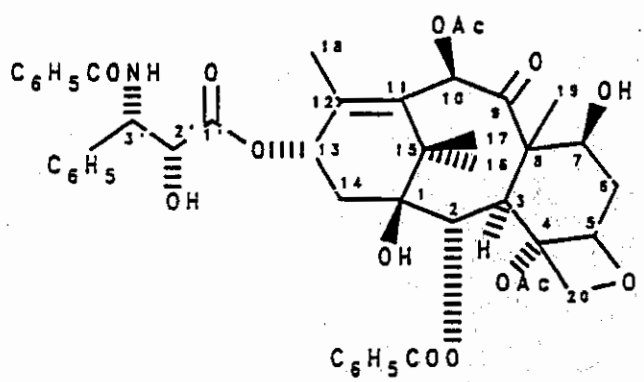
NOVEL TAXANES HAVING A FURYL OR THIENYL SUBSTITUTED SIDE-CHAIN AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

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

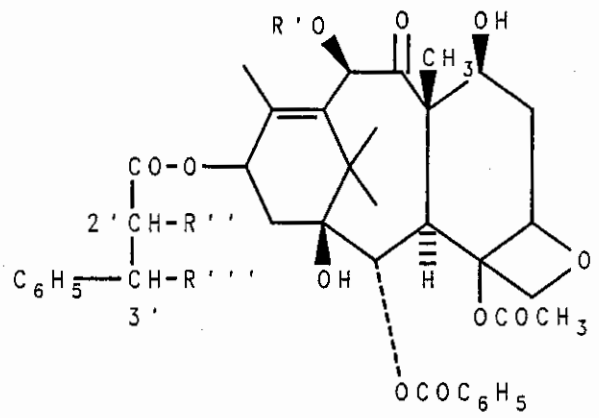
The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following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



(1)

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

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



(2)

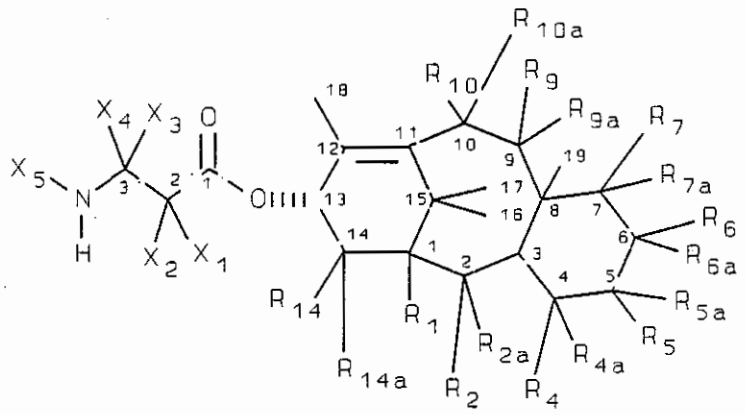
R′ represents hydrogen or acetyl and one of R′′ and R′′′ represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula **(2)** in which R′ is hydrogen, R′′ is hydroxy, R′′′ is tert-butoxycarbonylamino having the 2′R,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

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

SUMMARY OF THE INVENTION

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

Briefly, therefore, the present invention is directed to taxane derivatives having a C13 side chain which includes a furyl or thienyl 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 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, acyl or hetero-substituted alkyl, alkenyl, alkynyl, aryl or heteroaryl, provided, however, that X_3 and X_4 are not both acyl;

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_{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_{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_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_{7a} is hydrogen or together with R_7 forms an oxo;

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

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_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_4 is hydrogen, together with R_{4a} forms an oxo, 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_2 is hydrogen, hydroxy, or $-OCOR_{31}$;

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

R_1 is hydrogen, hydroxy, protected hydroxy;

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; and at least one of X_3, X_4 and X_{10} is furyl or thienyl.

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

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein "Ar" means aryl; "Ph" means phenyl; "Ac" means acetyl; "Et" means ethyl; "R" means alkyl unless otherwise defined; "Bu" means butyl; "Pr" means propyl; "TES" means triethylsilyl; "TMS" means trimethylsilyl; "TPAP" means tetrapropylammonium perruthenate; "DMAP" means p-dimethylamino pyridine; "DMF" means dimethylformamide; "LDA" means lithium diisopropylamide; "LAH" means lithium aluminum hydride; "Red-Al" means sodium bis(2-methoxyethoxy) aluminum hydride; FAR means 2-chloro-1,1,2-trifluorotriethylamine; "AIBN" means azo-(bis)-isobutyronitrile; "10-DAB" means 10-desacetylbaccatin III; 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 methoxy-methyl, thioesters, or thiocarbonates; "amine protecting group" includes, but is not limited to, carbamates, for example,

2,2,2-trichloroethylcarbamate or tertbutyl-carbamate; and "hydroxy protecting group" includes, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, 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 have from three to six carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates optionally substituted on the ring with one or more C_{1-6} alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine protecting groups may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981.

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

The alkenyl groups described herein, either alone or with the various substituents defined

hereinabove are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

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

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

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

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

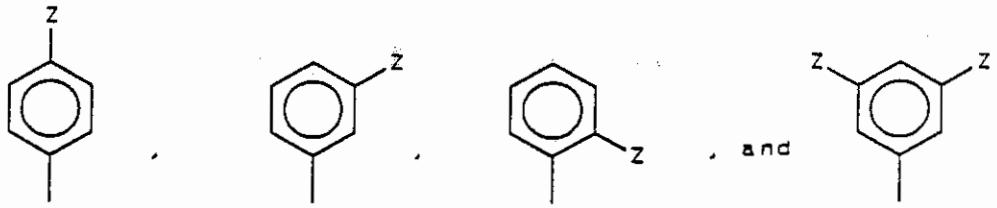
The substituents of the substituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups and moieties described herein, may be alkyl, alkenyl, alkynyl, aryl, heteroaryl and/or may contain nitrogen, oxygen, sulfur, halogens and include, for example, lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, nitro, amino, and keto.

In accordance with the present invention, it has been discovered that compounds corresponding to structural formula 3 show remarkable properties, in

vitro, and are valuable antileukemia and antitumor agents. Their biological activity has been determined in vitro, using tubulin assays according to the method of Parness et al., J. Cell Biology, 91: 479-487 (1981) and human cancer cell lines, and is comparable to that exhibited by taxol and taxotere.

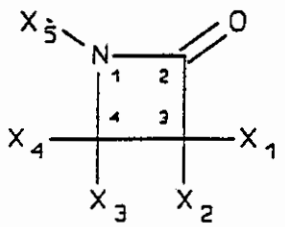
In one embodiment of the present invention, the substituents of the cyclic nucleus of the taxane (other than the C13 substituent) correspond to the substituents present on baccatin III or 10-DAB. That is, R_{10} is hydrogen, R_{10a} is hydroxy or acetoxy, R_9 and R_{9a} together form an oxo, R_{7a} is hydrogen, R_7 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_{2a} is hydrogen, R_2 is benzoyloxy, and R_1 is hydroxy and the C13 side-chain substituents (X_1-X_{11}) are as previously defined. Preferably, X_1 is -OH, X_2 is hydrogen, X_3 is furyl or thienyl, 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 furyl or thienyl, X_4 is hydrogen, X_5 is $-COX_{10}$ or $-COOX_{10}$ and X_{10} is furyl or thienyl, alkyl substituted furyl or thienyl, tert-, iso- or n-butoxy, ethoxy, iso- or n-propoxy, cyclohexyloxy, allyloxy, crotyloxy, 1,3-diethoxy-2-propoxy, 2-methoxyethoxy, neopentyloxy, $PhCH_2O$-, $-NPh_2$, -NHnPr, -NHPh, or -NHEt.

In other embodiments of the present invention, 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_2 may be hydroxy or $-OCOR_{31}$ wherein R_{31} is hydrogen, alkyl or selected from the group comprising



and Z is alkyl, hydroxy, alkoxy, halogen, or trifluoromethyl. R_{9a} may be hydrogen and R_9 may be hydrogen or hydroxy, R_{10a} may be hydrogen and R_{10} may be acetoxy or other acyloxy or R_{10} and R_{10a} may be oxo, X_3 may be selected from isobutenyl, isopropyl, cyclopropyl, n-butyl, t-butyl, cyclobutyl, amyl cyclohexyl, furyl, thienyl, pyridyl or the substituted derivatives thereof, X_5 may be $-COX_{10}$ or $-COOX_{10}$ and X_{10} may be selected from furyl, thienyl, alkyl substituted furyl or thienyl, pyridyl, tert-, iso- or n-butyl, ethyl, iso- or n-propyl, cyclopropyl, cyclohexyl, allyl, crotyl, 1,3-diethoxy-2-propyl, 2-methoxyethyl, amyl, neopentyl, $PhCH_2O-$, $-NPh_2$, -NHnPr, -NHPh, and -NHEt.

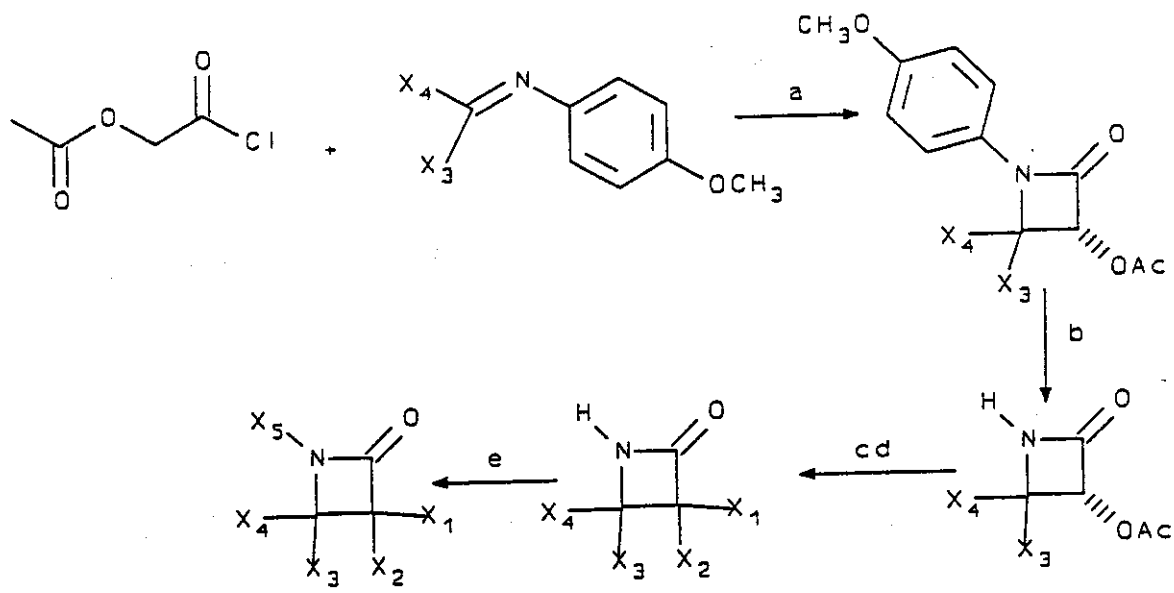
Taxanes having the general formula 3 may be obtained by reacting a ß-lactam with metal alkoxides having the taxane tricyclic or tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a ß-amido ester substituent at C-13. The ß-lactams have the following structural formula:



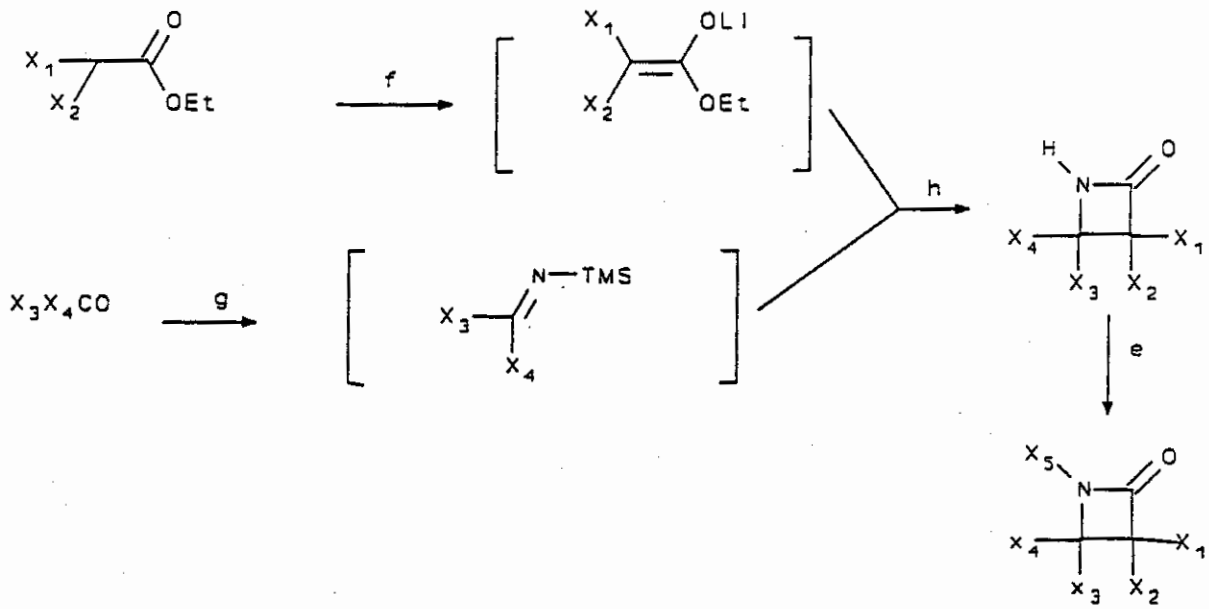
wherein X_1 - X_5 are as previously above.

The ß-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, 0°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.

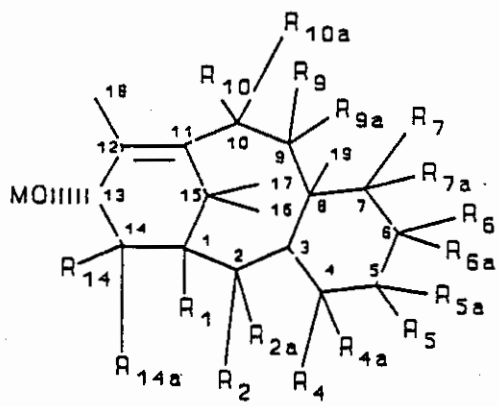
The starting materials are readily available. In scheme A, α-acetoxy acetyl chloride is prepared from glycolic acid, and, in the presence of a tertiary amine, it cyclocondenses with imines prepared from aldehydes and p-methoxyaniline to give 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-ones. The p-methoxyphenyl group can be readily removed through oxidation with ceric ammonium nitrate, and the acyloxy group can be hydrolyzed under

standard conditions familiar to those experienced in the art to provide 3-hydroxy-4-arylazetidin-2-ones. In Scheme B, ethyl-α-triethylsilyloxyacetate is readily prepared from glycolic acid.

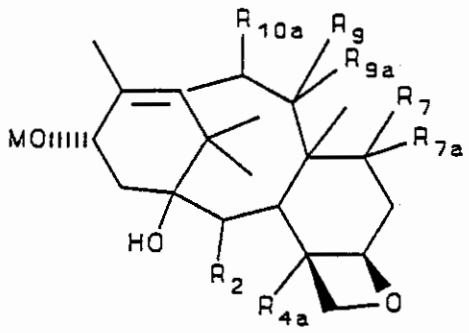
In Schemes A and B, X_1 is preferably $-OX_5$ and X_5 is a hydroxy protecting group. Protecting groups such as 2-methoxypropyl ("MOP"), 1-ethoxyethyl ("EE") are preferred, but a variety of other standard protecting groups such as the triethylsilyl group or other trialkyl (or aryl) silyl groups may be used. As noted above, additional hydroxy protecting groups and the synthesis thereof may be found in "Protective groups in Organic Synthesis" by T.W. Greene, John Wiley & Sons, 1981.

The racemic ß-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 ß-amido ester side chain is attached has the advantage of being highly diastereo-selective, thus permitting the use of a racemic mixture of side chain precursor.

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



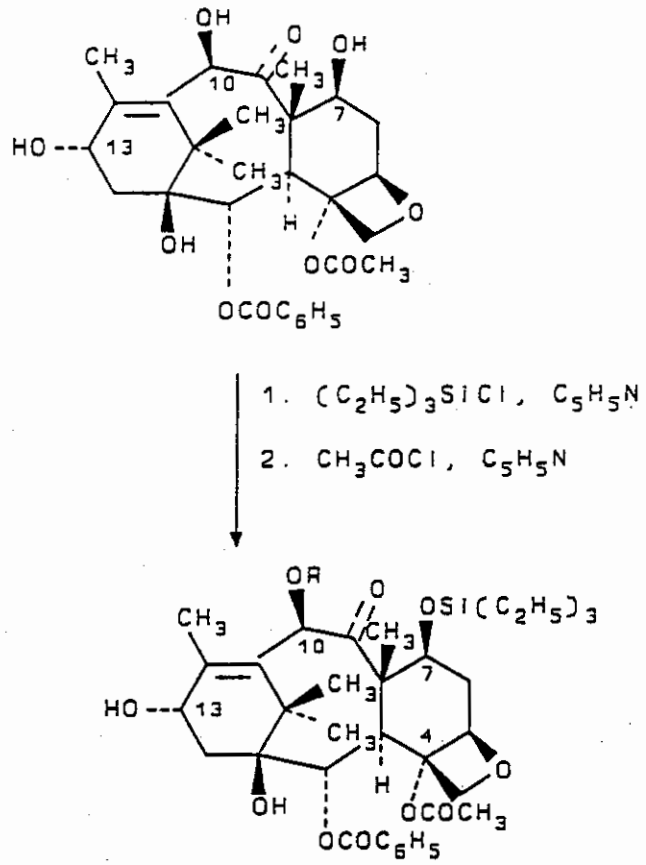
wherein R_1 - R_{14a} are as previously defined and M comprises ammonium or is a metal optionally selected from the group comprising Group IA, Group IIA and transition metals, and preferably, Li, Mg, Na, K or Ti. Most preferably, the alkoxide has the tetracyclic taxane nucleus and corresponds to the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



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

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

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

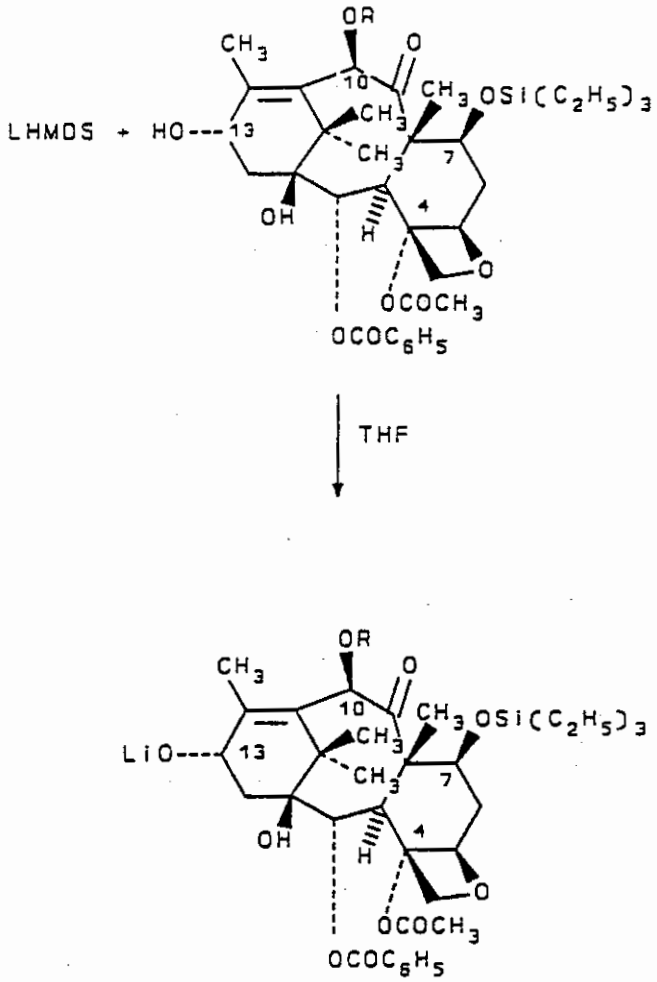


(4) a, R=H
b, R=$COCH_3$

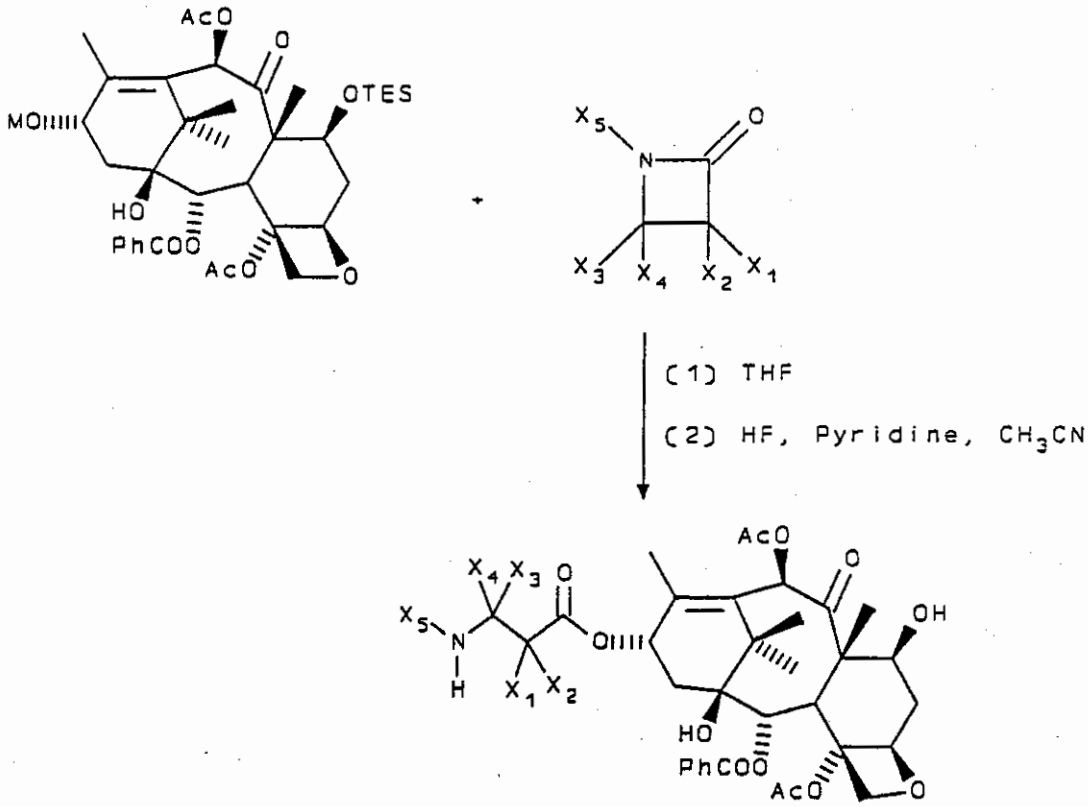
Under what is reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(C_2H_5)_3SiCl$ at 23°C under an argon atmosphere for 20 hours in the presence of 50 ml of pyridine/mmol of 10-deacetyl baccatin III to provide 7-triethylsilyl-10-deacetyl baccatin III **(4a)** as a reaction product in 84-86% yield after purification. The reaction product may then optionally be acetylated with 5 equivalents of CH_3COCl and 25 mL of pyridine/mmol of **4a** at 0 °C under an argon atmosphere for 48 hours to provide 86% yield of 7-O-triethylsilyl baccatin III **(4b)**. Greene, et al. in JACS 110, 5917 at 5918 (1988).

The 7-protected baccatin III **(4b)** is reacted with an organometallic compound such as LHMDS in a solvent such as tetrahydrofuran (THF), to form the metal

alkoxide 13-O-lithium-7-O-triethylsilyl baccatin III as shown in the following reaction scheme:



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



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

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

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

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

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

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

The water solubility of compounds of formula (3) may be improved by modification of the C2′ and/or C7 substituents. For instance, water solubility may be increased if X_1 is $-OX_6$ and R_7 is $-OR_{28}$, and X_6 and R_{28} are independently hydrogen or $-COGCOR^1$ wherein:

G is ethylene, propylene, -CH=CH-, 1,2-cyclohexylene, or 1,2-phenylene;

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

R^2 = hydrogen or methyl;

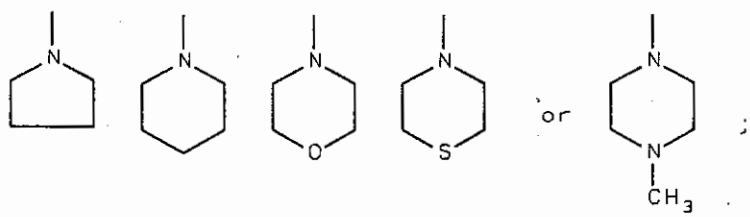
R^3 = $(CH_2)_nNR^6R^7$ or $(CH_2)_nN^{\oplus}R^6R^7R^8X^{\ominus}$;

n = 1 to 3;

R^4 = hydrogen or lower alkyl containing 1 to 4 carbons;

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

R^6 and R^7 = independently selected from lower alkyl containing 1 or 2 carbons or benzyl, or R^6 and R^7 together with the nitrogen atom of NR^6R^7 forms one of the following rings



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

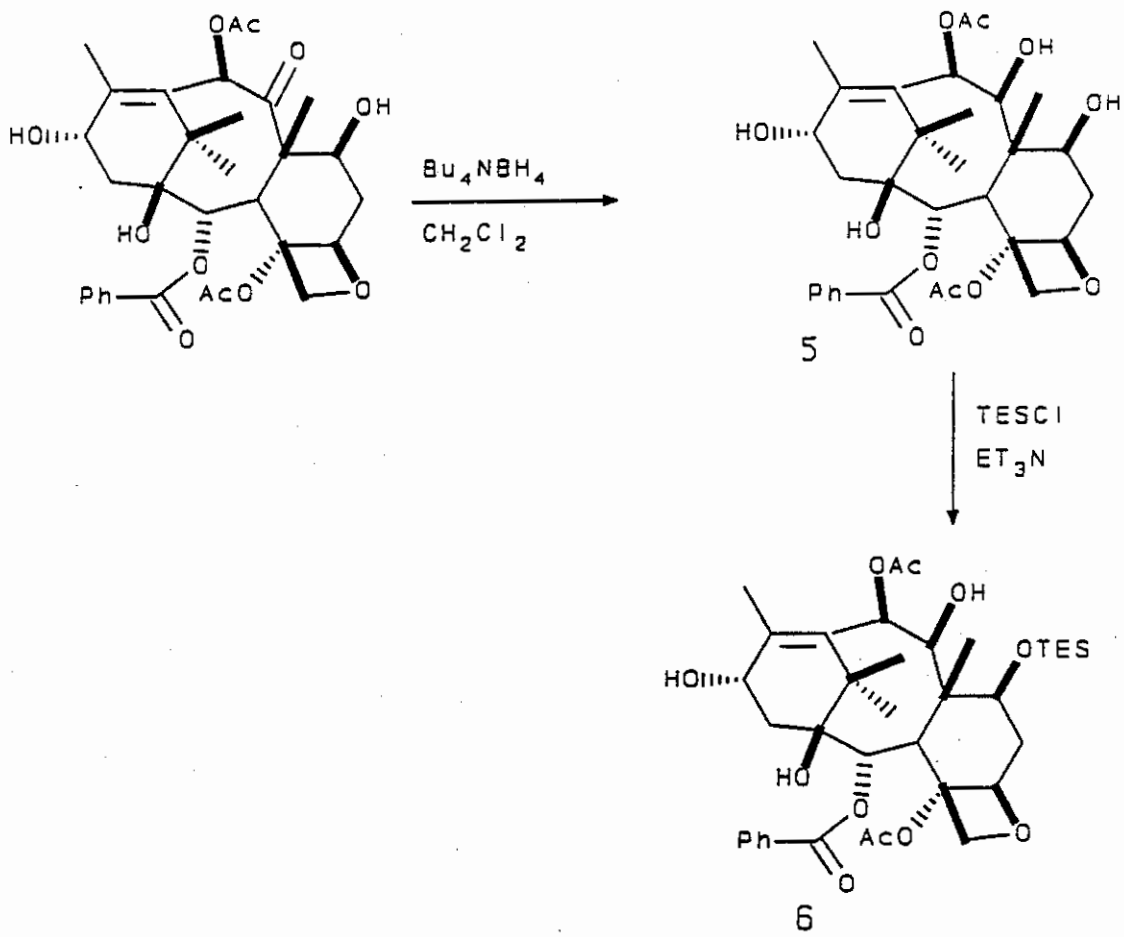
The preparation of compounds in which X_1 or X_2 is $-COGCOR^1$ is set forth in Hangwitz U.S. Patent 4,942,184 which is incorporated herein by reference.

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

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

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-9ß-hydroxy derivative 6 as elsewhere described herein. Removal of the remaining protecting groups thus yields 9ß-hydroxy-desoxo taxol or other 9β-hydroxytetracylic taxane having a C13 side chain.

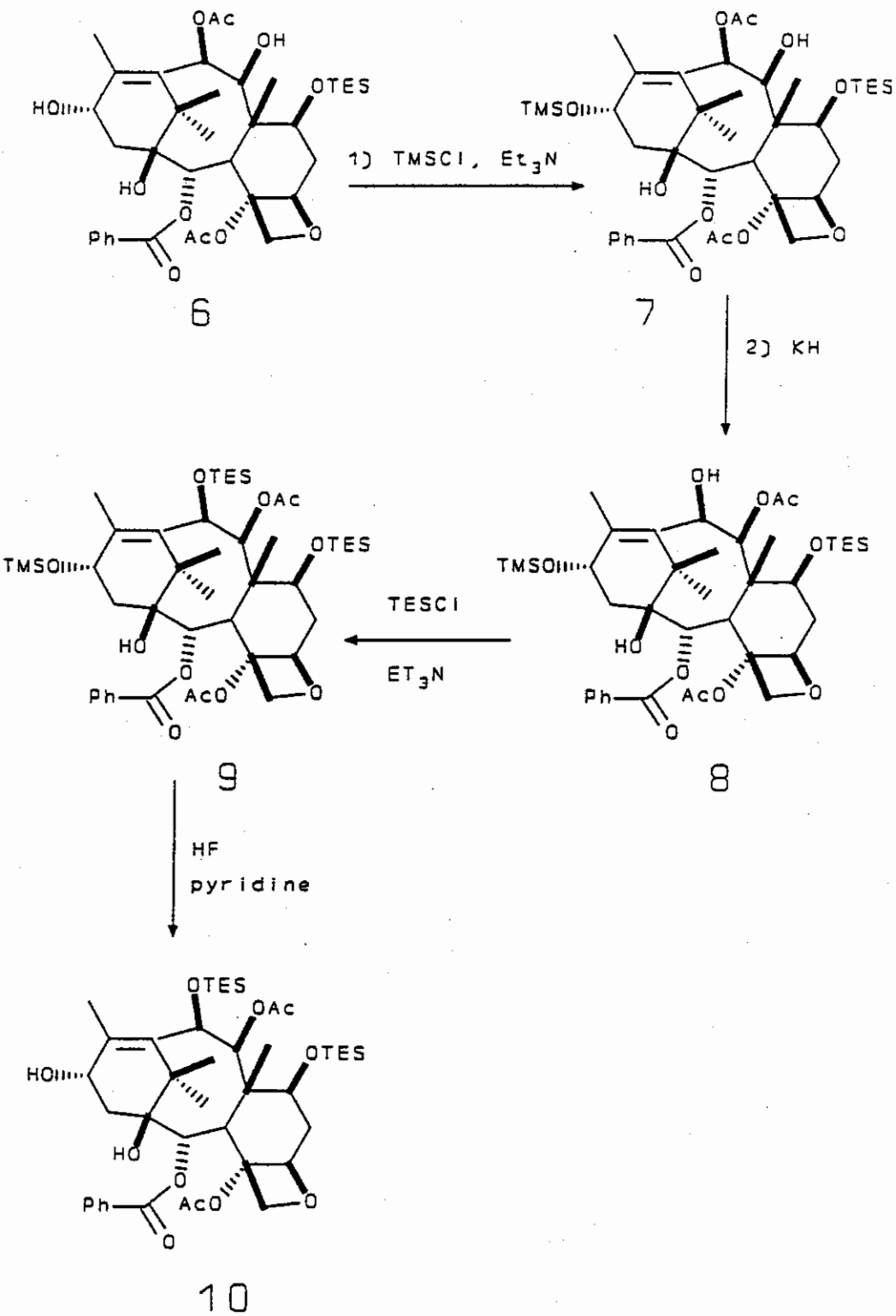
REACTION SCHEME 1



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

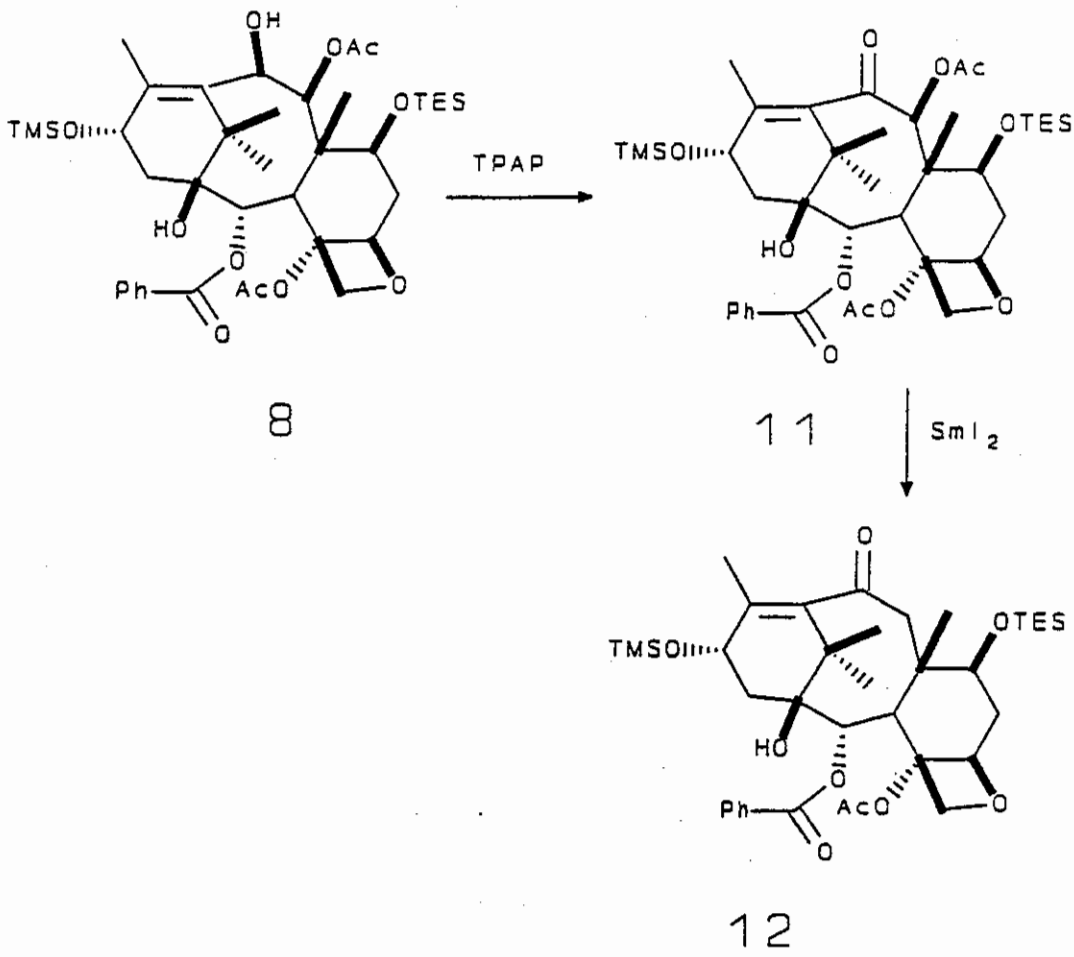
derivative **10** to which a suitable side chain may be attached as described above.

REACTION SCHEME 2



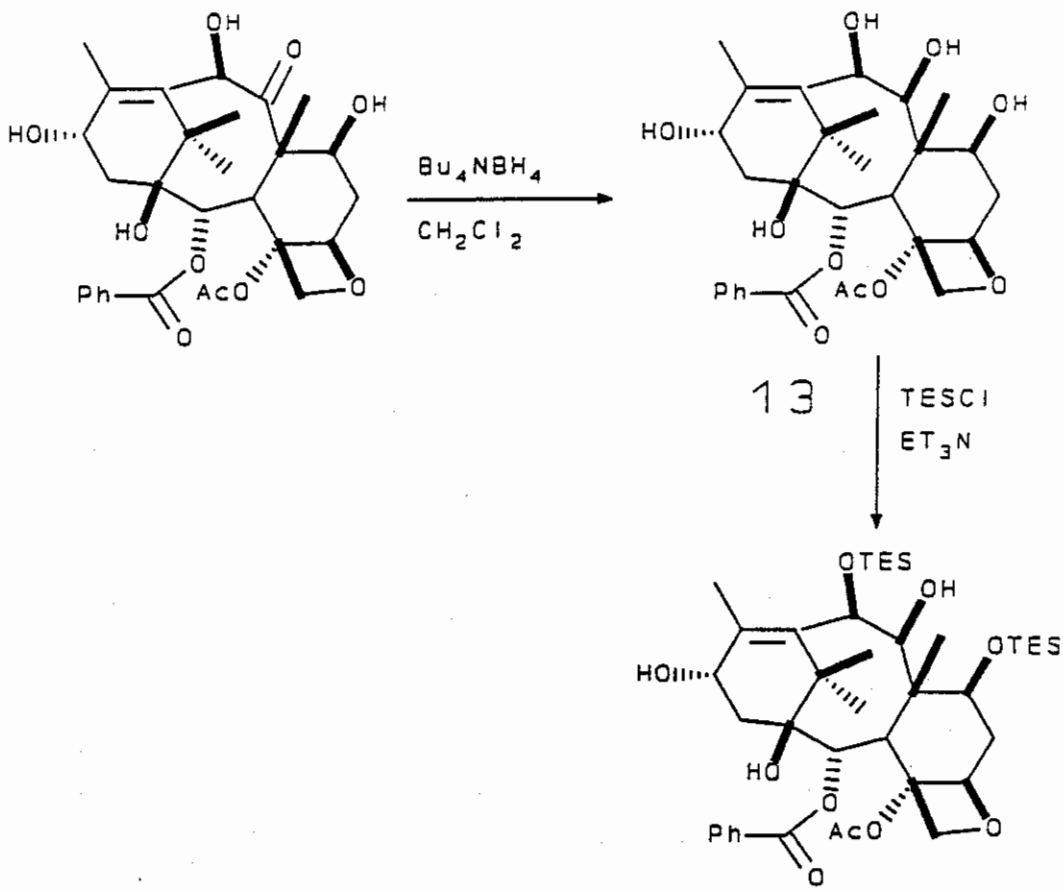
As shown in Reaction Scheme 3, 10-oxo derivative **11** can be provided by oxidation of 10-desacetyl derivative **8**. Thereafter, the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-acetoxy-10-oxo-taxol or other 9-acetoxy-10-oxotetracylic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

REACTION SCHEME 3



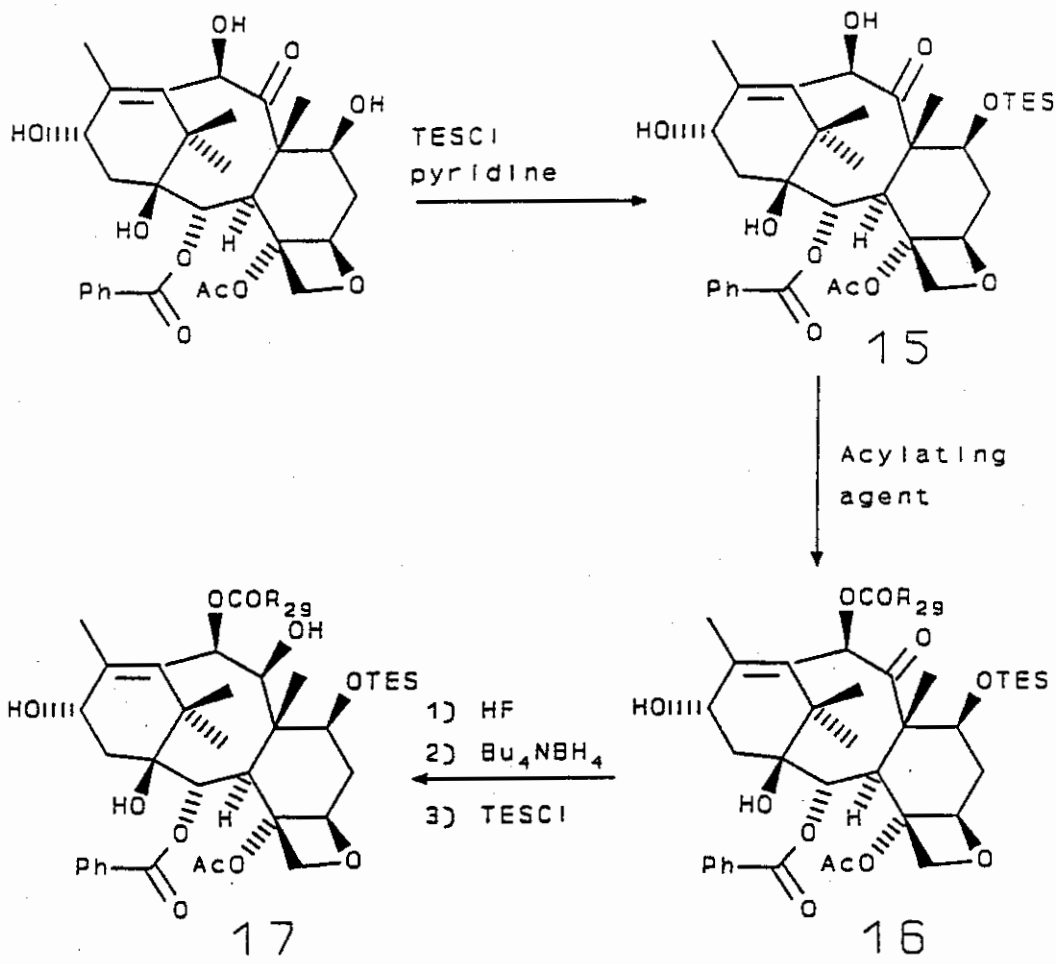
Reaction Scheme 4 illustrates a reaction in which 10-DAB is reduced to yield pentaol **13**. The C7 and C10 hydroxyl groups of pentaol **13** can then be selectively protected with the triethylsilyl or another protecting group to produce triol **14** to which a C13 side chain can be attached as described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

REACTION SCHEME 4



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 9ß-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



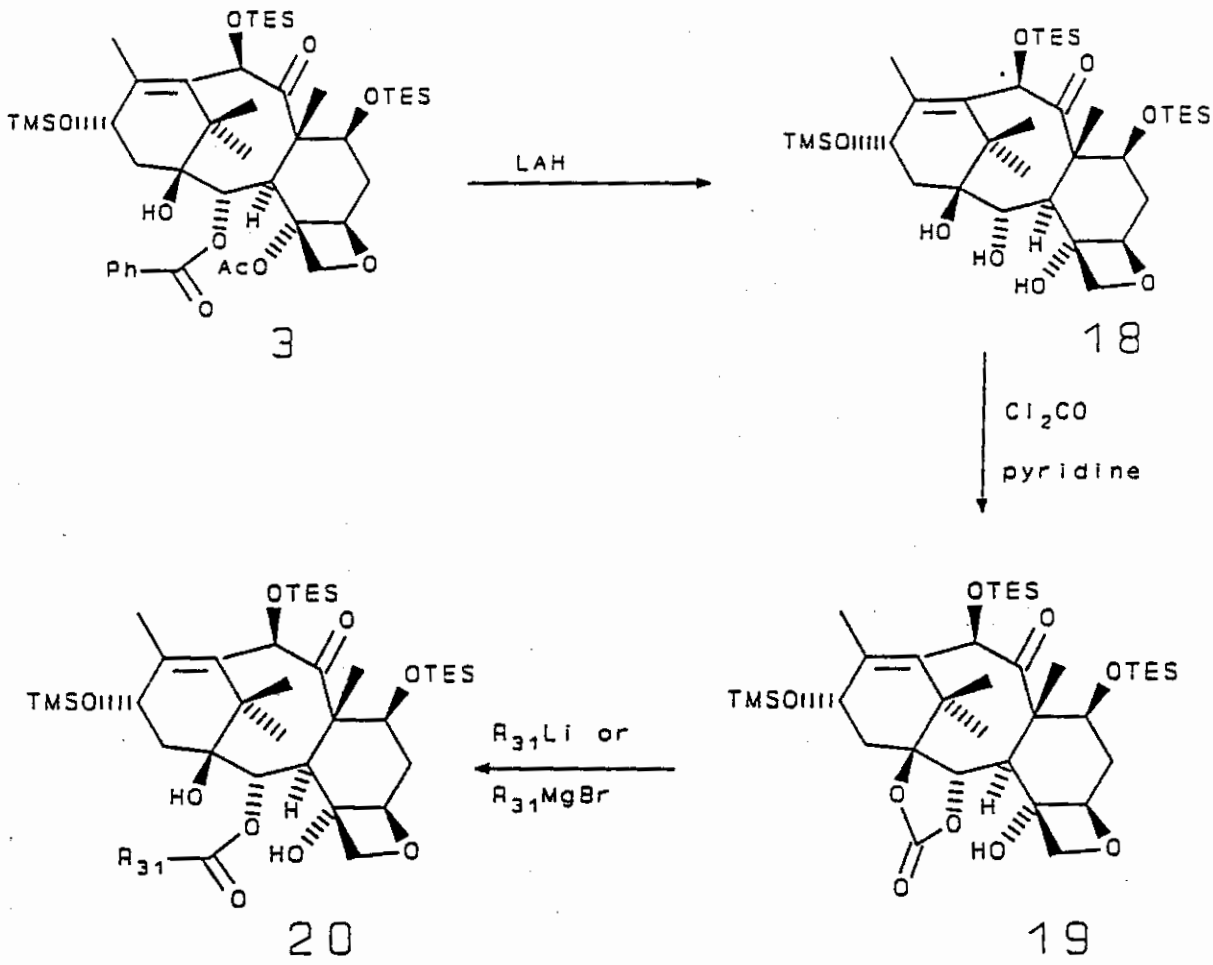
Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter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

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. Derivatives of the baccatin III and 10-DAB analogs having different substituents at C10 and at least one other position, for instance C1, C2, C4, C7, C9 and C13, can then be prepared by carrying out any of the other reactions described herein and any others which are within the level of skill in the art.

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).

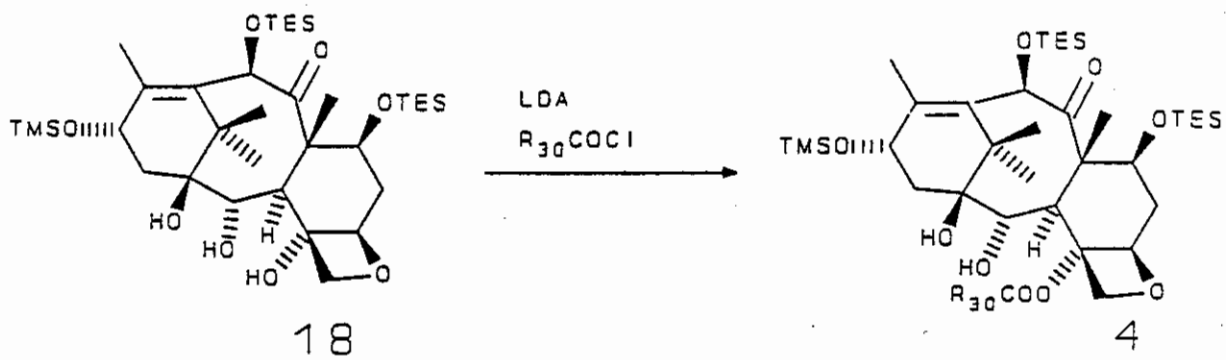
Scheme 6



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

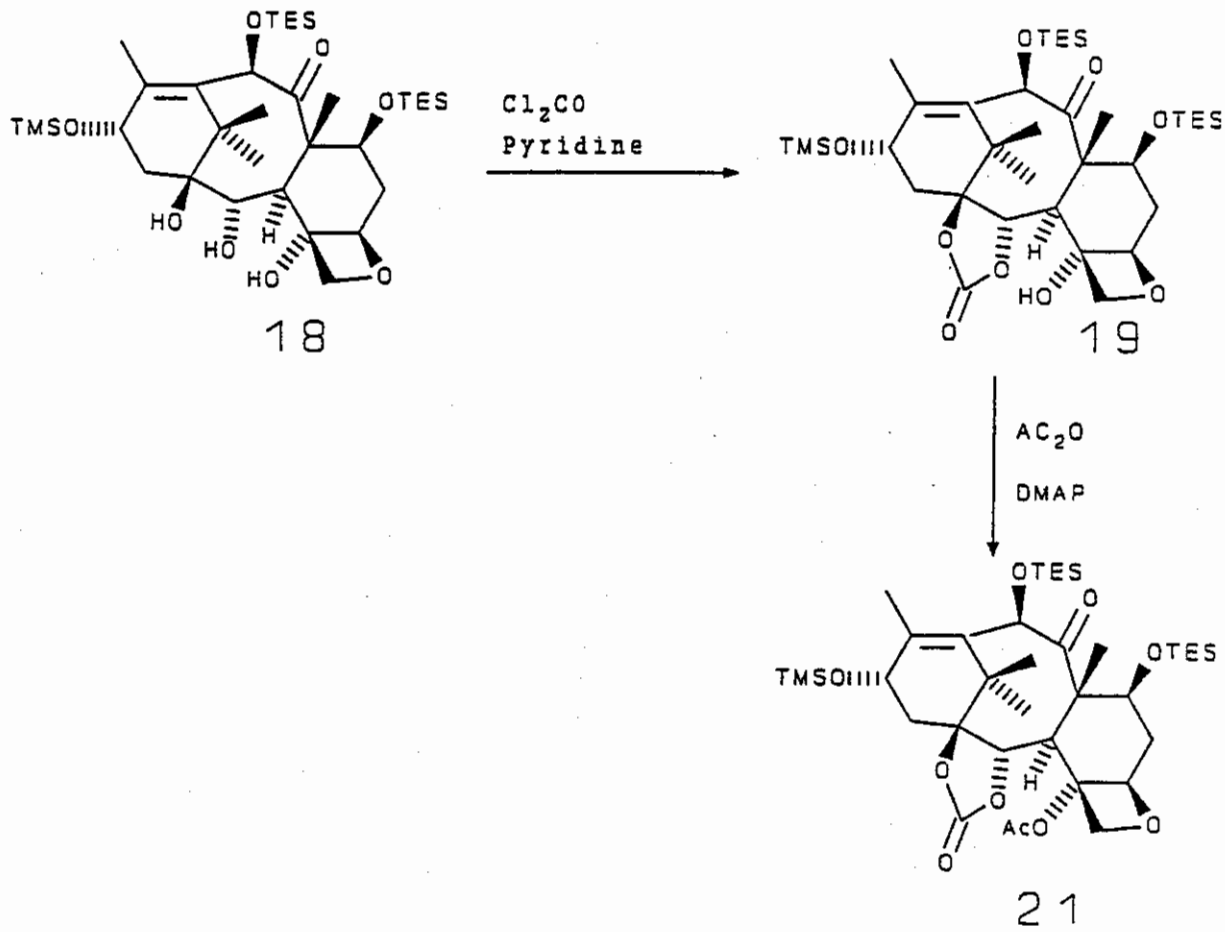
Triol **18** can also readily be converted to the 1,2 carbonate **19**. Acetylation of carbonate **19** under vigorous standard conditions provides carbonate **21** as described in Reaction Scheme 8; addition of alkyllithiums or Grignard reagents to carbonate **19** provides the C2 ester having a free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

Scheme 7



18 4

Scheme 8

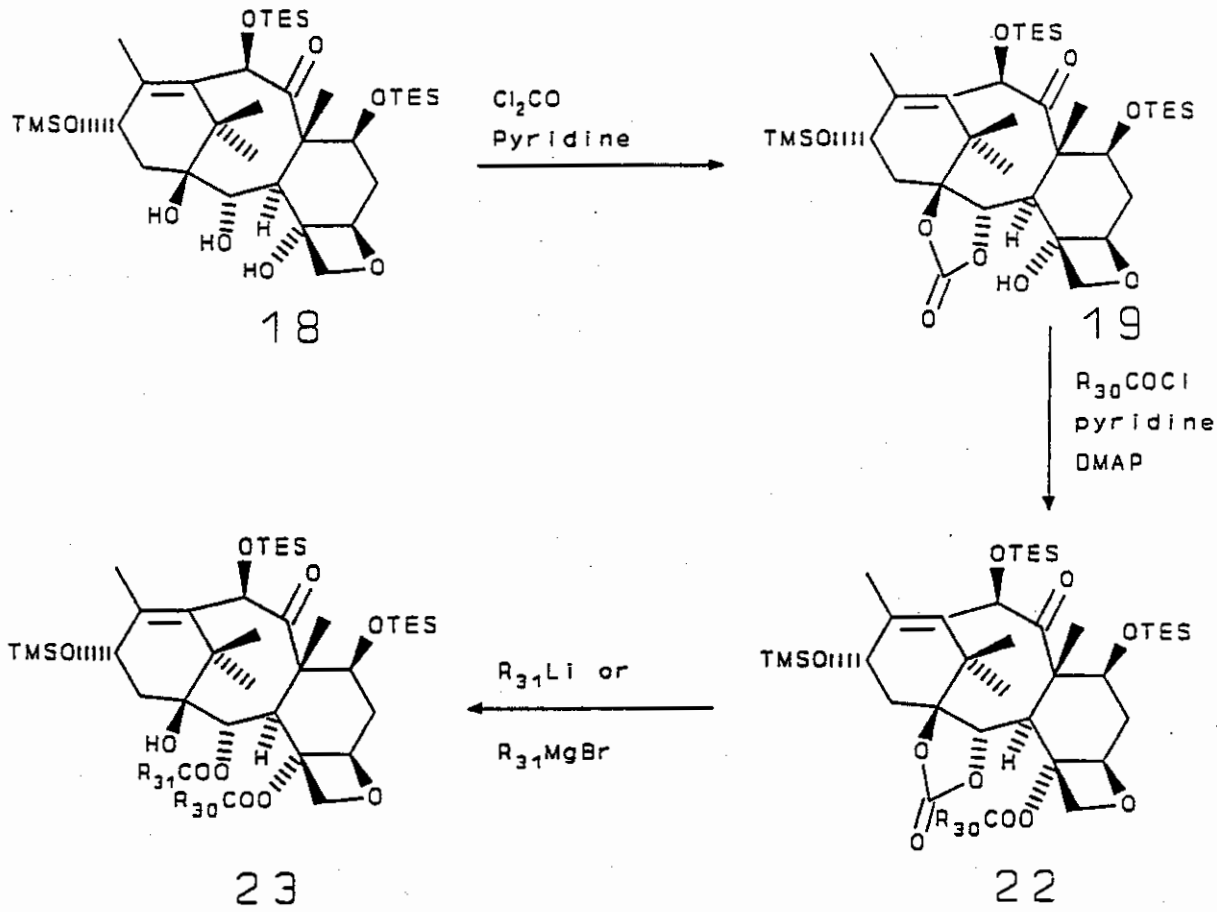


18 19 21

As set forth in Reaction Scheme 9, other C4 substituents can be provided by reacting carbonate **19** with an acid chloride and a tertiary amine to yield

carbonate **22** which is then reacted with alkyllithiums or Grignard reagents to provide 10-DAB derivatives having new substituents at C2.

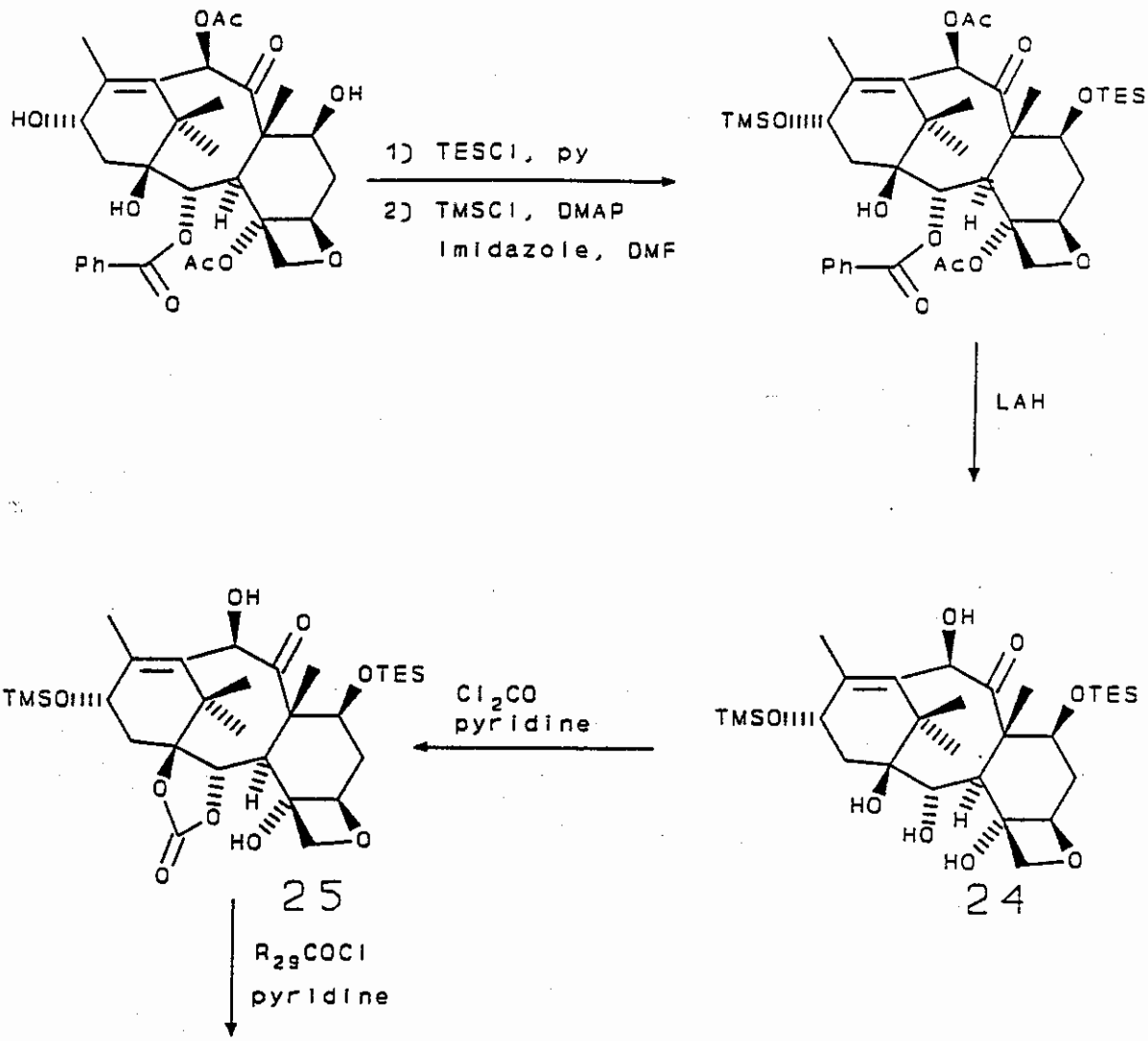
Scheme 9

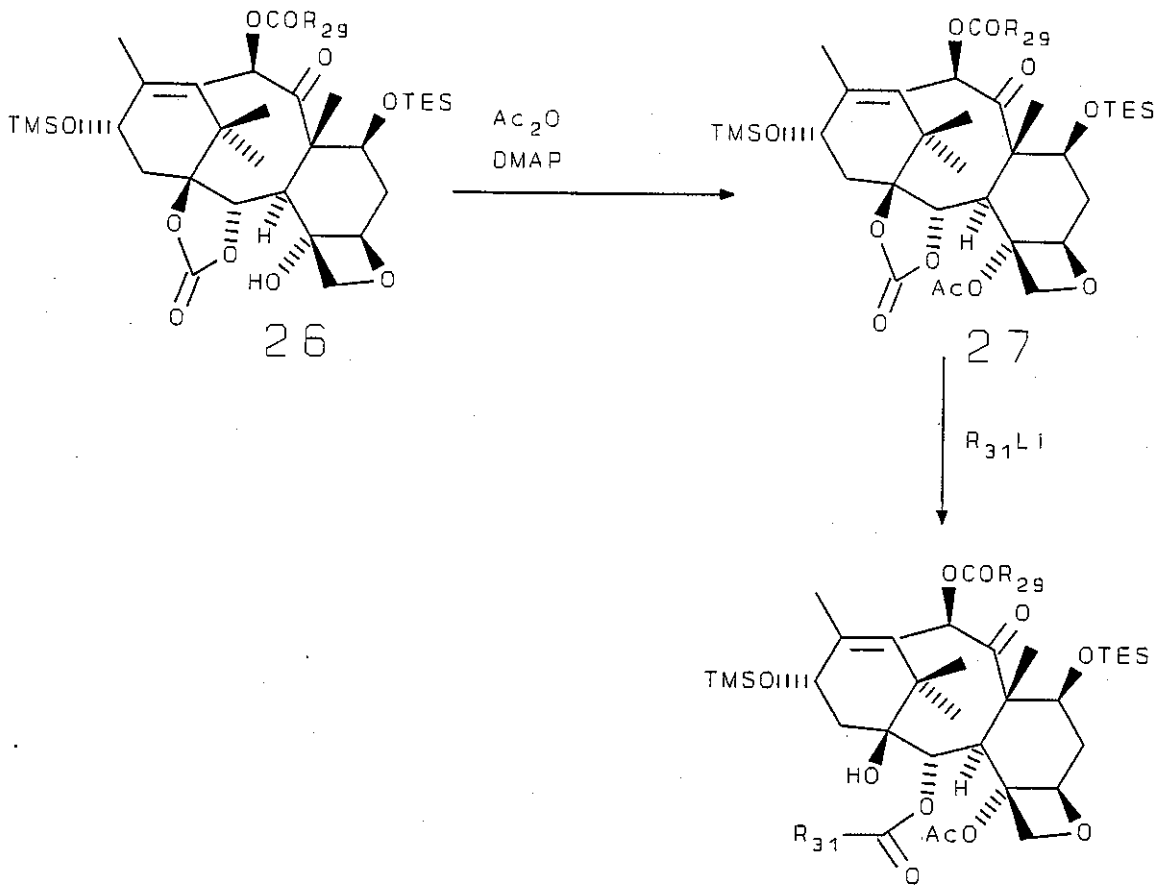


Alternatively, baccatin III may be used as a starting material and reacted as shown in Reaction Scheme 10. After being protected at C7 and C13, baccatin III is reduced with LAH to produce 1,2,4,10 tetraol **24**. Tetraol **24** is converted to carbonate **25** using Cl_2CO and pyridine, and carbonate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

provides carbonate **27** which is then reacted with alkyl lithiums to provide the baccatin III derivatives having new substituents at C2 and C10.

Scheme 10



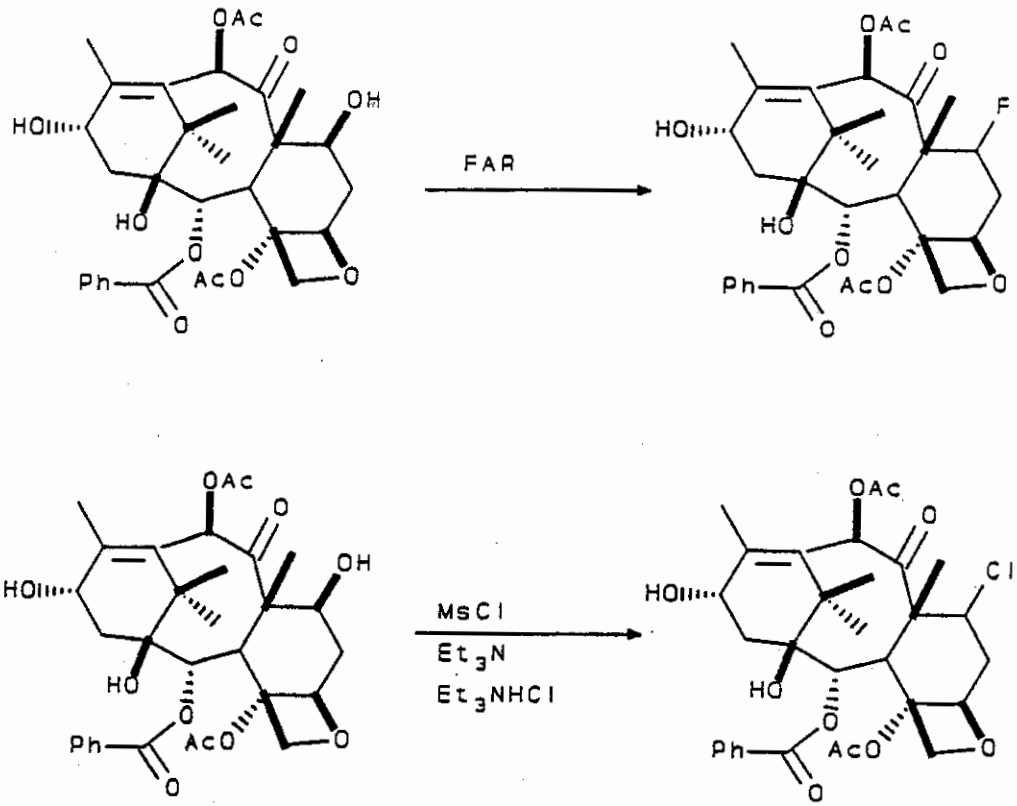


26

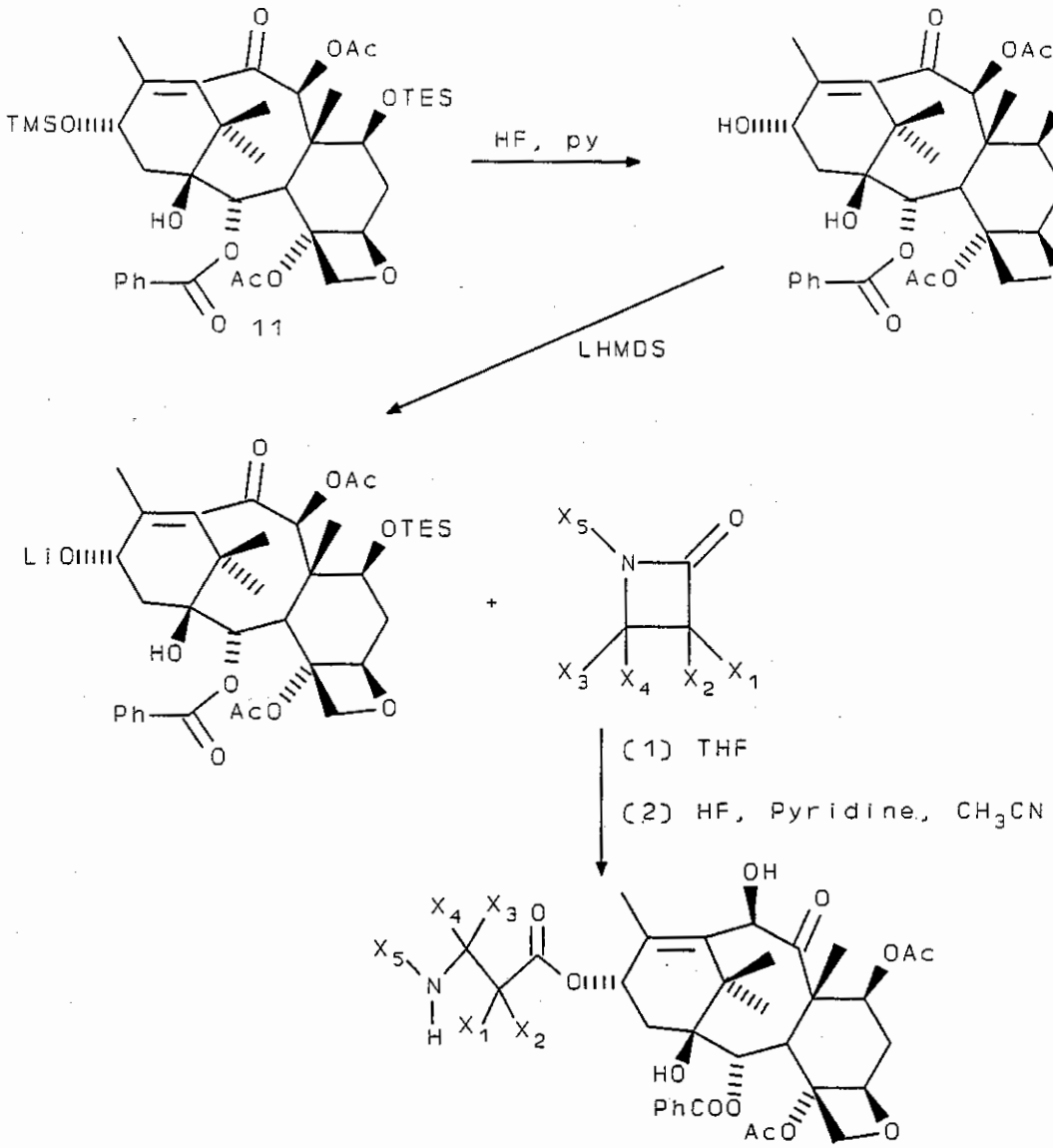
27

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.

REACTION SCHEME 12



REACTION SCHEME 12a

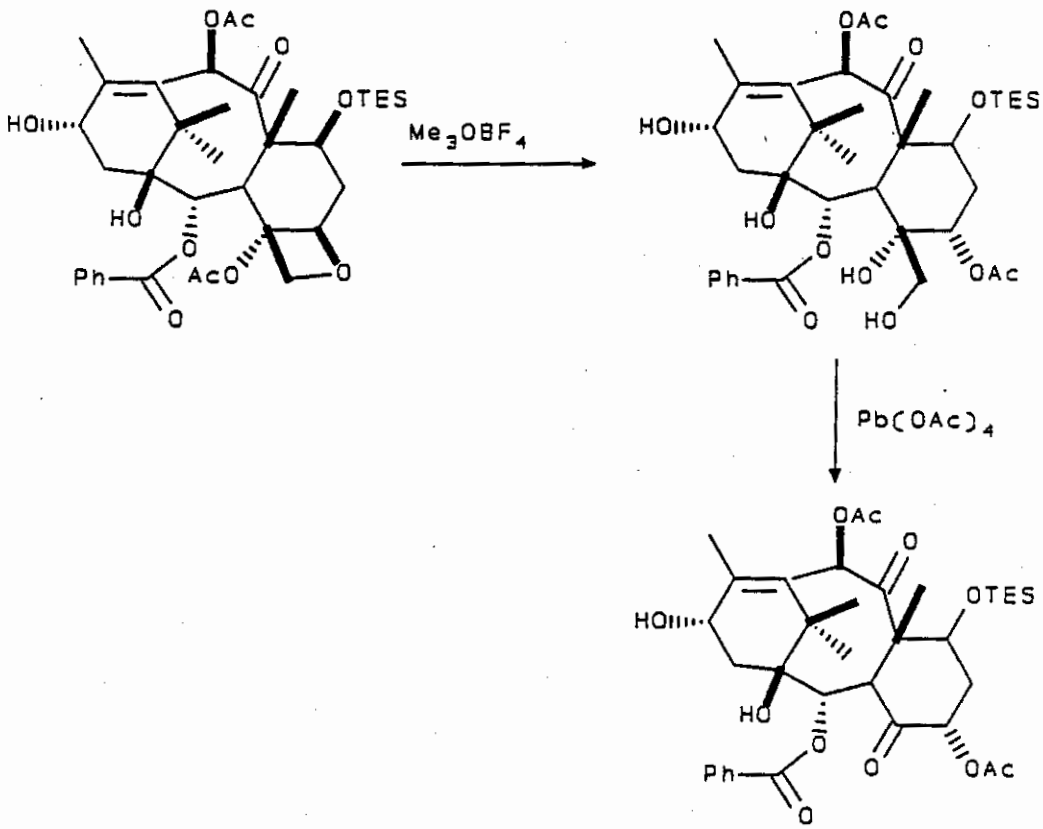


As shown in Reaction Scheme 12, Baccatin III may be converted into 7-fluoro baccatin III by treatment with FAR at room temperature in THF solution. Other baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-chloro baccatin III can be prepared by treatment of baccatin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

methylene chloride solution containing an excess of triethylamine hydro-chloride.

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

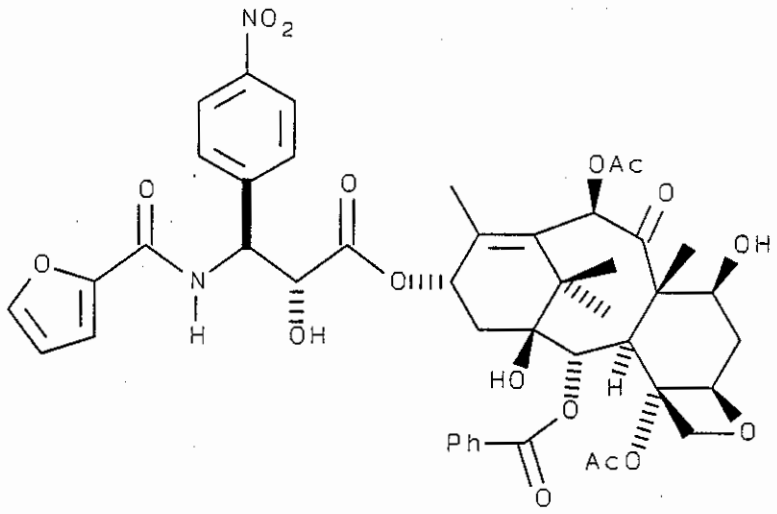


Recently a hydroxylated taxane (14-hydroxy-10-deacetylbaccatin III) has been discovered in an extract of yew needles (C&EN, p 36-37, April 12, 1993).

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, C7, C9, C10 and C13 substituents.

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

EXAMPLE 1



(26-4)

Preparation of N-debenzoyl-N-(2-furoyl)-3'-desphenyl-3'-(4-nitrophenyl) taxol.

To a solution of 7-triethylsilyl baccatin III (200 mg, 0.286 mmol) in 2 mL of THF at -45 °C was added dropwise 0.174 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45 °C, a solution of cis-1-(furoyl)-3-triethylsilyloxy-4-(4-nitrophenyl)azetidin-2-one (596 mg, 1.43 mmol) in 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 320 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-(furoyl)-3'-

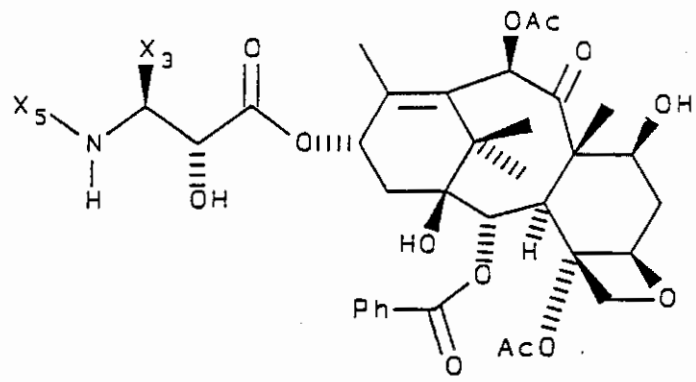
desphenyl-3'-(4-nitrophenyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 320 mg (0.286 mmol) of the mixture obtained from the previous reaction in 18 mL of acetonitrile and 0.93 mL of pyridine at 0 °C was added 2.8 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 254 mg of material which was purified by flash chromatography to give 187 mg (74%)N-debenzoyl-N-(furoyl)-3'-desphenyl-3'-(4-nitrophenyl) taxol, which was recrystallized from methanol/water.

m.p.184-185 °C; $[\alpha]^{25}_{Na}$-60.0° (c 0.006, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J = 8.79 Hz, 2H, Ar-NO_2), 8.12 (d, J=7.2 Hz, 2H, benzoate ortho), 7.68 (d, J=8.8 Hz 2H, benzamide ortho), 7.7-7.47 (m, 6 H, aromatic), 7.3 (d, J = 9.3 Hz, 1H, NH), 7.02(d, J=3.3 Hz, 1H, furyl), 6.48(dd, J=3.3 Hz, 1.65 Hz, 1H, furyl), 6.27 (s, 1H Hz, H10), 6.26 (dd, J = 8.5, 8.5 Hz, 1H, H13), 5.87 (dd, J = 8.8, 1.65 Hz, 1H, H3'), 5.65 (d, J = 6.6 Hz, 1H, H2β), 4.93 (d, J = 8.2 Hz, 1H, H5), 4.79 (dd, J = 2.7, 1.4 Hz, 1H, H2'), 4.38 (m, 1H, H7), 4.29 (d, J = 8.4 Hz, 1H, H20α), 4.18 (d, J = 8.4 Hz, 1H, H20β), 3.97 (d, J=3.3 Hz, 1H, 2'OH), 3.79 (d, J = 6.6 Hz, 1H, H3), 2.5 (m, 1H, H6α), 2.4(m, 1H, 7OH), 2.38 (s, 3H, 4Ac), 2.27 (m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.88 (m, 1H, H6β), 1.81 (br s, 3H, Me18), 1.78 (s, 1H, 1OH), 1.68 (s, 3H, Me19), 1.21 (s, 3H, Me17), 1.13(s, 3H, Me16).

EXAMPLE 2-43



Using the procedure set forth in Example 1 (except for the substituents of azetidin-2-one and the amounts of the reactants) a series of compounds were prepared having the structure shown above in which X_3 and X_{10} are as shown in the following table. The structures were confirmed by NMR.

TABLE 1

Example	Compound #	X_3	X_5
2	30-2	phenyl	2-furoyl
3	31-1	phenyl	2-thienoyl
4	31-4	2-furyl	t-butoxycarbonyl
5	32-1	2-furyl	ethoxycarbonyl
6	33-1	2-thienyl	cyclohexyloxycarbonyl
7	34-2	2-thienyl	t-butoxycarbonyl
8	34-3	2-thienyl	2-thienoyl
9	34-4	2-thienyl	2-furoyl
10	35-1	2-thienyl	n-butoxycarbonyl
11	35-2	2-thienyl	allyloxycarbonyl
12	35-4	2-thienyl	diethylcarbamyl

Example	Compound #	X_3	X_5
13	36-3	2-furyl	4-methylbenzoyl
14	37-1	2-furyl	isobutoxycarbonyl
15	37-2	2-furyl	butoxycarbonyl
16	37-3	2-furyl	diethylcarbamyl
17	37-4	2-furyl	isopropoxycarbonyl
18	38-1	2-furyl	allyloxycarbonyl
19	38-2	2-furyl	benzyloxycarbonyl
20	38-3	2-furyl	diphenylcarbamyl
21	39-3	2-thienyl	ethoxycarbonyl
22	39-4	2-thienyl	3-butynyloxycarbonyl
23	40-1	2-thienyl	crotyloxycarbonyl
24	40-2	2-thienyl	1,3-diethoxy-2-propoxycarbonyl
25	40-3	2-thienyl	methoxyethoxycarbonyl
26	40-4	2-thienyl	neopentyloxycarbonyl
27	41-1	2-thienyl	isopropoxycarbonyl
28	41-2	2-thienyl	isobutoxycarbonyl
29	42-3	2-furyl	2-thienylcarbonyl
30	42-4	2-furyl	2-methoxyethoxy-carbonyl
31	43-1	2-furyl	crotyloxycarbonyl
32	43-2	2-furyl	neopentyloxycarbonyl
33	43-3	2-furyl	cyclohexyloxycarbonyl
34	43-4	2-furyl	1,3-diethoxy-2-propyloxycarbonyl
35	44-1	2-furyl	3-butynyloxycarbonyl
36	44-2	2-furyl	N-methyl-N-phenyl-carbamoyl

Example	Compound #	X_3	X_5
37	44-3	2-furyl	N,N-dimethylcarbamoyl
38	44-4	2-furyl	4-morpholinocarbonyl
39	45-1	2-furyl	2-furoyl
40	46-2	2-furyl	N-n-propylcarbamoyl
41	46-3	2-furyl	N-phenylcarbamoyl
42	46-4	2-thienyl	N-phenylcarbamoyl
43	47-1	2-thienyl	N-n-propylcarbamoyl

EXAMPLE 44

The compounds of the preceding examples were in in vitro cytotoxicity activity against human colon carcinoma cells HCT-116 and HCT-116/VM46. The HCT116/VM cells are cells that have been selected for teniposide resistance and express the multidrug resistance phenotype, including resistance to taxol. Cytotoxicity was assessed in HCT116 and HCT VM46 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. The results are presented in Table 2 and are compared to taxol and taxotere. Lower numbers indicate greater activity.

TABLE 2

Example	Compound	IC_{50} HCT 116	HCT VM46
1	26-4	.002	.883
2	30-2	.003	.300
3	31-1	.002	.202
4	31-4	.001	.004
5	32-1	.001	.032
6	33-1	.001	<.017
7	34-2	.001	<.018
8	34-3	.001	.042
		.001	<.023
9	34-4	.001	.051
		.001	.034
10	35-1	.001	<.025
		.002	.016
11	35-2	.004	.022
12	35-4	.019	.581
13	36-3	.006	.150
14	37-1	.004	.022
		.001	.033
		<.001	.018
15	37-2	.005	<.021
		.001	.030
		.001	.021
16	37-3	.016	1.10
17	37-4	.005	<.015
		.004	.008
		.001	.008
18	38-1	.002	<.031
19	38-2	.003	.062
20	38-3	>.078	>7.8
21	39-3	.001	.019
22	39-4	.002	.163
23	40-1	.001	.011
24	40-2	.030	.597
25	40-3	.006	.251
26	40-4	.022	.090
27	41-1	.001	.008
28	41-2	.002	.023
29	42-3	.002	.034
30	42-4	.002	.216
31	43-1	.001	.010
32	43-2	.001	.009
33	43-3	.001	.009

TABLE 2 CONTINUED

		IC_{50}	
		HCT	HCT
Example	Compound	116	VM46
34	43-4	.005	.432
35	44-1	.001	.175
36	44-2	.018	.785
37	44-3	.010	2.11
38	44-4	.020	3.60
39	45-1	.001	.041
40	46-2	.013	.781
41	46-3	.008	.831
42	46-4	.005	.902
43	47-1	.008	.810
	taxol	.004	.536
		.002	.313
	taxotere	.007	.246
		.003	.189

EXAMPLES 45-57

Using the procedures set forth in Example 1 (except for the substituents of azetidin-2-one and the protected taxane and the amounts of the reactants) a series of compounds were prepared having the following structure in which X_3, X_{10}, R_2, R_{7a}, R_{9a}, and R_{10a} are as shown in Table 3. Unless otherwise indicated, R_2 is benzoyl, R_{7a} is hydroxy, R_{9a} is keto, and R_{10a} is acetoxy. The structures were confirmed by NMR.

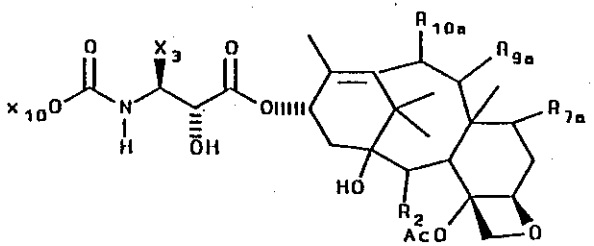


TABLE 3

Example	Compound	X_3	X_{10}	R_{10a}	R_{9a}	R_{7a}	R_2
45	68-3	2-thienyl	t-butyl	H			
46	69-2	2-furyl	t-butyl	H			
47	75-1	2-thienyl	t-butyl	keto	H		
48	72-2	2-thienyl	t-butyl	H		H	
49	72-3	2-furyl	t-butyl	H		H	
50	69-3	2-thienyl	t-butyl	HO-		acetoxy	
51	69-4	2-furyl	t-butyl	HO-		acetoxy	
52	71-1	2-thienyl	t-butyl			H	
53	71-3	2-furyl	t-butyl			H	
54	70-2	2-thienyl	t-butyl	-OH	-OH		
55	70-3	2-furyl	t-butyl	-OH	-OH		
56	73-2	3-furyl	t-butyl				
57	73-3	3-thienyl	t-butyl				

EXAMPLE 58

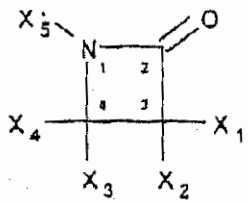
The taxanes of the Examples 45-57 were evaluated using the procedures set forth in Example 44. All compounds had an IC_{50} of less than 0.1, indicating that they are cytotoxically active.

In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

WHAT I CLAIM IS:

1. A ß-lactam corresponding to 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 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, acyl or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl, provided, however, that X_3 and X_4 are not both acyl;

X_5 is $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, 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, hetero-aryl, $-OX_{10}$, or $-NX_8X_{14}$;

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

at least one of X_3, X_4 and X_{10} is furyl or thienyl.

2. The β-lactam of claim 1 wherein X_1 is $-OX_6$, and X_6 is hydroxy protecting group.

3. The β-lactam of claim 1 wherein X_1 is $-OX_6$, and X_6 is triethylsilyl, 1-ethoxyethyl or 2,2,2-trichloroethoxymethyl.

4. The β-lactam of claim 1 wherein X_1 is $-OX_6$; X_2 is hydrogen or alkyl; and X_6 is hydroxy protecting group.

5. The β-lactam of claim 1 wherein X_1 is $-OX_6$; X_2 is hydrogen or alkyl; X_3 is hydrogen; and X_6 is hydroxy protecting group.

6. The β-lactam of claim 1 wherein X_3 is hydrogen.

7. The β-lactam of claim 1 wherein X_2 and X_3 are independently selected from hydrogen and alkyl.

8. The β-lactam of claim 1 wherein X_1 is $-OX_6$; X_2 is selected from hydrogen and alkyl; X_3 is hydrogen; X_4 is furyl or thienyl; X_5 is $-COOX_{10}$, or $-CONX_8X_{10}$; X_8 is

hydroxy protecting group; and X_8 and X_{10} are as defined in claim 1.

9. The β-lactam of claim 1 wherein X_6 is alkenyl, alkynyl, aryl, heteroaryl or hydroxy protecting group.

10. The β-lactam of claim 1 wherein X_2 is alkenyl, alkynyl, aryl, or heteroaryl.

11. The β-lactam of claim 1 wherein X_1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and X_4 is alkyl, alkynyl, or heteroaryl.