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(54) Titre : PROCEDE D'OBTENTION DE 10-DESACETOXYBACCATIN III
(54) Title: PROCESS FOR THE PREPARATION OF 10-DESACETOXYBACCATIN III

(57) Abrégé/Abstract:
A process for abstracting a C10 hydroxy, acyloxy or sulfonyloxy substituent from a taxane in which the C10 hydroxy, acyloxy or sulfonyloxy substituted taxane is reacted with samarium diiodide.

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(54) Title: PROCESS FOR THE PREPARATION OF 10-DESACETOXYBACCATIN III

(57) Abstract

A process for abstracting a C10 hydroxy, acyloxy or sulfonyloxy substituent from a taxane in which the C10 hydroxy, acyloxy or sulfonyloxy substituted taxane is reacted with samarium diiodide.

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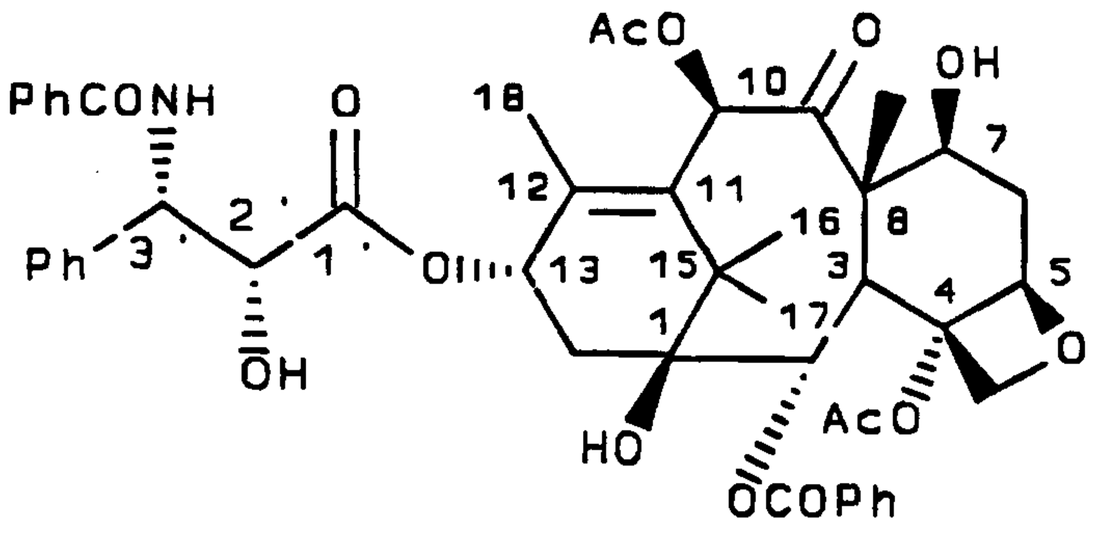
Process for the preparation of 10-desacetoxy baccatin III

BACKGROUND OF THE INVENTION

The present invention relates to a process for preparing 10-desacetoxytaxol, 10-desacetoxybaccatin III and derivatives of 10-desacetoxytaxol and 10-desacetoxy-baccatin III.

Taxol™ is a natural product extracted from the bark of yew trees. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is currently undergoing clinical trials against ovarian, breast and other types of cancer in the United States and France and preliminary results have confirmed it as a most promising chemo-therapeutic agent. The structure of taxol™ and the numbering system conventionally used is shown below; this numbering system is also applicable to compounds used in the process of the present invention.



In Colin U.S. Patent No. 4,814,470, it was reported that a taxol™ derivative, commonly referred to as taxotere™, has an activity significantly greater than taxol. Taxotere™ has the following structure:

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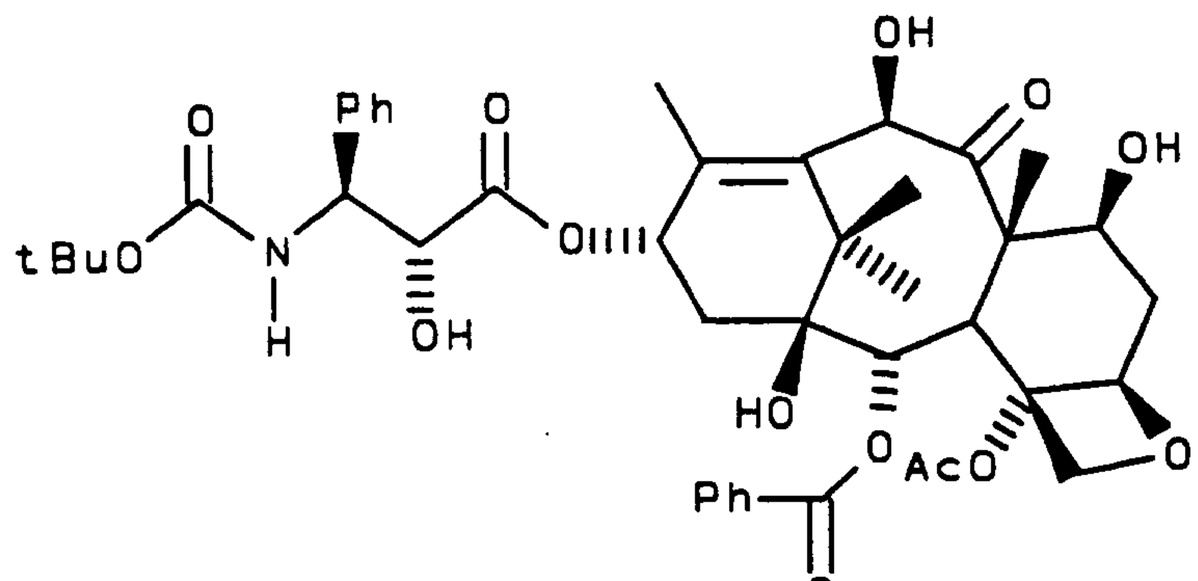

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Although taxol™ and taxotere™ are promising chemotherapeutic agents, a need remains for additional chemotherapeutic agents. The tetracyclic core of taxol™ bears a C10 acetoxy substituent and taxotere™ bears a C10 hydroxy substituent which, if modified, would lead to the preparation of a series of taxol™ analogs. To date, however, the selective manipulation of the C10 acetoxy and hydroxy groups has presented a formidable problem.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of an improved process for preparing 10-desacetoxytaxol, 10-desoxytaxotere, 10-desacetoxybaccatin III and derivatives of 10-desacetoxy-taxol and 10-desacetoxybaccatin III.

Briefly, therefore, the present invention is directed to a process for the preparation of 10-desacetoxy and 10-desoxy taxanes. According to this process, a taxane having a C10 leaving group such as hydroxy, acyloxy or sulfonyloxy is reacted with samarium diiodide. The C10 leaving group is selectively and nearly quantitatively removed from the taxane.

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

DETAILED DESCRIPTION OF THE INVENTION

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-trichloroethyl;

alkenyl carbonates having from two to six carbon atoms such as vinyl and allyl; cycloalkyl carbonates having from three to six carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates optionally substituted on the ring with one or more C_{1-6} alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine protecting groups may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981.

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

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

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

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

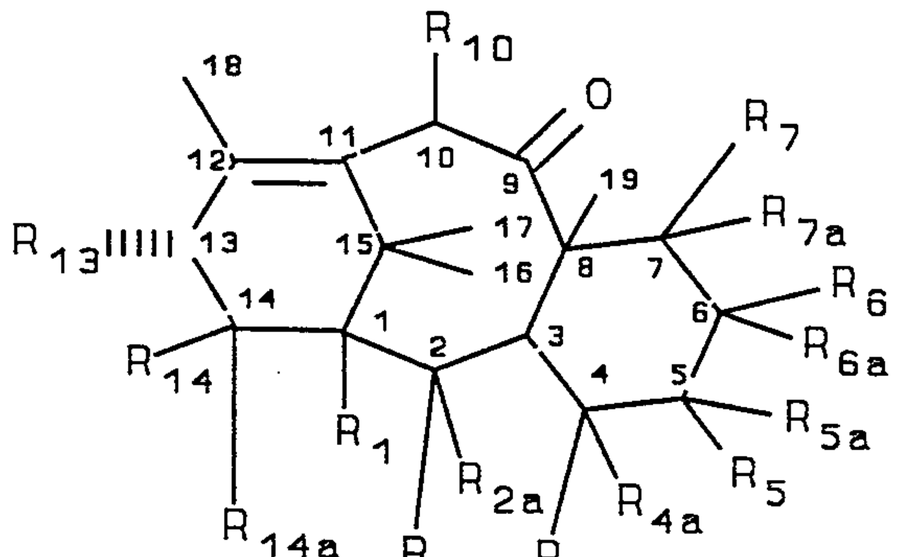
The heteroaryl moieties described herein, either alone or with various substituents, contain from 5 to 15 atoms and include, furyl, thienyl, pyridyl and the like. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido.

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

The sulfonyloxy 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.

Surprisingly, it has been discovered that taxanes possessing C10 hydroxy, acyloxy such as acetoxy or sulfonyloxy substituents may be selectively and nearly quantitatively converted to the corresponding 10-desacetoxy or 10-desoxytaxane. The C10 hydroxy, acyloxy or sulfonyloxy substituted taxane may have a tricyclic or tetracyclic core and corresponds to the formula:



(1)

wherein

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

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

R_{2a} is hydrogen or 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;

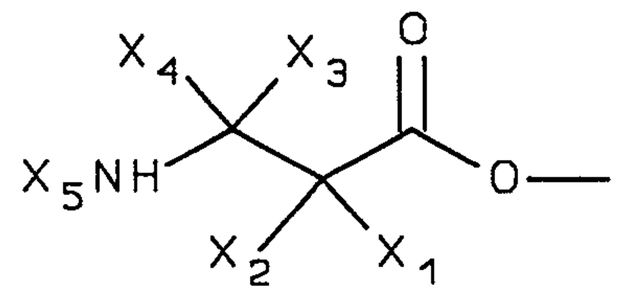
R_{6a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R_6 forms an oxo;

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_{10} is hydroxy, acyloxy or sulfonyloxy;

R_{13} is hydroxy, protected hydroxy or



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;

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

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, or heteroaryl;

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;

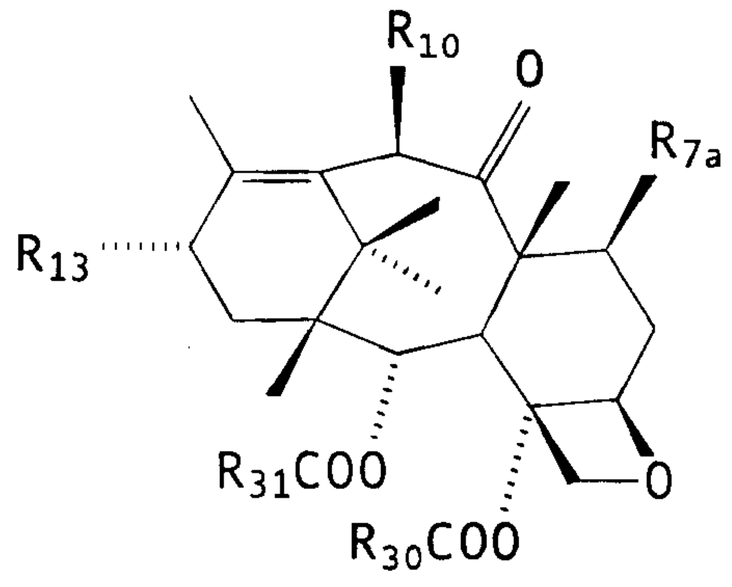
X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl;

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

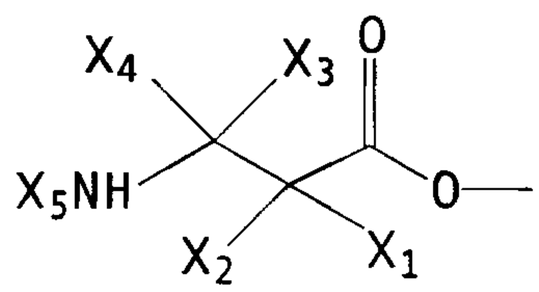
X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl.

According to one aspect of the present invention, there is provided a process for abstracting a C10 hydroxy, acyloxy or sulfonyloxy substituent from a taxane comprising reacting the C10 hydroxy, acyloxy or sulfonyloxy substituted taxane with samarium diiodide.

According to another aspect of the present invention, there is provided the process as described herein wherein the taxane has the formula



wherein R_{7a} is hydrogen, hydroxy, protected hydroxy or $-OR_{28}$; R_{10} is hydroxy or acetoxy; R_{13} is hydroxy, protected hydroxy or



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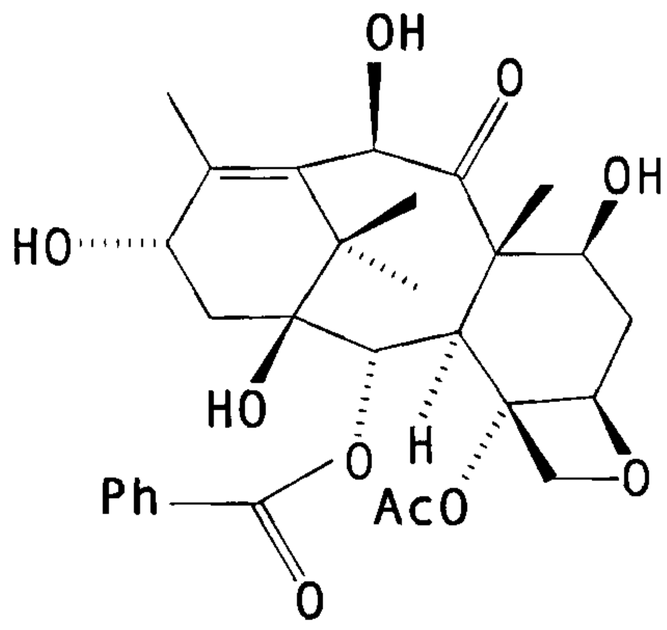
R_{28} is acyl; R_{30} is alkyl; R_{31} is monocyclic aryl; and X_1 - X_5 are as described above.

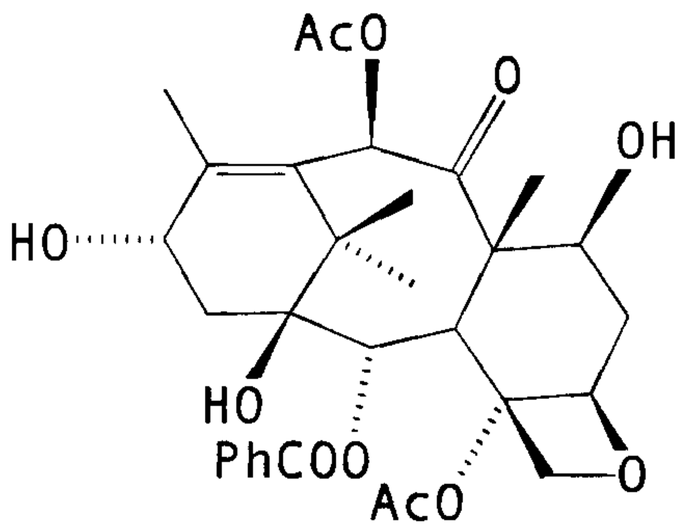
According to still another aspect of the present invention, there is provided the process as described herein wherein the taxane has a C10 hydroxy substituent.

According to yet another aspect of the present invention, there is provided the process as described herein wherein the taxane has a C10 acetoxy substituent.

According to a further aspect of the present invention, there is provided the process as described herein wherein the taxane has the formula

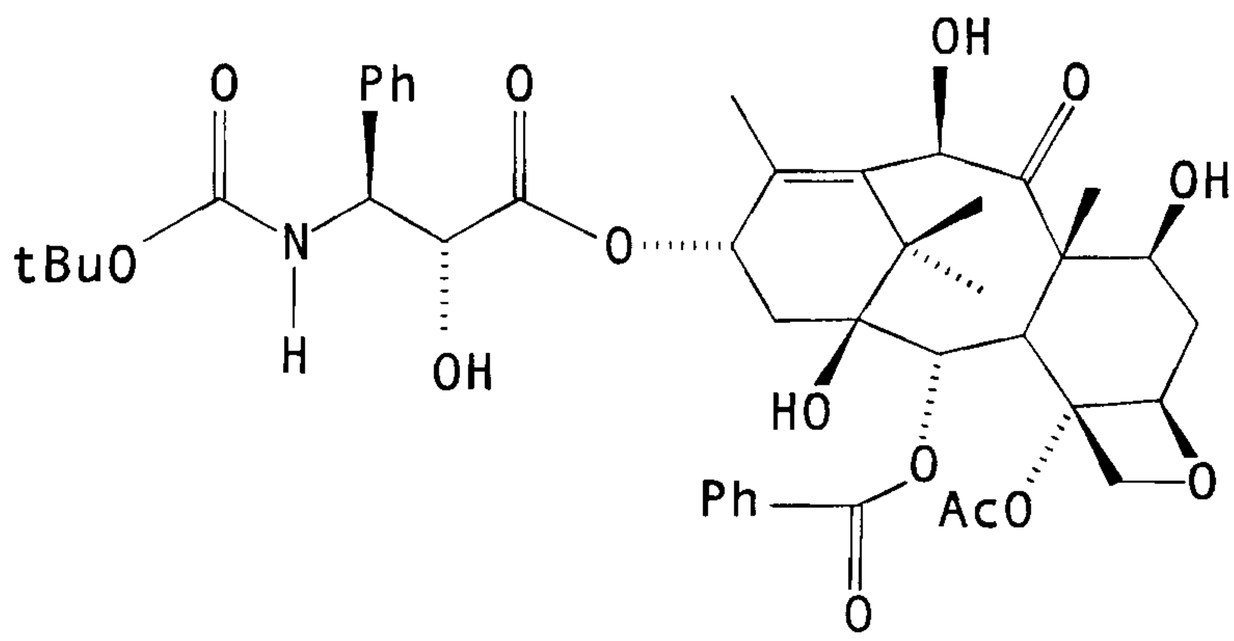


or



wherein Ac is acetyl and Ph is phenyl.

According to yet a further aspect of the present invention, there is provided the process as described herein wherein the taxane has the formula



or

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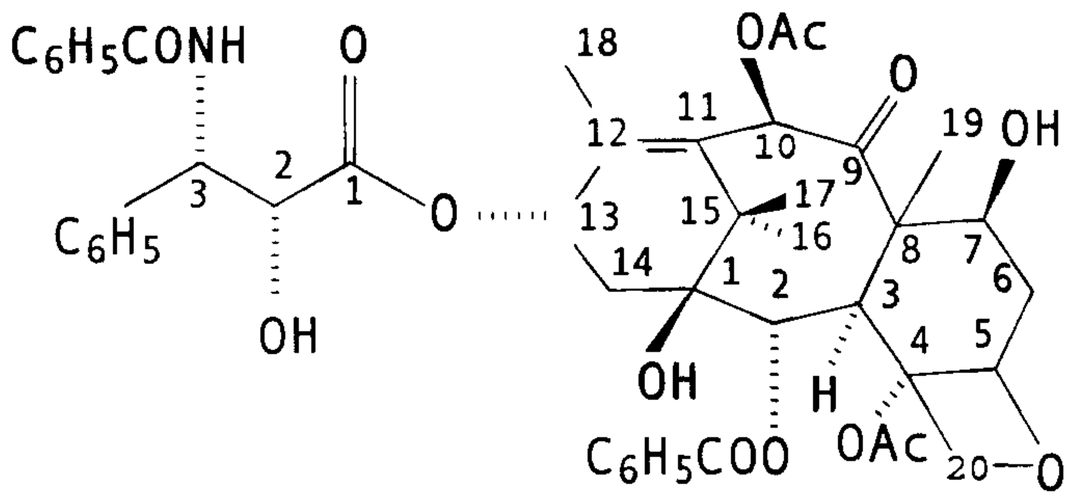
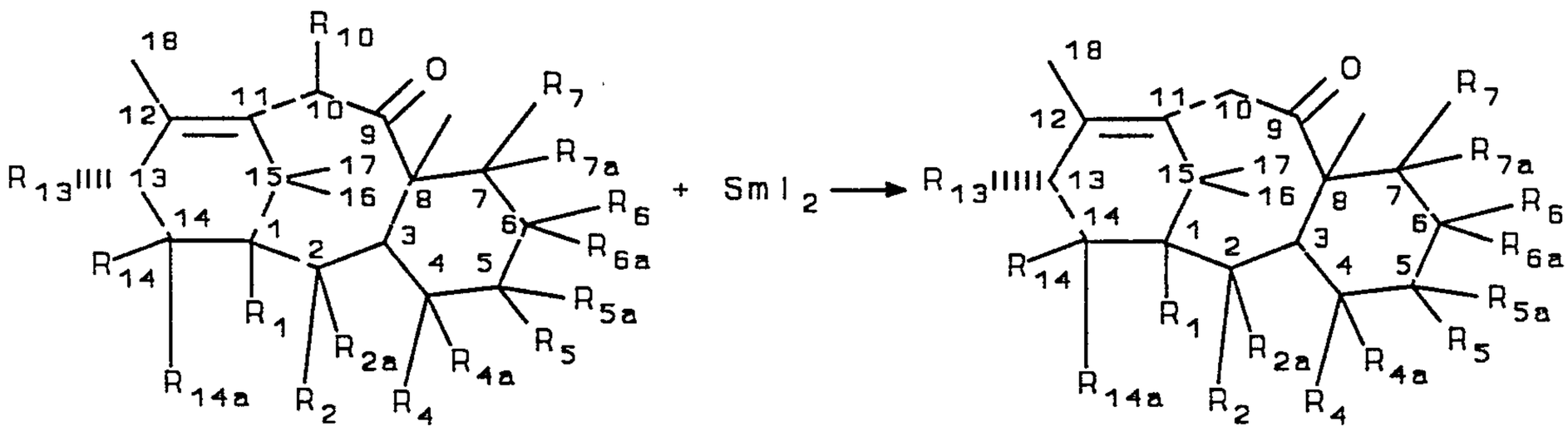


wherein Ac is acetyl, Ph is phenyl, and tBu is tert-butyl.

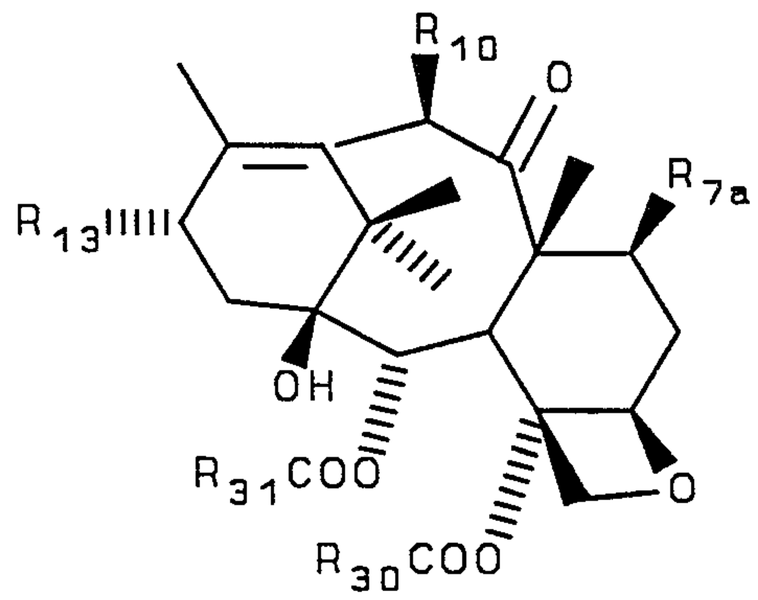
The reaction is illustrated in Reaction Scheme 1 wherein R_1 - R_{14a} are as previously defined. The reaction between the taxane and samarium diiodide may be carried out at a temperature between about -78°C and 100°C, preferably at or below 0°C, in a solvent, for

example, an ether such as tetrahydrofuran, a dipolar aprotic such as HMPA (hexamethylphosphoramide) or DMF (dimethylformamide), or combinations thereof. Advantageously, the samarium diiodide selectively abstracts the C10 leaving group; C13 side chains and other substituents on the nucleus remain undisturbed.

REACTION SCHEME 1



Preferably, the C10 hydroxy, acyloxy or sulfonyloxy substituted taxane is tetracyclic and corresponds to the formula

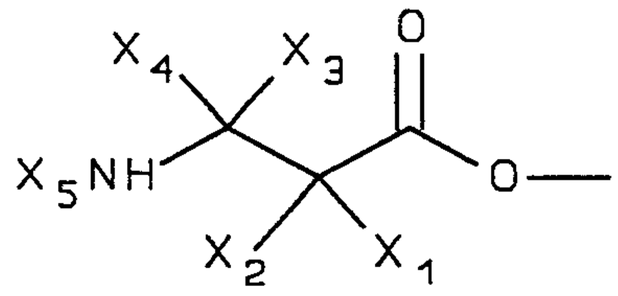


wherein

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

R_{10} is hydroxy or acetoxy;

R_{13} is hydroxy, protected hydroxy or



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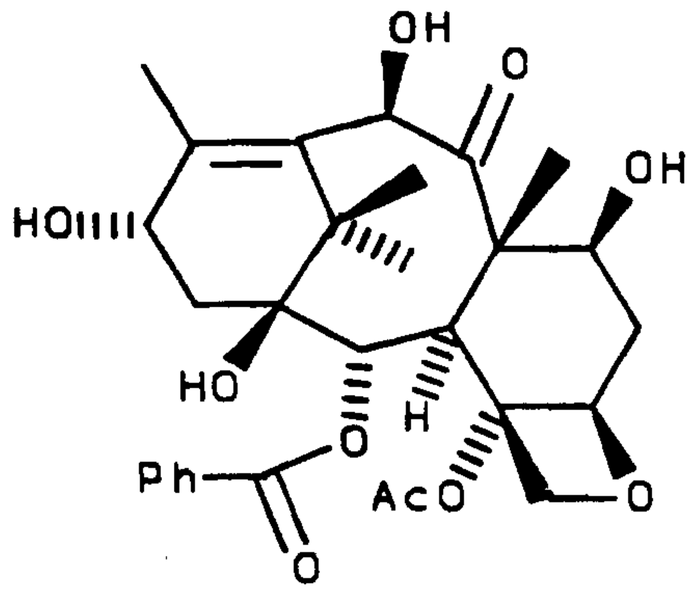
R_{28} is acyl;

R_{30} is alkyl;

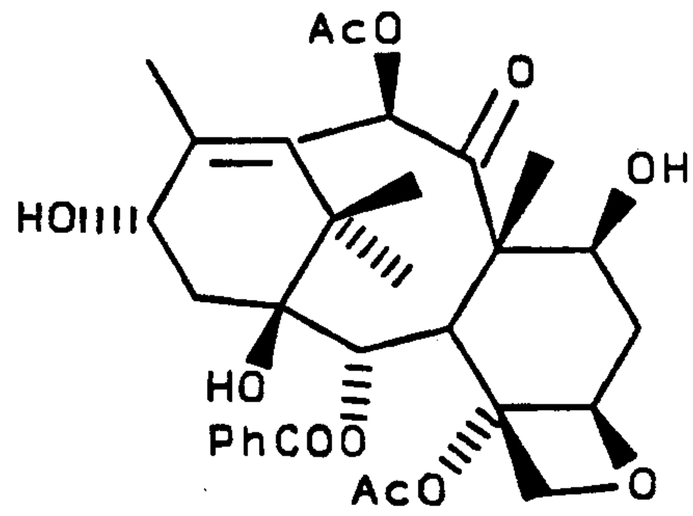
R_{31} is monocyclic aryl; and

X_1 - X_5 are as previously defined.

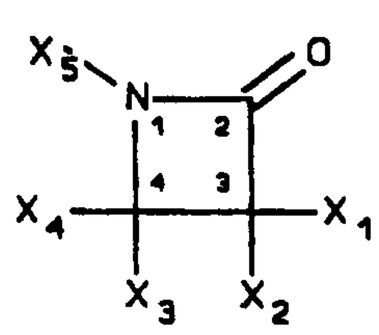
Most preferably, the taxane is baccatin III, 10-desacetyl baccatin III, taxol™, taxotere™, or other biologically active taxane having a comparable C13 side chain. Baccatin III and 10-desacetyl baccatin III have the following structures.



and



Baccatin III, 10-desacetyl baccatin III and taxol™ can be separated from mixtures extracted from natural sources such as the needles, stems, bark or heartwood of numerous Taxus species. Taxotere™ and other biologically active taxanes may be prepared semi-synthetically from baccatin III and 10-desacetyl baccatin III as set forth in U.S. Patent Nos. 4,924,011 and 4,924,012 or by the reaction of a β-lactam and an alkoxide having the taxane tricyclic or tetracyclic nucleus and a C13 metallic or ammonium oxide substituent. The ß-lactams have the following structural formula:



wherein X_1 - X_5 are as defined above and the alkoxides have the formula:

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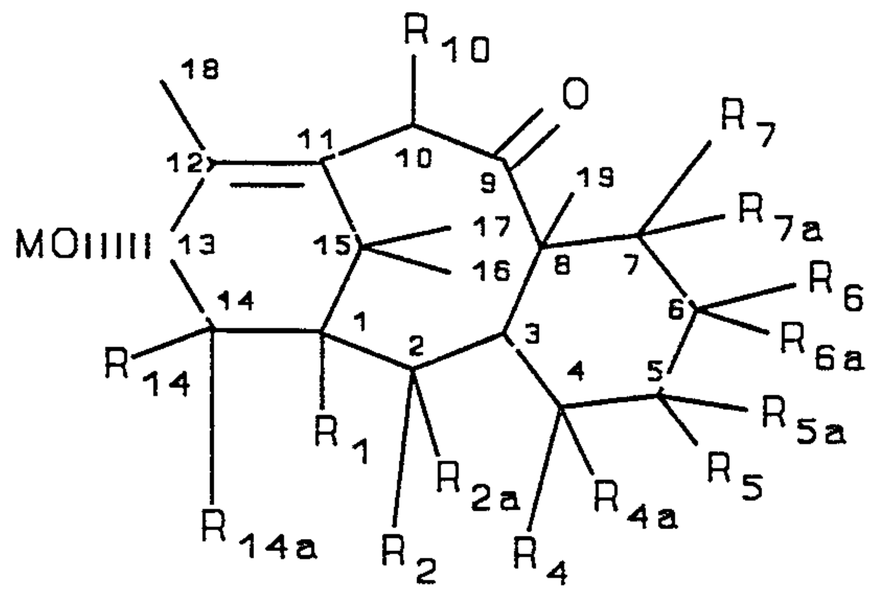
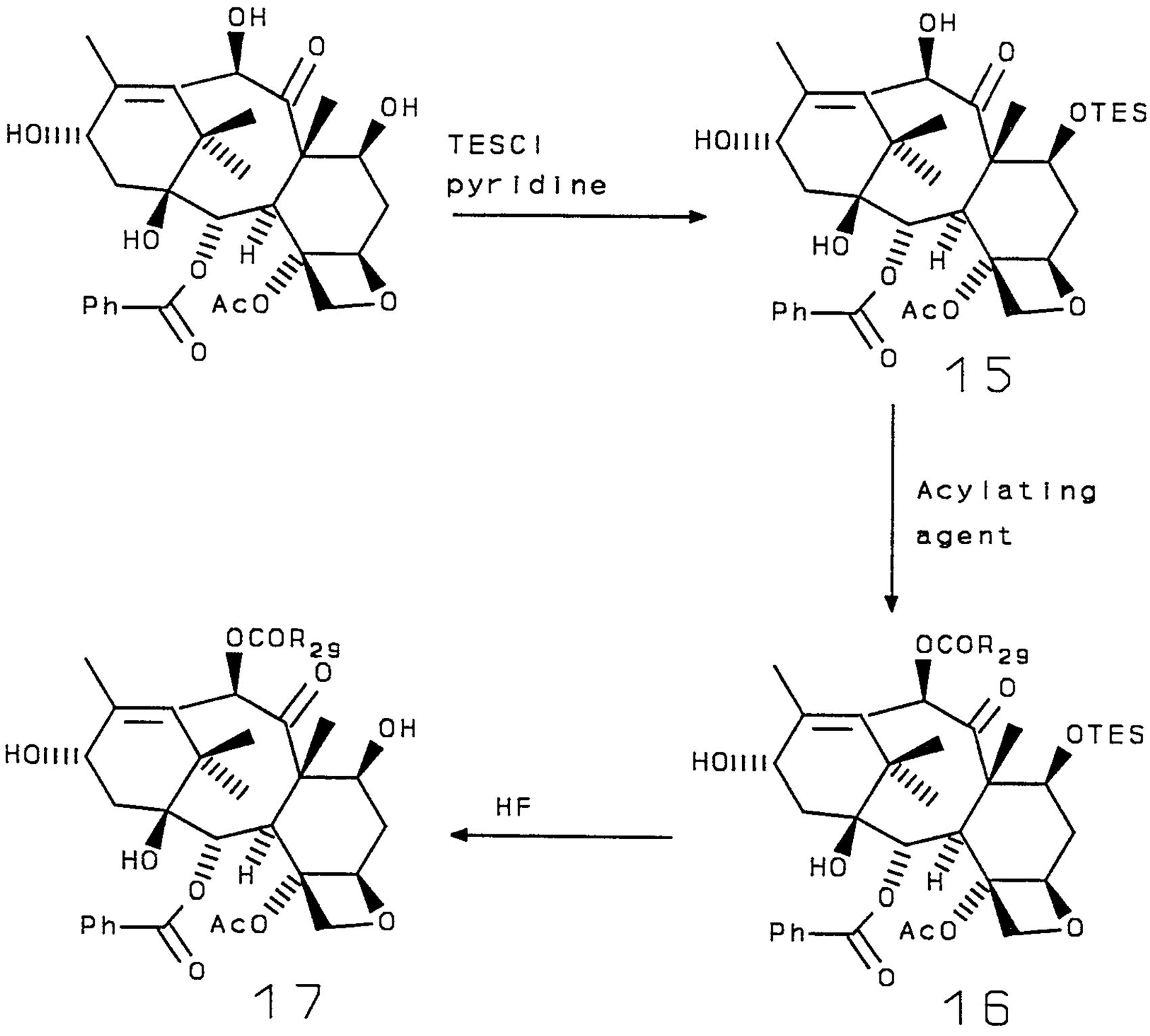


wherein R_1 - R_{14a} are as previously defined and M comprises ammonium or is a metal optionally selected from the group comprising Group IA, Group IIA and transition metals, and preferably, Li, Mg, Na, K or Ti.

Taxanes having a C10 sulfonyloxy substitutent may be prepared by reacting 10-desacetyl baccatin III or other C10 hydroxy substituted taxane with a sulfonyl chloride such as methanesulfonylchloride, benzene-sulfonylchloride or toluenesulfonylchloride and a tertiary amine.

Taxanes having C10 acyloxy substituents other than acetate can be prepared using 10-DAB as a starting material as illustrated in Reaction Scheme 2. 10-DAB may readily be protected with a variety of protecting groups at C7 with a silylchloride such as triethylsilylchloride or an acylating agent such as acetic anhydride to yield a 7-protected 10-DAB. 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 and, if desired, the C7 protecting group can readily be removed.

REACTION SCHEME 2

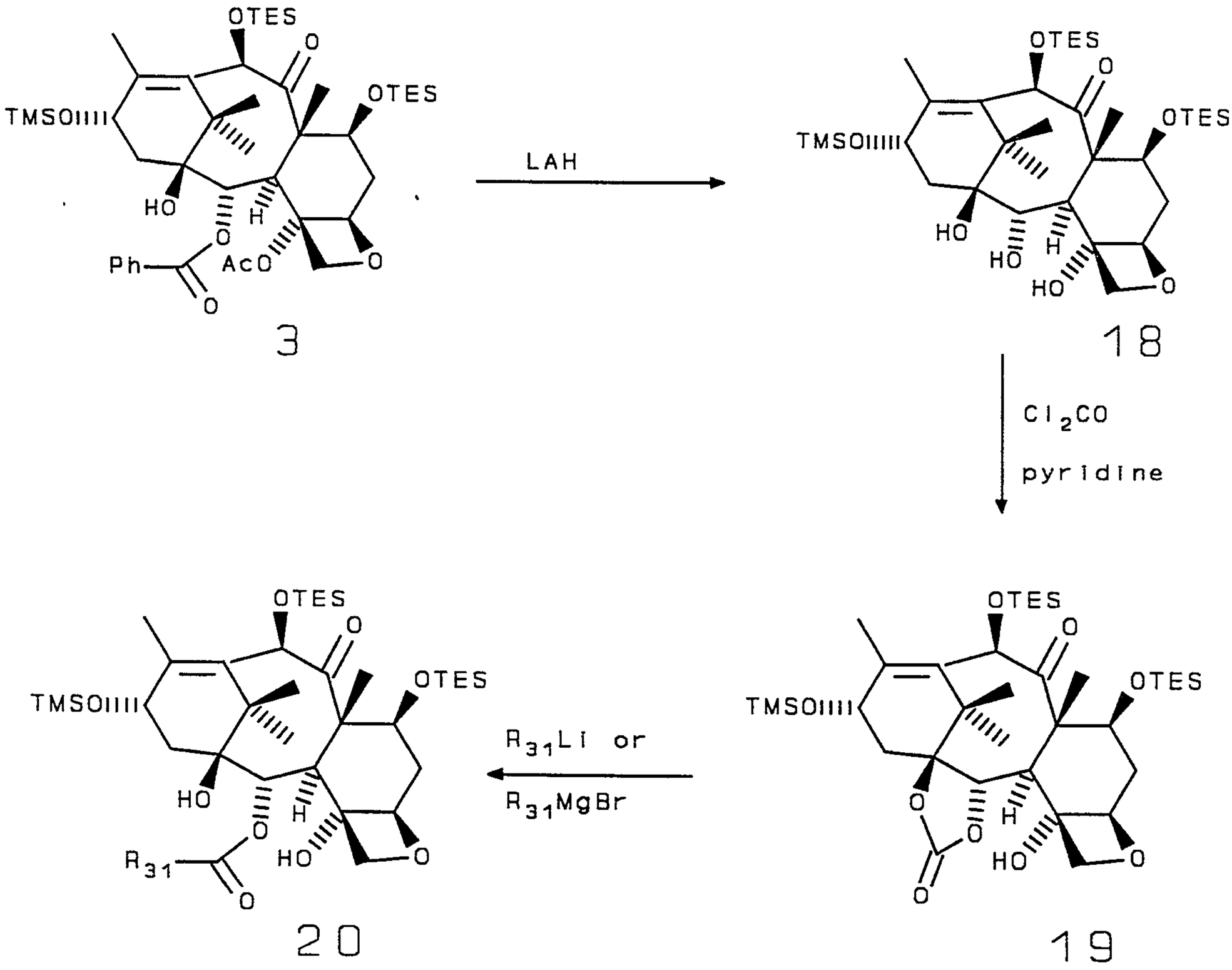


Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter 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 3-7. 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 various positions, for instance C1, C2, C4, C7, 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 3, 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).

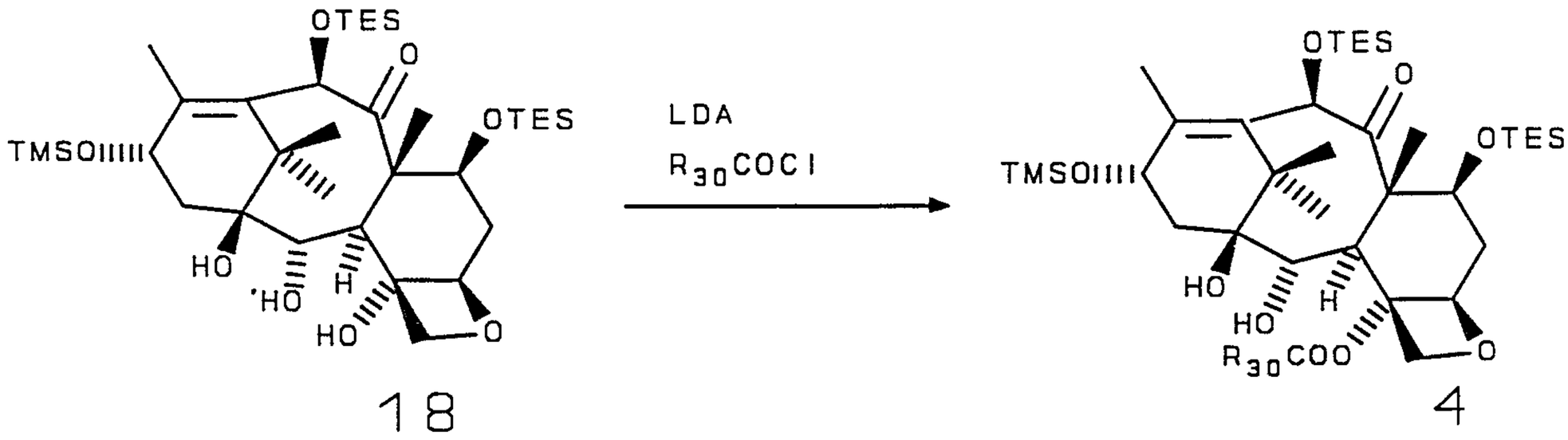
Scheme 3



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 4.

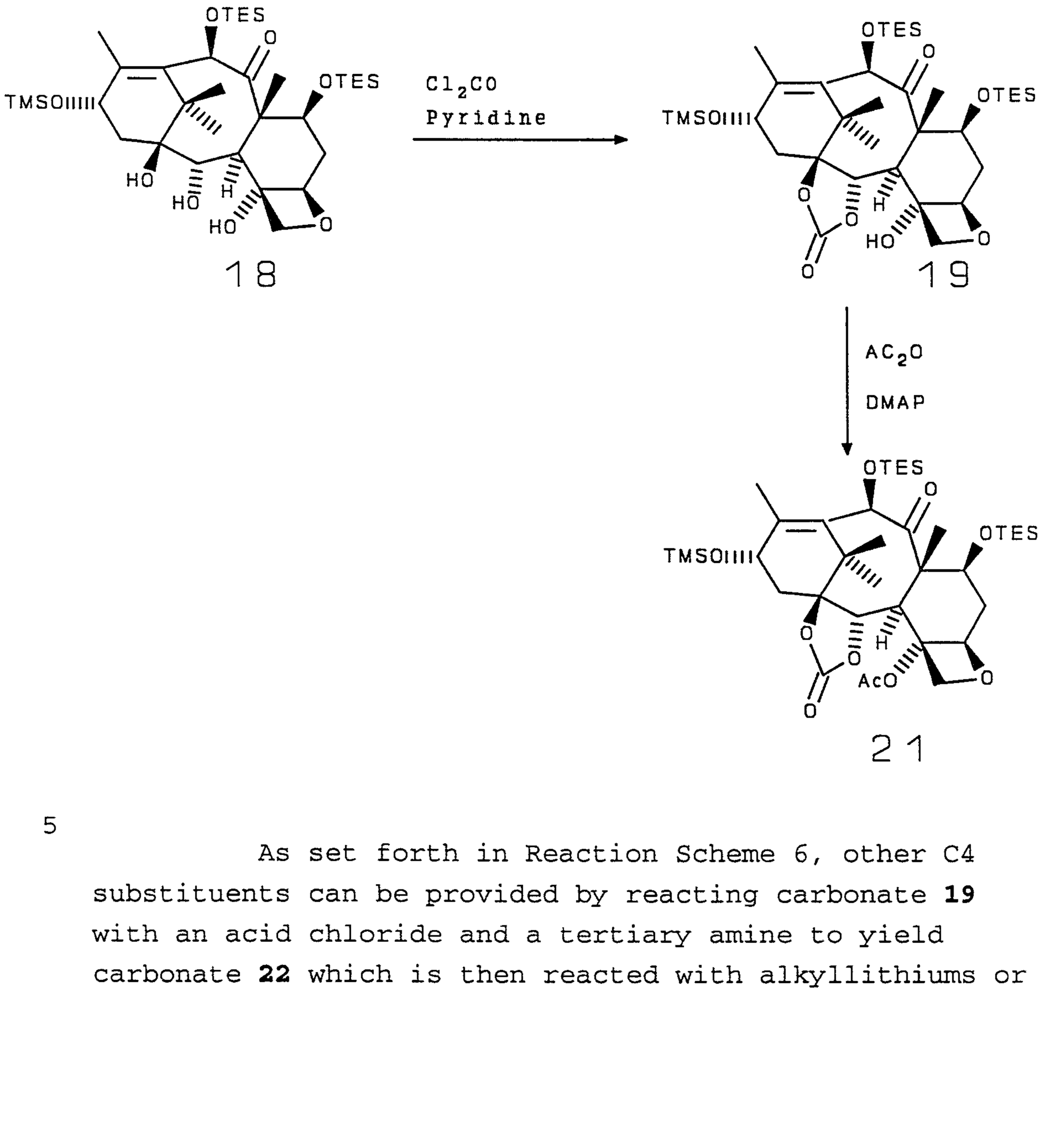
Triol **18** can also readily be converted to the 1,2 carbonate **19**. Acetylation of carbonate **19** under vigorous standard conditions provides carbonate **21** as described in Reaction Scheme 5; addition of alkyllithiums or Grignard reagents to carbonate **19** provides the C2 ester having a free hydroxyl group at C4 as set forth in Reaction Scheme 3.

Scheme 4



18 4

Scheme 5



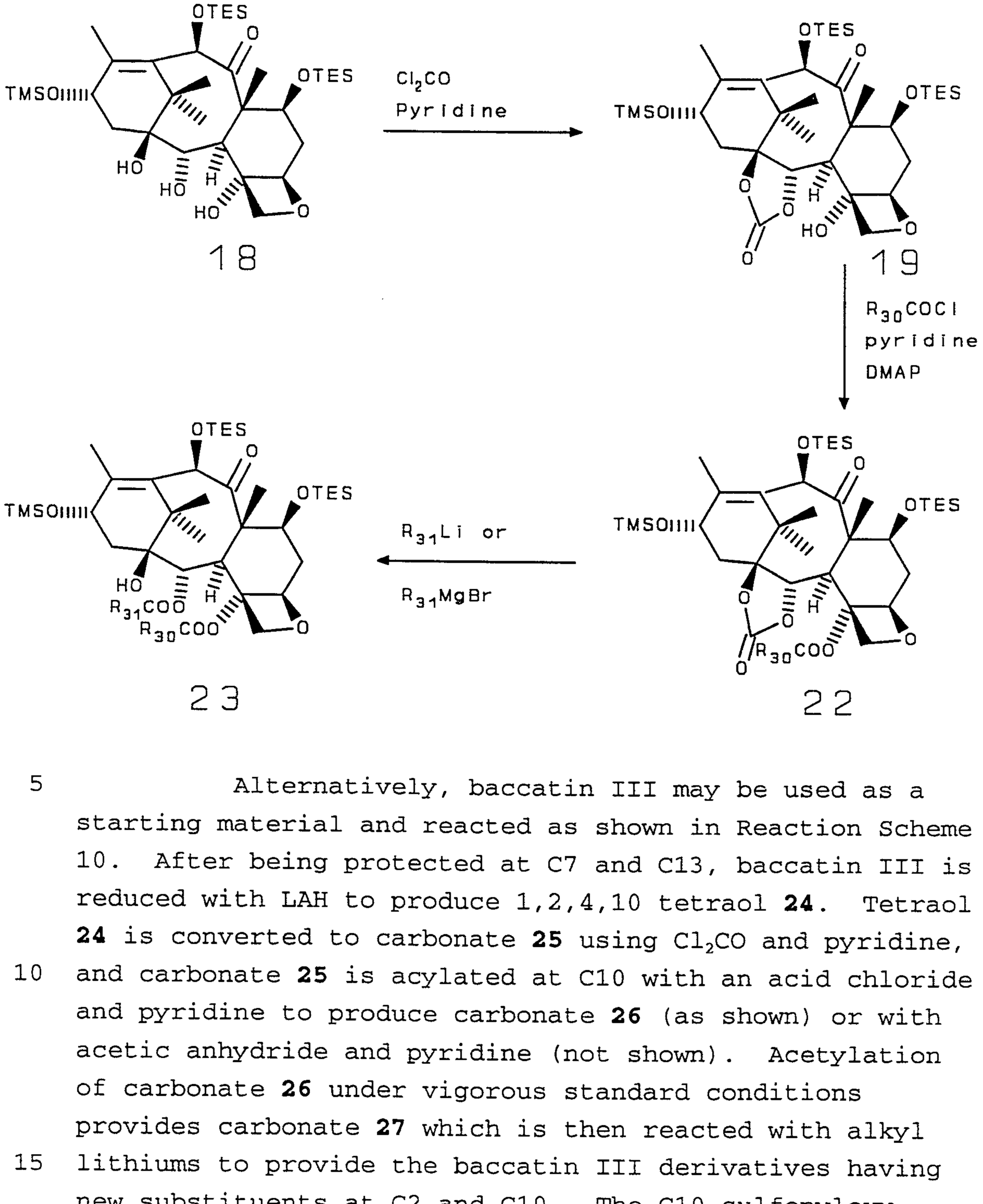
18 19

21

As set forth in Reaction Scheme 6, 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.

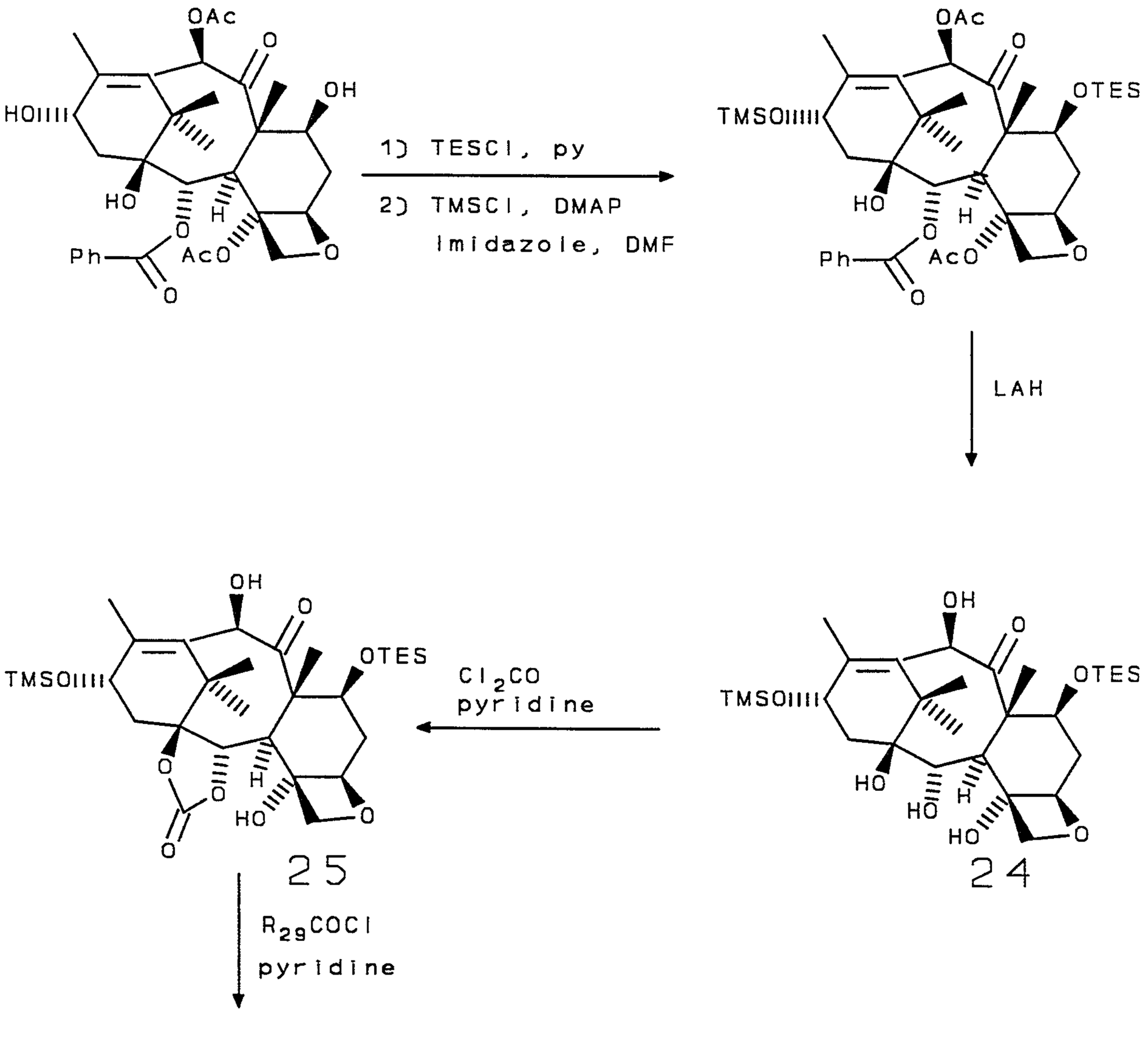
Scheme 6

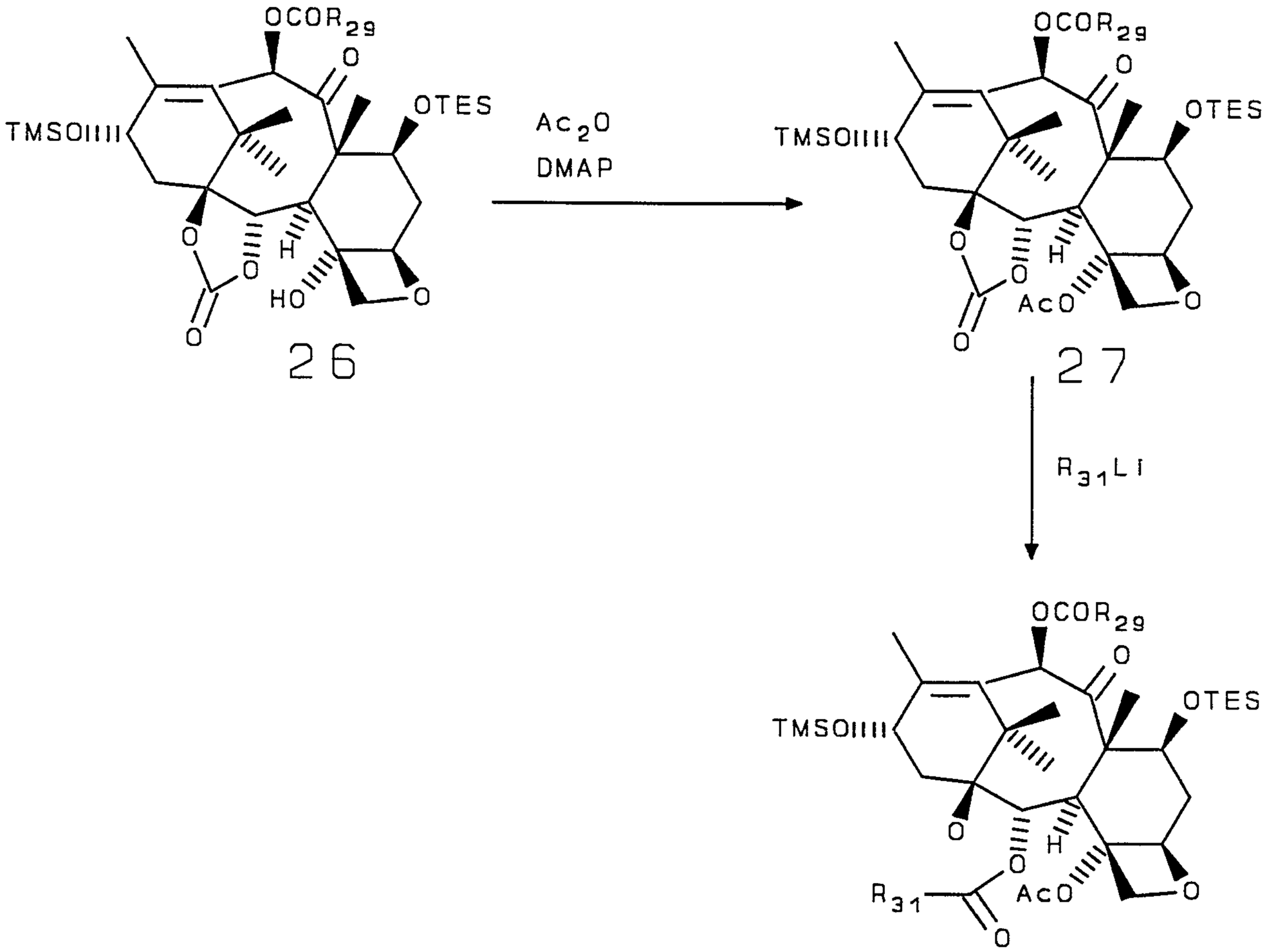


Alternatively, baccatin III may be used as a starting material and reacted as shown in Reaction Scheme 10. After being protected at C7 and C13, baccatin III is reduced with LAH to produce 1,2,4,10 tetraol **24**. Tetraol **24** is converted to carbonate **25** using Cl_2CO and pyridine, and carbonate **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. The C10 sulfonyloxy

analog may be prepared by reacting carbonate **25** with a sulfonylchloride instead of an acylating agent to produce a C10 sulfonyloxy analog of carbonate **26** and then proceeding as otherwise set forth in Reaction Scheme 10.

Scheme 7

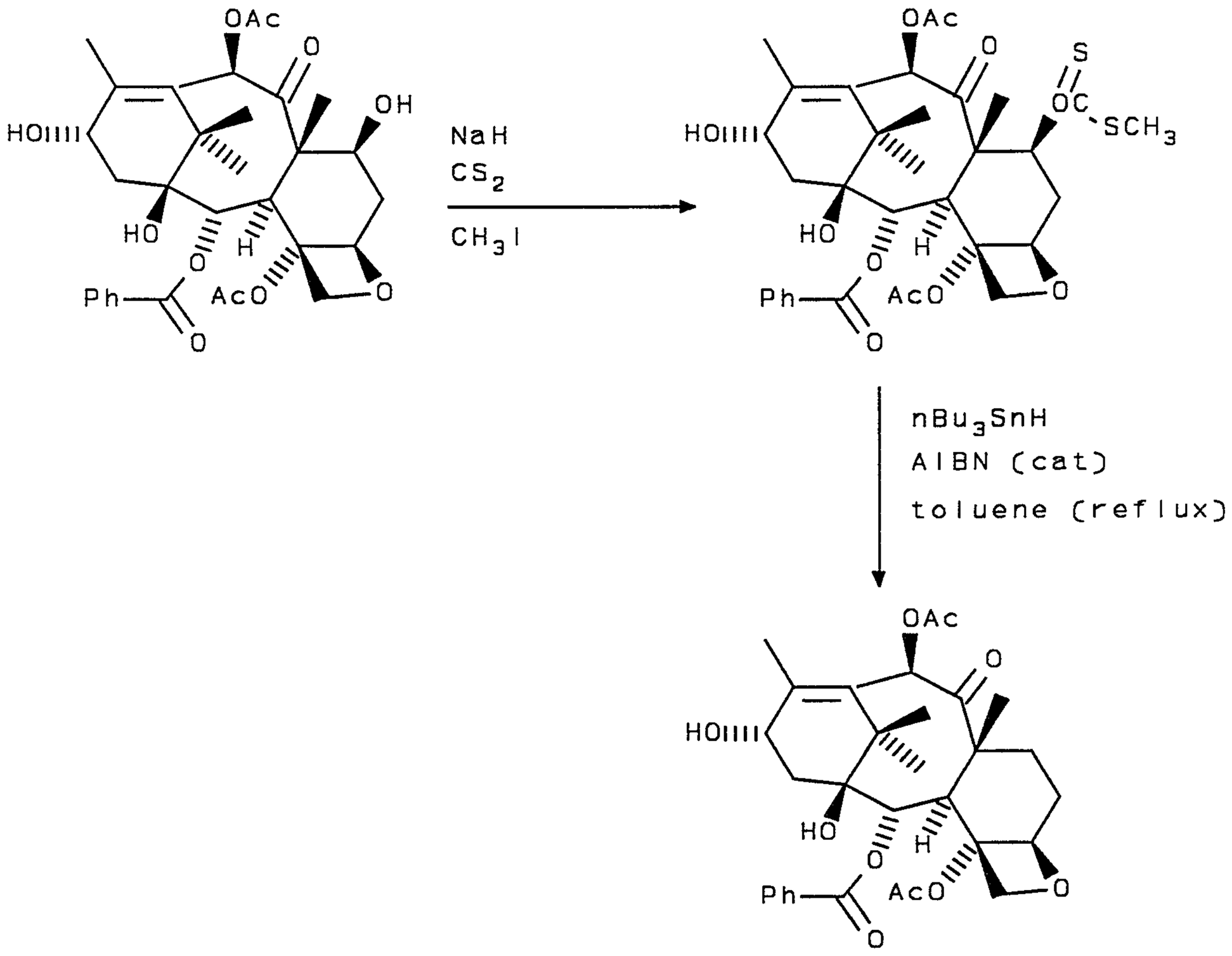




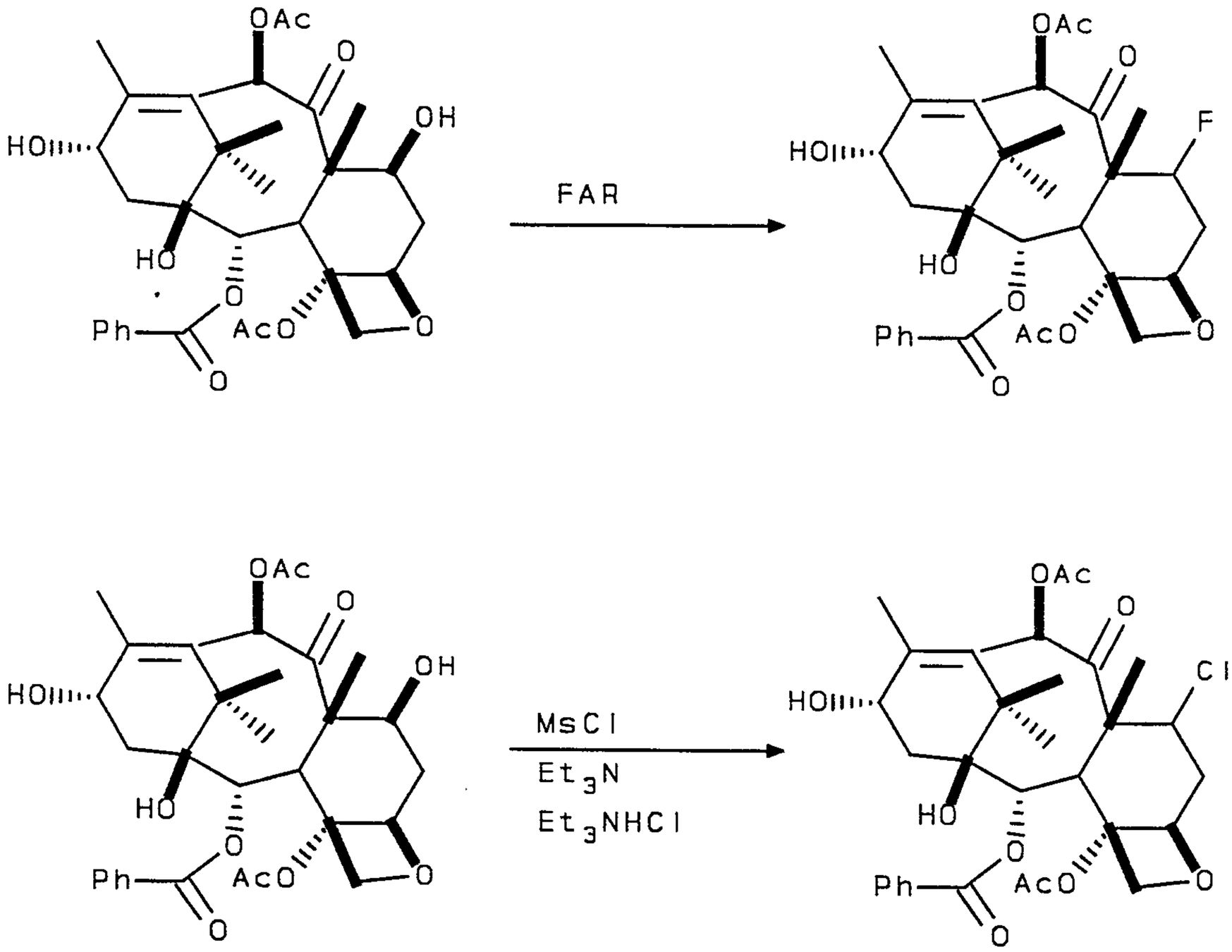
C7 dihydro and other C7 substituted taxanes can be prepared as set forth in Reaction Schemes 8 and 9.

As shown in Reaction Scheme 9, 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.

REACTION SCHEME 8

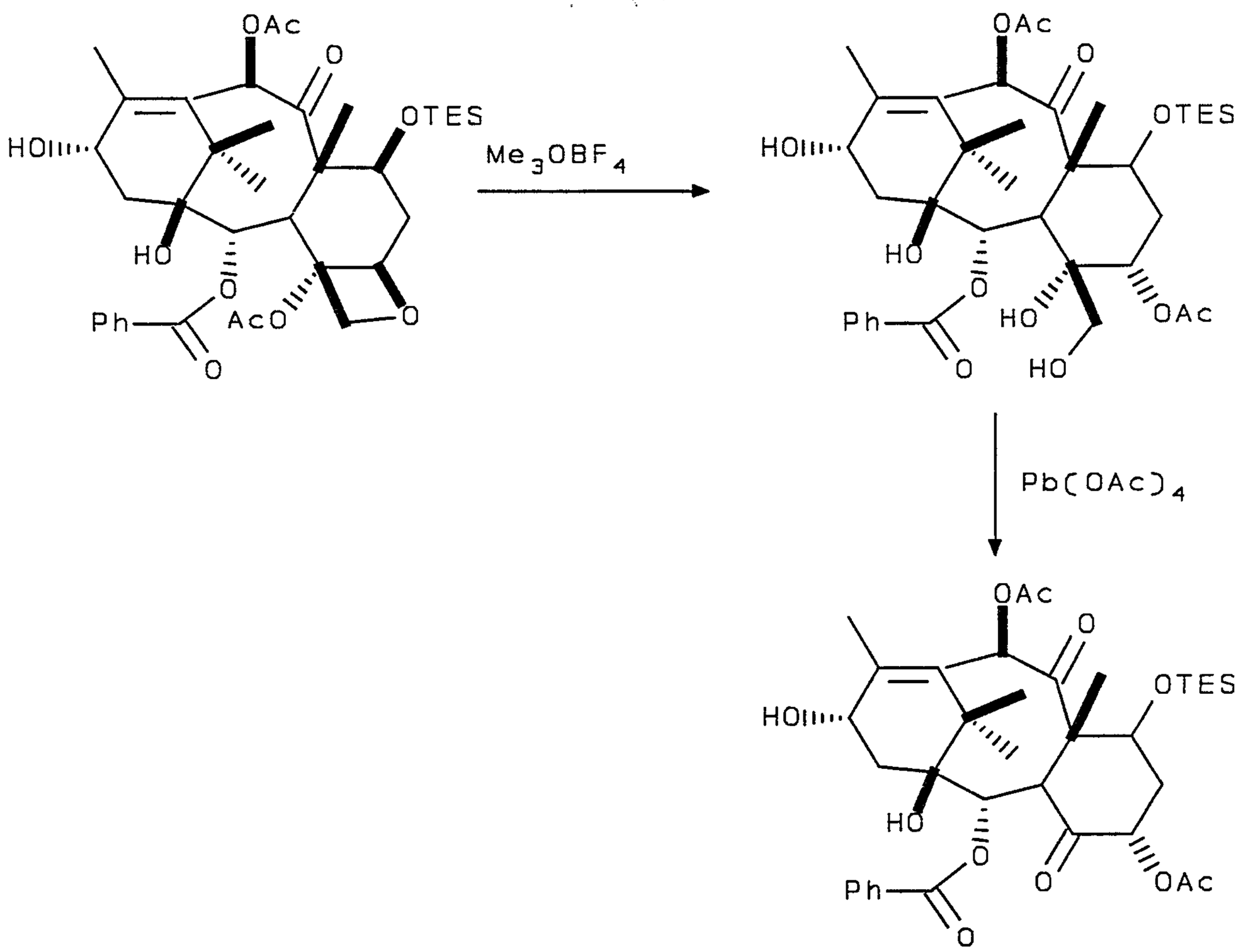


REACTION SCHEME 9



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 10, 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 10



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

10-Desacetoxybaccatin III:

To a solution of baccatin III (20 mg; 0.034 mmol) in THF (0.09 mL) at 0°C under nitrogen was added a solution of SmI_2 (0.1 M; 0.9 mL; 0.09 mmol) in THF. After stirring 45 minutes at 0°C the flask was opened to the air, and the reaction mixture diluted with ethyl acetate (10 mL). The mixture was poured into aqueous HCl (0.2N; 25 mL), extracted with ethyl acetate, and the extract was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The product was isolated by flash chromatography (SiO_2; 80% ethyl acetate-hexanes) affording 16.6 mg (92%) of 10-desacetoxybaccatin III which was recrystallized from $CHCl_3$-hexanes. mp 230-232 °C. $[\alpha]^{25}D$= -103.6 (c=0.00195, $CHCl_3$). IR (cm^{-1}): 3100, 2970, 2950, 2900, 1750, 1710, 1460, 1370, 1320, 1270, 1255, 1110, 980, 890, 760, 700. ^{1}H-nmr (500 MHz, $CDCl_3$) δ 8.11 (dd ; 2H; J=8.4, 1.2 Hz; o-Bz); 7.61 (dt; 1H; J=7.5,1.2 Hz; p-Bz); 7.48 (br t; 2H; J=7.8 Hz; m-Bz); 5.66 (br d; 1H; J=6.9 Hz; H-2β); 4.98 (br dd; 1H; J=9.4,2; H-5α); 4.83 (br; 1H; w1/2 19 Hz; H-13β); 4.34 (dt; 1H; J=11.2, 7.8Hz; H-7α); 4.31 (br d; 1H;J=8.4 Hz; H-20α); 4.17 (br d; 1H; J=6.9 Hz; H-3α); 4.15 (dd; 1H; J=8.4, 1Hz; H-20β); 3.84 (d; 1H; J=15.6 Hz; H-10α); 3.46 (ddd; 1H; J=15.6,3.7,1.6 Hz; H-10β); 2.64 (ddd; 1H; J=14.4,9.4,6.9 Hz; H-6α); 2.29 (s; 3H; 4-OAc); 2.28 (m; 2H; H-14α and H-14β); 1.95 (t; 3H; J=1.6 Hz; 18-Me); 1.94 (d, 1H; J=6.8 Hz; 13-OH); 1.79 (ddd; 1H; J=14.4, 11.2, 2.1 Hz; H-6β); 1.64 (s; 3H; 19-Me); 1.58 (s; 1H; 1-OH); 1.38 (d; 1H; J=7.8 Hz; 7-OH); 1.13 (s, 3H; 16-Me); 1.06 (s, 3H; 17-Me).

EXAMPLE 2

7-Triethylsilyl-10-desacetoxybaccatin III:

To a stirred solution of 10-desacetoxybaccatin III (10.0 mg; 0.019 mmol) in anhydrous pyridine (0.05 mL) at room temperature and under nitrogen, triethylchloro-

silane (15 L; 0.09 mmol) was added and the resulting mixture was stirred at room temperature for 48 h. After diluting with ethyl acetate (5 mL) the mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) and extracted with ethyl acetate. The extract was washed successively with water, 10% aqueous $CuSO_4$ and brine, dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography (SiO_2; 40% EA-hexanes) affording 11.1 mg (91%) of 7-triethylsilyl-10-desacetoxybaccatin III.

EXAMPLE 3

10-Desacetoxytaxol:

To a stirred solution of taxol (35 mg; 0.041 mmol) in THF (0.1 mL) at 0 °C under nitrogen was added a solution of SmI_2 (0.1 M; 1.0 mL; 0.10 mmol) in THF. After stirring 45 minutes at 0 °C the flask was opened to the air and the reaction mixture diluted with ethyl acetate (10 mL). The mixture was poured into aqueous HCl (0.2N; 25 mL), extracted with ethyl acetate, and the extract was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The product was isolated by flash chromatography (SiO_2; 80% ethyl acetate-hexanes) affording 29.4 mg (90%) of 10-desacetoxytaxol.

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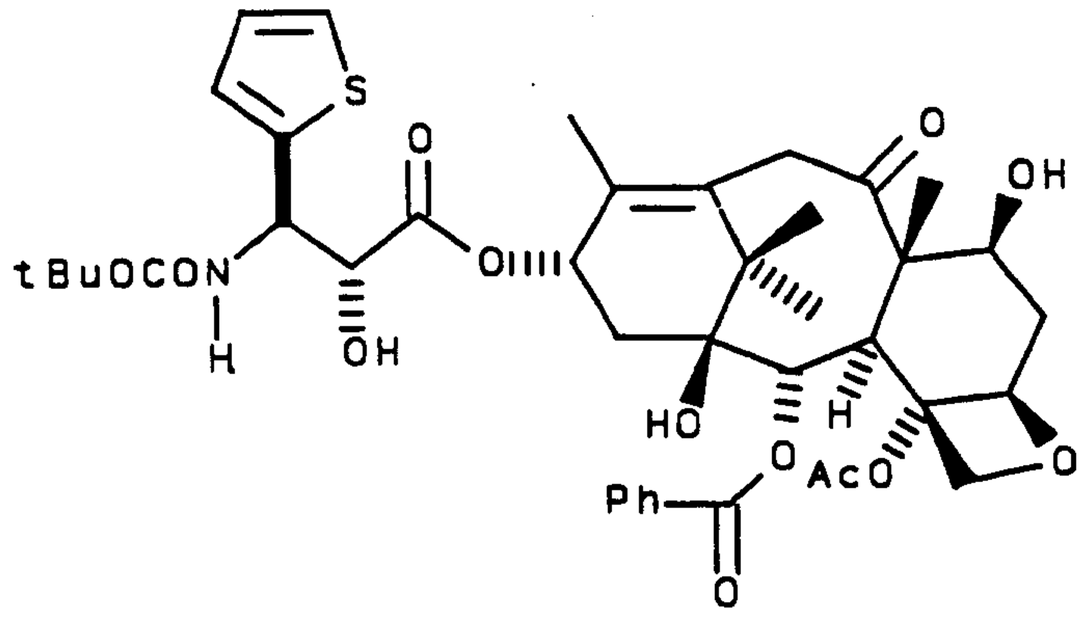
EXAMPLE 4



(68-3)

Preparation of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™.

To a solution of 7-O-triethylsilyl-10-desacetoxy baccatin (III) (47.5 mg, 0.073 mmol) in 0.7 mL of THF at -45°C was added dropwise 0.08 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsilyloxy-4-(2-thienyl)-azetidin-2-one (70.0 mg, 0.182 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 64.3 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxy-carbonyl)-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 64.3 mg (0.056 mmol) of the mixture obtained from the previous reaction in 3.2 mL of acetonitrile and 0.15 mL of pyridine at 0 °C was added 0.50 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25°C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 46.3 mg of

material which was purified by flash chromatography to give 40.1 mg (91%) of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™, which was recrystallized from methanol/water.

m.p.158-160°C; $[\alpha]^{25}_{Na}$ -58,4° (c 0.0028, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.11(d, J=6.9 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.50(m, 2H, benzoate meta), 7.27(dd, J=5.5, 1.2 Hz, 1H, thienyl), 7.06(d, J=3.3 Hz, 1H, thienyl), 7.01(dd, J=5.7, 3.9 Hz, 1H, thienyl), 6.13(td, J=6.3, 0.9 Hz, 1H, H13), 5.70(d, J=6.9 Hz, 1H, H2), 5.49(d, J=9.2 Hz, 1H, NH), 5.34(d, J=9.9 Hz, 1H, H3'), 4.62(dd, J=5.4 2.1 Hz, 1H, H5), 4.30(d, J=8.1 Hz, 1H, H20α), 4.29(s, 1H, H2'), 4.17(d, J=8.1 Hz, 1H, H20β), 4.06(d, J=6.9 Hz, 1H, H7), 3.81(d, J=15.3 Hz, H10α), 3.51(d, J=6.6 Hz, 1H, H3), 3.41(m, 1H, 2'OH), 2.61(m, 1H, H6α), 2.36(s, 3H, 4Ac), 2.30(m, 1H, H10β), 2.17(br s, 1H, 7 OH), 2.06(m, 1H, H14α), 1.81(m, 1H, H14β), 1.76(br s, 3H, Me18), 1.66(s, 1H, 1 OH), 1.62(m, 1H, H6β), 1.35(s, 9H, 3Me t-buthoxy), 1.25(s, 3H, Me17), 1.19(s, 3H, Me19), 1.17(s, 3H, Me16).

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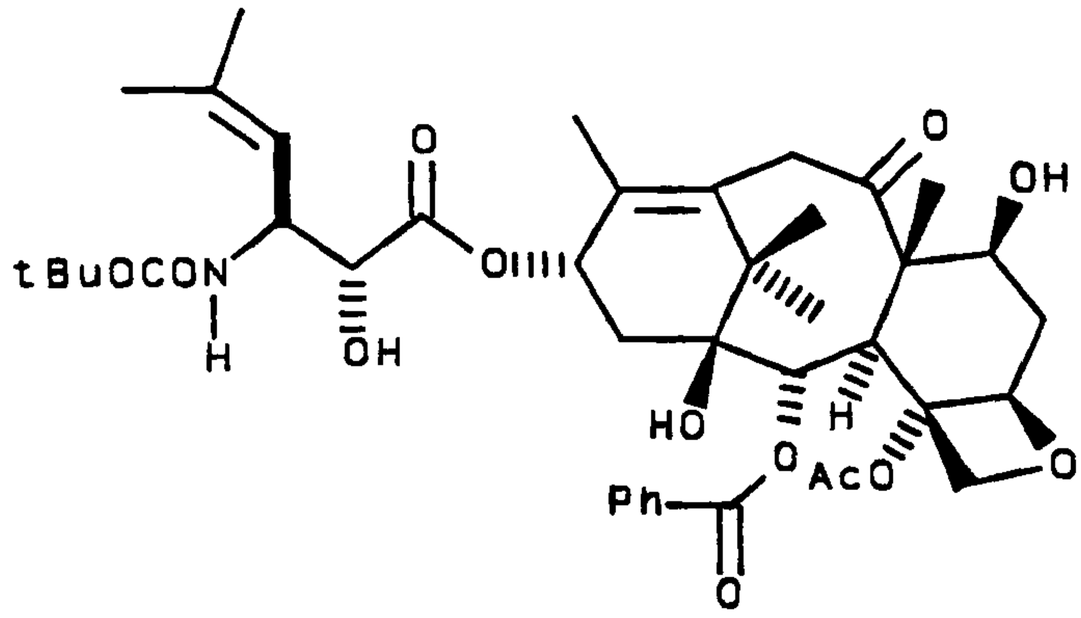
EXAMPLE 5



(68-4)

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

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

To a solution of 62.7 mg (0.059 mmol) of the mixture obtained from the previous reaction in 3.5 mL of acetonitrile and 0.16 mL of pyridine at 0 °C was added 0.55 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25°C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 51.5 mg of

material which was purified by flash chromatography to give 43.0 mg (95%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™, which was recrystallized from methanol/water.

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

^1H NMR ($CDCl_3$, 300 MHz) δ 8.10(d, J=7.3 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.47(m, 2H, benzoate meta), 6.15(td, J=8.5, 1.8 Hz, 1H, H13), 5.69(d, J=6.9 Hz, 1H, H2), 5.32(d, J= 9.2 Hz, 1H, NH), 4.93(dd, J=9.6, 1.8 Hz, 1H, H5), 4.82(d, J=8.7 Hz, 1H, $Me_2C=C\underline{H}$-), 4.76(td, J=8.7, 2.7 Hz, 1H, H3'), 4.37(d, J=8.7 Hz, 1H, H20α), 4.22(d, J=8.7 Hz, 1H, H20β), 4.18(d, J=2.7 Hz, 1H, H2'), 4.03(d, J=7.3 Hz, 1H, H7), 3.82(d, J=15.2 Hz, 1H, H10α), 3.47(m, 1H, 2'OH), 3.41(d, J=6.6 Hz, 1H, H3), 2.60(m, 1H, H6α), 2.39(m, 1H, H10β), 2.37(s, 3H, 4Ac), 2.18(s, 1H, 7 OH), 2.08(m, 1H, H14α), 1.78(m, 1H, H14β), 1.76(s, 3H, Me18), 1.74(s, 6H, 2Me from isobuthenyl), 1.63(m, 1H, H6β), 1.36(s, 9H, 3Me t-buthoxy) 1.26(s, 3H, Me17), 1.18(s, 3H, Me19), 1.15(s, 3H, Me16).

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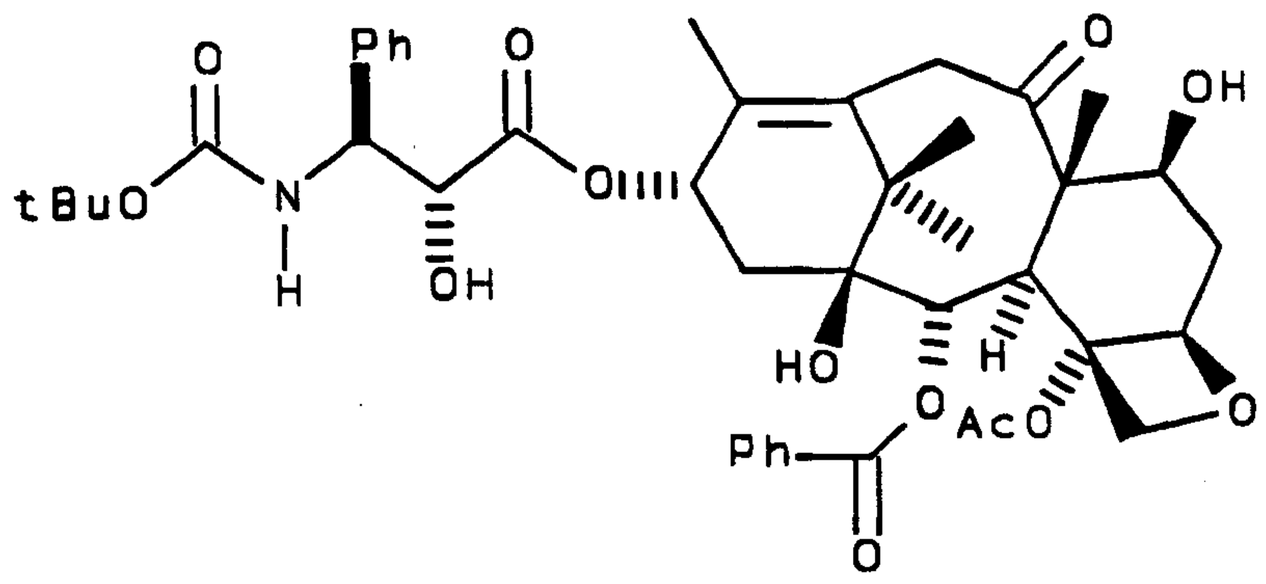
EXAMPLE 6



(69-1)

Preparation of N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™.

To a solution of 7-O-triethylsilyl-10-desacetoxy baccatin (III) (50.0 mg, 0.077 mmol) in 0.8 mL of THF at -45 °C was added dropwise 0.09 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsiloxy-4-phenylazetidin- 2-one (67.5 mg, 0.193 mmol) in 0.8 mL of THF was added dropwise to the mixture. The solution was warmed to 0°C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 72.0 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 72.0 mg (0.071 mmol) of the mixture obtained from the previous reaction in 3.8 mL of acetonitrile and 0.17 mL of pyridine at 0 °C was added 0.60 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25°C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 57.4 mg of material which was purified by flash chromatography to

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give 39.4 mg (71%) of N-desbenzoyl-N-(t-butoxycarbonyl)-10-desactoxy taxol™, which was recrystallized from methanol/water.

m.p.145-147°C; $[\alpha]^{25}_{Na}$ -54.4° (c 0.0027, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.11(d, J=7.1 Hz, 2H, benzoate ortho), 7.61-7.23(m, 8H, benzoate, phenyl), 6.13(td, J=6.3, 0.9 Hz, 1H, H13), 5.68(d, J=6.9 Hz, 1H, H2), 5.43(d, J=9.2 Hz, 1H, NH), 5.26(d, J=9.9 Hz, 1H, H3'), 4.96(dd, J=5.4 2.1 Hz, 1H, H5), 4.31(d, J=8.1 Hz, 1H, H20α), 4.22(s, 1H, H2'), 4.18(d, J=8.1 Hz, 1H, H20β), 4.03(d, J=6.9 Hz, 1H, H7), 3.81(d, J=15.1 Hz, H10α), 3.43(m, 1H, 2'OH), 3.40(d, J=6.6 Hz, 1H, H3), 2.60(m, 1H, H6α), 2.38(s, 3H, 4Ac), 2.32(m, 1H, H10β), 2.15(br s, 1H, 7 OH), 2.09(m, 1H, H14α), 1.83(m, 1H, H14β),1.78(br s, 3H, Me18), 1.66(s, 1H, 1 OH), 1.63(m, 1H, H6β), 1.36(s, 9H, 3Me t-butoxy), 1.25(s, 3H, Me17), 1.18(s, 3H, Me19), 1.16(s, 3H, Me16).

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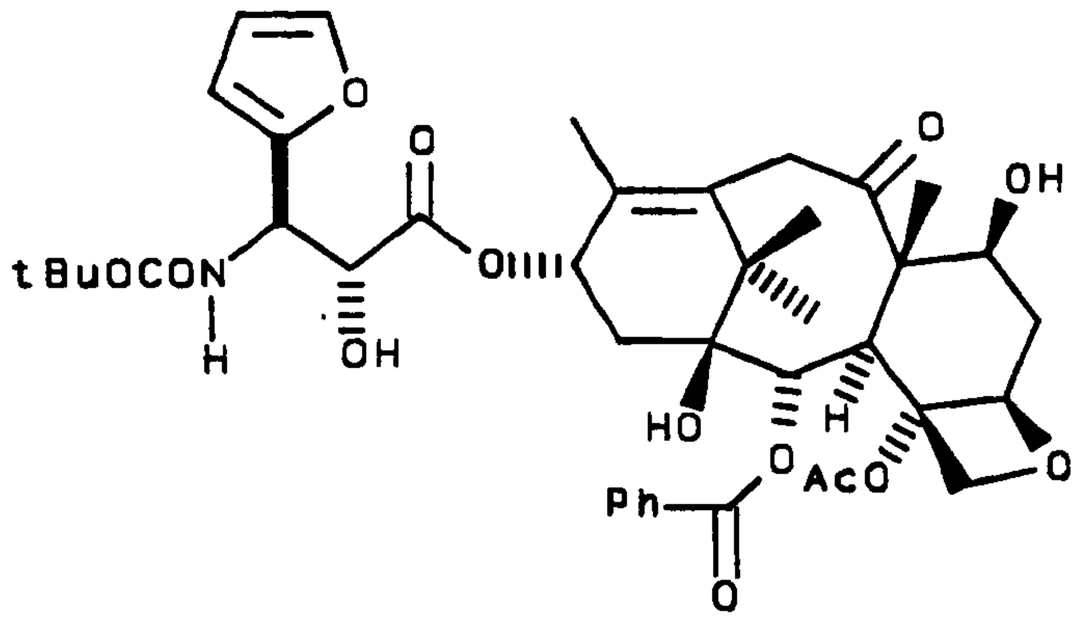
EXAMPLE 7



(69-2)

Preparation of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™.

To a solution of 7-O-triethylsilyl-10-desacetoxy baccatin (III) (50.0 mg, 0.077 mmol) in 0.8 mL of THF at -45 °C was added dropwise 0.09 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsiloxy-4-(2-furyl)azetidin-2-one (72.8 mg, 0.195 mmol) in 0.8 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 69.4 mg of a mixture containing (2'R,3'S)-2',7-(bis)-O-triethylsilyl-3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxy-carbonyl)-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 69.4 mg (0.068 mmol) of the mixture obtained from the previous reaction in 3.8 mL of acetonitrile and 0.17 mL of pyridine at 0 °C was added 0.60 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave

59.0 mg of material which was purified by flash chromatography to give 41.0 mg (76%) of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-10-desacetoxy taxol™, which was recrystallized from methanol/water.

m.p.151-153°C; $[\alpha]^{25}_{Na}$ -56.5° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.11(d, J=7.3 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.49(m, 2H, benzoate meta), 7.41(m, 1H, furyl), 6.37(m, 1H, furyl), 6.34(m, 1H, furyl), 6.13(dd, J=6.3, 0.9 Hz, 1H, H13), 5.69(d, J=6.6 Hz, 1H, H2), 5.49(d, J=9.2 Hz, 1H, NH), 5.34(d, J=9.9 Hz, 1H, H3'), 4.62(dd, J=5.4, 2.1 Hz, 1H, H5), 4.30(d, J=8.1 Hz, 1H, H20α), 4.29(s, 1H, H2'), 4.17(d, J=8.1 Hz, 1H, H20β), 4.06(d, J=6.9, 1H, H7), 3.81(d, J=15.3 Hz, 1H, H10α), 3.51(d, J=6.6 Hz, 1H, H3), 3.41(m, 1H, 2'OH), 2.61(m, 1H, H6α), 2.36(s, 3H, 4Ac), 2.32(m, 2H, H14α), 2.28(m, 1H, H10β), 2.17(br s, 1H, 7OH), 2.14(m, 1H, H14α), 1.82(m, 1H, H14β), 1.76(br s, 3H, Me18), 1.66(s, 1H, 1 OH), 1.62(m, 1H, H6β), 1.35(s, 9H, 3Me t-butoxy), 1.25(s, 3H, Me17), 1.19(s, 3H, Me19), 1.16(s, 3H, Me16).

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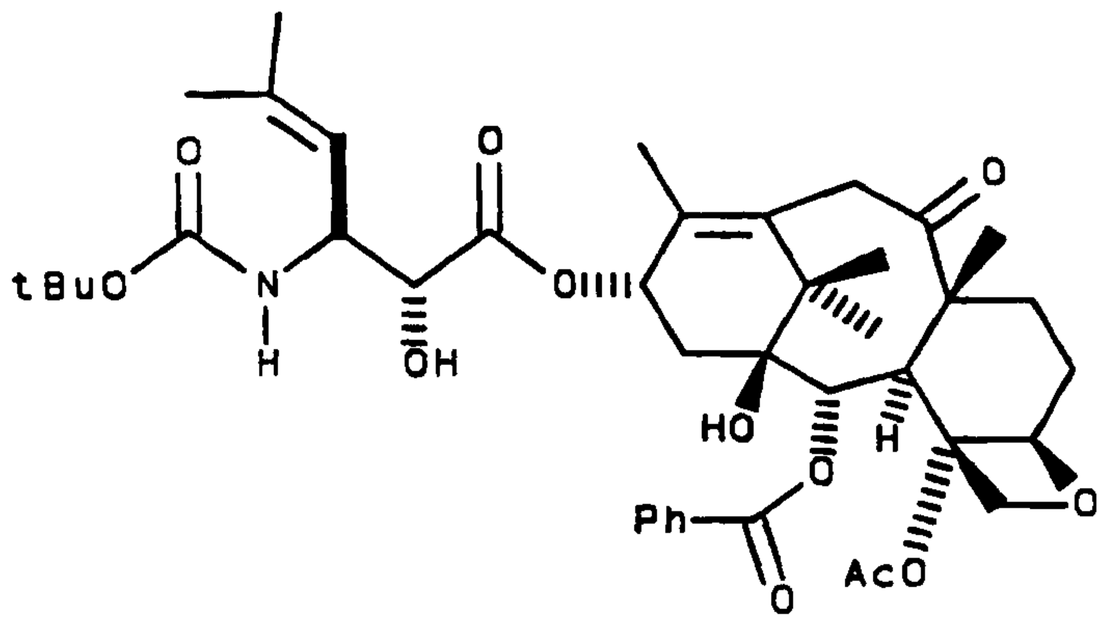
EXAMPLE 8



(72-1)

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

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

To a solution of 40.3 mg (0.046 mmol) of the mixture obtained from the previous reaction in 3.2 mL of acetonitrile and 0.15 mL of pyridine at 0 °C was added 0.47 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave

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35.2 mg of material which was purified by flash chromatography to give 24.0 mg (70%) of 3'-desphenyl-3'-(isobutenyl)-N-debenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™, which was recrystallized from methanol/water.

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

^1H NMR ($CDCl_3$, 300 MHz) δ 8.12(d, J=7.1 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 6.11(td, J=8.1, 1.8 Hz, 1H, H13), 5.68(d, J=6.9 Hz, 1H, H2), 5.23(d, J=9.9 Hz, 1H, NH), 5.12(d, J=9.9 Hz, 1H, H3'), 4.96(dd, J=9.1, 2.7 Hz, 1H, H5), 4.80(d, J=8.7 Hz, 1H, $Me_2C=C\underline{H}$-), 4.58(dd, J=5.7, 2.1 Hz, 1H, H2'), 4.30(d, J=8.1, 1H, H20α), 4.19(d, J=8.1 Hz, 1H, H20β), 3.97(d, J=6.9 Hz, H3), 3.83(d, J=16.5, 1H, H10α), 3.33(m, 1H, H10β), 3.30(m, 1H, 2'OH), 2.39(m, 1H, H14α), 2.35(s, 3H, 4Ac), 2.26(m, 1H, H14β), 2.19(m, 1H, H6α), 2.10(m, 1H, H7α), 1.95(m, 1H, H6β), 1.73(s, 3H, Me18), 1.69(s, 6H, 2Me from isobuthenyl), 1.63(s, 3H, Me19), 1.44(m, 1H, H7β), 1.39(br. s, 1H, 1 OH), 1.35(s, 9H, 3Me t-buthoxy), 1.25(s, 3H, Me16), 1.15(s, 3H, Me17).

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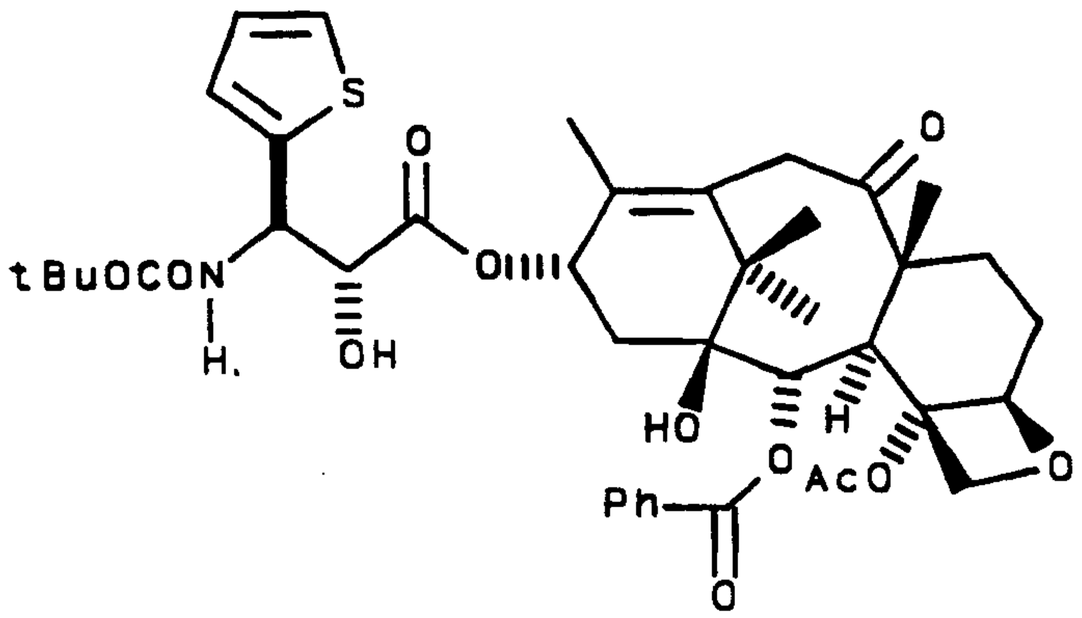
EXAMPLE 9



(72-2)

Preparation of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™.

To a solution of 7-deshydroxy-10-desacetoxy baccatin (III) (25.0 mg, 0.044 mmol) in 0.7 mL of THF at -45 °C was added dropwise 0.05 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsilyloxy-4-(2-thienyl)-azetidin-2-one (50.0 mg, 0.13 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0°C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 35.4 mg of a mixture containing (2'R,3'S)-2'-O-triethylsilyl-3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxy-carbonyl)-7-deshydroxy-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 35.4 mg (0.037 mmol) of the mixture obtained from the previous reaction in 3.2 mL of acetonitrile and 0.15 mL of pyridine at 0 °C was added 0.47 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave

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32.4 mg of material which was purified by flash chromatography to give 20.5 mg (71%) of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™, which was recrystallized from methanol/water.

m.p.132-134°C; $[\alpha]^{25}_{Na}$ -61.3° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.14(d, J=7.1 Hz, 2H, benzoate ortho), 7.61(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 7.29(dd, J=5.4, 1.2 Hz, 1H, thienyl), 7.09(d, J=3.3 Hz, 1H, thienyl), 7.01(dd, J=5.4, 3.3 Hz, 1H, thienyl), 6.14(td, J=8.4, 1.8 Hz, 1H, H13), 5.69(d, J=6.9 Hz, 1H, H2), 5.24(d, J=9.9 Hz, 1H, NH), 5.19(d, J=9.9 Hz, 1H, H3'), 4.93(dd, J=9.3, 2.7 Hz, 1H, H5), 4.62(dd, J=5.7, 2.1 Hz, 1H, H2'), 4.31(d, J=8.1, 1H, H20α), 4.21(d, J=8.1 Hz, 1H, H20β), 3.98(d, J=6.9 Hz, H3), 3.84(d, J=16.5, 1H, H10α), 3.38(m, 1H, H10β), 3.33(m, 1H, 2'OH), 2.40(m, 1H, H14α), 2.37(s, 3H, 4Ac), 2.27(m, 1H, H14β), 2.20(m, 1H, H6α), 2.11(m, 1H, H7α), 1.95(m, 1H, H6β), 1.74(s, 3H, Me18), 1.71(s, 3H, Me19), 1.46(m, 1H, H7β), 1.40(br. s, 1H, 1 OH), 1.34(s, 9H, 3Me t-buthoxy), 1.24(s, 3H, Me16), 1.13(s, 3H, Me17).

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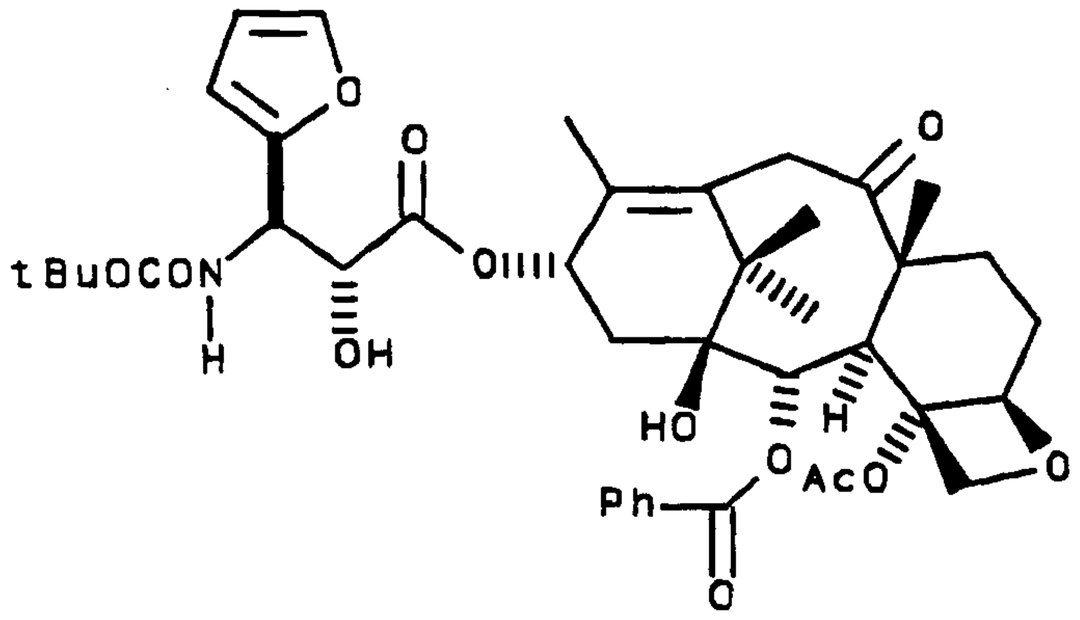
EXAMPLE 10



(72-3)

Preparation of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™

To a solution of 7-deshydroxy-10-desacetoxy baccatin (III) (35.0 mg, 0.061 mmol) in 0.8 mL of THF at -45°C was added dropwise 0.07 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsilyloxy-4-(2-furyl)-azetidin-2-one (68.0 mg, 0.18 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 56.3 mg of a mixture containing (2'R,3'S)-2'-O-triethylsilyl-3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 56.3 mg (0.06 mmol) of the mixture obtained from the previous reaction in 4.6 mL of acetonitrile and 0.22 mL of pyridine at 0 °C was added 0.68 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

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48.3 mg of material which was purified by flash chromatography to give 31.7 mg (69%) of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-7-des-hydroxy-10-desacetoxy taxol™, which was recrystallized from methanol/water.

m.p.128-131°C; $[\alpha]^{25}_{Na}$ -66.9° (c 0.0028, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.13(d, J=6.9 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.48(m, 2H, benzoate meta), 7.40(m, 1H, furyl), 6.38(m, 1H, furyl), 6.32(m, 1H, furyl), 6.12(td, J=8.1, 1.8 Hz, 1H, H13), 5.67(d, J=6.9 Hz, 1H, H2), 5.22(d, J=9.9 Hz, 1H, NH), 5.17(d, J=9.9 Hz, 1H, H3'), 4.91(dd, J=9.1, 2.7 Hz, 1H, H5), 4.60(dd, J=5.7, 2.1 Hz, 1H, H2'), 4.28(d, J=8.1, 1H, H20α), 4.21(d, J=8.1 Hz, 1H, H20β), 3.95(d, J=6.9 Hz, H3), 3.82(d, J=16.5, 1H, H10α), 3.33(m, 1H, H10β), 3.31(m, 1H, 2'OH), 2.38(m, 1H, H14α), 2.35(s, 3H, 4Ac), 2.23(m, 1H, H14β), 2.20(m, 1H, H6α), 2.11(m, 1H, H7α), 1.94(m, 1H, H6β), 1.73(s, 3H, Me18), 1.71(s, 3H, Me19), 1.43(m, 1H, H7β), 1.38(br. s, 1H, 1 OH), 1.32(s, 9H, 3Me t-buthoxy), 1.23(s, 3H, Me16), 1.12(s, 3H, Me17).

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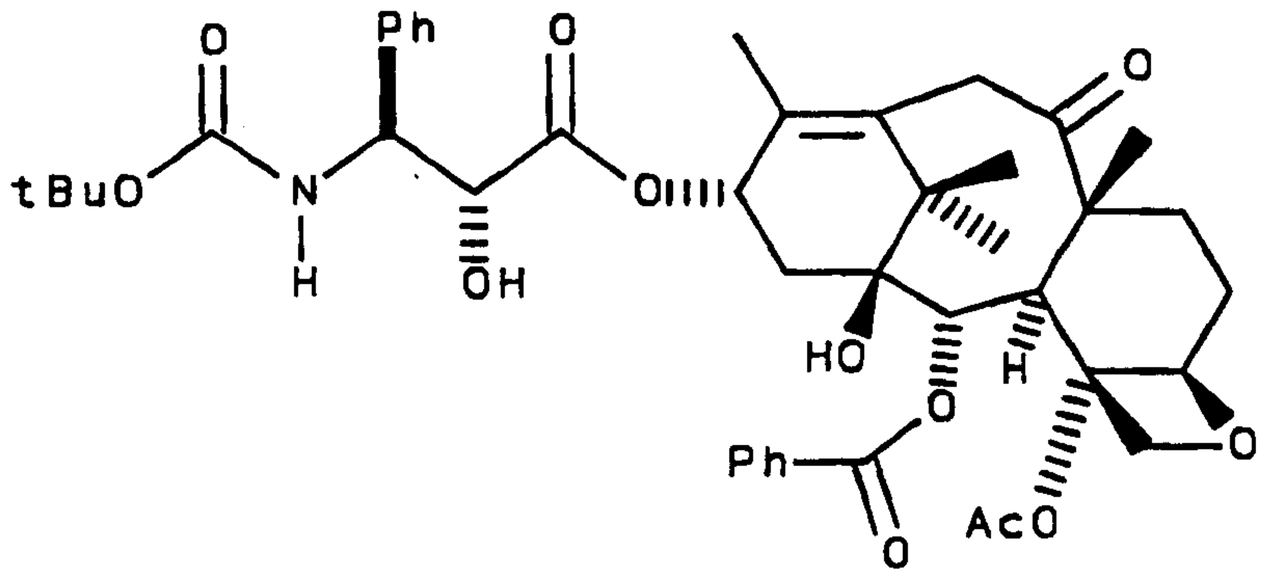
EXAMPLE 11



(72-4)

Preparation of N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™.

To a solution of 7-deshydroxy-10-desacetoxy baccatin (III) (28.0 mg, 0.049 mmol) in 0.7 mL of THF at -45 °C was added dropwise 0.06 mL of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h at -45 °C, a solution of *cis*-1-t-butoxycarbonyl-3-triethylsilyloxy-4-(phenyl)-azetidin-2-one (56.0 mg, 0.15 mmol) in 0.7 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 38.4 mg of a mixture containing (2'R,3'S)-2'-O-triethylsilyl-N-desbenzoyl-N-(t-butoxy-carbonyl)-7-deshydroxy-10-desacetoxy taxol™ and a small amount of the (2'S,3'R) isomer.

To a solution of 38.4 mg (0.041 mmol) of the mixture obtained from the previous reaction in 3.2 mL of acetonitrile and 0.15 mL of pyridine at 0 °C was added 0.46 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 33.8 mg of material which was purified by flash

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chromatography to give 27.4 mg (71%) of N-desbenzoyl-N-(t-butoxycarbonyl)-7-deshydroxy-10-desacetoxy taxol™, which was recrystallized from methanol/water.

m.p.135-138°C; $[\alpha]^{25}_{Na}$ -65.2° (c 0.0025, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.12(d, J=7.1 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 7.42-7.29(m, 5H, phenyl), 6.12(td, J=8.1, 1.8 Hz, 1H, H13), 5.66(d, J=6.9 Hz, 1H, H2), 5.21(d, J=9.9 Hz, 1H, NH), 5.16(d, J=9.9 Hz, 1H, H3'), 4.92(dd, J=9.1, 2.7 Hz, 1H, H5), 4.58(dd, J=5.7, 2.1 Hz, 1H, H2'), 4.30(d, J=8.1, 1H, H20α), 4.21(d, J=8.1 Hz, 1H, H20β), 3.97(d, J=6.9 Hz, H3), 3.82(d, J=16.5, 1H, H10α), 3.41(m, 1H, H10β), 3.36(m, 1H, 2'OH), 2.40(m, 1H, H14α), 2.38(s, 3H, 4Ac), 2.26(m, 1H, H14β), 2.20(m, 1H, H6α), 2.13(m, 1H, H7α), 1.93(m, 1H, H6β), 1.73(s, 3H, Me18), 1.70(s, 3H, Me19), 1.43(m, 1H, H7β), 1.38(br. s, 1H, 1 OH), 1.32(s, 9H, 3Me t-buthoxy), 1.25(s, 3H, Me16), 1.15(s, 3H, Me17).

EXAMPLE 12

Taxanes 68-3, 68-4, 69-1, 69-2, 72-1, 72-2, 72-3, and 72-4 of Examples 4-11 were evaluated in in vitro cytotoxicity activity against human colon carcinoma cells HCT-116. Cytotoxicity was assessed in HCT116 cells by XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide) assay (Scudiero et al, "Evaluation of a soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines", Cancer Res. 48:4827-4833, 1988). Cells were plated at 4000 cells/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37°C for 72 hours at which time the tetrazolium dye, XTT, was added. A dehydrogenase enzyme in live cells reduces the XTT to a

form that absorbs light at 450 nm which can be quantitated spectrophotometrically. The greater the absorbance the greater the number of live cells. The results are expressed as an IC_{50} which is the drug concentration required to inhibit cell proliferation (i.e. absorbance at 450 nm) to 50% of that of untreated control cells.

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

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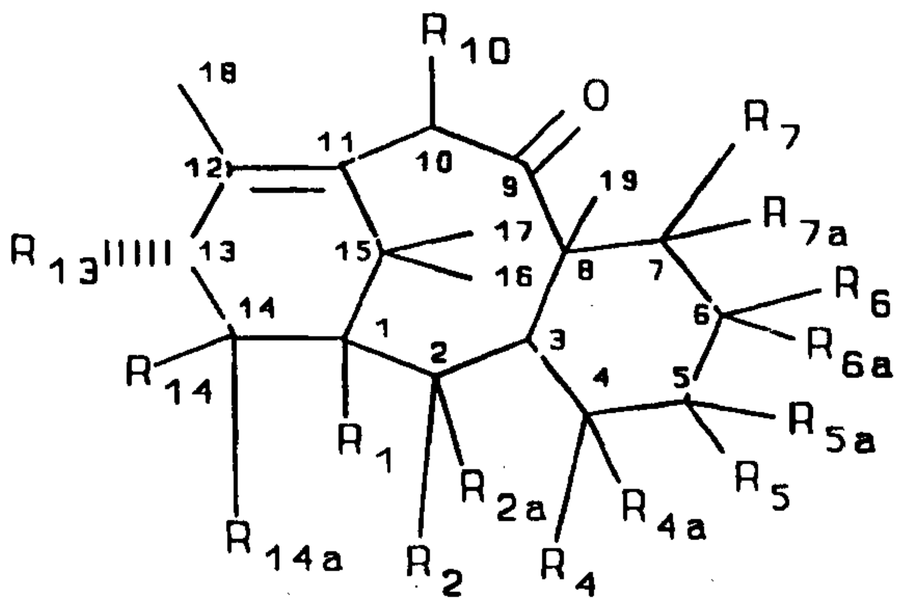
CLAIMS:

1. A process for abstracting a C10 hydroxy, acyloxy or sulfonyloxy substituent from a taxane comprising reacting the C10 hydroxy, acyloxy or sulfonyloxy substituted taxane with samarium diiodide.

2. The process of claim 1 wherein the taxane corresponds to the formula:



(1)

wherein

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

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

R_{2a} is hydrogen or 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;

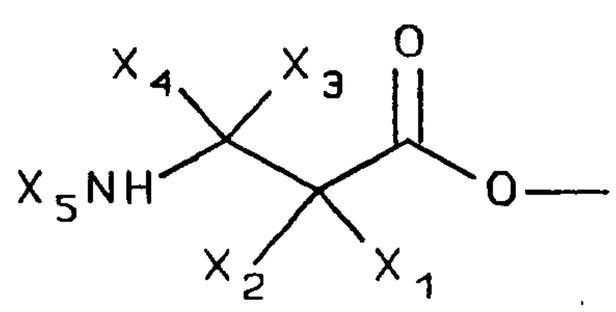
R_{6a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R_6 forms an oxo;

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_{10} is hydroxy, acyloxy or sulfonyloxy;

R_{13} is hydroxy, protected hydroxy or



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 or a functional group which increases the solubility of the taxane derivative;

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

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, or heteroaryl;

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;

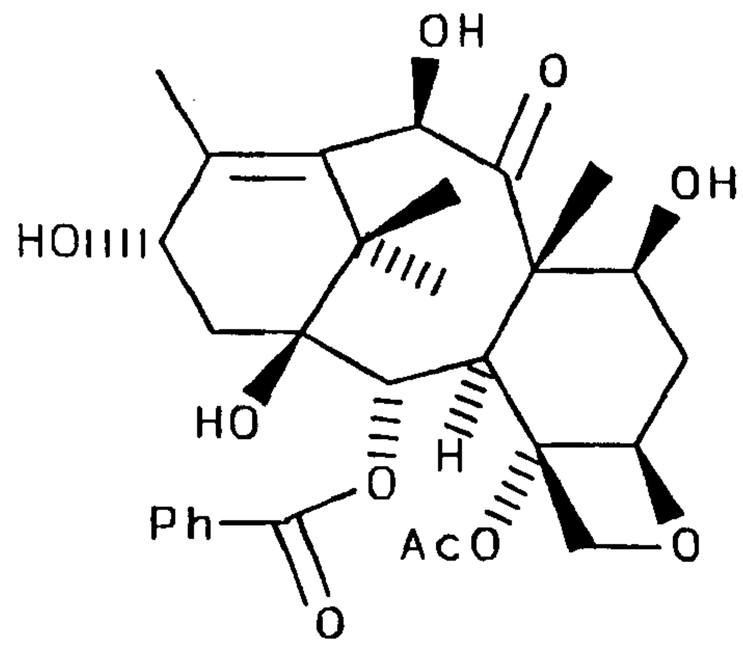
X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$; and

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

3. The process of any one of claims 1 and 2 wherein the taxane has a C10 hydroxy substituent.

4. The process of any one of claims 1 and 2 wherein the taxane has a C10 acetoxy substituent.

5. The process of claim 1 wherein the taxane has the formula



or

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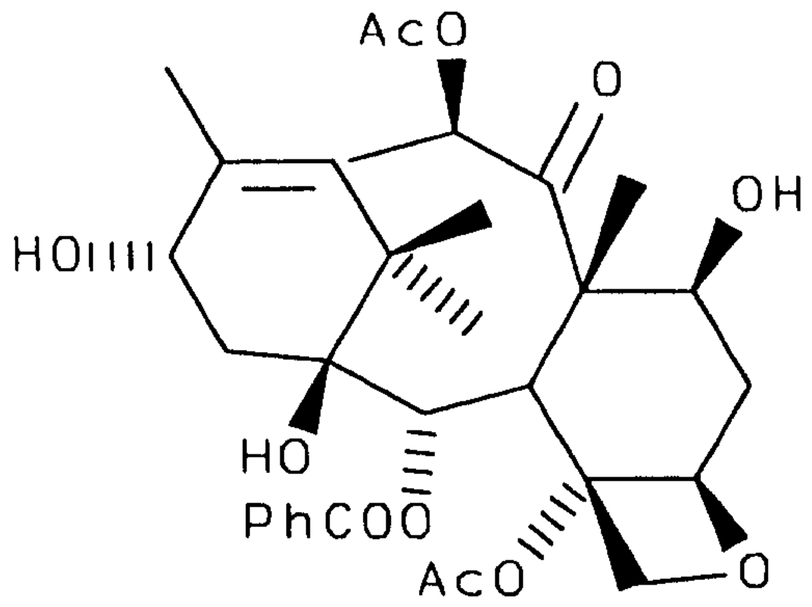
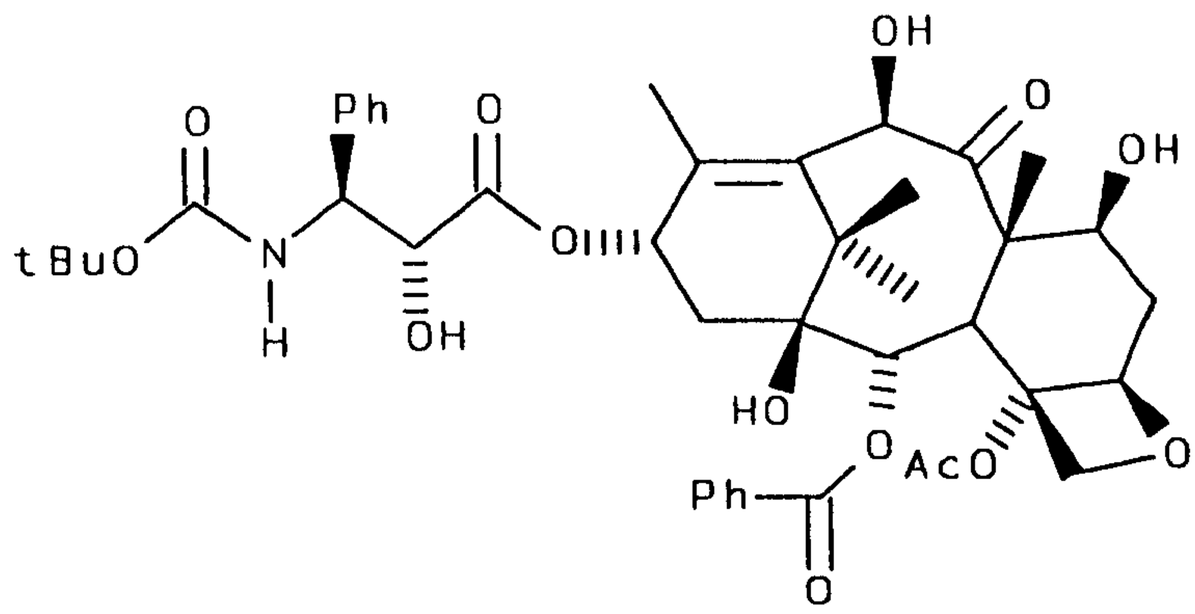
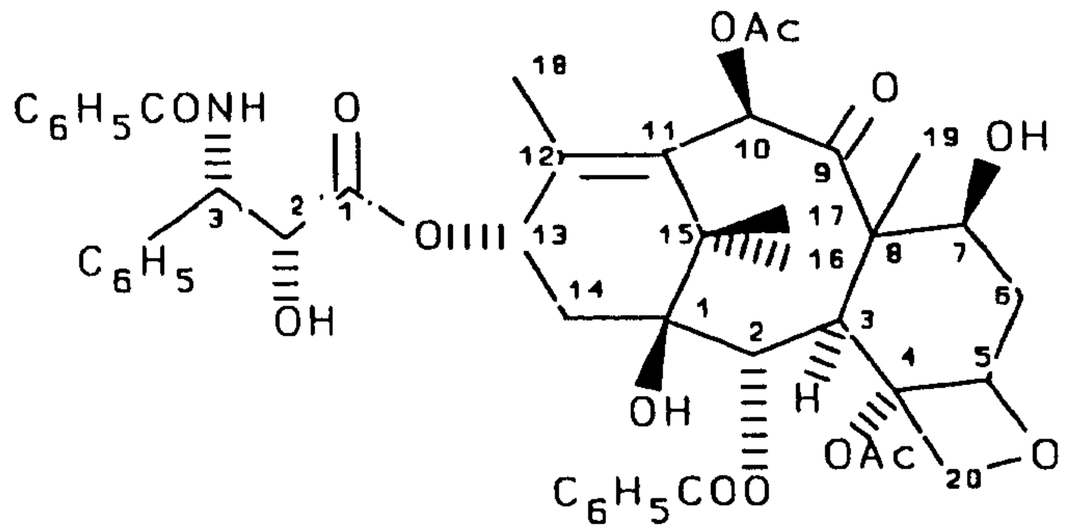


wherein Ac is acetyl and Ph is phenyl.

6. The process of claim 1 wherein the taxane has the formula



or



wherein Ac is acetyl, Ph is phenyl, and tBu is tert-butyl.

7. The process of claim 2 wherein the taxane has the formula

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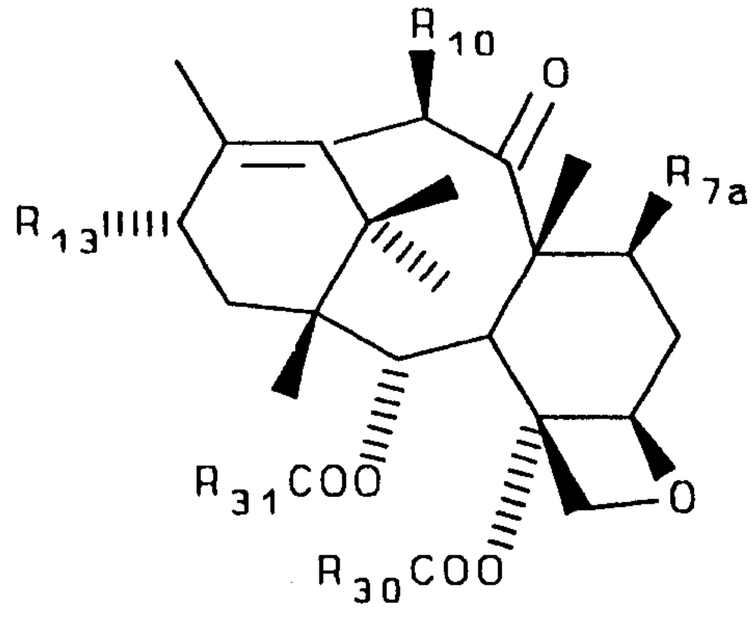
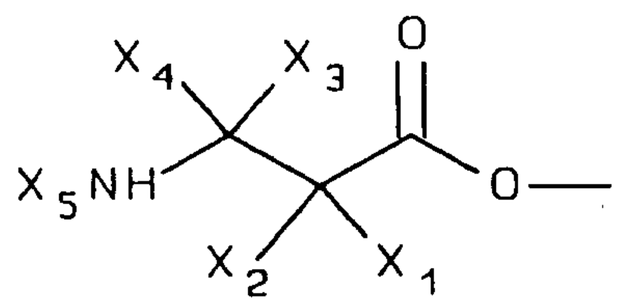


wherein

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

R_{10} is hydroxy or acetoxy;

R_{13} is hydroxy, protected hydroxy or



;

R_{28} is acyl;

R_{30} is alkyl;

R_{31} is monocyclic aryl; and

X_1 - X_5 are as defined in claim 2.

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PATENT AGENTS