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[54] **TAXANES HAVING A BUTENYL SUBSTITUTED SIDE-CHAIN AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

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[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,284,864.

[21] Appl. No.: **463,704**

[22] Filed: **Jun. 5, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 94,719, Jul. 20, 1993, abandoned, which is a continuation-in-part of Ser. No. 34,247, Mar. 22, 1993, Pat. No. 5,430,160, and Ser. No. 975,705, Nov. 13, 1992, Pat. No. 5,284,864, said Ser. No. 34,247, and Ser. No. 975,705, each is a continuation-in-part of Ser. No.949,107, Sep. 22, 1992, abandoned, which is a continuation-in-part of Ser. No. 863,849, Apr. 6, 1992, abandoned, which is a continuation-in-part of Ser. No. 862,955, Apr. 3, 1992, abandoned, which is a continuation-in-part of Ser. No. 763,805, Sep. 23, 1991, abandoned.

[51] **Int. Cl.**[6] **C07D 305/14**; A61K 31/335

[52] **U.S. Cl.** **549/510**; 549/511; 514/449

[58] **Field of Search** 549/510, 511; 544/449

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,680,391	7/1987	Firestone et al.	540/355
4,814,470	3/1989	Colin et al.	514/499
4,857,653	8/1989	Colin et al.	549/511
4,876,399	10/1989	Holton et al.	568/817
4,924,011	5/1990	Denis et al.	549/510
4,924,012	5/1990	Colin et al.	549/510
4,942,184	7/1990	Haugwitz et al.	514/449
4,960,790	10/1990	Stella et al.	514/449
5,015,744	5/1991	Holton	549/510
5,059,699	10/1991	Kingston et al.	549/511
5,136,060	8/1992	Holton	549/510
5,175,315	12/1992	Holton	549/510
5,227,400	7/1993	Holton et al.	514/444
5,229,526	7/1993	Holton	544/60
5,243,045	9/1993	Holton et al.	544/60
5,254,703	10/1993	Holton	549/510
5,272,171	12/1993	Ueda et al.	514/449
5,274,124	12/1993	Holton	549/214
5,283,253	2/1994	Holton et al.	514/444
5,284,864	2/1994	Holton et al.	514/449
5,284,865	2/1994	Holton et al.	549/449
5,336,785	8/1994	Holton	549/214
5,338,872	8/1994	Holton et al.	549/510
5,350,866	9/1994	Holton et al.	549/510
5,384,399	1/1995	Holton	544/97
5,399,726	3/1995	Holton et al.	549/510
5,405,972	4/1995	Holton et al.	549/214
5,430,160	7/1995	Holton	549/510
5,466,834	11/1995	Holton	549/510
5,489,601	2/1996	Holton et al.	514/337
5,532,363	7/1996	Holton	544/97
5,539,103	7/1996	Holton	540/354

FOREIGN PATENT DOCUMENTS

0247378 B1	12/1987	European Pat. Off. .
0253738 A1	1/1988	European Pat. Off. .
0253739 A1	1/1988	European Pat. Off. .
0336840 A1	10/1989	European Pat. Off. .
0336841 A1	10/1989	European Pat. Off. .
0400971 A2	12/1990	European Pat. Off. .
0428376 A1	5/1991	European Pat. Off. .
0534707 A1	9/1992	European Pat. Off. .
0534708 A1	9/1992	European Pat. Off. .
0534709 A1	9/1992	European Pat. Off. .
919224	11/1993	South Africa .
WO 92/09589	6/1992	WIPO .
WO 93/02065	3/1993	WIPO .

OTHER PUBLICATIONS

International Search Report issued for PCT/US93/10813 dated Mar. 11, 1994.

Holton et al., "A Synthesis of Taxusin", JACS 110:6558 (1988).

Samaranayake et al., "Modified Taxols. 5.1 Reaction of Taxol with Electrophilic Reagents and Preparation of a Rearranged Taxol Derivative with Tubulin Assembly Activity3", J. Org. Chem. 1991, 56, pp. 5114–5119.

Wani et al., "Plant Antitumor Agents. VI. The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor Agent from *Texus Brevifolia*", JACS 93:9, pp. 2325–2327 (May 5,1971).

Holton, "Synthesis of the Taxane Ring System", JACS 106, pp. 5731–5732 (1984).

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

Science/Technology "New Family of Taxol, Taxotere Analogs Developed", Chem. & Engineering News, pp. 26–27 (Apr. 12, 1993).

Schultz et al., "Synthesis of New N–radicals of Tetrazon–1–yl", Chem. Abstr. vol. 108, No. 37298C, p. 581 (1988).

Senilh et al., "Chime Organique Biologique—Hemisynthese de nouveaux analogues du taxol. Etude de leur interaction avec la tubuline", C.R. Acad. Sc. Paris, t. 299, Serie II, No. 15, pp. 1039–1043 (1984).

Ojima et al., "New and Efficient Approaches to the Semisynthesis of Taxol and its C–13 Side Chain Analogs by Means of β–Lactam Synthon Method", Tetrahedron vol. 48, No. 34, pp. 6985–7012 (1992).

Denis & Green, "A Highly Efficient, Practical Approach to Natural Taxol", JACS 110:5917–5919 (1988).

(List continued on next page.)

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[57] **ABSTRACT**

Taxane derivatives having a 3' butenyl substituted C13 side chain.

29 Claims, No Drawings

OTHER PUBLICATIONS

Witherup et al., "High Performance Liquid Chromatographic Separation of Taxol and Related Compounds From *Taxus Brevifolia*", Jour. of Liquid Chromatography, 12(11), pp. 2117–2132 (1989).

Kaiser et al., "Synthesis of Esters of Acid–Unstable Alcohols by Means of n–butyllithium", J. Org. Chem. vol. 35, p. 1198, (1970).

Bartholomew et al., "A Novel Rearrangement Reaction Conversion of 3–(chloromethyl)azetidin–2–ones to Azetidine–3–carboxylic Acid Esters", Tetrahedron Letters, vol. 32, No. 36, pp. 4795–4798 (1991).

N.F. Magri et al., "Modified Taxols, 4. Synthesis and Biological Activity of Taxols Modified in the Side Chain", vol. 51, No. 2, pp. 298–306, (1988).

H.M. Deutsch et al., "Synthesis of Congeners and Prodrugs. 3. Water–Soluble Prodrugs of Taxol with Potent Antitumour Activity", Journal of Medicinal Chem., vol. 32, No. 4, pp. 788–792, (Apr. 1989).

TAXANES HAVING A BUTENYL SUBSTITUTED SIDE-CHAIN AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

REFERENCE TO RELATED APPLICATIONS

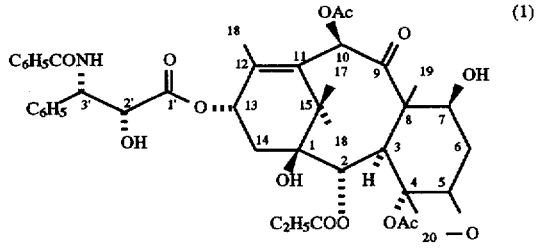
This is a continuation of application Ser. No. 08/094,719 filed on Jul. 20, 1993, now abandoned, which is a continuation-in-part application of U.S. Ser. No. 08/034,247 filed Mar. 22, 1993 now U.S. Pat. No. 5,430,160 which is a continuation-in-part of U.S. Ser. No. 07/949,107, filed Sep. 22, 1992, now abandoned which is a continuation-in-part application of U.S. Ser. No. 07/863,849, filed Apr. 6, 1992, now abandoned, which is a continuation-in-part application of U.S. Ser. No. 07/862,955, filed Apr. 3, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/763,805, filed Sep. 23, 1991, now abandoned. The application U.S. Ser. No. 08/094,719, filed Jul. 20, 1993, now abandoned, is also a continuation-in-part application of U.S. Ser. No. 07/975,705, filed Nov. 13, 1992 now U.S. Pat. No. 5,284,804 which is a continuation-in-part application of U.S. Ser. No. 07/949,107, filed Sep. 22, 1992 now abandoned, which is a continuation-in-part application of U.S. Ser. No. 07/863,849, filed Apr. 6, 1992 now abandoned, which is a continuation-in-part application of U.S. Ser. No. 07/862,955, filed Apr. 3, 1992 now abandoned which is a continuation-in-part of U.S. Ser. No. 07/763,805, filed Sep. 23, 1991, now abandoned.

This invention was made with Government support under NIH Grant #CA 42031 and NIH Grant #CA 55131 awarded by the National Institutes of Health. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The present invention is directed to novel taxanes which have utility as antileukemia and antitumor agents.

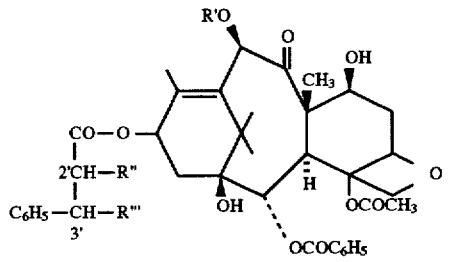
The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following structural formula:



(1)

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

Colin et al. reported in U.S. Pat. No. 4,814,470 that taxol derivatives having structural formula (2) below, have an activity significantly greater than that of taxol (1).



(2)

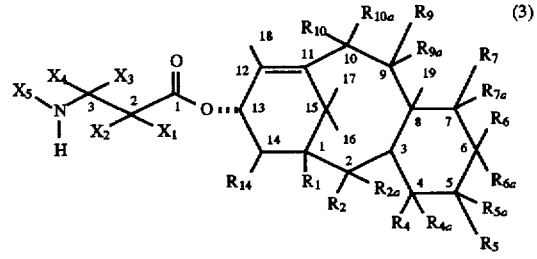
R' represents hydrogen or acetyl and one of R" and R'" represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula (2) in which R' is hydrogen R" is hydroxy, R'" is tert-butoxycarbonylamino having the 2'R, 3'S configuration is commonly referred to as taxotere.

Although taxol and taxotere are promising chemotherapeutic agents, they are not universally effective. Accordingly, a need remains for additional chemotherapeutic agents.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of novel taxane derivatives which are valuable antileukemia and antitumor agents.

Briefly, therefore, the present invention is directed to taxane derivatives having a C13 side chain which includes an alkyl substituent. In a preferred embodiment, the taxane derivative has a tricyclic or tetracyclic core and corresponds to the formula:



(3)

wherein

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 is hydrogen;

X_4 is butenyl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$;

X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

R_1 is hydrogen, hydroxy, protected hydroxy or together with R_{14} forms a carbonate;

R_2 is hydrogen, hydroxy, —$OCOR_{31}$ or together with R_{2a} forms an oxo;

R_{2a} is hydrogen or taken together with R_2 forms an oxo or;

R_4 is hydrogen, together with R_{4a} forms an oxo, oxirane or methylene, or together with R_{5a} and the carbon atoms to which they are attached form an oxetane ring;

R_{4a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyano, hydroxy, —$OCOR_{30}$, or together with R_4 forms an oxo, oxirane or methylene;

R_5 is hydrogen or together with R_{5a} forms an oxo,

R_{5a} is hydrogen, hydroxy, protected hydroxy, acyloxy, together with R_5 forms an oxo, or together with R_4 and the carbon atoms to which they are attached form an oxetane ring;

R_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R_{6a} forms an oxo;

R_{6a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R_6 forms an oxo;

R_7 is hydrogen or together with R_{7a} forms an oxo,

R_{7a} is hydrogen, halogen, protected hydroxy, —OR_{28}, or together with R_7 forms an oxo;

R_9 is hydrogen or together with R_{9a} forms an oxo,

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo,

R_{10a} is hydrogen, —$OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{14a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

R_{28} is hydrogen, acyl, hydroxy protecting group or a functional group which increases the solubility of the taxane derivative; and

R_{29}, R_{30}, and R_{31} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl.

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

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein "Ar" means aryl; "Ph" means phenyl; "Ac" means acetyl; "Et" means ethyl; "R" means alkyl unless otherwise defined; "Bu" means butyl; "Pr" means propyl; "TES" means triethylsilyl; "TMS" means trimethylsilyl; "TPAP" means tetrapropylammonium perruthenate; "DMAP" means p-dimethylamino pyridine; "DMF" means dimethylformamide; "LDA" means lithium diisopropylamide; "LHMDS" means lithium hexamethyldisilazide; "LAH" means lithium aluminum hydride; "Red-Al" means sodium bis(2-methoxyethoxy) aluminum hydride; "AIBN" means azo-(bis)-isobutyronitrile; "10-DAB" means 10-desacetylbaccatin III; FAR means 2-chloro-1,1,2-trifluorotriethylamine; protected hydroxy means —OR wherein R is a hydroxy protecting group; sulfhydryl protecting group" includes, but is not limited to, hemithioacetals such as 1-ethoxyethyl and methoxymethyl, thioesters, or thiocarbonates; "amine protecting group" includes, but is not limited to, carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate; and "hydroxy protecting group" includes, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, 2-methoxypropyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, dimethylarylsilyl ether, triisopropylsilyl ether and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates including but not limited to alkyl carbonates having from one to six carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl; isobutyl, and n-pentyl; alkyl carbonates having from one to six carbon atoms and substituted with one or more halogen atoms such as 2,2,2-trichloroethoxymethyl and 2,2,2-trichloro-ethyl; alkenyl carbonates having from two to six carbon atoms such as vinyl and allyl; cycloalkyl carbonates having from three to six carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates optionally substituted on the ring with one or more C_{1-6} alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine protecting groups may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981.

The alkyl groups described herein, either alone or with the various substituents defined herein are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be substituted, straight, branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl and the like.

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

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

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

The heteroaryl moieties described herein, either alone or with various substituents, contain from 5 to 15 atoms and include, furyl, thienyl, pyridyl and the like. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido.

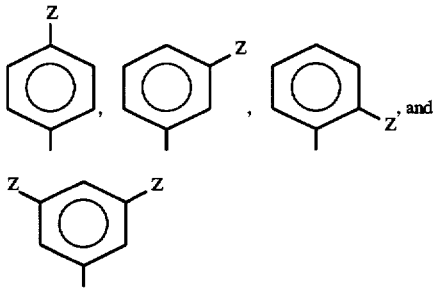
The acyloxy groups described herein contain alkyl, alkenyl, alkynyl, aryl or heteroaryl groups.

The substituents of the substituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups and moieties described herein, may be alkyl, alkenyl, alkynyl, aryl, heteroaryl and/or may contain nitrogen, oxygen, sulfur, halogens and include, for

example, lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, nitro, amino, and keto.

In accordance with the present invention, it has been discovered that compounds corresponding to structural formula 3 show remarkable properties, in vitro, and are valuable antileukemia and antitumor agents. Their biological activity has been determined in vitro, using tubulin assays according to the method of Parness et al., *J. Cell Biology*, 91: 479–487 (1981) and human cancer cell lines, and is comparable to that exhibited by taxol and taxotere.

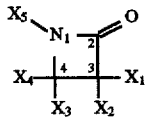
In one embodiment of the present invention, the substituents of the cyclic nucleus of the taxane (other than the C13 substituent) correspond to the substituents present on baccatin III or 10-DAB. That is, R_{14} and R_{14a} are hydrogen, R_{10} is hydrogen, R_{10a} is hydroxy or acetoxy, R_9 and R_{9a} together form an oxo, R_7 is hydrogen, R_{7a} is hydroxy, R_5 is hydrogen, R_{5a} and R_4 and the carbons to which they are attached form an oxetane ring, R_{4a} is acetoxy, R_2 is hydrogen, R_{2a} is benzoyloxy, and R_1 is hydroxy. In other embodiments, the taxane has a structure which differs from that of taxol or taxotere with respect to the C13 side chain and at least one other substituent. For example, R_{14} may be hydroxy, R_2 may be hydroxy or —$OCOR_{31}$ wherein R_{31} is hydrogen, alkyl or selected from the group comprising



and Z is alkyl, hydroxy, alkoxy, halogen, or trifluoromethyl. R_{9a} may be hydrogen and R_9 may be hydrogen or hydroxy, R_{7a} may be hydrogen and R_7 may be acetoxy or other acyloxy or halogen, or R_{10} and R_{10a} may each be hydrogen or together form an oxo.

With respect to the C13 side-chain, in a preferred embodiment X_1 is —OH, X_2 is hydrogen, X_3 is hydrogen, X_4 is butenyl, X_5 is —COX_{10} or —$COOX_{10}$, and X_{10} is alkyl, alkenyl, alkynyl, aryl, furyl, thienyl or other heteroaryl and the taxane has the 2'R, 3'S configuration. In a particularly preferred embodiment, X_4 is isobutenyl, X_5 is —COX_{10} or —$COOX_{10}$ and X_{10} is furyl, thienyl, alkyl substituted furyl or thienyl, pyridyl, tert-, iso- or n-butyl, ethyl, iso- or n-propyl, cyclopropyl, cyclohexyl, allyl, crotyl, 1,3-diethoxy-2-propyl, 2-methoxyethyl, amyl, neopentyl, $PhCH_2O$—, —NPh_2, —NHnPr, —NHPh, or —NHEt.

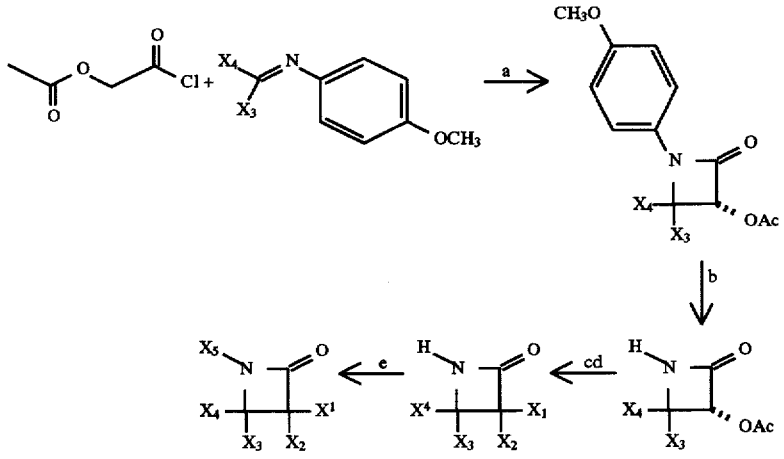
Taxanes having the general formula 3 may be obtained by reacting a β-lactam with alkoxides having the taxane tricyclic or tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a β-amido ester substituent at C-13. The β-lactams have the following structural formula:



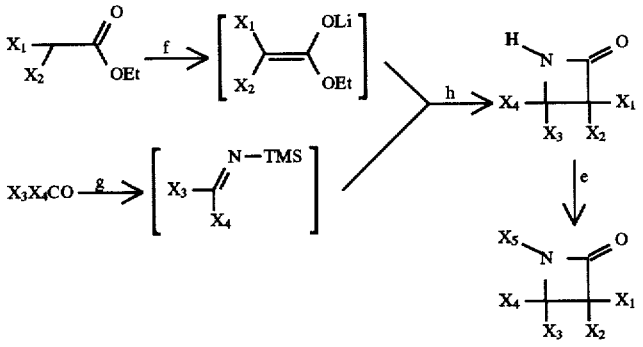
wherein X_1—X_5 are as defined above.

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

Scheme A



Scheme B



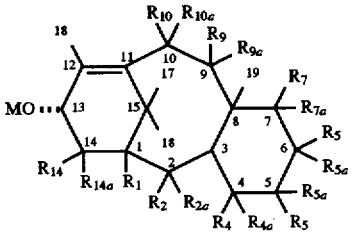
reagents: (a) triethylamine, CH_2Cl_2, 25° C., 18 h; (b) 4 equiv ceric ammonium nitrate, CH_3CN, −10° C., 10 min; (c) KOH, THF, H_2O, 0° C., 30 min, or pyrrolidine, pyridine, 25° C., 3 h, (d) TESCl, pyridine, 25° C., 30 min or 2-methoxypropene toluene sulfonic acid (cat.), THF, 0° C., 2 h; (e) n-butyllithium, THF, −78° C., 30 min; and an acyl chloride or chloroformate (X_5=—COX_{10}), sulfonyl chloride (X_5=—$COSX_{10}$) or isocyanate (X_5=—$CONX_8X_{10}$); (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-acetoxy 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. In Scheme B, ethyl-α-triethylsilyloxyacetate is readily prepared from glycolic acid.

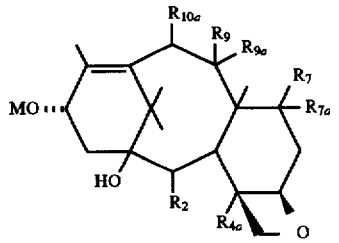
In Schemes A and B, X_1 is preferably —OX_6 and X_6 is a hydroxy protecting group. Protecting groups such as 2-methoxypropyl ("MOP"), 1-ethoxyethyl ("EE") are preferred, but a variety of other standard protecting groups such as the triethylsilyl group or other trialkyl (or aryl) silyl groups may be used. As noted above, additional hydroxy protecting groups and the synthesis thereof may be found in "Protective groups in Organic Synthesis" by T. W. Greene, John Wiley & Sons, 1981.

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 alkoxides having the tricyclic or tetracyclic taxane nucleus and a C-13 metallic oxide or ammonium oxide substituent have the following structural formula:



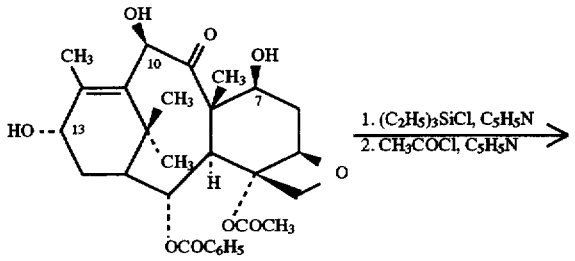
wherein R_1–R_{14a} are as previously defined and M comprises ammonium or is a metal optionally selected from the group comprising Group IA, Group IIA and transition metals, and preferably, Li, Mg, Na, K or Ti. Most preferably, the alkoxide has the tetracyclic taxane nucleus and corresponds to the structural formula:

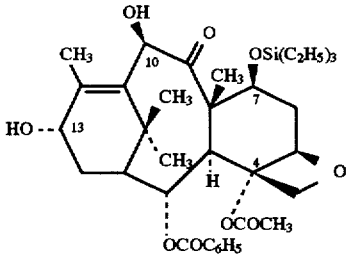


wherein M, R_2, R_{4a}, R_7, R_{7a}, R_9, R_{9a}, R_{10}, and R_{10a} are as previously defined.

The alkoxides can be prepared by reacting an alcohol having 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:

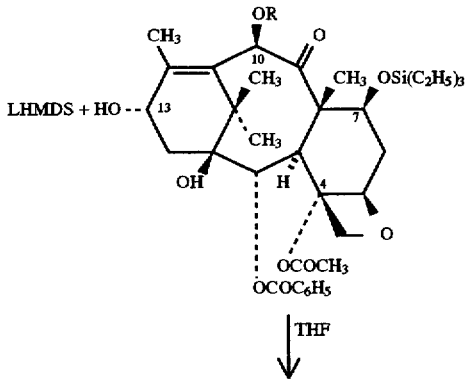




(4) a, R = H
b, R = $COCH_3$

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 may then optionally be 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). Greene, et al. in JACS 110, 5917 at 5918 (1988).

The 7-protected baccatin III (4b) is reacted with an organometallic compound such as LHMDS in a solvent such as tetrahydrofuran (THF), to form the metal alkoxide 13-O-lithium-7-O-triethylsilyl baccatin III as shown in the following reaction scheme:



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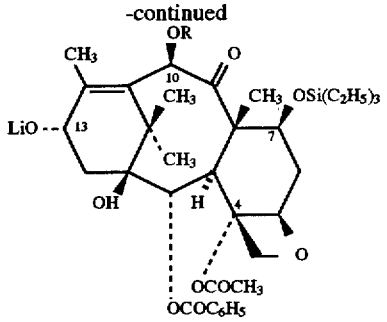
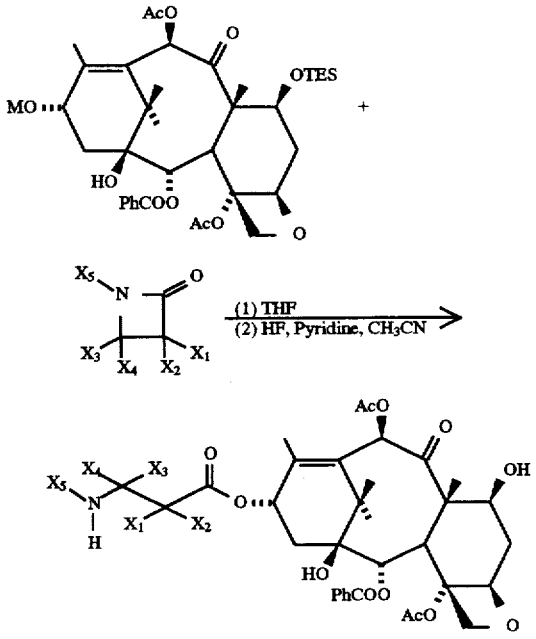


As shown in the following reaction scheme, 13-O-lithium-7-O-triethylsilyl baccatin III reacts with a β-lactam in which X_1 is preferably —OX_6, (X_6 being a hydroxy protecting group) and X_2—X_5 are as previously defined to provide an intermediate in which the C-7 and C-2' hydroxyl groups are protected. The protecting groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents.



Both the conversion of the alcohol to the alkoxide and the ultimate synthesis of the taxane derivative can take place in the same reaction vessel. Preferably, the β-lactam is added to the reaction vessel after formation therein of the alkoxide.

Compounds of formula 3 of the instant invention are useful for inhibiting tumor growth in animals including humans and are preferably administered in the form of a pharmaceutical composition comprising an effective antitumor amount of compound of the instant invention in combination with a pharmaceutically acceptable carrier or diluent.

Antitumor compositions herein may be made up in any suitable form appropriate for desired use; e.g., oral, parenteral or topical administration. Examples of parenteral administration are intramuscular, intravenous, intraperitoneal, rectal and subcutaneous administration.

The diluent or carrier ingredients should not be such as to diminish the therapeutic effects of the antitumor compounds.

Suitable dosage forms for oral use include tablets, dispersible powders, granules, capsules, suspensions, syrups, and elixirs. Inert diluents and carriers for tablets include, for example, calcium carbonate, sodium carbonate, lactose and talc. Tablets may also contain granulating and disintegrating agents such as starch and alginic acid, binding agents such as starch, gelatin and acacia, and lubricating agents such as magnesium stearate, stearic acid and talc. Tablets may be uncoated or may be coated by unknown techniques; e.g., to delay disintegration and absorption. Inert diluents and carriers which may be used in capsules include, for example, calcium carbonate, calcium phosphate and kaolin. Suspensions, syrups and elixirs may contain conventional excipients, for example, methyl cellulose, tragacanth, sodium alginate; wetting agents, such as lecithin and polyoxyethylene stearate; and preservatives, e.g., ethyl-p-hydroxybenzoate.

Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions and the like. They may also be manufactured in the form of sterile solid compositions which can be dissolved or suspended in sterile injectable medium immediately before use. They may contain suspending or dispersing agents known in the art.

The water solubility of compounds of formula (3) may be improved by modification of the C2' and/or C7 substituents. For instance, water solubility may be increased if X_1 is $-OX_6$ and R_{7a} is $-OR_{28}$, and X_6 and R_{28} are independently hydrogen or —COGCOR^1 wherein

G is ethylene, propylene, —CH=CH—, 1,2-cyclohexane, or 1,2-phenylene,

R^1=OH base, NR^2R^3, OR^3, SR^3, $OCH_2CONR^4R^5$, OH

R^2=hydrogen, methyl

R^3=$(CH_2)_nNR^6R^7$; $(CH_2)_nN^{\oplus}R^6R^7R^8X^{\ominus}$

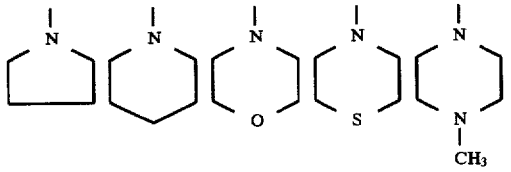
n=1 to 3

R^4=hydrogen, lower alkyl containing 1 to 4 carbons

R^5=hydrogen, lower alkyl containing 1 to 4 carbons, benzyl, hydroxyethyl, CH_2CO_2H, dimethylaminoethyl

R^6R^7=lower alkyl containing 1 or 2 carbons, benzyl or R^6 and

R^7 together with the nitrogen atom of NR^6R^7 form the following rings



R^8=lower alkyl containing 1 or 2 carbons, benzyl

$X^{\ominus}$=halide

base=NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4OH)_2$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH, KOH.

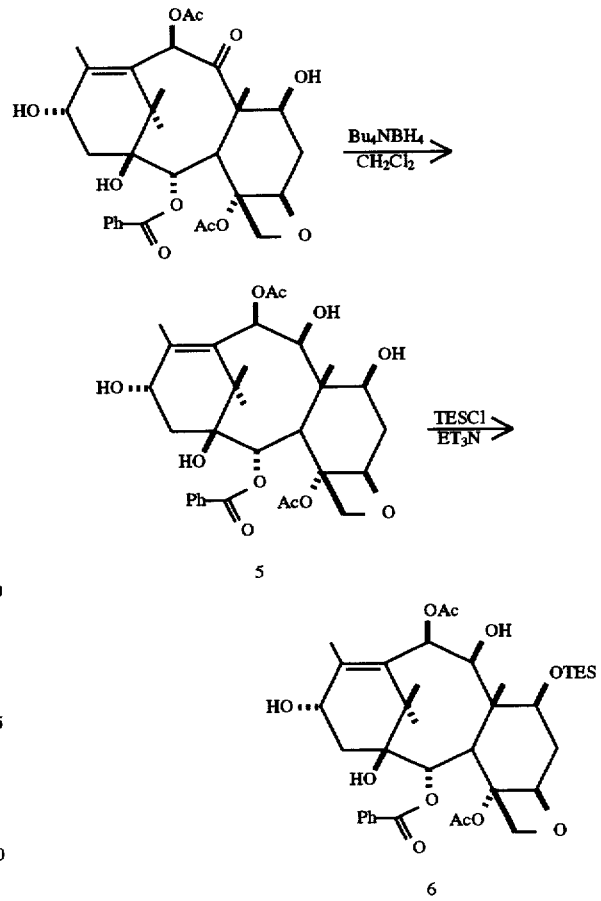
The preparation of compounds in which X_1 or X_2 is —COGCOR^1 is set forth in Haugwitz U.S. Pat. No. 4,942,184 which is incorporated herein by reference.

Alternatively, solubility may be increased when X_1 is $-OX_6$ and X_6 is a radical having the formula —COCX=CHX or —COX—CHX—CHX—SO_2O—M wherein X is hydrogen, alkyl or aryl and M is hydrogen, alkaline metal or an ammonio group as described in Kingston et al., U.S. Pat. No. 5,059,699 (incorporated herein by reference).

Taxanes having alternative C9 keto substituent may be prepared by selectively reducing to yield the corresponding C9 β-hydroxy derivative. The reducing agent is preferably a borohydride and, most preferably, tetrabutylammoniumborohydride (Bu_4NBH_4) or triacetoxyborohydride.

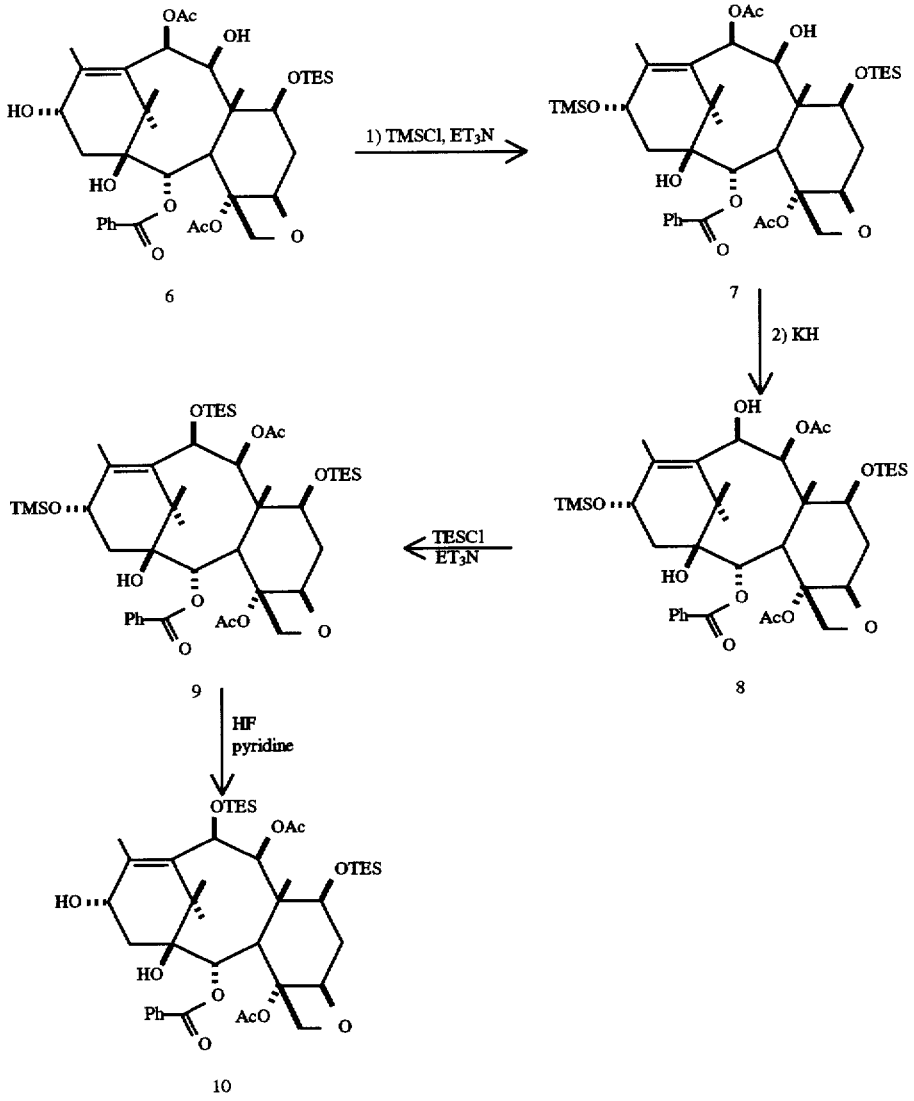
As illustrated in Reaction Scheme 1, the reaction of baccatin III with Bu_4NBH_4 in methylene chloride yields 9-desoxo-9β-hydroxybaccatin III 5. After the C7 hydroxy group is protected with the triethylsilyl protecting group, for example, a suitable side chain may be attached to 7-protected-9β-hydroxy derivative 6 as elsewhere described herein. Removal of the remaining protecting groups thus yields 9β-hydroxy-desoxo taxol or other 9β-hydroxytetracylic taxane having a C13 side chain.

REACTION SCHEME 1



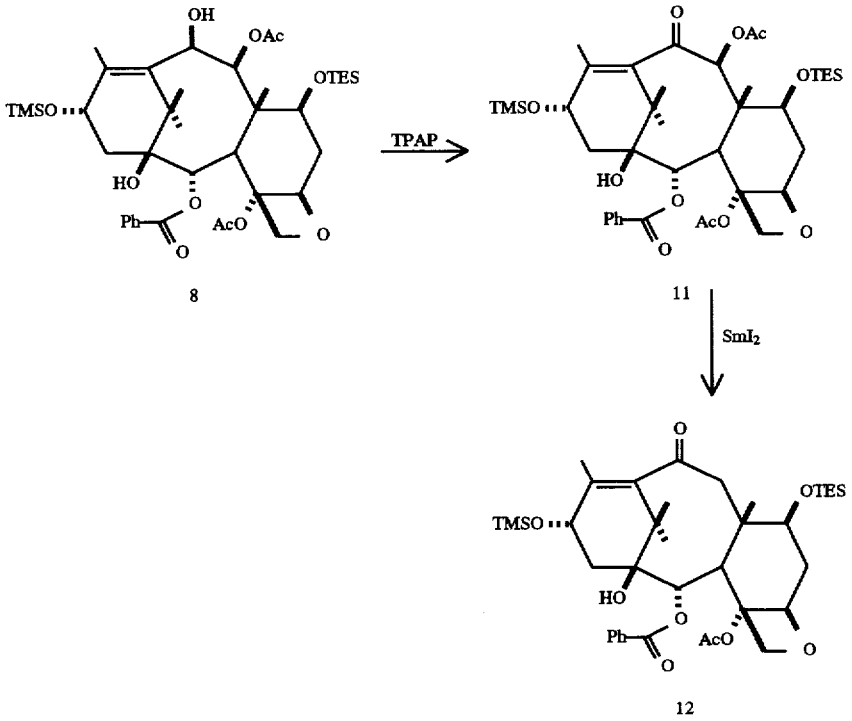
Alternatively, the C13 hydroxy group of 7-protected-9β-hydroxy derivative 6 may be protected with trimethylsilyl or other protecting group which can be selectively removed relative to the C7 hydroxy protecting group as illustrated in Reaction Scheme 2, to enable further selective manipulation of the various substituents of the taxane. For example, reaction of 7,13-protected-9β-hydroxy derivative 7 with KH causes the acetate group to migrate from C10 to C9 and the hydroxy group to migrate from C9 to C10, thereby yielding 10-desacetyl derivative 8. Protection of the C10 hydroxy group of 10-desacetyl derivative 8 with triethylsilyl yields derivative 9. Selective removal of the C13 hydroxy protecting group from derivative 9 yields derivative 10 to which a suitable side chain may be attached as described above.

REACTION SCHEME 2



As shown in Reaction Scheme 3, 10-oxo derivative 11 can be provided by oxidation of 10-desacetyl derivative 8. Thereafter, the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-acetoxy-10-oxo-taxol or other 9-acetoxy-10-oxotetracylic taxanes having a C13 side chain. Alternatively, the C9 acetate group can be selectively removed by reduction of 10-oxo derivative 11 with a reducing agent such as samarium diiodide to yield 9-desoxo-10-oxo derivative 12 from which the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-desoxo-10-oxo-taxol or other 9-desoxo-10-oxotetracylic taxanes having a C13 side chain.

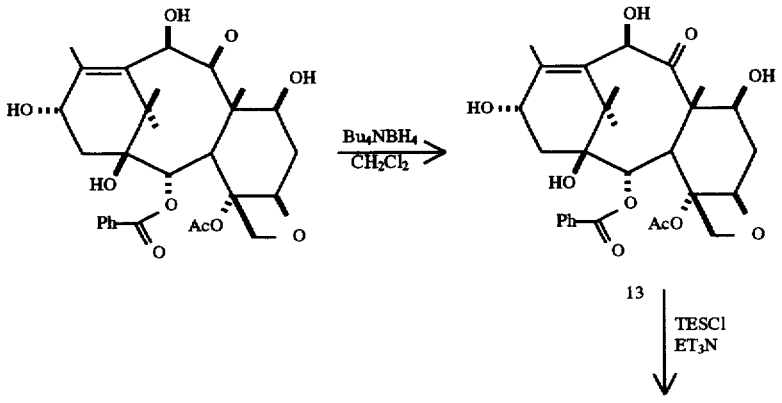
REACTION SCHEME 3



8 11 12

Reaction Scheme 4 illustrates a reaction in which 10-DAB is reduced to yield pentaol 13. The C7 and C10 hydroxyl groups of pentaol 13 can then be selectively protected with the triethylsilyl or another protecting group to produce triol 14 to which a C13 side chain can be attached as described above or, alternatively, after further modification of the tetracylic substituents.

REACTION SCHEME 4



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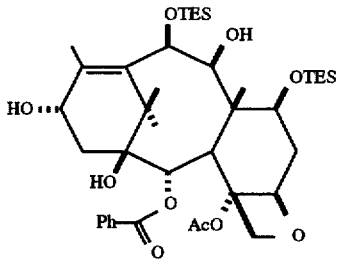
REACTION SCHEME 4



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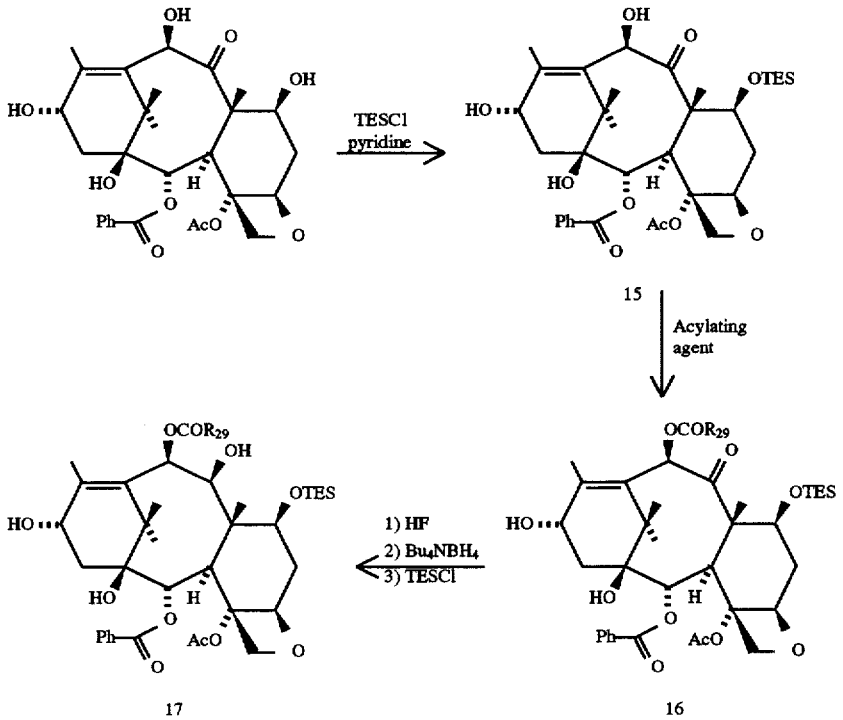
Taxanes having C9 and/or C10 acyloxy substituents other than acetate can be prepared using 10-DAB as a starting material as illustrated in Reaction Scheme 5. Reaction of 10-DAB with triethylsilyl chloride in pyridine yields 7-protected 10-DAB 15. The C10 hydroxy substituent of 7-protected 10-DAB 15 may then be readily acylated with any standard acylating agent to yield derivative 16 having a new C10 acyloxy substituent. Selective reduction of the C9 keto substituent of derivative 16 yields 9β-hydroxy derivative 17 to which a C13 side chain may be attached. Alternatively, the C10 and C9 groups can be caused to migrate as set forth in Reaction Scheme 2, above.

such as anhydrides and acid chlorides in combination with an amine such as pyridine, triethylamine, DMAP, or diisopropyl ethyl amine. Alternatively, the C2 and/or C4 alcohols may be converted to new C2 and/or C4 esters through formation of the corresponding alkoxide by treatment of the alcohol with a suitable base such as LDA followed by an acylating agent such as an acid chloride.

Baccatin III and 10-DAB analogs having different substituents at C2 and/or C4 can be prepared as set forth in Reaction Schemes 6–10. To simplify the description, 10-DAB is used as the starting material. It should be understood, however, that baccatin III derivatives or analogs

REACTION SCHEME 5



17 16

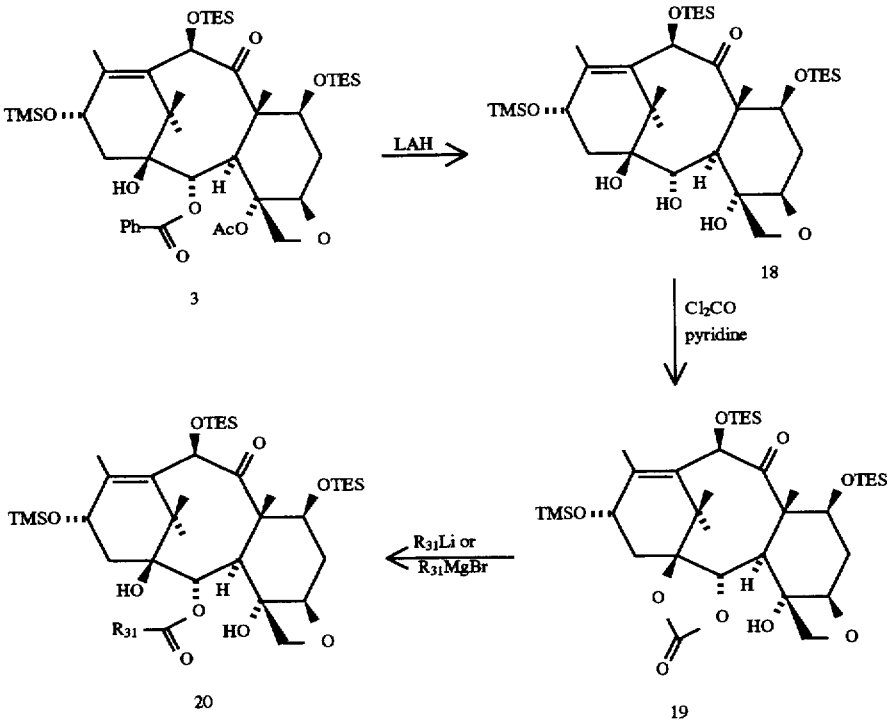
Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter be substituted using standard acylating agents

may be produced using the same series of reactions (except for the protection of the C10 hydroxy group) by simply replacing 10-DAB with baccatin III as the starting material. 9-desoxo derivatives of the baccatin III and 10-DAB analogs having different substituents at C2 and/or C4 can then be

prepared by reducing the C9 keto substituent of these analogs and carrying out the other reactions described above.

In Reaction Scheme 6, protected 10-DAB 3 is converted to the triol 18 with lithium aluminum hydride. Triol 18 is then converted to the corresponding C4 ester using Cl_2CO in pyridine followed by a nucleophilic agent (e.g., Grignard reagents or alkyllithium reagents).

Scheme 6

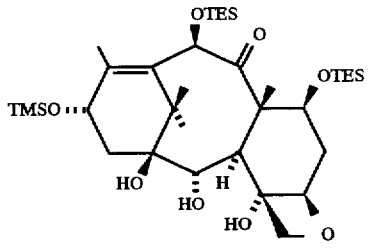


3 18 20 19

Deprotonation of triol 18 with LDA followed by introduction of an acid chloride selectively gives the C4 ester. For example, when acetyl chloride was used, triol 18 was converted to 1,2 diol 4 as set forth in Reaction Scheme 7.

Triol 18 can also readily be converted to the 1,2 carbonate 19. Acetylation of carbonate 19 under vigorous standard conditions provides carbonate 21 as described in Reaction Scheme 8; addition of alkyllithiums or Grignard reagents to carbonate 19 provides the C2 ester having a free hydroxyl group at C4 as set forth in Reaction Scheme 6.

Scheme 7



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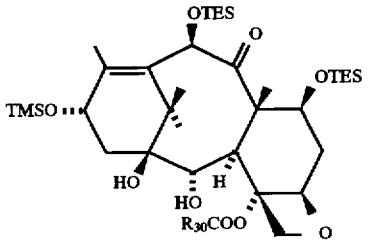
Scheme 7



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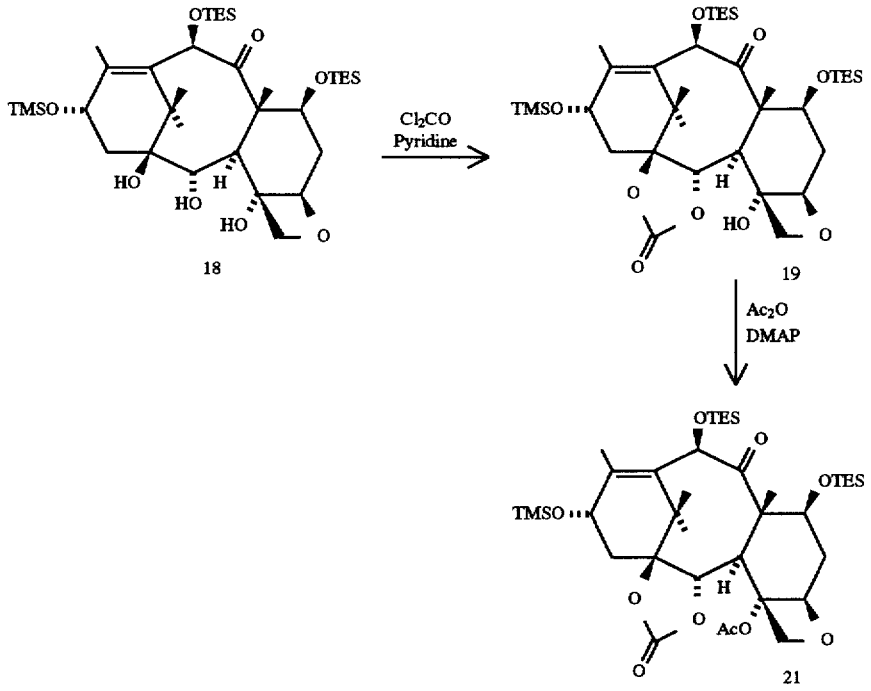
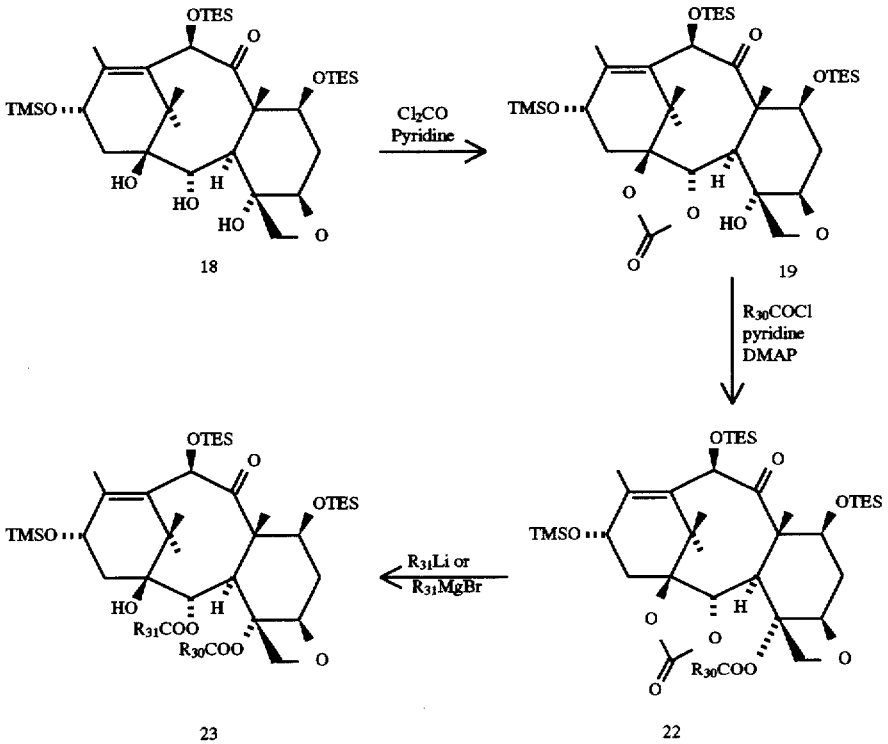
Scheme 8



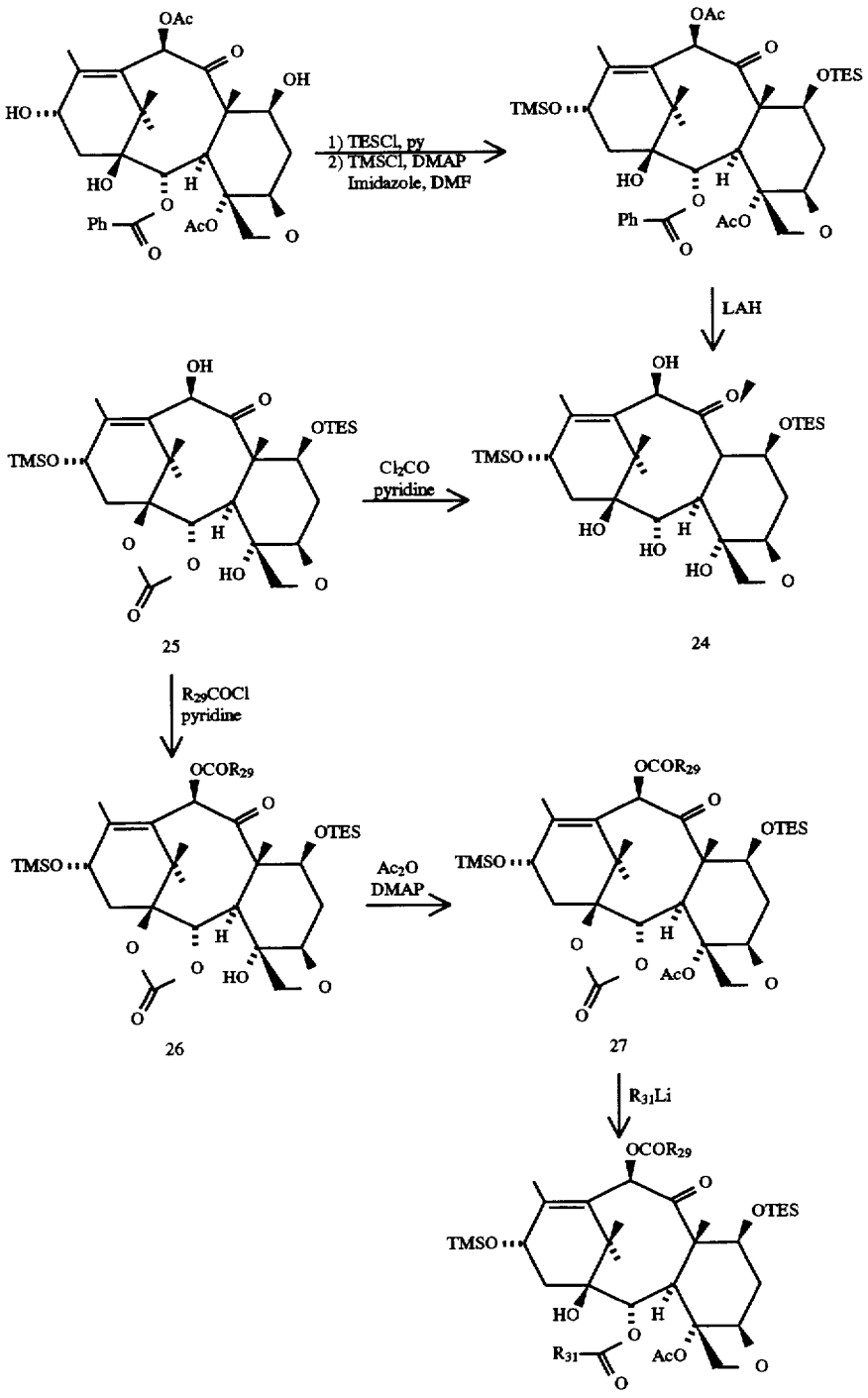
As set forth in Reaction Scheme 9, other C4 substituents can be provided by reacting carbonate 19 with an acid chloride and a tertiary amine to yield carbonate 22 which is then reacted with alkyllithiums or Grignard reagents to provide 10-DAB derivatives having new substituents at C2.

Scheme 9



Alternatively, baccatin III may be used as a starting material and reacted as shown in Reaction Scheme 10. After being protected at C7 and C13, baccatin III is reduced with LAH to produce 1,2,4,10 tetraol 24. Tetraol 24 is converted to carbonate 25 using Cl_2CO and pyridine, and carbonate 25 is acylated at C10 with an acid chloride and pyridine to produce carbonate 26 (as shown) or with acetic anhydride and pyridine (not shown). Acetylation of carbonate 26 under vigorous standard conditions provides carbonate 27 which is then reacted with alkyl lithiums to provide the baccatin III derivatives having new substituents at C2 and C10.

Scheme 10

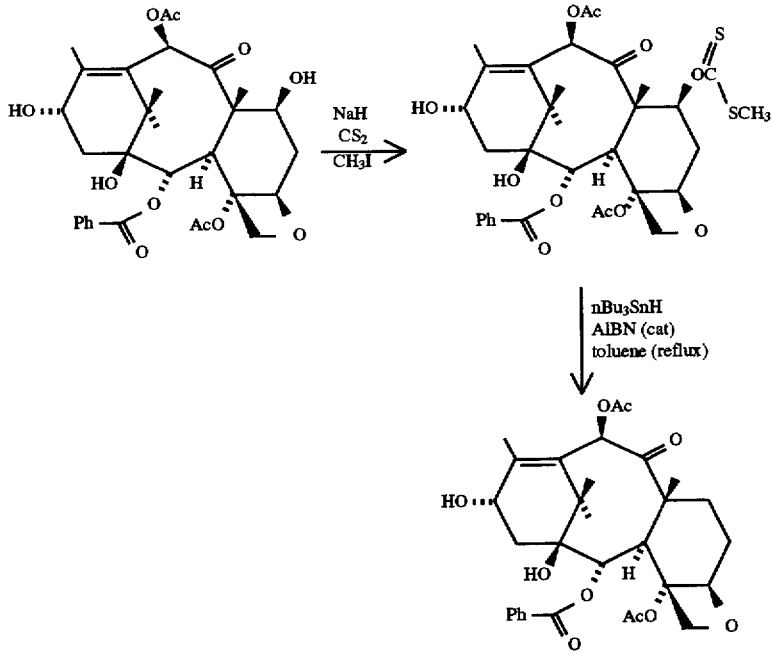


10-desacetoxy derivatives of baccatin III and 10-desoxy derivatives of 10-DAB may be prepared by reacting baccatin III or 10-DAB (or their derivatives) with samarium diiodide. Reaction between the tetracyclic taxane having a C10 leav-

ing group and samarium diiodide may be carried out at 0° C. in a solvent such as tetrahydrofuran. Advantageously, the samarium diiodide selectively abstracts the C10 leaving group; C13 side chains and other substituents on the tetracyclic nucleus remain undisturbed. Thereafter, the C9 keto substituent may be reduced to provide the corresponding 9-desoxo-9β-hydroxy-10-desacetyoxy or 10-desoxy derivatives as otherwise described herein.

C7 dihydro and other C7 substituted taxanes can be prepared as set forth in Reaction Schemes 11, 12 and 12a.

REACTION SCHEME 11



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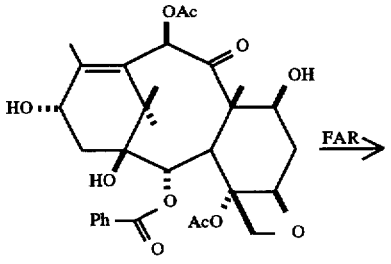
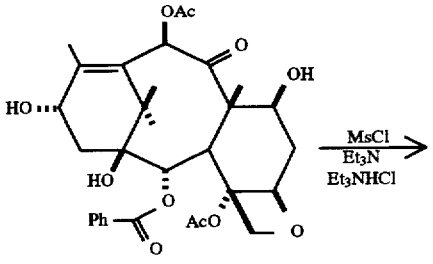
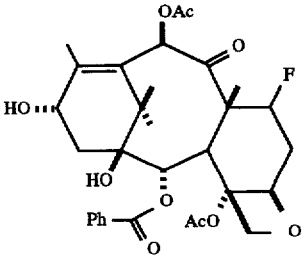
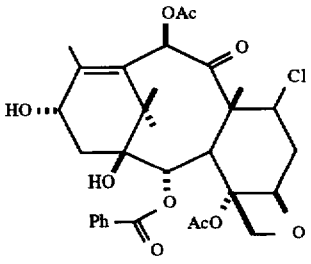
REACTION SCHEME 12



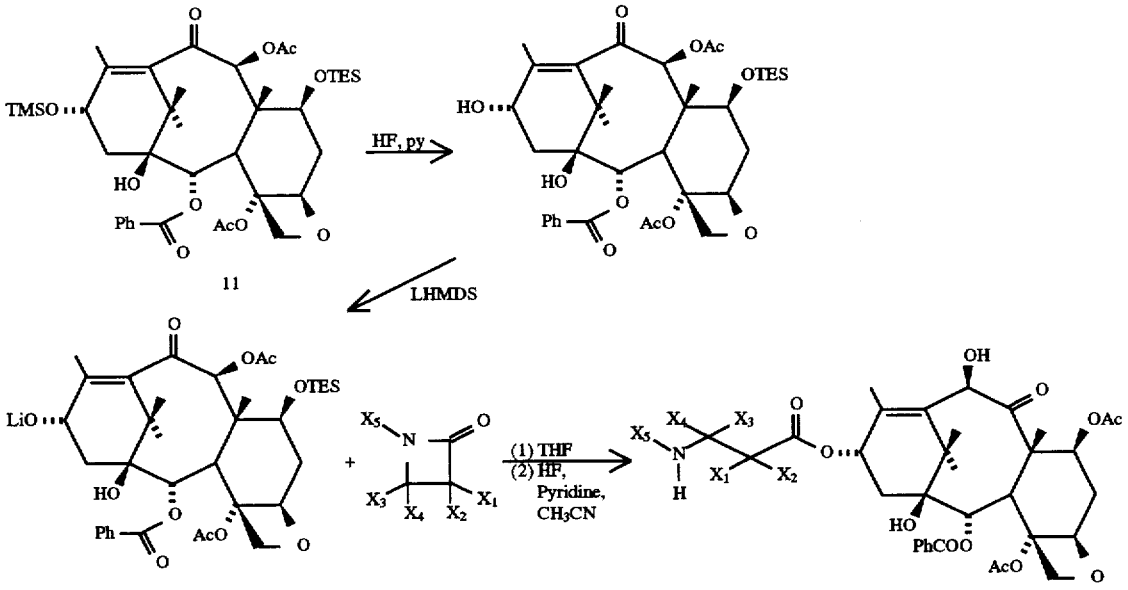
REACTION SCHEME 12







REACTION SCHEME 12a

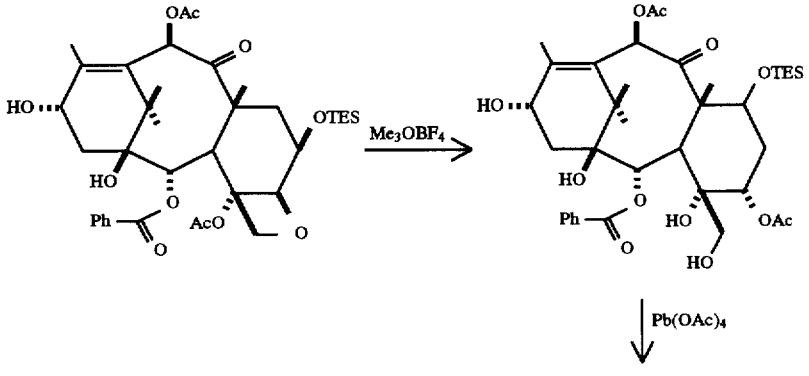


As shown in Reaction Scheme 12, Baccatin III may be converted into 7-fluoro baccatin III by treatment with FAR at room temperature in THF solution. Other baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-chloro baccatin III can be prepared by treatment of baccatin III with methane sulfonyl chloride and triethylamine in methylene chloride solution containing an excess of triethylamine hydrochloride.

Taxanes having C7 acyloxy substituents can be prepared as set forth in Reaction Scheme 12a, 7,13-protected 10-oxo-derivative 11 is converted to its corresponding C13 alkoxide by selectively removing the C13 protecting group and replacing it with a metal such as lithium. The alkoxide is then reacted with a β-lactam or other side chain precursor. Subsequent hydrolysis of the C7 protecting groups causes a migration of the C7 hydroxy substituent to C10, migration of the C10 oxo substituent to C9, and migration of the C9 acyloxy substituent to C7.

A wide variety of tricyclic taxanes are naturally occurring, and through manipulations analogous to those described herein, an appropriate side chain can be attached to the C13 oxygen of these substances. Alternatively, as shown in Reaction Scheme 13, 7-O-triethylsilyl baccatin III can be converted to a tricyclic taxane through the action of trimethyloxonium tetrafluoroborate in methylene chloride solution. The product diol then reacts with lead tetraacetate to provide the corresponding C4 ketone.

REACTION SCHEME 13



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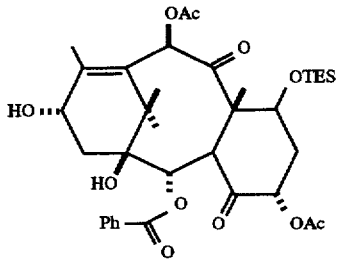
REACTION SCHEME 13

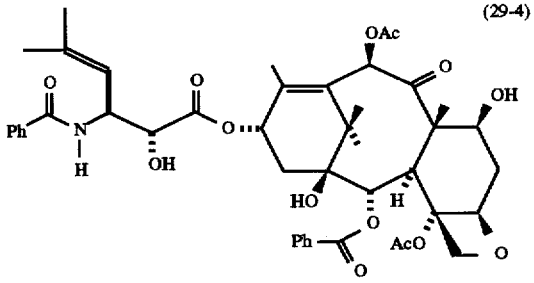


Recently a hydroxylated taxane (14-hydroxy-10-deacetylbaccatin III) has been discovered in an extract of yew needles (C&EN, p 36–37, Apr. 12, 1993). Derivatives of this hydroxylated taxane having the various C2, C4, etc. functional groups described above may also be prepared by using this hydroxylated taxane. In addition, the C14 hydroxy group together with the C1 hydroxy group of 10-DAB can be converted to a 1,2-carbonate as described in C&EN or it may be converted to a variety of esters or other functional groups as otherwise described herein in connection with the C2, C4, C9 and C10 substituents.

The following examples are provided to more fully illustrate the invention.

EXAMPLE 1

(29-4)



Preparation of 3'-desphenyl-3'-(2-methyl-1-propenyl) taxol.

To a solution of 7-triethylsilyl baccatin III (120 mg, 0.171 mmol) in 1.2 mL of THF at –45° C. was added dropwise 0.104 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at –45° C., a solution of cis-1-benzoyl-3-triethylsilyloxy-4-(2-methyl-1-propenyl)azetidin-2-one (295 mg, 0.885 mmol) in 1.2 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 179 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-(2-methyl-1-propenyl) taxol and a small amount of the (2'S,3'R) isomer.

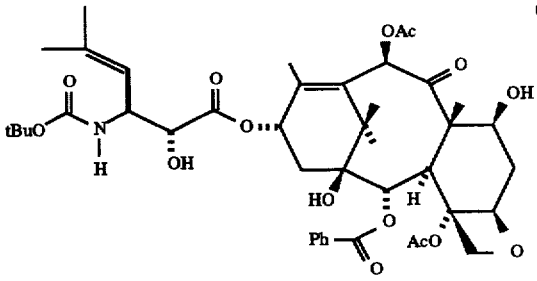
To a solution of 179 mg (0.171 mmol) of the mixture obtained from the previous reaction in 11 mL of acetonitrile and 0.55 mL of pyridine at 0° C. was added 1.7 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 140 mg of material which was purified by flash chromatography to give 109.0 mg (78%) of 3'-desphenyl-3'-(2-methyl-1-propenyl) taxol, which was recrystallized from methanol/water.

m.p.143°–144° C.; $[\alpha]^{25}_{Na}$–61.0° (c 0.0065, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.1 Hz, 2H, benzoate ortho),7.69(d, J=8.3 Hz, 2H, benzamide ortho), 7.64–7.36(m, 6H, aromatic), 6.45(d, J=8.2 Hz, 1H, NH), 6.29(s, 1H, H10), 6.20 (dd, J=7.7, 7.7 Hz, 1H, H13), 5.68(d, J=7.1 Hz, 1H, H2β), 5.46(m, 1H, vinyl), 5.27(ddd, J=8.8, 8.8, 3.3 Hz, 1H, H3'), 4.96 (d, J=7.7 Hz, 1H, H5), 4.40(m, 1H, H7),4.36(m, 1H, H2'), 4.32(d, J=7.8 Hz, 1H, H20α), 4.22 (d, J=7.8 Hz, 1H, H20β), 3.82(d, J=7.1 Hz, 1H, H3), 3.63(d, J=6.6 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.48(d, J=3.9 Hz, 1H, 7OH), 2.42(m, 2H, H14), 2.39(s, 3H, 4 Ac), 2.23 (s, 3H, 10 Ac), 2.16(br s, 3H, Me18), 1.89 (m, 1H, H6β), 1.88 (s, 3H, Me19), 1.80(s, 4H, Me thienyl+1OH), 1.24(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 2

(51-3)



Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol.

To a solution of 7-triethylsilyl baccatin III (30.0 mg, 0.043 mmol) in 0.5 mL of THF at –45° C. was added dropwise 0.047 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 0.5 h at –45° C., a solution of cis-1-(t-butoxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (44.2 mg, 0.13 mmol) in 0.4 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 40.3 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 40.3 mg (0.038 mmol) of the mixture obtained from the previous reaction in 2 mL of acetonitrile and 0.1 mL of pyridine at 0° C. was added 0.3 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 34.2 mg of material which was

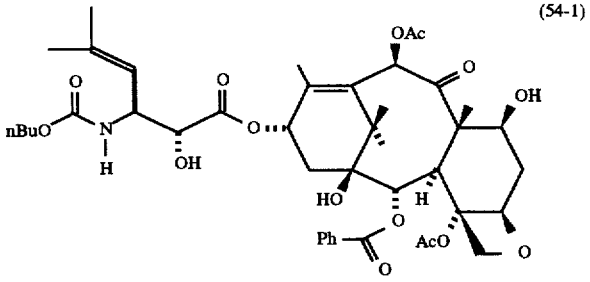
purified by flash chromatography to give 22.4 mg (72%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.147°–149° C.; $[\alpha]^{25}_{Na}$–65.2° (c 0.0023, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.1 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48 (m, 2H, benzoate meta), 6.45(s, 1H, NH), 6.30(d, J=8.3 Hz, 1H, H10), 6.18 (dd, J=7.7, 7.7 Hz, 1H, H13), 5.68(d, J=7.1 Hz, 1H, H2β), 5.31(m, 1H, vinyl), 5.01(ddd, J=8.8, 8.8, 3.3 Hz, 1H, H3'), 4.95 (d, J=7.7 Hz, 1H, H5), 4.76(m, 1H, H7),4.43 (m, 1H, H2'), 4.32(d, J=7.8 Hz, 1H, H20α), 4.19 (d, J=7.8 Hz, 1H, H20β), 3.81(d, J=7.1 Hz, 1H, H3), 3.74(d, J=6.6 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.48(d, J=3.9 Hz, 1H, 7OH), 2.44(m, 2H, H14), 2.39(s, 3H, 4 Ac), 2.26(s, 3H, Me vinyl), 2.25(s, 3H, Me vinyl), 2.23 (s, 3H, 10 Ac), 1.98(br s, 3H, Me18), 1.86 (m, 1H, H6β), 1.76 (s, 3H, Me19), 1.43(s, 9H, 3Me t-butoxy) 1.25(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 3

(54-1)



Preparation of N-debenzoyl-N-(n-butoxycarbonyl)-3'-desphenyl-3'-isobutenyl taxol.

To a solution of 7-triethylsilyl baccatin III (70.0 mg, 0.086 mmol) in 0.7 mL of THF at –45° C. was added dropwise 0.10 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at –45° C., a solution of cis-1-(n-butoxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobutenyl azetidin-2-one (94.2 mg, 0.214 mmol) in 0.5 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 82.8 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-7-triethylsilyl-N-debenzoyl-N-(n-butoxycarbonyl)-3'-desphenyl-3'-isobutenyl taxol and a small amount of the (2'S,3'R) isomer.

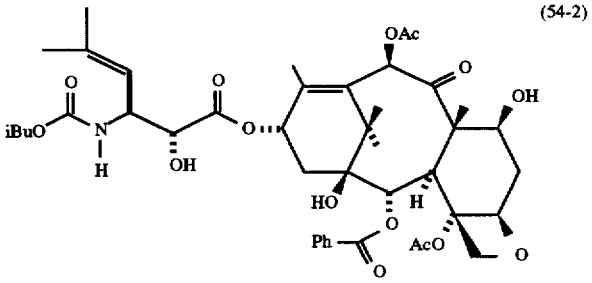
To a solution of 82.8 mg (0.083 mmol) of the mixture obtained from the previous reaction in 6.0 mL of acetonitrile and 0.3 mL of pyridine at 0° C. was added 0.7 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 67.7 mg of material which was purified by flash chromatography to give 53.2 mg (77%) of N-debenzoyl-N-(n-butoxycarbonyl)-3'-desphenyl-3'-isobutenyl taxol, which was recrystallized from methanol/water.

m.p.132°–134° C.; $[\alpha]^{25}_{Na}$–64.0° (c 0.0023, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.21(dd, J=7.5, 7.5 Hz, 1H, H13), 5.67(d, J=7.2 Hz, 1H, H2β), 5.33(m, 1H, olefine of isobutenyl), 4.97(d, J=7.8, 1H, H5), 4.91(d, J=8.2 Hz, 1H, NH), 4.78(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.43(m, 1H, H2'), 4.31(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.96(q, J=6.6 Hz, 2H, n-butyloxy), 3.81(d, J=7.2 Hz, 1H, H3), 3.34(d, J=6.6 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.36(s, 3H, 4 Ac), 2.33(m, 2H, H14), 2.26(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.89(s, 3H, Me19), 1.87(m, 1H, H6β), 1.77(s, 3H, Me isobutenyl), 1.75(s, 1H, 1OH), 1.68(s, 3H, Me isobutenyl), 1.56(m, 2H, n-butyloxy), 1.32(m, 2H, n-butyloxy), 1.26(s, 3H, Me17), 1.15(s, 3H, Me16), 0.85(t, J=6.6 Hz, 3H, Me of n-butyloxy).

EXAMPLE 4

(54-2)



Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(isobutyloxycarbonyl) taxol.

To a solution of 7-triethylsilyl baccatin III (40.0 mg, 0.042 mmol) in 0.5 mL of THF at –45° C. was added dropwise 0.05 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at –45° C., a solution of cis-1-(isobutyloxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (43.0 mg, 0.13 mmol) in 0.5 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 0.5 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 31.2 mg of a mixture containing (2'R,3'S)-2'-(2methoxy-2-propoxy)-7-triethylsilyl-3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(isobutyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

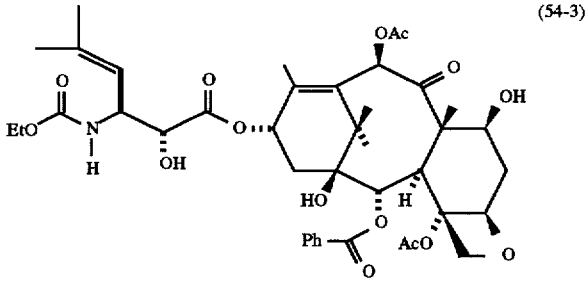
To a solution of 31.2 mg (0.030 mmol) of the mixture obtained from the previous reaction in 2.0 mL of acetonitrile and 0.12 mL of pyridine at 0° C. was added 0.25 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 27.7 mg of material which was purified by flash chromatography to give 20.7 mg (83%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(isobutyloxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.147°–148° C.; $[\alpha]^{25}_{Na}$–58.2° (c 0.0016, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.22(dd, J=7.5, 7.5 Hz, 1H, H13), 5.65(d, J=7.2 Hz, 1H, H2β), 5.31(m, 1H, olefine of isobuthenyl), 4.95(d, J=7.8, 1H, H5), 4.91(d, J=8.2 Hz, 1H, NH), 4.76(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.41(m, 1H, H2'), 4.33(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.81(d, J=7.2 Hz, 1H, H3), 3.71(dd, J=10.2, 6.6 Hz, 1H, isobuthyl), 3.60(dd, J=10.2, 6.6 Hz, 1H, isobuthyl), 3.31(d, J=6.6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.37(s, 3H, 4 Ac), 2.31(m, 2H, H14), 2.26(s, 3H, 10 Ac), 2.23(br s, 3H, Me18), 1.89(s, 3H,

Me19), 1.87(m, 1H, H6β), 1.77(s, 3H, Me isobuthenyl), 1.75(s, 1H, 1OH), 1.66(s, 3H, Me isobuthenyl), 1.25(s, 3H, Me17), 1.15(s, 3H, Me16), 0.76(d, J=7.2 Hz, 3H, Me of isobuthyl), 0.70(d, J=6.6 Hz, 3H, Me of isobuthyl).

EXAMPLE 5



Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(ethoxycarbonyl) taxol.

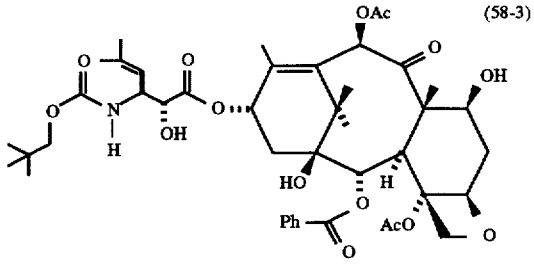
To a solution of 7-triethylsilyl baccatin III (100.0 mg, 0.142 mmol) in 1.0 mL of THF at −45° C. was added dropwise 0.16 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(ethoxycarbonyl)-3-(2'-2"-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (155 mg, 0.43 mmol) in 1.0 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 112.2 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(ethoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 112.2 mg (0.109 mmol) of the mixture obtained from the previous reaction in 7.0 mL of acetonitrile and 0.4 mL of pyridine at 0° C. was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 98.7 mg of material which was purified by flash chromatography to give 81.4 mg (93%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(ethoxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.137°–140° C.; $[\alpha]^{25}_{Na}$−56.2.0° (c 0.0023, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.19(dd, J=7.5, 7.5 Hz, 1H, H13), 5.65(d, J=7.2 Hz, 1H, H2β), 5.31(m, 1H, olefine of isobuthenyl), 4.98(d, J=7.8, 1H, H5), 4.90(d, J=8.2 Hz, 1H, NH), 4.75(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.45(m, 1H, H2'), 4.31(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.93(q, J=7.2 Hz, 2H, ethyl), 3.81(d, J=7.2 Hz, 1H, H3), 3.34(d, J=6.6 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.36(s, 3H, 4 Ac), 2.33(m, 2H, H14), 2.26(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.89(s, 3H, Me19), 1.87(m, 1H, H6β), 1.78 s, 3H, Me isobuthenyl), 1.73(s, 1H, 1OH), 1.68(s, 3H, Me isobuthenyl), 1.26(s, 3H, Me17), 1.15(s, 3H, Me16), 1.08(t, J=7.2 Hz, 3H, Me of ethyl).

EXAMPLE 6



Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(neopentyloxycarbonyl) taxol.

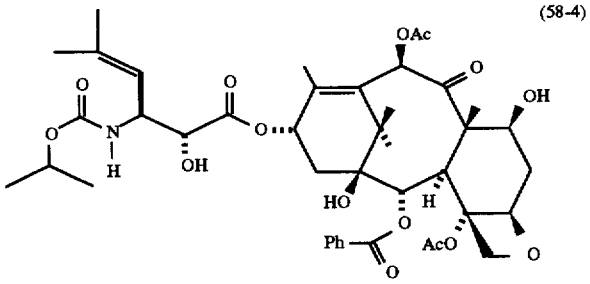
To a solution of 7-triethylsilyl baccatin III (50.0 mg, 0.071 mmol) in 0.7 mL of THF at −45° C. was added dropwise 0.08 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(neopentyloxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobuthenylazetidin-2-one (68.9 mg, 0.21 mmol) in 1.0 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 65.1 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(neopentyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 65.1 mg (0.057 mmol) of the mixture obtained from the previous reaction in 6.0 mL of acetonitrile and 0.3 mL of pyridine at 0° C. was added 0.7 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 58.2 mg of material which was purified by flash chromatography to give 31.2 mg (65%) of 3'-desphenyl-3'-(isobutenyl)-N-debenzoyl-N-(neopentyloxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.147°–149° C.; $[\alpha]^{25}_{Na}$−58.5° (c 0.0019, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.15(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.22(dd, J=7.5, 7.5 Hz, 1H, H13), 5.68(d, J=7.2 Hz, 1H, H2β), 5.32(m, 1H, olefine of isobuthenyl), 4.98(d, J=7.8, 1H, H5), 4.89(d, J=8.2 Hz, 1H, NH), 4.76(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.43(m, 1H, H2'), 4.29(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.76(s, 2H, neopenthyloxy), 3.81(d, J=7.2 Hz, 1H, H3), 3.34(d, J=6.6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.33(s, 3H, 4 Ac), 2.30(m, 2H, H14), 2.26(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.89(s, 3H, Me19), 1.87 (m, 1H, H6β), 1.77 (s, 3H, Me isobuthenyl), 1.75(s, 1H, 1OH), 1.68(s, 3H, Me isobuthenyl), 1.26(s, 3H, Me17), 1.20(s, 9H, Me of neopenthyloxy) 1.15(s, 3H, Me16).

EXAMPLE 7



(58-4)

Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(isopropyloxycarbonyl) taxol.

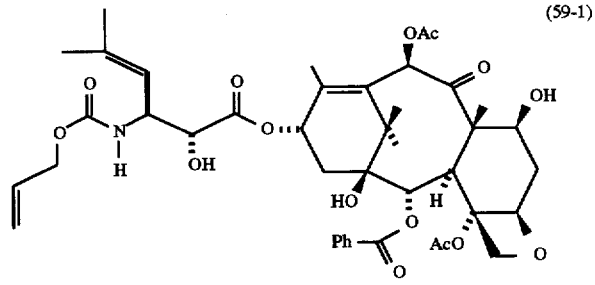
To a solution of 7-triethylsilyl baccatin III (50.0 mg, 0.071 mmol) in 0.7 mL of THF at −45° C. was added dropwise 0.08 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(isopropyloxycarbonyl) -3-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (56.3 mg, 0.22 mmol) in 1.0 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 63.4 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(isopropyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 63.4 mg (0.057 mmol) of the mixture obtained from the previous reaction in 5.5 mL of acetonitrile and 0.3 mL of pyridine at 0° C. was added 0.66 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 49.2 mg of material which was purified by flash chromatography to give 38.2 mg (82%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(isopropyloxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.145°–147° C.; $[\alpha]^{25}_{Na}$–58.3° (c 0.0019, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.12(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.20(dd, J=7.5, 7.5 Hz, 1H, H13), 5.65(d, J=7.2 Hz, 1H, H2β), 5.31(m, 1H, olefine of isobuthenyl), 4.96(d, J=7.8, 1H, H5), 4.90(d, J=8.2 Hz, 1H, NH), 4.77(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.69(m, 1H, isopropyloxy), 4.43 (m, 1H, H2'), 4.31 (d, J=7.8 Hz, 1H, H20α), 4.24(m, 1H, H7), 4.15(d, J=7.8 Hz, 1H, H20β), 3.81(d, J=7.2 Hz, 1H, H3), 3.33(d, J=6.6 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.34(s, 3H, 4 Ac), 2.30(m, 2H, H14), 2.24(s, 3H, 10 Ac), 2.21(br s, 3H, Me18), 1.88(s, 3H, Me19), 1.87(m, 1H, H6β), 1.77(s, 3H, Me isobuthenyl), 1.75(s, 1H, 1OH), 1.66(s, 3H, Me isobuthenyl), 1.25(s, 3H, Me17), 1.16(s, 3H, Me16), 1.14(d, J=6.6 Hz, 3H, Me of isopropyloxy), 1.12(d, J=6.6 Hz, 3H, Me of isopropyloxy).

EXAMPLE 8



(59-1)

Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(allyloxycarbonyl) taxol.

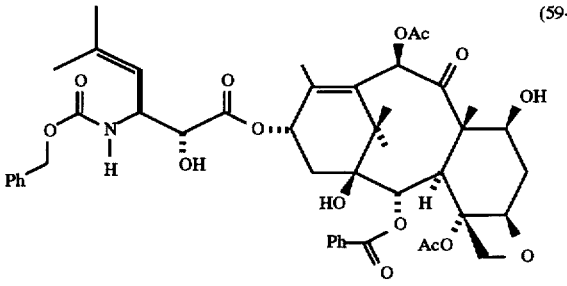
To a solution of 7-triethylsilyl baccatin III (50.0 mg, 0.071 mmol) in 0.7 mL of THF at −45° C. was added dropwise 0.08 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(allyloxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (65.4 mg, 0.22 mmol) in 1.0 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 64.4 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobuthenyl-7-triethylsilyl-N-debenzoyl-N-(allyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 64.4 mg (0.058 mmol) of the mixture obtained from the previous reaction in 6.0 mL of acetonitrile and 0.28 mL of pyridine at 0° C. was added 0.7 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 53.2 mg of material which was purified by flash chromatography to give 33.3 mg (71%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(allyloxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.137°–139° C.; $[\alpha]^{25}_{Na}$=–59.1° (c 0.0022, $CHCl_3$).

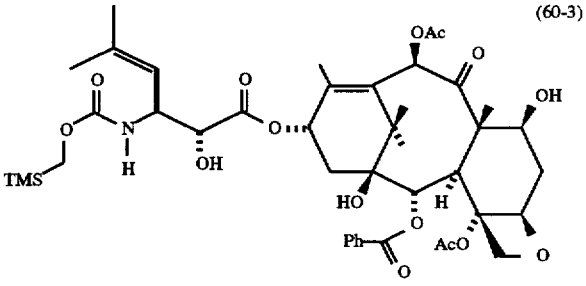
^1H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.2 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.29(s, 1H, H10), 6.21(dd, J=7.5, 7.5 Hz, 1H, H13), 5.78(m, 1H, allyl), 5.67(d, J=7.2 Hz, 1H, H2β), 5.33(m, 1H, olefine of isobuthenyl), 5.14(m, 2H, allyl), 4.97(d, J=7.8, 1H, H5), 4.91(d, J=8.2 Hz, 1H, NH), 4.78 (ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.43(m, 1H, H2'), 4.31(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.18(d, J=7.8 Hz, 1H, H20β), 4.08(d, J=6.6 Hz, 2H, allyl) 3.79(d, J=7.2 Hz, 1H, H3), 3.34(d, J=6.6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.36(s, 3H, 4 Ac), 2.33(m, 2H, H14), 2.26(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.88(s, 3H, Me19), 1.85(m, 1H, H6β), 1.72(s, 3H, Me isobuthenyl), 1.69(s, 1H, 1OH), 1.61(s, 3H, Me isobuthenyl), 1.25(s, 3H, Me17), 1.15(s, 3H, Me16).

EXAMPLE 9



(59-2)

EXAMPLE 10



(60-3)

Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(benzoyloxycarbonyl) taxol.

To a solution of 7-triethylsilyl baccatin III (50.0 mg, 0.071 mmol) in 0.7 mL of THF at −4° C. was added dropwise 0.08 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −4° C., a solution of cis-1-(benzoyloxycarbonyl)-3-(2-methoxy-2-propoxy)-4-isobutenylazetidin-2-one (63 mg, 0.21 mmol) in 0.5 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 60.4 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(benzoyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 60.4 mg (0.053 mmol) of the mixture obtained from the previous reaction in 5.0 mL of acetonitrile and 0.3 mL of pyridine at 0° C. was added 0.65 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 48.2 mg of material which was purified by flash chromatography to give 34.1 mg (74%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(benzoyloxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.148°–149° C.; $[\alpha]^{25}_{Na}$–53.2.0° (c 0.0026, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ8.15(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 7.22–7.20 (m, 3H, benzyl), 7.10–7.05(m, 2H, benzyl), 6.29(s, 1H, H10), 6.21(dd, J=7.5, 7.5 Hz, 1H, H13), 5.63(d, J=7.2 Hz, 1H, H2b), 5.33(m, 1H, olefine of isobuthenyl), 5.06(d, J=12.3 Hz, 1H, benzyl), 4.97(d, J=7.8, 1H, H5), 4.91(d, J=8.2 Hz, 1H, NH), 4.85(d, J=12.3 Hz, 1H, benzyl), 4.76(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.48(m, 1H, H2'), 4.30(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.81(d, J=7.2 Hz, 1H, H3), 3.34(d, J=6.6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.49(d, J=3.9 Hz, 1H, 7OH), 2.36(s, 3H, 4 Ac), 2.32(m, 2H, H14), 2.27(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.90(s, 3H, Me19), 1.86(m, 1H, H6β), 1.77(s, 3H, Me isobuthenyl), 1.75(s, 1H, 1OH), 1.67(s, 3H, Me isobuthenyl), 1.27(s, 3H, Me17), 1.16(s, 3H, Me16).

Preparation of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(trimethylsilylmethoxycarbonyl) taxol.

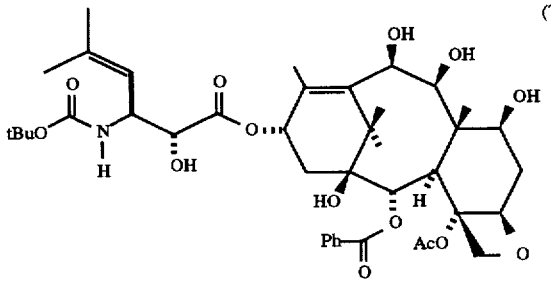
To a solution of 7-triethylsilyl baccatin III (50.0 mg, 0.71 mmol) in 0.7 mL of THF at −45° C. was added dropwise 0.08 mL of a 1.0M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(trimethylsilylmethoxycarbonyl)-3-(2-methoxy-2-propoxy)-4-(isobuthenyl)azetidin-2-one (77.0 mg, 0.22 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1.0 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 58.4 mg of a mixture containing (2'R,3'S)-2'-(2-methoxy-2-propoxy)-3'-desphenyl-3'-isobutenyl-7-triethylsilyl-N-debenzoyl-N-(trimethylsilylmethoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 58.4 mg (0.51 mmol) of the mixture obtained from the previous reaction in 5.0 mL of acetonitrile and 0.30 mL of pyridine at 0° C. was added 0.60 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 51.2 mg of material which was purified by flash chromatography to give 31.1 mg (71%) of 3'-desphenyl-3'-isobutenyl-N-debenzoyl-N-(trimethylsilylmethoxycarbonyl) taxol, which was recrystallized from methanol/water.

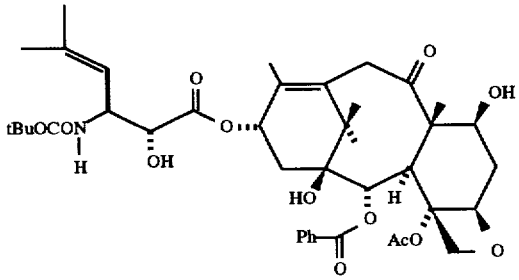
m.p.149°–151° C.; $[\alpha]^{25}_{Na}$–58.0° (c 0.0018, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ8.11(d, J=7.2 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.30(s, 1H, H10), 6.21(dd, J=7.5, 7.5 Hz, 1H, H13), 5.67(d, J=7.2 Hz, 1H, H2β), 5.33(m, 1H, olefine of isobuthenyl), 4.97(d, J=7.8, 1H, H5), 4.88(d, J=8.2 Hz, 1H, NH), 4.76(ddd, J=8.7, 8.7, 2.7 Hz, 1H, H3'), 4.41(m, 1H, H2'), 4.28(d, J=7.8 Hz, 1H, H20α), 4.25(m, 1H, H7), 4.16(d, J=7.8 Hz, 1H, H20β), 3.76(d, J=7.2 Hz, 1H, H3), 3.68(d, J=14.1 Hz, 1H, C$\underline{H}_2$TMS), 3.51(d, J=14.1 Hz, 1H, C$\underline{H}_2$TMS), 3.41(d, J=6.6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.50(d, J=3.9 Hz, 1H, 7OH), 2.29(s, 3H, 4 Ac), 2.25(m, 2H, H14), 2.21(s, 3H, 10 Ac), 2.24(br s, 3H, Me18), 1.89(s, 3H, Me19), 1.87(m, 1H, H6β), 1.77(s, 3H, Me isobuthenyl), 1.75(s, 1H, 1OH), 1.68(s, 3H, Me isobuthenyl), 1.18(s, 3H, Me17), 1.15(s, 3H, Me16), −0.04(s, 9H, Me_3Si—).

(70-4)



(68-4)



Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-desacetyl taxol.

To a solution of 7,10-(bis)-O-triethylsilyl-9-desoxo-9β-hydroxy-10-deacetyl baccatin (III) (70.0 mg, 0.09 mmol) in 1.0 mL of THF at −45° C. was added dropwise 0.10 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-(t-butoxycarbonyl)-3-(2-methoxyisopropyloxy)-4-(isobutenyl)azetidin-2-one (84.5 mg, 0.27 mmol) in 1.0 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 88.3 mg of a mixture containing (2'R,3'S)-2',7,10-(tris)-O-triethylsilyl-3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-desacetyl taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 88.3 mg (0.080 mmol) of the mixture obtained from the previous reaction in 13.5 mL of acetonitrile and 0.55 mL of pyridine at 0° C. was added 1.90 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 67.2 mg of material which was purified by flash chromatography to give 52.7 mg (82%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-desacetyl taxol, which was recrystallized from methanol/water.

m.p.138°–140° C.; $[\alpha]^{25}_{Na}$−55.2° (c 0.0026, $CHCl_3$).

^1H NMR (MeOH, 300 MHz) δ8.11(d, J=7.1 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.13(m, 1H, H13), 6.12(m, 1H, H2), 5.21(br s., 1H, H3'), 5.02(d, J=5.3 Hz, 1H, H10), 4.93(d, J=8.1 Hz, 1H, H5), 4.85(d, J=9.1 hz, 1H, NH), 4.84(d, J=8.5 Hz, 1H, Me_2C=CH—), 4.50(br s, 1H, H2'), 4.50(d, J=5.5 Hz, 1H, H9), 4.22(d, J=8.1, 1H, H20α), 4.18(d, J=8.1 Hz, 1H, H20β), 3.89(dd, J=9.4, 7.5 Hz, 1H, H7), 3.12(d, J=5.5 Hz, H3), 2.45(m, 1H, H6α), 2.31(m, 1H, H14α), 2.29(s, 3H, 4 Ac), 2.18(m, 1H, H14β), 1.85(ddd, J=15.1, 9.4, 1.2 Hz, H6β), 1.81(s, 3H, Me16), 1.76(s, 3H, Me18), 1.72(s, 6H, 2Me from isobuthenyl), 1.61(s, 3H, Me19), 1.39(s, 9H, 3Me t-buthoxy), 1.26(s, 3H, Me17).

Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol.

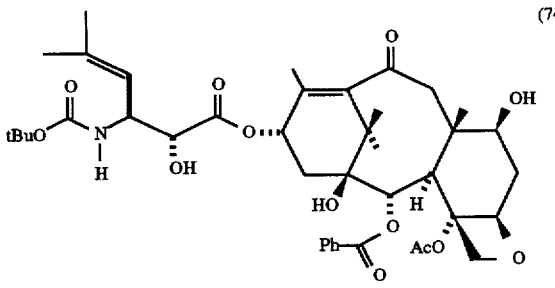
To a solution of 7-O-triethylsilyl-10-desacetoxy baccatin (III) (50.0 mg, 0.077 mmol) in 0.8 mL of THF at −45° C. was added dropwise 0.09 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-t-butoxycarbonyl-3-(2-methoxyisopropyloxy)-4-(isobutenyl)azetidin-2-one (58.0 mg, 0.193 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 62.7 mg of a mixture containing (2'R,3'S)-2'-O-(2-methoxyisopropyl)-7-O-triethylsilyl-3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 62.7 mg (0.059 mmol) of the mixture obtained from the previous reaction in 3.5 mL of acetonitrile and 0.16 mL of pyridine at 0° C. was added 0.55 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 51.5 mg of material which was purified by flash chromatography to give 43.0 mg (95%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol, which was recrystallized from methanol/water.

m.p.153°–155° C.; $[\alpha]^{25}_{Na}$−56.3° (c 0.003, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.10(d, J=7.3 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.47(m, 2H, benzoate meta), 6.15(td, J=8.5, 1.8 Hz, 1H, H13), 5.69(d, J=6.9 Hz, 1H, H2), 5.32(d, J=9.2 Hz, 1H, NH), 4.93(dd, J=9.6, 1.8 Hz, 1H, H5), 4.82(d, J=8.7 Hz, 1H, Me_2C=CH—), 4.76(td, J=8.7, 2.7 Hz, 1H, H3'), 4.37(d, J=8.7 Hz, 1H, H20α), 4.22(d, J=8.7 Hz, 1H, H20β), 4.18(d, J=2.7 Hz, 1H, H2'), 4.03(d, J=7.3 Hz, 1H, H7), 3.82(d, J=15.2 Hz, 1H, H10α), 3.47(m, 1H, 2'OH), 3.41(d, J=6.6 Hz, 1H, H3), 2.60(m, 1H, H6α), 2.39(m, 1H, H10β), 2.37(s, 3H, 4 Ac), 2.18(s, 1H, 7OH), 2.08(m, 1H, H14α), 1.78(m, 1H, H14β), 1.76(s, 3H, Me18), 1.74(s, 6H, 2Me from isobuthenyl), 1.63(m, 1H, H6β), 1.36(s, 9H, 3Me t-buthoxy) 1.26(s, 3H, Me17), 1.18(s, 3H, Me19), 1.15(s, 3H, Me16).

EXAMPLE 13



(74-4)

Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol.

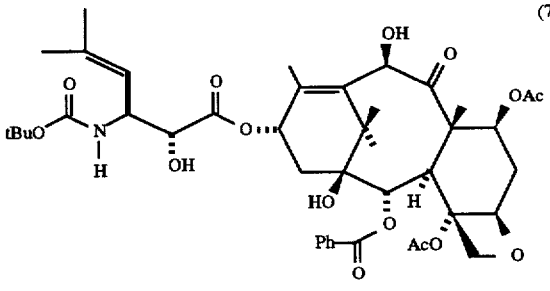
To a solution of 7-O-triethylsilyl-9-desoxo-10-desacetoxy-10-keto baccatin (III) (30.0 mg, 0.047 mmol) in 0.5 mL of THF at −45° C. was added dropwise 0.05 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-t-butoxycarbonyl-3-(2-methoxyisopropyloxy)-4-(isobutenyl) azetidin-2-one (44.1 mg, 0.141 mmol) in 0.5 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 40.8 mg of a mixture containing (2'R,3'S)-2'-O-(2-methoxyisopropyl)-7-O-triethylsilyl-3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 40.8 mg (0.043 mmol) of the mixture obtained from the previous reaction in 4 mL of acetonitrile and 0.2 mL of pyridine at 0° C. was added 0.5 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 34.4 mg of material which was purified by flash chromatography to give 23.0 mg (70%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol, which was recrystallized from methanol/water.

m.p.149°–153° C.; $[\alpha]^{25}_{Na}$–56.3° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.12(d, J=7.2 Hz, 2H, benzoate ortho), 7.64(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 6.12(t, J=7.5 Hz, 1H, H13), 5.95(d, J=6.2 Hz, 1H, H2), 5.30(d, J=8.9 Hz, 1H, NH), 4.94(d, J=8.2 Hz, 1H, H5), 4.88(d, J=8.9 Hz, 1H, Me_2C=CH—), 4.79(td, J=8.9, 2.4 Hz, 1H, H3'), 4.34(d, J=8.2 Hz, 1H, H20α), 4.27(dd, J=5.5, 2.7 Hz, 1H, H2'), 4.19(d, J=8.2 Hz, 1H, H20β), 3.73(m, 1H, H7), 3.67(br s, 1H, 2'OH), 3.13(d, J=5.1 Hz, 1H, H3), 3.12(d, J=15.7 Hz, 1H, H9α), 2.90(d, J=15.7 Hz, 1H, H9β), 2.55(m, 1H, H6α), 2.47(m, 1H, H14β), 2.32(s, 3H, 4 Ac), 2.28(m, 1H, H14α), 2.04(br s, 1H, 7OH), 1.88(s, 1H, 1OH), 1.82(m, 1H, H6β), 1.79(s, 3H, Me18), 1.76(s, 6H, 2Me from isobuthenyl), 1.57(s, 3H, Me16), 1.47 (s, 3H, Me19), 1.40(s, 9H, 3Me t-buthoxy) 1.30 (s, 3H, Me17).

EXAMPLE 14



(70-1)

Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-O-acetyl-10-desacetyl taxol.

To a solution of 7-O-triethylsilyl-9-desoxy-9β-acetoxy-10-desacetoxy-10-keto baccatin (III) (33.0 mg, 0.047 mmol) in 0.5 mL of THF at −45° C. was added dropwise 0.05 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-t-butoxycarbonyl-3-(2-methoxyisopropyloxy)-4-isobutenylazetidin-2-one (44.1 mg, 0.141 mmol) in 0.5 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 41.9 mg of a mixture containing (2'R,3'S)-2'-O-(2-methoxyisopropyl)-7-O-triethylsilyl-3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxy-9β-acetoxy-10-desacetoxy-10-keto taxol and a small amount of the (2'S,3'R) isomer.

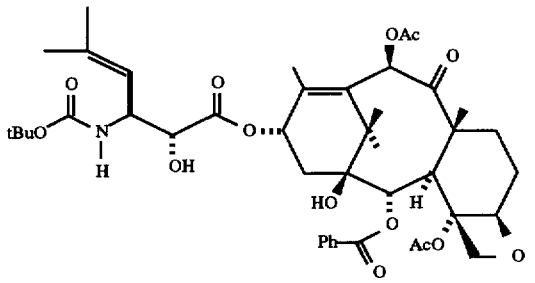
To a solution of 41.9 mg (0.045 mmol) of the mixture obtained from the previous reaction in 3.5 mL of acetonitrile and 0.15 mL of pyridine at 0° C. was added 0.50 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 32.4 mg of material which was stirred with 1.0 g of silica gel in 5 mL of methylene chloride at room temperature in 48 hrs. The organic layer was purified by filtration through silica gel to give 26.2 mg (70%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-O-acetyl-10-desacetyl taxol.

m.p.1136°–139° C.; $[\alpha]^{25}_{Na}$–60.2° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.10(d, J=7.3 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.16(td, J=8.7, 1.8 Hz, 1H, H13), 5.68(d, J=6.9 Hz, 1H, H2), 5.48(dd, J=10.5, 7.3 Hz, 1H, H7), 5.33{d, J=1.8 Hz, 1H, H10), 5.32(d, J=9.2 Hz, 1H, NH), 4.94(dd, J=9.6, 1.8 Hz, 1H, H5), 4.80(d, J=8.7 Hz, 1H, Me_2C=CH—), 4.75(td, J=8.7, 2.7 Hz, 1H, H3'), 4.33(d, J=8.7 Hz, 1H, H20α), 4.23(d, J=2.7 Hz, 1H, H2'), 4.22(d, J=8.7 Hz, 1H, H20β), 4.01(d, J=6.9 Hz, 1H, H3), 3.98(d, J=1.8 Hz, 1H, 10OH), 3.68(m, 1H, 2'OH), 2.54(m, 1H, H6α), 2.37(s, 3H, 4 Ac), 2.35(m, 1H, H14α), 2.01(m, 1H, H14β), 1.99(s, 3H, 7 Ac), 1.98(br s, 3H, Me18), 1.93(m, 1H, H6β), 1.85(s, 3H, Me19), 1.77(s, 6H, 2 Me from isobuthenyl), 1.61(s, 1H, 7OH), 1.37(s, 9H, 3Me t-butoxy), 1.23(s, 3H, Me17), 1.10(s, 3H, Me16).

EXAMPLE 15

(71-2)



Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy taxol.

To a solution of 7-deshydroxy baccatin (III) (38.7 mg, 0.063 mmol) in 0.8 mL of THF at −45° C. was added dropwise 0.08 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-t-butoxycarbonyl-3-(2-methoxyisopropyloxy)-4-(isobutenyl) azetidin-2-one (59.0 mg, 0.19 mmol) in 0.8 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 43.4 mg of a mixture containing (2'R,3'S)-2'-O-(2-methoxyisopropyl)-3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7- deshydroxy taxol and a small amount of the (2'S,3'R) isomer.

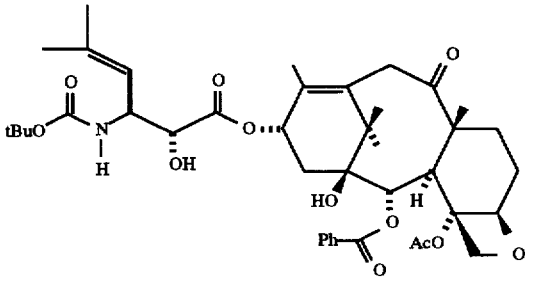
To a solution of 43.4 mg (0.049 mmol) of the mixture obtained from the previous reaction in 3.5 mL of acetonitrile and 0.15 mL of pyridine at 0° C. was added 0.5 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 40.2 mg of material which was purified by flash chromatography to give 34.1 mg (86%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy taxol, which was recrystallized from methanol/water.

m.p.142°–144° C.; $[\alpha]^{25}_{Na}$–53.3° (c 0.0024, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.13(d, J=7.3 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.47(m, 2H, benzoate meta), 6.41(s, 1H, H10), 6.20(dd, J=9.0, 0.9 Hz, 1H, H13), 5.67(d, J=7.2 Hz, 1H, H2), 5.39(d, J=6.9 Hz, 1H, NH), 5.32(d, J=9.0 Hz, 1H, H3'), 4.93(dd, J=8.7, 2.1 Hz, 1H, H5), 4.81(d, J=8.7 Hz, 1H, $Me_2C{=}C\underline{H}$—), 4.61(d, J=3.3 Hz, 1H, H2'), 4.30(d, J=8.1 Hz, 1H, H20α), 4.17(d, J=8.1 Hz, 1H, H20β), 3.75(d, J=6.6 Hz, 1H, H3), 3.41(m, 1H, 2'OH), 2.36(s, 3H, 4 Ac), 2.33(m, 1H, H14α), 2.30(m, 1H, H14β), 2.26(m, 1H, H6α), 2.08(m, 1H, H7α), 1.94(m, 1H, H6β), 1.85(br s, 3H, Me18), 1.73(s, 6H, 2Me from isobuthenyl), 1.70(s, 3H, Me19), 1.66(s, 1H, 1OH), 1.53(m, 1H, H7β), 1.41(s, 9H, 3Me t-buthoxy), 1.25(s, 3H, Me16), 1.15(s, 3H, Me17).

EXAMPLE 16

(72-1)



Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol.

To a solution of 7-deshydroxy-10-desacetoxy baccatin (III) (28.7 mg, 0.051 mmol) in 0.7 mL of THF at −45° C. was added dropwise 0.06 mL of a 0.98M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at −45° C., a solution of cis-1-t-butoxycarbonyl-3-(2-methoxyisopropyloxy)-4-(isobutenyl)azetidin-2-one (47.3 mg, 0.15 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0° C. and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 40.3 mg of a mixture containing (2'R,3'S)-2'-O-(2-methoxyisopropyl)-3'-desphenyl-3'-(isobutenyl)-N-debenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 40.3 mg (0.046 mmol) of the mixture obtained from the previous reaction in 3.2 mL of acetonitrile and 0.15 mL of pyridine at 0° C. was added 0.47 mL of 48% aqueous HF. The mixture was stirred at 0° C. for 3 h, then at 25° C. for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 35.2 mg of material which was purified by flash chromatography to give 24.0 mg (70%) of 3'-desphenyl-3'-(isobutenyl)-N-debenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol, which was recrystallized from methanol/water.

m.p.122°–125° C.; $[\alpha]^{25}_{Na}$–64.3° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ8.12(d, J=7.1 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.11(td, J=8.1, 1.8 Hz, 1H, H13), 5.68(d, J=6.9 Hz, 1H, H2), 5.23(d, J=9.9 Hz, 1H, NH), 5.12(d, J=9.9 Hz, 1H, H3'), 4.96(dd, J=9.1, 2.7 Hz, 1H, H5), 4.80(d, J=8.7 Hz, 1H, $Me_2C{=}C\underline{H}$—), 4.58(dd, J=5.7, 2.1 Hz, 1H, H2'), 4.30(d, J=8.1, 1H, H20α), 4.19(d, J=8.1 Hz, 1H, H20β), 3.97(d, J=6.9 Hz, H3), 3.83(d, J=16.5, 1H, H10α), 3.33(m, 1H, H10β), 3.30(m, 1H, 2'OH), 2.39(m, 1H, H14α), 2.35(s, 3H, 4 Ac), 2.26(m, 1H, H14β), 2.19(m, 1H, H6α), 2.10(m, 1H, H7α), 1.95(m, 1H, H6β), 1.73(s, 3H, Me18), 1.69(s, 6H, 2Me from isobuthenyl), 1.63(s, 3H, Me19), 1.44(m, 1H, H7β), 1.39(br. s, 1H, 1OH), 1.35(s, 9H, 3Me t-buthoxy), 1.25(s, 3H, Me16), 1.15(s, 3H, Me17).

EXAMPLE 17

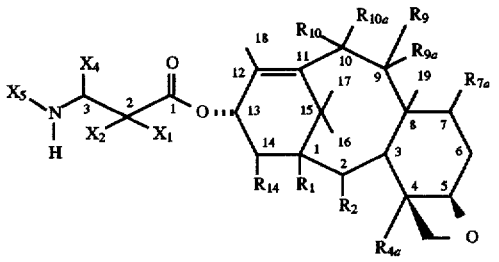
Taxanes 29-4, 51-3, 54-1, 54-2, 54-3, 58-3, 58-4, 59-1, 59-2, 60-3, 70-4, 68-4, 74-4, 70-1, 71-2, and 72-1 of Examples 1–16 were evaluated in in vitro cytotoxicity activity against human colon carcinoma cells HCT-116. Cytotoxicity was assessed in HCT116 human colon carcinoma cells by XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium

hydroxide) assay (Scudiero et al, "Evaluation of a 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.

All compounds had an IC_{50} of less than 0.1, indicating that they are cytotoxically active.

What we claim is:

1. A taxane having the formula



wherein

X_1 is $—OX_6$, $—SX_7$, or $—NX_8X_9$;

X_2 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl; or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

X_4 is substituted or unsubstituted butenyl;

X_5 is $—COX_{10}$, $—COOX_{10}$, $—COSX_{10}$, $—CONX_8X_{10}$, or $—SO_2X_{11}$;

X_6 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or hydroxy protecting group;

X_7 is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or sulfhydryl protecting group;

X_8 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted heteroaryl; substituted aryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{11} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; $—OX_{10}$; or $—NX_8X_{14}$;

X_{14} is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

R_1 is hydroxy, protected hydroxy or together with R_{14} forms a carbonate;

R_2 is hydroxy or $—OCOR_{31}$;

R_{4a} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; cyano; hydroxy; or $—OCOR_{30}$;

R_{7a} is hydrogen, halogen, protected hydroxy, or $—OR_{28}$;

R_9 is hydrogen or together with R_{9a} forms an oxo;

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, $—OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{14} is hydrogen, hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{28} is hydrogen, acyl, or hydroxy protecting group or a functional group which increases the solubility of the taxane derivative; and

R_{29}, R_{30}, and R_{31} are independently hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

2. The taxane derivative of claim **1** wherein X_5 is $—COX_{10}$ or $—COOX_{10}$, and X_{10} is substituted or unsubstituted heteroaryl or substituted, unsubstituted, straight, branch chained or cyclic alkyl.

3. The taxane derivative of claim **1** wherein X_5 is $—COX_{10}$ and X_{10} is substituted or unsubstituted heteroaryl.

4. The taxane derivative of claim **1** wherein X_5 is $—COOX_{10}$ and X_{10} is, substituted, unsubstituted, straight, branch chained or cyclic alkyl.

5. The taxane of claim **1** wherein

R_{9a} is hydrogen, acyloxy or together with R_9 forms an oxo;

R_{7a} is hydrogen, halogen or $—OR_{28}$;

R_{4a} is hydroxy or $—OCOR_{30}$,

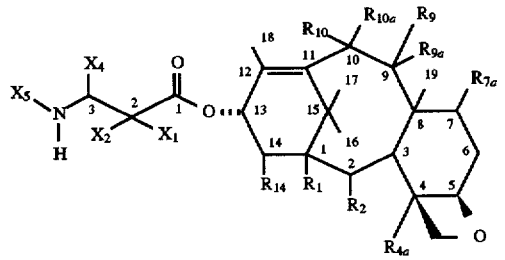
R_2 is hydroxy or $—OCOR_{31}$;

R_1 is hydroxy or protected hydroxy;

R_{28} is hydrogen, acyl, or hydroxy protecting group; and

R_{29}, R_{30}, and R_{31} are independently hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

6. A taxane having the formula



wherein

X_1 is —OX_6;

X_2 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

X_4 is substituted or unsubstituted isobutenyl;

X_5 is —COX_{10}, —$COOX_{10}$, —$COSX_{10}$, —$CONX_8X_{10}$, or —SO_2X_{11};

X_6 is hydrogen or hydroxy protecting group;

X_8 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{11} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; —OX_{10}; or —NX_8X_{14};

X_4 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

R_1 is hydroxy, protected hydroxy or together with R_{14} forms a carbonate;

R_2 is hydroxy or —$OCOR_{31}$;

R_{4a} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; cyano; hydroxy; or —$OCOR_{30}$;

R_{7a} is hydrogen, halogen, protected hydroxy, or —OR_{28};

R_9 is hydrogen or together with R_{9a} forms an oxo;

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, —$OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{14} is hydrogen, hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{28} is hydrogen, acyl, or hydroxy protecting group; and

R_{29}, R_{30}, and R_{31} are independently hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

7. The taxane of claim 6 wherein

X_5 is —COX_{10}, —$COOX_{10}$, or —$CONX_8X_{10}$; and

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl; substituted or unsubstituted heteroaryl; or heterosubstituted alkyl.

8. A pharmaceutical composition which contains the taxane derivative of claim 1 and one or more pharmacologically acceptable, inert or physiologically active diluents or adjuvants.

9. The taxane of claim 1 wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{14} is hydrogen;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

10. The taxane of claim 6 wherein X_5 is —COX_{10}, —$COOX_{10}$ or —$CONX_8X_{10}$; and

X_6 is hydrogen or hydroxy protecting group.

11. The taxane of claim 10 wherein X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; or substituted or unsubstituted heteroaryl.

12. The taxane of claim 6 wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{14} is hydrogen;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

13. The taxane of claim 10 wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

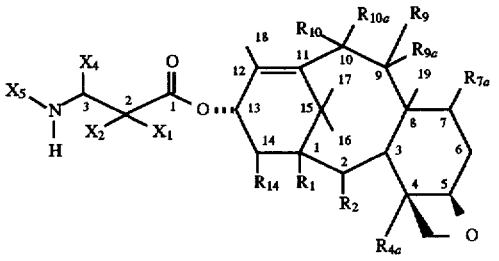
R_{14} is hydrogen;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

14. A pharmaceutical composition which contains the taxane derivative of claim 6 and one or more pharmacologically acceptable, inert or physiologically active diluents or adjuvants.

15. A taxane having the formula



wherein

X_1 is —OX_6, —SX_7, or —NX_8X_9;

X_2 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

X_4 is substituted or unsubstituted butenyl;

X_5 is —COX_{10}, —$COOX_{10}$, —$COSX_{10}$, —$CONX_8X_{10}$, or —SO_2X_{11};

X_6 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or hydroxy protecting group;

X_7 is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or sulfhydryl protecting group;

X_8 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{11} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; —OX_{10}; or —NX_8X_{14};

X_{14} is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

R_1 is hydroxy, protected hydroxy or together with R_{14} forms a carbonate;

R_2 is hydroxy or —$OCOR_{31}$;

R_{4a} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; cyano; hydroxy; or —$OCOR_{30}$;

R_{7a} is hydrogen, halogen, protected hydroxy, or —OR_{28};

R_9 is hydrogen or together with R_{9a} forms an oxo;

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, —$OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{14} is hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{28} is hydrogen, acyl, or hydroxy protecting group; and

R_{29}, R_{30}, and R_{31} are independently hydrogen; substituted, unsubstituted, straight, chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

16. The taxane of claim 15 wherein

X_1 is —OX_6;

X_5 is —COX_{10}, —$COOX_{10}$ or —$CONX_8X_{10}$; and

X_6 is hydrogen or hydroxy protecting group.

17. The taxane of claim 16 wherein X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl or heteroaryl.

18. The taxane of claim 15 wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

19. The taxane of claim 16 wherein

R_1 is hydroxy;

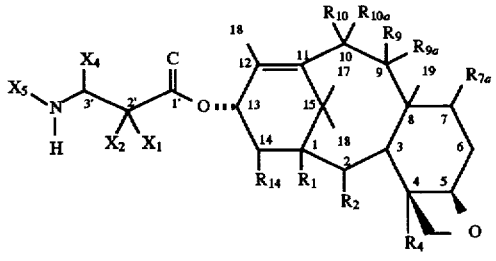
R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

20. A taxane having the formula



wherein

X_1 is —OX_6, —SX_7, or —NX_8X_9;

X_2 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl; or heteroaryl;

X_4 is substituted or unsubstituted butenyl;

X_5 is —COX_{10}, —$COOX_{10}$, —$COSX_{10}$, —$CONX_8X_{10}$, or —SO_2X_{11};

X_6 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or hydroxy protecting group;

X_7 is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or sulfhydryl protecting group;

X_8 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{11} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; $—OX_{10}$; or $—NX_8X_{14}$;

X_{14} is hydrogen, substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

R_1 together with R_{14} forms a carbonate;

R_2 is hydroxy or $—OCOR_{31}$;

R_{4a} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; cyano; hydroxy; or $—OCOR_{30}$;

R_{7a} is hydrogen, halogen, protected hydroxy, or $—OR^{28}$;

R_9 is hydrogen or together with R_{9a} forms an oxo;

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, $—OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{28} is hydrogen, acyl, or hydroxy protecting group; and

R_{29}, R_{30}, and R_{31} are independently hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

21. The taxane of claim **20** wherein

X_1 is $—OX_6$;

X_5 is $—COX_{10}$, $—COOX_{10}$ or $—CONX_8X_{10}$; and

X_6 is hydrogen or hydroxy protecting group.

22. The taxane of claim **21** wherein X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; or substituted or unsubstituted heteroaryl.

23. The taxane of claim **20** wherein

R_2 is $—OCOR_{31}$;

R_{4a} is $—OCOR_{30}$;

R_{14} is hydrogen;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

24. The taxane of claim **22** wherein

R_2 is $—OCOR_{31}$;

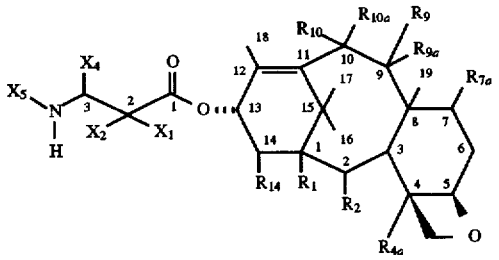
R_{4a} is $—OCOR_{30}$;

R_{14} is hydrogen;

R_{30} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

25. A taxane having the formula



wherein

X_1 is $—OX_6$, $—SX_7$, or $—NX_8X_9$;

X_2 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

X_4 is substituted or unsubstituted butenyl;

X_5 is $—COX_{10}$, $—COOX_{10}$, $—COSX_{10}$, $—CONX_8X_{10}$, or $—SO_2X_{11}$;

X_6 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or hydroxy protecting group;

X_7 is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or sulfhydryl protecting group;

X_8 is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{11} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; $—OX_{10}$; or $—NX_8X_{14}$;

X_{14} is hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted aryl or heteroaryl;

R_1 is hydroxy, protected hydroxy or together with R_{14} forms a carbonate;

R_2 is hydroxy or —$OCOR_{31}$;

R_{4a} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; substituted or unsubstituted aryl or heteroaryl; cyano; hydroxy; or —$OCOR_{30}$;

R_{7a} is hydrogen, halogen, protected hydroxy, or —OR_{28};

R_9 is hydrogen or together with R_{9a} forms an oxo;

R_{9a} is hydrogen, hydroxy, protected hydroxy, acyloxy, or together with R_9 forms an oxo;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, —$OCOR_{29}$, hydroxy, or protected hydroxy, or together with R_{10} forms an oxo;

R_{14} is hydrogen, hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{28} is hydrogen, acyl, or hydroxy protecting group;

R_{29} and R_{31} are independently hydrogen; substituted, unsubstituted, straight, branch chained or cyclic alkyl; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl;

R_{30} is hydrogen; substituted, unsubstituted, straight or branch chained alkenyl or alkynyl; or substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

26. The taxane of claim **25** wherein

X_1 is —OX_6;

X_5 is —COX_{10}, —$COOX_{10}$ or —$CONX_8X_{10}$; and

X_6 is hydrogen or hydroxy protecting group.

27. The taxane of claim **26** wherein X_{10} is substituted, unsubstituted, straight, branch chained or cyclic alkyl; or substituted or unsubstituted heteroaryl.

28. The taxane of claim **25** wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{14} is hydrogen; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

29. The taxane of claim **26** wherein

R_1 is hydroxy;

R_2 is —$OCOR_{31}$;

R_{4a} is —$OCOR_{30}$;

R_{14} is hydrogen; and

R_{31} is substituted or unsubstituted monocyclic aryl or monocyclic heteroaryl.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

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

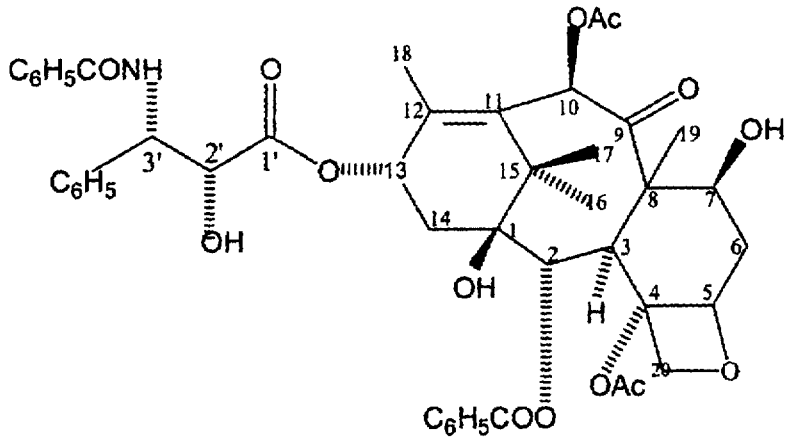
Title page,

Item [63], **Related U.S. Application Data**, should read:

-- Continuation of Ser. No. 08/094,719, Jul. 20, 1993, abandoned, which is a continuation-in-part of Ser. No. 08/034,247, Mar. 22, 1993, Pat. No. 5,430,160 which is a continuation-in-part of Ser. No. 07/949,107, Sep. 22, 1992, abandoned, which is a continuation-in-part of Ser. No. 07/863,849, Apr. 6, 1992, abandoned, which is a continuation-in-part of Ser. No. 07/862,955, Apr. 3, 1992, abandoned, which is a continuation-in-part of Ser. No. 07/763,805, Sep. 23, 1991, abandoned. This application is also a continuation-in-part of Ser. No. 07/975,705, Nov. 13, 1992, Pat. No. 5,284,864, which is a continuation-in-part of Ser. No. 07/949,107, which is a continuation-in-part of Ser. No. 07/863,849, which is a continuation-in-part of Ser. No. 07/862,955, which is a continuation-in-part of Ser. No. 07/763,805. --

Column 1,

Lines 50-60, structure (1) should read:

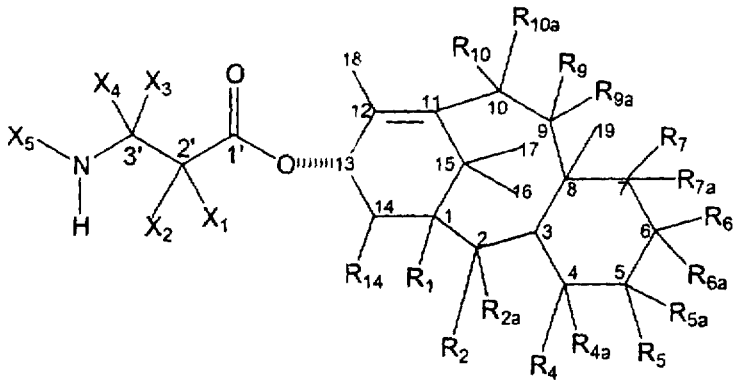


CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

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

Column 2,
Line 16, "hydrogen R" should read -- hydrogen, R" --.
Lines 35-43, structure (3) should read:

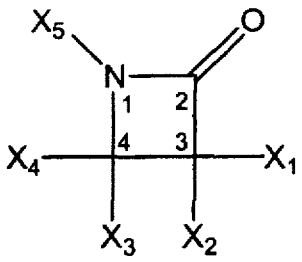


(3)

Line 65, "alkenyl alkynyl" should read -- alkenyl, alkynyl --.

Column 3,
Lines 7-8 "oxo or;" should read -- oxo; --.

Column 6,
Lines 37-33, the structure should read:

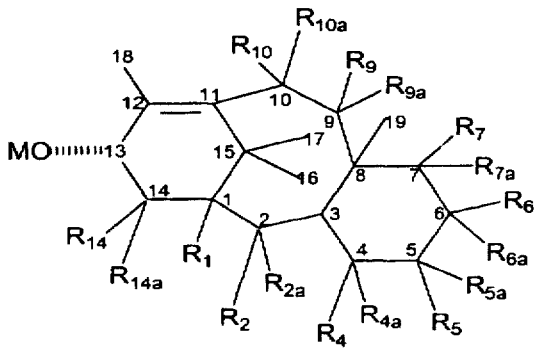


CERTIFICATE OF CORRECTION

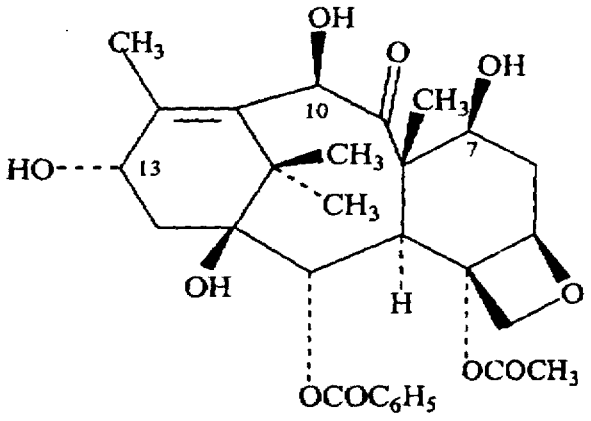
PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

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

Column 8,
Lines 20-28, the structure should read:



Column 9,
Lines 1-10, the structure should read:

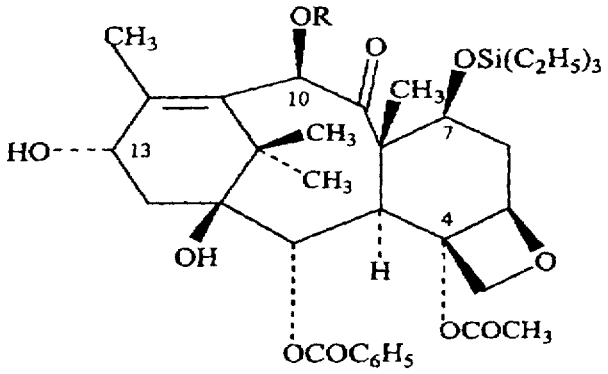


CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

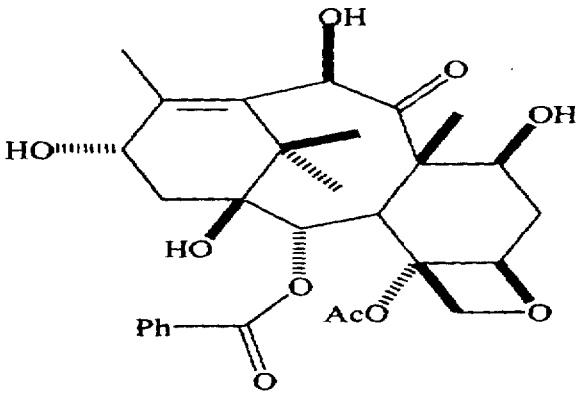
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 9 cont'd.,
Lines 14-23, the structure should read:



Column 12,
Line 2, "reducing" should read -- reducing the C_9 keto substituent --.

Column 16,
Reaction Scheme 4, the first recited structure should read:

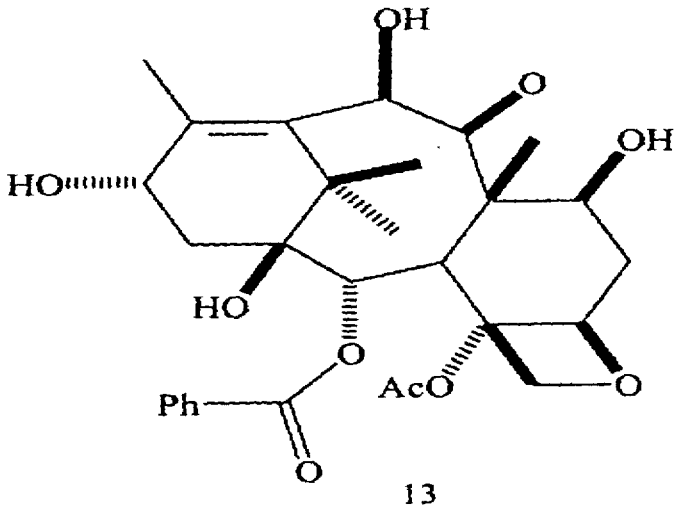


CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

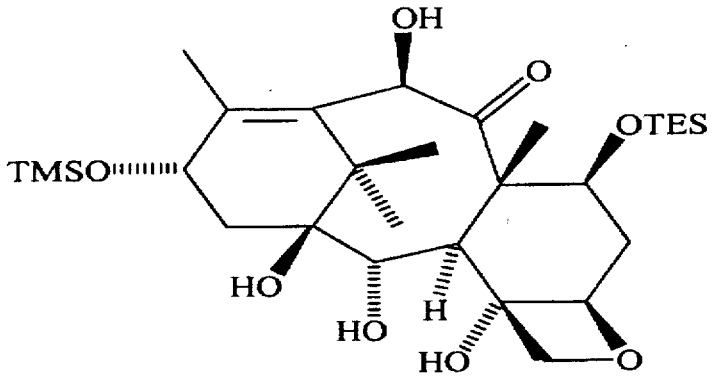
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Reaction Scheme 4, the second recited structure should read:



13

Column 24,
Scheme 10, structure 24 should read:



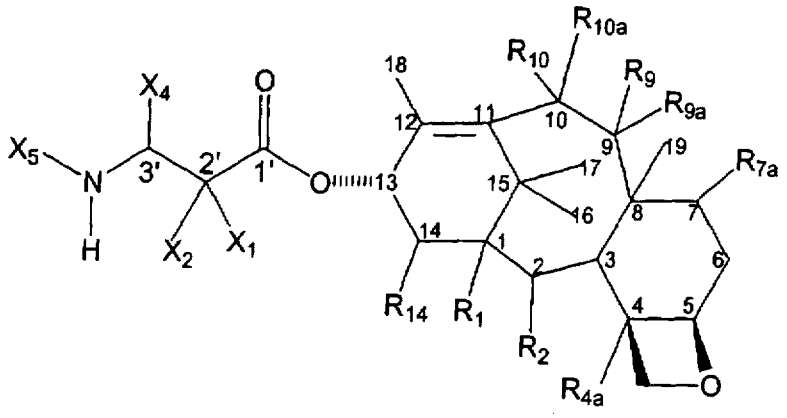
24

CERTIFICATE OF CORRECTION

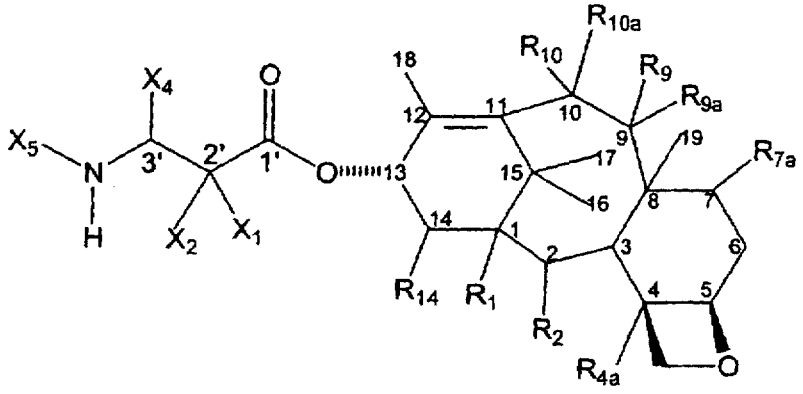
PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

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

Column 45,
Lines 20-30, the structure should read:



Column 47,
Lines 3-13, the structure should read:



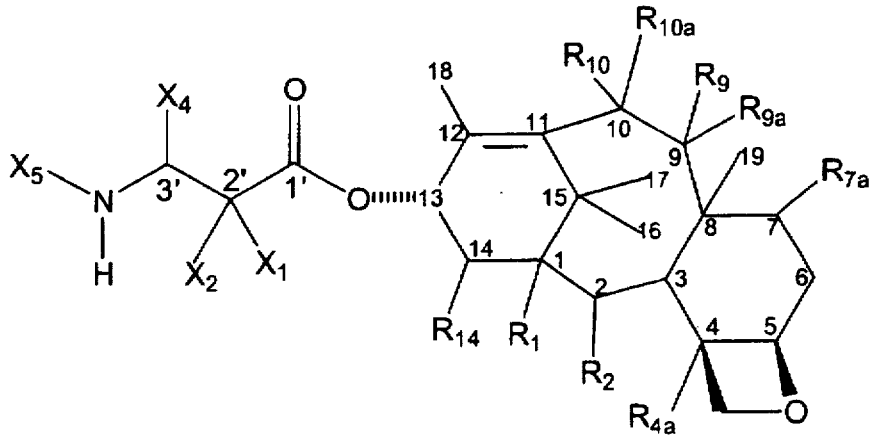
CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

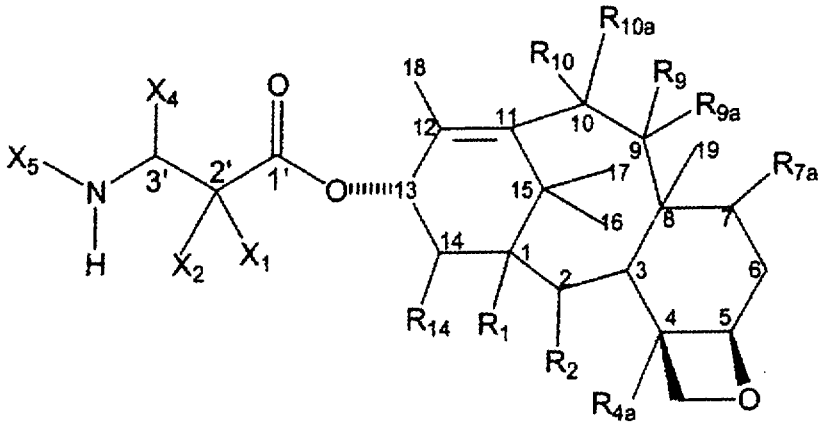
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 47,
Line 43, "X_4" should read -- X_{14} --.

Column 49,
Lines 3-13, the structure should read:



Column 50,
Line 10, "straight, chained" should read -- straight, branch chained --.
Lines 42-50, the structure should read:



UNITED STATES PATENT AND TRADEMARK OFFICE

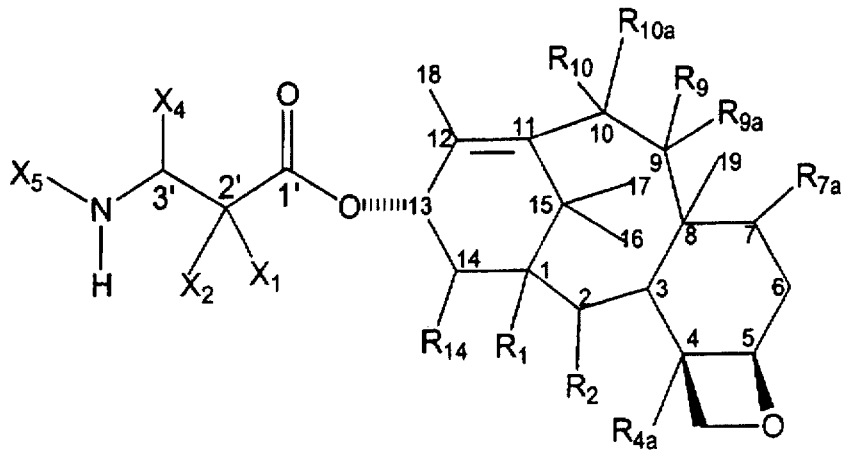
CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton, Ki-byung Chai and Hossain Nadizadeh

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

Column 51,
Line 37, "OR^{28};" should read -- $-OR_{28}$; --.

Column 52,
Lines 13-21, the structure should read:



Signed and Sealed this

Seventh Day of May, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

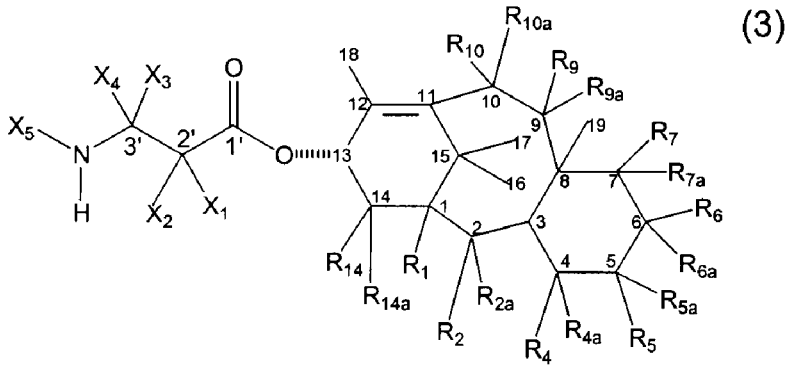
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,728,850
DATED : March 17, 1998
INVENTOR(S) : Robert A. Holton

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

Column 2,
Lines 35-43, structure (3) should read:



Signed and Sealed this

Third Day of February, 2004

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office