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(54) TAXANES HAVING AN ALKYL SUBSTITUTED SIDE-CHAIN AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

TAXANE, DIE EINE ALKYL-SUBSTITUIERTE SEITENKETTE HABEN, UND DIESE ENTHALTENDE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN

TAXANES A CHAINE LATERALE A SUBSTITUTION ALKYLE ET COMPOSITIONS PHARMACEUTIQUES LES CONTENANT

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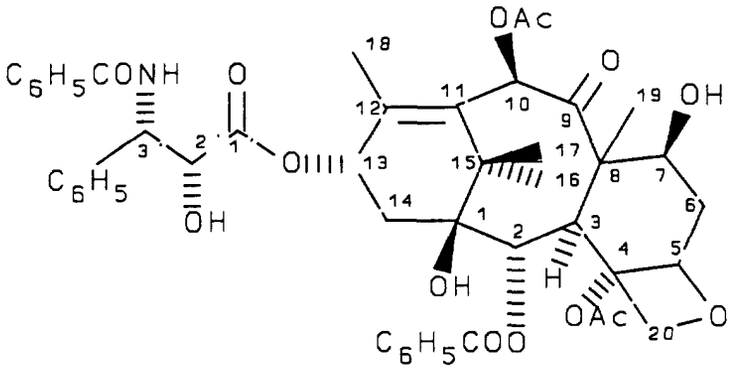
Description

BACKGROUND OF THE INVENTION

[0001] The present invention is directed to novel taxanes which have utility as antileukemia and antitumor agents.

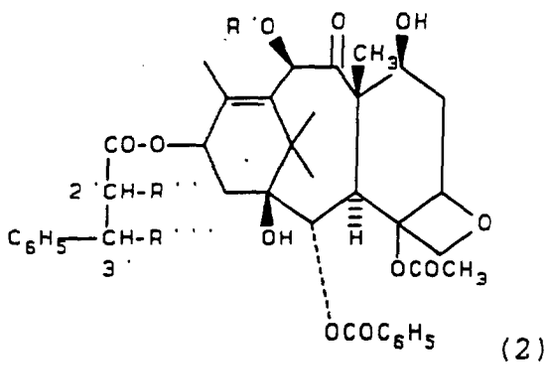
[0002] The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and 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.

[0003] Colin et al. reported in U.S. Patent No. 4,814,470 that taxol derivatives having structural formula **(2)** below, have an activity significantly greater than that of taxol **(1)**.



(2)

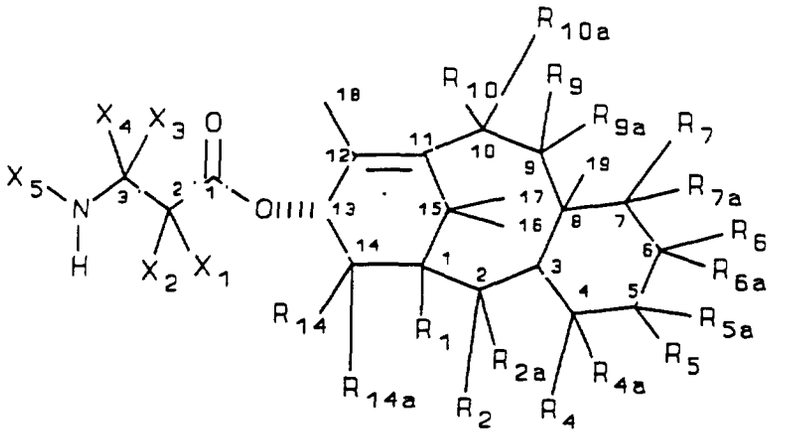
R' represents hydrogen or acetyl and one of R'' and R''' represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula **(2)** in which R'' is hydroxy, R''' is tert-butoxycarbonylamino having the 2'R, 3'S configuration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

[0004] 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

[0005] Among the objects of the present invention, therefore, is the provision of novel taxane derivatives which are valuable antileukemia and antitumor agents.

[0006] Briefly, therefore, the present invention is directed to taxane derivatives having a C13 side chain which includes an optionally substituted cycloalkyl 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 optionally substituted cycloalkyl;
X_4 is hydrogen;
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, $-OCOR_{31}$ together with R_{2a} forms an oxo;
R_{2a} is hydrogen or taken together with R_2 forms an oxo;
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, or 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.

[0007] Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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.

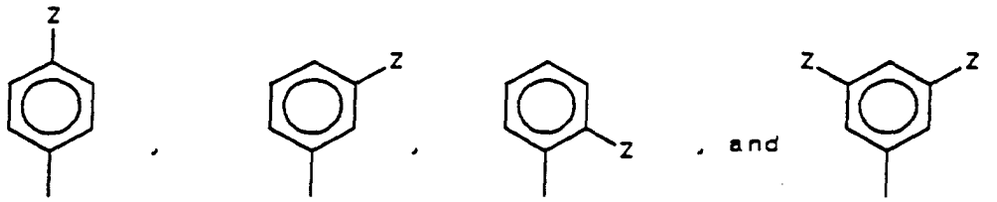
[0013] The heteroaryl moieties described herein, either alone or with various substituents, contain from 5 to 15 atoms and include, furyl, thienyl, pyridyl and the like. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido.

[0014] The acyloxy groups described herein contain alkyl, alkenyl, alkynyl, aryl or heteroaryl groups.

[0015] 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.

[0016] In accordance with the present invention, it has been discovered that compounds corresponding to structural formula b 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.

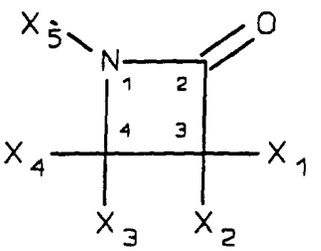
[0017] In one embodiment of the present invention, the substituents of the cyclic nucleus of the taxane (other than the C13 substituent) correspond to the substituents present on baccatin III or 10-DAB. That is, R_{14} and R_{14a} are hydrogen, R_{10} is hydrogen, R_{10a} is hydroxy or acetoxy, R_9 and 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



wherein 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.

[0018] With respect to the C13 side-chain, in a preferred embodiment X_1 is -OH, X_2 is hydrogen, X_3 is cycloalkyl, X_4 is hydrogen, 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_3 is cyclopropyl, cyclobutyl, cyclohexyl or the substituted analogs thereof, X_5 is $-COX_{10}$ or $-COOX_{10}$ and X_{10} is furyl, thienyl, pyridyl, alkyl substituted furyl or thienyl, 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.

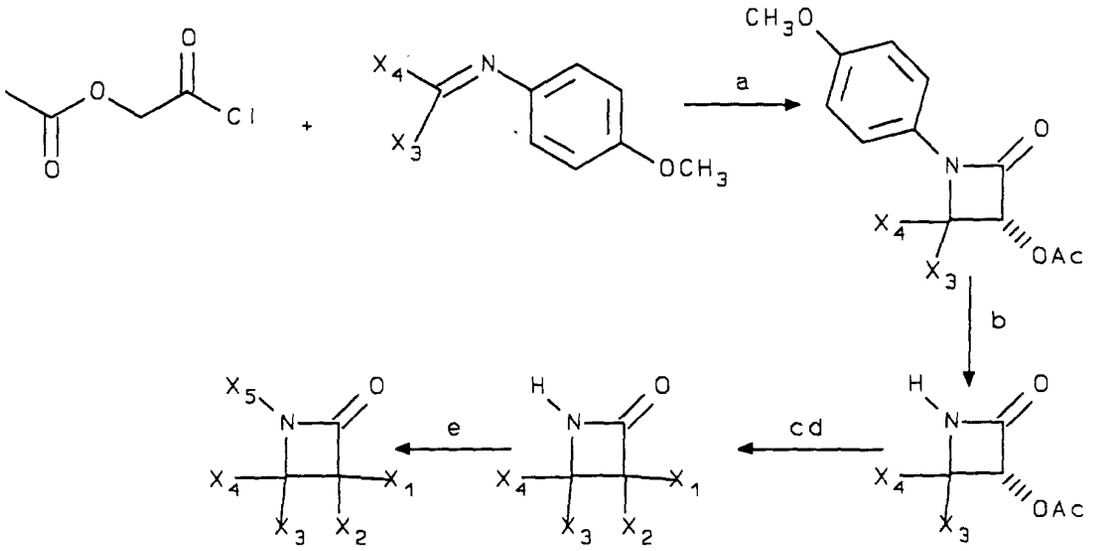
[0019] Taxanes having the general formula **3** may be obtained by reacting a β-lactam with alkoxides having the taxane tricyclic or tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a β-amido ester substituent at C-13. The β-lactams have the following structural formula:



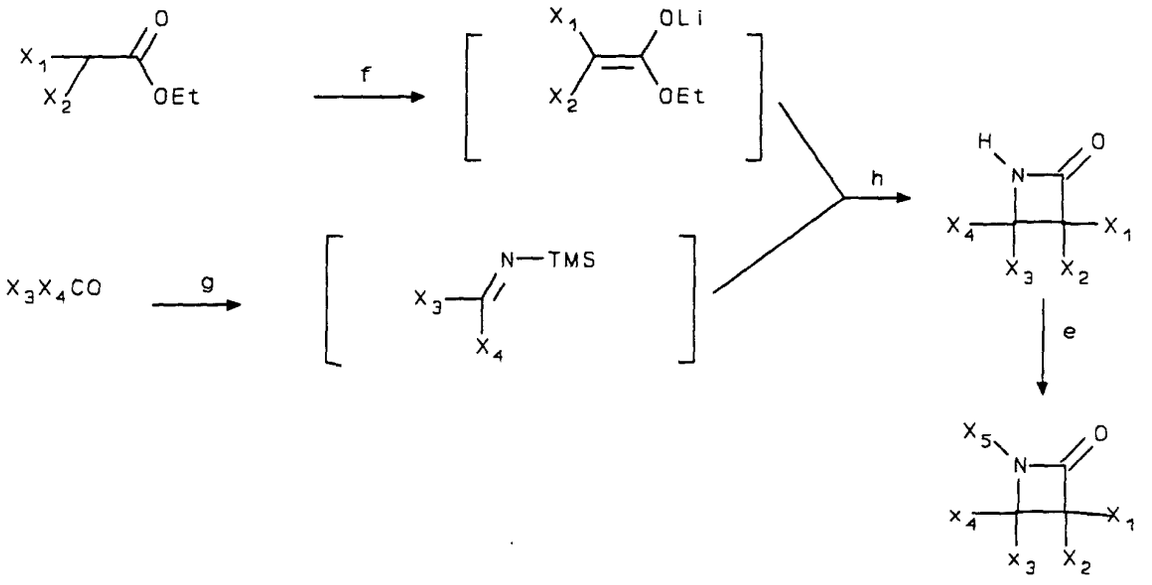
wherein X_1 - X_5 are as defined above.

[0020] 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, 18h; (b) 4 equiv ceric ammonium nitrate, CH_3CN, -10°C, 10 min; (c) KOH, THF, H_2O, O°C 30 min, or pyrolidine, pyridine, 25 °C, 3h, (d) TESCl, pyridine, 25 °C, 30 min or 2-methoxypropene toluene sulfonic acid (cat.), THF, 0°C, 2h; (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, 12h.

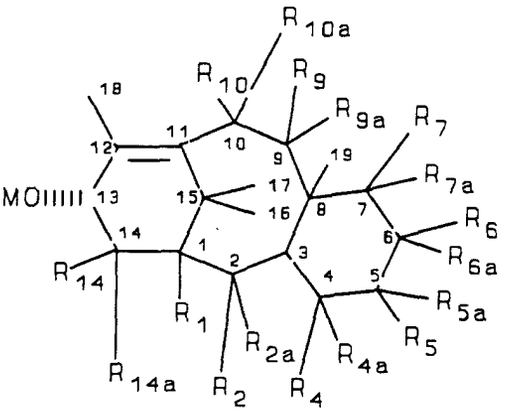
[0021] The starting materials are readily available. In scheme A, α-acetoxy acetyl chloride is prepared from glycolic acid, and, in the presence of a tertiary amine, it cyclocondenses with imines prepared from aldehydes and p-methoxyaniline to give 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-ones. The 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-tri-

ethylsilyloxyacetate is readily prepared from glycolic acid.

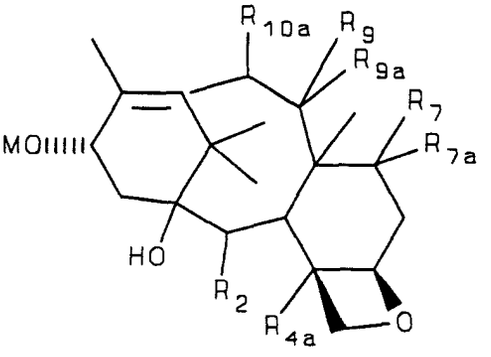
[0022] In Schemes A and B, X_1 is preferably $-OX_6$ and X_6 is a hydroxy protecting group. Protecting groups such as 2-methoxypropyl ("MOP"), 1-ethoxyethyl ("EE") are preferred, but a variety of other standard protecting groups such as the triethylsilyl group or other trialkyl (or aryl) silyl groups 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.

[0023] 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.

[0024] The alkoxides having the tricyclic or tetracyclic taxane nucleus and a C-13 metallic oxide or ammonium oxide substituent have the following structural formula:



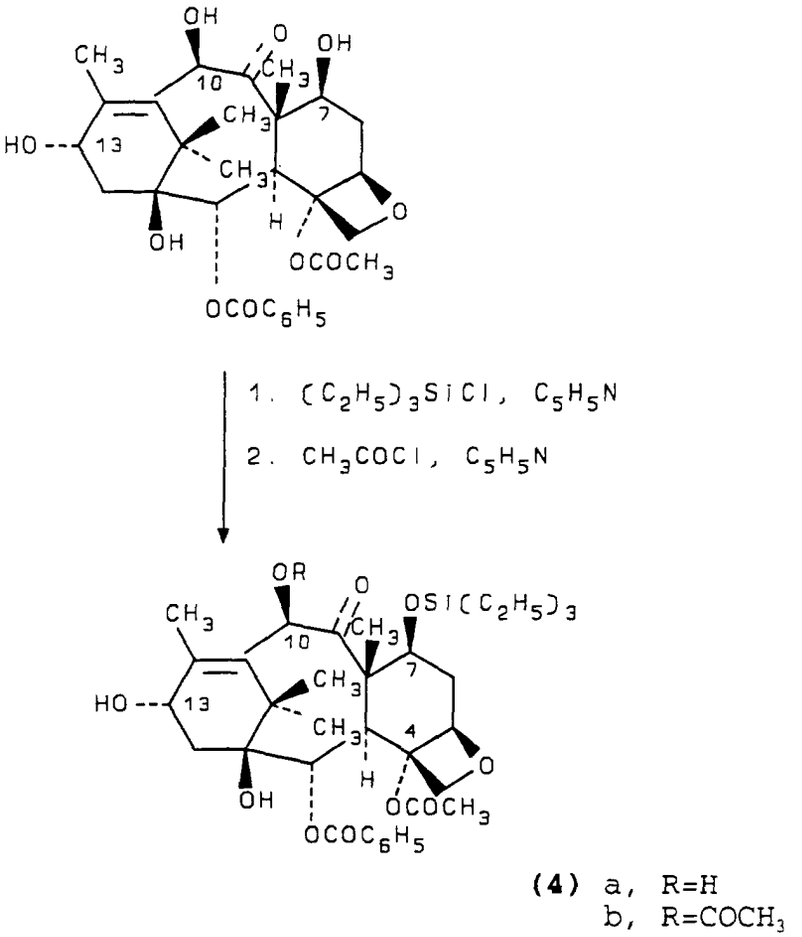
wherein R_1 - R_{14a} are as previously defined and M comprises ammonium or is a metal optionally selected from the group comprising Group IA, Group IIA and transition metals, and preferably, Li, Mg, Na, K or Ti. Most preferably, the alkoxide has the tetracyclic taxane nucleus and corresponds to the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

[0025] 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.

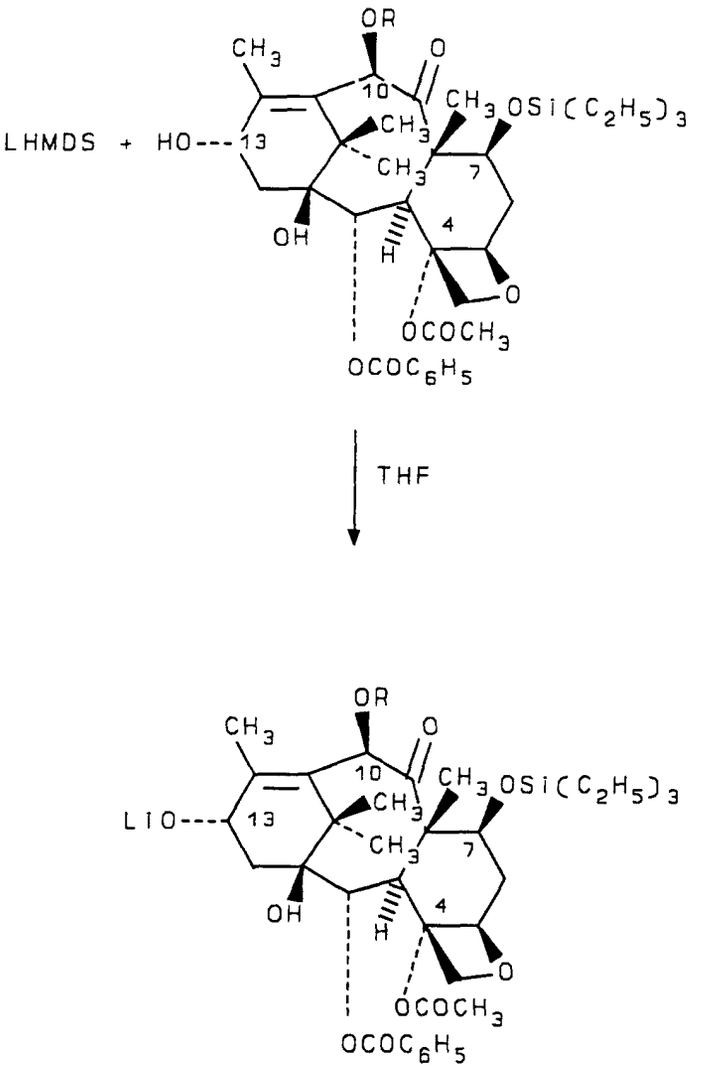
[0026] As reported in Greene et al., 10-deacetyl baccatin III is converted to 7-O-triethylsilyl-10-deacetyl baccatin III according to the following reaction scheme:



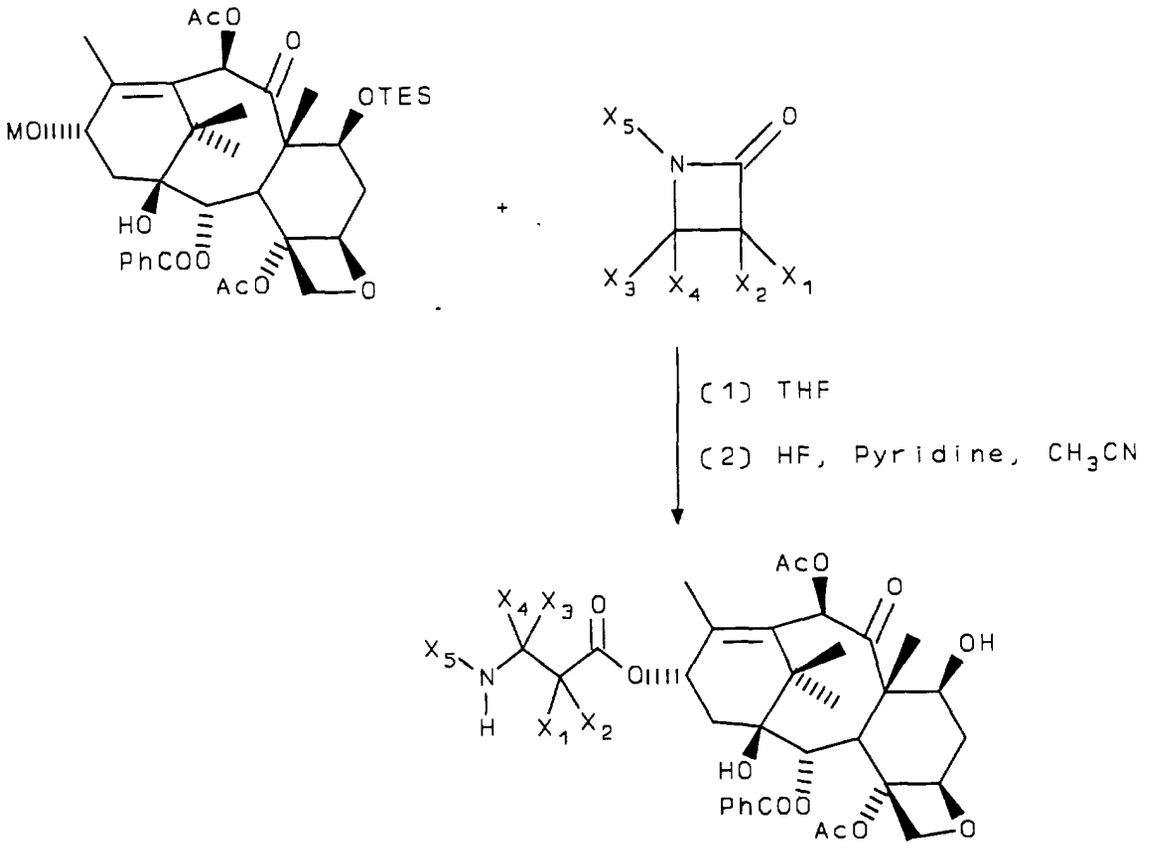
(4) a, R=H
b, R=$COCH_3$

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).

[0027] 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:



[0028] 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.



[0029] 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.

[0030] 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.

[0031] 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.

[0032] The diluent or carrier ingredients should not be such as to diminish the therapeutic effects of the antitumor compounds.

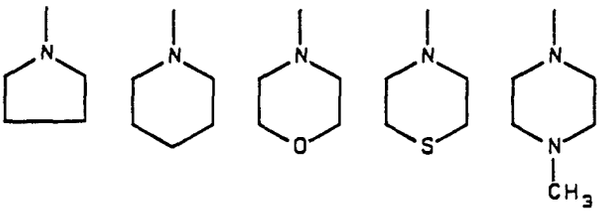
[0033] Suitable dosage forms for oral use include tablets, dispersible powders, granules, capsules, suspensions, syrups, and elixirs. Inert diluents and carriers for tablets include, for example, calcium carbonate, sodium carbonate, lactose and talc. Tablets may also contain granulating and disintegrating 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.

[0034] 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.

[0035] 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.

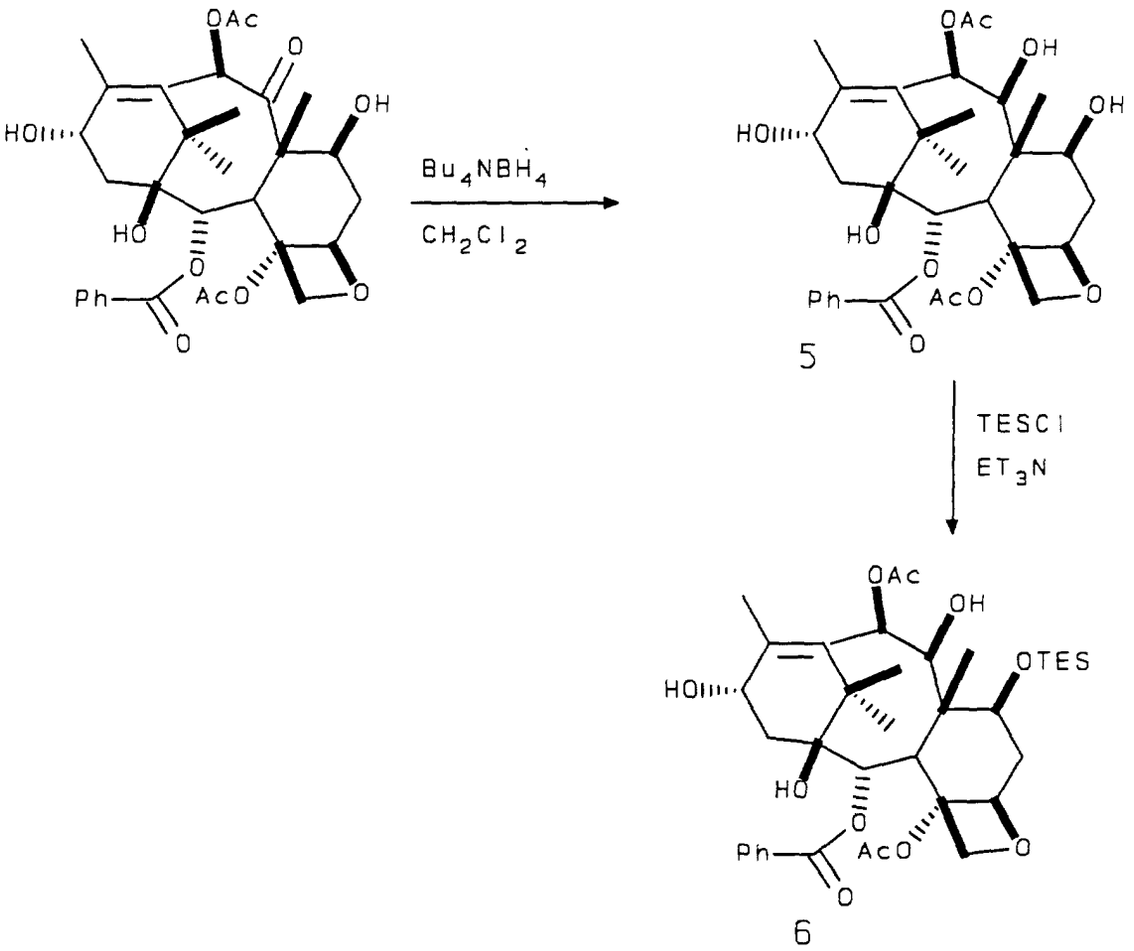
The preparation of compounds in which X_1 or X_2 is -COGCOR[1] is set forth in Haugwitz U.S. Patent 4,942,184 which is incorporated herein by reference.

[0036] Alternatively, solubility may be increased when X_1 is $-OX_6$ and X_6 is a radical having the formual - 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. Patent No. 5,059,699 (incorporated herein by reference).

[0037] Taxanes having alternative C9 keto substituent may be prepared by selectively reduced to yield the corresponding C9 β-hydroxy derivative. The reducing agent is preferably a borohydride and, most preferably, tetrabutylammoniumboro-hydride (Bu_4NBH_4) or triacetoxyborohydride.

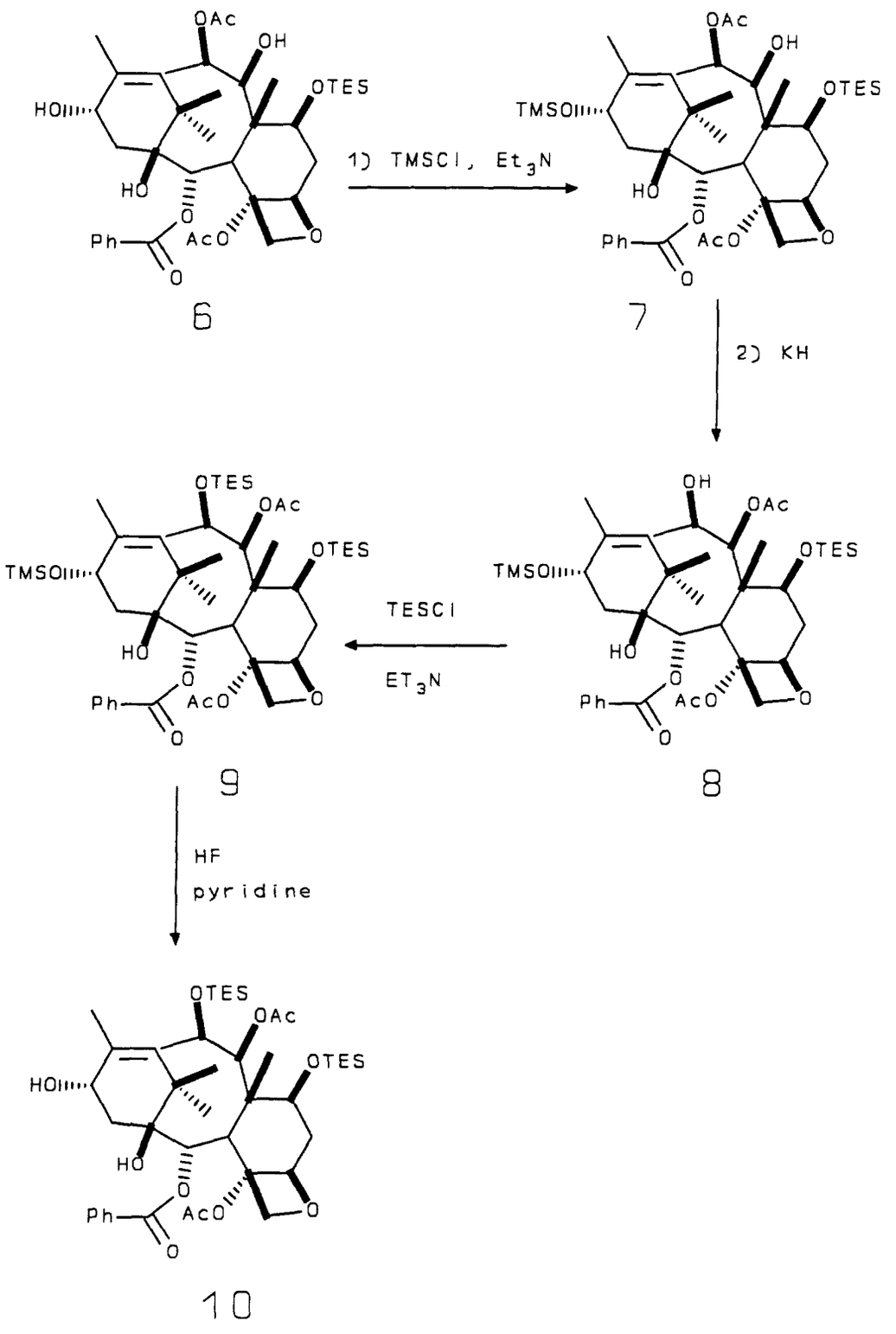
[0038] As illustrated in Reaction Scheme 1, the reaction of baccatin III with Bu_4NBH_4 in methylene chloride yields 9-desoxo-9β-hydroxybaccatin III 5. After the C7 hydroxy group is protected with the triethylsilyl protecting group, for example, a suitable side chain may be attached to 7-protected-9β-hydroxy 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



[0039] 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.

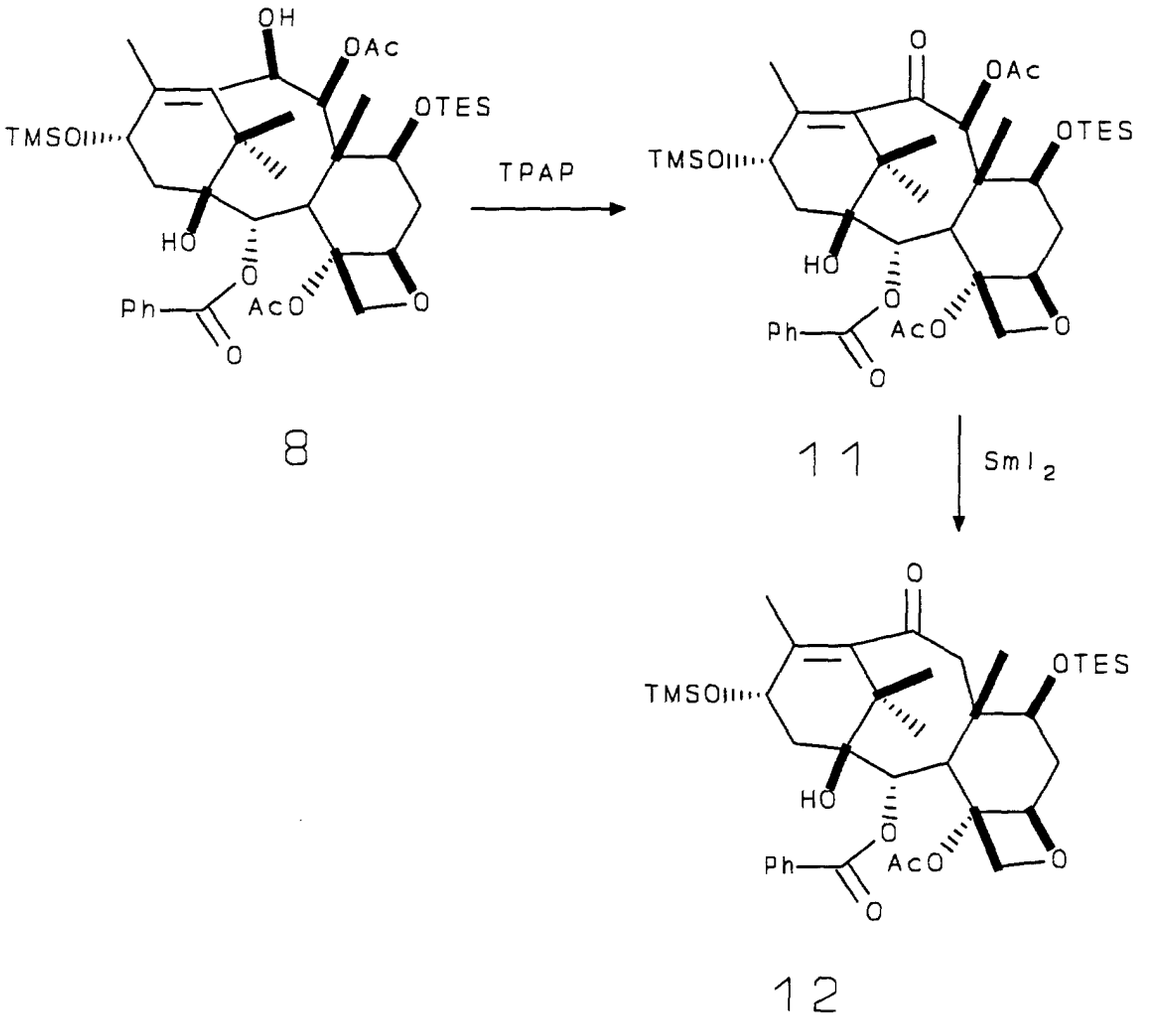
REACTION SCHEME 2



[0040] 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.

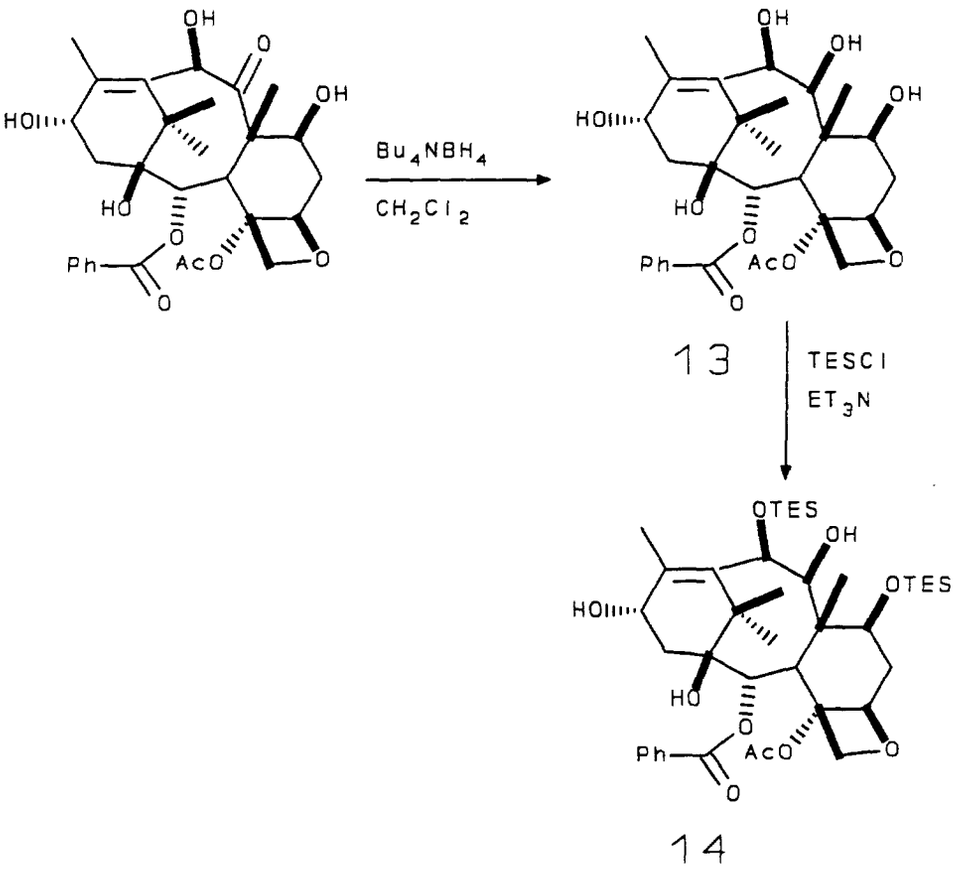
Alternatively, the C9 acetate group can be selectively removed by reduction of 10-oxo derivative **11** with a reducing agent such as samarium diiodide to yield 9-desoxo-10-oxo derivative **12** from which the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain 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



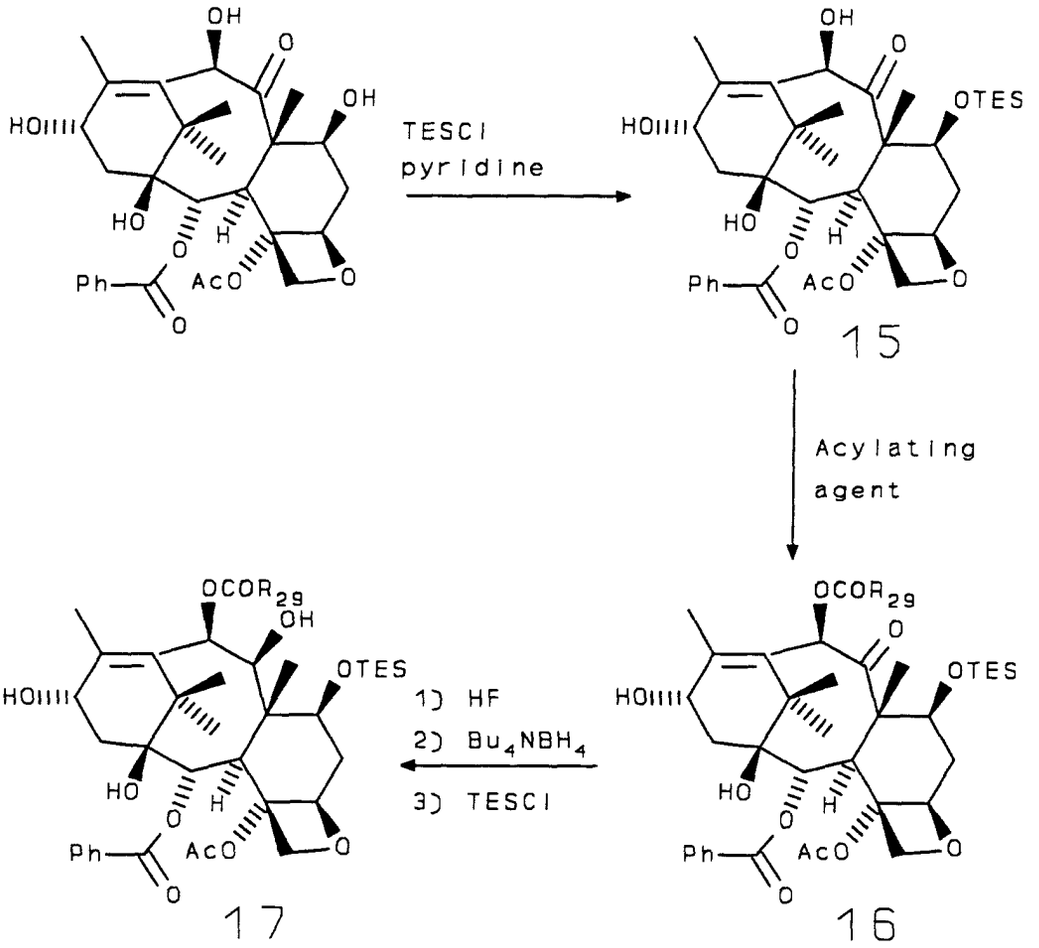
[0041] Reaction Scheme 4 illustrates a reaction in which 10-DAB is reduced to yield pentaol **13**. The C7 and C10 hydroxyl groups of pentaol **13** can then be selectively protected with the triethylsilyl or another protecting group to produce triol **14** to which a C13 side chain can be attached as described above or, alternatively, after further modification of the tetracylic substituents.

REACTION SCHEME 4



[0042] 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.

REACTION SCHEME 5

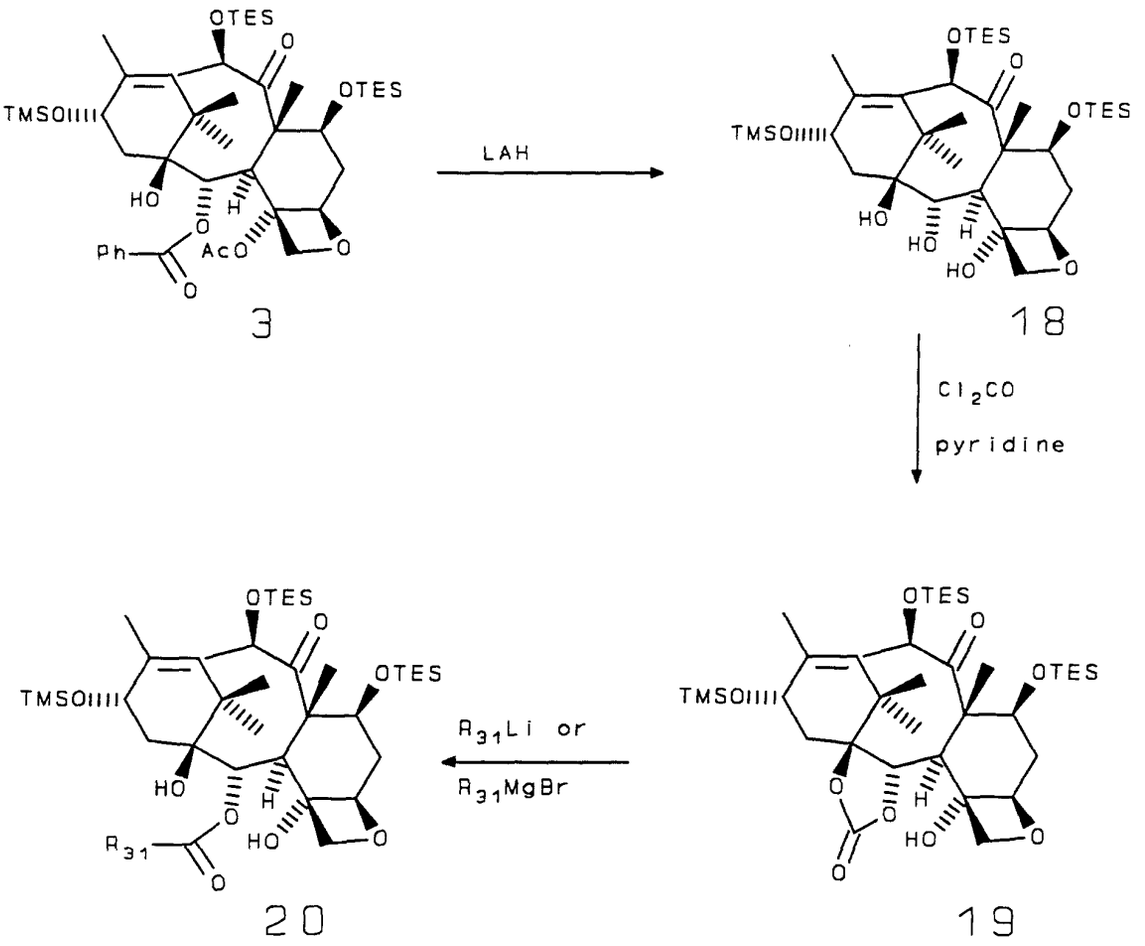


[0043] Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol (s) using reducing agents such as LAH or Red-Al, and new esters can thereafter be substituted using standard acylating agents 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.

[0044] 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 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.

[0045] 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).

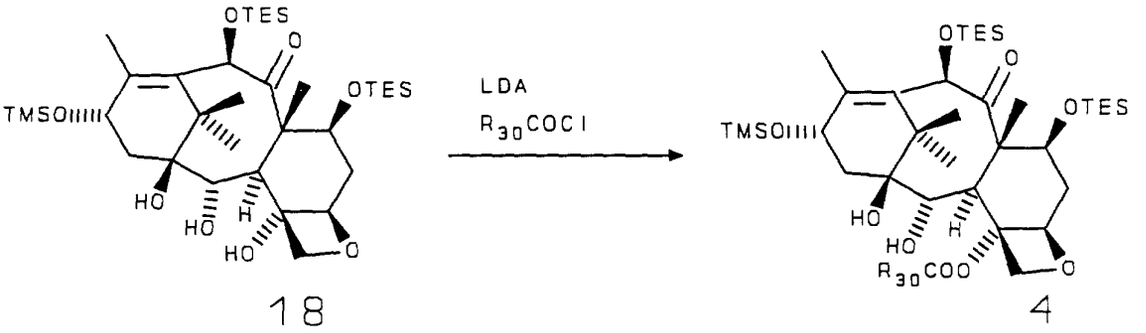
Scheme 6



[0046] 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.

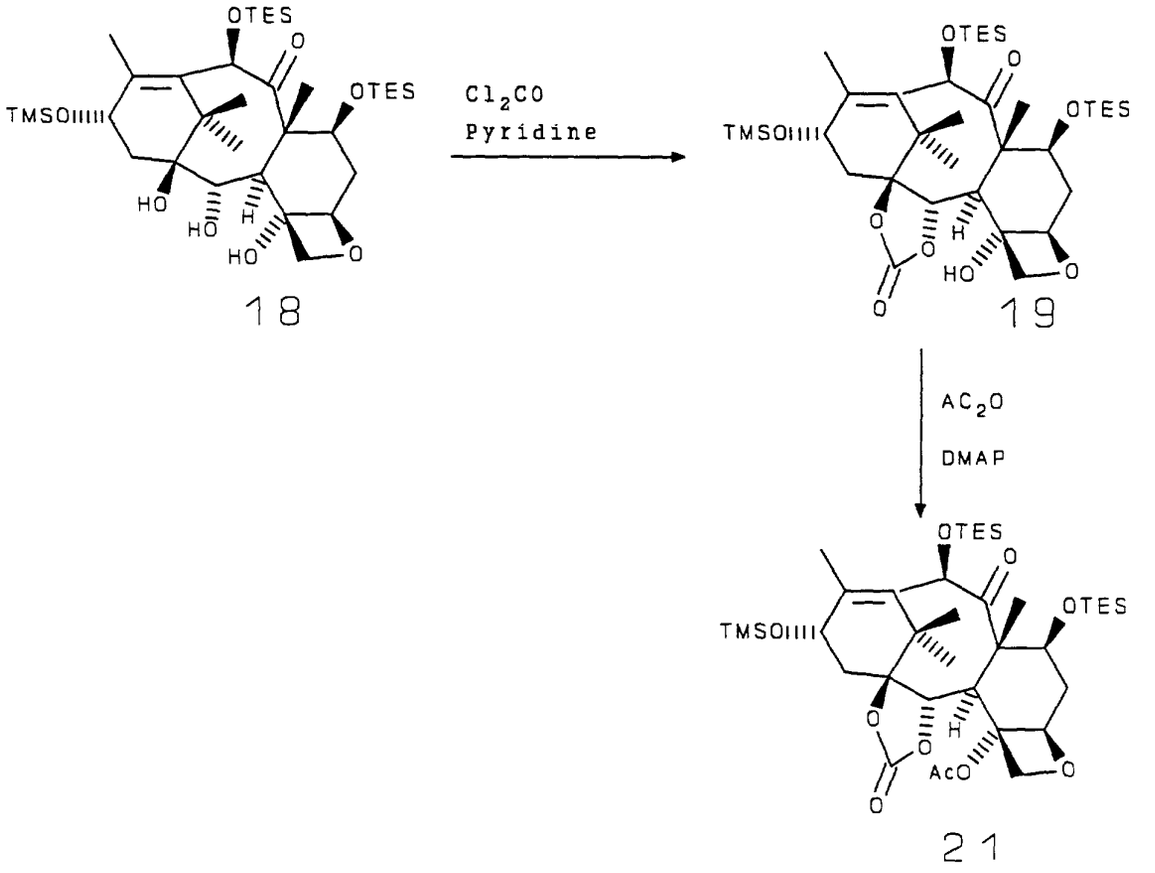
[0047] Triol **18** can also readily be converted to the 1,2 carbonate **19**. Acetylation of carbonate **19** under vigorous standard conditions provides carbonate **21** as described in Reaction Scheme 8; addition of alkyllithiums or Grignard reagents to carbonate **19** provides the C2 ester having a free hydroxyl group at C4 as set forth in Reaction Scheme 6.

Scheme 7



18 4

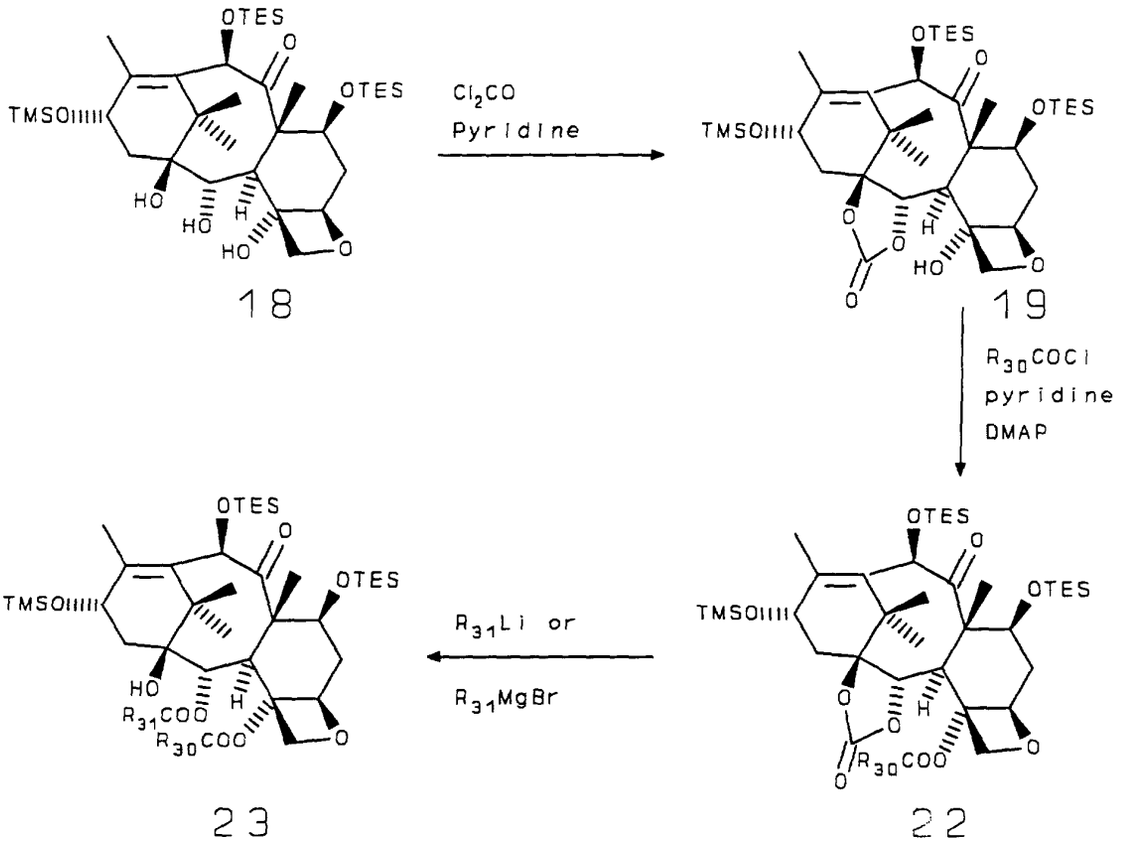
Scheme 8



18 19 21

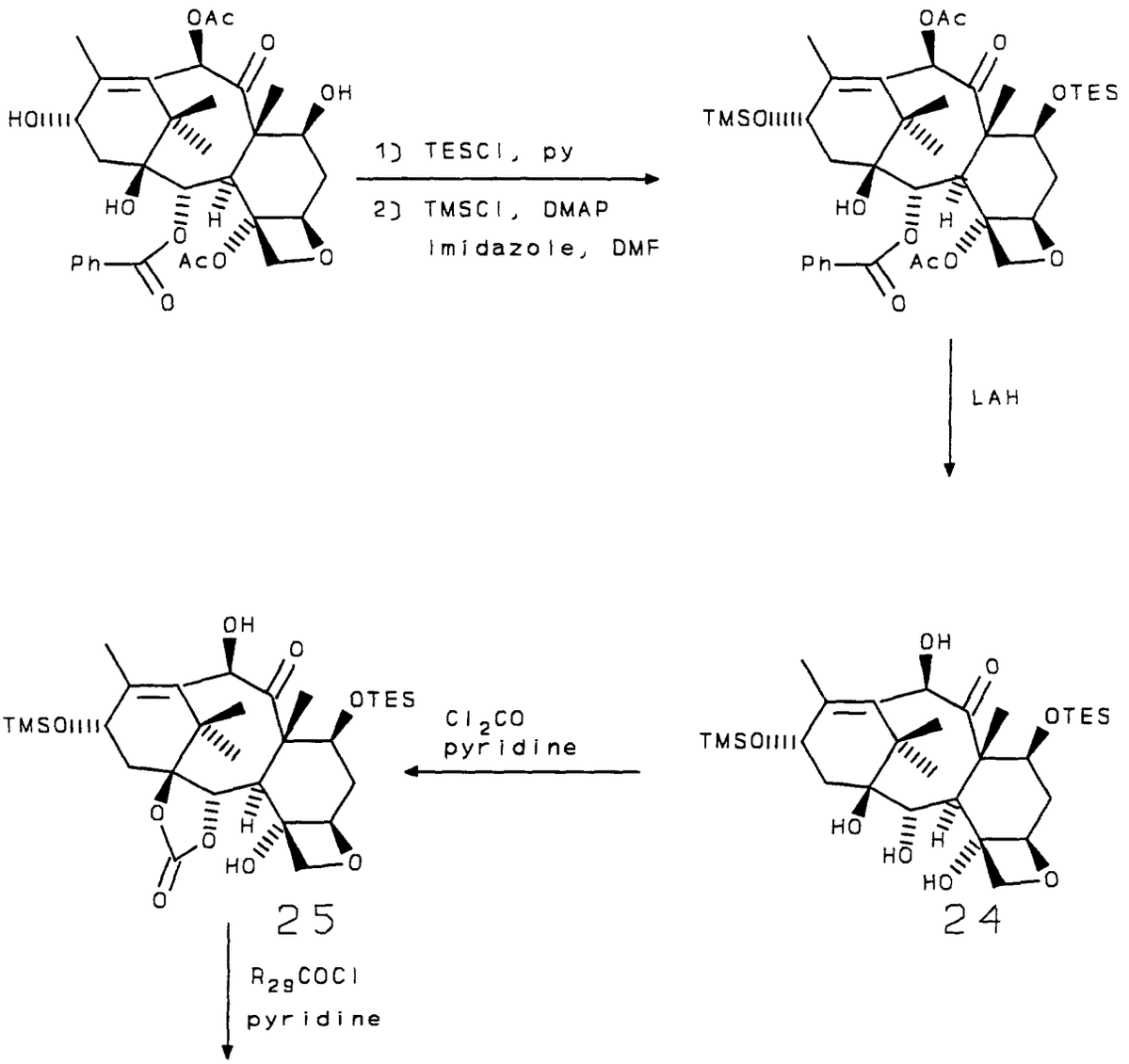
[0048] As set forth in Reaction Scheme 9, other C4 substituents can be provided by reacting carbonate **19** with an acid chloride and a tertiary amine to yield carbonate **22** which is then reacted with alkyllithiums or Grignard reagents to provide 10-DAB derivatives having new substituents at C2.

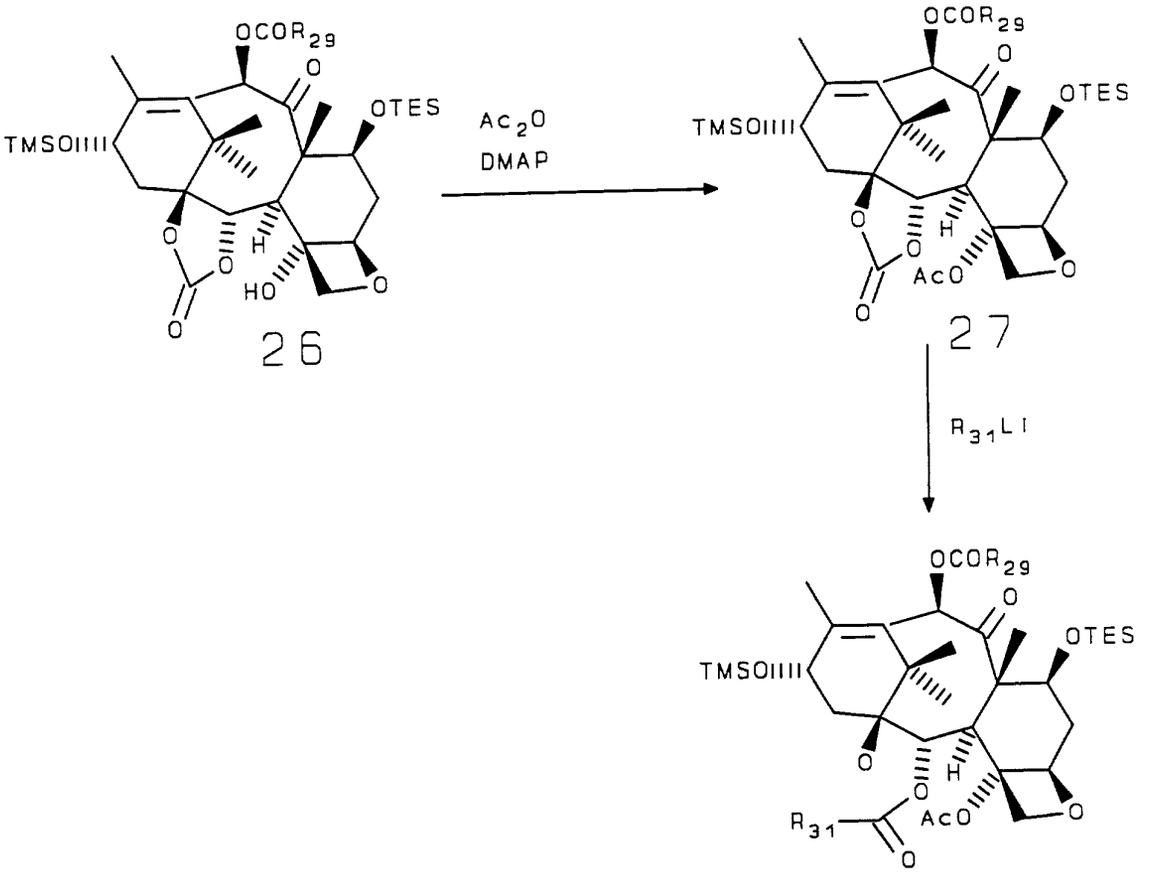
Scheme 9



[0049] 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

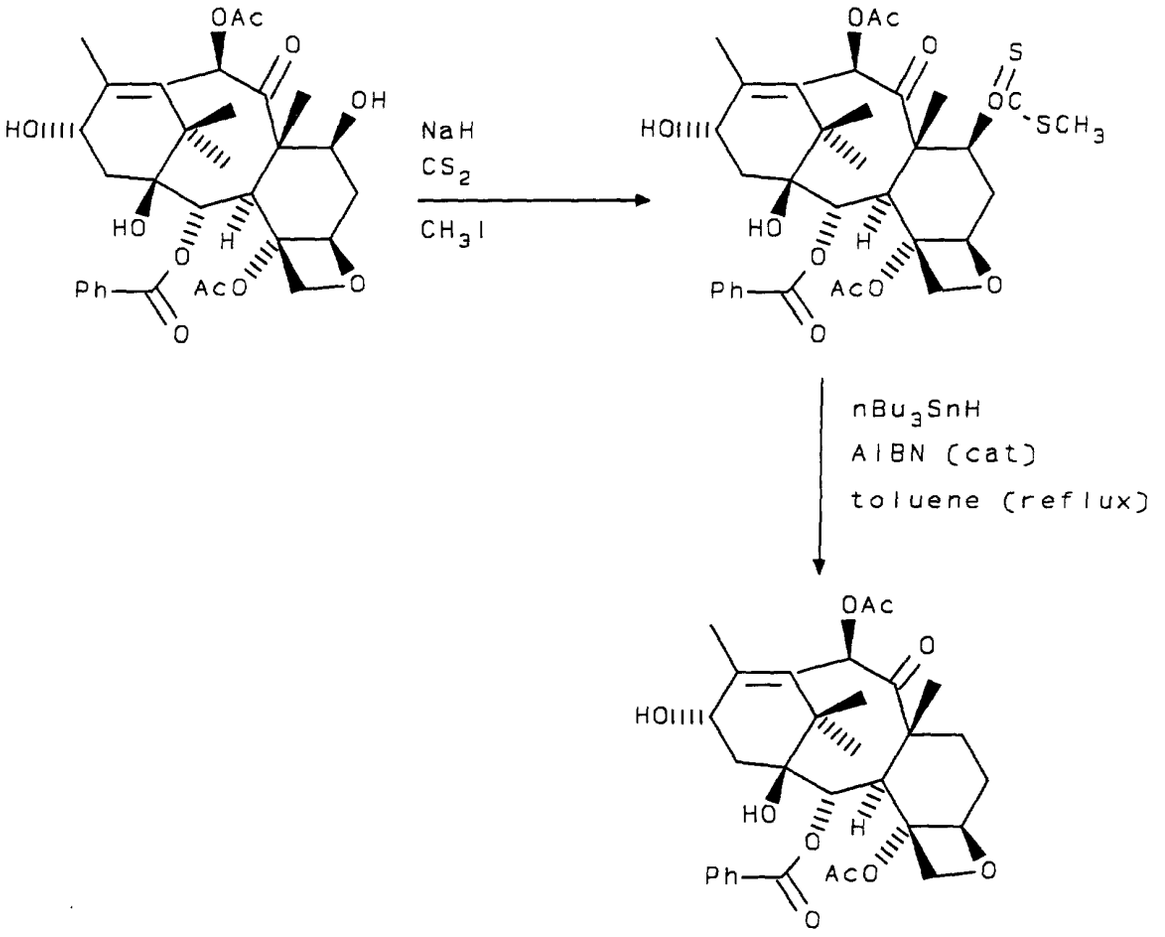

OAc
OH
HO
HO
Ph
AcO
1) TESCl, py
2) TMSCl, DMAP
imidazole, DMF
OTES
TMSO
LAH
24
25
Cl_2CO
pyridine
$R_{29}COCl$
pyridine



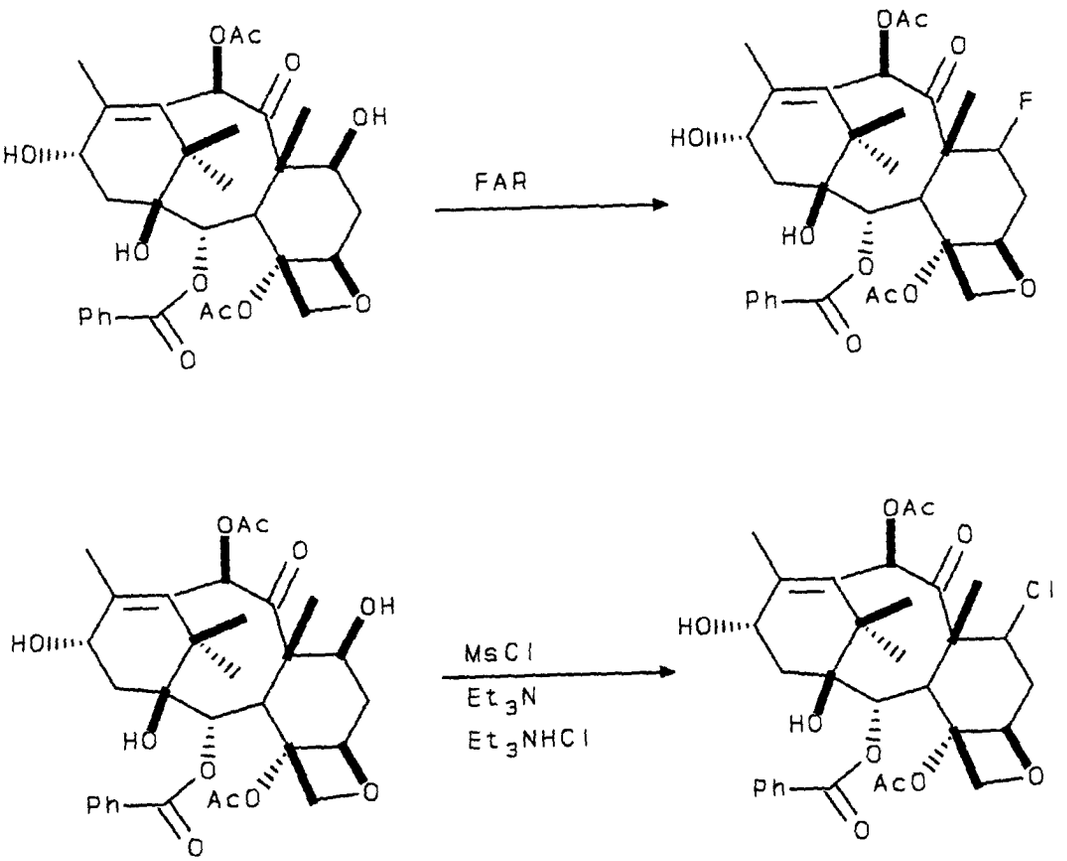
[0050] 10-desacetoxy derivatives of baccatin III and 10-desoxy derivatives of 10-DAB may be prepared by reacting baccatin III or 10-DAB (or their derivatives) with samarium diiodide. Reaction between the tetracyclic taxane having a C10 leaving group and samarium diiodide may be carried out at 0°C in 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.

[0051] C7 dihydro and other C7 substituted taxanes can be prepared as set forth in Reaction Schemes 11, 12 and 12a.

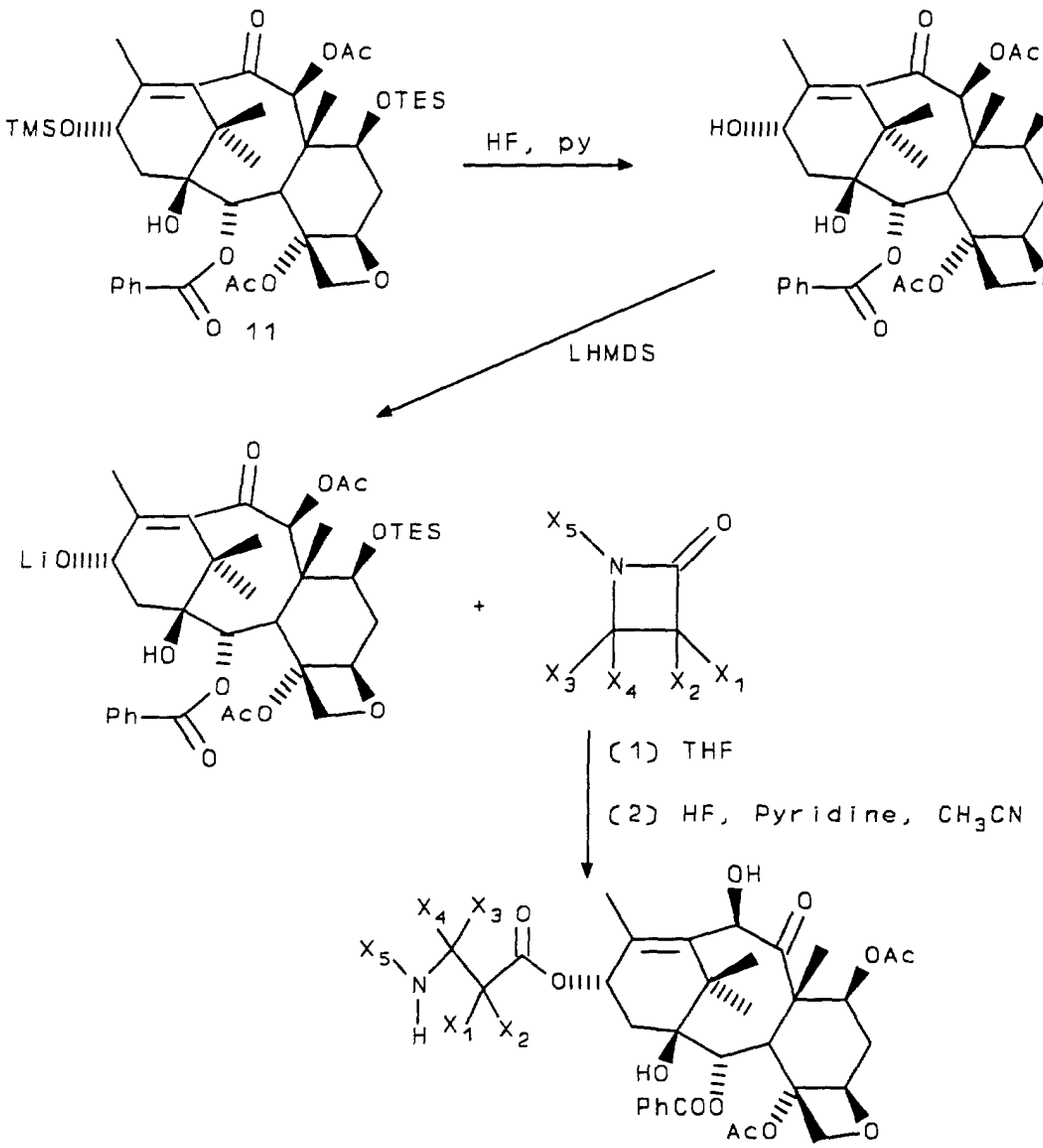
REACTION SCHEME 11



REACTION SCHEME 12



REACTION SCHEME 12a

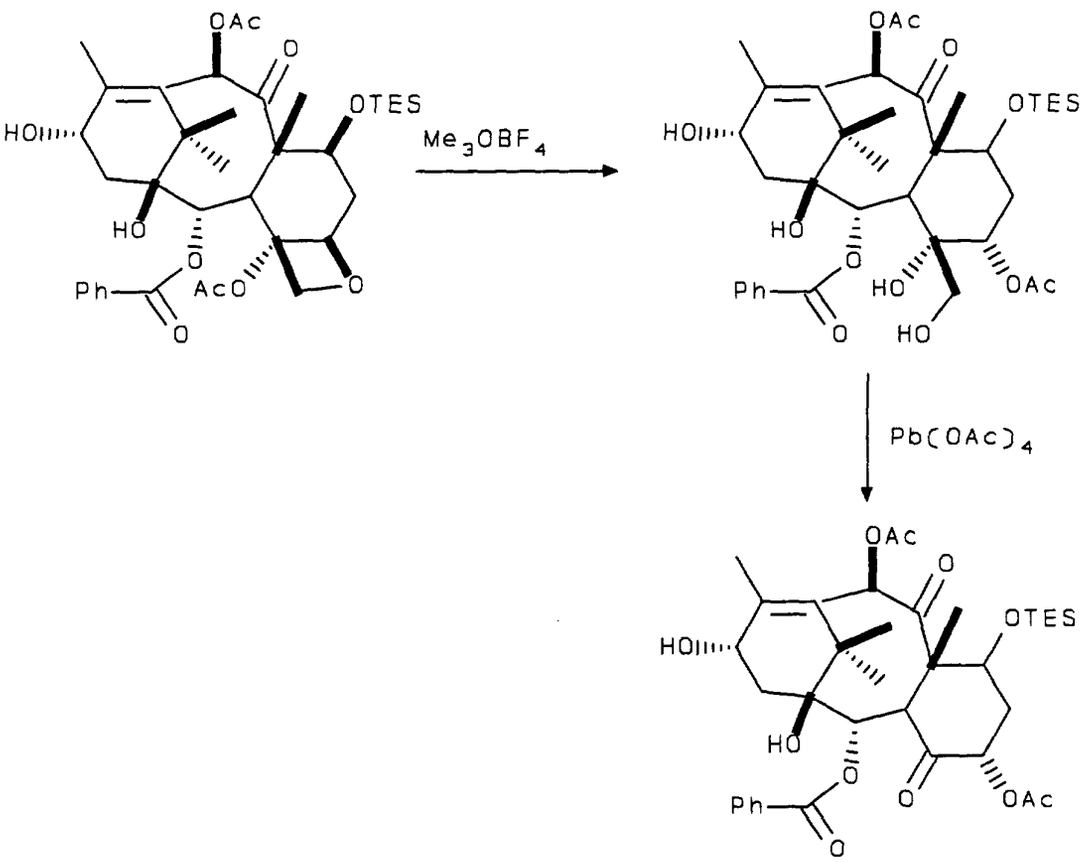


[0052] As shown in Reaction Scheme 12, Baccatin III may be converted into 7-fluoro baccatin III by treatment with FAR at room temperature in THF solution. Other baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-chloro baccatin III can be prepared by treatment of baccatin III with methane sulfonyl chloride and triethylamine in methylene chloride solution containing an excess of triethylamine hydrochloride.

[0053] 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.

[0054] 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

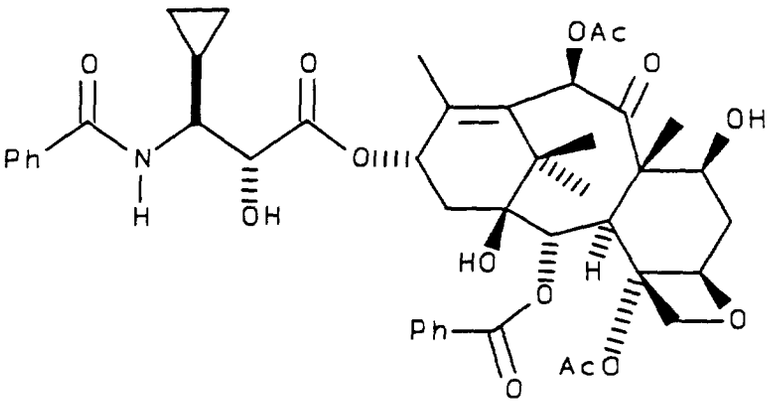


[0055] Recently a hydroxylated taxane (14-hydroxy-10-deacetylbaccatin III) has been discovered in an extract of yew needles (C&EN, p 36-37, April 12, 1993). Derivatives of this hydroxylated taxane having the various C2, C4, etc. functional groups described above may also be prepared by using this hydroxylated 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.

[0056] The following examples are provided to more fully illustrate the invention. ***[deletion(s)]***

EXAMPLE 1

[0057]



(67-4)

Preparation of 3'-desphenyl-3'-cyclopropyl taxol.

[0058] To a solution of 7-triethylsilyl baccatin III (50 mg, 0.071 mmol) in 0.5 mL of THF at -45 °C was added dropwise 0.086 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(benzoyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (240 mg, 0.696 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 10h 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 52 mg of a mixture containing (2'R,3'S)-2', 7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclopropyl taxol and a small amount of the (2'S,3'R) isomer.

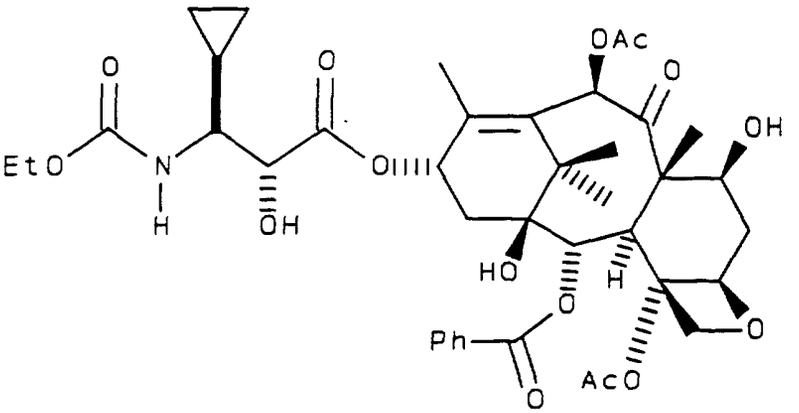
[0059] To a solution of 52 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 109 mg of material which was purified by flash chromatography to give 33 mg (81%) of 3'-desphenyl-3'- cyclopropyl taxol, which was recrystallized from ether/hexane.

m.p. 161-163 °C; $[\alpha]^{25}_{Na}$ -50.0 ° (c 0.13 , $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (m, 2H, benzoate *ortho*), 7.69 (m, 2H, benzamide, ortho), 7.61 (m, 1H, benzoate, *para*), , 7.50 (m, 3H, benzoate, *meta,* and benzamide, *para*), 7.39 (m, 2H, benzamide, *meta*), 6.52 (d, *J* = 8.8 Hz, 1H, NH), 6.28 (s, 1H, H10), 6.20 (br t, *J* = 9.0 Hz, 1H, H13), 5.68 (d, *J* = 6.9 Hz, 1H, H2β), 4.97 (dd, *J* = 9.6, 1.8 Hz, 1H, H5), 4.54 (dd, *J* = 5.5, 2.2 Hz, 1H, H2'), 4.42 (m, 1H, H7), 4.32 (d, *J* = 8.4 Hz, 1H, H20α), 4.20 (d, *J* = 8.4 Hz, 1H, H20β), 3.84 (br t, *J* = 9.9 Hz, 1H, H3'), 3.80 (d, *J* = 6.9 Hz, 1H, H3), 3.63 (d, *J* = 6.0 Hz, 1H, 2'OH), 2.56 (m, 1H, H6α), 2.42 (s, 3H, 4Ac), 2.32 (m, 2H, H14α and H14β),2.23 (s, 3H, 10Ac), 1.87 (d, *J*= 1.1 Hz,3H, Me18), 1.83 (s, 1H, 1 OH), 1.68 (s, 3H, Me19), 1.39 (m, 1H, cyclopropyl), 1.23 (s, 3H, Me17), 1.13 (s, 3H, Me16), 0.68 (m, 2H, cyclopropyl), 0.52 (m, 1H, cyclopropyl), 0.39 (m, 1H, cyclopropyl).

EXAMPLE 2

[0060]



(56-2)

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

[0061] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 2 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(ethoxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (225 mg, 0.715 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h 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 125 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-debenzoy 1-N-(ethoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

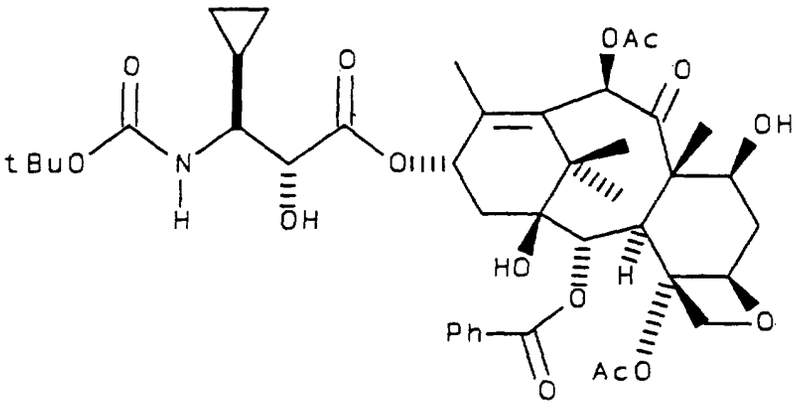
[0062] To a solution of 125 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 93 mg of material which was purified by flash chromatography to give 82 mg (85%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(ethoxy-carbonyl) taxol, which was recrystallized from ether/hexane.

m.p. 140-142 °C; $[\alpha]^{25}_{Na}$ -65.0° (c 0.08, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, *J* = 7.2 Hz, 2H, benzoate *ortho),* 7.60 (m, 1H, benzoate, *para),* 7.49 (t, *J* = 7.2 Hz, 2H, benzoate, *meta*), 6.29 (s, 1H, H10), 6.22 (br t, *J* = 8.7 Hz, 1H, H13), 5.66 (d, *J* = 6.9 Hz, 1H, H2β), 5.08 (d, *J* = 9.3 Hz, 1H, NH), 4.95 (dd, *J* = 9.3, 1.5 Hz, 1H, H5), 4.43 (dd, *J* = 6.0, 2.1 Hz, 1H, H2'), 4.40 (m, 1H, H7), 4.30 (d, *J* = 8.1 Hz, 1H, H20α), 4.17 (d, *J* = 8.1 Hz, 1H, H20β), 3.96 (q, *J* = 7.2 Hz, 2H, OCH2), 3.79 (d, *J* = 6.9 Hz, 1H, H3), 3.47 (d, *J* = 6.0 Hz, 1H, 2'OH), 3.35 (dt, *J* = 9.3, 2.1 Hz, 1H, H3'), 2.52 (m, 2H, H6α, 7OH), 2.36 (s, 3H, 4Ac), 2.23 (s, 3H, 10Ac), 1.88 (s, 3H, Me18), 1.67 (s, 3H, Me19), 1.47 (m, 2H, CH2), 1.24 (s, 3H, Me17), 1.14 (s, 3H, Me16), 1.11 (t, *J* = 7.2 Hz, Me), 0.64 (m, 2H, cyclopropyl), 0.47 (m, 1H, cyclopropyl), 0.29 (m, 1H, cyclopropyl).

EXAMPLE 3

[0063]



(49-1)

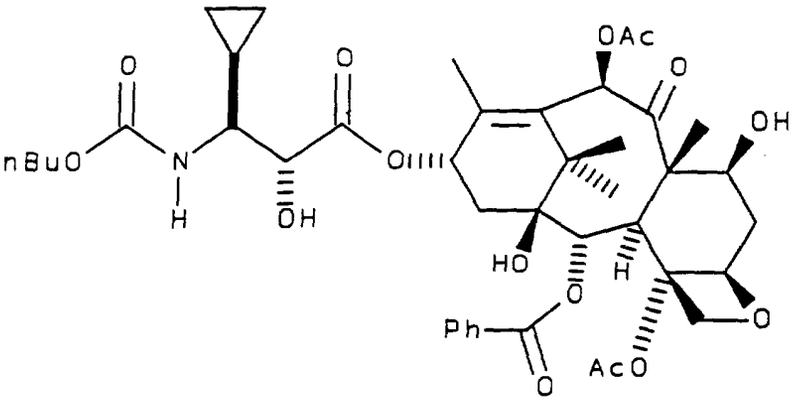
Preparation of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol.

[0064] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(t-butoxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (170 mg, 0.5 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h 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 140 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0065] To a solution of 140 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 109 mg of material which was purified by flash chromatography to give 106 mg (97%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol, which was recrystallized from ether/hexane.
m.p. 167-169 °C; $[\alpha]^{25}_{Na}$ -74.0° (c 0.1, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, *J* = 7.5 Hz, 2H, benzoate *ortho),* 7.61 (m, 1H, benzoate, *para),* 7.49 (t, *J* = 7.5 Hz, 2H, benzoate, *meta*), 6.30 (s, 1H, H10), 6.16 (br t, *J* = 8.7 Hz, 1H, H13), 5.67 (d, *J* = 7.2 Hz, 1H, H2β), 4.96 (dd, *J* = 9.3, 1.5 Hz, 1H, H5), 4.91 (d, *J* = 9.3 Hz, 1H, NH), 4.41 (m, 1H, H7), 4.39 (dd, *J* = 6.6, 1.8 Hz, 1H, H2'), 4.31 (d, *J* = 8.1 Hz, 1H, H20α), 4.16 (d, *J* = 8.1 Hz, 1H, H20β), 3.79 (d, *J* = 7.2 Hz, 1H, H3), 3.37 (d, *J* = 6.6 Hz, 1H, 2'OH), 3.29 (dt, *J* = 9.3, 1.8 Hz, 1H, H3'), 2.55 (m, 1H, H6α), 2.50 (d, *J*= 3.9 Hz, 1H, 7OH), 2.35 (s, 3H, 4Ac), 2.30 (br d, *J* = 9.3 Hz, 2H, H14), 2.23 (s, 3H, 10Ac), 1.89 (d, *J* = 0.9 Hz, 3H, Me18), 1.74 (s, 1H, 1OH), 1.66 (s, 3H, Me19), 1.31 (s, 9H, t-Bu), 1.24 (s, 3H, Me17), 1.14 (s, 3H, Me16), 0.63 (m, 2H, cyclopropyl), 0.46 (m, 1H, cyclopropyl), 0.25 (m, 1H, cyclopropyl).

EXAMPLE 4

[0066]



(56-3)

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

[0067] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1.5 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(n-butoxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (170 mg, 0.5 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h 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 145 mg of a mixture containing (2'R,3'S)-2',7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(n-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

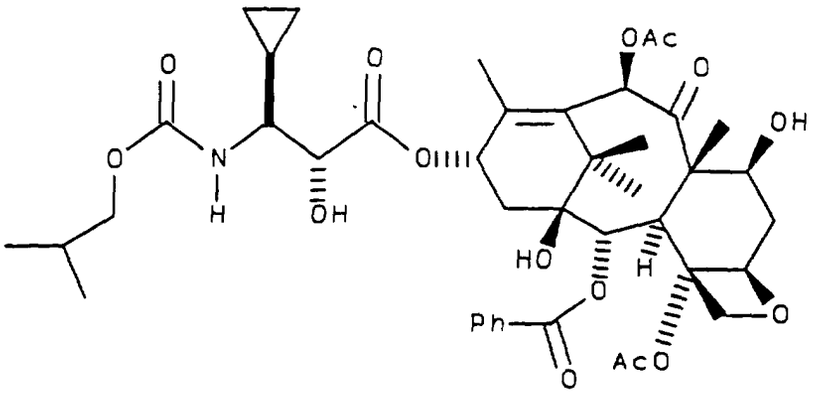
[0068] To a solution of 145 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 108 mg of material which was purified by flash chromatography to give 98 mg (87%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(n-butoxycarbonyl) taxol, which was recrystallized from ether/hexane.

m.p. 132-134 °C; $[\alpha]^{25}_{Na}$-64.0° (c 0.175, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, *J* = 7.8 Hz, 2H, benzoate *ortho*), 7.60 (m, 1H, benzoate, *para*), 7.49 (t, *J* = 7.8 Hz, 2H, benzoate, *meta*), 6.29 (s, 1H, H10), 6.22 (br t, *J* = 9.3 Hz, 1H, H13), 5.66 (d, *J* = 6.9 Hz, 1H, H2β), 5.04 (d, *J* = 9.3 Hz, 1H, NH), 4.95 (dd, *J* = 9.6, 1.8 Hz, 1H, H5), 4.43 (dd, *J* = 5.4, 2.1 Hz, 1H, H2'), 4.40 (m, 1H, H7), 4.30 (d, *J* = 8.7 Hz, 1H, H20α), 4.17 (d, *J* = 8.7 Hz, 1H, H20β), 3.89 (m, 2H, OCH2), 3.79 (d, *J*= 6.9 Hz, 1H, H3), 3.43 (d, *J* = 5.4 Hz, 1H, 2'OH), 3.36 (dt, *J* = 9.3, 2.1 Hz, 1H, H3'), 2.55 (m, 1H, H6α), 2.49 (d, *J* = 4.5 Hz, 1H, 7OH), 2.36 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac), 1.88 (s, 3H, Me18), 1.75 (s, 1H, 1OH), 1.67 (s, 3H, Me19), 1.47 (m, 2H, CH2), 1.26 (s, 3H, Me17), 1.23 (m, 2H, CH2), 1.14 (s, 3H, Me16), 0.82 (t, *J* = 7.2 Hz, 3H, Me), 0.64 (m, 2H, cyclopropyl), 0.47 (m, 1H, cyclopropyl), 0.29 (m, 1H, cyclopropyl).

EXAMPLE 5

[0069]



(63-1)

Preparation of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol.

[0070] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 2 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(isobutoxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (244 mg, 0.715 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous NaHCO3 and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 145 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

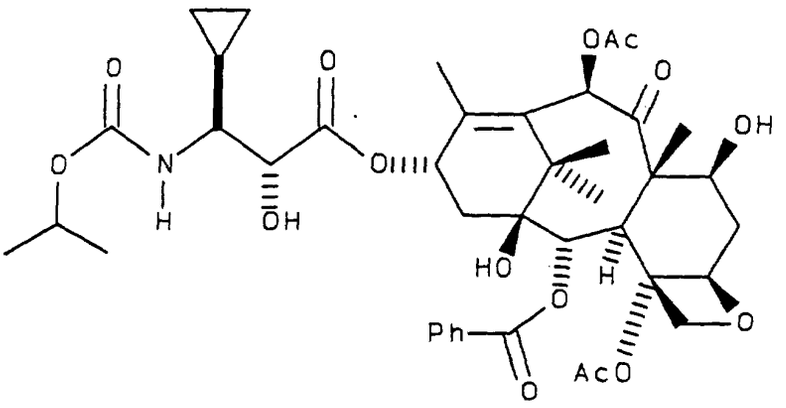
[0071] To a solution of 145 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 95 mg of material which was purified by flash chromatography to give 87 mg (85%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol, which was recrystallized from ether/hexane.

m.p. 130-132 °C; $[\alpha]^{25}_{Na}$ -64.0° (c 0.15, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 7.2 Hz, 2H, benzoate *ortho*), 7.61 (m, 1H, benzoate, *para*), 7.50 (t, *J* = 7.2 Hz, 2H, benzoate, *meta*), 6.29 (s, 1H, H10), 6.22 (br t, *J* = 8.7 Hz, 1H, H13), 5.67 (d, *J* = 7.2 Hz, 1H, H2β), 5.05 (d, *J* = 9.6 Hz, 1H, NH), 4.96 (dd, *J* = 9.3, 1.8 Hz, 1H, H5), 4.43 (dd, *J* = 5.4, 2.1 Hz, 1 H, H2'), 4.41 (m, 1H, H7), 4.30 (d, *J* = 8.4 Hz, 1H, H20α), 4.17 (d, *J* = 8.4 Hz, 1H, H20β), 3.79 (d, *J* = 7.2 Hz, 1H, H3), 3.67 (m, 2H, i-Bu), 3.39 (d, *J* = 5.4 Hz, 1H, 2'OH), 3.37 (dt, *J* = 9.3, 2.1 Hz, 1H, H3'), 2.55 (m, 1H, H6α), 2.48 (d, *J* = 3.9 Hz, 1H, 7OH), 2.37 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac) 1.88 (s, 3H, Me18), 1.67 (s, 3H, Me19), 1.25 (s, 3H, Me17), 1.14 (s, 3H, Me16), 0.80 (d, *J* = 6.6 Hz, 3H, Me), 0.76 (d, *J* = 6.6 Hz, 3H, Me), 0.64 (m, 2H, cyclopropyl), 0.48 (m, 1H, cyclopropyl), 0.29 (m, 1H, cyclopropyl).

EXAMPLE 6

[0072]



(62-3)

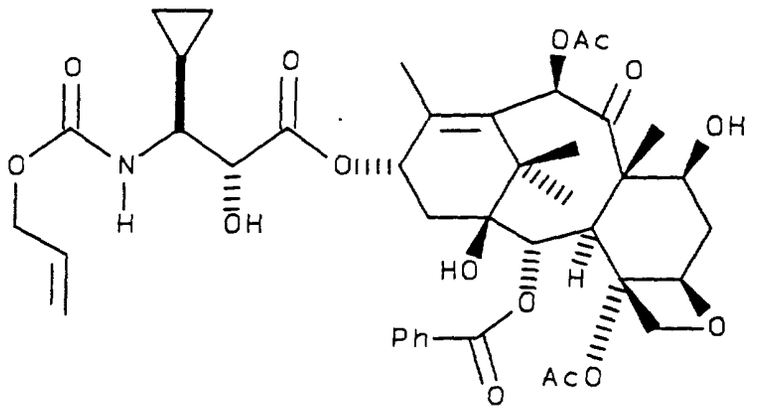
Preparation of 3'-desphenyl-3'-cyclopropyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol.

[0073] To a solution of 7-O-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 2 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(isopropoxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (145 mg, 0.429 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 9h 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 145 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0074] To a solution of 145 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 111 mg of material which was purified by flash chromatography to give 95 mg (84%) of 3'-desphenyl-3'-cyclopropyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol, which was recrystallized from ether/hexane.
m.p. 142-144 °C; $[\alpha]^{25}_{Na}$ -77.06° (c 0.17, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, *J* = 7.2 Hz, 2H, benzoate *ortho*), 7.61 (m, 1H, benzoate, *para*), 7.49 (t, *J* = 7.2 Hz, 2H, benzoate, *meta*), 6.29 (s, 1H, H10), 6.20 (br t, *J* = 9.0 Hz, 1H, H13), 5.67 (d, *J* = 7.2 Hz, 1H, H2β), 4.97 (d, *J* = 9.6 Hz, 1H, NH), 4.96 (dd, *J* = 9.3, 1.8 Hz, 1H, H5), 4.71 (m, 1H, isopropyl), 4.42 (m, 2H, H7 and H2'), 4.31 (d, *J* = 8.4 Hz, 1H, H20α), 4.17 (d, *J* = 8.4 Hz, 1H, H20β), 3.79 (d, *J* = 7.2 Hz, 1H, H3), 3.39 (d, *J* = 6.0 Hz, 1H, 2'OH), 3.35 (dt, *J* = 9.3, 2.1 Hz, 1H, H3'), 2.55 (m, 1H, H6α), 2.48 (d, *J* = 3.9 Hz, 1H, 7OH), 2.36 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac), 1.88 (s, 3H, Me18), 1.67 (s, 3H, Me19), 1.25 (s, 3H, Me17), 1.14 (s, 3H, Me16), 1.14 (d, *J* = 6.0 Hz, 3H, isopropyl), 1.05 (d, *J* = 6.0 Hz, 3H, isopropyl), 0.64 (m, 2H, cyclopropyl), 0.47 (m, 1H, cyclopropyl), 0.28 (m, 1H, cyclopropyl).

EXAMPLE 7

[0075]



(56-4)

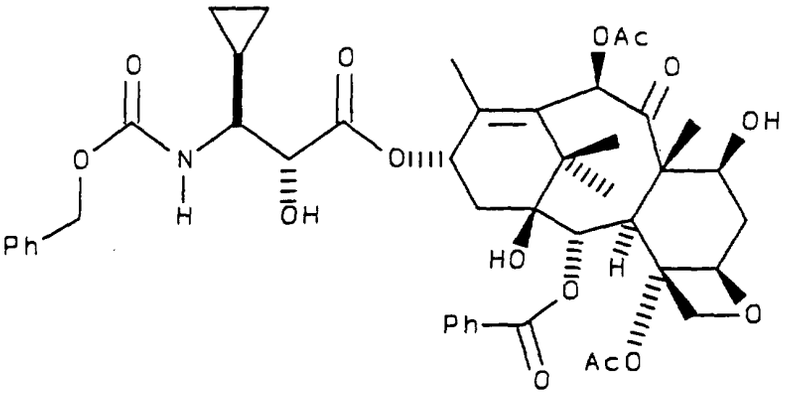
Preparation of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(allyloxycarbonyl) taxol.

[0076] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 2 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(allyloxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (220 mg, 0.672 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h 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 125 mg of a mixture containing (2'R,3'S)-2',7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(allyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0077] To a solution of 120 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 87 mg of material which was purified by flash chromatography to give 79 mg (85%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(allyloxycarbonyl) taxol, which was recrystallized from ether/hexane.
m.p. 138-140 °C; $[\alpha]^{25}_{Na}$ -68.2° (c 0.085, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 7.2 Hz, 2H, benzoate *ortho),* 7.61 (m, 1H, benzoate, *para),* 7.50 (t, *J* = 7.2 Hz, 2H, benzoate, *meta*), 6.29 (s, 1H, H10), 6.22 (br t, *J* = 8.4 Hz, 1H, H13), 5.78 (m, 1H, allyl), 5.67 (d, *J* = 7.2 Hz, 1H, H2β), 5.14 (m, 2H, allyl), 5.09 (d, *J* = 9.6 Hz, 1H, NH), 4.96 (dd, *J* = 9.3, 2.4 Hz, 1H, H5), 4.43 (m, 4H, OCH2, H7 and H2'), 4.30 (d, *J* = 8.4 Hz, 1H, H20α), 4.18 (d, *J* = 8.4 Hz, 1H, H20β), 3.79 (d, *J* = 6.9 Hz, 1H, H3), 3.39 (dt, *J* = 9.6, 1.8 Hz, 1H, H3'), 3.35(d, *J* = 5.4 Hz, 1H, 2'OH), 2.55 (m, 1H, H6α), 2.45 (d, *J* = 3.9 Hz, 1H, 7OH), 2.36 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac), 1.88 (s, 3H, Me18), 1.68 (s, 3H, Me19), 1.26 (s, 3H, Me17), 1.14 (s, 3H, Me16), 0.64 (m, 2H, cyclopropyl), 0.48 (m, 1H, cyclopropyl), 0.29 (m, 1H, cyclopropyl).

EXAMPLE 8

[0078]



(62-4)

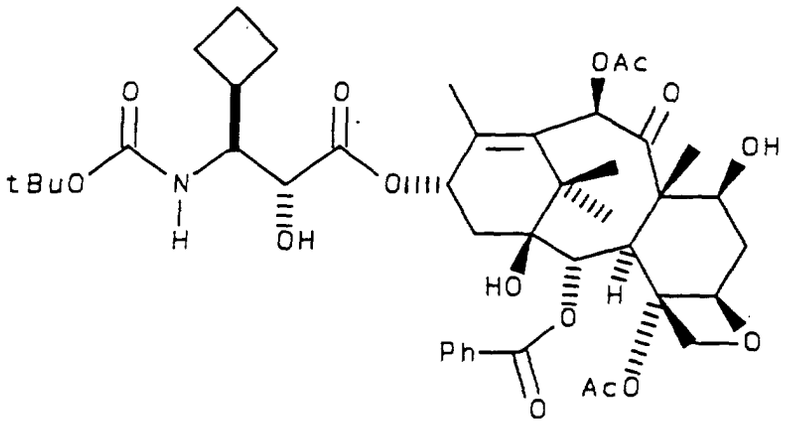
Preparation of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(benzyloxycarbonyl) taxol.

[0079] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 2 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0M solution of $(TMS)_2NLi$ in THF. After 1 h at -45 °C, a solution of *cis*-1-(benzyloxycarbonyl)-3-triethylsilyloxy-4-cyclopropylazetidin-2-one (264 mg, 0.715 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 10h 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 144 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-esphenyl-3'-cyclopropyl-N-debenzoyl-N-(benzyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0080] To a solution of 144 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 109 mg of material which was purified by flash chromatography to give 97 mg (86%) of 3'-desphenyl-3'-cyclopropyl-N-debenzoyl-N-(benzyloxycarbonyl) taxol, which was recrystallized from ether/hexane.
m.p. 128-130 °C; $[\alpha]^{25}_{Na}$ -64.21° (c 0.19, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, *J* = 7.2 Hz, 2H, benzoate *ortho),* 7.60 (m, 1H, benzoate, *para),* 7.49 (t, *J* = 7.2 Hz, 2H, benzoate, *meta*), 7.25 (m, 3H, benzyl), 7.14 (m, 2H, benzyl), 6.26 (s, 1H, H10), 6.18 (br t, *J* = 8.7 Hz, 1H, H13), 5.64 (d, *J* = 7.2 Hz, 1H, H2β), 5.24 (d, *J* = 9.3 Hz, 1H, NH), 5.01 (d, *J* = 12.6 Hz, 1H, benzyl), 4.94 (dd, *J* = 9.3, 1.5 Hz, 1H, H5), 4.91 (d, *J* = 12.6 Hz, 1H, benzyl), 4.44 (br s, 1 H, H2'), 4.40 (dd, *J* = 11.1, 6,6 Hz, 1H, H7), 4.28 (d, *J* = 8.4 Hz, 1H, H20α), 4.18 (d, *J* = 8.4 Hz, 1H, H20β), 3.75 (d, *J* = 7.2 Hz, 1H, H3), 3.44 (br s, 1H, 2'OH), 3.41 (dt, *J* = 9.3, 2.1 Hz, 1H, H3'), 2.53 (m, 1H, H6α), 2.36 (s, 3H, 4Ac), 2.23 (s, 3H, 10Ac), 1.83 (s, 3H, Me18), 1.67 (s, 3H, Me19), 1.21 (s, 3H, Me17), 1.12 (s, 3H, Me16), 0.64 (m, 2H, cyclopropyl), 0.47 (m, 1H, cyclopropyl), 0.29 (m, 1H, cyclopropyl).
[deletion(s)]

EXAMPLE 9

[0081]



(61-3)

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

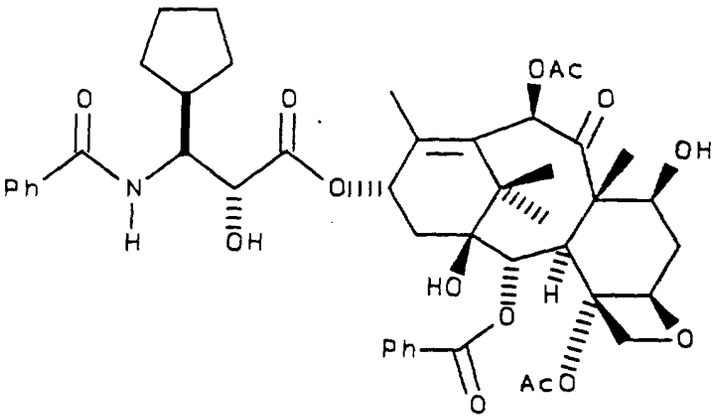
[0082] To a solution of 7-triethylsilyl baccatin III (120 mg, 0.171 mmol) in 1.2 mL of THF at -45 °C was added dropwise 0.188 mL of a 1.00 M solution of lithium bis(trimethylsilyl)-amide in THF. After 0.5 h at -45 °C, a solution of *cis*-1-(t-butoxycarbonyl)-3-triethylsilyloxy-4-cyclobutylazetidin-2-one (303 mg, 0.855 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 180.5 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclobutyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0083] To a solution of 180.5 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 141 mg of material which was purified by flash chromatography to give 133 mg (92%) of 3'-desphenyl-3'-cyclobutyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.168-169 °C; $[\alpha]^{25}_{Na}$ -41.0° (c 0.006, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13(d, J=7.7 Hz, 2H, benzoate, ortho), 7.62-7.48(m, 3H, aromatic), 6.30(s, 1H, H10), 6.18(dd, *J* = 8.9, 8.9 Hz, 1H, H13), 5.68(d, *J* = 7.1 Hz, 1H, H2β), 4.98(d, *J* = 9.9 Hz, 1H, H5), 4.57(d, J=9.3 Hz, 1H, NH),4.42(m, 1H, H7), 4.33(d, J=8.8 Hz, 1H, H20α), 4.22-4.16(m, 2H, H20β, H2'), 3.94(dd, J=9.3,6.0 Hz, 1H, H3'), 3.80 (d, J=6.6 Hz, 1H, H3), 3.13(d, J= 6 Hz, 1H, 2'OH), 2.60(m, 1H, H6α), 2.45(d, J=4.5 Hz, 1H, 7OH), 2.43(s, 3H, 4Ac), 2.35(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.95 (m, 1H, H6β), 1.88(br s, 3H, Me18), 1.80-1.78 (m, 7H,cyclobutyl), 1.77(s, 1H, 1OH), (1.67, s, 3H, Me19), 1.30 (s, 9H, t-butoxy), 1.25(s, 3H, Me17), 1.15(s, 3H, Me16).

EXAMPLE 10

[0084]



(57-1)

Preparation of 3'-desphenyl-3'-(cyclopentyl) taxol.

[0085] 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 0.188 mL of a 1.00 M solution of lithium bis(trimethyl-silyl)amide in THF. After 0.5 h at -45 °C, a solution of cis-1-benzoyl-3-triethylsilyloxy-4-cyclopentylazetidin-2-one (319 mg, 0.855 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 183 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-(cyclopentyl) taxol and a small amount of the (2'S, 3'R) isomer.

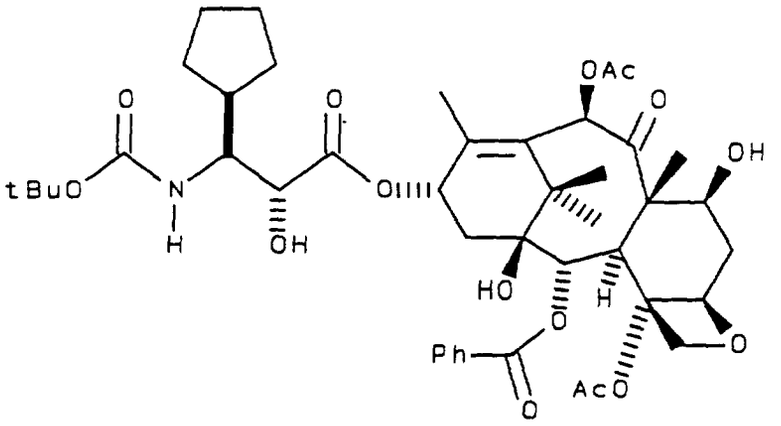
[0086] To a solution of 183mg (0.171 mmol) of the mixture obtained from the previous reaction in 11 mL of acetonitrile and 0.55 mL of pyridine at 0 °C was added 1.7 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 144.5 mg of material which was purified by flash chromatography to give 123 mg (85%) of 3'-desphenyl-3'-(cyclopentyl) taxol, which was recrystallized from methanol/water.

m.p.165-166 °C; $[\alpha]\ ^{25}_{Na}$ -35.0° (c 0.0052, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J=8.2 Hz, 2H, benzoate, ortho), 7.6-7.3(m, 8H, aromatic), 6.32(s, J=9.3 Hz, 1H, NH), 6.27(s, 1H, H10), 6.21(dd, *J* = 8.8, 8.8 Hz,1H, H13), 5.68(d, *J* = 7.7 Hz, 1H, H2β), 4.96 (d, *J* = 7.1 Hz, 1H, H5), 4.48-4.20(m, 5H, H20's, H2',H3',H7), 3.80(d, J= 7.7 Hz, 1H, H3), 3.62(d, J= 5.5 Hz, 1H, 2'OH), 2.54(m, 1H, H6α), 2.48 (s, 3H, 4Ac), 2.45(d, J=4.4 Hz, 1H, 7OH), 2.33(m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.89 (m, 1H, H6β), 1.84(br s, 3H, Me18), 1.79(s, 1H, 10H), 1.68 (s, 3H, Mel9), 1.32-1.23(m, 9H, cyclopentyl), 1.22(s, 3H, Me17), 1.13(s, 3H, Me16).

EXAMPLE 11

[0087]



(61-1)

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

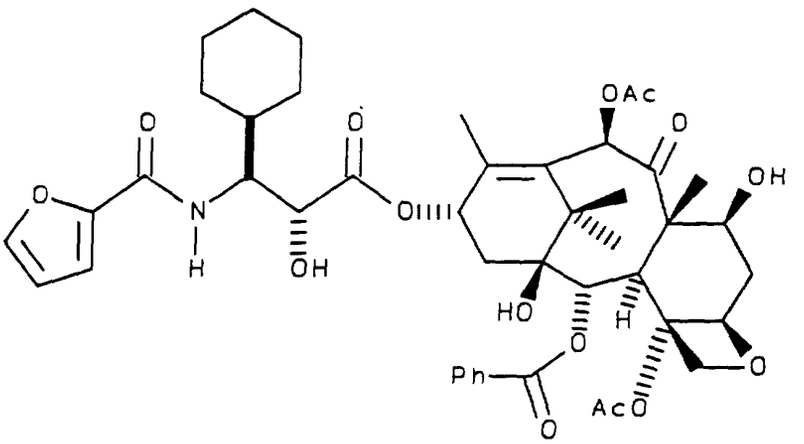
[0088] To a solution of 7-triethylsilyl baccatin III (120 mg, 0.171 mmol) in 1.2 mL of THF at -45 °C was added dropwise 0.188 mL of a 1.00 M solution of lithium bis(trimethylsilyl)-amide in THF. After 0.5 h at -45 °C, a solution of *cis*-1- (t-butoxycarbonyl)-3-triethylsilyloxy-4-cyclopentylazetidin- 2-one (316 mg, 0.855 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 183 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclopentyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0089] To a solution of 183mg (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 144 mg of material which was purified by flash chromatography to give 136 mg (94%) of 3'-desphenyl-3'-cyclopentyl-N-debenzoyl-N-(t-butoxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.164-165 °C; $[\alpha]^{25}_{Na}$ -37.0° (c 0.0055, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J=8.2 Hz, 2H, benzoate, ortho), 7.61-7.47(m, 3H, aromatic), 6.30(s, 1H, H10), 6.20(dd, *J* = 8.9, 8.9 Hz, 1H, H13), 5.67(d, *J* = 7.1 Hz, 1H, H2β), 4.95(d, *J* = 7.7 Hz, 1H, H5), 4.72(d, J=9.3 Hz, 1H, NH)4.40(m, 1H, H7), 4.35-4.16(m, 3H, H20's, H3'), 3.79(m, 2H, H3, H2'), 3.23(d, J= 6 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.40(s, 3H, 4Ac), 2.45(d, J=4.5 Hz, 1H, 7OH), 2.35(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.95 (m, 1H, H6β), 1.88(br s, 3H, Me18), 1.79(s, 1H, 1OH), (1.67,s, 3H, Me19), 1.32-1.23(m, 18H, cyclopentyl, butoxy), 1.21(s, 3H, Me17), 1.12(s, 3H, Me16).

EXAMPLE 12

[0090]



(62-2)

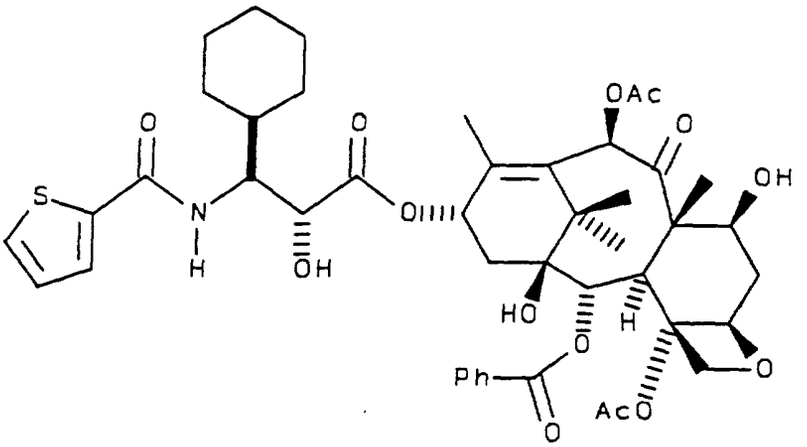
Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-furoyl) taxol.

[0091] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1- (2-furoyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (270 mg, 0.715 mmol) in 1 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 154.2 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-furoyl) taxol and a small amount of the (2'S,3'R) isomer.

[0092] To a solution of 154.2 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 121.5 mg of material which was purified by flash chromatography to give 83.5 mg (68.7 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-furoyl) taxol, which was recrystallized from methanol/water.
m.p.171-173°C; $[\alpha]^{25}_{Na}$ -24.3° (c 0.0028, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17(d, J=7.15 Hz, 2H, benzoate ortho), 7.63(m, 1H, benzoate para), 7.53(m, 2H, benzoate meta), 7.42(d, J= 1.65 Hz, 1H, furyl), 6.92(d, J= 2.74 Hz, 1H, furyl), 6.5(d, J= 9.34 Hz, 1H, NH), 6.43(dd, J= 2.74 Hz, 1.65 Hz, 1H, furyl) ,6.26(s, 1H, H10), 6.22(m, 1H, H13), 5.67(d, J = 7.15 Hz, 1H, H2β), 4.96(dd, J = 9.34 Hz, 2.2 Hz, 1H, H5), 4.59(bs, 1H, H2'), 4.41(dd, J= 10.71 Hz, 6.6 Hz, 1H, H7), 4.31(d, J= 8.24 Hz, 1H, H20α), 4.26(m, 1H, H3'), 4.21 (d, J=8.24 Hz, 1H, H20β), 3.79(d, J= 7.14 Hz, 1H, H3), 3.63(bs, 1H, 2'OH), 2.55(m, 1H, H6α), 2.48(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.87 (s, 3H, Me18), 1.83(m, 1H, H6β), 1.73-1.64(m, 6H, cyclohexyl), 1.68(s, 3H, Mel9), 1.37-1.2(m, 5H, cyclohexyl), 1.25(s, 3H, Me17), 1.13(s, 3H, Me16).

EXAMPLE 13

[0093]



(57-2)

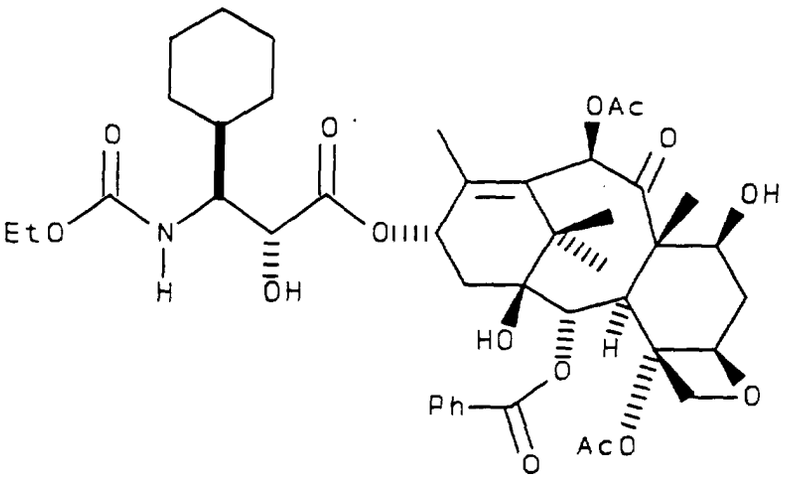
Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-thienoyl) taxol.

[0094] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethyl-silyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(2-thienoyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (281 mg, 0.715 mmol) in 1 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 156.5 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-thienoyl) taxol and a small amount of the (2'S,3'R) isomer.

[0095] To a solution of 156.5 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 121.5 mg of material which was purified by flash chromatography to give 87.4 mg (70.5 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(2-thienoyl) taxol, which was recrystallized from methanol/water.
m.p.162-164°C; $[\alpha]^{25}_{Na}$ -29.2° (c 0.0026, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16(d, J=7.14 Hz, 2H, benzoate ortho), 7.62(m, 1H, benzoate para), 7.53(m, 2H, benzoate meta), 7.42(d, J= 4.39 Hz, 2H, thienyl), 7.02(m, 1H, thienyl), 6.26(s, 1H, H10), 6.22(m, 1H, H13), 6.17(d, J= 9.89 Hz, 1H, NH), 5.67(d, J = 7.15 Hz, 1H, H2β), 4.96(dd, J = 9.61 Hz, 2.2 Hz, 1H, H5), 4.60(d, J= 2.2 Hz, 1H, H2'), 4.41(dd, J= 10.99 Hz, 6.6 Hz, 1H, H7), 4.30(d, J= 8.24 Hz, 1H, H20α), 4.25(m, 1H, H3'), 4.21 (d, J=8.24 Hz, 1H, H20β), 3.78 (d, J= 7.14 Hz, 1H, H3), 2.55(m, 1H, H6α), 2.48(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.86(m, 1H, H6β) 1.83(s, 3H, Me18), 1.73-1.64(m, 6H, cyclohexyl), 1.68(s, 3H, Me19), 1.37-1.2(m, 5H, cyclohexyl), 1.24(s, 3H, Me17), 1.12(s, 3H, Me16).

EXAMPLE 14

[0096]



(51-4)

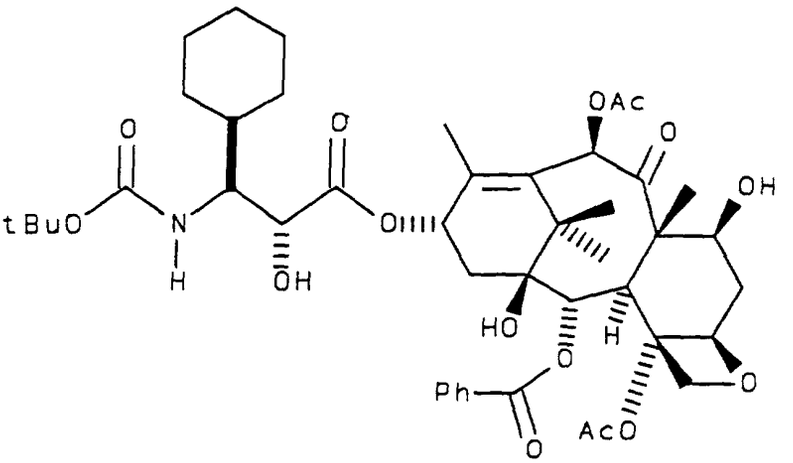
Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-ethoxycarbonyl taxol.

[0097] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1- (ethoxycarbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (254 mg, 0.715 mmol) in 1 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 151 mg of a mixture containing (2'R,3'S)-2',7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-ethoxycarbonyl taxol and a small amount of the (2'S,3'R) isomer.

[0098] To a solution of 151 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 118 mg of material which was purified by flash chromatography to give 100.6 mg (85 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-ethoxycarbonyl taxol, which was recrystallized from methanol/water.
m.p.157-160 °C; $[\alpha]^{25}_{Na}$ -62.6° (c 0.0027, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14(d, J=7.15 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.28 (s, 1H, H10), 6.27(m, 1H, H13), 5.67(d, J = 7.14 Hz, 1H, H2β), 4.96 (dd, J = 8.8, 1.1 Hz, 1H, H5), 4.81(d, J= 9.89 Hz, 1H, NH), 4.50(b s, 1H, H2'), 4.42(dd, J= 10.99, 6.59 Hz, 1H, H7), 4.30(d, J= 8.24 Hz, 1H, H20α), 4.19 (d, J=8.79 Hz, 1H, H20β), 3.93(q, J= 7.14 Hz, 2H, CH_2, ethyl), 3.79(d, J= 6.59 Hz, 1H, H3),3.76(m, 1H, H3'), 3.36(m, 1H, 2'OH), 2.55(m, 1H, H6α), 2.43(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.24 (s, 3H, 10Ac), 1.87 (s, 3H, Me18), 1.83(m, 1H, H6β),1.73-1.64(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.33-1.17(m, 5H, cyclohexyl), 1.26(s, 3H, Me17), 1.14(s, 3H, Me16), 1.09 (t, J= 7.14 Hz, 3H, Me, ethyl).

EXAMPLE 15

[0099]



(47-3)

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

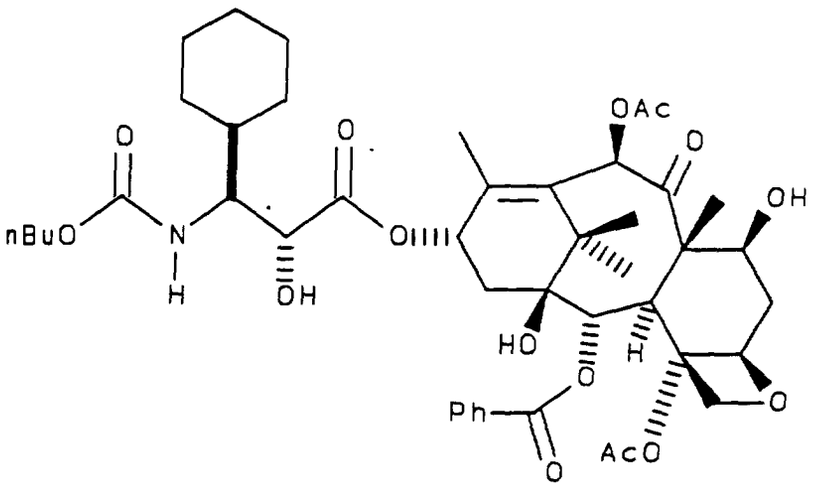
[0100] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethyl-silyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(t-butoxycarbonyl)-3-triethylsilyloxy-4-(cyclohexyl)-azetidin-2-one (274 mg, 0.715 mmol) in 1 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, and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 155 mg of a mixture containing (2'R,3'S)-2',7- (bis)triethylsilyl-3'-desphenyl-3'-(cyclohexyl)-N-debenzoyl- N-(t-butoxycarbonyl)taxol and a small amount of the (2'S,3'R) isomer.

[0101] To a solution of 155 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 122 mg of material which was purified by flash chromatography to give 106 mg (86.6 %) of 3'-desphenyl-3'-(cyclohexyl)-N-debenzoyl-N-(t-butoxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.163-166 °C; $[\alpha]\ ^{25}_{Na}$ -71.0° (c 0.00255, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12(d, J=7.14 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.5(m, 2H, benzoate meta), 6.29 (s, 1H, H10), 6.20(bt, J=8.8 Hz, 1H, H13), 5.67(d, J = 7.14 Hz, 1H, H2β), 4.96 (dd, J = 9.61, 2.2 Hz, 1H, H5), 4.67(d,J= 9.89 Hz, 1H, NH), 4.47(dd, J= 4.94, 1.65 Hz, 1H, H2'), 4.41(m, 1H, H7), 4.31(d, J= 8.24 Hz, 1H, H20α), 4.17 (d, J=8.24 Hz, 1H, H20β), 3.79(d, J= 7.14 Hz, 1H, H3),3.71(m, 1H, H3'), 3.25(d, J= 4.95 Hz, 1H, 2'OH), 2.55(m, 1H, H6α),2.47(m, 1H, 7OH), 2.41(s, 3H, 4Ac), 2.32(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.87 (s, 3H, Me18), 1.83(m, 1H, H6β),1.73-1.58(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.37-1.2(m, 5H, cyclohexyl), 1.28(s, 9H, tert-butyl), 1.25(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 16

[0102]



48-3

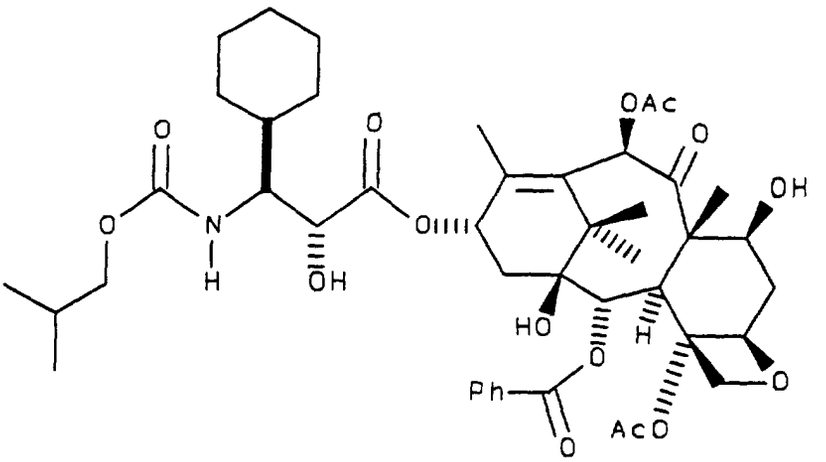
Preparation of 3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(n-butoxycarbonyl) taxol.

[0103] To a solution of 7-O-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 10 M solution of lithium bis(tri-methylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(n-butoxycarbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (274 mg, 0.715 mmol) in 1 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 155 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(n-butoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0104] To a solution of 155 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 122 mg of material which was purified by flash chromatography to give 111 mg (90 %) of 3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(n-butoxycarbonyl) taxol, which was recrystallized from methanol/water.
m.p.140-143 °C; $[\alpha]^{25}_{Na}$ -62.9° (c 0.0031, $CHCl_3$).
^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J=7.69 Hz, 2H, benzoate ortho) ,7.60(m, 1H, benzoate para), 7.49(m, 2H, benzoate meta) , 6.27(s, 1H, H10), 6.25 (m, 1H, H13), 5.66(d, *J* = 7.14 Hz, 1H, H2β), 4.95(d, *J* = 8.24 Hz, 1H, H5), 4.87 (d,J= 9.89 Hz, 1H, NH), 4.50(b s, 1H, H2'), 4.41(dd, J = 10.98, 6.6 Hz, 1H, H7), 4.29(d, *J*= 8.24 Hz, 1H, H20α), 4.17 (d, J=8.25 Hz, 1H, H20β), 3.87(m, 2H, n-butyl), 3.78(d, J= 7.14 Hz, 1H, H3),3.76(m, 1H, H3'), 3.44(bs, 1H, 2'OH), 2.55 (m, 1H, H6α), 2.43(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.23(s, 3H, 10Ac), 1.86(s, 3H, Me18) 1.83(m, 1H, H6β), 1.75(s, 1H, 10H), 1.73-1.64(m, 6H, cyclohexyl), 1.66 (s, 3H, Me19),1.43(m, 2H, n-butyl), 1.31-1.1.13(m, 7H, cyclohexyl, n-butyl), 1.26(s, 3H, Me17), 1.14(s, 3H, Me16), 0.791(t, J= 7.14 Hz, 3H, n-butyl).

EXAMPLE 17

[0105]



(48-2)

Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol.

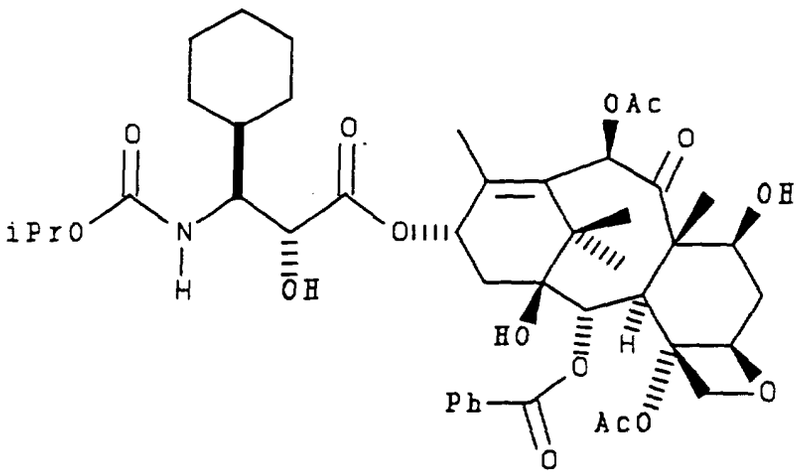
[0106] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethyl-silyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(isobutoxycarbonyl)-3-triethylsilyloxy-4-cyclohexyl azetidin-2-one (274 mg, 0.715 mmol) in 1 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 155 mg of a mixture containing (2'R,3'S)-2',7- (bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0107] To a solution of 155 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 122 mg of material which was purified by flash chromatography to give 110 mg (90 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(isobutoxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.145-148 °C; $[\alpha]^{25}_{Na}$ -54.0° (c 0.0025, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, J=7.14 Hz, 2H, benzoate ortho) ,7.60 (m, 1H, benzoate para), 7.50 (m, 2H, benzoate meta), 6.28 (s, 1H, H10), 6.26 (m, 1H, H13), 5.66(d, *J* = 7.14 Hz, 1H, H2β), 4.95(dd, *J* = 9.61,2.2 Hz, 1H, H5), 4.84(d,J= 9.89 Hz, 1H, NH), 4.51(d, J=1.65 Hz, 1H, H2'), 4.42(dd, J = 10.44, 6.59 Hz, 1H, H7), 4.30(d, J= 8.24 Hz, 1H, H20α), 4.18 (d, J=8.24 Hz, 1H, H20β), 3.78(d, J= 7.69 Hz, 1H, H3),3.73(m, 1H, H3'),3.70(dd, J= 10.44 Hz, 6.59 Hz, 1H, isobutyl), 3.60(dd, J= 10.44 Hz, 6.59 Hz, 1H, isobutyl), 3.35(b s, 1H, 2'OH), 2.55(m, 1H, H6α), 2.44(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.23(s, 3H, 10Ac), 1.86 (s, 3H, Me18), 1.83(m, 1H, H6β), 1.75(m, 1H, isobutyl), 1.73-1.58 (m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.37-1.2(m, 5H, cyclohexyl), 1.25(s, 3H, Me17), 1.13(s, 3H, Me16), 0.76(d, J=7.15 Hz, 3H, Me, isobutyl), 0.71(d, J=6.59 Hz, 3H, Me, isobutyl).

EXAMPLE 18

[0108]



48-4

Preparation of 3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol.

[0109] To a solution of 7-O-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 10 M solution of lithium bis(trimethylsilyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(isopropoxycarbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (264 mg, 0.715 mmol) in 1 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 153 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

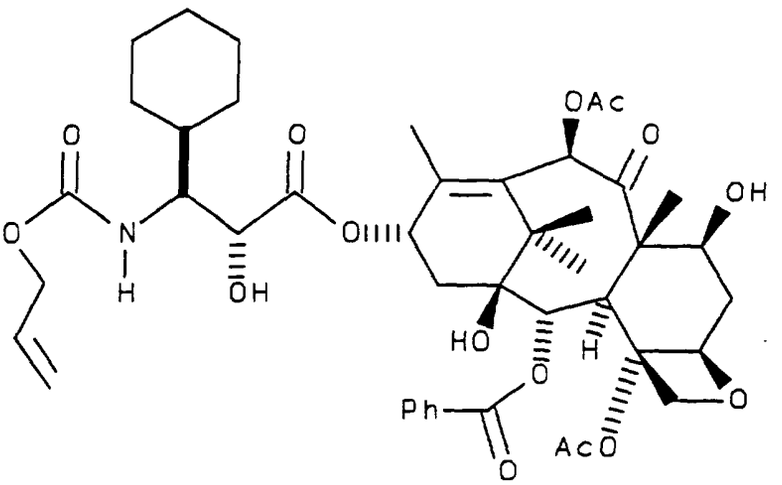
[0110] To a solution of 153 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 122 mg of material which was purified by flash chromatography to give 109.4 mg (90.8 %) of 3'-desphenyl-3'-cyclohexyl-N-desbenzoyl-N-(isopropoxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.150-153 °C; $[\alpha]^{25}_{Na}$ -64.1° (c 0.0031, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14(d, J=7.14 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta) , 6.29(s, 1H, H10), 6.25(m, 1H, H13), 5.67(d, *J* = 7.14 Hz, 1H, H2β), 4.96(dd, *J* = 10.01,2.2 Hz, 1H, H5), 4.76 (d,J= 9.89 Hz, 1H, NH),4.69(m, 1H, isopropyl) 4.49(d, J= 1.65 Hz, 1H, H2'), 4.41(dd, J = 10.99, 6.59 Hz, 1H, H7), 4.30 (d, J= 8.24 Hz, 1H, H20α), 4.18 (d, J= 8.24 Hz, 1H, H20β), 3.79(d, J= 6.6 Hz, 1H, H3), 3.76(m, 1H, H3'), 3.32(b s, 1H, 2'OH), 2.55(m, 1H, H6α), 2.43(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.87(s, 3H, Me18), 1.83(m, 1H, H6β), 1.73-1.64(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.37-1.2(m, 5H, cyclohexyl), 1.26(s, 3H, Me17), 1.14(s, 3H, Me16), 1.11(d, J= 6.04 Hz, 3H, isopropyl), 1.01(d, J= 6.04 Hz, 3H, isopropyl).

EXAMPLE 19

[0111]



(62-1)

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

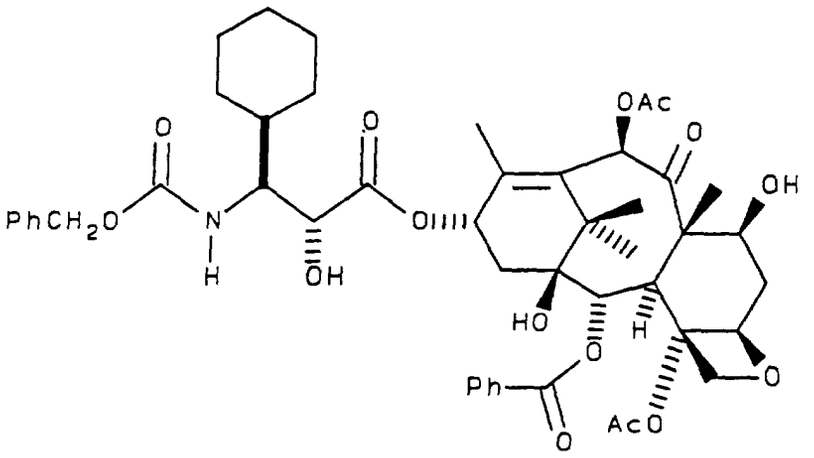
[0112] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(allyloxy-carbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin- 2-one (262.8 mg, 0.715 mmol) in 1 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 152.8 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(allyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0113] To a solution of 152.8 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 120 mg of material which was purified by flash chromatography to give 110.7 mg (92 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(allyloxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.136-138 °C; $[\alpha]^{25}_{Na}$ -61.1° (c 0.0026, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.13(d, J=7.14 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.28(s, 1H, H10), 6.25(m, 1H, H13), 5.75(m, 1H, allyl), 5.66(d, J = 7.15 Hz, 1H, H2β), 5.15(m, 1H, allyl), 5.09 (m, 1H, allyl), 4.95 (m, 1H, H5), 4.92 (d, J= 10.24 Hz, 1H, NH), 4.51(d, J= 1.64 Hz, 1H, H2'), 4.41(m, 1H, H7), 4.39(m, 2H, allyl), 4.29(d, J= 8.79 Hz, 1H, H20α), 4.19 (d, J=8.79 Hz, 1H, H20β), 3.79(m, 1H, H3'), 3.78(m, 1H, H3), 3.25(bs, 1H, 2'OH), 2.55(m, 1H, H6α), 2.42(s, 3H, 4Ac), 2.34(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.86 (s, 3H, Me18), 1.83(m, 1H, H6β),1.73-1.58(m, 6H, cyclohexyl), 1.67 (s, 3H, Mel9), 1.37-1.2(m, 5H, cyclohexyl), 1.24(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 20

[0114]



(52-1)

Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-benzyloxycarbonyl taxol.

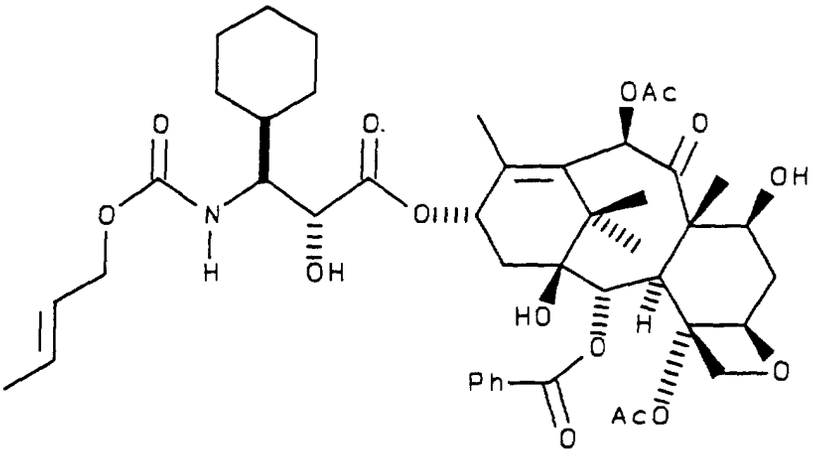
[0115] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethyl-silyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(benzyloxycarbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin-2-one (298 mg, 0.715 mmol) in 1 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 160 mg of a mixture containing (2'R,3'S)-2',7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-benzyloxycarbonyl taxol and a small amount of the (2'S,3'R) isomer.

[0116] To a solution of 160 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 127 mg of material which was purified by flash chromatography to give 110 mg (86 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-benzyloxycarbonyl taxol, which was recrystallized from methanol/water. m.p.149-152 °C; $[\alpha]^{25}_{Na}$ -46.5° (c 0.0023, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14(d, J=8.8 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 7.24-7.21(m, 3H, benzyl), 7.10-7.06(m, 2H, benzyl), 6.24 (s, 1H, H10), 6.21(m, 1H, H13), 5.63(d, J = 7.15 Hz, 1H, H2β), 5.01(d, J= 12.64 Hz, 1H, benzyl),5.00(d,J= 8.79 Hz, 1H, NH),4.94 (dd, J = 9.61, 2.2 Hz, 1H, H5),4.87(d, J= 12.64 Hz, 1H, benzyl), 4.51(b s, 1H, H2'), 4.4(dd, J= 11, 7 Hz, 1H, H7), 4.28(d, J= 8.79 Hz, 1H, H20α), 4.20 (d, J=8.79 Hz, 1H, H20β), 3.82(m, 1H, H3') 3.74(d, J= 7.15 Hz, 1H, H3), 3.37(m, 1H, 2'OH), 2.53(m, 1H, H6α), 2.43(s, 3H, 4Ac), 2.31(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.83(m, 1H, H6β) 1.81 (s, 3H, Me18), 1.73-1.60(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.33-1.2(m, 5H, cyclohexyl), 1.24(s, 3H, Me17), 1.11(s, 3H, Me16).

EXAMPLE 21

[0117]



(66-3)

Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(crotyloxycarbonyl) taxol.

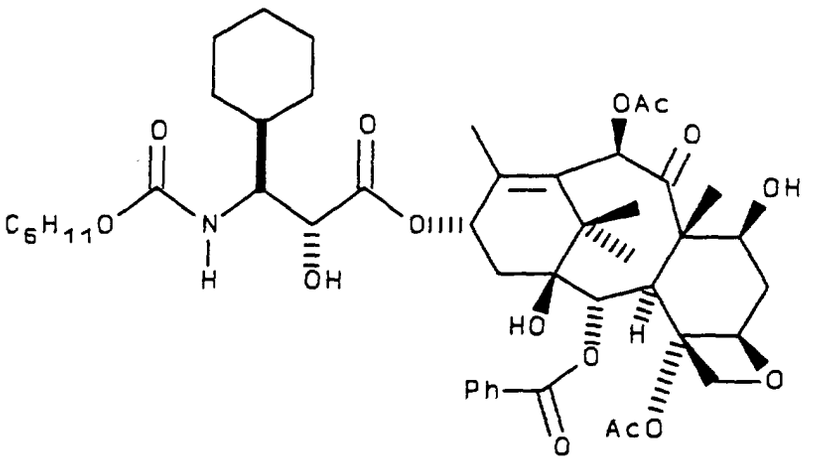
[0118] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 10 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1- (crotyloxycarbonyl)-3-triethylsilyloxy-4-cyclohexylazetidin- 2-one (273 mg, 0.715 mmol) in 1 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 154.8 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(crotyloxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

[0119] To a solution of 154.8 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 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 122 mg of material which was purified by flash chromatography to give 113 mg (92.5 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(crotyloxycarbonyl) taxol, which was recrystallized from methanol/water. m.p.139-141 °C; $[\alpha]^{25}_{Na}$ -66.8° (c 0.00265, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13(d, J=8.79 Hz, 2H, benzoate ortho) ,7.60(m, 1H, benzoate para),7.50(m, 2H, benzoate meta), 6.28 (s, 1H, H10), 6.26 (m, 1H, H13), 5.66(d, *J* = 7.15 Hz, 1H, H2β),5.58(m, 1H, crotyl), 5.44(m, 1H, crotyl), 4.95(dd, J = 9.89 Hz, 2.2 Hz, 1H, H5), 4.86(d,J= 9.89 Hz,1H,NH), 4.50(dd, J= 4.9 Hz, 1.92 Hz, 1H, H2'), 4.42(m, 1H, H7), 4.31(m, 2H, crotyl), 4.29(d, J= 8.24 Hz, 1H, H20α), 4.18 (d, J=8.24 Hz, 1H, H20β), 3.79(d, J= 7.69 Hz, 1H, H3), 3.75(m, 1H, H3'), 3.39(d, J= 4.9 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.43(s, 3H, 4Ac), 2.31(m, 2H, H14), 2.23 (s, 3H, 10Ac),1.86(s, 3H, Me18), 1.83 (m, 1H, H6β), 1.73-1.64(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19),1.60 (d, J= 6.6 Hz, 3H, crotyl), 1.33-1.17(m, 5H, cyclohexyl), 1.26(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 22

[0120]



(52-2)

Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-cyclohexyloxycarbonyl taxol.

[0121] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1- (cyclohexyloxycarbonyl)-3-triethylsilyloxy-4-cyclohexyl-azetidin-2-one (293 mg, 0.715 mmol) in 1 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 159 mg of a mixture containing (2'R,3'S)-2',7-(bis)-triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-cyclohexyloxycarbonyl taxol and a small amount of the (2'S,3'R) isomer.

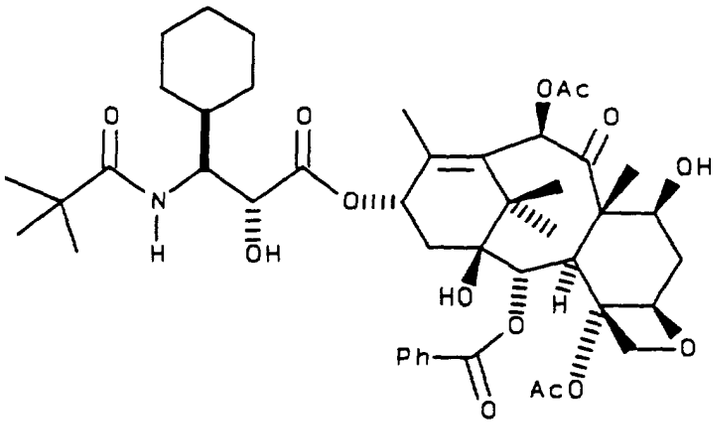
[0122] To a solution of 159 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 126 mg of material which was purified by flash chromatography to give 120 mg (95 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-cyclohexyloxycarbonyl taxol, which was recrystallized from methanol/water.

m.p.164-167 °C; $[\alpha]^{25}_{Na}$ -56.5° (c 0.0026, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15(d, J=8.8 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 6.28 (s, 1H, H10), 6.25(m, 1H, H13), 5.66(d, J = 7.15 Hz, 1H, H2β),4.96 (dd, J = 8,79, 1.65 Hz, 1H, H5) 4.76 (d,J= 9.89 Hz, 1H, NH), 4.50(b s, 1H, H2'), 4.41(m, 2 H, H7, cyclohexyl), 4.29(d, J= 8.79 Hz, 1H, H20α), 4.18 (d, J=8.79 Hz, 1H, H20β), 3.79(d, J= 7.15 Hz, 1H, H3),3.78(m, 1H, H3'), 3.27(m, 1H, 2'OH), 2.53(m, 1H, H6α), 2.44(s, 3H, 4Ac), 2.31(m, 2H, H14), 2.24 (s, 3H, 10Ac),1.87 (s, 3H, Me18) 1.83(m, 1H, H6β),1.9-0.9 (m, 21H, cyclohexyl), 1.67 (s, 3H, Me19), 1.2(s, 3H, Me17), 1.14(s, 3H, Me16).

EXAMPLE 23

[0123]



(61-4)

Preparation of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(neopentoxycarbonyl) taxol.

[0124] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(neopentoxycarbonyl)-3-triethylsilyloxy-4-cyclohexyl-azetidin-2-one (284.3 mg, 0.715 mmol) in 1 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 157 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(neopentoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

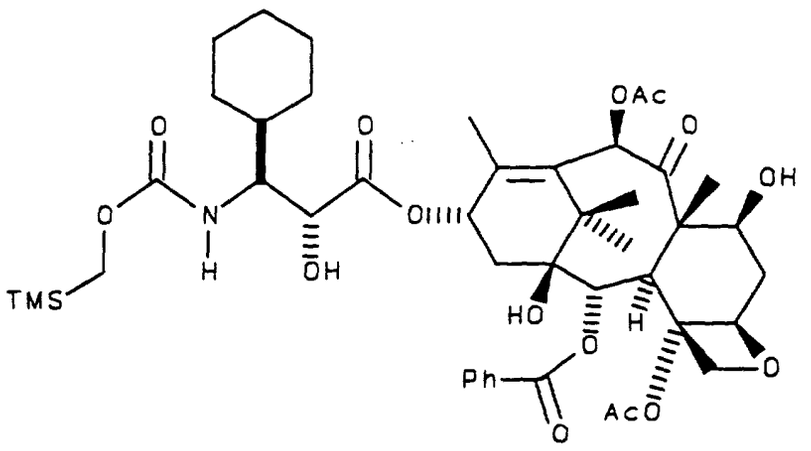
[0125] To a solution of 157 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 124.4 mg of material which was purified by flash chromatography to give 106 mg (85.2 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(neopentoxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.159-161°C; $[\alpha]^{25}_{Na}$ -60.0° (c 0.0026, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.15(d, J=7.14 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.28(s, 1H, H10), 6.25(m, 1H, H13), 5.66(d, J = 7.15 Hz, 1H, H2β), 4.95(dd, J = 9.61, 1.65 Hz, 1H, H5), 4.86 (d,J= 9.89 Hz, 1H, NH), 4.52(d, J= 1.65 Hz, 1H, H2'), 4.42(dd, J= 10.99 Hz, 6.6 Hz, 1H, H7), 4.30(d, J= 8.24 Hz, 1H, H20α), 4.18(d, J=8.24 Hz, 1H, H20β), 3.79(d, J= 7.15 Hz, 1H, H3), 3.78(m, 1H, H3'), 3.65(d, J= 10.44 Hz, 1H, neopentyl),3.52(d, J= 10.44 Hz, 1H, neopentyl), 3.25(bs, 1H, 2'OH), 2.55(m, 1H, H6α), 2.44(s,3H, 4Ac), 2.32(m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.86 (s, 3H, Me18), 1.83(m, 1H, H6β), 1.73-1.58 (m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.37-1.2 (m, 5H, cyclohexyl), 1.25(s, 3H, Me17), 1.13(s, 3H, Me16), 0.76(s, 9H, neopentyl).

EXAMPLE 24

[0126]



(57-3)

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

[0127] To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol) in 1 mL of THF at -45 °C was added dropwise 0.157 mL of a 1.0 M solution of lithium bis(trimethyl-silyl)amide in THF. After 1 h at -45 °C, a solution of *cis*-1-(trimethylsilylmethoxycarbonyl)-3-triethylsilyloxy-4- cyclohexylazetidin-2-one (295.8 mg, 0.715 mmol) in 1 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 159.4 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(trimethylsilylmethoxycarbonyl) taxol and a small amount of the (2'S,3'R) isomer.

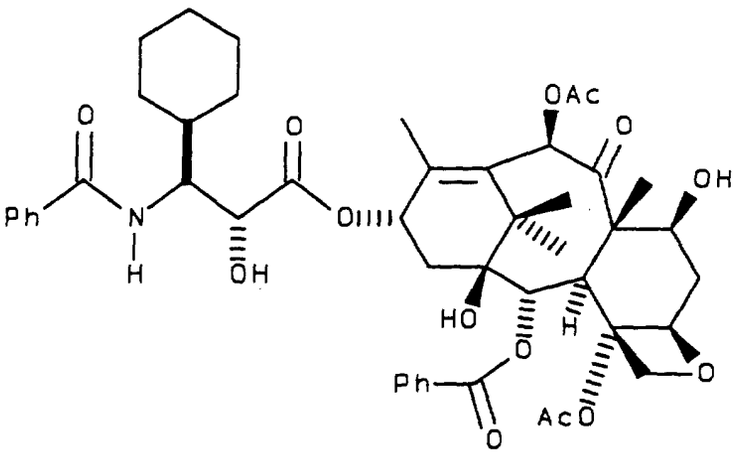
[0128] To a solution of 159.4 mg (0.143 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 126.7 mg of material which was purified by flash chromatography to give 116 mg (91.5 %) of 3'-desphenyl-3'-cyclohexyl-N-debenzoyl-N-(trimethylsilylmethoxycarbonyl) taxol, which was recrystallized from methanol/water.

m.p.147-149°C; $[\alpha]^{25}_{Na}$ -56.4° (c 0.0025, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15(d, J=7.15 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 6.28(s, 1H, H10), 6.26(m, 1H, H13), 5.67(d, J = 7.15 Hz, 1H, H2β), 4.96 (dd, J = 9.61, 2.2 Hz, 1H, H5), 4.80(d, J= 9.89 Hz, 1H, NH), 4.51(dd, J= 4.95, 1.65 Hz, 1H, H2'), 4.42(m, 1H, H7), 4.30(d, J= 8.24 Hz, 1H, H20α), 4.18(d, J=8.24 Hz, 1H, H20β), 3.79(d, J= 7.14 Hz, 1H, H3), 3.76 (m, 1H, H3'), 3.62(d, J= 14.28 Hz, 1H, CH2TMS),3.53(d, J= 14.28 Hz, 1H, CH2TMS), 3.41(d, J= 4.95 Hz, 1H, 2'OH), 2.55(m, 1H, H6α), 2.47(m, 1H, 7OH), 2.44(s, 3H, 4Ac), 2.32 (m, 2H, H14), 2.23(s, 3H, 10Ac), 1.86(s, 3H, Me18), 1.83(m, 1H, H6β), 1.73-1.58(m, 6H, cyclohexyl), 1.67 (s, 3H, Me19), 1.37-1.2(m, 5H, cyclohexyl), 1.26(s, 3H, Me17), 1.14(s, 3H, Me16), -0.05(s, 9H, (CH3)3Si).

EXAMPLE 25

[0129]



(29-2)

Preparation of 3'-desphenyl-3'-(cyclohexyl) taxol.

[0130] 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-(cyclohexyl)azetidin-2-one (331 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 186 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-(cyclohexyl) taxol and a small amount of the (2'S,3'R) isomer.

[0131] To a solution of 186 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 147 mg of material which was purified by flash chromatography to give 107 mg (73%) of 3'-desphenyl-3'-(cyclohexyl) taxol, which was recrystallized from methanol/water.
m.p.163-164 °C; $[a]^{25}_{Na}$ -32.0° (c 0.0049, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz) w 8.16 (d, J=7.2 Hz, 2H, benzoate ortho),7.65(d, J=7.4 Hz, 2H, benzamide ortho), 7.64-7.33 (m, 6H, aromatic), 6.29(s, J=9.9 Hz, 1H, NH), 6.26 (s, 1H, H10), 6.20(dd, J = 9.35, 9.35 Hz, 1H, H13), 5.68(d, J = 7.7 Hz, 1H, H2β), 4.97 (d, J = 7.7 Hz, 1H, H5), 4.60(dd, J= 4.9,1.4 Hz, 1H, H2'), 4.40(m, 1H, H7), 4.27(m, 1H, H3'), 4.26 (d, J= 8.2 Hz, 1H, H20α), 4.21 (d, J=8.2 Hz, 1H, H20β), 3.78(d, J= 7.7 Hz, 1H, H3), 3.66(d, J= 4.9 Hz, 1H, 2'OH), 2.58 (m, 1H, H6α), 2.50(s, 3H, 4Ac), 2.45(d, J=3.9 Hz, 1H, 7OH), , 2.31(m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.86 (m, 1H, H6β), 1.83(br s, 3H, Me18), 1.75(s, 1H, 1OH), 1.68 (s, 3H, Me19), 1.27-1.2(m, 11H, cyclohexyl), 1.20(s, 3H, Me17), 1.11(s, 3H, Me16). ***[deletion(s)]***

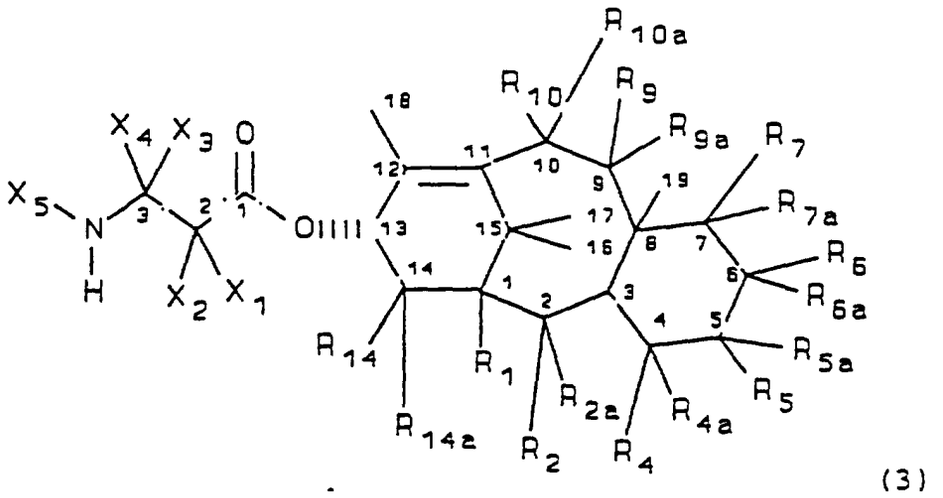
EXAMPLE 26

[0132] The taxanes of the preceding examples 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.

[0133] All compounds had an IC_{50} of less than 0.1 indicating that they are cytotoxically active.

Claims

1. A taxane derivative having 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 optionally substituted cycloalkyl;
X_4 is hydrogen;
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, $-OCOR_{31}$ 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;
R_{29}, R_{30}, and R_{31} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl; and
alkyl may be substituted, straight, branched chain or cyclic.

2. The taxane derivative of claim 1 wherein X_3 is cyclohexyl, cyclopentyl, cyclopropyl, or cyclobutyl.

3. The taxane derivative of claim 1 wherein

R_{14} and R_{14a} are hydrogen;
R_{10} is hydrogen or together with R_{10a} forms an oxo;
R_{10a} is hydrogen, hydroxy, -$OCOR_{29}$, or together with R_{10} forms an oxo;
R_9 is hydrogen or together with R_{9a} forms an oxo;
R_{9a} is hydrogen, acyloxy or together with R_9 forms an oxo;
R_7 is hydrogen;
R_{7a} is hydrogen, halogen or -OR_{28};
R_6 and R_{6a} are hydrogen;
R_5 is hydrogen;
R_{5a} together with R_4 and the carbon atoms to which they are attached form an oxetane ring;
R_{4a} is hydroxy, or -$OCOR_{30}$;
R_2 is hydroxy, or -$OCOR_{31}$;
R_{2a} is hydrogen;
R_1 is hydrogen or hydroxy;
R_{28} is hydrogen, acyl, or hydroxy protecting group; and
R_{29}, R_{30}, and R_{31} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl.

4. The taxane derivative of claim 2 wherein X_5 is -COX_{10} and X_{10} is alkoxy, furyl or thienyl.

5. The taxane derivative of claim 1 wherein X_5 is -COX_{10}, X_{10} is as defined in claim 1, and X_3 is cyclohexyl, cyclopentyl, cyclopropyl, or cyclobutyl.

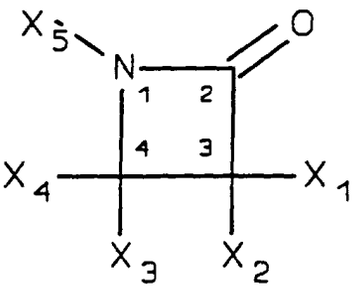
6. The taxane derivative of claim 2 wherein

R_{14} and R_{14a} are hydrogen;
R_{10} is hydrogen or together with R_{10a} forms an oxo;
R_{10a} is hydrogen, hydroxy, -$OCOR_{29}$, or together with R_{10} forms an oxo;
R_9 is hydrogen or together with R_{9a} forms an oxo;
R_{9a} is hydrogen, acyloxy or together with R_9 forms an oxo;
R_7 is hydrogen;
R_{7a} is hydrogen, halogen or -OR_{28};
R_6 and R_{6a} are hydrogen;
R_5 is hydrogen;
R_{5a} together with R_4 and the carbon atoms to which they are attached form an oxetane ring;
R_{4a} is hydroxy, or -$OCOR_{30}$;
R_2 is hydroxy, or -$OCOR_{31}$;
R_{2a} is hydrogen;
R_1 is hydrogen or hydroxy;
R_{28} is hydrogen, acyl, or hydroxy protecting group; and
R_{29}, R_{30}, and R_{31} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl.

7. A pharmaceutical composition which contains the taxane derivative of claim 1 and one or more pharmacologically

acceptable, inert or physiologically active diluents or adjuvants.

8. A β-lactam of the formula

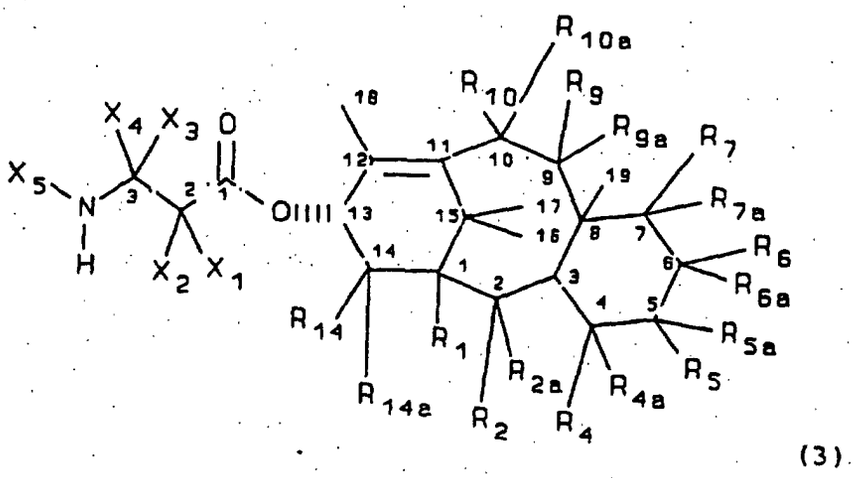


wherein

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;
X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;
X_3 is optionally substituted cycloalkyl;
X_4 is hydrogen;
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; and
alkyl may be substituted, straight, branched chain or cyclic.

Patentansprüche

1. Taxanderivat mit der Formel



(3)

worin

X_1 $-OX_6$, $-SX_7$ oder $-NX_8X_9$ ist;
X_2 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_3 wahlweise substituiertes Cycloalkyl ist;
X_4 Wasserstoff ist;
X_5 $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$ oder $-SO_2X_{11}$ ist;
X_6 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, Hydroxy-Schutzgruppe oder eine funktionelle Gruppe ist, die die Wasserlöslichkeit des Taxanderivats erhöht;
X_7 Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder Sulfhydryl-Schutzgruppe ist;
X_8 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder heterosubstituiertes Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_9 eine Amino-Schutzgruppe ist;
X_{10} Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder heterosubstituiertes Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_{11} Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, $-OX_{10}$ oder $-NX_8X_{14}$ ist;
X_{14} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
R_1 Wasserstoff, Hydroxy, geschütztes Hydroxy ist oder zusammen mit R_{14} ein Carbonat bildet;
R_2 Wasserstoff, Hydroxy, $-OCOR_{31}$ist oder zusammen mit R_{2a} ein Oxo bildet;
R_{2a} Wasserstoff ist oder zusammen mit R_2 ein Oxo bildet;
R_4 Wasserstoff ist, zusammen mit R_{4a} ein Oxo, Oxiran oder Methylen bildet oder zusammen mit R_{5a} und den Kohlenstoffatomen, an denen sie hängen, einen Oxetanring bildet;
R_{4a} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, Cyano, Hydroxy, $-OCOR_{30}$ ist oder zusammen mit R_4 ein Oxo, Oxiran oder Methylen bildet;
R_5 Wasserstoff ist oder zusammen mit R_{5a} ein Oxo bildet;
R_{5a} Wasserstoff, Hydroxy, geschütztes Hydroxy, Acyloxy ist, zusammen mit R_5 ein Oxo bildet oder zusammen mit R_4 und den Kohlenstoffatomen, an denen sie hängen, einen Oxetanring bildet;
R_6 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl, Hydroxy, geschütztes Hydroxy ist oder zusammen mit R_{6a} ein Oxo bildet;
R_{6a} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl , Hydroxy oder geschütztes Hydroxy ist oder zusammen mit R_6 ein Oxo bildet;
R_7 Wasserstoff ist oder zusammen mit R_{7a} ein Oxo bildet;
R_{7a} Wasserstoff, Halogen, geschütztes Hydroxy, $-OR_{28}$ ist oder zusammen mit R_7 ein Oxo bildet;
R_9 Wasserstoff ist oder zusammen mit R_{9a} ein Oxo bildet;
R_{9a} Wasserstoff, Hydroxy, geschütztes Hydroxy, Acyloxy ist oder zusammen mit R_9 ein Oxo bildet;
R_{10} Wasserstoff ist oder zusammen mit R_{10a} ein Oxo bildet;
R_{10a} Wasserstoff, $-OCOR_{29}$, Hydroxy oder geschütztes Hydroxy ist oder zusammen mit R_{10} ein Oxo bildet;
R_{14} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, Hydroxy, geschütztes Hydroxy ist oder zusammen mit R_1 ein Carbonat bildet;
R_{14a} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
R_{28} Wasserstoff, Acyl, Hydroxy-Schutzgruppe oder eine funktionelle Gruppe ist, die die Löslichkeit des Taxanderivats erhöht;
R_{29}, R_{30} und R_{31} unabhängig Wasserstoff, Alkyl, Alkenyl, Alkynyl, monocyclisches Aryl oder monocyclisches Heteroaryl sind; und
Alkyl substituiert, gerade, verzweigtkettig oder cyclisch sein kann.

2. Taxanderivat des Anspruchs 1, bei dem X_3 Cyclohexyl, Cyclopentyl, Cyclopropyl oder Cyclobutyl ist.

3. Taxanderivat des Anspruchs 1, bei dem

R_{14} und R_{14a} Wasserstoff sind;
R_{10} Wasserstoff ist oder zusammen mit R_{10a} ein Oxo bildet;
R_{10a} Wasserstoff, Hydroxy, $-OCOR_{29}$ ist oder zusammen mit R_{10} ein Oxo bildet;
R_9 Wasserstoff ist oder zusammen mit R_{9a} ein Oxo bildet;
R_{9a} Wasserstoff, Acyloxy ist oder zusammen mit R_9 ein Oxo bildet;
R_7 Wasserstoff ist;
R_{7a} Wasserstoff, Halogen oder $-OR_{28}$ ist;
R_6 und R_{6a} Wässerstoff sind;
R_5 Wasserstoff ist;
R_{5a} zusammen mit R_4 und den Kohlenstoffatomen, an denen sie hängen, einen Oxetanring bildet;

R_{4a} Hydroxy oder -$OCOR_{30}$ ist;
R_2 Hydroxy oder -$OCOR_{31}$ ist;
R_{2a} Wasserstoff ist;
R_1 Wasserstoff oder Hydroxy ist;
R_{28} Wasserstoff, Acyl oder eine Hydroxy-Schutzgruppe ist; und
R_{29}, R_{30} und R_{31} unabhängig Wasserstoff, Alkyl, Alkenyl, Alkynyl, monocyclisches Aryl oder monocyclisches Heteroaryl sind.

4. Taxanderivat des Anspruchs 2, bei dem X_5 -COX_{10} ist und X_{10} Alkoxy, Furyl oder Thienyl ist.

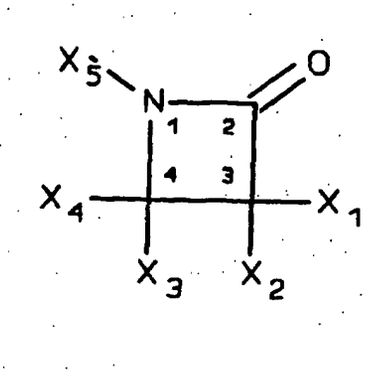
5. Taxanderivat des Anspruchs 1, bei dem X_5 -COX_{10} ist, X_{10} wie in Anspruch 1 definiert ist und X_3 Cyclohexyl, Cyclopentyl, Cyclopropyl oder Cyclobutyl ist.

6. Taxanderivat des Anspruchs 2, bei dem

R_{14} und R_{14a} Wasserstoff sind;
R_{10} Wasserstoff ist oder zusammen mit R_{10a} ein Oxo bildet;
R_{10a} Wasserstoff, Hydroxy, -$OCOR_{29}$ ist oder zusammen mit R_{10} ein Oxo bildet;
R_9 Wasserstoff ist oder zusammen mit R_{9a} ein Oxo bildet;
R_{9a} Wasserstoff oder Acyloxy ist oder zusammen mit R_9 ein Oxo bildet;
R_7 Wasserstoff ist;
R_{7a} Wasserstoff, Halogen oder -OR_{28} ist
R_6 und R_{6a} Wasserstoff sind;
R_5 Wasserstoff ist;
R_{5a} zusammen mit R_4 und den Kohlenstoffatomen, an denen sie hängen, einen Oxetanring bildet;
R_{4a} Hydroxy oder -$OCOR_{30}$ ist;
R_2 Hydroxy oder -$OCOR_{31}$ ist;
R_{2a} Wasserstoff ist;
R_1 Wasserstoff oder Hydroxy ist;
R_{28} Wasserstoff, Acyl oder eine Hydroxy-Schutzgruppe ist; und
R_{29} , R_{30} und R_{31} unabhängig Wasserstoff, Alkyl, Alkenyl, Alkynyl, monocyclisches Aryl oder monocyclisches Heteroaryl sind.

7. Pharmazeutische Zusammensetzung, die das Taxanderivat des Anspruchs 1 und ein oder mehrere pharmakologisch zulässige, inerte oder physiologisch aktive Verdünnungsmittel oder Hilfsmittel enthält.

8. β-Lactam der Formel



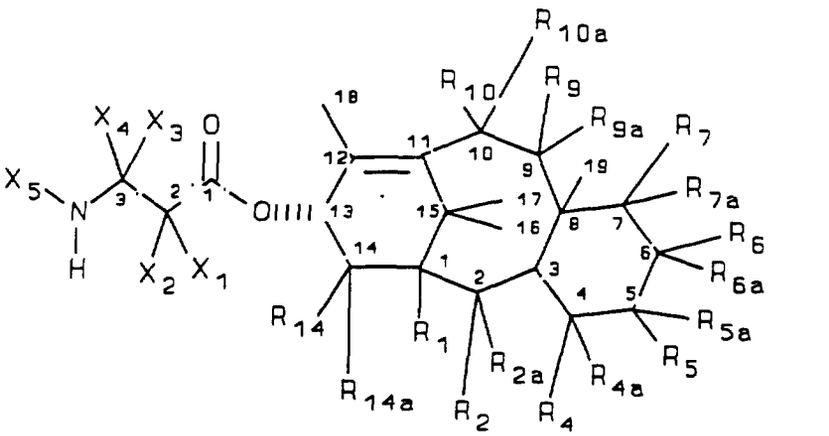
worin

X_1 -OX_6, -SX_7 oder -NX_8 X_9 ist;
X_2 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_3 wahlweise substituiertes Cycloalkyl ist;
X_4 Wasserstoff ist;

X_5 $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$ oder $-SO_2X_{11}$ ist;
X_6 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, eine Hydroxy-Schutzgruppe oder eine funktionelle Gruppe ist, die die Wasserlöslichkeit des Taxanderivats erhöht;
X_7 Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder eine Sulfhydryl-Schutzgruppe ist
X_8 Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder heterosubstituiertes Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_9 eine Amino-Schutzgruppe ist;
X_{10} Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl oder heterosubstituiertes Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist;
X_{11} Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, $-OX_{10}$ oder $-NX_8X_{14}$ ist;
X_{14} Wasserstoff, Alkyl, Alkenyl, Alkynyl, Aryl oder Heteroaryl ist; und
Alkyl substituiert, gerade, verzweigtkettig oder cyclisch sein kann.

Revendications

1. Dérivé de taxane de formule



(3)

dans laquelle

X_1 est $-OX_6$, $-SX_7$, ou $-NX_8X_9$;
X_2 est hydrogène, alkyle, alcényle, alcynyle, aryle ; ou hétéroaryle ;
X_3 est cycloalkyle éventuellement substitué;
X_4 est hydrogène ;
X_5 est $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, ou $-SO_2X_{11}$;
X_6 est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle, un groupe de protection hydroxy, ou un groupe fonctionnel qui accroît la solubilité dans l'eau du dérivé de taxane ;
X_7 est alkyle, alcényle, alcynyle, aryle, hétéroaryle, ou un groupe de protection sulfhydryle ;
X_8 est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle ; ou alkyle, alcényle, alcynyle, aryle ou hétéroaryle hétérosubstitué ;
X_9 est un groupe de protection amino ;
X_{10} est alkyle, alcényle, alcynyle, aryle, hétéroaryle ; ou alkyle, alcényle, alcynyle, aryle ou hétéroaryle hétérosubstitué ;
X_{11} est alkyle, alcényle, alcynyle, aryle, hétéroaryle, $-OX_{10}$, ou $-NX_8X_{14}$;
X_{14} est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle ;
R_1 est hydrogène, hydroxy, hydroxy protégé ou, avec R_{14}, il forme un carbonate ;
R_2 est hydrogène, hydroxy, $-OCOR_{31}$ ou avec R_{2a}, il forme un oxo ;
R_{2a} est hydrogène ou avec R_2, il forme un oxo ;
R_4 est hydrogène, avec R_{4a}, il forme un oxo, oxirane ou méthylène, ou avec R_{5a} et les atomes de carbone auxquels ils sont liés, ils forment un cycle oxétane ;
R_{4a} est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle, cyano, hydroxy, $-OCOR_{30}$, ou avec R_4, il

forme un oxo, oxirane ou méthylène ;
R_5 est hydrogène, ou avec R_{5a}, il forme un oxo ;
R_{5a} est hydrogène, hydroxy, hydroxy protégé, acyloxy, avec R_5, il forme un oxo, ou avec R_4 et les atomes de carbone auxquels ils sont liés, ils forment un cycle oxétane ;
R_6 est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle, hydroxy, hydroxy protégé ou avec R_{6a}, il forme un oxo ;
R_{6a} est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle, hydroxy, hydroxy protégé ou avec R_6, il forme un oxo ;
R_7 est hydrogène, ou avec R_{7a}, il forme un oxo ;
R_{7a} est hydrogène, halogène, hydroxy protégé, $-OR_{28}$, ou avec R_7, il forme un oxo ;
R_9 est hydrogène ou avec R_{9a}, il forme un oxo ;
R_{9a} est hydrogène, hydroxy, hydroxy protégé, acyloxy, ou avec R_9, il forme un oxo ;
R_{10} est hydrogène ou avec R_{10a}, il forme un oxo ;
R_{10a} est hydrogène, $-OCOR_{29}$, hydroxy, ou hydroxy protégé, ou avec R_{10}, il forme un oxo ;
R_{14} est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle, hydroxy, hydroxy protégé ou avec R_1, il forme un carbonate ;
R_{14a} est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle ;
R_{28} est hydrogène, acyle, un groupe de protection hydroxy ou un groupe fonctionnel qui accroît la solubilité dans l'eau du dérivé de taxane ;
R_{29}, R_{30} et R_{31} sont, indépendamment, hydrogène, alkyle, alcényle, alcynyle, aryle monocyclique ou hétéroaryle monocyclique ; et l'alkyle peut être substitué, à chaîne droite, ramifiée ou cyclique.

2. Dérivé de taxane selon la revendication 1, dans lequel X est cyclohexyle, cyclopentyle, propyle, ou butyle.

3. Dérivé de taxane selon la revendication 1, dans lequel

R_{14} et R_{14a} sont hydrogène ;
R_{10} est hydrogène ou avec R_{10a}, il forme un oxo ;
R_{10a} est hydrogène, hydroxy, $-OCOR_{29}$, ou avec R_{10}, il forme un oxo ;
R_9 est hydrogène ou avec R_{9a}, il forme un oxo ;
R_{9a} est hydrogène, acyloxy ou avec R_9, il forme un oxo ;
R_7 est hydrogène ;
R_{7a} est hydrogène, halogène ou $-OR_{28}$;
R_6 et R_{6a} sont hydrogène ;
R_5 est hydrogène ;
R_{5a} avec R_4 et les atomes de carbone auxquels ils sont liés forment un cycle oxétane ;
R_{4a} est hydroxy, ou $-OCOR_{30}$;
R_2 est hydroxy, ou $-OCOR_{31}$;
R_{2a} est hydrogène ;
R_1 est hydrogène ou hydroxy ;
R_{28} est hydrogène, acyle, ou un groupe de protection hydroxy ; et
R_{29}, R_{30} et R_{31} sont, indépendamment, hydrogène, alkyle, alcényle, alcynyle, aryle monocyclique ou hétéroaryle monocyclique.

4. Dérivé de taxane selon la revendication 2, dans lequel X_5 est $-COX_{10}$ et X_{10} est alcoxy, furyle ou thiényle.

5. Dérivé de taxane selon la revendication 1, dans lequel X_5 est $-COX_{10}$, X_{10} est tel que défini dans la revendication 1, et X_3 est cyclohexyle, cyclopentyle, cyclopropyle, ou cyclobutyle.

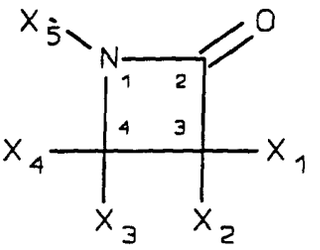
6. Dérivé de taxane selon la revendication 2, dans lequel

R_{14} et R_{14a} sont hydrogène ;
R_{10} est hydrogène ou avec R_{10a}, il forme un oxo ;
R_{10a} est hydrogène, hydroxy, $-OCOR_{29}$, ou avec R_{10}, il forme un oxo ;
R_9 est hydrogène ou avec R_{9a}, il forme un oxo ;
R_{9a} est hydrogène, acyloxy ou avec R_9, il forme un oxo ;
R_7 est hydrogène ;
R_{7a} est hydrogène, halogène ou $-OR_{28}$;

R_6 et R_{6a} sont hydrogène ;
R_5 est hydrogène ;
R_{5a} avec R_4 et les atomes de carbone auxquels ils sont liés forment un cycle oxétane ;
R_{4a} est hydroxy, ou -$OCOR_{30}$;
R_2 est hydroxy, ou -$OCOR_{31}$;
R_{2a} est hydrogène ;
R_1 est hydrogène ou hydroxy ;
R_{28} est hydrogène, acyle, ou un groupe de protection hydroxy ; et
R_{29}, R_{30} et R_{31} sont, indépendamment, hydrogène, alkyle, alcényle, alcynyle, aryle monocyclique ou hétéroaryle monocyclique.

7. Composition pharmaceutique qui contient le dérivé de taxane selon la revendication 1 et un ou plusieurs diluants ou adjuvants acceptables du point de vue pharmacologique, inertes ou physiologiquement actifs.

8. β-lactame de formule :



dans laquelle

X_1 est -OX_6, -SX_7, ou -NX_8X_9 ;
X_2 est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle ;
X_3 est cycloalkyle, éventuellement substitué ;
X_4 est hydrogène ;
X_5 est -COX_{10}, -$COOX_{10}$, -$COSX_{10}$, -$CONX_8X_{10}$, ou -SO_2X_{11} ;
X_6 est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle, un groupe de protection hydroxy, ou un groupe fonctionnel qui accroît la solubilité dans l'eau du dérivé de taxane ;
X_7 est alkyle, alcényle, alcynyle, aryle, hétéroaryle, ou un groupe de protection sulfhydryle ;
X_8 est hydrogène, alkyle, alcényle, alcynyle, aryle, hétéroaryle ; ou alkyle, alcényle, alcynyle, aryle ou hétéroaryle hétérosubstitué ;
X_9 est un groupe de protection amino ;
X_{10} est alkyle, alcényle, alcynyle, aryle, hétéroaryle ; ou alkyle, alcényle, alcynyle, aryle ou hétéroaryle hétérosubstitué ;
X_{11} est alkyle, alcényle, alcynyle, aryle, hétéroaryle, -OX_{10}, ou -NX_8X_{14} ;
X_{14} est hydrogène, alkyle, alcényle, alcynyle, aryle, ou hétéroaryle ; et
l'alkyle peut être substitué, à chaîne droite, ramifiée ou cyclique.