrant dans les compositions selon l'invention doivent être purs et non toxiques pour les quantités utilisées.

Les compositions peuvent contenir au moins 0,01 % de produit thérapeutiquement actif. La quantité de produit actif dans une composition est telle qu'une posologie convenable puisse être prescrite. De préférence, les compositions sont préparées de telle façon qu'une dose unitaire contienne de 0,01 à 1000 mg environ de produit actif pour l'administration par voie parentérale.

Le traitement thérapeutique peut être effectué concurremment avec d'autres traitements thérapeutiques incluant des médicaments antinéoplastiques , des anticorps monoclonaux, des thérapies immunologiques ou des radiothérapies ou des modificateurs des réponses biologiques. Les modificateurs des réponses incluent, de manière non limitative, les lymphokines et les cytokines telles que les interleukines, les interférons (α, β ou δ) et le TNF. D'autres agents chimiothérapeutiques utiles dans le traitement des désordres dus à la prolifération anormale des cellules incluent, de manière non limitative, les agents alkylants tels que les moutardes à l'azote comme la mechloretamine, le cyclophosphamide, le melphalan et le chlorambucil, des sulfonates d'alkyle comme le busulfan, les nitrosourées comme la carmustine, la lomustine, la sémustine et la streptozocine, les triazènes comme la dacarbazine, les antimétabolites comme les analogues de l'acide folique tel que le méthotrexate, les analogues de pyrimidine comme le fluorouracil et la cytarabine, des analogues de purines comme la mercaptopurine et la thioguanine, des produits naturels tels que les alcaloïdes de vinca comme la vinblastine, la vincristine et la vendésine, des épipodophyllotoxines comme l'étoposide et le teniposide, des antibiotiques comme la dactinomycine, la daunorubicine, la doxorubicine, la bléomycine, la plicamycine et la mitomycine, des enzymes comme la L-asparaginase, des agents divers comme les complexes de coordination du platine tel que le cisplatine, les urées substituées telles que l'hydroxyurée, les dérivés de méthylhydrazine comme la procarbazine, les suppresseurs adrénocoticoïques comme le mitotane et l'aminoglutéthymide, les hormones et les antagonistes comme les adrénocorticostéroïdes comme la prednisone, les progestines comme le caproate d'hydroxyprogestérone, l'acétate de méthoxyprogestérone et l'acétate de megestrol, les oestrogènes comme le

diéthylstilbestrol et l'éthynylestradiol, les antioestrogènes comme le tamoxifène, les androgènes comme le propionate de testostérone et la fluoxymesterone.

Les doses utilisées pour mettre en oeuvre les méthodes selon l'invention sont celles qui permettent un traitement prophylactique ou un maximum de réponse thérapeutique. Les doses varient selon la forme d'administration, le produit particulier sélectionné et les caractéristiques propres du sujet à traiter. En général, les doses sont celles qui sont thérapeutiquement efficaces pour le traitement des désordres dus à une prolifération cellulaire anormale. Les produits selon l'invention peuvent être administrés aussi souvent que nécessaire pour obtenir l'effet thérapeutique désiré. Certains malades peuvent répondre rapidement à des doses relativement fortes ou faibles puis avoir besoin de doses d'entretien faibles ou nulles. Généralement, de faibles doses seront utilisées au début du traitement et, si nécessaire, des doses de plus en plus fortes seront administrées jusqu'à l'obtention d'un effet optimum. Pour d'autres malades il peut être nécessaire d'administrer des doses d'entretien 1 à 8 fois par jour, de préférence 1 à 4 fois, selon les besoins physiologiques du malade considéré. Il est aussi possible que pour certains malades il soit nécessaire de n'utiliser qu'une à deux administrations journalières.

Chez l'homme, les doses sont généralement comprises entre 0,01 et 200 mg/kg. Par voie intrapéritonéale, les doses seront en général comprises entre 0,1 et 100 mg/kg et, de préférence entre 0,5 et 50 mg/kg et, encore plus spécifiquement entre 1 et 10 mg/kg. Par voie intraveineuse, les doses sont généralement comprises entre 0,1 et 50 mg/kg et, de préférence entre 0,1 et 5 mg/kg et, encore plus spécifquement entre 1 et 2 mg/kg. Il est entendu que, pour choisir le dosage le plus approprié, devront être pris en compte la voie d'administration, le poids du malade, son état de santé général, son âge et tous les facteurs qui peuvent influer sur l'efficacité du traitement.

L'exemple suivant illustre une composition selon l'invention.

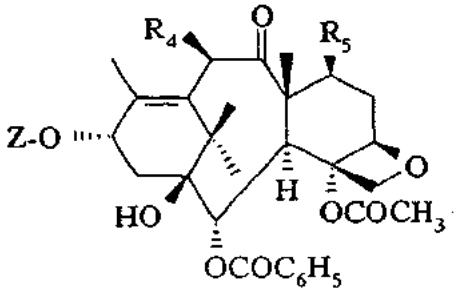
EXEMPLE

On dissout 40 mg du produit obtenu à l'exemple 1 dans 1 cm3 d'Emulphor EL 620 et 1 cm3 d'éthanol puis la solution est diluée par addition de 18 cm3 de sérum physiologique.

La composition est administrée par perfusion pendant 1 heure par introduction dans du soluté physiologique.

REVENDICATIONS

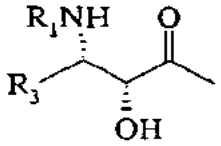
1 - Nouveaux taxoïdes de formule générale :



(I)

dans laquelle

Z représente un atome d'hydrogène ou un radical de formule générale :



(II)

dans laquelle :

R_1 représente un radical benzoyle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone, alcoxy contenant 1 à 4 atomes de carbone ou trifluorométhyle, thénoyle ou furoyle ou un radical R_2-O-CO- dans lequel R_2 représente :

- un radical alcoyle contenant 1 à 8 atomes de carbone, alcényle contenant 2 à 8 atomes de carbone, alcynyle contenant 3 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, bicycloalcoyle contenant 7 à 10 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs substituants choisis parmi les atomes d'halogène et les radicaux hydroxy, alcoxy contenant 1 à 4 atomes de carbone, dialcoylamino dont chaque partie alcoyle contient 1 à 4 atomes de carbone, pipéridino, morpholino, pipérazinyl-1 (éventuellement substitué en -4 par un radical alcoyle contenant 1 à 4 atomes de carbone ou par un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone), cycloalcoyle contenant 3 à 6 atomes de carbone, cycloalcényle contenant 4 à 6 atomes de carbone, phényle (éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de

carbone), cyano, carboxy ou alcoxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone,

- un radical phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles contenant 1 à 4 atomes de carbone ou alcoxy contenant 1 à 4 atomes de carbone ou un radical hétérocyclique aromatique à 5 chaînons choisi de préférence parmi les radicaux furyle et thiényle,

- ou un radical hétérocyclyle saturé contenant 4 à 6 atomes de carbone éventuellement substitué par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone,

R_3 représente un radical alcoyle droit ou ramifié contenant 1 à 8 atomes de carbone, alcényle droit ou ramifié contenant 2 à 8 atomes de carbone, alcynyle droit ou ramifié contenant 2 à 8 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle ou α- ou β-naphtyle éventuellement substitué par un ou plusieurs atomes ou radicaux choisis parmi les atomes d'halogène et les radicaux alcoyles, alcényles, alcynyles, aryles, aralcoyles, alcoxy, alcoylthio, aryloxy, arylthio, hydroxy, hydroxyalcoyle, mercapto, formyle, acyle, acylamino, aroylamino, alcoxycarbonylamino, amino, alcoylamino, dialcoylamino, carboxy, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, cyano, nitro et trifluorométhyle, ou un hétérocycle aromatique ayant 5 chaînons et contenant un ou plusieurs hétéroatomes, identiques ou différents, choisis parmi les atomes d'azote, d'oxygène ou de soufre et éventuellement substitué par un ou plusieurs substituants, identiques ou différents, choisis parmi les atomes d'halogène et les radicaux alcoyles, aryles, amino, alcoylamino, dialcoylamino, alcoxycarbonylamino, acyle, arylcarbonyle, cyano, carboxy, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle ou alcoxycarbonyle, étant entendu que, dans les substituants des radicaux phényle, α- ou β-naphtyle et hétérocyclyles aromatiques, les radicaux alcoyles et les portions alcoyles des autres radicaux contiennent 1 à 4 atomes de carbone et que les radicaux alcényles et alcynyles contiennent 2 à 8 atomes de carbone et que les radicaux aryles sont des radicaux phényles ou α- ou β-naphtyles,

R_4 représente un atome d'hydrogène ou un radical hydroxy ou un radical alcoxy contenant 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcényloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynyloxy contenant 3 à 6 atomes de carbone en chaîne droite ou ramifiée, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, alcanoyloxy dont la partie alcanoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée,

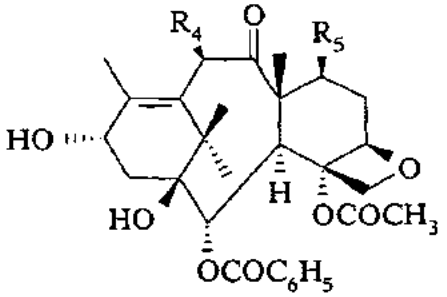
alcénoyloxy dont la partie alcénoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcynoyloxy dont la partie alcynoyle contient 3 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoxyacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoylthioacétyle dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, alcoyloxycarbonyloxy dont la partie alcoyle contient 1 à 6 atomes de carbone en chaîne droite ou ramifiée, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone, ou bien R_4 représente un radical benzoyloxy ou hétérocyclylcarbonyloxy dans lequel la partie hétérocyclique représente un hétérocycle aromatique 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi les atomes d'oxygène, de soufre ou d'azote,

R_5 représente un radical alcoxy contenant 1 à 6 atomes ce carbone en chaîne droite ou ramifiée éventuellement substitué par un radical alcoxy contenant 1 à 4 atomes de carbone, alcényloxy contenant 3 à 6 atomes de carbone, alcynyloxy contenant 3 à 6 atomes de carbone, cycloalcoyloxy contenant 3 à 6 atomes de carbone, cycloalcényloxy contenant 3 à 6 atomes de carbone, ces radicaux étant éventuellement substitués par un ou plusieurs atomes d'halogène ou par un radical alcoxy contenant 1 à 4 atomes de carbone, alcoylthio contenant 1 à 4 atomes de carbone, ou un radical carboxy, alcoyloxycarbonyle dont la partie alcoyle contient 1 à 4 atomes de carbone, cyano, carbamoyle, N-alcoylcarbamoyle ou N,N-dialcoylcarbamoyle dont chaque partie alcoyle contient 1 à 4 atomes de carbone ou forme avec l'atome d'azote auquel elle est liée un radical hétérocyclique saturé contenant 5 ou 6 chaînons et éventuellement un second hétéroatome choisi parmi les atomes d'oxygène, de soufre ou d'azote éventuellement substitué par un radical alcoyle contenant 1 à 4 atomes de carbone ou un radical phényle ou un radical phénylalcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone.

2 - Nouveaux taxoïdes selon la revendication pour lesquels Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical alcoyle contenant 1 à 6 atomes de carbone, alcényle contenant 2 à 6 atomes de carbone, cycloalcoyle contenant 3 à 6 atomes de carbone, phényle éventuellement substitué par un ou plusieurs atomes ou radicaux, identiques ou différents choisis parmi les atomes d'halogène et les radicaux alcoyles, alcoxy, dialcoylamino, acylamino, alcoxycarbonylamino ou trifluorométhyle ou un radical furyle-2 ou -3, thiényle-2 ou -3 ou thiazolyle-2, -4 ou -5 et R_4 et R_5, identiques ou différents, représentent un radical alcoxy droit ou ramifié contenant 1 à 6 atomes de carbone.

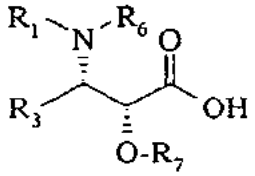
3 - Nouveaux taxoïdes selon la revendication 1 pour lesquels Z représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle R_1 représente un radical benzoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical tert-butyle et R_3 représente un radical isobutyle, isobutényle, butényle, cyclohexyle, phényle, furyle-2, furyle-3, thiényle-2, thiényle-3, thiazolyle-2, thiazolyle-4 ou thiazolyle-5, R_4 et R_5 représentent chacun un radical méthoxy.

4 - Procédé de préparation des taxoïdes selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un radical de formule générale (II) caractérisé en ce que l'on estérifie un produit de formule générale :



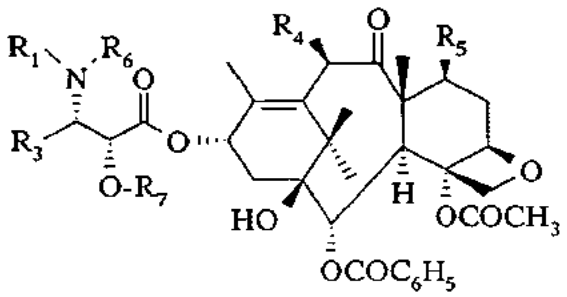
(III)

dans laquelle R_4 et R_5 sont définis comme dans l'une des revendications 1, 2 ou 3, au moyen d'un acide de formule générale :



(IV)

dans laquelle R_1 et R_3 sont définis comme précédemment, ou bien R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, et ou bien R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons, ou d'un dérivé de cet acide pour obtenir un ester de formule générale :



(V)

dans laquelle R_1, R_3, R_4, R_5, R_6 et R_7 sont définis comme précédemment, dont on remplace les groupements protecteurs représentés par R_7 et/ou R_6 et R_7 par des atomes d'hydrogène.

5 - Procédé selon la revendication 4 caractérisé en ce que l'estérification est effectuée au moyen d'un acide de formule générale (IV) en présence d'un agent de condensation et d'un agent d'activation dans un solvant organique à une température comprise entre -10 et 90°C.

6 - Procédé selon la revendication 4 caractérisé en ce que l'estérification est effectuée au moyen d'un acide de formule générale (IV) sous forme d'anhydride symétrique en opérant en présence d'un agent d'activation dans un solvant organique à une température comprise entre 0 et 90°C.

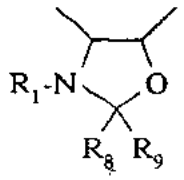
7 - Procédé selon la revendication 4 caractérisé en ce que l'estérification est effectuée en utilisant l'acide de formule générale (IV) sous forme d'halogénure ou sous forme d'anhydride mixte avec un acide aliphatique ou aromatique, éventuellement préparé in situ, en présence d'une base en opérant dans un solvant organique à une température comprise entre 0 et 80°C.

8 - Procédé selon la revendication 4 caractérisé en ce que l'on remplace les groupements protecteurs R_7 et/ou R_6 et R_7 par des atomes d'hydrogène en opérant, selon leur nature de la manière suivante :

1) lorsque R_6 représente un atome d'hydrogène et R_7 représente un groupement protecteur de la fonction hydroxy, on remplace les groupements protecteurs par des

atomes d'hydrogène au moyen d'un acide minéral ou organique utilisé seul ou en mélange en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés, les hydrocarbures aromatiques ou les nitriles à une température comprise entre -10 et 60°C,

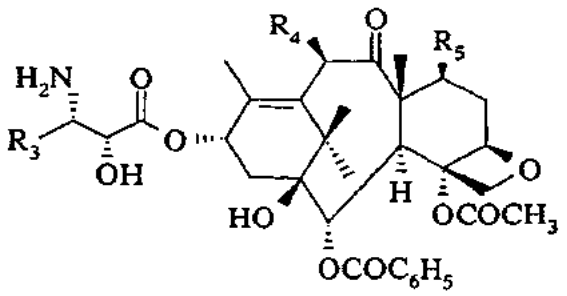
2) lorsque R_6 et R_7 forment ensemble un hétérocycle saturé à 5 ou 6 chaînons de formule générale :



(VI)

dans laquelle R_1 est défini comme précédemment, R_8 et R_9, identiques ou différents, représentent un atome d'hydrogène ou un radical alcoyle contenant 1 à 4 atomes de carbone, ou un radical aralcoyle dont la partie alcoyle contient 1 à 4 atomes de carbone et la partie aryle représente, de préférence, un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou un radical aryle représentant, de préférence un radical phényle éventuellement substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone, ou bien R_8 représente un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical trihalométhyle tel que trichlorométhyle ou un radical phényle substitué par un radical trihalométhyle tel que trichlorométhyle et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble avec l'atome de carbone auquel ils sont liés un cycle ayant 4 à 7 chaînons, on remplace le groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène en opérant, selon les significations de R_1, R_8 et R_9, de la manière suivante :

a) lorsque R_1 représente un radical tert-butoxycarbonyle, R_8 et R_9, identiques ou différents, représentent un radical alcoyle ou un radical aralcoyle ou aryle, ou bien R_8 représente un radical trihalométhyle ou un radical phényle substitué par un radical trihalométhyle, et R_9 représente un atome d'hydrogène, ou bien R_8 et R_9 forment ensemble un cycle ayant de 4 à 7 chaînons, on traite l'ester de formule générale (V) par un acide minéral ou organique éventuellement dans un solvant organique tel qu'un alcool pour obtenir le produit de formule générale :



(VII)

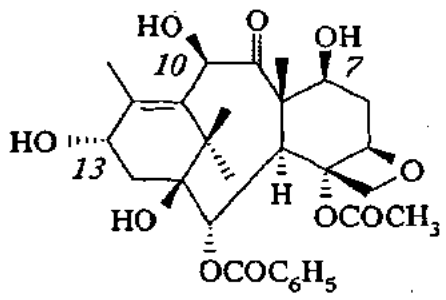
dans laquelle R_3, R_4 et R_5 sont définis comme précédemment, que l'on acyle au moyen de chlorure de benzoyle dans lequel le noyau phényle est éventuellement substitué, de chlorure de thénoyle, de chlorure de furoyle ou d'un produit de formule générale :

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

dans laquelle R_2 est défini comme précédemment et X représente un atome d'halogène ou un reste -O-R_2 ou -O-CO-O-R_2, pour obtenir un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II),

b) lorsque R_1 représente un radical benzoyle éventuellement substitué, thénoyle ou furoyle ou un radical R_2O-CO- dans lequel R_2 est défini comme précédemment, R_8 représente un atome d'hydrogène ou un radical alcoxy contenant 1 à 4 atomes de carbone ou un radical phényle substitué par un ou plusieurs radicaux alcoxy contenant 1 à 4 atomes de carbone et R_9 représente un atome d'hydrogène, on remplace le groupement protecteur formé par R_6 et R_7 par des atomes d'hydrogène s'effectue en présence d'un acide minéral ou organique utilisé seul ou en mélange en quantité stoechiométrique ou catalytique, en opérant dans un solvant organique choisi parmi les alcools, les éthers, les esters, les hydrocarbures aliphatiques, les hydrocarbures aliphatiques halogénés et les hydrocarbures aromatiques à une température comprise entre -10 et 60°C, de préférence entre 15 et 30°C.

9 - Procédé de préparation d'un nouveau taxoïde selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un atome d'hydrogène, R_4 est défini comme dans l'une des revendications 1, 2 ou 3 mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on traite la 10-désacétyl-baccatine III de formule :

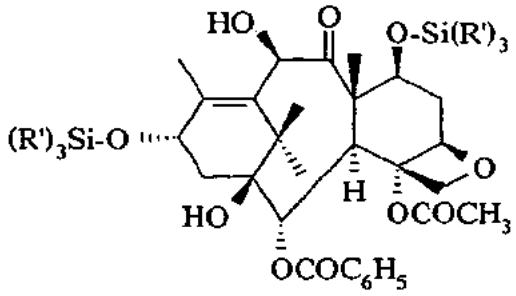


(IX)

par un halogénure de silyle de formule générale :

$$(R')_3\text{-Si-Hal} \qquad (X)$$

dans laquelle les symboles R', identiques ou différents, représentent un radical alcolyle contenant 1 à 4 atomes de carbone éventuellement substitué par un radical phényle, ou un radical phénylе pour obtenir un produit de formule générale :

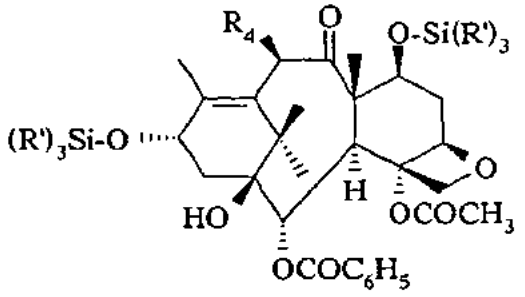


(XI)

dans laquelle R' est défini comme précédemment, que l'on traite par un produit de formule générale :

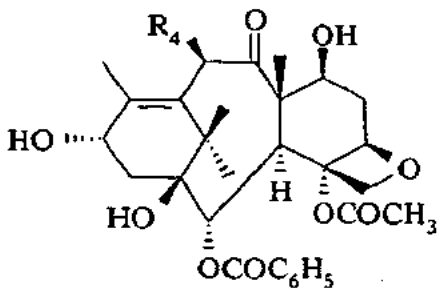
$$R_4\text{-}X_1 \qquad (XII)$$

dans laquelle R_4 est défini comme dans l'une des revendications 1, 2 ou 3 et X_1 représente un atome d'halogène ou un reste d'ester réactif tel qu'un reste d'ester sulfurique ou sulfonique pour obtenir un produit de formule générale :



(XIII)

dans laquelle R' et R_4 sont définis comme précédemment, dont on remplace les groupements protecteurs silylés par des atomes d'hydrogène pour obtenir un produit de formule générale :



(XIV)

dans laquelle R_4 est défini comme précédemment, qui est éthérifié sélectivement en position 7 par action d'un produit de formule générale :

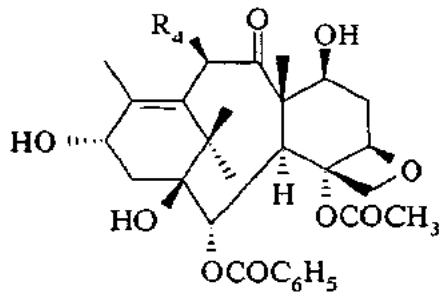
$$R_5\text{-}X_2 \qquad \text{(XV)}$$

dans laquelle R_5 est défini comme dans l'une des revendications 1, 2 ou 3 et X_2 représente un reste d'ester réactif ou un atome d'halogène pour donner le produit de formule générale (I) dans laquelle Z représente un atome d'hydrogène.

10 - Procédé de préparation d'un nouveau taxoïde selon la revendication 1 pour lequel Z représente un atome d'hydrogène, R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on fait réagir un produit de formule générale :

$$R_5\text{-}X_2 \qquad \text{(XV)}$$

sur un produit de formule générale :

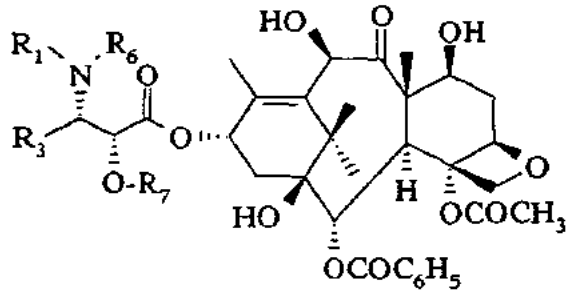


(XIV)

dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy, après métallation de la fonstion hydroxy en position 7, en opérant dans un solvant organique à une température comprise entre 0 et 50°C.

11 - Procédé de préparation d'un produit selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un radical de formule générale (II), R_4 est défini comme dans l'une des revendications 1, 2 ou 3 mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des

revendications 1, 2 ou 3 caractérisé en ce que l'on traite un produit de formule générale :

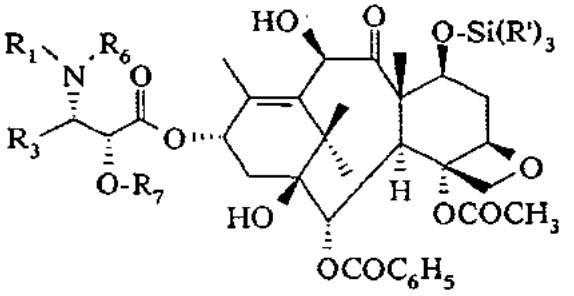


(XVI)

dans laquelle R_1, R_3, R_6 et R_7 sont définis comme dans l'une des revendications 1, 2, 3 ou 4 au moyen d'un produit de formule générale :

$$(R')_3Si\text{-}Hal \quad (X)$$

dans laquelle les symboles R', identiques ou différents, représentent un radical alcoyle contenant 1 à 4 atomes de carbone, éventuellement substitué par un radical phényle, ou un radical phényle pour obtenir un produit de formule générale :

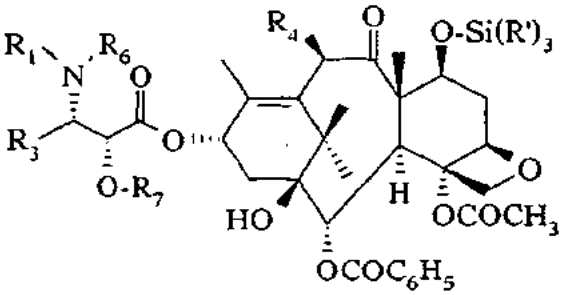


(XVII)

dans laquelle R', R_1, R_3, R_6 et R_7 sont définis comme précédemment, qui est fonctionnalisé en position 10 au moyen d'un produit de formule générale :

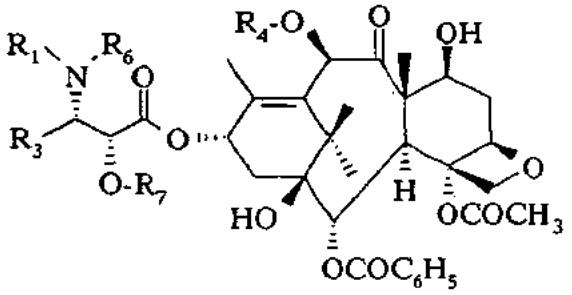
$$R_4\text{-}X_1 \qquad (XII)$$

dans laquelle R_4 est défini comme dans l'une des revendications 1, 2 ou 3 et X_1 représente un atome d'halogène ou un reste d'ester réactif pour donner un produit de formule générale :



(XVIII)

dans laquelle R', R_1, R_3, R_4, R_6 et R_7 sont définis comme précédemment dont le groupement protecteur silylé est remplacé par un atome d'hydrogène pour donner un produit de formule générale :



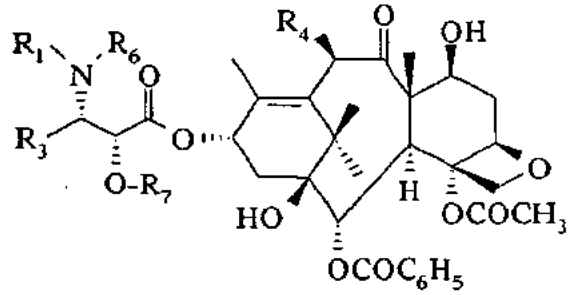
(XIX)

qui, par action d'un produit de formule générale (XV) conduit au produit de formule générale (V) dont les groupements protecteurs sont remplacés par des atomes d'hydrogène pour donner un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II).

12 - Procédé de préparation d'un produit selon la revendications 1 pour lequel Z représente un radical de formule générale (I), R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on fait réagir un produit de formule générale :

$$R_5\text{-}X_2 \qquad (XV)$$

dans laquelle R_5 est défini comme dans l'une des revendications 1, 2 ou 3 et X_2 représente un atome d'halogène ou un reste d'ester réactif, sur un produit de formule générale :



(XIX)

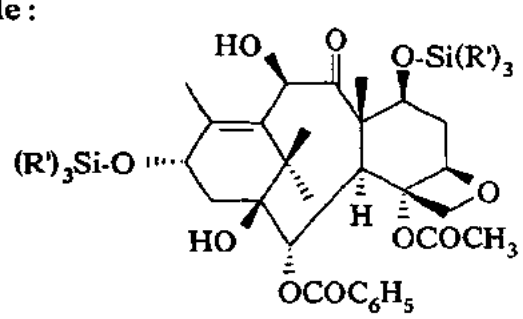
dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy, R_1, R_3 sont définis comme dans l'une des revendications 1, 2 ou 3, R_6 et R_7 sont définis comme dans la revendication 4 en opérant dans un solvant organique à une température comprise entre 0 et 50°C, suivie du remplacement des groupements protecteurs par des atomes d'hydrogène pour obtenir un produit de formule générale (I) dans laquelle

Z représente un radical de formule générale (II) et R_4 représente un atome d'hydrogène ou un radical hydroxy.

13 - Composition pharmaceutique caractérisée en ce qu'elle contient au moins un produit selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un radical de formule générale (II) en association avec un ou plusieurs diluants ou adjuvants pharmaceutiquement acceptables et éventuellement un ou plusieurs composés compatibles et pharmacologiquement actifs.

ORIGINAL

ou un radical phényle, sur la 10-désacétyl-baccatine III pour obtenir un produit de formule générale :

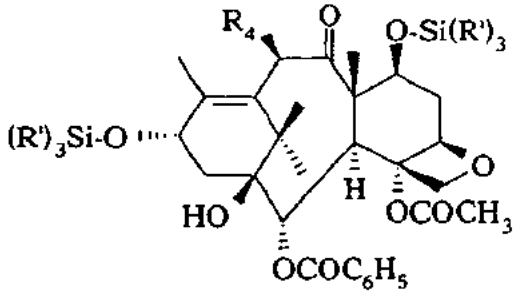


(XI)

dans laquelle R' est défini comme précédemment, puis action d'un produit de formule générale :

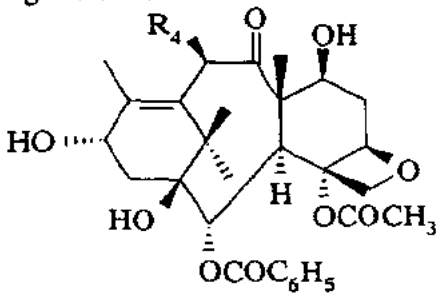
$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

dans laquelle R'_4 représente un radical alcoyle, alcényle,alcynyle, cycloalcoyle, cycloalcényle, alcanoyle, alcénoyle, alcynoyle, alcoxyacétyle, alcoylthioacétyle ou alcoyloxycarbonyle éventuellement substitué, ou un radical benzoyle ou hétérocyclylcarbonyle, ces différents radicaux et substituants ayant une définition identique à celle donnée dans la définition de R_4 et X_1 représente un reste d'ester réactif ou un atome d'halogène pour obtenir un produit de formule générale :



(XIII)

dans laquelle R' et R_4 sont définis comme précédemment dont les groupements protecteurs silylés sont remplacés par des atomes d'hydrogène pour obtenir un produit de formule générale :



(XIV)

dans laquelle R_4 est défini comme précédemment, qui est éthérifié sélectivement en position 7 par action d'un produit de formule générale :

R'_5-X_2 (XV)

dans laquelle R'_5 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle éventuellement substitué, ces différents radicaux et substituants ayant une définition identique à celle donnée dans la définition de R_5 et X_2 représente atome d'halogène ou un reste d'ester réactif tel qu'un reste d'ester sulfurique ou sulfonique pour donner le produit de formule générale (III).

Généralement, l'action d'un dérivé silylé de formule générale (X) sur la 10-désacétyl-baccatine III est effectuée dans la pyridine ou la triéthylamine éventuellement en présence d'un solvant organique tel qu'un hydrocarbure aromatique comme le benzène, le toluène ou les xylènes à une température comprise entre 0°C et la température de reflux du mélange réactionnel.

Généralement, l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI), est effectuée, après métallation de la fonction hydroxy en position 10 au moyen d'un hydrure de métal alcalin tel que l'hydrure de sodium, un amidure de métal alcalin tel que l'amidure de lithium ou d'un alcoylure de métal alcalin tel que le butyllithium, en opérant dans un solvant organique tel que le diméthylformamide ou le tétrahydrofurane à une température comprise entre 0 et 50°C.

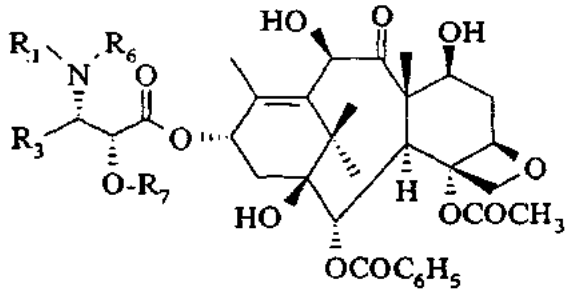
Généralement le remplacement des groupements protecteurs silylés du produit de formule générale (XIII) par des atomes d'hydrogène s'effectue au moyen d'un acide tel que l'acide fluorhydrique ou l'acide trifluoroacétique en présence d'une base telle que la triéthylamine ou la pyridine éventuellement substituée par un ou plusieurs radicaux alcoyles contenant 1 à 4 atomes de carbone, éventuellement associée à un solvant organique inerte tel qu'un nitrile comme l'acétonitrile ou un hydrocarbure aliphatique halogéné comme le dichlorométhane à une température comprise entre 0 et 80°C.

Généralement l'action d'un produit de formule générale (XV) sur un produit de formule générale (XIV) s'effectue dans les conditions indiquées précédemment pour l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI).

Les produits de formule générale (III) dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus par action d'un produit de formule générale (XV) sur un produit de formule générale (XIV) dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy dans les conditions décrites précédemment pour l'action d'un produit de formule générale (XII) sur un produit de formule générale (XI).

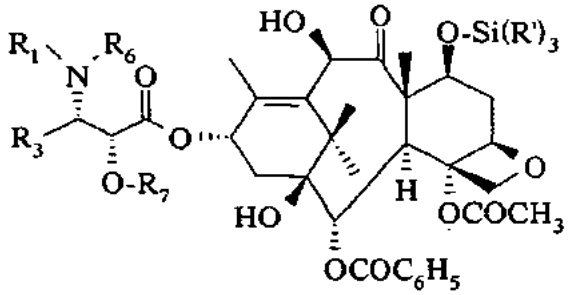
Les produits de formule générale (XIV) dans laquelle R_4 représente un atome d'hydrogène peuvent être obtenus dans les conditions décrites dans des demandes internationales PCT WO 94/11547 et PCT WO 93/06093.

Selon l'invention, les produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II), R_4 est défini comme précédemment mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme précédemment, peuvent être obtenus à partir d'un produit de formule générale :



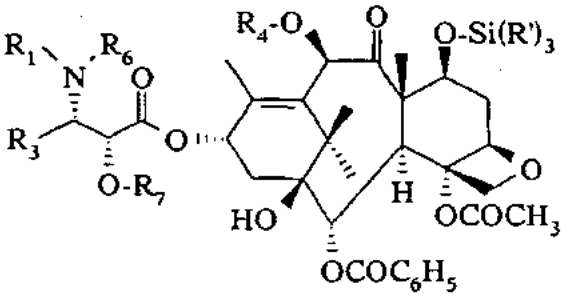
(XVI)

dans laquelle R_1, R_3, R_6 et R_7 sont définis comme précédemment par silylation en position 7 au moyen d'un produit de formule générale (X) pour obtenir un produit de formule générale :

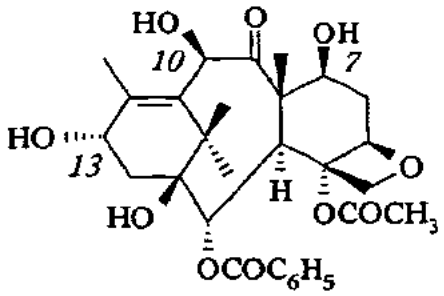


(XVII)

dans laquelle R', R_1, R_3, R_6 et R_7 sont définis comme précédemment, qui est fonctionnalisé en position 10 au moyen d'un produit de formule générale (XII) pour donner un produit de formule générale :



(XVIII)

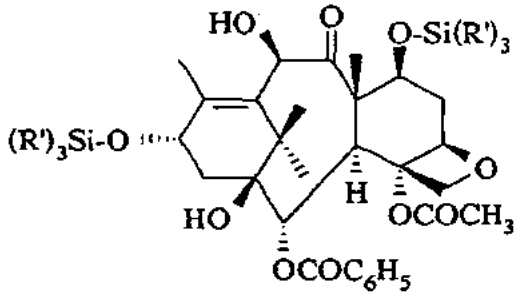


(IX)

par un halogénure de silyle de formule générale :

$$(R')_3\text{-Si-Hal} \qquad (X)$$

dans laquelle les symboles R', identiques ou différents, représentent un radical alcolyle contenant 1 à 4 atomes de carbone éventuellement substitué par un radical phényle, ou un radical phényle pour obtenir un produit de formule générale :

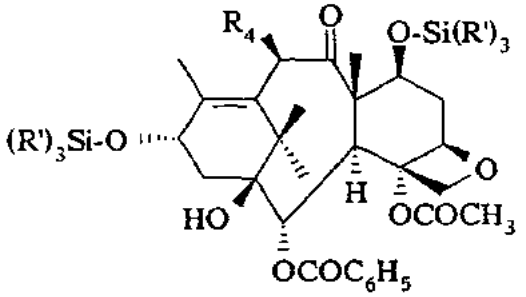


(XI)

dans laquelle R' est défini comme précédemment, que l'on traite par un produit de formule générale :

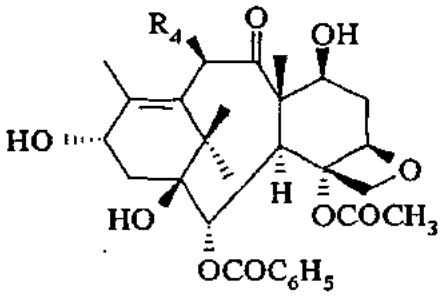
$$R'_4\text{-}X_1 \qquad (XII)$$

dans laquelle R'_4 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle, alcanoyle, alcénoyle, alcynoyle, alcoxyacétyle, alcoylthioacétyle ou alcoyloxycarbonyle éventuellement substitué, ou un radical benzoyle ou heterocyclylcarbonyle, ces radicaux et substituants ayant une définition identique à celle donnée dans la définition de R_4 dans les revendications 1, 2 ou 3 et X_1 représente un atome d'halogène ou un reste d'ester réactif tel qu'un reste d'ester sulfurique ou sulfonique pour obtenir un produit de formule générale :



(XIII)

dans laquelle R' et R_4 sont définis comme précédemment, dont on remplace les groupements protecteurs silylés par des atomes d'hydrogène pour obtenir un produit de formule générale :



(XIV)

dans laquelle R_4 est défini comme précédemment, qui est éthérifié sélectivement en position 7 par action d'un produit de formule générale :

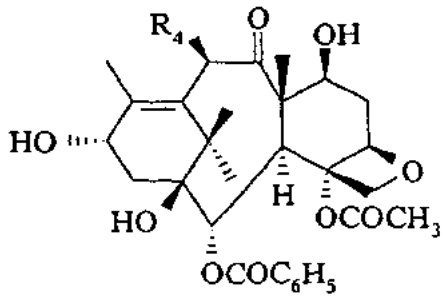
$$R'_5\text{-}X_2 \qquad (XV)$$

dans laquelle R'_5 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle éventuellement substitué, ces différents radicaux et substituants ayant une définition identique à celle donnée dans la définition de R_5 dans l'une des revendications 1, 2 ou 3 et X_2 représente un reste d'ester réactif ou un atome d'halogène pour donner le produit de formule générale (I) dans laquelle Z représente un atome d'hydrogène.

10 - Procédé de préparation d'un nouveau taxoïde selon la revendication 1 pour lequel Z représente un atome d'hydrogène, R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on fait réagir un produit de formule générale :

$$R'_5\text{-}X_2 \qquad (XV)$$

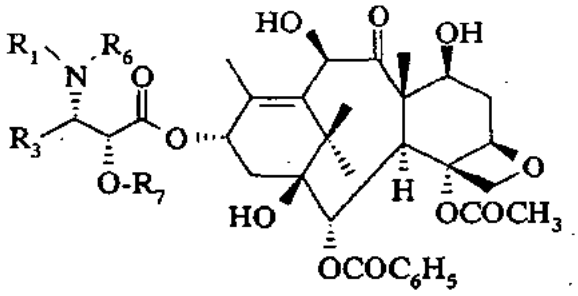
sur un produit de formule générale :



(XIV)

dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy, après métallation de la fonstion hydroxy en position 7, en opérant dans un solvant organique à une température comprise entre 0 et 50°C.

11 - Procédé de préparation d'un produit selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un radical de formule générale (II), R_4 est défini comme dans l'une des revendications 1, 2 ou 3 mais ne peut pas représenter un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on traite un produit de formule générale :

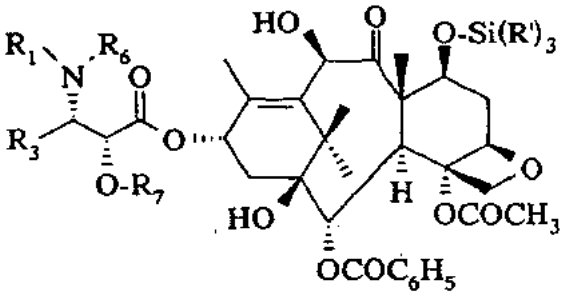


(XVI)

dans laquelle R_1, R_3, R_6 et R_7 sont définis comme dans l'une des revendications 1, 2, 3 ou 4 au moyen d'un produit de formule générale :

$$(R')_3Si\text{-}Hal \quad (X)$$

dans laquelle les symboles R', identiques ou différents, représentent un radical alcoyle contenant 1 à 4 atomes de carbone, éventuellement substitué par un radical phényle, ou un radical phényle pour obtenir un produit de formule générale :

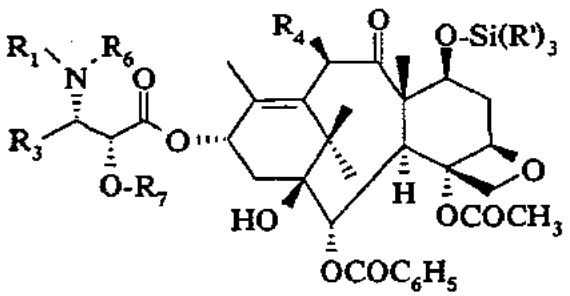


(XVII)

dans laquelle R', R_1, R_3, R_6 et R_7 sont définis comme précédemment, qui est fonctionnalisé en position 10 au moyen d'un produit de formule générale :

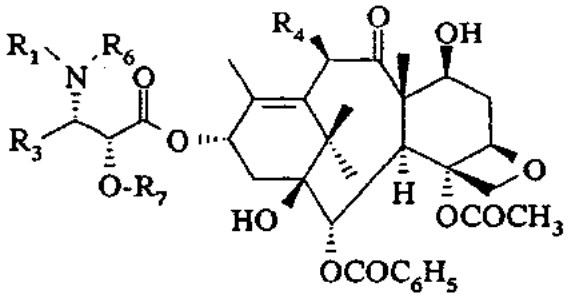
$$R'_4\text{-}X_1 \qquad (XII)$$

dans laquelle R_4 est défini comme dans la revendication 9 et X_1 représente un atome d'halogène ou un reste d'ester réactif pour donner un produit de formule générale :



(XVIII)

dans laquelle R', R_1, R_3, R_4, R_6 et R_7 sont définis comme précédemment dont le groupement protecteur silylé est remplacé par un atome d'hydrogène pour donner un produit de formule générale :



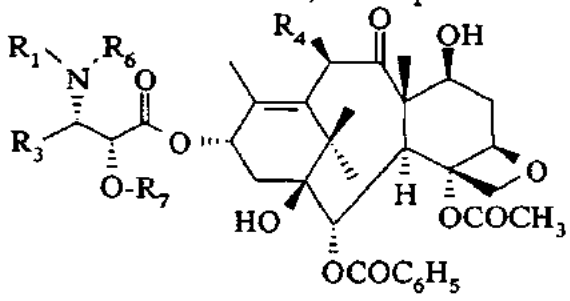
(XIX)

qui, par action d'un produit de formule générale (XV) conduit au produit de formule générale (V) dont les groupements protecteurs sont remplacés par des atomes d'hydrogène pour donner un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II).

12 - Procédé de préparation d'un produit selon la revendications 1 pour lequel Z représente un radical de formule générale (I), R_4 représente un atome d'hydrogène ou un radical hydroxy et R_5 est défini comme dans l'une des revendications 1, 2 ou 3 caractérisé en ce que l'on fait réagir un produit de formule générale :

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

dans laquelle R_5 est défini comme dans la revendication 9 et X_2 représente un atome d'halogène ou un reste d'ester réactif, sur un produit de formule générale :



(XIX)

dans laquelle R_4 représente un atome d'hydrogène ou un radical hydroxy, R_1, R_3 sont définis comme dans l'une des revendications 1, 2 ou 3, R_6 et R_7 sont définis comme dans la revendication 4 en opérant dans un solvant organique à une température comprise entre 0 et 50°C, suivie du remplacement des groupements protecteurs par des atomes d'hydrogène pour obtenir un produit de formule générale (I) dans laquelle Z représente un radical de formule générale (II) et R_4 représente un atome d'hydrogène ou un radical hydroxy.

13 - Composition pharmaceutique caractérisée en ce qu'elle contient au moins un produit selon l'une des revendications 1, 2 ou 3 pour lequel Z représente un radical de formule générale (II) en association avec un ou plusieurs diluants ou adjuvants pharmaceutiquement acceptables et éventuellement un ou plusieurs composés compatibles et pharmacologiquement actifs.

[redacted]

5847178

ISSUE CLASSIFICATION: Class 514 | Subclass 510

69652 U.S. PTO 08622011

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER
08/622,011	DEC 08 1998	5847178

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/622,011	03/26/96	196		1802	TRI

APPLICANTS: HERVE BOUCHARD, IVRY-SUR-SEINE, FRANCE; JEAN-DOMINIQUE BOURZAT, VINCENNES, FRANCE; ALAIN COMMERCON, VITRY-SUR-SEINE, FRANCE.

CONTINUING DATA********
VERIFIED PROVISIONAL APPLICATION NO. 60/010,144 01/17/96

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FOREIGN APPLICATIONS********
VERIFIED

FRANCE	95 03540	03/27/95
FRANCE	95 15381	12/22/95

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Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged	Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
[X] yes [ ] no	[X] yes [ ] no	GD		FRX	0	31	9	$1,590.00	9806.0367-

ADDRESS:
FINNEGAN, HENDERSON FARABOW GARRETT AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

TITLE: NEW TAXOIDS, THEIR PREPARATION AND PHARACEUTICAL COMPOSITIONS CONTAINING THEM

U.S. DEPT. OF COMM./ PAT. & TM — PTO-436L (Rev

CERTIFICATE OF CORRECTION

PARTS OF APPLICATION FILED SEPARATELY

SEP 7 1999

Applications Examiner

NOTICE OF ALLOWANCE MAILED	CLAIMS ALLOWED	
June 9, 1998	Total Claims: 28	Print Claim: 1

Assistant Examiner

ISSUE FEE		DRAWING		
Amount Due	Date Paid	Sheets Drwg.	Figs. Drwg.	Print Fig.
$1300.00	9-2-98			

BA K. TRINH
PRIMARY EXAMINER
GROUP 1200 1802
Primary Examiner

ISSUE BATCH NUMBER: 517

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ISSUE FEE IN FILE

(FACE)

SEARCHED			
Class	Sub.	Date	Exmr.
549	510 511	3.97	BJ
update		6.98	BT

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
549	510 511	6.98	BT

SEARCH NOTES	
	Date / Exmr.

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POSITION		ID NO.	DATE
CLASSIFIER		50	4/18/96
EXAMINER		CPP	5/2-96
TYPIST		38	5/1
VERIFIER			
CORPS CORR.			
SPEC. HAND		38	5/1/96
FILE MAINT.		335	5/3/96
DRAFTING			

INDEX OF CLAIMS

Claim Final	Claim Original	Date 3/97	Date 7/98	Date 6/98
	1	✓	✓	
	2	✓		
	3	✓		
	4	✓	✓	
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SYMBOLS

✓ ..... Rejected
= ..... Allowed
- (Through numbers) Canceled
* ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim Final	Claim Original	Date
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