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NEW AND EFFICIENT APPROACHES TO THE SEMISYNTHESIS OF TAXOL AND ITS C-13 SIDE CHAIN ANALOGS BY MEANS OF β–LACTAM SYNTHON METHOD

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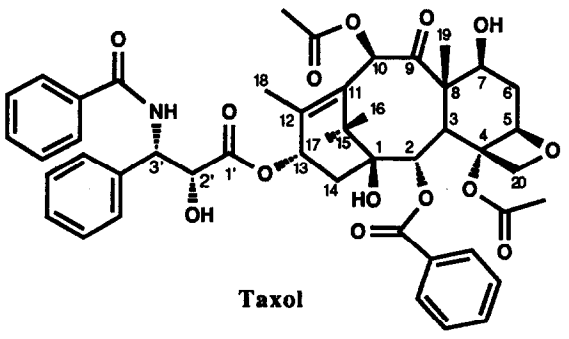
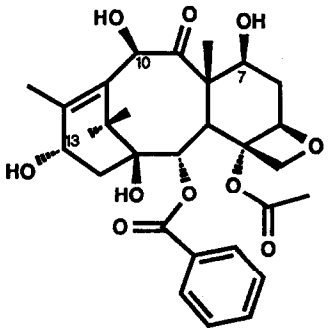
Summary: Highly efficient chiral ester enolate-imine condensation giving 3-hydroxy-4-aryl-β-lactams with excellent enantiomeric purity is successfully applied to the asymmetric synthesis of the enantiomerically pure taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenyl-isoserine and its analogs. (3*R*,4*S*)-*N*-benzoyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone readily derived from the 3-hydroxy-4-phenyl-β-lactam is coupled with protected baccatin IIIs, followed by deprotection to give optically pure taxol and 10-deacetyl-7,10-bis(Troc)-taxol in good yields. Fully assigned ^{1}H, ^{13}C, and 2D (COSY and HETCOR) NMR spectra of taxol thus synthesized are shown and discussed.

Taxol, a complex diterpene,[1] 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 trial for advanced overian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.[2] At present, the supply of taxol is solely dependent on the extraction from the bark of *Taxus brevifolia* (Pacific yew), which is a very slowly growing tree in old growth forests in the Northwest of the United States and the total number is estimated to one million. For the set of clinical trials only, more than 25,000 trees are required because of the low concentration of taxol in the bark. The harvest of those trees endangers not only the old growth forest in the Northwest of the United States, but also the future supply of taxol.



Taxol



10-Deacetylbaccatin III (1)

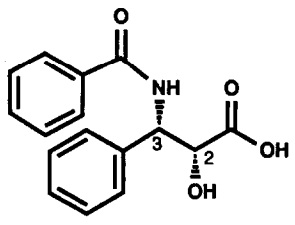
Accordingly, it is obviously an absolute necessity to develop practical cell culture or synthesis for this extremely promising anticancer drug. A couple of reports have appeared for the cell culture approach,[3] but the efficiency and practicality of those reported methods are still unknown. The total synthesis of taxol has already been attempted by a number of synthetic chemists without success so far, and requires much further elaborations.[4]

However, it has recently been found that the most complicated tetracyclic diterpene moiety of taxol, i.e., 10-deacetylbaccatin III (**1**), which is the most demanding in total synthesis, is more readily available from the leaves of *Taxus baccata* (European yew).[5] The extraction of the fresh leaves yields 10-deacetylbaccatin III in a very good yield, i.e., 1g/1Kg. The leaves are reproduced quickly, and thus it is unnecessary to cut down the trees to obtain the bark, which makes a sharp contrast to the case of taxol.

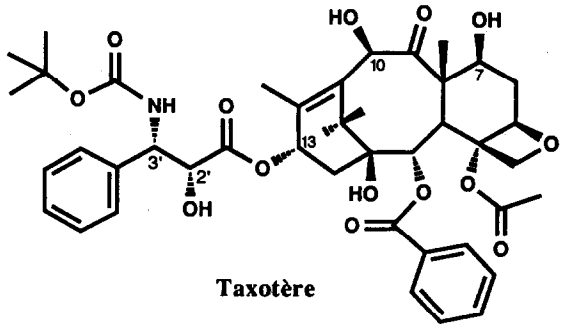
With the availability of 10-deacetylbaccatin III (**1**), it appears that sufficient supplies of taxol can now be produced in a semisynthetic fashion. Namely, if the C-13 side chain can be synthesized effectively and coupled to 10-deacetylbaccatin III (**1**) with proper protective groups, the semisynthetic process would be the most practical approach to the production of taxol and sufficient supplies of taxol may well be secured.

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem in solubility in aqueous media, which may impose some serious limitation in its use. Also, it is common that better drugs can 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 unnatural compound was named "taxotère", which has t-butoxycarbonyl instead of benzoyl on the amino group of (2*R*,3*S*)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of acetoxy group at C-10.[6] 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-(2*R*,3*S*)-3-phenylisoserine (**2**) with 10-deacetylbaccatin III (**1**) with proper protecting groups.[7]

It is known that the C-13 side chain, i.e., *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**3**) moiety, is crucial for the strong antitumor activity of taxol.[8] 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. Accordingly, it is quite promising to investigate the structure-activity relationship (SAR) for the C-13 side chain analogs of taxol with some modification of the baccatin III moiety in order to find more effective anticancer agents with better pharmacological property.[9]



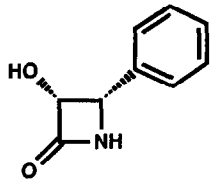
Taxol C-13 side chain (3)



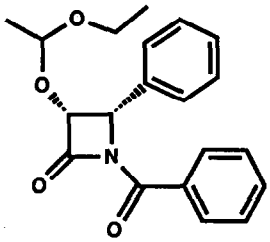
Taxotère

Accordingly, the development of an efficient method which can be applied not only to taxol, but also to taxotère and other analogs, i.e, the method having flexibility and wide applicability is extremely important and of current demand to promote the research in this area. We describe here an efficient and practical approach to the semisynthesis of the C-13 side chain analogs of taxol on the basis of the "β-Lactam Synthon Method",[10] which has the desired flexibility and wide applicability.

The first enantioselective synthesis of the important side chain **3** was obtained in 8 steps and 23% yield via a Sharpless epoxidation from cis-cinnamyl alcohol with an enantiomeric excess of 76-80%.[11] The obtained **3** was coupled with 7-triethylsilylbaccatin III (**4a**) by esterification.[12] A recent publication describes the chemo-enzymatic synthesis of a derivative of **3**, in which the racemic mixture was resolved by enzymatic hydrolysis with lipases.[13] We successfully applied lithium chiral ester enolate - imine cyclocondensation strategy[14] to the asymmetric synthesis of **3** via a (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one (**5a**) as the key-intermediate.[15] Based on this protocol, **3** can be obtained in 3 steps in high yield with virtually 100% e.e. Quite recently, it was found that 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (**6a**), readily derived from the hydroxy-β-lactam (**5a**), served as the key-intermediate for the synthesis of taxol.[16] Therefore, our β-lactam intermediate **5a** serves as the key-intermediate for both coupling methods.



5a

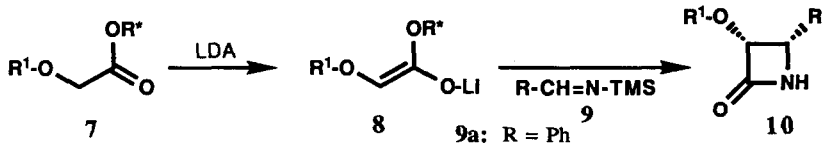


6a

RESULTS AND DISCUSSION

Synthesis of C-13 side chain of taxol and its analogs

First, we carried out the reactions of chiral lithium ester enolates (**8**) generated in situ from silyloxyacetates (**7**) (**Chart 1**) with *N*-trimethylsilylimines (**9**), which gave the corresponding chiral β-lactams **10** (eq. 1). Results are summarized in Table 1.



7 **8** **9** **10** (1)

9a: R = Ph
9b: R = 4-(MeO)C_6H_4
9c: R = 3,4-$(MeO)_2C_6H_3$

Chart 1

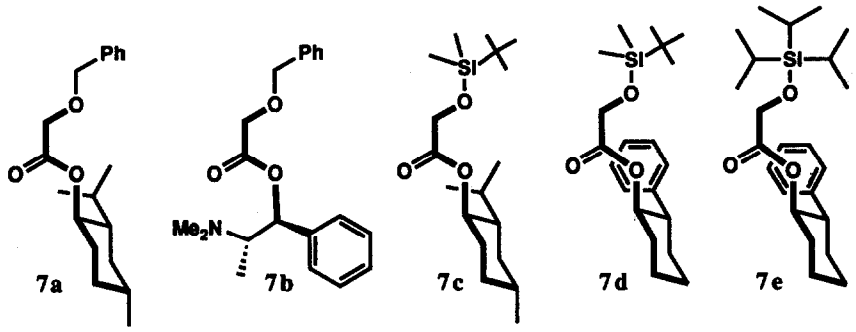


Table 1. Asymmetric synthesis of β-lactams (**10**) through chiral enolate - imine cyclocondensation

Entry	Ester	Imine	β-Lactam	Isolated Yield (%)	Configuration	Enantiomeric Purity (% e.e.)[a]
1	**7a**	**9a**	(-)**10-A**	18	3R,4S	15
2	**7b**	**9a**	(+)**10-A**	20	3S,4R	67
3	**7c**	**9a**	**10-B**	52	3R,4S	50
4	**7d**	**9a**	**10-B**	90	3R,4S	76
5	(-)**7e**	**9a**	(+)**10-C**	85	3R,4S	96
6	(+)**7e**	**9a**	(-)**10-C**	80	3S,4R	97
7	(-)**7e**	**9b**	(+)**10-D**	80	3R,4S	96
8	(-)**7e**	**9c**	(+)**10-E**	80	3R,4S	98

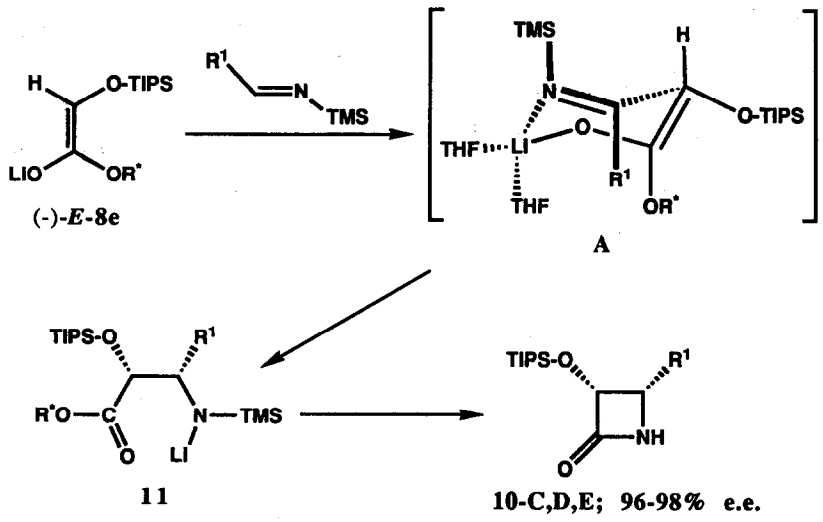
[a] Determined by ^{1}H NMR analysis using a chiral shift reagent, (+)-Eu(hfc)$_3$, (Entries 1-3) and by HPLC analysis on a chiral column - DAICEL CHIRACEL OD using n-hexane - 2-propanol as the solvent (Entries 4-8).

As Table 1 shows, the chiral auxiliary and the *O*-protecting group exert marked effects on the enantioselectivity as well as on the chemical yield of the reaction.[17] For example, the reactions of **7e**, bearing (-)- or (+)-trans-2-phenyl-1-cyclohexyl as the chiral auxiliary[19] and triisopropylsilyl (TIPS) as the *O*-protecting group, with **9a-c** give exclusively the corresponding cis-β-lactams **10** in high yields with extremely high enantiomeric purity (96-98% e.e.) (Entries 5-8). However, the reaction of **7d** bearing t-butyldimethylsilyl (TBDMS) as the *O*-protecting group with **9a** gives **10-B** in 90% yield, but with 76% e.e. (Entry 4). When (-)-menthyl is used as the chiral auxiliary and t-butyldimethylsilyl as the *O*-protecting group (**7c**), the reaction with **9a** gives **10-B** in 52% yield with only 50% enantiomeric purity (Entry 3). The use of benzyl as the *O*-protecting group and (-)-menthyl or ephedrinyl, **7a** and **7b**, gives (-)**10-A** (18% e.e.) or (+)**10-A** (67% e.e.) in low yield (15-20%) (Entries 1,2).

Absolute configurations of β-lactams (**10**) were determined by chemical correlation with authentic samples: **10-B** and (+)**10-C** were converted to (*R*)-3-phenyllactic acid via hydrogenolysis on 10% Pd-C followed by hydrolysis[10d-f] and to (2*R*,3*S*)-3-phenylisoserine by hydrolysis with 6N hydrochloric acid (*vide infra*), respectively. For (+)**10-D** and (+)**10-E**, absolute configurations were assigned by analogy with (+)**10-C** based on specific rotations and retention times on HPLC analyses on a chiral column (see Experimental Section). The absolute configuration of (-)**10-A** and (+)**10-A** were determined on the basis of the fact that **7d** bearing (-)-menthyl group gives (3*R*,4*S*)-β-lactam (**10-B**), i.e, (-)**10-A** should have (3*R*,4*S*) configuration and (+)**10-B** (3*S*,4*R*). The chiral auxiliaries, (+)- and (-)-trans-2-phenyl-1-cyclohexanol were recovered >90% yield in the Entries 5-8.

The exclusive formation of cis-β-lactams (+)**10-C,D,E** with 96-98% e.e. is rationalized by taking into account the highly selective generation of (*E*)-lithium enolates, (-)-*E*-**8e**, and the transition state **A** depicted in Scheme 1 on the basis of analysis discussed below.

Scheme 1



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