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(54) Title: PREPARATION OF TAXANES FROM 9-DIHYDRO-13-ACETYLBACCATIN III

(57) Abstract: The present invention relates to a new process for the preparation of 9-dihydrobaccatin III intermediates as useful precursors for the preparation of paclitaxel, 1, docetaxel, 2, and analogues thereof. More particularly, the process comprises the steps of (i) concomitantly deacetylating esters at the 10-position and 13-position of 9-dihydro-13-acetylbaccatin III to form 9-dihydro-10-deacetylbaccatin III; (ii) protecting a hydroxy group at the 7-position of 9-dihydro-10-deacetylbaccatin III; and (iii) acylating a hydroxy group at the 10-position to form a compound of formula II.



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PREPARATION OF TAXANES FROM 9-DIHYDRO-13-
ACETYLBACCATIN III

CROSS-REFERENCE TO RELATED APPLICATIONS

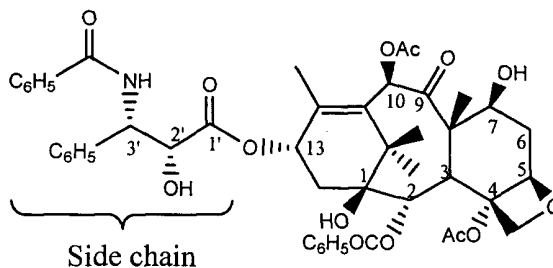
[0001] This application claims the benefit of U.S. provisional application No. 60/666,728 filed March 31, 2005 which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention is directed towards a new method for the preparation of derivatives of 9-dihydrobaccatin III from 9-DHAB-III. It is also directed towards a new method to convert such derivatives of 9-dihydrobaccatin III into biologically active taxanes through coupling of suitable taxane side chains followed by oxidation of the 9 position. Such derivatives of 9-dihydrobaccatin III can be used as starting material for the synthesis of paclitaxel, docetaxel and analogs thereof.

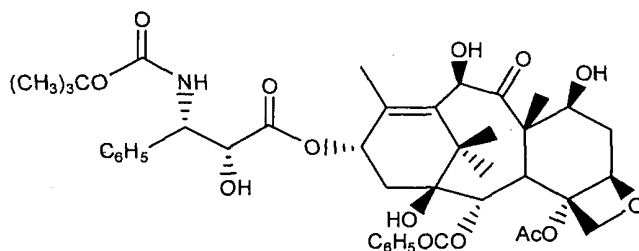
BACKGROUND OF THE INVENTION

[0003] Paclitaxel, a naturally occurring diterpenoid extracted from yew trees, has demonstrated great potential as an anti-cancer drug. It is unique among antimetabolic drugs in that it promotes the assembly of stable microtubules from tubulin. It binds strongly to microtubules, thus preventing depolymerisation of the tubulin and inhibiting mitosis. The structure of paclitaxel 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.

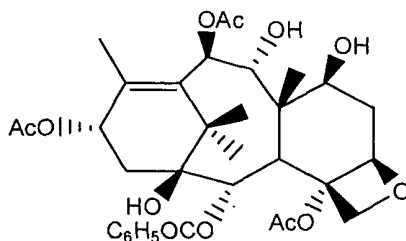


[0004] The acyclic portion attached to the 13-hydroxy group is commonly referred to as "side chain" of a taxane compound.

[0005] Docetaxel, a paclitaxel derivative, has also demonstrated excellent antitumor activity over the past few years. Docetaxel has the following structure:



[0006] The chemical conversion of naturally occurring precursors such as 10-deacetylbaccatin III to paclitaxel and docetaxel have been reported. However, another potential precursor, 9-dihydro-13-acetylbaccatin III (9-DHAB-III), is abundant in needles and stems of the Canada yew, *Taxus canadensis*. The taxane structure of naturally occurring 9-DHAB-III has the carbon skeleton of paclitaxel and docetaxel except for the lack of a side chain and an alpha-hydroxyl group at C9. 9-DHAB-III has the following structure:



[0007] Synthetic routes that have been proposed for the synthesis of biologically active taxanes from 9-DHAB-III involve its conversion to baccatin III, 10-deacetylbaccatin III and 7-protected derivatives thereof. In this approach, a 7-protected-9-DHAB-III is oxidised at C9 followed by deacetylation at C10 and/or C13 (US Patent 6,197,981). Others have used 9-DHAB-III as starting material to produce novel 9-dihydro taxanes with potentially greater therapeutic benefits.

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[0008] Important limitations and difficulties associated with existing methods using 9-DHAB-III as starting material include the difficult and low yield of deacetylation at 13-hydroxy group, poor scalability and the limited versatility of synthetic intermediates.

[0009] Earlier methods for the transformation of 9-DHAB III to 9-ketotaxanes bearing side chains involved the oxidation of the 9-hydroxy group prior to connecting the side chain to the baccatin A ring. A major difficulty with this approach is that the 13-acetoxy group of 7-protected-9-keto-baccatin III resists hydrolysis. Its removal requires strong bases such as alkyl lithium and the prior hydrolysis of the 10-acetoxy group resulting in overall low yield.

[0010] Another disadvantage is that the protection of the 7- hydroxy and 10-hydroxy groups in the synthesis of docetaxel and analogs thereof requires a separate step for protection of each position.

[0011] Therefore, additional routes for the production of biologically active taxanes are still needed.

[0012] It would thus be highly desirable to be provided with a new process for the preparation of paclitaxel, docetaxel, 9-dihydrobaccatin III, baccatin III and other taxanes from 9-DHAB-III.

SUMMARY OF THE INVENTION

[0013] One aim of the present invention is to provide a process for the preparation of paclitaxel, docetaxel, and analogs thereof where naturally occurring 9-DHAB-III or derivatives thereof are used as starting material.

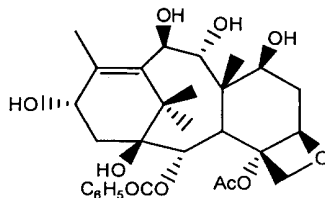
[0014] Another aim of the present invention is to provide novel and versatile 9-dihydrobaccatin III derivatives as intermediates for the preparation of paclitaxel, docetaxel and other taxanes.

[0015] Another aim of the present invention is to provide a process for the preparation of 9-ketotaxane intermediates useful in the preparation of paclitaxel,

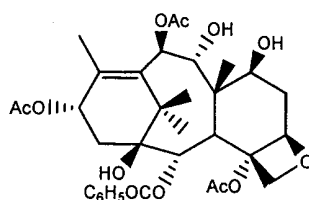
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docetaxel and analogs thereof using mild oxidation of the corresponding 9-dihydrotaxanes intermediates bearing protected side chains.

[0016] In one aspect of the invention, there is provided a process for the preparation of 9-dihydro-10-deacetylbaccatin III

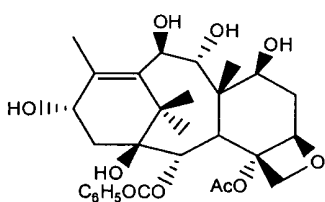


which comprises the step of reacting 9-dihydro-13-acetylbaccatin III having the formula:

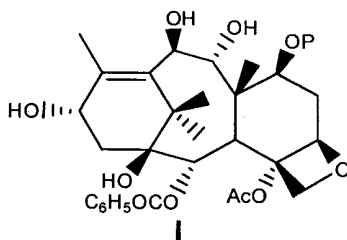


with a deacetylating agent in absence of a solvent to concomitantly deacetylate 10- and 13- positions and produce 9-dihydro-10-deacetylbaccatin III.

[0017] In accordance with the present invention, the process is further comprising the step of protecting the 7-hydroxy group of 9-dihydro-10-deacetylbaccatin III



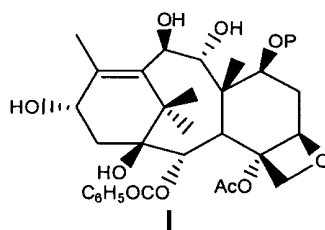
to produce a taxane of formula I



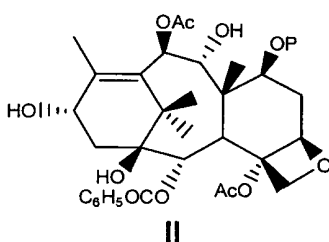
wherein P is a hydroxy protecting group.

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[0018] In accordance with the present invention, the process is further comprising the step of acetylating the 10-hydroxy group of the taxane of formula I:

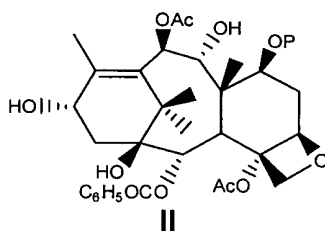


to produce a taxane of formula II:

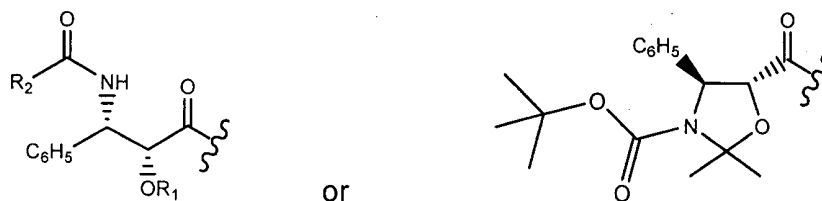


[0019] In accordance with the present invention, the process is further comprising the steps of:

i) reacting the 13-hydroxy group of the compound of formula II



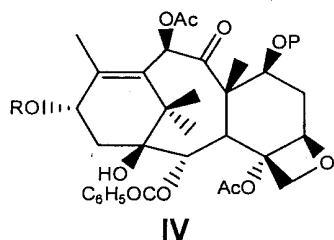
with a taxane side chain precursor of formula R-X, wherein X is a leaving group and R is



wherein R₁ is selected from the group consisting of ethoxyethyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl and tert-butyloxycarbonyl and R₂ is phenyl or tert-butoxy; and

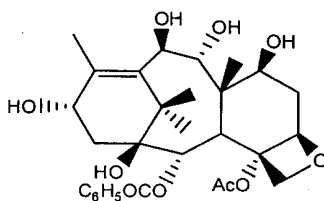
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ii) oxidizing the 9-hydroxy group with an oxidizing agent to produce a taxane of formula IV

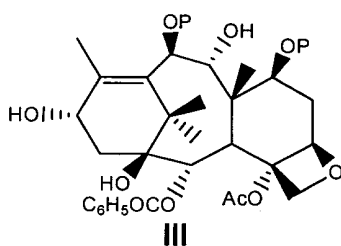


[0020] In one aspect of the invention, there is provided a process for the preparation of 9-dihydro-10-deacetylbaccatin III as described herein; and

further comprising the step of concomitantly protecting 10-hydroxy and 7-hydroxy groups of the 9-dihydro-10-deacetylbaccatin III



to produce a taxane of formula III

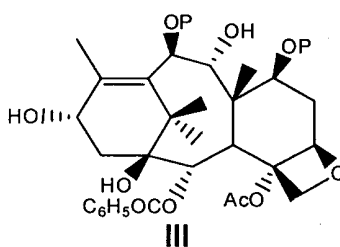


wherein each P is the same and is a hydroxy protecting group.

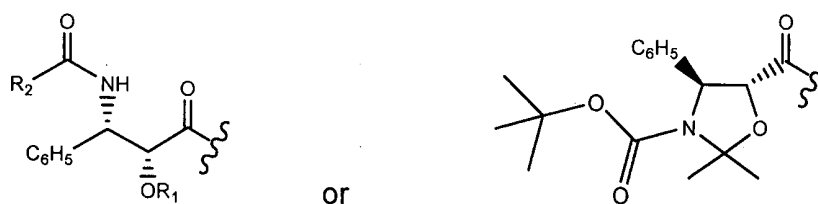
[0021] In accordance with the present invention, the process is further comprising the steps of:

i) reacting the 13-hydroxy group of the compound of formula III

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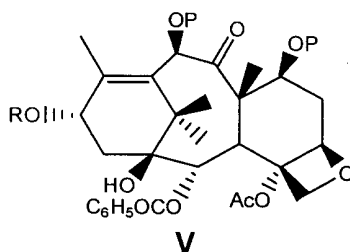


with a taxane side chain precursor of formula R-X, wherein X is a leaving group and R is

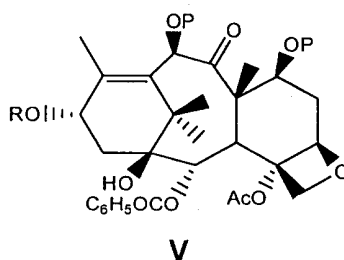


wherein R₁ is selected from the group consisting of ethoxyethyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl and tert-butyloxycarbonyl and R₂ is phenyl or tert-butoxy; and

ii) oxidizing the 9-hydroxy group with an oxidizing agent to produce a taxane of formula V



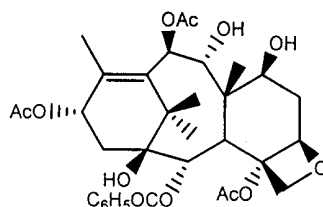
[0022] In accordance with the present invention, there is provided a process for the preparation of compound of formula V



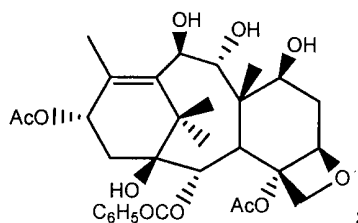
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wherein P is a hydroxy protecting group and R is acetyl, said process comprising the steps of :

i) selectively deacetylating the 10-hydroxy group of 9-dihydro-13-acetylbaccatin III having the formula:



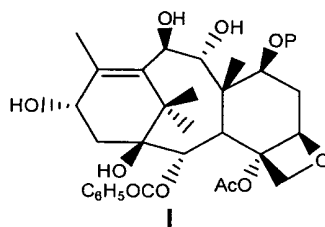
with N,N-dimethylethylenediamine to form 9-dihydro-10-deacetyl-13-acetylbaccatin III of formula:



ii) concomitantly protecting 7-hydroxy and 10-hydroxy groups of the reaction product of step i); and

iii) oxidizing the 9-hydroxy group of the reaction product of step ii) with an oxidizing agent to form the compound of formula V.

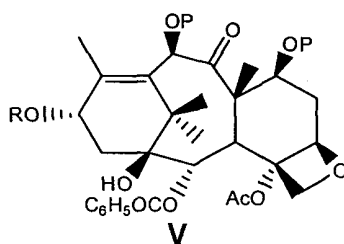
[0023] In accordance with the present invention, there is also provided a compound of formula I



wherein P is a hydroxy protecting group.

[0024] In accordance with the present invention, there is also provided a compound of formula V

- 9 -



wherein P is a hydroxy protecting group and R is acetyl.

In accordance with the present invention, there is provided a process for producing a pharmaceutically active taxane which comprises the steps of i) producing a taxane of formula IV by the process as described herein; and ii) transforming said compound of formula IV into the pharmaceutically active taxane.

In accordance with the present invention, there is provided a process for producing a pharmaceutically active taxane, which comprises the steps of i) producing a taxane of formula V by the process as described herein; and ii) transforming said compound of formula V into the pharmaceutically active taxane.

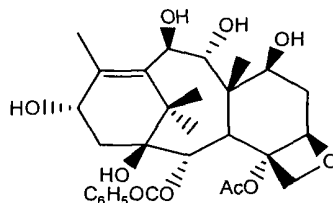
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0025] In one embodiment, the present invention provides a new method for the preparation of 9-dihydro-10-deacetylbaccatin III from 9-DHAB III in one step and nearly quantitative yield. In the new method, no attempt is made to solubilize 9-DHAB III in preparation for deacetylation. Concentrated mixtures of 9-DHAB-III in hydrazine monohydrate or hydrazine hydrate in which 9-DHAB-III is insoluble or very sparingly soluble allow its complete conversion into 9-dihydro-10-deacetylbaccatin III, which is also insoluble in these conditions.

[0026] The use of solvents such as ethanol used by other groups allows for the deacetylation of 10-hydroxy group only and requires an additional reaction step with strong nucleophiles such as methyllithium or n-butyllithium to deacetylate 13-hydroxy group.

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[0027] In accordance with the present invention, there is also provided a process for the preparation of 9-dihydro-10-deacetylbaaccatin III

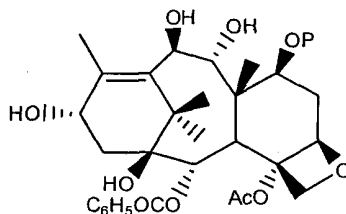


which comprises the step of reacting 9-dihydro-13-acetylbaaccatin III with a deacetylating agent, such as for example, hydrazine monohydrate, in absence of a solvent.

[0028] In one embodiment, the process is further comprising the step of washing the 9-dihydro-10-deacetylbaaccatin III with an aqueous solvent.

[0029] In one embodiment, the aqueous solvent is water.

[0030] It is a further object of this invention to provide a simple and efficient method of preparing 7-protected-9-dihydro-10-deacetylbaaccatin III of formula I



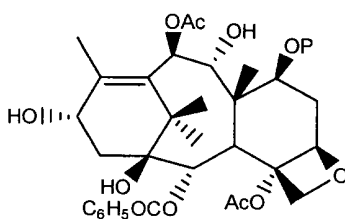
I

wherein P is a hydroxy protecting group, which comprises the step of reacting 9-dihydro-10-deacetylbaaccatin III with a hydroxy protecting group to form a compound of formula I.

In one embodiment, the 7-hydroxy group protection is highly regioselective.

[0031] The present invention also provides a process for the preparation of compound of formula II

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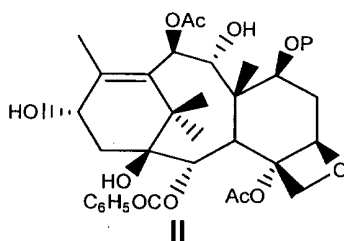


II

which comprises the step of acylating a compound of formula I.

In one embodiment, the 10-hydroxy acetylation is highly regioselective.

[0032] In accordance with the present invention there is provided a process for the preparation of a taxane of formula II



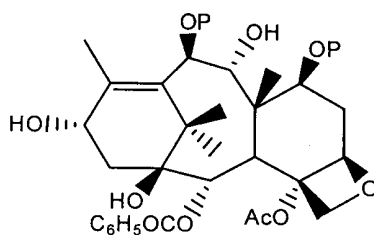
II

wherein P is a hydroxy protecting group, said process comprising the steps of:

- concomitantly deacetylating esters at the 10-position and 13-position of 9-dihydro-13-acetylbaccatin III to form 9-dihydro-10-deacetylbaccatin III;
- protecting a hydroxy group at the 7-position of 9-dihydro-10-deacetylbaccatin III; and
- acylating a hydroxy group at the 10-position to form a compound of formula II.

[0033] The present invention also provides a process for the selective and concomitant protection of 9-dihydro-10-deacetylbaccatin III at both C7 and C10 to afford a compound of formula III

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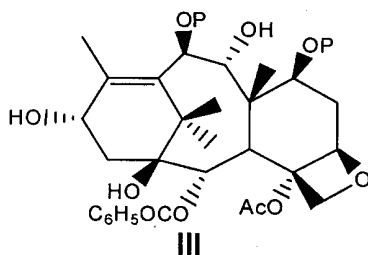


III

wherein P is a hydroxy protecting group, which comprises the step of reacting 9-dihydro-10-deacetylbaccatin III with a hydroxy protecting group to form a compound of formula III.

In one embodiment, the 7-, 10- bishydroxy group protection is highly regioselective.

[0034] In accordance with the present invention, there is also provided a process for the preparation of a taxane of formula III



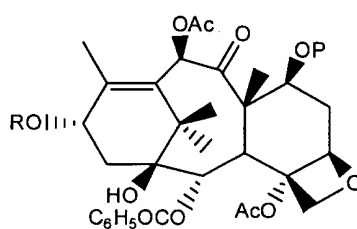
III

wherein P is a hydroxy protecting group, said process comprising the steps of:

- concomitantly deacetylating esters at the 10-position and 13-position of 9-dihydro-13-acetylbaccatin III to produce 9-dihydro-10-deacetylbaccatin III; and
- concomitantly protecting hydroxy groups at the 7-position and 10 position of 9-dihydro-10-deacetylbaccatin III to form a compound of formula III.

[0035] The present invention further provides a process for the preparation of compound of formula IV

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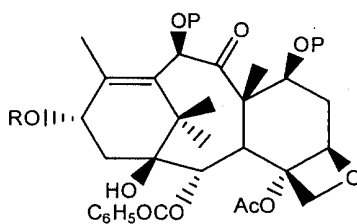


IV

wherein P is a hydroxy protecting group and R is protected side chain, which comprises the step of : (i) reacting a compound of formula II at the 13 position with a suitable taxane side chain precursor; and (ii) oxidizing the hydroxyl group at the 9 position.

[0036] Compounds of formula IV can be converted to paclitaxel and analogs thereof.

[0037] The present invention further provides a process for the preparation of compound of formula V



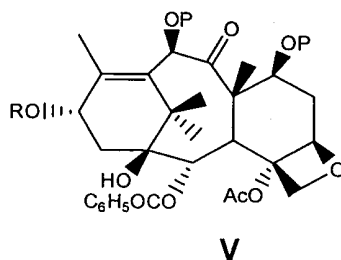
V

wherein P is a hydroxy protecting group and R is protected side chain, which comprises the step of : (i) reacting a compound of formula III at the 13 position with a suitable taxane side chain precursor; (ii) oxidizing the hydroxyl group at the 9 position.

[0038] Compounds of formula V can be converted to docetaxel and analogs thereof.

[0039] Still in accordance with the present invention, there is also provided a process for the preparation of compound of formula V

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wherein P is a hydroxy protecting group and R is acetyl,

said process comprising the steps of :

- selectively deacetylating the ester at the 10-position of 9-dihydro-13-acetylbaccatin III with N,N-dimethylethylenediamine to form 9-dihydro-10-deacetyl-13-acetyl-baccatin III;
- concomitantly protecting hydroxy groups at the 7-position and 10-position of 9-dihydro-10-deacetyl-13-acetyl-baccatin III; and
- oxidizing the hydroxy group at the 9 position with an oxidizing agent to form a compound of formula V.

[0040] In accordance with the present invention, there is provided a process for producing a pharmaceutically active taxane which comprises the steps of i) producing a taxane of formula IV by the process as described herein; and ii) transforming said compound of formula IV into the pharmaceutically active taxane. In one embodiment, the pharmaceutically active taxane is paclitaxel.

[0041] In further embodiments, paclitaxel is paclitaxel anhydrous or trihydrates.

[0042] In accordance with the present invention, there is provided a process for producing a pharmaceutically active taxane, which comprises the steps of i) producing a taxane of formula V by the process as described herein; and ii) transforming said compound of formula V into the pharmaceutically active taxane. In one embodiment, the pharmaceutically active taxane is docetaxel.

[0043] In further embodiments, docetaxel is docetaxel anhydrous or trihydrates.

[0044] The present invention provides the advantage that starting material for the preparation of intermediates, 9-DHAB-III, is abundant in needles and twigs of the Canada yew, *Taxus Canadensis*.

[0045] For the purpose of the present invention the following terms are defined below.

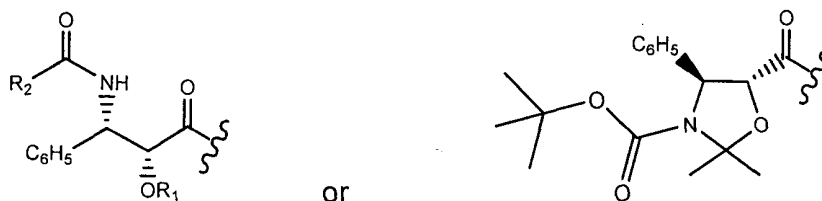
[0046] The term "hydroxy protecting group" is intended to mean a group that is attached to the oxygen of the hydroxyl group, for protecting said group from reacting in a subsequent reaction. Such group are well known in the art.

[0047] In one embodiment, the protecting group is triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl or tert-butyloxycarbonyl,

[0048] In one embodiment, the protecting group is triethylsilyl.

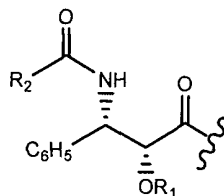
[0049] The term "protected taxane side chain" is intended to mean a side chain which when attached to the core molecules described herein will result in a taxane. The protected taxane side chain is said to be protected such that any reactive group on said side chain are prevented from reacting in any subsequent reaction until the protective group is removed. Such protective group is well known in the art. Moreover, the person skilled in the art will readily recognize the side chain required to produce a specific taxane when attached to the core molecules.

[0050] In one embodiment of the present invention, the taxane side chain precursor is of formula R-X, wherein R is

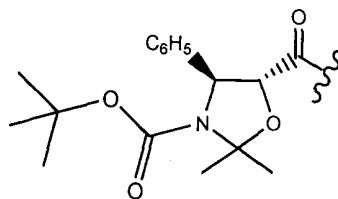


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[0051] In one embodiment R is



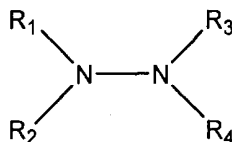
[0052] In one embodiment R is



[0053] The term "deacetylating agent" means a reagent that has the ability to remove an acetyl group from the C-10 and C-13 hydroxyl of 9-dihydro-13-acetylbaccatin III. The deacetylating agent is a weak base being sufficiently nucleophilic to remove acetyl group. An appropriate agent should not have detrimental effect on other functionalities of the 9-dihydro-13-acetylbaccatin III and in particular C-2 benzoate or C-4 acetoxy groups. Non-limiting examples include hydrazine, methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, 1,2-diethylhydrazine, phenylhydrazine or their hydrate thereof.

[0054] In one embodiment, the deacetylating agent is a nucleophilic weak base.

[0055] In one embodiment, the deacetylating agent is a hydrazine compound or its corresponding hydrate having the formula:



wherein each R₁ to R₄ is independently a hydrogen, an optionally substituted C₁-C₆ alkyl or an optionally substituted C₆ aryl.

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[0056] In a further embodiment, each R₁ to R₄ is independently a hydrogen, a C₁-C₄ alkyl or a phenyl.

[0057] In a further embodiment, each R₁ to R₄ is independently a hydrogen, a methyl, an ethyl or a phenyl.

[0058] In one embodiment, the deacetylating agent is hydrazine, methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, 1,2-diethylhydrazine, phenylhydrazine or their hydrate thereof.

[0059] In one embodiment, the deacetylating agent is hydrazine monohydrate.

[0060] As used herein, the term "solvent" means a liquid that partially or totally dissolves 9-dihydro-13-acetylbaccatin III.

[0061] The term "alkyl" represents a linear, branched or cyclic hydrocarbon moiety having 1 to 6 carbon atoms, which is optionally substituted. Examples include but are not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, neoheptyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term alkyl is also meant to include alkyls in which one or more hydrogen atom is replaced by a halogen, ie. an alkylhalide. Examples include but are not limited to trifluoromethyl, trichloromethyl, trifluoroethyl, trichloroethyl.

[0062] The term "aryl" represents a carbocyclic moiety containing one benzenoid-type ring and which may be optionally substituted with one or more substituents. Examples include but are not limited to phenyl, tolyl, dimethylphenyl, aminophenyl, anilinyll.

[0063] The term "independently" means that a substituent can be the same or a different definition for each item.

[0064] The terms "substituted" or "substituant" represent one or more halogen, amino, cyano, hydroxyl, nitro or acyl.

[0065] As used herein, the term "hydrate" in relation with "hydrazine" means that hydrazine incorporates water. Illustrative non-limiting examples include monohydrate, dihydrate, trihydrate and tetrahydrate or semi-hydrate. The hydration may be assessed by methods known in the art such as Loss on Drying techniques (LOD) and Karl Fisher titration.

[0066] The term "leaving group" herein refers to an atom or molecule that detaches from the group R- when exposed to an hydroxyl group of a taxane compound under usual reaction conditions. Examples include halogens such as chloride, bromide and iodide, sulfonates such as trifluoromethanesulfonate and methanesulfonate, azide, a derivative resulting from a carbodiimide such as N,N'-dicyclohexylcarbodiimide (DCC) N,N'-diisopropylcarbodiimide (DIC) or 1-ethyl-3-(3-dimethylaminopropyl) or carbodiimidehydrochloride (EDC).

[0067] "Oxidizing agent" that can be used in accordance with the present invention are for example, without limitation, o-iodoxybenzoic acid (IBX), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane), iodosobenzene, iodozobenzene diacetate, CrO₃/ H₂SO₄ (Jones reagent), pyridinium dichromate, pyridinium chlorochromate, potassium permanganate and Swern reagent. Preferably, the oxidizing agent is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one.

[0068] The term "Swern reagent" herein refers to a reagent for oxidizing primary or secondary alcohols (hydroxyl groups) involving dimethylsulfoxide (DMSO) and anyone of a number of electrophilic molecule including but not limited to dicyclohexylcarbodiimide (DCC), acetic anhydride, trifluoroacetic anhydride, oxalyl chloride and sulphur trioxide.

[0069] In accordance with one embodiment of the present invention, it has been discovered that 9-DHAB-III can be deacetylated at both 10-hydroxy and 13-hydroxy groups under mild conditions and in near quantitative yields with hydrazine monohydrate. Surprisingly, it was discovered that neat hydrazine monohydrate (i.e. in the absence of a solvent) in which 9-DHAB-III is only sparingly soluble allows for complete deacetylation of the acetate at position C-

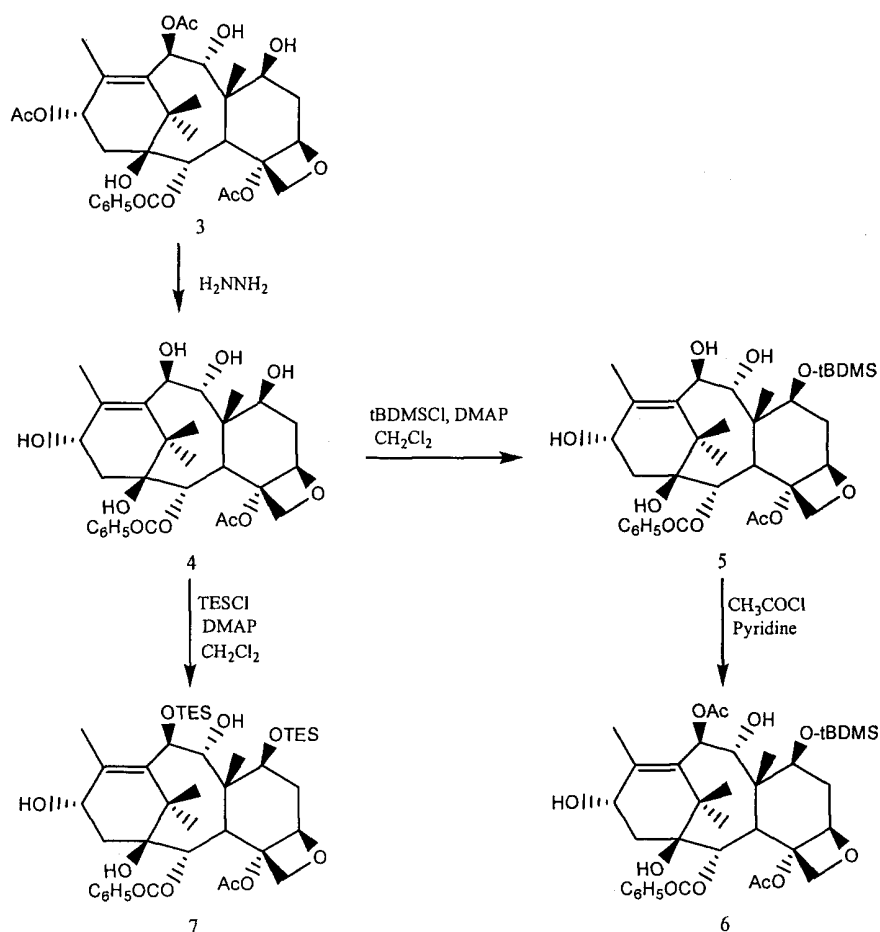
13. Hydrazinolysis is highly selective and both 10- and 13-acetate are removed while the 4-acetoxy and 2-benzoate groups remain intact. That is in clear contrast with the techniques known in the art.

[0070] With reference to scheme 1. 1, 9-DHAB-III (compound 3) was treated with neat hydrazine monohydrate, in accordance with the present invention, to yield the 9-dihydro-10-deacetylbaaccatin III, (compound 4), that is also sparingly soluble in neat hydrazine monohydrate, and was then easily recovered by simple filtration. The 7-hydroxy group requires no protection during removal of the 10- and 13-acetate groups with base since the absence of a keto group at the 9-position prevents epimerisation of the 7-hydroxy group through a retro-aldol mechanism

[0071] Compound 4 was converted to C-7-hydroxy-protected-10-acetoxy taxanes in two steps. First, the C-7 hydroxy group was protected with a hydroxy protecting group which in a preferred embodiment comprises silyl protecting groups in the presence of a catalyst such as 4-dimethylaminopyridine to yield compound 5. Second, the C-10 hydroxy group was acetylated selectively by reaction with acetyl chloride in pyridine to give compound 6.

[0072] Compound 4 was also converted into 7-,10-bis-protected taxanes 7 in a single step. In a preferred embodiment, trialkylsilylchloride was reacted with compound 4 in the presence 4-dimethylaminopyridine to yield compound 7.

Scheme 1

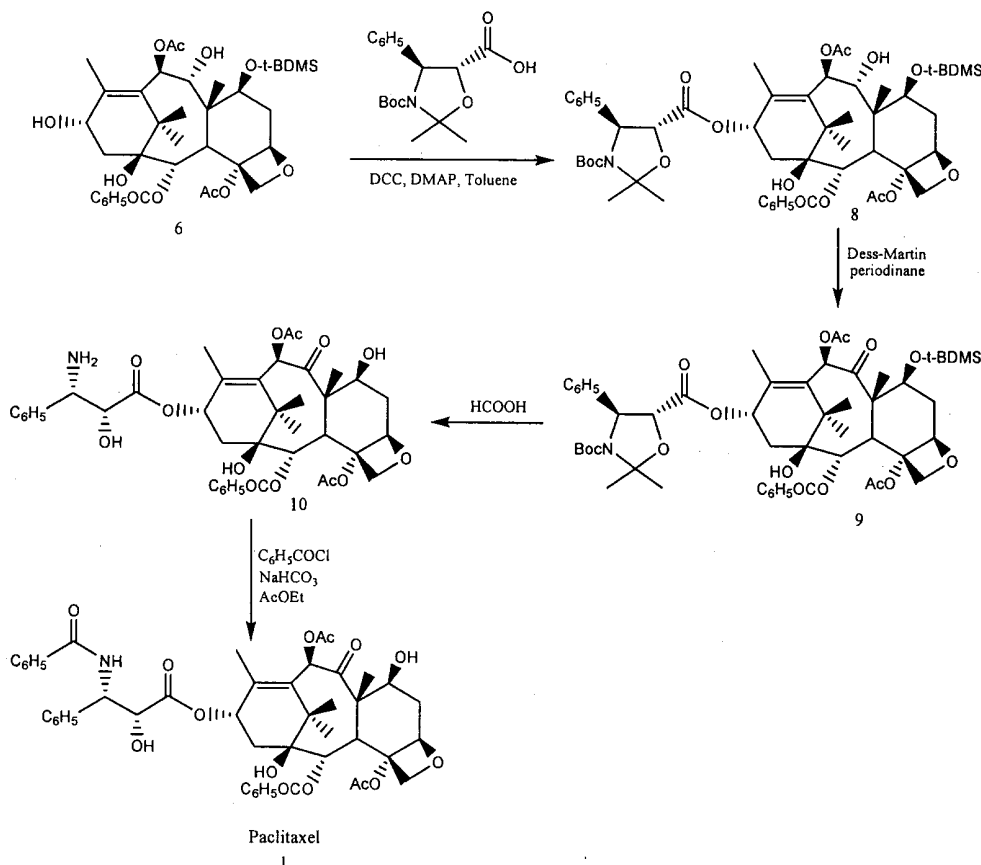


[0073] With reference to scheme 2, 7-protected-10-acetyl taxanes such as compound 6 can be converted to biologically active taxanes such as paclitaxel bearing a side chain at the C-13-position, an acetyl group at the C-10-hydroxy group position and a carbonyl group at the C-9-position. This was accomplished in four steps: (1) coupling of compound 6 with a suitable side chain precursor; (2) oxidizing the 9-hydroxy group to a carbonyl group; (3) concomitant deprotection of the side chain and 7-position; and (4) acylation of the side chain amino group. In a preferred embodiment of the present invention, compound 6 was reacted with (4S,5R)-3-tert-butyloxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid in the presence of an activating agent which in a preferred embodiment comprises dicyclocarbodiimide and 4-dimethylaminopyridine to yield compound 8. Compound 8 was then converted to compound 9 shown in scheme 2 by reaction with the Dess-Martin

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periodinane. Compound **9** can then be converted to paclitaxel or other 10-acetyl taxanes in two steps using well-established chemistry for the de-protection of side chain and 7-position followed by the acylation of the amino group.

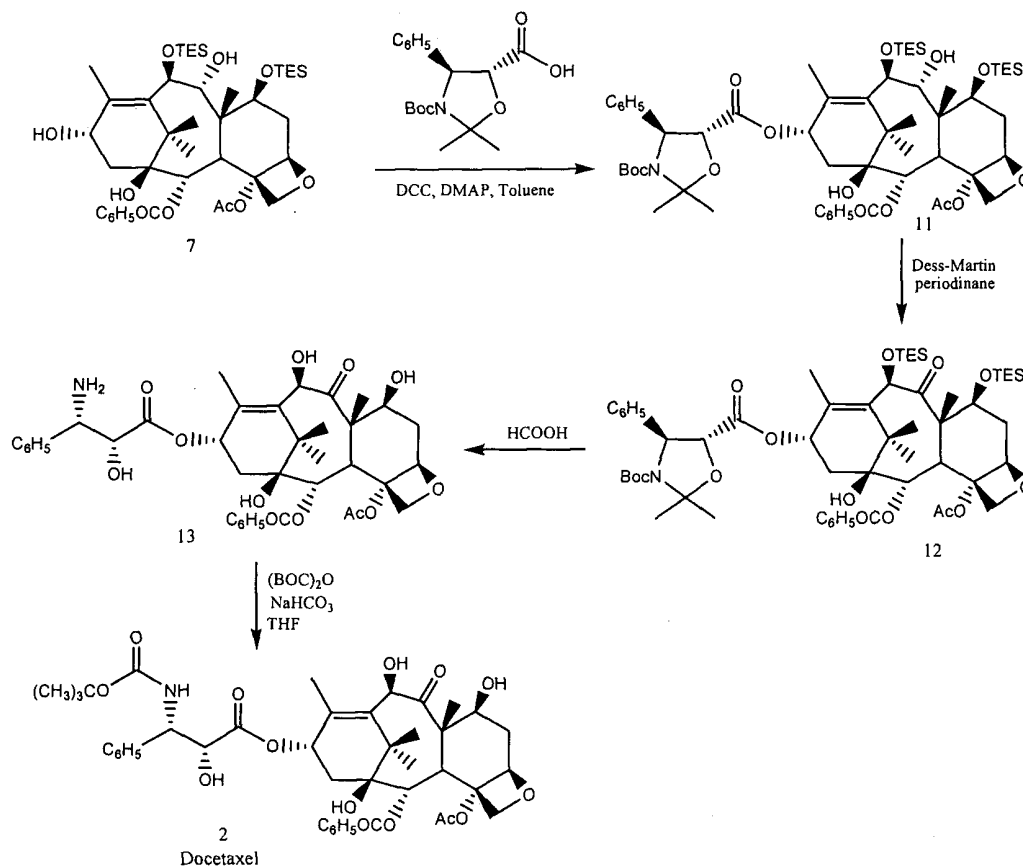
Scheme 2



[0074] With reference to scheme 3, it is shown that 7,10-bis-protected-9-dihydro taxanes such as compound **7** can be converted to biologically active taxanes such as docetaxel bearing a side chain at the C-13-position, a carbonyl group at the C-9-position and free hydroxy groups at the C-7 and C-10 positions. This is accomplished in four steps: (1) coupling of compound **7** with a suitable side chain precursor; (2) oxidizing the 9-hydroxy group to a carbonyl group; (3) concomitant de-protection of the side chain and the C-7- and C-10-positions; and (4) acylation of the side chain amino group. In a preferred embodiment of the present invention, compound **7** was reacted with (4S,5R)-3-tert-butyloxyxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid in the presence of an activating agent which in a preferred embodiment comprises

dicyclocarbodiimide and 4-dimethylaminopyridine to yield compound **11**. Compound **11** was then converted to compound **12** shown in scheme 3 by reaction with the Dess-Martin periodinane. Compound **12** can then be converted to docetaxel or other 10-deacetyl taxanes in two steps using well-established chemistry for the de-protection of side chain and C-7- and C-10-position followed by the acylation of the amino group.

[0075] Scheme 3



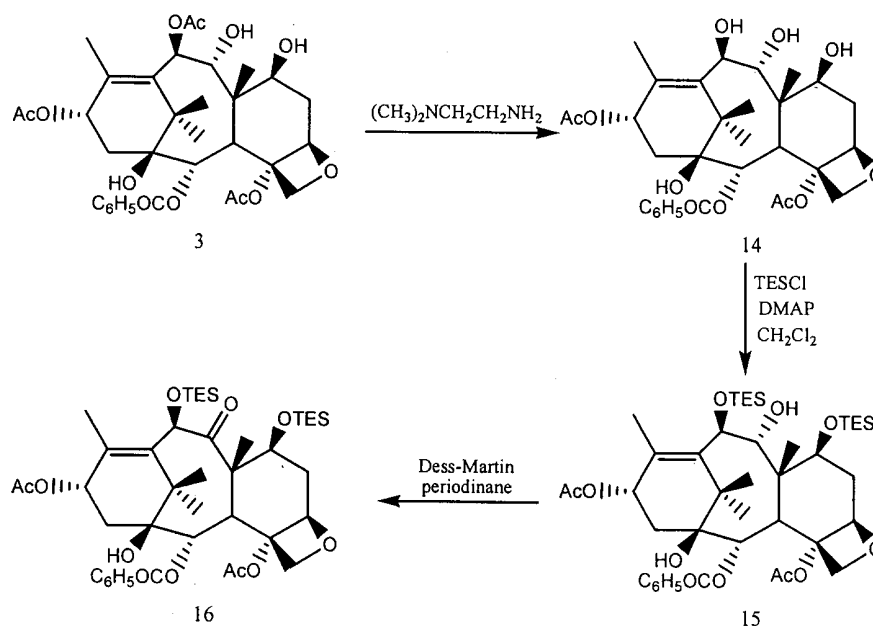
[0076] With reference to scheme 4, this invention includes a process for the preparation of 7,10-bis-protected-13-acetyl-10-deacetylbaaccatin III from 9-DHAB-III. Such compounds can be versatile precursors in the preparation of docetaxel and other taxanes. For example, they can be reacted with a side chain precursor at the C-13-position in the presence of an alkyl lithium according to known chemistry. The conversion from 9-DHAB-III is accomplished in three steps: (1) selective hydrolysis of the 10-acetyl group of 9-DHAB-III; (2)

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concomitant and selective protection at the C-7-, and C-10-positions; and (3) oxidation of the C-9-position.

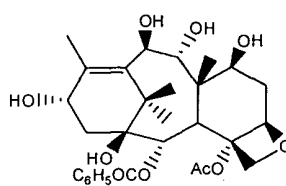
[0077] It was discovered that N,N-dimethylethylenediamine is an excellent reagent for the removal of the 10-acetyl group of 9-DHAB-III. N,N-dimethylethylenediamine deacetylates 9-DHAB-III selectively and in nearly quantitative yields leaving the 13-acetoxy group intact. Furthermore, it requires no solvent and is removed easily from the reaction mixture by simple evaporation due to its relatively low boiling point. In a preferred embodiment of the present invention, the resulting product, compound **14** was reacted with triethylsilylchloride in the presence of 4-dimethylaminopyridine to yield compound **15**. Compound **15** was then converted to compound **16** by reaction with Dess-Martin periodinane.

Scheme 4

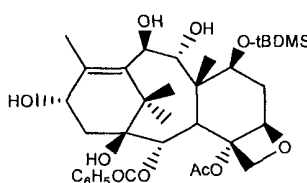


[0078] The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

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EXAMPLE I**9-Dihydro-10-deacetylbaccatin III**

[0079] 9-Dihydro-13-acetylbaccatin III (200.0 g, 317 mmol) was added to 666 mL of hydrazine monohydrate. The heterogeneous mixture was stirred for 48 hours at room temperature. The mixture was filtered on sintered glass funnel and washed with cold water (2 x 333 mL) and the solid was dried under vacuum for 48 hours affording 168 g (97%) of 9-dihydro-10-deacetylbaccatin III. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.11 (dd; 2H; J=8.4, 1.2 Hz; o-Bz); 7.63 (br t; 2H; J=7.7 Hz; m-Bz); 7.52 (br t; 1H; J=7.5 Hz; p-Bz); 5.75 (d; 1H; J=5.9 Hz; H2); 5.61 (br s; 1H; 9-OH); 5.53 (br d; 1H; J=6.6 Hz; 7-OH); 4.88 (d; 1H; J=9.6 Hz; H5); 4.88 (d; 1H; J=9.6 Hz; H10); 4.84 (br t; 1H; J=8.1 Hz; H13); 4.41 (br m; 1H; J=9.6 Hz; H7); 4.30 (d; 1H; J=9.6 Hz; H9); 4.25 (d; 1H; J=5.1 Hz; 13-OH); 4.14 (d; 1H; J=7.9 Hz; H20a); 4.11 (d; 1H; J=7.9 Hz; H20b); 3.91 (br s; 1H; 10-OH); 3.31 (s; 1H; 1-OH); 3.18 (d; 1H; J=5.9 Hz; H3); 2.40 (o m; 1H; H6a); 2.40 (o m; 1H; H14a); 2.29 (dd; 1H; J=15.3, 9.6 Hz; H14b); 2.17 (s; 3H; Ac); 1.94 (d; 3H; J=1.1 Hz; Me-18); 1.81 (ddd; 1H; J=14.3, 10.1, 1.5 Hz; H6b); 1.77 (s; 3H; Me-19); 1.63 (s; 3H; Me-17); 1.15 (s; 3H; Me-16).

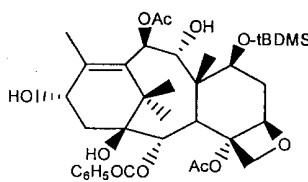
EXAMPLE II**9-Dihydro-10-deacetyl-7-t-butyldimethylsilyl-baccatin III**

[0080] To a stirred solution of 9-dihydro-10-deacetylbaccatin III (1.10 g, 2.01 mmol), triethylamine (2.02 g, 20.0 mmol) and DMAP (122 mg, 1.0 mmol) in 15 mL of dry dichloromethane was added t-butyldimethylsilylchloride (1.67 g, 5.5 mmol) and the reaction mixture was stirred for 24 hours at room temperature. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (1x100 mL and 2x50 mL). The combined organic extracts were

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washed with water (3x50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue which was crystallized in 5:1 hexanes – acetone to afford 840 mg (63%) of 9-dihydro-10-deacetyl-7-t-butyldimethylsilyl-baccatin III. ^1H NMR (Acetone- d_6 , 600 MHz) δ 8.11 (dd; 2H; $J=8.2, 1.2$ Hz; o-Bz); 7.63 (tt; 1H; $J=7.4, 1.2$ Hz; p-Bz); 7.52 (t; 2H; $J=7.7$ Hz; m-Bz); 5.73 (d; 1H; $J=6.0$ Hz; H2); 5.21 (d; 1H; $J=9.6$ Hz; 9-OH); 4.85 (br m; 1H; H13); 4.90 (d; 1H; $J=9.3$ Hz; H5); 4.81 (d; 1H; $J=10.6$ Hz; H10); 4.60 (dd; 1H; $J=10.4, 7.0$ Hz; H7); 4.34 (d; 1H; $J=5.1$ Hz; 13-OH); 4.21 (t; 1H; $J=10.1$ Hz; H9); 4.15 (d; 1H; $J=7.9$ Hz; H20a); 4.11 (d; 1H; $J=7.9$ Hz; H20b); 3.49 (s; 1H; 10-OH); 3.34 (s; 1H; 1-OH); 3.20 (d; 1H; $J=6.0$ Hz; H3); 2.45 (o m; 1H; H6a); 2.42 (o m; 1H; H14a); 2.31 (dd; 1H; $J=14.9, 10.2$ Hz; H14b); 2.18 (s; 3H; Ac); 1.98 (d; 3H; $J=1.1$ Hz; Me-18); 1.86 (ddd; 1H; $J=14.1, 10.5, 1.6$ Hz; H6b); 1.79 (s; 3H; Me-19); 1.63 (s; 3H; Me-17); 1.15 (s; 3H; Me-16); 0.96 (s; 9H; tBu); 0.29 (s; 3H; SiMe); 0.23 (s; 3H; SiMe).

EXAMPLE III

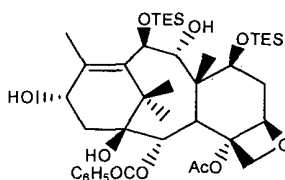


9-Dihydro-7-t-butyldimethylsilyl-baccatin III

[0081] Pyridine (50.0 mL) was cooled to 4 °C under argon and acetylchloride (4.04g, 51.5 mmol) was added dropwise. The mixture was stirred for 10 min and a cold solution of 9-dihydro-10-deacetyl-7-t-butyldimethylsilyl-baccatin III (2.27 g, 3.43 mmol) in 10 mL of pyridine was added dropwise over 3 min. The reaction mixture was stirred for 6 hours at 4 °C under argon, quenched with water (50 mL) and extracted with ethyl acetate (1x500 mL and 2x100 mL). The combined organic extracts were washed with cold 1% HCl (3x25 mL), saturated aqueous sodium bicarbonate (1x50 mL) and water (3x100mL). The resulting solution was dried over anhydrous Na_2SO_4 and evaporated. The product was isolated by flash chromatography (SiO_2 ; 2 to 20% acetone gradient in hexanes) affording 1.30 g (54%) of 9-dihydro-7-t-butyldimethylsilyl-baccatin III. ^1H NMR (Acetone- d_6 , 600 MHz) δ 8.12 (dd; 2H; $J=8.1, 1.1$ Hz; o-Bz); 7.63 (tt; 1H; $J=7.4, 1.2$ Hz; p-Bz); 7.53 (t; 2H; $J=7.7$ Hz; m-Bz); 6.05 (d; 1H; $J=11.1$ Hz; H10); 5.73

(d; 1H; J=6.6 Hz; H2); 5.00 (d; 1H; J=9.8 Hz; 9-OH); 4.91 (d; 1H; J=9.4 Hz; H5); 4.84 (br m; 1H; H13); 4.65 (dd; 1H; J=10.2, 7.2 Hz; H7); 4.38 (d; 1H; J=5.1 Hz; 13-OH); 4.36 (o t; 1H; H9); 4.16 (d; 1H; J=7.9 Hz; H20a); 4.12 (d; 1H; J=7.7 Hz; H20b); 3.48 (s; 1H; 1-OH); 3.17 (d; 1H; J=6.1 Hz; H3); 2.49 (ddd; 1H; J=14.3, 9.4, 7.2 Hz; H6a); 2.43 (dd; 1H; J=15.1, 6.2 Hz; H14a); 2.32 (m; 1H; H14b); 2.18 (s; 3H; Ac); 2.12 (d; 3H; J=1.3 Hz; Me-18); 2.02 (s; 3H; Ac); 1.85 (o m; 1H; H6b); 1.81 (s; 3H; Me-19); 1.62 (s; 3H; Me-17); 1.11 (s; 3H; Me-16); 0.92 (s; 9H; tBu); 0.30 (s; 3H; SiMe); 0.22 (s; 3H; SiMe).

EXAMPLE IV

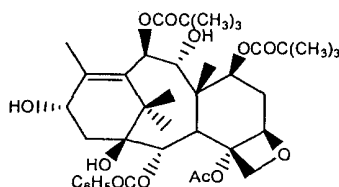


9-Dihydro-7,10-bis-triethylsilyl-10-deacetyl-baccatin III

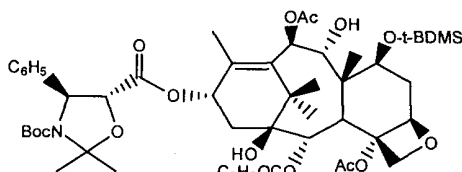
[0082] To a stirred solution of 9-dihydro-10-deacetylbaccatin III (1.0 g, 1.83 mmol), triethylamine (1.85 g, 18.3 mmol) and DMAP (112 mg, 0.92 mmol) in 15 mL of dry dichloromethane was added triethylsilylchloride (1.21 g, 8.03 mmol) and the reaction mixture was stirred for 72 hours at room temperature. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (1x100 mL and 2x50 mL). The combined organic extracts were washed with water (3x50 mL), dried over anhydrous Na₂SO₄ and concentrated to give a residue which was crystallized in 5:1 hexanes – acetone to afford 714 mg (50.4%) of 9-dihydro-7,10-bis-triethylsilyl-10-deacetyl-baccatin III. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.10 (dd; 2H; J=8.2, 1.2 Hz; o-Bz); 7.63 (tt; 1H; J=7.4, 1.2 Hz; p-Bz); 7.52 (t; 2H; J=7.8 Hz; m-Bz); 5.75 (d; 1H; J=6.0 Hz; H2); 5.04 (d; 1H; J=9.6 Hz; 9-OH); 4.89 (d; 1H; J=9.3 Hz; H5); 4.84 (o m; 1H; H13); 4.84 (o d; 1H; J=10.0 Hz; H10); 4.62 (dd; 1H; J=10.2, 7.0 Hz; H7); 4.31 (d; 1H; J=5.1 Hz; 13-OH); 4.15 (o m; 1H; H9); 4.15 (o m; 1H; H20a); 4.11 (d; 1H; J=7.9 Hz; H20b); 3.30 (s; 1H; 1-OH); 3.19 (d; 1H; J=6.0 Hz; H3); 2.54 (ddd; 1H; J=14.0, 9.4, 7.2 Hz; H6a); 2.41 (ddd; 1H; J=15.3, 6.4, 2.0 Hz; H14a); 2.29 (dd; 1H; J=15.1, 10.0; H14b); 2.18 (s; 3H; Ac); 1.97 (d; 3H; J=1.1 Hz; Me-18); 1.88 (ddd; 1H; J=14.1, 10.3, 1.5 Hz; H6b); 1.79 (s; 3H; Me-19); 1.67 (s; 3H; Me-17); 1.16

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(s; 3H; Me-16); 1.06 (t; 3H; J=7.9 Hz; SiCH₂CH₃); 1.00 (t; 3H; J=7.9 Hz; SiCH₂CH₃); 0.79 (q; 2H; J=7.7; SiCH₂CH₃); 0.69 (AB-q; 2H; SiCH₂CH₃).

EXAMPLE V**9-Dihydro-7,10-bis-*tert*-butyloxycarbonyl-10-deacetyl-baccatin III**

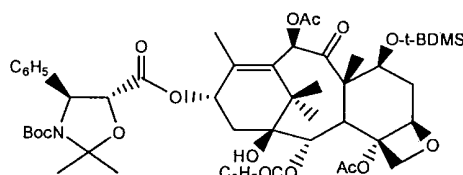
[0083] To a stirred solution of 9-dihydro-10-deacetyl-baccatin III (100 mg, 0.18 mmol) and DMAP (11 mg, 0.09 mmol) in 3 mL of dry dichloromethane was added di-*tert*-butyldicarbonate (94 mg, 0.43 mmol) and the reaction mixture was stirred for 48 hours at room temperature. The resulting mixture was quenched with water (50 mL) and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with water (3x50 mL), dried over anhydrous Na₂SO₄ and evaporated. The product was isolated by flash chromatography (SiO₂; 0 to 25% acetone gradient in hexanes) affording 65 mg (48%) of 9-dihydro-7,10-bis-*tert*-butyloxycarbonyl-10-deacetyl-baccatin III. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.11 (dd; 2H; J=8.1, 1.1 Hz; o-Bz); 7.64 (tt; 1H; J=7.4, 1.2 Hz; p-Bz); 7.53 (t; 2H; J=7.8 Hz; m-Bz); 6.02 (d; 1H; J=11.1 Hz; H10); 5.75 (d; 1H; J=5.9 Hz; H2); 5.38 (dd; 1H; J=10.1, 7.5 Hz; H7); 4.95 (d; 1H; J=8.9 Hz; H5); 4.88 (br t; 1H; J=8.3; H13); 4.41 (d; 1H; J=5.1 Hz; 13-OH); 4.37 (m; 1H; H9); 4.17 (d; 1H; J=7.9; H20a); 4.11 (d; 1H; J=7.7 Hz; H20b); 3.59 (s; 1H; 1-OH); 3.54 (d; 1H; J=9.4 Hz; 9-OH); 3.21 (d; 1H; J=6.0 Hz; H3); 2.55 (ddd; 1H; J=14.5, 8.9, 7.7 Hz; H6a); 2.43 (ddd; 1H; J=15.3, 6.3, 1.9 Hz; H14a); 2.34 (dd; 1H; J=15.8, 10.5; H14b); 2.20 (s; 3H; Ac); 2.12 (br s; 3H; Me-18); 1.80 (ddd; 1H; J=14.4, 10.2, 1.3 Hz; H6b); 1.83 (s; 3H; Me-19); 1.58 (s; 3H; Me-17); 1.50 (s; 9H, tBu); 1.46 (s; 9H, tBu); 1.13 (s; 3H; Me-16).

EXAMPLE VI

13-[(2R,3S)-N-t-Butyloxycarbonyl-N,O-(1-methylethylidene)-3-phenylisoserine]-9-dihydro-7-t-butyldimethylsilyl-baccatin III

[0084] To a stirred solution of 9-dihydro-7-t-butyldimethylsilyl-baccatin III (225 mg, 0.32 mmol), (4S,5R)-3-tert-butyloxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid (154 mg, 0.50 mmol) and DMAP (20 mg, 0.16 mmol) in 3 mL of dry toluene was added N,N-dicyclohexylcarbodiimide (105 mg, 0.51 mmol). The solution was stirred for 45 minutes under argon at room temperature and filtered. Water (50 mL) was added and the solution was extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with water (3x50 mL), sodium bicarbonate (1x50 mL) and water (3x50 mL). The solution was dried over anhydrous Na₂SO₄ and evaporated to dryness affording 320 mg (99%) of compound 8. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.06 (d; 2H; J=7.7 Hz; o-Bz); 7.65 (t; 1H; J=7.5 Hz; p-Bz); 7.54 (t; 2H; J=7.7 Hz; m-Bz); 7.43-7.40 (m; 5H; 3'-Ph); 6.27 (br t; 1H; J=8.8 Hz; H13); 6.04 (d; 1H; J=11.0 Hz; H10); 5.78 (d; 1H; J=6.0 Hz; H2); 5.14 (br s; 1H; H3'); 5.04 (d; 1H; J=9.8 Hz; 9-OH); 4.84 (d; 1H; J=9.1 Hz; H5); 4.65 (o d; 1H; J= 6.2 Hz; H2'); 4.60 (dd; 1H; J=9.8, 7.6 Hz; H7); 4.40 (t; 1H; J=10.5 Hz; H9); 4.11 (s; 2H; H20ab); 3.90 (s; 1H, 1-OH); 3.07 (d; 1H; J=6.0 Hz; H3); 2.48 (ddd; 1H; J=14.3, 9.1, 7.6 Hz; H6a); 2.39 (dd; 1H; J=15.1, 9.8 Hz; H14a); 2.32 (o m; 1H; H14b); 2.04 (s; 3H; Ac); 2.04 (s; 3H; Me-18); 1.85 (o m; 1H; H6b); 1.81 (s; 3H; Ac); 1.81 (o s; 3H; Me-19); 1.79 (o s; 3H; NCMe₂); 1.69 (s; 3H; Me-17); 1.72 (s; 3H; NCMe₂); 1.26 (s; 3H; Me-16); 1.11 (br s; 9H, BOC tBu); 0.92 (s; 9H; TBDMS tBu); 0.29 (s; 3H; SiMe); 0.22 (s; 3H; SiMe).

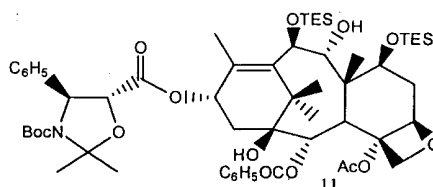
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EXAMPLE VII

13-[(2R,3S)-N-t-Butyloxycarbonyl-N,O-(1-methylethylidene)-3-phenylisoserine]-7-t-butyldimethylsilyl-baccatin III

[0085] To a stirred mixture of Dess-Martin periodinane (227 mg, 268 mmol) in 5.0 mL of dichloromethane was added pyridine (0.3 mL) until the mixture became clear. Compound 8 (300 mg, 0.28 mmol) was dissolved in 2.0 mL of dichloromethane and added to the periodinane solution. The reaction mixture was gently stirred for 5 hours at room temperature and cold saturated sodium hydrogensulfite (50 mL) was added. The mixture was extracted with ethyl acetate (3x50 mL) and the combined organic extracts were washed with water (3x50 mL), dried over anhydrous Na₂SO₄ and evaporated to dryness. The product was isolated by flash chromatography (SiO₂; 2 to 12% acetone gradient in hexanes) affording 276 mg (92%) of compound 9. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.06 (dd; 2H; J=8.1, 1.1 Hz; o-Bz); 7.67 (t; 1H; J=7.5 Hz; p-Bz); 7.56 (t; 2H; J=7.7 Hz; m-Bz); 7.49-7.43 (m; 5H; 3'-Ph); 6.27 (br t; 1H; J=8.8 Hz; H13); 6.40 (s; 1H; H10); 5.70 (d; 1H; J=6.8 Hz; H2); 5.11 (br s; 1H; H3'); 4.87 (d; 1H; J=9.1 Hz; H5); 4.64 (d; 1H; J=6.4 Hz; H2'); 4.45 (dd; 1H; J=10.2, 7.0 Hz; H7); 4.10 (d AB; 2H; J=8.5 Hz; H20ab); 3.83 (d; 1H; J=7.2 Hz; H3); 2.51 (ddd; 1H; J=14.3, 9.4, 7.0 Hz; H6a); 2.42 (dd; 1H; J=15.8, 9.0 Hz; H14a); 2.34 (dd; 1H; J=15.0, 9.2 Hz; H14b); 2.12 (d; 3H; J=0.9 Hz; Me-18); 2.10 (s; 3H; Ac); 1.90 (s; 3H; Ac); 1.80 (s; 3H; NCMe₂); 1.73 (o m; 1H; H6b); 1.73 (s; 3H; NCMe₂); 1.68 (s; 3H; Me-19); 1.25 (s; 3H; Me-17); 1.21 (s; 3H; Me-16); 1.10 (br s; 9H, BOC tBu); 0.79 (s; 9H; TBDMS tBu); 0.12 (s; 3H; SiMe); 0.08 (s; 3H; SiMe).

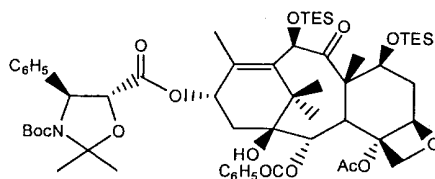
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EXAMPLE VIII

13-[(2R,3S)-N-t-Butyloxycarbonyl-N,O-(1-methylethylidene)-3-phenylisoserine]-9-dihydro-7,10-bis-triethylsilyl-10-deacetyl-baccatin III

[0086] To a stirred solution of 9-dihydro-7,10-bis-triethylsilyl-10-deacetyl-baccatin III (714 mg, 0.92 mmol), (4S,5R)-3-tert-butyloxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid (451 mg, 1.46 mmol) and DMAP (57 mg, 0.47 mmol) in 10 mL of dry toluene was added N,N-dicyclohexylcarbodiimide (308 mg, 1.49 mmol). The solution was stirred for 30 minutes under argon at room temperature and filtered. Water (50 mL) was added and the solution was extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with water (3x50 mL), sodium bicarbonate (1x50 mL) and water (3x50 mL). The solution was dried over anhydrous Na₂SO₄ and evaporated to dryness affording 957 mg (96%) of compound 11. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.05 (d; 2H; J=7.4 Hz; o-Bz); 7.64 (t; 1H; J=7.5 Hz; p-Bz); 7.52 (t; 2H; J=7.9 Hz; m-Bz); 7.42-7.32 (m; 5H; 3'-Ph); 6.26 (br t; 1H; J=8.8 Hz; H13); 5.77 (d; 1H; J=6.0 Hz; H2); 5.14 (br s; 1H; H3'); 5.06 (d; 1H; J=9.6 Hz; 9-OH); 4.84 (o d; 1H; J=9.8 Hz; H10); 4.82 (o d; 1H; J=8.5 Hz; H5); 4.61 (d; 1H; J= 6.0 Hz; H2'); 4.57 (dd; 1H; J=9.4, 7.7 Hz; H7); 4.17 (o m; 1H; H9); 4.10 (s; 2H; H20ab); 3.08 (d; 1H; J=5.9 Hz; H3); 2.53 (m; 1H; H6a); 2.34 (m; 2H; H14ab); 1.88 (s; 3H; Me-18); 1.88 (o m; 1H; H6b); 1.79 (s; 3H; Ac); 1.79 (o s; 3H; Me-19); 1.79 (o s; 3H; NCMe₂); 1.72 (s; 3H; Me-17); 1.71 (o s; 3H; NCMe₂); 1.33 (s; 3H; Me-16); 1.10 (br s; 9H, tBu); 1.05 (t; 3H; J=8.0 Hz; SiCH₂CH₃); 1.00 (t; 3H; J=7.9 Hz; SiCH₂CH₃); 0.79 (m; 2H; SiCH₂CH₃); 0.68 (m; 2H; SiCH₂CH₃).

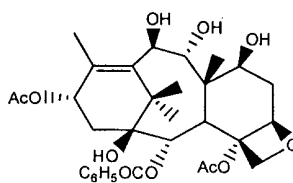
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EXAMPLE IX

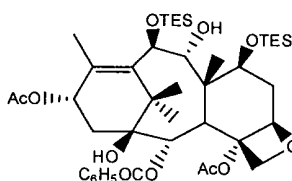
13-[(2R,3S)-N-t-Butyloxycarbonyl-N,O-(1-methylethylidene)-3-phenylisoserine]-7,10-bis-triethylsilyl-10-deacetyl-baccatin III

[0087] To a stirred mixture of Dess-Martin periodinane (1.11 g, 1.31 mmol) in 30.0 mL of dichloromethane was added pyridine (2.0 mL) until the mixture became clear. Compound 11 (1.40 g, 1.30 mmol) was dissolved in 10.0 mL of dichloromethane and added to the periodinane solution. The reaction mixture was gently stirred for 3 hours at room temperature and cold saturated sodium hydrogensulfite (50 mL) was added. The mixture was extracted with ethyl acetate (3x50 mL) and the combined organic extracts were washed with water (3x50 mL), dried over anhydrous Na₂SO₄ and evaporated to dryness affording 1.30 g (93%) of compound 12. ¹H NMR (Acetone-d₆, 600 MHz) δ 8.05 (d; 2H; J=8.3 Hz; o-Bz); 7.55 (t; 2H; J=7.7 Hz; m-Bz); 7.46 (t; 1H; J=7.5 Hz; p-Bz); 7.43 (m; 5H; 3'-Ph); 6.27 (t; 1H; J=8.6 Hz; H13); 5.67 (o d; 1H; J=7.2 Hz; H2); 5.24 (s; 1H; H10); 5.10 (br s; 1H; H3'); 4.86 (d; 1H; J=8.9 Hz; H5); 4.63 (d; 1H; J= 6.6 Hz; H2'); 4.46 (dd; 1H; J=10.4, 6.8 Hz; H7); 4.11 (d; 1H; J= 8.3 Hz; H20a); 4.08 (d; 1H; J= 8.1 Hz; H20b); 3.85 (d; 1H; J=7.2 Hz; H3); 2.55 (ddd; 1H; J=14.1, 9.4, 6.9 Hz; H6a); 2.38 (dd; 1H; J=15.1, 9.1 Hz H14a); 2.33 (dd; 1H; J=15.2, 9.2 Hz H14b); 1.96 (s; 3H; Me-18); 1.86 (br s; 3H; Ac); 1.80 (o m; 1H; H6b); 1.80 (s; 3H; NCM₂); 1.72 (s; 3H; NCM₂); 1.64 (s; 3H; Me-19); 1.25 (s; 3H; Me-17); 1.25 (s; 3H; Me-16); 1.1 (br s; 9H, tBu); 1.03 (t; 3H; J=7.9 Hz; SiCH₂CH₃); 0.99 (t; 3H; J=8.0 Hz; SiCH₂CH₃); 0.69 (m; 2H; SiCH₂CH₃); 0.63 (q; 2H; J=7.9 Hz; SiCH₂CH₃).

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EXAMPLE X**9-dihydro-10-deacetyl-13-acetylbaccatin III**

[0088] A solution of 9-dihydro-13-acetylbaccatin III (500 mg, 0.79 mmol) in 4.0 mL of N,N- dimethylethylenediamine was stirred for 48 hours at room temperature. The solution was evaporated and the residue was taken up in 1.5 mL of toluene and evaporated to dryness. The solid was separated by chromatography (Alumina; 2 to 20% methanol gradient in chloroform) affording 397 mg (85%) of 9-dihydro-10-deacetyl-13-acetylbaccatin III. ^1H NMR (Acetone- d_6 , 600 MHz) δ 8.10 (dd; 2H; $J=8.1, 1.1$ Hz; o-Bz); 7.63 (t; 1H; $J=7.5$ Hz; p-Bz); 7.52 (t; 2H; $J=7.7$ Hz; m-Bz); 6.16 (br t; 1H; $J=8.5$ Hz; H13); 5.80 (d; 1H; $J=6.0$ Hz; H2); 4.90 (d; 1H; $J=10.2$ Hz; H5); 4.90 (d; 1H; $J=10.2$ Hz; H10); 4.37 (dd; 1H; $J=9.8, 7.7$ Hz; H7); 4.33 (d; 1H; $J=10.4$ Hz; H9); 4.15 (d; 1H; $J=7.9$ Hz; H20a); 4.13 (d; 1H; $J=7.7$ Hz; H20b); 3.67 (s; 1H; 1-OH); 3.10 (d; 1H; $J=5.9$ Hz; H3); 2.43 (ddd; 1H; $J=14.8, 9.2, 7.7$ Hz; H6a); 2.38 (dd; 1H; $J=15.1, 7.7$ Hz; H14a); 2.25 (dd; 1H; $J=15.0, 9.3$ Hz; H14b); 2.29 (s; 3H; Ac); 2.16 (s; 3H; Ac); 1.81 (d; 3H; $J=1.3$ Hz; Me-18); 1.82 (o m; 1H; H6b); 1.78 (s; 3H; Me-19); 1.69 (s; 3H; Me-17); 1.27 (s; 3H; Me-16).

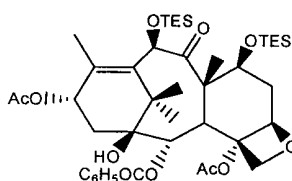
EXAMPLE XI**9-Dihydro-7,10-bis-triethylsilyl-10-deacetyl-13-acetyl-baccatin III**

[0089] To a stirred solution of 9-dihydro-10-deacetyl-13-acetylbaccatin III (1.0 g, 1.70 mmol), triethylamine (1.72 g, 17.0 mmol) and DMAP (104 mg, 0.85 mmol) in 15 mL of dry dichloromethane was added triethylsilylchloride (1.13 g, 7.5 mmol) and the reaction mixture was stirred for 72 hours at room temperature. The resulting mixture was quenched with water (100 mL) and extracted with ethyl acetate (1x100 mL and 2x50 mL). The combined organic

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extracts were washed with water (3x50 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue which was crystallized in 5:1 hexanes – acetone to afford 626 mg (45%) of 9-dihydro-7,10-bis-triethylsilyl-10-deacetyl-13-acetyl-baccatin III. ^1H NMR (Acetone- d_6 , 600 MHz) δ 8.10 (dd; 2H; $J=8.3, 1.1$ Hz; o-Bz); 7.63 (tt; 1H; $J=7.4, 1.2$ Hz; p-Bz); 7.52 (t; 2H; $J=7.7$ Hz; m-Bz); 6.14 (tq; 1H; $J=9.0, 1.0$ Hz; H13); 5.79 (d; 1H; $J=6.0$ Hz; H2); 5.05 (d; 1H; $J=9.6$ Hz; 9-OH); 4.91 (d; 1H; $J=9.3$ Hz; H5); 4.84 (d; 1H; $J=10.0$ Hz; H10); 4.57 (dd; 1H; $J=9.7, 7.5$ Hz; H7); 4.12 (o m; 1H; H9); 4.15 (o m; 2H; H20ab); 3.75 (s; 1H; 1-OH); 3.12 (d; 1H; $J=6.0$ Hz; H3); 2.57 (ddd; 1H; $J=14.2, 9.2, 7.4$ Hz; H6a); 2.37 (dd; 1H; $J=15.1, 7.9$ Hz; H14a); 2.28 (dd; 1H; $J=15.2, 10.4$; H14b); 2.30 (s; 3H; Ac); 2.17 (s; 3H; Ac); 1.90 (ddd; 1H; $J=14.1, 10.3, 1.3$ Hz; H6b); 1.84 (d; 3H; $J=1.3$ Hz; Me-18); 1.81 (s; 3H; Me-19); 1.71 (s; 3H; Me-17); 1.28 (s; 3H; Me-16); 1.06 (t; 3H; $J=8.0$ Hz; SiCH_2CH_3); 1.00 (t; 3H; $J=7.9$ Hz; SiCH_2CH_3); 0.79 (q; 2H; $J=8.2$; SiCH_2CH_3); 0.69 (m; 2H; SiCH_2CH_3).

EXAMPLE XII



7,10-bis-Triethylsilyl-10-deacetyl-13-acetyl-baccatin III

[0090] To a stirred mixture of Dess-Martin periodinane (66 mg, 0.16 mmol) in 2.0 mL of dichloromethane was added pyridine (0.1 mL) until the mixture became clear. 9-dihydro-7,10-bis-triethylsilyl-10-deacetyl-13-acetyl-baccatin III (100 mg, 0.12 mmol) was dissolved in 1.0 mL of dichloromethane and added to the periodinane solution. The reaction mixture was gently stirred for 18 hours at room temperature and cold saturated sodium hydrogensulfite (2 mL) was added. The mixture was extracted with ethyl acetate (1x50 mL and 2x25 mL) and the combined organic extracts were washed with water (3x25 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was isolated by flash chromatography (SiO_2 ; 2 to 10% acetone gradient in hexanes) affording 82 mg (82%) of 7,10-bis-Triethylsilyl-10-deacetyl-13-acetyl-baccatin III. ^1H NMR (Acetone- d_6 , 600 MHz) δ 8.08 (dd; 2H; $J=8.2, 1.0$ Hz; o-Bz); 7.63 (t; 1H; $J=7.5$

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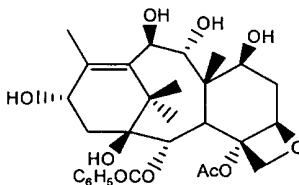
Hz; p-Bz); 7.52 (t; 2H; J=7.7 Hz; m-Bz); 6.13 (t; 1H; J=8.4 Hz; H13); 5.69 (d; 1H; J=7.0 Hz; H2); 5.26 (s; 1H; H10); 4.94 (d; 1H; J=8.9 Hz; H5); 4.49 (dd; 1H; J=10.6, 6.8 Hz; H7); 4.15 (s; 2H; H20ab); 3.91 (d; 1H; J=7.0 Hz; H3); 3.69 (s; 1H; 1-OH); 2.59 (ddd; 1H; J=14.1, 9.5, 6.8 Hz; H6a); 2.41 (ddd; 1H; J=15.3, 8.6, 1.3 Hz; H14a); 2.36 (s; 3H; Ac); 2.33 (dd; 1H; J=15.3, 9.4; H14b); 2.19 (s; 3H; Ac); 1.94 (d; 3H; J=1.3 Hz; Me-18); 1.82 (o m; 1H; H6b); 1.67 (s; 3H; Me-19); 1.24 (s; 3H; Me-17); 1.20 (s; 3H; Me-16); 1.03 (t; 3H; J=7.9 Hz; SiCH₂CH₃); 1.00 (t; 3H; J=7.7 Hz; SiCH₂CH₃); 0.70 (m; 2H; SiCH₂CH₃); 0.64 (q; 2H; J=8.0 Hz; SiCH₂CH₃).

[0091] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

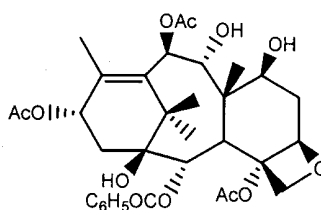
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WHAT IS CLAIMED IS:

1. A process for the preparation of 9-dihydro-10-deacetylbaccatin III

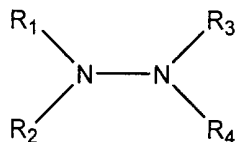


which comprises the step of reacting 9-dihydro-13-acetylbaccatin III having the formula:



with a deacetylating agent in absence of a solvent to concomitantly deacetylate 10- and 13- positions and produce 9-dihydro-10-deacetylbaccatin III.

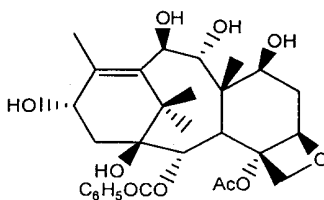
2. The process of claim 1, wherein the deacetylating agent is a nucleophilic weak base.
3. The process of claim 1, wherein the deacetylating agent is a hydrazine compound having the formula:



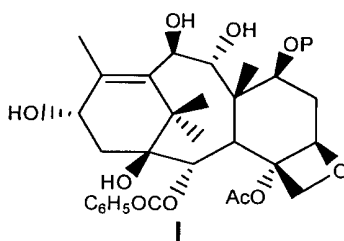
or its corresponding hydrate, wherein each R_1 to R_4 is independently a hydrogen, an optionally substituted C_1 - C_6 alkyl or an optionally substituted C_6 aryl.

4. The process of claim 3, wherein R_1 to R_4 is independently a hydrogen, a C_1 - C_4 alkyl or a phenyl.

5. The process of claim 3, wherein R_1 to R_4 is independently a hydrogen, a methyl, an ethyl or a phenyl.
6. The process of claim 1, wherein the deacetylating agent is hydrazine, methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, 1,2-diethylhydrazine, phenylhydrazine or their hydrates thereof.
7. The process of claim 1, wherein the deacetylating agent is hydrazine monohydrate.
8. The process as defined in any one of claims 1 to 7, further comprising the step of protecting the 7-hydroxy group of 9-dihydro-10-deacetylbaicatin III

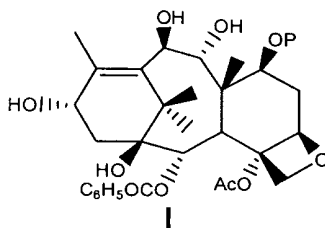


to produce a taxane of formula I



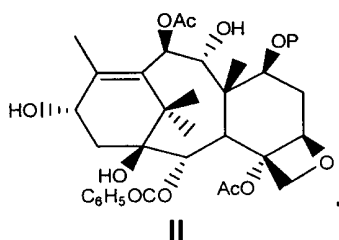
wherein P is a hydroxy protecting group.

9. The process as defined in claim 8, further comprising the step of acetylating the 10-hydroxy group of the taxane of formula I;



to produce a taxane of formula II:

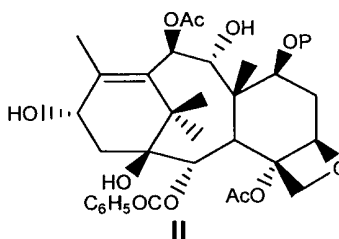
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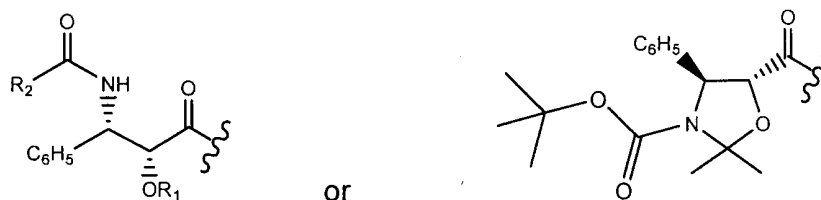
wherein P is as defined in claim 8.

10. The process as defined in claim 9, further comprising the steps of:

i) reacting the 13-hydroxy group of the compound of formula II

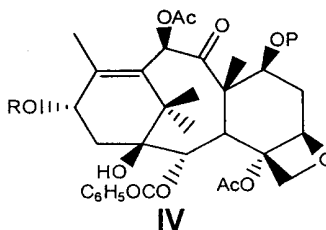


with a taxane side chain precursor of formula R-X, wherein X is a leaving group and R is



wherein R₁ is selected from the group consisting of ethoxyethyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl and tert-butyloxycarbonyl and R₂ is phenyl or tert-butoxy; and

ii) oxidizing the 9-hydroxy group with an oxidizing agent to produce a taxane of formula IV



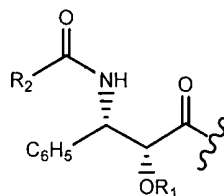
wherein R is as defined previously and P is as defined in claim 8.

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11. The process of claim 10, wherein the oxidizing agent is selected from the group consisting of o-iodoxybenzoic acid (IBX), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane), iodosobenzene, iodozobenzene diacetate, $\text{CrO}_3/\text{H}_2\text{SO}_4$ (Jones' reagent), pyridinium dichromate, pyridinium chlorochromate, potassium permanganate and Swern reagent.

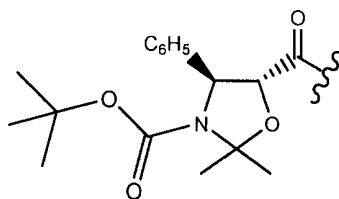
12. The process of claim 10, wherein the oxidizing agent is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane).

13. The process as defined in any one of claims 10 to 12, wherein R is



wherein R_1 and R_2 are as defined in claim 10.

14. The process of as defined in any one of claims 10 to 12, wherein R is

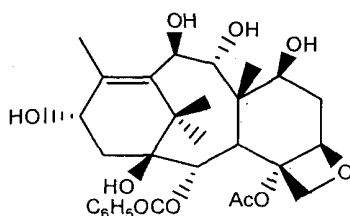


15. The process as defined in claim 8, wherein the hydroxy protecting group is selected from the group consisting of triethylsilyl, triisopropylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, benzyl and tert-butyloxycarbonyl.

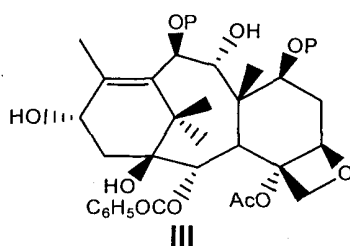
16. The process as defined in claim 8, wherein the hydroxy protecting group is triethylsilyl.

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17. The process as defined in any one of claims 1 to 7, further comprising the step of concomitantly protecting 10-hydroxy and 7-hydroxy groups of the 9-dihydro-10-deacetylbaccatin III



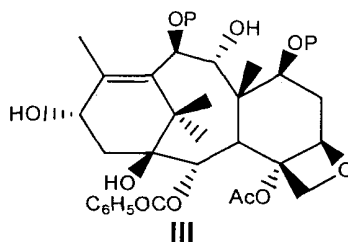
to produce a taxane of formula III



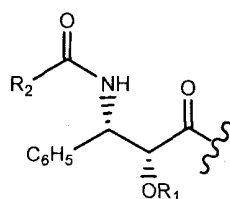
wherein each P is the same and is a hydroxy protecting group.

18. The process as defined in claim 17, further comprising the steps of:

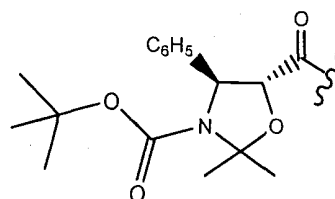
i) reacting the 13-hydroxy group of the compound of formula III



with a taxane side chain precursor of formula R-X, wherein X is a leaving group and R is

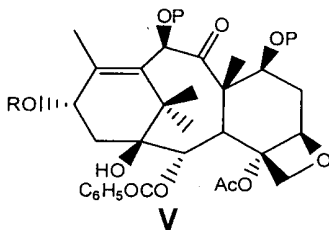


or



wherein R_1 is selected from the group consisting of ethoxyethyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl and tert-butyloxycarbonyl and R_2 is phenyl or tert-butoxy; and

ii) oxidizing the 9-hydroxy group with an oxidizing agent to produce a taxane of formula V

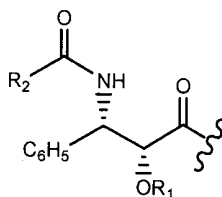


wherein R is as defined previously and P is as defined in claim 17.

19. The process of claim 18, wherein the oxidizing agent is selected from the group consisting of o-iodoxybenzoic acid (IBX), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane), iodosobenzene, iodozobenzene diacetate, $\text{CrO}_3/\text{H}_2\text{SO}_4$ (Jones' reagent), pyridinium dichromate, pyridinium chlorochromate, potassium permanganate and Swern reagent.

20. The process of claim 18, wherein the oxidizing agent is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane).

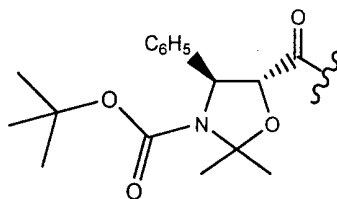
21. The process as defined in any one of claims 18 to 20, wherein R is



wherein R_1 and R_2 are as defined in claim 18.

22. The process as defined in any one of claims 18 to 20, wherein R is

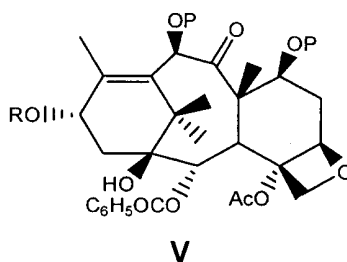
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23. The process as defined in claim 18, wherein the hydroxy protecting group is selected from the group consisting of triethylsilyl, triisopropylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, benzyl and tert-butyloxycarbonyl.

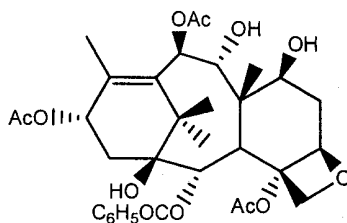
24. The process as defined in claim 18, wherein the hydroxy protecting group is triethylsilyl.

25. A process for the preparation of compound of formula V



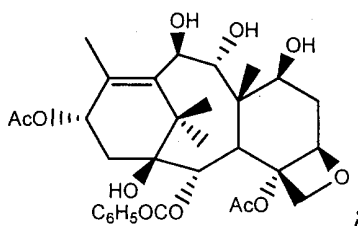
wherein P is a hydroxy protecting group and R is acetyl, said process comprising the steps of :

i) selectively deacetylating the 10-hydroxy group of 9-dihydro-13-acetylbaccatin III having the formula:



with N,N-dimethylethylenediamine to produce 9-dihydro-10-deacetyl-13-acetylbaccatin III of formula:

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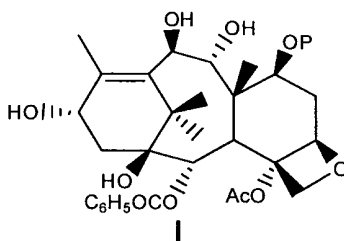
ii) concomitantly protecting 7-hydroxy and 10-hydroxy groups of the reaction product of step i); and

iii) oxidizing the 9-hydroxy group of the reaction product of step ii) with an oxidizing agent to produce the compound of formula V.

26. The process of claim 25, wherein the oxidizing agent is selected from the group consisting of o-iodoxybenzoic acid (IBX), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane), iodosobenzene, iodozobenzene diacetate, CrO₃/ H₂SO₄ (Jones' reagent), pyridinium dichromate, pyridinium chlorochromate, potassium permanganate and Swern reagent.

27. The process of claim 25, wherein the oxidizing agent is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane).

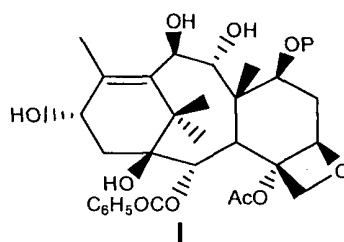
28. A compound of formula I



wherein P is a hydroxy protecting group.

29. A compound of formula I

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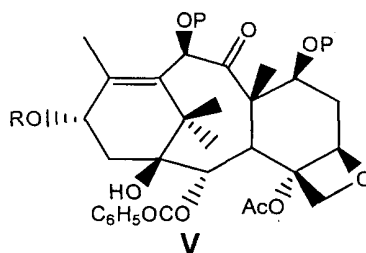


wherein P is a hydroxy protecting group prepared by the process as defined in claim 8.

30. The compound of claim 28 or 29, wherein the hydroxy protecting group is selected from the group consisting of triethylsilyl, triisopropylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, benzyl and tert-butyloxycarbonyl.

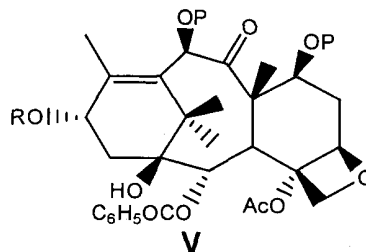
31. The compound of claim 28 or 29, wherein the hydroxy protecting group is triethylsilyl.

32. A compound of formula V



wherein P is a hydroxy protecting group and R is acetyl.

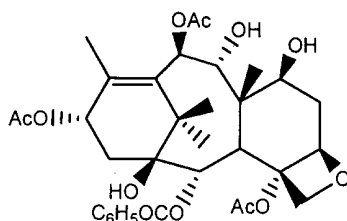
33. A compound of formula V



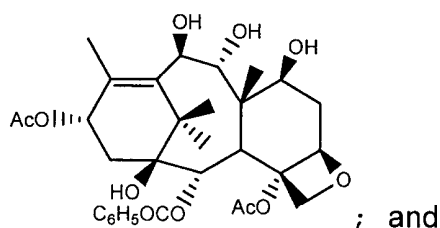
wherein P is a hydroxy protecting group and R is acetyl; prepared by the process comprising the steps of :

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i) selectively deacetylating 10-hydroxy group of 9-dihydro-13-acetylbaccatin III having the formula:



with N,N-dimethylethylenediamine to produce 9-dihydro-10-deacetyl-13-acetyl-baccatin III of formula:



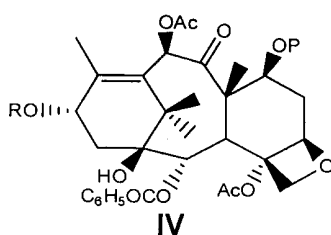
ii) concomitantly protecting 7-hydroxy and 10-hydroxy groups of the reaction product of step i) to produce the compound of formula V.

34. The compound of claim 32 or 33, wherein P is selected from the group consisting of triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl and tert-butyloxycarbonyl.

35. The compound of claim 32 or 33, wherein the hydroxy protecting group is triethylsilyl.

36. A process for producing a pharmaceutically active taxane which comprise the steps of:

i) producing a taxane of formula IV



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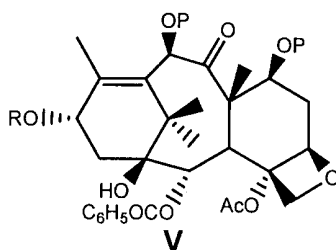
by the process as defined in claim 10; and

ii) transforming said compound of formula IV into the pharmaceutically active taxane.

37. The process of claim 36, wherein the pharmaceutically active taxane is paclitaxel.

38. A process for producing a pharmaceutically active taxane, which comprise the steps of:

i) producing a taxane of formula V



by the process as defined in claims 18; and

ii) transforming said compound of formula V into the pharmaceutically active taxane.

39. The process of claim 38, wherein the pharmaceutically active taxane is docetaxel.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000480

A. CLASSIFICATION OF SUBJECT MATTER IPC: C07D 305/14 (2006.01) , A61K 31/337 (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC: C07D 305/14 (2006.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) STN (structure), Canadian Patent Database		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bioorganic & Medicinal Chemistry, 2000, vol 8, p. 1269-1280 NIKOLAKAKIS et al. See compound 8 and 14	32, 34-35
X	J. Med. Chem., 2005, vol. 48, p.2218-2228 OJIMA et al. See Tables 2-8 and CAS Registry Numbers 848250-69-1, 848251-58-1, 848251-59-2, 848251-54-7, 848251-57-0, 848251-60-5, 848251-61-6, 848250-98-6	32, 34-35
X Y	J. Org. Chem., 2001, vol. 66, p. 3330-3337 DeMATTEI et al. See Scheme 1	1-6, 17 25-27
X Y	CA 2.403.429 KASITU et al. 27 September 2001 (27-09-2001) whole document	1-10, 32, 34-35 25-27
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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Date of the actual completion of the international search 5 June 2006 (05-06-2006)	Date of mailing of the international search report 14 July 2006 (14-07-2006)	
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Sophie Beaudoin (819) 956-6128	

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CA 2.204.197 LIU 1 November 1998 (01-11-1998) whole document, namely CAS Registry Number 351885-34-2	25, 28-31
X	CA 2.214.319 BOUCHARD et al. 3 October 1996 (03-10-1996) whole document	36-39
X	CA 2.165.328 BOURZAT et al. 22 December 1994 (22-12-1994) whole document	36-39
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