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Holton

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[54] **METAL ALKOXIDES**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 763,805, Sep. 23, 1991, abandoned.

[51] **Int. Cl.**[5] **C07D 305/14**; C07F 5/02; C07F 7/02

[52] **U.S. Cl.** **549/213**; 549/214; 549/510; 549/511

[58] **Field of Search** 549/214, 510, 511, 213

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,814,470	3/1989	Colin et al.	514/449
4,857,653	8/1989	Colin et al.	549/511
4,924,011	5/1990	Denis et al.	849/510
4,924,012	5/1990	Colin et al.	849/510
4,942,184	7/1990	Haugwitz et al.	514/449
5,015,744	5/1991	Holton	549/510

FOREIGN PATENT DOCUMENTS

253738	7/1987	European Pat. Off. .
253739	7/1987	European Pat. Off. .
336840	4/1989	European Pat. Off. .
336841	4/1989	European Pat. Off. .

OTHER PUBLICATIONS

Denis and Greene, "A Highly Efficient, Practical Approach to Natural Taxol", J. Am. Chem. Soc. 1988, 110, 5917–5919.

Holton et al., "A Synthesis of Taxusin", J. Am. Chem. Soc., 1988, 110, pp. 6558–6560.

Holton, "Synthesis of the Taxane Ring System", J. Am. Chem. Soc., 1984, 106, pp. 5731–5732.

Mukerjee et al., "β-Lactams: Retrospect and Prospect", Tetrahedron vol. 34, Report No. 52, pp. 1731–1767 (1978).

Wani et al., "Plant Antitumor Agents. VI. The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor Agent from *Taxus brevifolia*", J. Am. Chem. Soc. 93:9, May 5, 1971, pp. 2325–2327.

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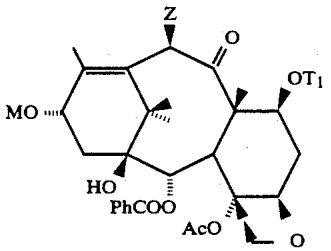
[57] **ABSTRACT**

A metal alkoxide having the following formula:



(1)

wherein T_1 is hydrogen or a hydroxy protecting group, Z is $—OT_2$, or $—OCOCH_3$, T_2 is hydrogen or a hydroxy protecting group, and M is selected from the group comprising Group IA, IIA and transition metals are useful in the preparation of biologically active derivatives of baccatin III and 10-deacetyl baccatin III.

15 Claims, No Drawings

METAL ALKOXIDES

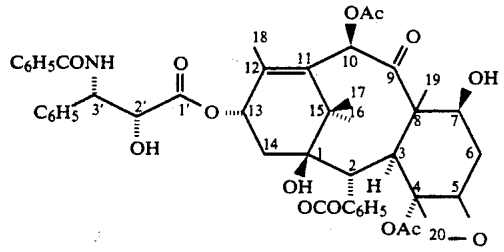
REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Ser. No. 07/763,805, filed Sep. 23, 1991, now abandoned.

BACKGROUND OF THE INVENTION

The present invention is directed to novel metal alkoxides useful in the preparation of derivatives of baccatin III and 10-deacetyl baccatin III such as taxol, taxotere and other taxane derivatives which have biological activity.

The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has the following structure:



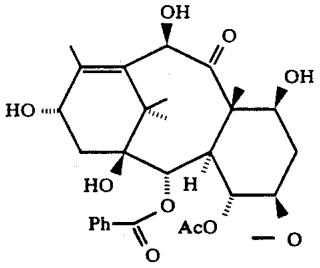
(I)

Because of this promising activity, taxol is currently undergoing clinical trials in both France and the United States.

The supply of taxol for these clinical trials is presently being provided by the bark from *Taxus brevifolia* (Western Yew). However, taxol is found only in minute quantities in the bark of these slow growing evergreens, causing considerable concern that the limited supply of taxol will not meet the demand. Consequently, chemists in recent years have expended their energies in trying to find a viable synthetic route for the preparation of taxols. So far, the results have not been entirely satisfactory.

One synthetic route that has been proposed is directed to the synthesis of the tetracyclic taxane nucleus from commodity chemicals. A synthesis of the taxol congener taxusin has been reported by Holton, et al. in JACS 110, 6558 (1988). Despite the progress made in this approach, the final total synthesis of taxol is, nevertheless, likely to be a multi-step, tedious, and costly process.

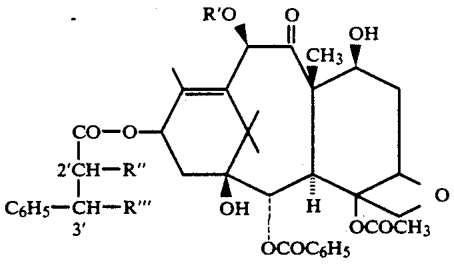
An alternate approach to the preparation of taxol has been described by Greene, et al. in JACS 110, 5917 (1988), and involves the use of a congener of taxol, 10-deacetyl baccatin III which has the structure of formula II shown below:



(II)

10-deacetyl baccatin III is more readily available than taxol since it can be obtained from the needles of *Taxus baccata*. According to the method of Greene et al., 10-deacetyl baccatin III is converted to taxol by attachment of the C-10 acetyl group and by attachment of the C-13 β-amido ester side chain through the esterification of the C-13 alcohol with a β-amido carboxylic acid unit. Although this approach requires relatively few steps, the synthesis of the β-amido carboxylic acid unit is a multi-step process which proceeds in low yield, and the coupling reaction is tedious and also proceeds in low yield. However, this coupling reaction is a key step which is required in every contemplated synthesis of taxol or biologically active derivative of taxol, since it has been shown by Wani, et al. in JACS 93, 2325 (1971) that the presence of the β-amido ester side chain at C13 is required for anti-tumor activity.

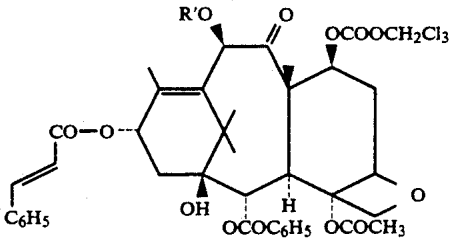
More recently, it has been reported in Colin et al. U.S. Pat. No. 4,814,470 that taxol derivatives of the formula III below, have an activity significantly greater than that of taxol (I).



(III)

R′ represents hydrogen or acetyl and one of R″ and R‴ represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof.

According to Colin et al., U.S. Pat. No. 4,418,470, the products of general formula (III) are obtained by the action of the sodium salt of tert-butyl N-chlorocarbamate on a product of general formula:

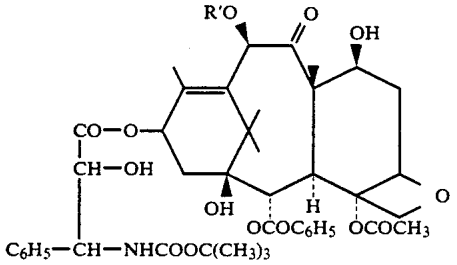


(IV)

in which R′ denotes an acetyl or 2,2,2-trichloroethoxycarbonyl radical, followed by the replacement of the 2,2,2-trichloroethoxycarbonyl group or groups by hy-

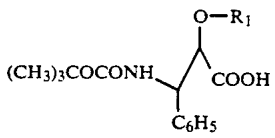
drogen. It is reported by Denis et al. in U.S. Pat. No. 4,924,011, however, that this process leads to a mixture of isomers which has to be separated and, as a result, not all the baccatin III or 10-deactylbaccatin III employed for the preparation of the product of general formula (IV) can be converted to a product of general formula (III).

In an effort to improve upon the Colin et al. process, Denis et al. disclose a different process for preparing derivatives of baccatin III or of 10-deactylbaccatin III of general formula



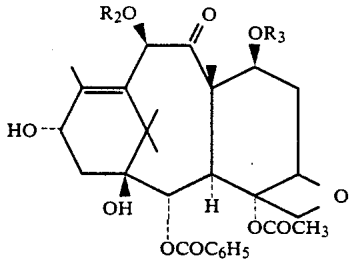
(V)

in which R' denotes hydrogen or acetyl wherein an acid of general formula:



(VI)

in which R_1 is a hydroxy-protecting group, is condensed with a taxane derivative of general formula:



(VII)

in which R_2 is an acetyl hydroxy-protecting group and R_3 is a hydroxy-protecting group, and the protecting groups R_1, R_3 and, where appropriate, R_2 are then replaced by hydrogen. However, this method employs relatively harsh conditions, proceeds with poor conversion, and provides less than optimal yields.

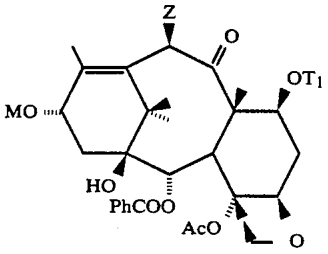
A major difficulty remaining in the synthesis of taxol and other potential anti-tumor agents is the lack of baccatin III and 10-deacetyl baccatin III derivatives which have been activated at the C-13 oxygen. Development of such derivatives would permit attachment of the β-amido ester side chain in high yield and thus, facilitate the synthesis of taxol as well as related anti-tumor agents having a modified set of nuclear substituents or a modified C-13 side chain.

Another major difficulty encountered in the synthesis of taxol is that known processes for the attachment of the β-amido ester side chain at C-13 are generally not sufficiently diastereoselective. Therefore the side chain precursor must be prepared in optically active form to obtain the desired diastereomer during attachment.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of activated baccatin III and 10-deacetyl baccatin III derivatives which permit attachment of the β-amido ester side chain in high yield, the provision of such derivatives which permit the use of a racemic mixture of side chain precursor, eliminating the need for the expensive, time-consuming process of separating the precursor into its respective isomeric forms, and the provision of such derivatives which permit the preparation of taxanes having greater variety in the side-chain.

Briefly, therefore, the present invention is directed to a metal alkoxide having the formula:



(1)

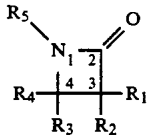
wherein T_1 is hydrogen or a hydroxy protecting group, Z is —OT_2, or —$OCOCH_3$, T_2 is hydrogen or a hydroxy protecting group, and M is a metal, preferably, Li, Mg, Na, K or Ti.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION

Metal alkoxides (1) are activated derivatives of baccatin III and/or 10-deacetyl baccatin III and have particular utility in a process for the preparation of taxol, taxotere and other biologically active taxane derivatives. In accordance with the present invention, metal alkoxides (1) are reacted with β-lactam (2) to form a β-amido ester intermediate. The intermediate is then converted to a biologically active taxane derivative.

β-lactam (2) has the general formula:



(2)

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 alkyl, alkenyl, alkynyl, aryl, heteroaryl, or hydroxy protecting group;

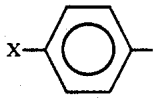
R_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

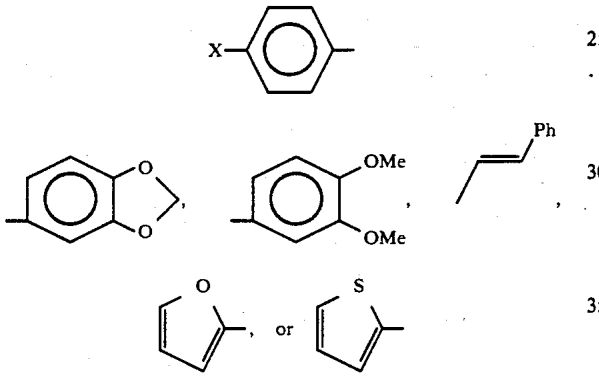
R_9 is an amino protecting group;

R_{10} is alkyl, alkenyl, alkynyl, aryl, or 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 $—NR_8R_{14}$; and
R_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl.

In accordance with the present invention, R_5 of β-lactam (2) is preferably $—COR_{10}$ with R_{10} being aryl, p-substituted phenyl, or lower alkoxy, and most preferably, phenyl, methoxy, ethoxy, tert-butoxy ("tBuO"; $(CH_3)_3CO—$) or



wherein X is Cl, Br, F, $CH_3O—$, or $NO_2—$. Preferably R_2 and R_4 are hydrogen or lower alkyl. R_3 is preferably aryl, most preferably, naphthyl, phenyl,



wherein X is as previously defined, Me is methyl and Ph is phenyl. Preferably, R_1 is selected from $—OR_6$, $—SR_7$ or $—NR_8R_9$ wherein R_6, R_7 and R_9, are hydroxy, sulfhydryl, and amine protecting groups, respectively, and R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl. Most preferably, R_1 is $—OR_6$ wherein R_6 is triethylsilyl ("TES"), 1-ethoxyethyl ("EE") or 2,2,2-trichloroethoxymethyl.

The β-lactam alkyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, aryl, hexyl, and the like.

The β-lactam alkenyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, aryl, hexenyl, and the like.

The β-lactam alkynyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, aryl, hexynyl, and the like.

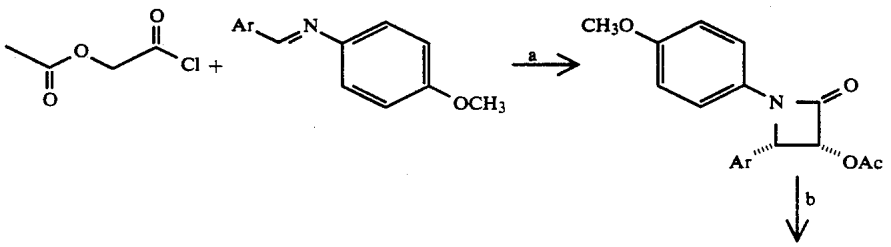
The β-lactam aryl moieties described, either alone or with various substituents, contain from 6 to 15 carbon atoms and include phenyl, α-naphthyl or β-naphthyl, etc. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, amido, etc. Phenyl is the more preferred aryl.

As noted above, R_1 of β-lactam (2) may be $-OR_6$ with R_6 being alkyl, acyl, ethoxyethyl ("EE"), triethylsilyl ("TES"), 2,2,2-trichloroethoxymethyl, or other hydroxyl protecting group such as acetals and ethers, i.e., methoxymethyl ("MOM"), benzyloxymethyl; esters, such as acetates; carbonates, such as methyl carbonates; and alkyl and aryl silyl such as triethylsilyl, trimethylsilyl, dimethyl-t-butylsilyl, dimethylarylsilyl, dimethylheteroarylsilyl, and triisopropylsilyl, and the like. A variety of protecting groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981. 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.

Also as noted previously, R_7 may be a sulfhydryl protecting group and R_9 may be an amine protecting group. Sulfhydryl protecting groups include hemithioacetals such as 1-ethoxyethyl and methoxymethyl, thioesters, or thiocarbonates. Amine protecting groups include carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate. A variety of sulfhydryl and amine protecting groups may be found in the above-identified text by T. W. Greene.

The β-lactams (2) can be prepared from readily available materials, as is illustrated in schemes A and B below:

Scheme A



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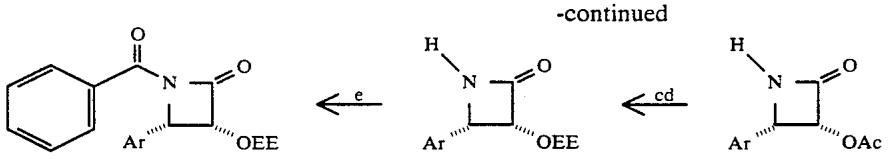
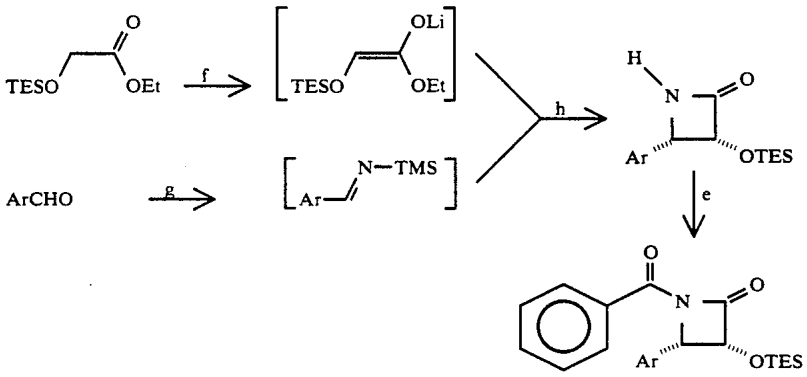


Scheme B



reagents: (a) triethylamine, CH_2Cl_2, 25° C., 18 h; (b) 4 equiv ceric ammonium nitrate, CH_3CN, −10° C., 10 min; (c) KOH, THF, H_2O, 0° C., 30 min; (d) ethyl vinyl ether, THF, toluene sulfonic acid (cat.), 0° C., 1.5 h; (e) n-butyllithium, ether, −78° C., 10 min; benzoyl chloride, −78° C., 1 h; (f) lithium diisopropyl amide, THF −78° C. to −50° C.; (g) lithium hexamethyldisilazide, THF −78° C. to 0° C.; (h) THF, −78° C. to 25° C., 12 h.

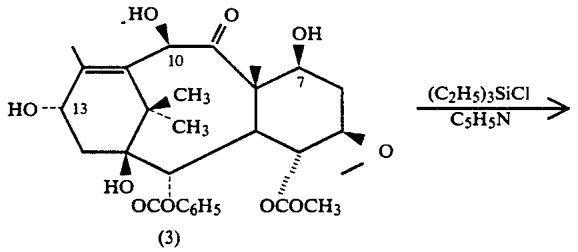
The starting materials are readily available. In scheme A, α-Acyloxy acetyl chloride is prepared from glycolic acid, and, in the presence of a tertiary amine, it cyclocondenses with imines prepared from aldehydes and p-methoxyaniline to give 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-ones. The p-methoxyphenyl group can be readily removed through oxidation with ceric ammonium nitrate, and the acyloxy group can be hydrolyzed under standard conditions familiar to those experienced in the art to provide 3-hydroxy-4-arylazetidin-2-ones. The 3-hydroxyl group is protected with 1-ethoxyethyl, but may be protected with variety of standard protecting groups such as the triethylsilyl group or other trialkyl (or aryl) silyl groups. In Scheme B, ethyl-α-triethylsilyloxyacetate is readily prepared from glycolic acid.

The racemic β-lactams may be resolved into the pure enantiomers prior to protection by recrystallization of the corresponding 2-methoxy-2-(trifluoromethyl) phenylacetic esters. However, the reaction described hereinbelow in which the β-amido ester side chain is attached has the advantage of being highly diastereoselective, thus permitting the use of a racemic mixture of side chain precursor.

The 3-(1-ethoxyethoxy)-4-phenylazetidin-2-one of Scheme A and the 3-(1-triethylsilyl)-4-phenylazetidin-2-one of Scheme B can be converted to β-lactam (2), by treatment with a base, preferably n-butyllithium, and an acyl chloride, sulfonyl chloride, phosphinyl chloride, phosphoryl chloride or an alkyl chloroformate at −78° C. or less.

Preferably, the metal alkoxides are prepared by reacting an alcohol having two to four rings of the taxane nucleus and a C-13 hydroxyl group with an organometallic compound in a suitable solvent. Most preferably, the alcohol is a protected baccatin III, in particular, 7-O-triethylsilyl baccatin III (which can be obtained as described by Greene, et al. in JACS 110, 5917 (1988) or by other routes) or 7,10-bis-O-triethylsilyl baccatin III.

As reported in Greene et al., 10-deacetyl baccatin III is converted to 7-O-triethylsilyl-10-deacetyl baccatin III according to the following reaction scheme:



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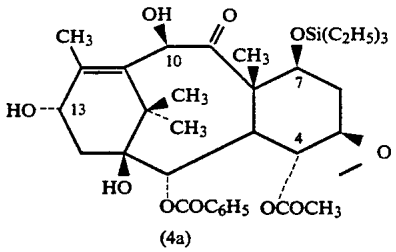

(4a)

Under what is reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(C_2H_5)_3SiCl$ at 23° C. under an argon atmosphere for 20 hours in the presence of 50 ml of pyridine/mmol of 10-deacetyl baccatin III to provide 7-triethylsilyl-10-deacetyl baccatin III (4a) as a reaction product in 84–86% yield after purification.

The reaction product (4a) is then acetylated with 5 equivalents of CH_3COCl and 25 mL of pyridine/mmol of 4a at 0° C. under an argon atmosphere for 48 hours to provide 86% yield of 7-O-triethylsilyl baccatin III (4b) as reported by Greene, et al. in JACS 110, 5917 at 5918 (1988).

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