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REYES & REYES

A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-108806-00004-0000

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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y CC

E.

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REF:

Expediente 06-108-806

**TÍTULO SOLICITADO: "UN MÉTODO FÁCIL PARA SINTETIZAR
COMPUESTOS DE BACATINA III."**

**PUBLICACIÓN: Gaceta 579 de 31 de Agosto de 2007, número de
publicación 311.**

PRIORIDAD: US 60/570,834 de mayo 14 de 2004

SOLICITANTE: IMMUNOGEN, INC.

APODERADO: HUMBERTO RUBIO CAMACHO

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

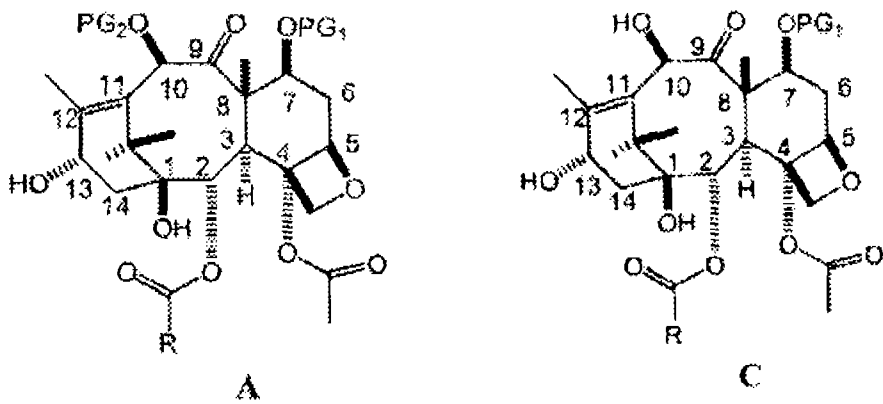
I. RATIFICACIÓN

Comedidamente me permito presentar los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de en trámite incumple los requisitos de patentabilidad establecidos por los artículos

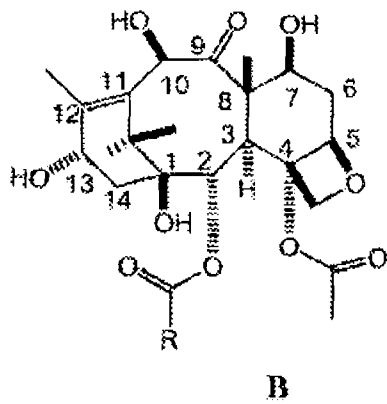
14 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN.

La solicitud colombiana 06-108-806 en trámite que se refiere a un proceso de obtención de derivados de bacatina III:



a partir de 10-deacetilbacatina III:



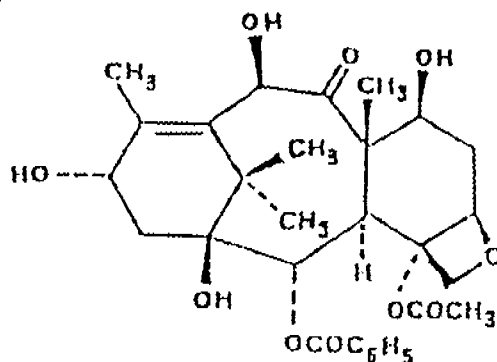
y que utiliza un agente de protección (compuesto de organosilano tal como clorotriethylsilano) y un agente de asilación en presencia de una amina secundaria y un compuesto que contiene nitrógeno seleccionado de una trialquilamina o un heterociclo con nitrógeno (piridina o piperazina sustituidas o no), carece tanto de novedad como de nivel inventivo, tal y como se demuestra a través de los siguientes argumentos:

- En primer lugar, el intermediario **“10-deacetilbacatina III”** a partir del cual se obtienen los compuestos de formula (A) y (C) es un compuesto que se ha venido utilizando y que pertenece al estado de la técnica, veamos:

- ❖ La publicación internacional WO 94/04519 publicada el 03 de Marzo de 1994 y titulada "PROCESS OF CONVERTING TAXANES INTO BACCATIN III AND 10-DEACETYLBACCATIN III" revela:

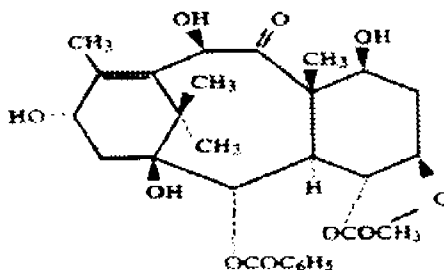
An object of the present invention is to convert partially purified organic by-products of the taxane extraction process into 10-deacetylbaccatin III.

22. A process for the preparation of a compound of formula (II)



- ❖ La patente americana US 5,256,801 publicada el 26 de octubre de 1996 y titulada "PROCESSES OF CONVERTING TAXANES INTO 10-DEACETYLBACCATIN III" revela:

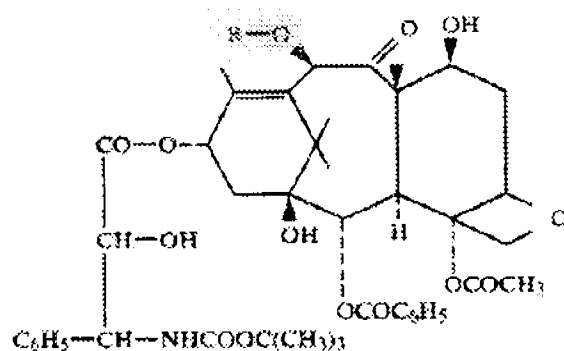
A process for the preparation of a compound of formula (I)



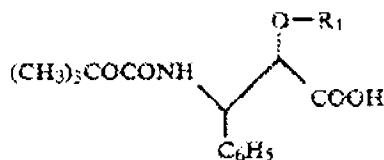
comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

- ❖ La patente americana US 4,924,012 publicada el 08 de mayo de 1990 y titulada "PROCESS FOR PREPARING DERIVATIVES OF BACCATINE III AND OF 10-DEACETYLBACCATINE III" revela:

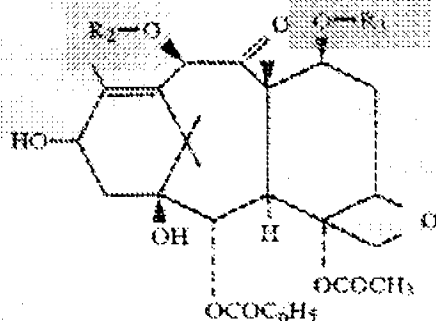
1. A process for preparing a derivative of baccatine III or of 10-deacetylbaccatine III, of general formula:



in which R denotes hydrogen or acetyl, wherein an acid of general formula:



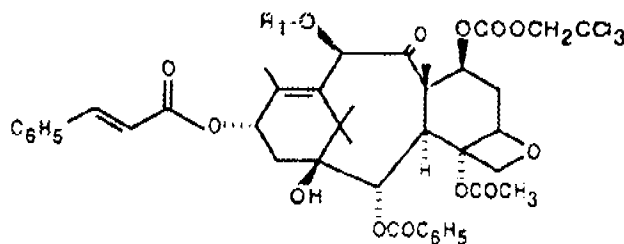
in which R₁ is a hydroxy-protecting group, is condensed with a taxane derivative of general formula



in which R₂ is an acetyl group or a hydroxy-protecting group and R₃ is a hydroxy-protecting group, and the protecting groups R₁, R₃ and, where appropriate, R₂ are then replaced by hydrogen.

- ❖ La patente europea EP 0526311 publicada el 03 de febrero de 1993 y titulada "PROCEDE DE PREPARATION DE LA CINNAMOYL-13ALPHA BACCATINE III OU DESACETIL-10 BACCATINE III" revela:

1 - Procédé de préparation d'un dérivé du taxane de formule générale :



90 am

4 - Procédé selon la revendication 3 caractérisé en ce que la base est choisie parmi la pyrrolidinopyridine ou la diméthylaminopyridine.

5 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que l'on utilise une mole d'anhydride mixte par mole de dérivé de la baccatine III ou de la désacétyl-10 baccatine III.

❖ La publicación científica "¹³C NMR INVESTIGATION OF SOLID-STATE POLYMORPHISM IN 10-DEACETYL BACCATIN III¹" revela:

Abstract: To investigate the origins of solid-state NMR shift differences in polymorphs, carbon NMR chemical shift tensors are measured for two forms of solid 10-deacetyl baccatin III, a dimethyl sulfoxide (DMSO) solvate and an unsolvated form. A comparison of ab initio computed tensors that includes and omits the DMSO molecules demonstrates that lattice interactions cannot fully account for the shift differences in the two forms. Instead, conformational differences in the cyclohexenyl, benzoyl, and acetyl moieties are postulated to create the differences observed. X-ray analysis of six baccatin III analogues supports the suggested changes in the cyclohexenyl and benzoyl systems. The close statistical match of the ¹³C chemical shifts of both polymorphic forms with those calculated using the X-ray geometry of 10-deacetyl baccatin III supports the contention that the B, C, and D rings are fairly rigid. Therefore, the observed tensor differences appear to arise primarily from conformational variations in ring substituents and the cyclohexenyl ring.

Como se puede observar, en todos estos documentos no sólo se encuentran detalladamente descritas varias maneras de obtener el intermediario inicial de la solicitud colombiana en trámite (10-deacetil baccatina II) e importantes características fisicoquímicas (como las de sus estado sólido), sino que dicho intermediario se encuentra incluido en procesos de síntesis de compuestos similares a los obtenidos por la presente solicitud, específicamente refiriéndonos a los compuestos mencionados en la patente americana US 4,924,012 y la patente europea EP 0526311 cuando sus radicales R, R1, R2 y/o R3 representan un grupo acetilo o un grupo protector de un grupo hidroxilo, características mencionadas en las reivindicaciones 1, 16, 17, 18, 19, 39, 54 y 55 de la solicitud colombiana en trámite.

Adicionalmente, en la patente europea EP 0526311 se hace uso de pirrolidinopiridina o de dimetilaminopiridina en la obtención de dichos compuestos de baccatina similares a los de la presente solicitud, lo que evidencia específicamente el uso o la presencia de un compuesto que contiene nitrógeno seleccionado de un heterociclo que contiene nitrógeno, como piridina sustituida o

¹ ¹³C NMR Investigation of Solid-State Polymorphism in 10-Deacetyl Baccatin III. Harper, J.K., Facelli, J.C., Barich, D.H., McGeorge, G., Mulgrew, A.E., and Grant, D.M. J. Am. Chem. Soc., 124, 35, 10589 - 10595, 2002, 10.1021/ja020371a.

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no sustituida, tal y como se menciona en las reivindicaciones 1 y 39 de la misma solicitud en trámite.

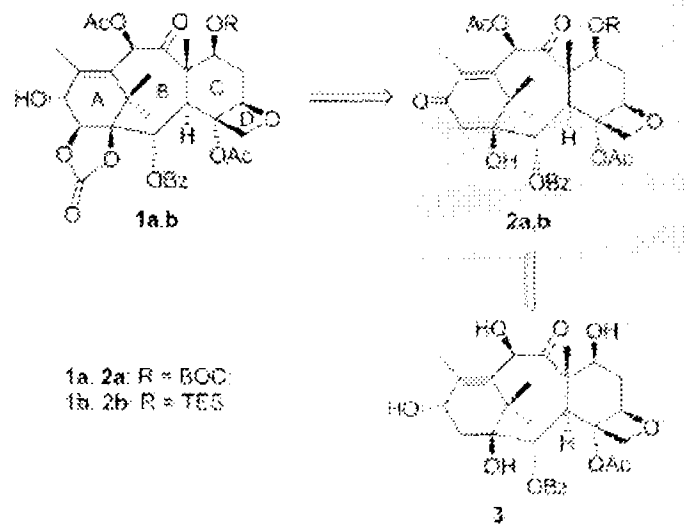
➤ En segunda instancia, es importante citar otras anterioridades que involucran no solo el compuesto de partida y compuestos relacionados a los obtenidos por la solicitud colombiana en trámite, si no que además contienen información acerca de los reactivos empleados en dicha solicitud, veamos:

❖ La publicación científica “DIASTEREOSELECTIVE 14 α -HYDROXYLATION OF BACCATIN III DERIVATIVES²” revela:

Abstract: 14 α -Hydroxybaccatin III, a compound with limited availability by natural sources, is the starting material for the synthesis of the second-generation anticancer taxoid ortataxel. The 7-tert-butoxycarbonyl (1a) and 7-triethylsilyl (1b) derivatives of 14 α -hydroxybaccatin III 1,14-carbonate were synthesized from 10-deacetyl baccatin III (3). The crucial steps were (a) the C14 α hydroxylation of the corresponding 13-oxobaccatin III derivatives by oxaziridine-mediated electrophilic oxidation and (b) the reduction of the C13 carbonyl group with sodium or alkylammonium borohydrides. This protocol provides a practical way for the semisynthesis of ortataxel from 10-deacetyl baccatin III, a compound readily available from various yews.

(...)

CHART 4. Retrosynthetic Analysis of 1a and 1b



(...)

Such an intermediate would allow direct coupling with the appropriate C13 side chain. This would require protection of C7-OH as either the 7-tert-

² Diastereoselective 14 α -Hydroxylation of Baccatin III Derivatives Baldelli, E., Battaglia, A., Bombardelli, E., Carenzi, G., Fontana, G., Gambini, A., Gelmi, M.L., Guerrini, A., and Pocar, D.J. Org. Chem., 68, 25, 9773 - 9779, 2003, 10.1021/jo0347112

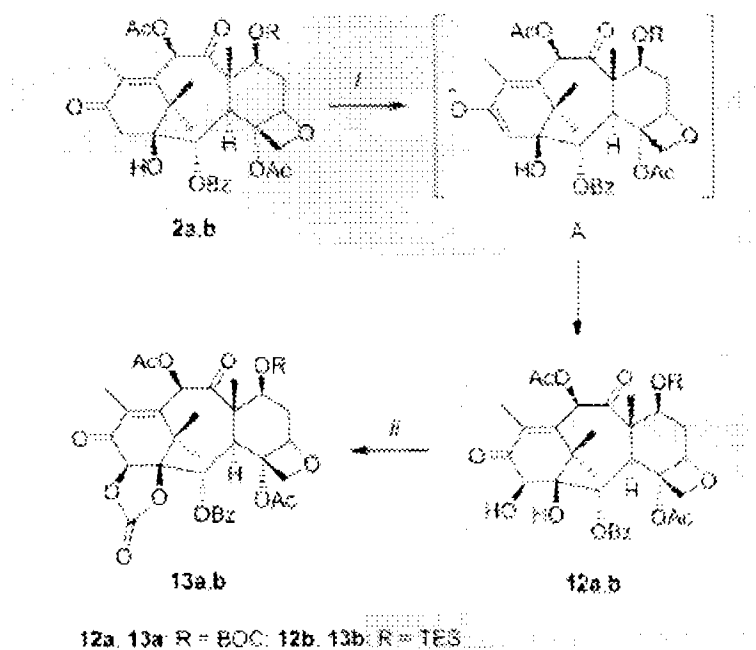
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butoxycarbonyl (7-BOC) or 7-triethylsilyl (7-TES) derivatives of 14 α -OHbaccatin III 1,14-carbonate (1a and 1b, respectively).
(...)

Results and Discussion

The formation of the 13-oxo-7-TES-baccatin III (2b) from 10-DAB 3 was previously reported, by sequential transformation of 3 via selective silylation and acetylation of the C7 and C10 hydroxy groups followed by MnO₂oxidation to give 2b.¹³ However, a protocol for preparation of the 7-BOC analogue 2a was not available; thus, we studied two different routes to obtain it (Scheme 1).
(...)

SCHEME 2 Conversion of 2a,b to 12a,b²



Como se puede observar, en este documento se hace uso de los compuestos de organosilano como protectores del hidroxilo de la posición 7 sobre el núcleo de 10-deacetil baccatina, específicamente el uso de trimetilsililo y trietilsililo (TES), que son trialquilsililos, clase de organosilanos que se mencionan en las reivindicaciones 16, 22, 54 y 58 de la solicitud colombiana en trámite.

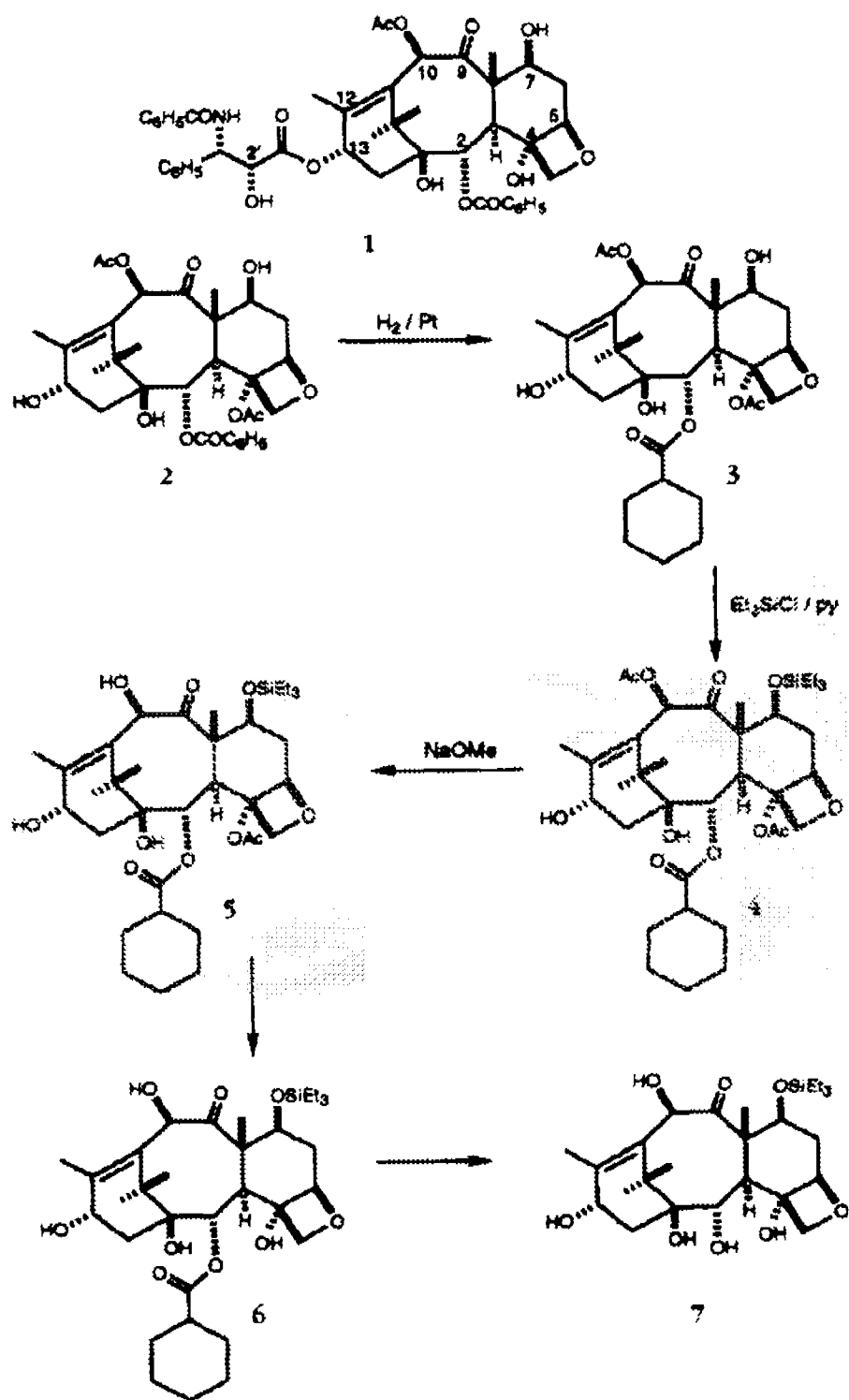
❖ La publicación científica MODIFIED TAXOLS, DEACYLATION AND REACYLATION OF BACCATIN III³ revela:

ABSTRACT: Hydrogenation of baccatin 111 over platinum converted it to its hexahidro derivative, and deacylation of this as its 7-triethylsilyl derivative was achieved with methoxide ion. The 10-acetate was hydrolyzed first, followed by the C-4 acetate and then the C-2cyclohexylcarboxylate; an explanation for this

³ Modified Taxols, 8. Deacylation and Reacylation of Baccatin III Samaranayake, Gamini, Neidigh, Kurt A., and Kingston, David G. I. J. Nat. Prod., 56, 6, 884 - 898, 1993, 10.1021/np50096a012

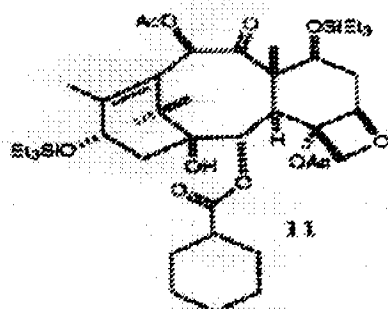
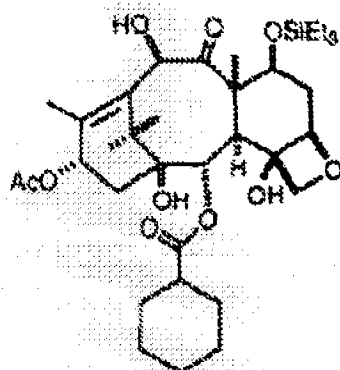
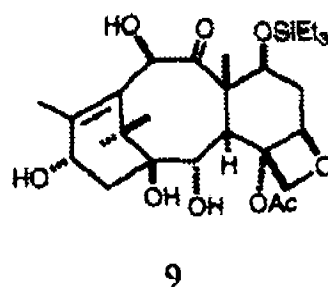
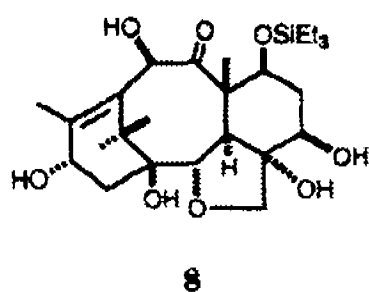
unexpected order is presented. Base treatment also yielded a rearranged analogue with a tetrahydrofuran ring in place of the oxetane ring of baccatin III. Acetylation of 4,10-bis(deacetyl)-2-debenzoyl-7-triethylsilyl-baccatin I proceeded readily at the C-13 position, in contrast to baccatin III which is only acetylated with difficulty at this position. Further acylation could be carried out selectively at the C-2 and C-10 positions, but acetylation at C-4 was possible only under vigorous conditions.

(...)

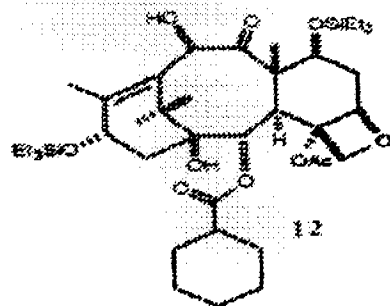


SCHEME 1

(...)



NaOMe



(...)

Como se puede observar, esta publicación incluye los compuestos de la solicitud colombiana en tramite (A y C), utilizando el mismo agente de protección tipo organosilano en presencia de un compuesto que contiene nitrógeno,

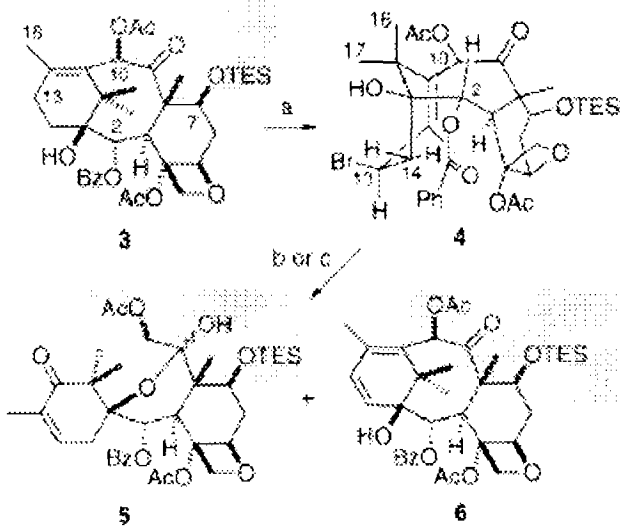
específicamente trietilsilil (TES) en presencia de piridina (PY), tal y como se menciona en las reivindicaciones 1 y 39 de la solicitud colombiana en tramite.

❖ La publicación científica "SYNTHETIC STUDIES WITH 13-DEOXYBACCATIN III⁴" revela:

Abstract: An efficient synthesis of 13-epi-7-O-(triethylsilyl)-baccatin III from 13-deoxybaccatin III is described. Oxidation of 13-deoxy-7-O-(triethylsilyl)baccatin III with tert-butyl peroxide, followed by reduction with SmI2, produced 13-epi-7-O-(triethylsilyl)baccatin III in good overall yield. The preparation of 13-oxo-7-O-(triethylsilyl)baccatin III from 13-epi-7-O-(triethylsilyl)baccatin III using tetrapropylammonium perruthenate and N-methylmorpholine N-oxide is also reported.

(...)

SCHEME 1^a

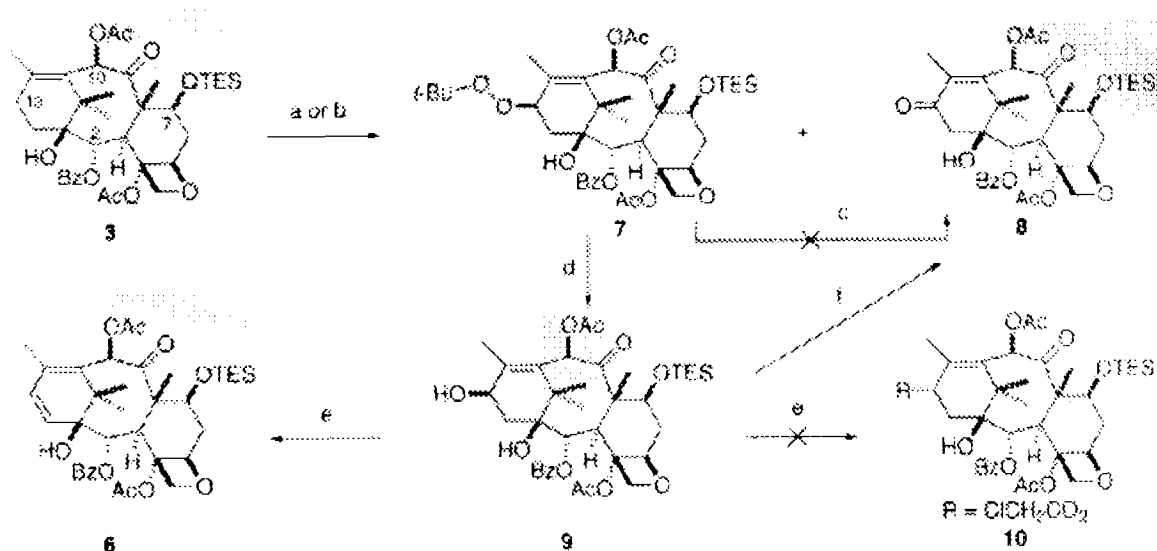


(...)

The 7-hydroxy group of 13-deoxybaccatin III was protected with triethylsilyl chloride (TESCl) to provide 13-deoxy-7-O-(triethylsilyl)baccatin III (3)^{10,11} in 95% yield.

(...)

¹ Synthetic Studies with 13-Deoxybaccatin III Ahn, Y.M., Vander Velde, D.G., and Georg, G.I. J. Org. Chem., 67, 20, 7140 - 7143, 2002. 10.1021/jo011183q



Si bien es cierto que los compuestos no son idénticos a los contenidos en la solicitud colombiana en trámite, se puede apreciar las mismas sustituciones con grupo acetilo en la posición 10 y la protección del hidroxilo de la posición 7 con un grupo trietilsililo (obtenido de la reacción con clortrietilsilano) sobre un núcleo de baccatina III, tal y como sucede en lo reivindicado por la solicitud colombiana en cuestión.

- ❖ La patente europea EP 1022284 publicada el 26 de Julio de 2000 y titulada "TAXOID DERIVATIVES AND PROCESS FOR PRODUCING THE SAME" revela:

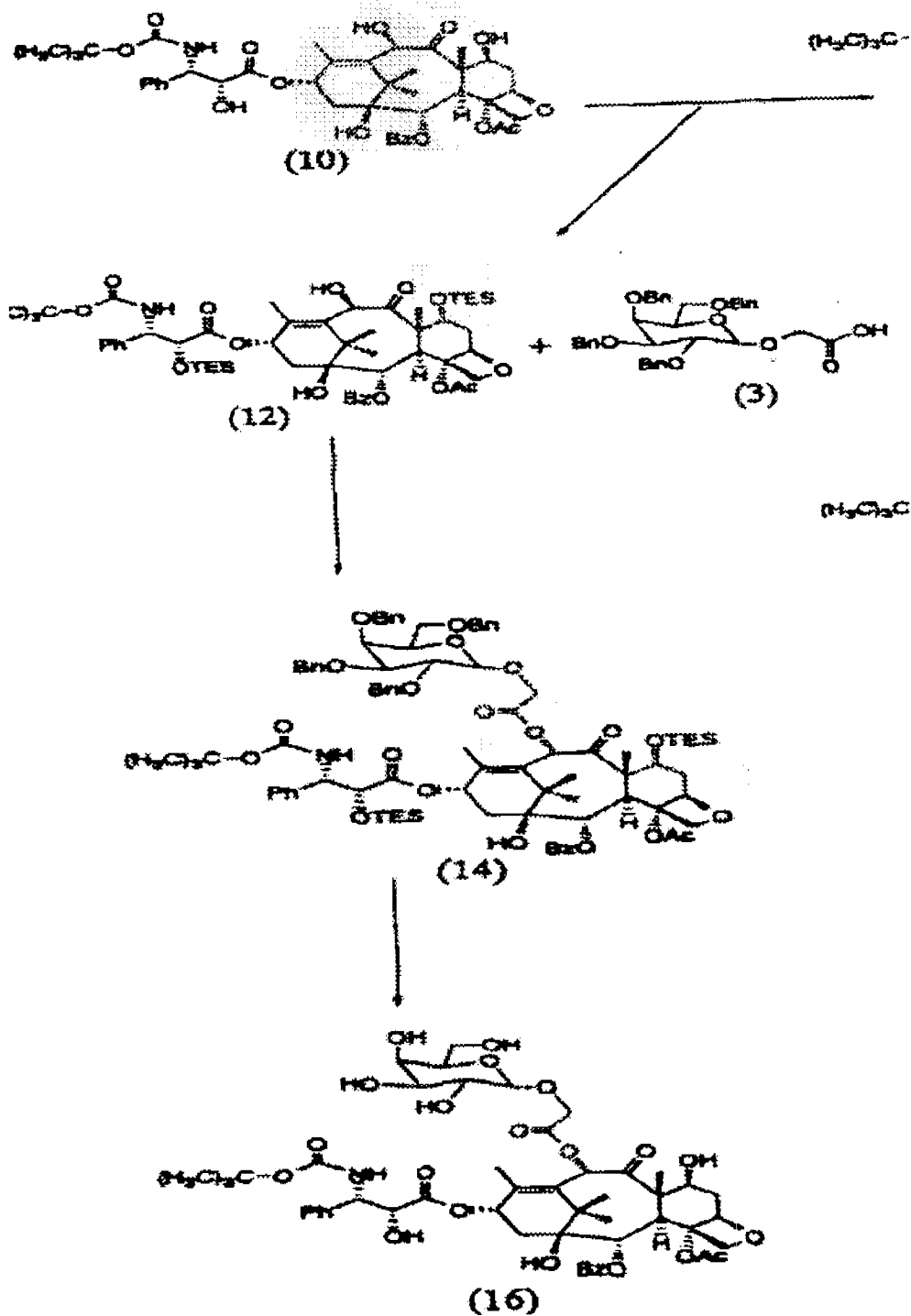
(57) An object of the invention is to develop galactose or mannose derivatives of docetaxel, etc. having improved solubility and physiological activity, to alleviate burden imposed on patients and to provide effective therapeutic drug for tumors.

The present invention provides taxoid derivatives comprising any of paclitaxel, docetaxel and 10-deacetyl-baccatin III to which galactose or mannose is linked through a spacer, and methods for producing taxoid derivatives comprising reacting paclitaxel, docetaxel or 10-deacetyl-baccatin III with tetrabenzyl acetyloxygalactoside or tetrabenzyl acetyloxymannoside, subjecting the product to debenzylation reaction, and optionally to triethylsilylation reaction.

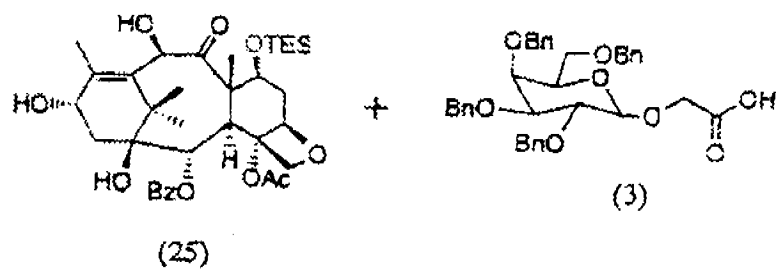
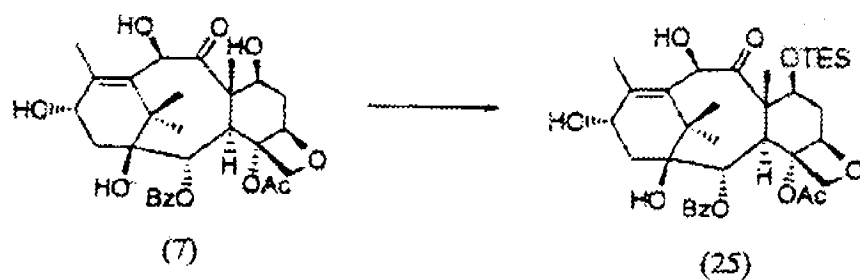
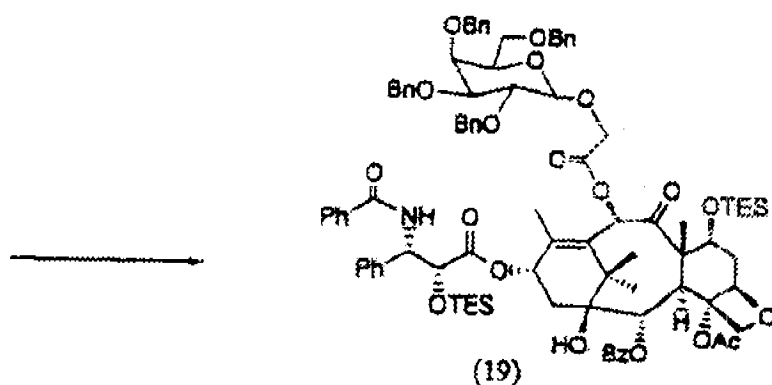
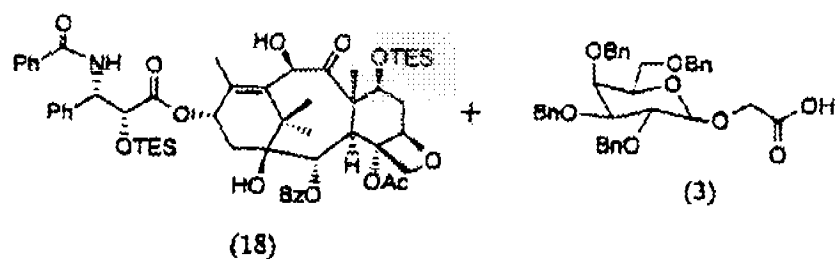
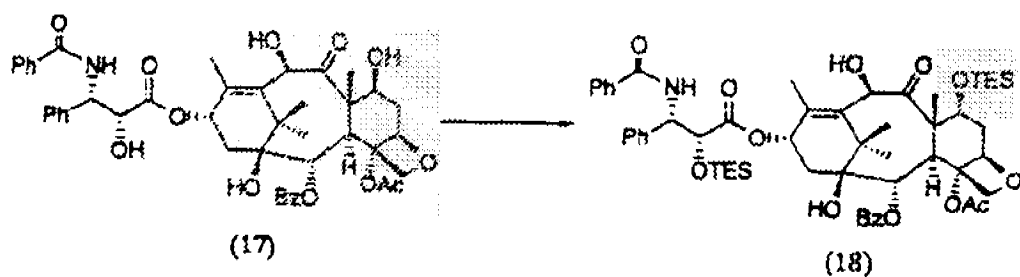
(...)

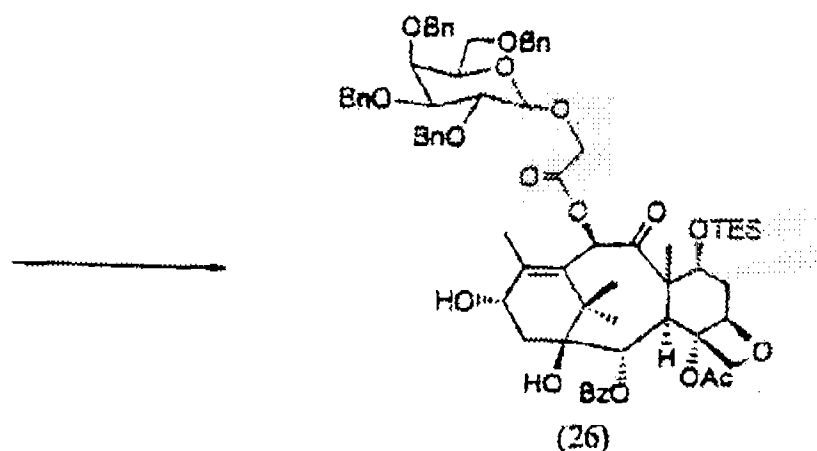
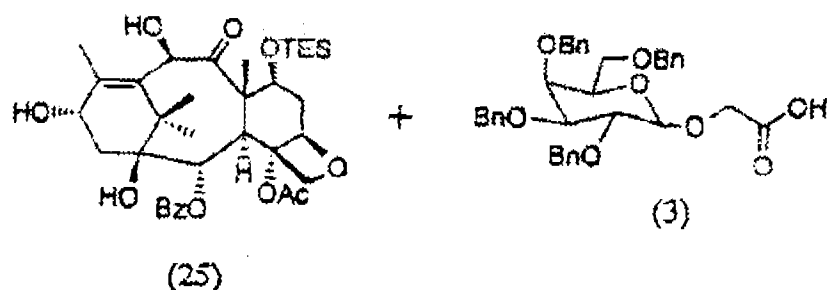
[0010] The present inventors have made intensive research with view to developing derivatives of paclitaxel and as a result found that there can be obtained paclitaxel derivatives that consists of paclitaxel, and galactose or mannose linked thereto via an ester bond through a spacer and that the resulting derivatives show improved solubility in water and physiological activity. The present invention has been accomplished based on this discovery. Also, as for docetaxel and 10-deacetyl-baccatin III described above, the present inventors have established methods for preparing taxoid derivatives in which galactose or mannose is linked via an ester bond in a similar manner.

(...)



(...)

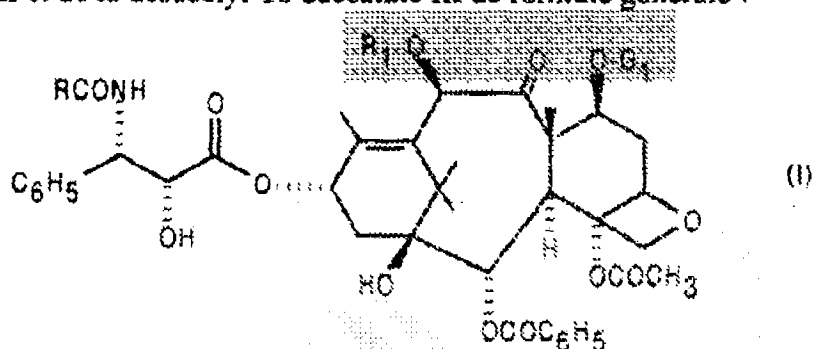




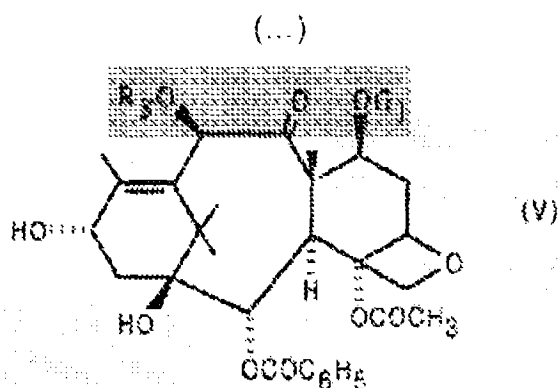
Si bien es cierto los compuestos de la anterioridad que aquí se mencionan no corresponden idénticamente a los de la solicitud colombiana en trámite, se puede evidenciar que se utilizan sobre el mismo núcleo de 10-deacetil baccatina III los compuestos protectores de grupo hidroxilo de organosilano, específicamente el residuo de dicho agente en la posición 7 (TES o trietilsilano) así como la sustitución con un grupo acetilo que sirve como conector con el sacárido en el caso de la anterioridad aquí expuesta y que hace las veces de grupo protector de la función hidroxilo.

- ❖ La publicación internacional WO 93/01179 publicada el 21 de enero de 1993 y titulada "PROCESS FOR THE PREPARATION OF BACCATIN III AND 10-DEACETYL BACCATIN III DERIVATIVES" revela:

La présente invention concerne un procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III de formule générale :



dans laquelle R représente un radical t.butoxy ou phényle, R_1 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate et G_1 représente un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate sous forme 2'R,3'S ou 2'S,3'S.



dans laquelle R_3 représente un radical acétyle ou un groupement protecteur de la fonction hydroxy choisi parmi les radicaux trichloro-2,2,2 éthoxycarbonyle ou trialkylsilyle dont chaque partie alcoyle contient 1 à 3 atomes de carbone et G_1 représente un groupement protecteur de la fonction hydroxy choisi parmi les radicaux trichloro-2,2,2 éthoxycarbonyle ou trialkylsilyle dont chaque partie alkyle contient 1 à 3 atomes de carbone, suivie du remplacement des groupements protecteurs des fonctions hydroxy par des atomes d'hydrogène.

Claramente se evidencia el uso de los mismos agentes protectores de grupo hidroxilo derivados de organosilano, específicamente trialquilsilanos, sobre el núcleo de 10-deacetil baccatina III, tal y como lo menciona en su capítulo reivindicatorio la solicitud colombiana en trámite.

- ❖ La patente americana US 6,706,896 publicada el 16 de marzo de 2004 y titulada "PROCESS FOR SELECTIVE DERIVATION OF TAXANES" revela:

16
106
102

(57)

ABSTRACT

Processes for the preparation of taxol and other taxanes through selective derivatization of the C(7) and C(10) hydroxyl groups of 10-DAB, particularly a novel process using a new strategy in which the C(10) hydroxyl group is protected or derivatized prior to the C(7) hydroxyl group; and the provision of C(7) and C(10) derivatized 10-DAB compounds.

(...)

The present invention is further directed to a process for the silylation of the C(10) hydroxy group of a taxane having a C(10) hydroxy group. The process comprises treating the taxane with a silylamide or a bis-silylamide to form a C(10) silylated taxane.

(...)

Among other things, the present invention enables the selective derivatization of the C(10) hydroxyl group of a taxane without first protecting the C(7) hydroxyl group. Stated another way, it has been discovered that the reactivities previously reported for the C(7) and C(10) hydroxyl groups can be reversed, that is, the reactivity of the C(10) hydroxyl group becomes greater than the reactivity of the C(7) hydroxyl group under certain conditions.

(...)

In accordance with the process of the present invention, it has been discovered that the C(10) hydroxyl group of a taxane can be selectively acylated in the absence of an amine base. Preferably, therefore, amine bases such as pyridine, triethylamine, dimethylaminopyridine and 2,6-lutidine, if present at all, are present in the reaction mixture in relatively low concentration. Stated another way, if an amine base is present in the reaction mixture, the molar ratio of the amine base to the taxane is preferably less than 1:1, more preferably less than 10:1, and most preferably less than 100:1.

(...)

ride. Zinc chloride or cerium trichloride is particularly preferred when the acylating agent is an anhydride or dicarbonate. Cuprous chloride is particularly preferred when the acylating agent is an isocyanate.

(...)

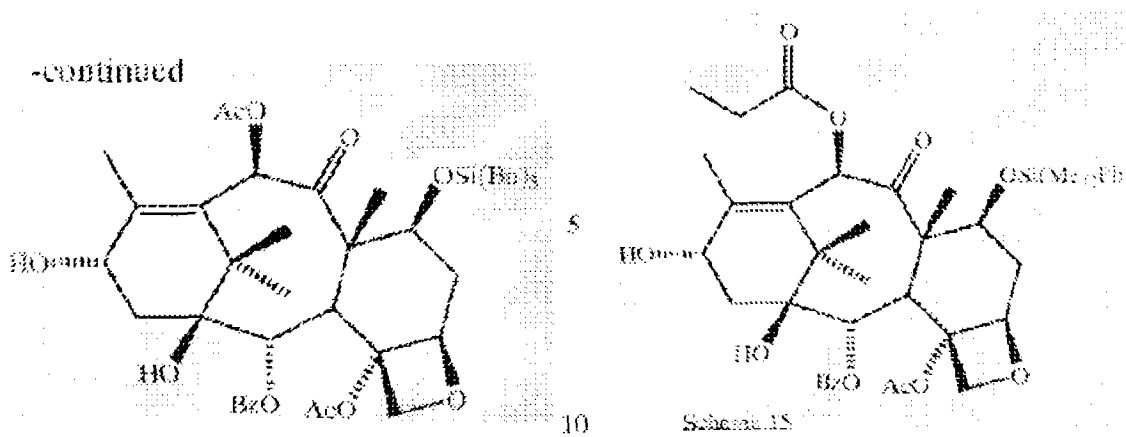
102 103

For purposes of illustration, acylating reactions involving dibenzyl dicarbonate, diallyl dicarbonate, acetic anhydride, chloroacetic anhydride and phenyl isocyanate are illustrated in Reaction Schemes 1 through 5 below. In this series of reaction schemes, the taxane which is selectively acylated at the C(10) position is 10-deacetylbaccatin III. It should be

(...)

In another aspect of the present invention, the C(10) hydroxyl group of a taxane may be selectively silylated. In general, the silylating agent is selected from the group consisting of silylamides and bissilylamides. Preferred silylamides and bissilylamides correspond to structures 6 and 7, respectively:

(...)



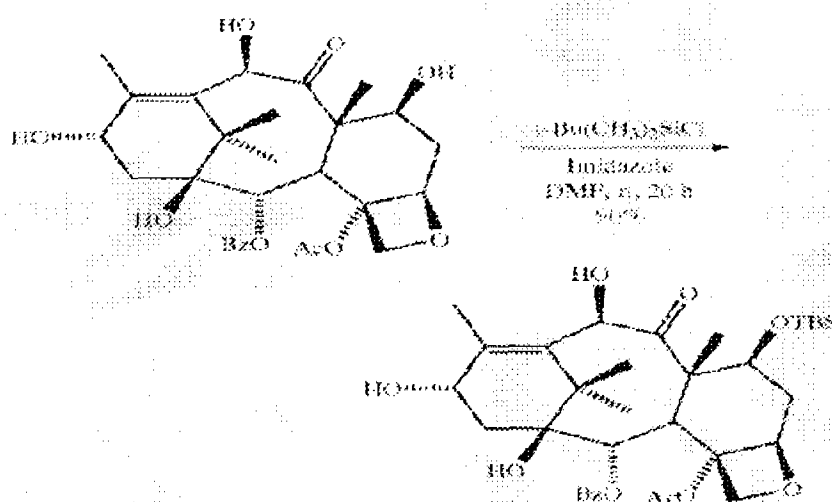
(...)

In general, the C(7) hydroxyl group of a taxane can be selectively silylated with a silylating agent which includes the $\text{—SiR}_j\text{R}_k\text{R}_l$ moiety wherein R_j , R_k and R_l are independently substituted or unsubstituted hydrocarbyl or heteroaryl, provided that any substituents are other than hydroxyl. In one embodiment of the present invention, if each of R_j , R_k and R_l is alkyl, then at least one of R_j , R_k , and R_l comprises a carbon skeleton (i.e., carbon chain or ring(s)) having at least four carbon atoms. Suitable silylating agents include silyl halides and silyl triflates, for example, tri(hydrocarbyl)silyl halides and tri(hydrocarbyl)silyl triflates. The hydrocarbyl substituents of these silylating agents may be substituted or unsubstituted and preferably are substituted or unsubstituted alkyl or aryl.

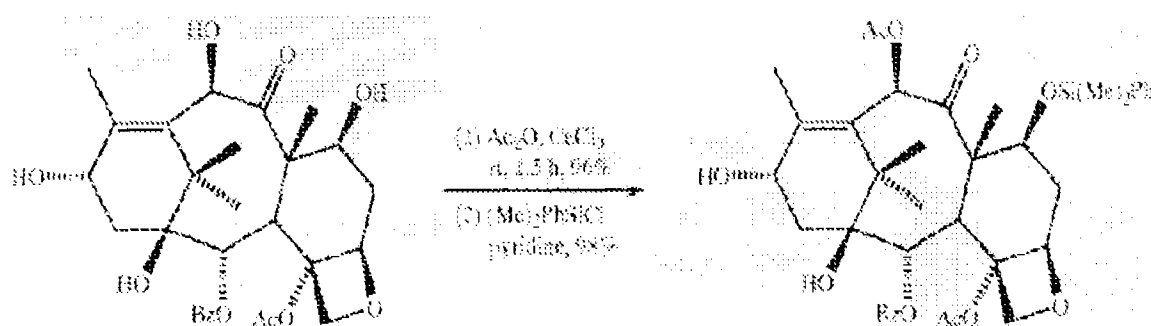
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The selective silylation of the C(7) hydroxy group may be carried out in a solvent, such as dimethyl formamide ("DMF") or pyridine and in the presence of an amine base, such as imidazole or pyridine. Reaction Schemes 17-20 illustrate the silylation of the C(7) hydroxy group of 10-DAB in high yield by treating 10-DAB with 1-butyltrimethylsilyl chloride, tribenzylsilyl chloride, dimethyl-isopropylsilyl chloride, and dimethylphenylsilyl chloride, respectively. Silylation under these conditions was

(...)



(...)



Este documento nos permite observar toda la información necesaria para obtener tanto el compuesto A como el compuesto C, a partir del mismo intermediario (10-deacetil baccatina III), específicamente en lo que se refiere a l uso de compuestos de organosilano como agentes protectores de los grupos hidroxilo, el uso de anhídrido acético como agente de acilación, la presencia de pirazina o piridina para conseguir la protección en la posición 7, y en general, todas las condiciones necesarias para hacer selectiva la sustitución en los hidroxilos de la posición 7 y/o 10 de la 10-deacetil-baccatina III, tal como se pretende en el capítulo reivindicatorio de la solicitud en trámite.

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En conclusión, la solicitud colombiana en trámite pretende reivindicar un proceso de obtención de derivados de 10-deacetil baccatina III, a través de procedimientos, reactivos y condiciones que se encuentran ampliamente descritos en el estado de la técnica, tal como es la protección selectiva de los grupos hidroxilo de las posiciones 7 y 10 con compuestos organosilanos.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

III. ANEXOS

- La publicación internacional WO 94/04519 publicada el 03 de Marzo de 1994 y titulada "PROCESS OF CONVERTING TAXANES INTO BACCATIN III AND 10-DEACETYLBACCATIN III" pagina 4 y capítulo reivindicatorio.
- La patente americana US 5,256,801 publicada el 26 de octubre de 1996 y titulada "PROCESSES OF CONVERTING TAXANES INTO 10-DEACETYLBACCATIN III" capítulo reivindicatorio.
- La patente americana US 4,924,012 publicada el 08 de mayo de 1990 y titulada "PROCESS FOR PREPARING DERIVATIVES OF BACCATINE III AND OF 10-DEACETYL BACCATINE III" capítulo reivindicatorio.
- La patente europea EP 0526311 publicada el 03 de febrero de 1993 y titulada "PROCEDE DE PREPARATION DE LA CINNAMOYL-13ALPHA BACCATINE III OU DESACETIL-10 BACCATINE III" capítulo reivindicatorio.
- Abstract de la publicación científica "¹³C NMR INVESTIGATION OF SOLID-STATE POLYMORPHISM IN 10-DEACETYL BACCATIN III"
- La patente europea EP 1022284 publicada el 26 de Julio de 2000 y titulada "TAXOID DERIVATIVES AND PROCESS FOR PRODUCING THE SAME" paginas 4, 10, 11, 13, 18, 20, 24 y capítulo reivindicatorio.
- La patente americana US 6706896 publicada el 16 de marzo de 2004 y titulada "PROCESS FOR SELECTIVE DERIVATION OF TAXANES" columnas 1 a 5, 7, 11, 13, 15, 16 y capítulo reivindicatorio.
- La publicación internacional WO 93/01179 publicada el 21 de enero de 1993 y titulada "PROCESS FOR THE PREPARATION OF BACCATIN III AND 10-

DEACETYL BACCATIN III DERIVATIVES" paginas 1, 3 y capitulo reivindicatorio.

- La publicación científica "DIASTEREOSELECTIVE 14^Å-HYDROXYLATION OF BACCATIN III DERIVATIVES".
- La publicación científica "SYNTHETIC STUDIES WITH 13-DEOXYBACCATIN III"

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P. 44655 del C. S de la J.

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containing low percentages of taxol, 10-deacetyltaxol and cephalomannine are converted into baccatin III or 10-deacetylbaccatin III.

In large scale processing of taxol for commercial use, the cost associated with achieving the Magris, et al. yield is not economically feasible. The Magris, et al. process uses tetrabutylammonium borohydride, an expensive reducing salt. Furthermore, this procedure is run at 0°C which adds refrigeration costs to the final product. Most taxane extraction processes result in by-products containing some taxol, 10-deacetyltaxol, cephalomannine and significant amounts of other substances. Therefore, there remains a need for a high yield inexpensive process of converting these partially purified mixtures of taxanes including but not limited to taxol, 10-deacetyltaxol and/or cephalomannine into baccatin III and/or 10-deacetylbaccatin III.

SUMMARY OF THE INVENTION

An object of the present invention is to convert partially purified organic by-products of the taxane extraction process into 10-deacetylbaccatin III.

An object of the present invention is to convert partially purified organic by-products of the taxane extraction process into Baccatin III.

Another object of the present invention is to provide a method of converting selected taxanes into Baccatin III.

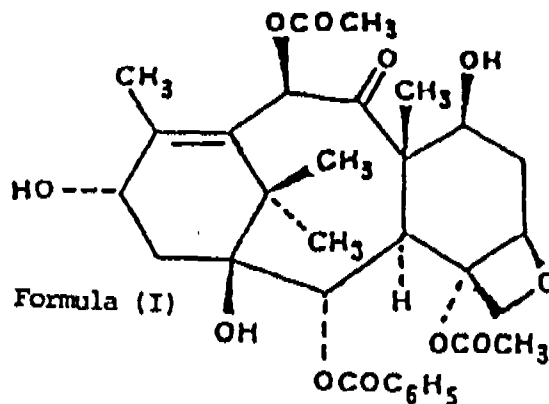
A further object of the present invention is to provide a simple, high-yield method of preparing Baccatin III at room temperature.

A further object of the present invention is to provide a simple, method of preparing 10-deacetylbaccatin III at room temperature.

Still a further object is to provide an inexpensive method of converting a partially purified mixture of taxol, cephalomannine, 10-deacetyltaxol and other substances into baccatin III or 10-deacetylbaccatin III.

I claim:

1. A process for the preparation of a compound of formula (I)



comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

2. The process of claim 1 conducted at a range temperature of from room temperature to -30°C.

3. The process of claim 1 wherein the borohydride reducing salt is sodium borohydride.

4. The process of claim 1 wherein the borohydride reducing salt is tetrabutylammonium borohydride.

5. The process of claim 1 wherein the reaction solvent is selected from the group consisting of: CH₃OCH₂CH₂OCH₂, CH₃OCH₂CH₂OCH₂CH₂OCH₃, CH₃OCH₂CH₂OCH₂CH₂OCH₂CH₂OCH₃.

6. The process of claim 1 wherein the reaction solvent is tetrahydrofuran.

7. The process of claim 1 wherein the reaction solvent is dichloromethane.

8. The process of claim 1 wherein the mixture contains at least 15% - 50% taxanes which are taxol and the reaction solvent is tetrahydrofuran.

9. The process of claim 1 wherein the mixture

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contains greater than 50% by weight of taxanes which are taxol and the reaction solvent is dichloromethane.

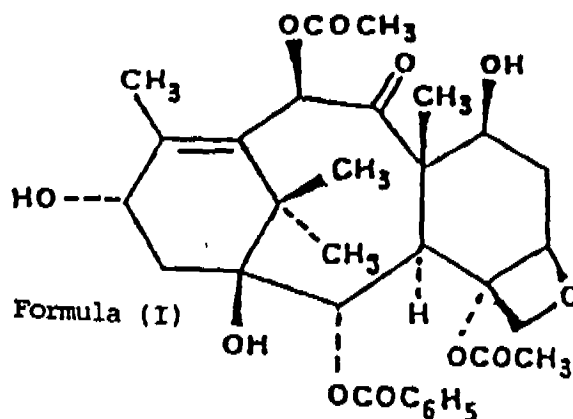
10. The process of claim 1 wherein the mixture contains less than 15% by weight of taxanes which are taxol and the reaction solvent is selected from the group consisting of $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})\text{CH}_3$, $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$.

11. The process of claim 1 wherein the Lewis acid is a metal halide.

12. The process of claim 12 wherein the metal halide is Tin chloride.

13. The process of claim 12 wherein the metal halide is cobalt chloride.

14. A process for the preparation of a compound of formula (I)



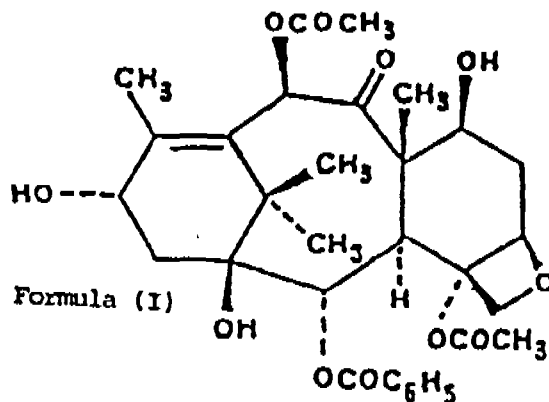
comprising contacting a mixture containing at least one taxane compound constituent having an ester linkage at the C-13 position with a borohydride reducing salt in aromatic hydrocarbons.

15. The process according to claim 14 wherein said aromatic hydrocarbon is toluene.

16. The process according to claim 14 wherein said borohydride reducing salt is tetrabutylammonium borohydride.

17. The process according to claim 14 is conducted at a temperature of 0°C.

18. A process for the preparation of a compound of formula (I)



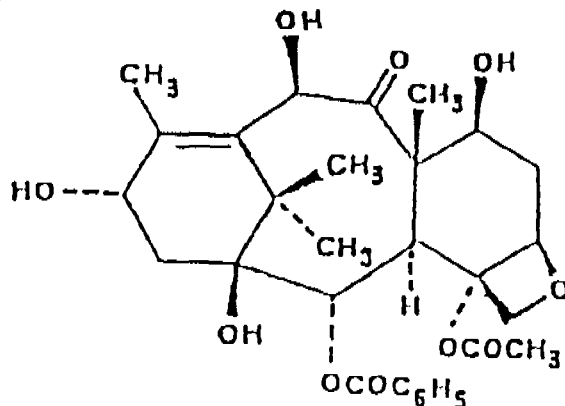
comprising contacting a mixture containing a taxane compound which is taxol and at least one other taxane compound having an ester linkage at the C-13 position that is not taxol with a borohydride reducing salt in a reaction solvent wherein the taxane compound which is taxol in the mixture is not converted to formula I as defined above.

19. The process according to claim 18 wherein the reducing salt is sodium borohydride.

20. The process according to claim 19 wherein the reaction solvent is ethanol.

21. The process according to claim 20 conducted at a temperature of -30°C.

22. A process for the preparation of a compound of formula (II)



comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

23. The process of claim 22 wherein the borohydride reducing salt is sodium borohydride.

24. The process of claim 22 wherein the reaction solvent is selected from $\text{CH}_3(\text{OCH}_2\text{CH}_2)_x\text{OCH}_3$, where x is an integer from 1 to 5.

25. The process of claim 22 wherein the reaction solvent is tetrahydrofuran.

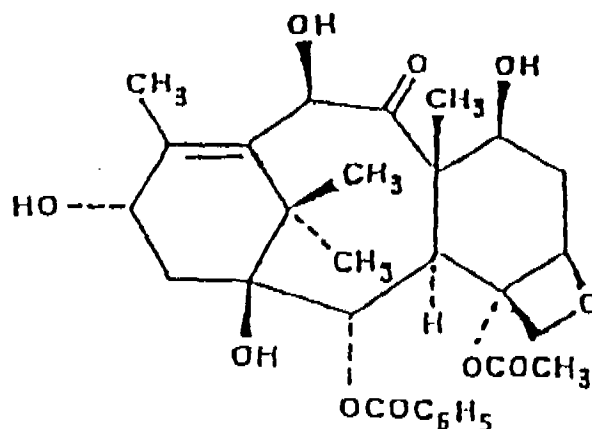
26. The process of claim 22 wherein the reaction solvent is dichloromethane.

27. The process of claim 22 wherein the Lewis acid is a metal halide.

28. The process of claim 27 wherein the metal halide is tin chloride.

29. The process of claim 27 wherein the metal halide is cobalt chloride.

30. A process for the preparation of a compound of formula (II)



comprising contacting a mixture containing at least one taxane compound constituent having an ester linkage at the C-13 position with a borohydride reducing salt in triglyme.

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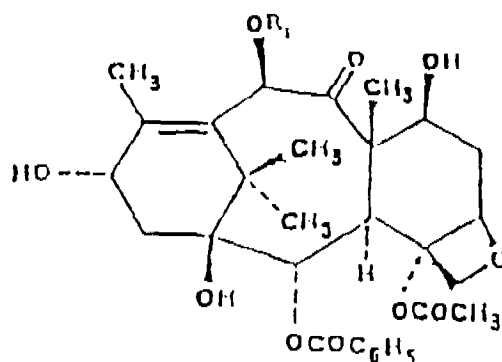
31. The process according to claim 30 wherein said borohydride reducing salt is sodium borohydride.

32. The process according to claim 30 is conducted at a temperature of 22°-27°C.

[received by the International Bureau on 28 December 1993 (28.12.93);
new claim 33 added; other claims unchanged (1 page)]

32. The process according to claim 30 is conducted at a temperature of 22'-27'C.

33. A process for the preparation of a compound of formula



where R₁ is selected from H and COCH₃, comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.



US005256801A

United States Patent [19]
Carver et al.

[11] **Patent Number:** **5,256,801**
[45] **Date of Patent:** **Oct. 26, 1993**

[54] **PROCESSES OF CONVERTING TAXANES INTO 10-DEACETYLBACCATIN III**

[75] **Inventors:** **David R. Carver; Timothy R. Prout,** both of Boulder; **Hernita A. Ewald,** Denver; **Donia L. Henderson,** Boulder, all of Colo.

[73] **Assignee:** **NaPro BioTherapeutics, Inc.,** Boulder, Colo.

[21] **Appl. No.:** **986,852**

[22] **Filed:** **Dec. 4, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 930,840, Aug. 14, 1992, Pat. No. 5,202,448.

[51] **Int. Cl.⁵** **C07D 305/14**

[52] **U.S. Cl.** **549/510**

[58] **Field of Search** **549/510**

[56] **References Cited**

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Tetrahedron, vol. 42, F. Gueritte-Voegelein, V. Senilii,

B. David, D. Guenard and P. Potier, Chemical Studies of 10-Deacetyl Baccatin III, Hemisynthesis of Taxol Derivatives, pp. 4451-4460, No. 16, 1986.

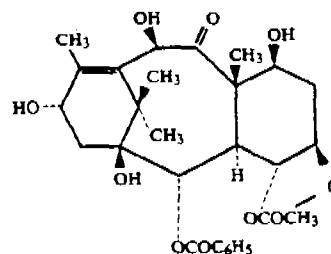
Primary Examiner—Marianne M. Cintins

Assistant Examiner—Michael B. Hydorn

Attorney, Agent, or Firm—Timothy J. Martin; Dana S. Rewoldt

[57] **ABSTRACT**

A process for the preparation of a compound of formula (I)



comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

11 Claims, No Drawings

SnBr_2 , SnI_2 and CoBr_2 would be selected Lewis acids under the two step test.

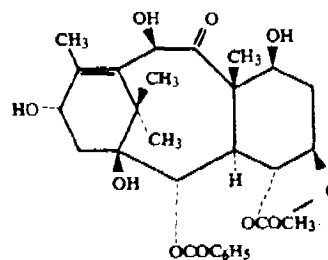
Various experiments indicate that large scale production of 10-deacetylbaccatin III may require more than 0.1% of the Lewis acid. Furthermore, when large quantities of starting material are used it is extremely important to closely monitor the reaction by TLC and to be certain that the mixture is being well agitated so that the cleavage reaction can readily occur.

The present invention discloses new high yield processes for converting partially purified taxane mixtures into both baccatin III and 10-deacetylbaccatin III. These processes result in good yield of 10-deacetylbaccatin III which is essentially pure after further purification by methods known to those skilled in the art. Characterization of the resultant species confirms the structure of the resultant product to be 10-deacetylbaccatin III. In addition to the good yield of 10-deacetylbaccatin III these processes are commercially viable, inexpensive, and run at room temperature. The use of the borohydride reducing salts other than sodium borohydride and tetrabutylammonium borohydride and the use of other Lewis acids are contemplated by this invention.

Accordingly, the present invention has been described with some degree of particularity directed to the processes of the present invention. It should be appreciated, though, that the present invention is defined by the following claims construed in light of the prior art so that modifications or changes may be made to the processes of the present invention without departing from the inventive concepts contained herein. It is understood that the invention may be practiced otherwise than as specifically described.

We claim:

1. A process for the preparation of a compound of formula (I)



comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

2. The process of claim 1 wherein the borohydride reducing salt is sodium borohydride.

3. The process of claim 1 wherein the reaction solvent is selected from $\text{CH}_3(\text{OCH}_2\text{CH}_2)_x\text{OCH}_3$, where x is an integer from 1 to 5.

4. The process of claim 1 wherein the reaction solvent is tetrahydrofuran.

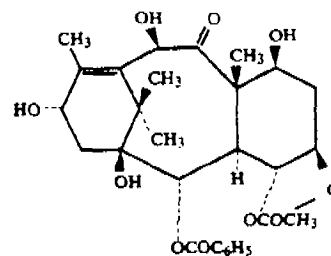
5. The process of claim 1 wherein the reaction solvent is dichloromethane.

6. The process of claim 1 wherein the Lewis acid is a metal halide.

7. The process of claim 6 wherein the metal halide is tin chloride.

8. The process of claim 6 wherein the metal halide is cobalt chloride.

9. A process for the preparation of a compound of formula (I)



comprising contacting a mixture containing at least one taxane compound constituent having an ester linkage at the C-13 position with a borohydride reducing salt in triglyme.

10. The process according to claim 9 wherein said borohydride reducing salt is sodium borohydride.

11. The process according to claim 9 is conducted at a temperature of 22°-27° C.

- [54] PROCESS FOR PREPARING DERIVATIVES
OF BACCATINE III AND OF 10-DEACETYL
BACCATINE III

- [75] Inventors: Michel Colla, Thoiry; Daniel Guenard, Montrouge; Françoise Gueritte-Voegelein, Les Ulis; Pierre Potier, Paris, all of France

- [73] Assignee: **Rhone-Poulenc Sante, Antony, France**

- [21] Appl. No.: 331,758

- [22] Filed: Apr. 3, 1989

- [30] Foreign Application Priority Data

Apr. 6, 1988 [FR] France 88 04513

- [51] **Int. Cl.**⁵ C07D 305/14

- [52] U.S. Cl. 549/510; 549/511

- [58] **Field of Search** 549/\$10, 511

- ## [56] References Cited

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|-----------|--------|--------------|---------|
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Primary Examiner--Glennon H. Hollrah

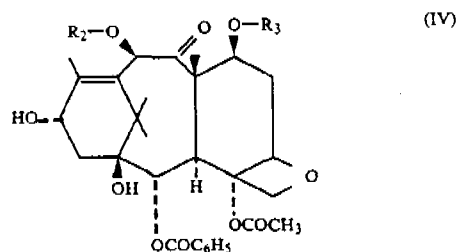
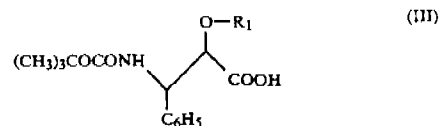
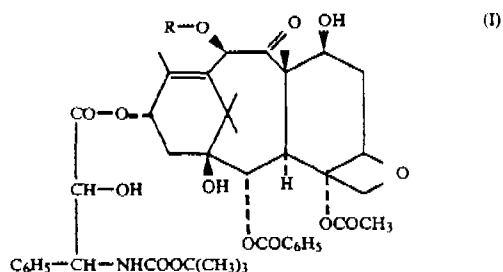
Assistant Examiner—Ba K. Trinh

Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

- [57]
- ABSTRACT**

Process for preparing derivatives of baccatine III and of

10-deacetyl bacattine III, of general formula (I), in which R is hydrogen or acetyl, by condensation of an acid of general formula (II) with a derivative of bacattine III or of 10-deacetyl bacattine III of general formula (III), R₁, R₂ and R₃ denoting hydroxy-protecting groups, followed by the replacement of the protecting groups by hydrogen.



11 Claims, No Drawings

below 30° C. After 1 hour, the flask is purged with argon. The reaction mixture is filtered on celite and then rinsed with ethanol. After concentration to dryness, an oil is obtained, which crystallizes to give, in a 92% yield, ethyl threo-2-hydroxy-3-amino-3-phenylpropionate (146 g), the structure of which is confirmed by the proton nuclear magnetic resonance spectrum and the mass spectrum.

Ethyl threo-2-hydroxy-3-amino-3-phenylpropionate may be prepared in the following manner:

tert-Butyl threo-2-hydroxy-3-amino-3-phenylpropionate (194 g) is dissolved in absolute ethanol (1 liter) in a 4-liter three-necked round-bottomed flask. A freshly prepared solution (550 cc) of hydrochloric acid in ethanol at a concentration of 13% by weight is added. After 3 hours at a temperature in the region of 20° C., the ethanol is evaporated off under reduced pressure. The residue is taken up with methylene chloride (1.5 liter). The methylene chloride solution is washed with saturated sodium bicarbonate solution (200 cc) and then with water. After drying and evaporation of the solvent, ethyl threo-2-hydroxy-3-amino-3-phenylpropionate (180 g) is obtained in a 99.7% yield, its structure being confirmed by the proton nuclear magnetic resonance spectrum and by the mass spectrum.

tert-Butyl threo-2-hydroxy-3-amino-3-phenylpropionate may be prepared in the following manner:

tert-Butyl 3-phenylglycidate (189 g), dissolved in ethanol (3 liters), is introduced into a 6-liter three-necked flask equipped with a stirrer, a thermometer and a condenser. Sodium azide (95 g) and ammonium chloride (75 g) are added and the mixture is then heated to 75° C. for 20 hours. Two-thirds of the ethanol are distilled off under reduced pressure at 50° C., water (4 liters) is then added and the evaporation of the ethanol is finally completed. After the aqueous suspension is cooled, a crystalline precipitate is obtained, which is separated by filtration and washed with water. After drying under reduced pressure in the presence of a phosphorus pentoxide, tert-butyl threo-2-hydroxy-3-amino-3-phenylpropionate (186.4 g) is obtained in an 82.4% yield, its structure being confirmed by the proton nuclear magnetic resonance spectrum and by the mass spectrum.

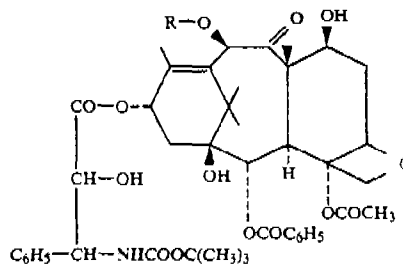
tert-Butyl 3-phenylglycidate may be prepared according to the process described by F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, 34, 3600 (1969). The product obtained is purified by chromatography on Merck 7734 silica, so as to obtain tert-butyl cis-3-phenylglycidate (200 g).

The product of general formula (IV) in which R₂ and R₃ each denote a 2,2,2-trichloroethoxycarbonyl radical may be prepared according to the process described in European patent application EP No. 253,738.

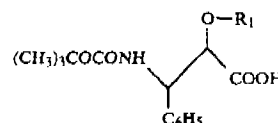
We claim:

1. A process for preparing a derivative of baccatine III or of 10-deacetyl baccatine III, of general formula:

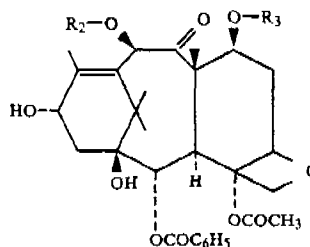
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in which R denotes hydrogen or acetyl, wherein an acid of general formula:



in which R₁ is a hydroxy-protecting group, is condensed with a taxan derivative of general formula



in which R₂ is an acetyl group or a hydroxy-protecting group and R₃ is a hydroxy-protecting group, and the protecting groups R₁, R₃ and, where appropriate, R₂ are then replaced by hydrogen.

2. A process according to claim 1, wherein R₁ is chosen from the group comprising methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (β-trimethylsilyloxy)methyl, tetrahydropyranyl and 2,2,2-trichloroethoxycarbonyl.

3. A process according to claim 2, wherein R₁ is 1-ethoxyethyl.

4. A process according to claim 1, wherein the hydroxy-protecting groups R₂ and R₃ which may be the same or different are each chosen from 2,2,2-trichloroethoxycarbonyl or trialkylsilyl groups in which each alkyl portion contains 1 to 3 carbon atoms.

5. A process according to claim 4, wherein the hydroxy-protecting group is 2,2,2-trichloroethoxycarbonyl.

6. A process according to claim 1, wherein the condensation is performed in the presence of a condensing agent and an activating agent.

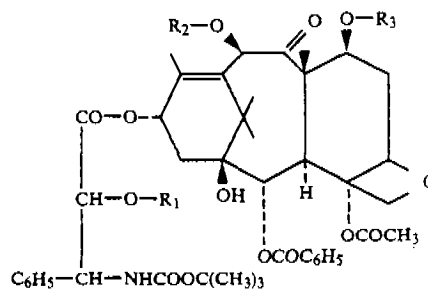
7. A process according to claim 6, wherein the condensing agent is chosen from carbodiimides and reactive carbonates and the activating agent is chosen from dialkylaminopyridines.

8. A process according to claim 7, wherein the condensing agent is chosen from dicyclohexylcarbodiimide and di-2-pyridyl carbonate, and the activating agent is 4-dimethylaminopyridine.

9. A process according to claim 1, wherein the condensation is preformed in an aromatic solvent chosen from benzene, toluene, xylenes, ethylbenzene, isopropylbenzene and chlorobenzene.

10. A process according to claim 1, wherein the condensation is performed at a temperature of between 60° and 90° C.

11. A process according to claim 1, for replacing by hydrogen of the protecting groups R_1 , R_3 and, where appropriate, R_2 on the intermediate product of general formula:



comprising treating said intermediate with zinc in the presence of acetic acid or with an inorganic or organic acid dissolved in an aliphatic alcohol containing 1 to 3 carbon atoms.

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DEMANDE DE BREVET EUROPEEN

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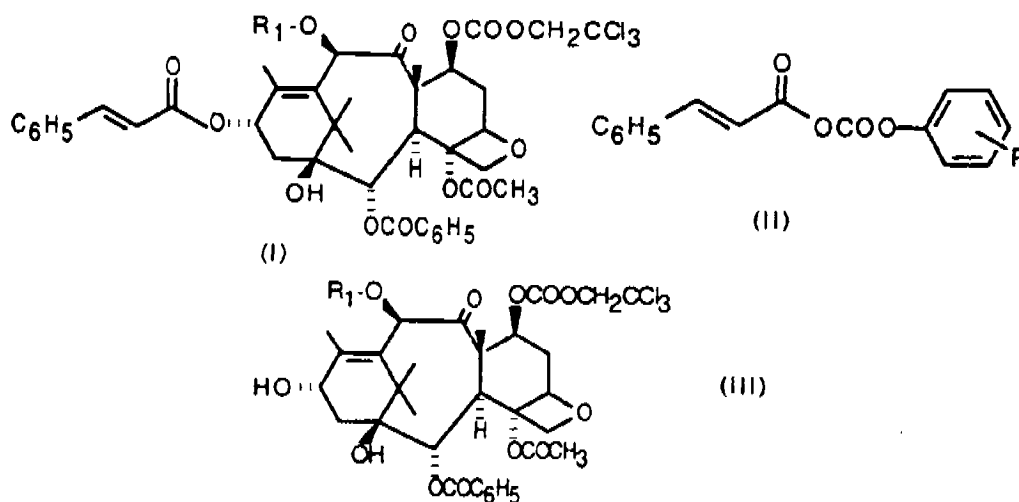
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(54) **Procédé de préparation de la cinnamoyl-13 α baccatine III ou désacétyl-10 baccatine III.**

(57) Procédé de préparation de la cinnamoyl-13 α baccatine III ou désacétyl-10 baccatine III de formule (I) par condensation d'un anhydride mixte de formule générale (II) sur un dérivé de la baccatine III ou de la désacétyl-10 baccatine III de formule générale (III).

Dans les formules (I) et (III), R₁ représente un radical acétyle ou trichloro-2,2,2 éthoxycarbonyle.

Dans la formule (II), R représente 1 à 5 substituants, identiques ou différents (halogène, nitro, méthyle, méthoxy).



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2,4,6 benzoïque.

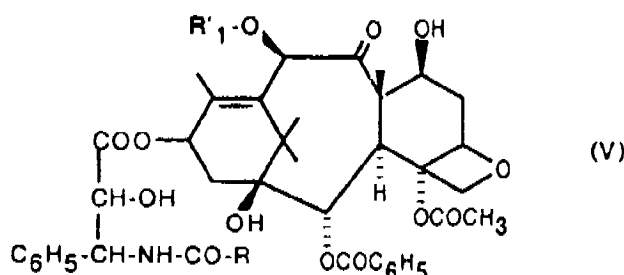
Généralement, l'anhydride mixte de formule générale (III) est obtenu par action du chlorure d'acide de formule générale (IV) sur l'acide cinnamique en solution dans un solvant organique convenable tel que le tétrahydrofurane en présence d'une base organique telle qu'une amine tertiaire comme la triéthylamine à une température comprise entre 0 et 30°C.

De préférence, afin d'éviter les réactions secondaires, la réaction de l'anhydride mixte de formule générale (III) sur le dérivé de la baccatine III ou de la désacétyl-10 baccatine III est effectuée en ajoutant lentement une solution de l'anhydride mixte dans un solvant organique convenable à une solution du dérivé de la baccatine III ou de la désacétyl-10 baccatine III dans le même solvant en présence d'un agent de condensation tel que la pyrrolidinopyridine ou la diméthylaminopyridine. Il est particulièrement avantageux d'opérer sous une atmosphère inerte telle qu'une atmosphère d'argon.

Comme solvant, on utilise de préférence un hydrocarbure aromatique, choisi parmi le benzène, le toluène ou les xylènes, ou un éther tel que le tétrahydrofurane.

Il est particulièrement avantageux d'opérer à une température comprise entre 40 et 110°C et de préférence à 80°C.

Le produit de formule générale (I) obtenu par le procédé selon la présente invention peut être transformé en produit de formule générale :



dans laquelle R représente un radical t.butoxy ou phényle et R'1 représente un atome d'hydrogène ou un radical acétyle selon les procédés décrits dans les demandes de brevet européen EP-A-0 253 738 et EP-A-0 253 739.

L'exemple suivant illustre la présente invention.

EXEMPLE

A 0,605 g d'acide cinnamique (4 mmoles) en solution dans 10 cm³ de tétrahydrofurane anhydre, on ajoute 0,580 ml de méthylamine anhydre. On ajoute alors, sous atmosphère d'azote, 0,640 ml de chlorure de trichloro-2,4,6 benzoyle (4,1 mmoles) dans 10 cm³ de tétrahydrofurane anhydre. On agite pendant 1 heure à une température voisine de 20°C. Le chlorhydrate de triéthylamine est séparé par filtration sur verre fritté. Le tétrahydrofurane est éliminé sous pression réduite. L'anhydride mixte ainsi obtenu est repris par 50 cm³ de toluène anhydre.

Dans un tricol, on dissout, sous atmosphère d'argon, 4,02 g de bis[(trichloro-2,2,2 éthoxy) carbonyloxy]-7β,10β désacétyl-10 baccatine III (4,48 mmoles) et 1,16 g de pyrrolidinopyridine (7,83 mmoles) dans 50 cm³ de toluène anhydre en chauffant à 80°C. On ajoute alors, goutte à goutte, l'anhydride mixte au moyen d'une ampoule à égalisation de pression. L'évolution de la réaction est suivie par chromatographie en couche mince. Après 3 heures à 80°C, il se forme 70 % d'ester.

La phase toluénique est lavée par de l'acide chlorhydrique N, par de l'hydrogénocarbonate de sodium en solution aqueuse à 2,5 % puis est séchée sulfate de sodium. Après filtration et concentration à sec sous pression réduite, le résidu obtenu est purifié par chromatographie sur silice (0,015-0,025 mm) en éluant par un mélange toluène-éther (95-5 en volumes).

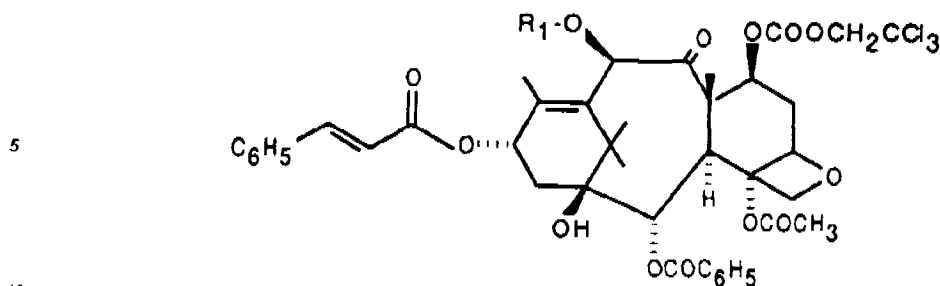
On obtient, avec un rendement de 61,9 %, 2,5 g de cinnamoyl-13α bis[(trichloro-2,2,2 éthoxy) carbonyloxy]-7β,10β désacétyl-10 baccatine III dont les caractéristiques sont identiques à celles qui sont décrites par F. GUE-
RITTE-VOEGELEIN et coll., Tetrahedron, Vol. 42, N° 16, 4451-4460 (1986).

Revendications

1 - Procédé de préparation d'un dérivé du taxane de formule générale :

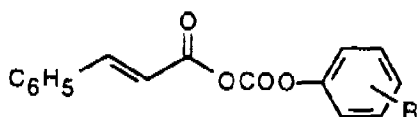
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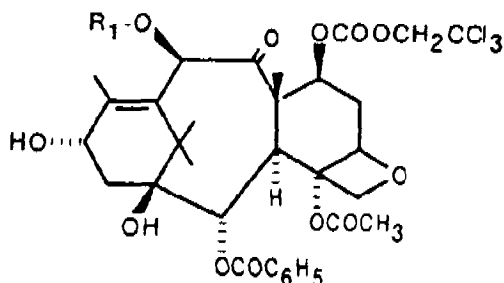
dans laquelle R_1 représente un radical acétyle ou un radical trichloro-2,2,2 éthoxycarbonyle caractérisé en ce que l'on fait réagir un anhydride mixte de formule générale :

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dans laquelle R représente 1 à 5 substituants choisis parmi les atomes d'halogène et les radicaux nitro, méthyle ou méthoxy, sur un dérivé de la baccatine III ou désacétyl-10 baccatine III de formule générale :

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35 dans laquelle R_1 représente un radical acétyle ou trichloro-2,2,2 éthoxycarbonyle.

2 - Procédé selon la revendication 1 caractérisé en ce que l'on opère dans un solvant organique choisi parmi les hydrocarbures aromatiques et les éthers.

3 - Procédé selon l'une des revendications 1 ou 2 caractérisé en ce que l'on opère en présence d'une base organique.

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4 - Procédé selon la revendication 3 caractérisé en ce que la base est choisie parmi la pyrrolidinopyridine ou la diméthylaminopyridine.

5 - Procédé selon l'une des revendications 1 à 4 caractérisé en ce que l'on utilise une mole d'anhydride mixte par mole de dérivé de la baccatine III ou de la désacétyl-10 baccatine III.

6 - Procédé selon l'une des revendications 1 à 5 caractérisé en ce que l'on opère à une température comprise entre 40 et 110°C.

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¹³C NMR Investigation of Solid-State Polymorphism in 10-Deacetyl Baccatin III

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Abstract: To investigate the origins of solid-state NMR shift differences in polymorphs, carbon NMR chemical shift tensors are measured for two forms of solid 10-deacetyl baccatin III: a dimethyl sulfoxide (DMSO) solvate and an unsolvated form. A comparison of *ab initio* computed tensors that includes and omits the DMSO molecules demonstrates that lattice interactions cannot fully account for the shift differences in the two forms. Instead, conformational differences in the cyclohexenyl, benzoyl, and acetyl moieties are postulated to create the differences observed. X-ray analysis of six baccatin III analogues supports the suggested changes in the cyclohexenyl and benzoyl systems. The close statistical match of the ¹³C chemical shifts of both polymorphic forms with those calculated using the X-ray geometry of 10-deacetyl baccatin III supports the contention that the B, C, and D rings are fairly rigid. Therefore, the observed tensor differences appear to arise primarily from conformational variations in ring substituents and the cyclohexenyl ring.

Introduction

Molecular conformation in many compounds strongly affects bioactivity. This phenomenon has been extensively examined in proteins, peptides, and smaller bioactive compounds where marked differences in activities are observed for differing stable conformations. In the case of prion proteins, a conformational change is proposed to create an infectious protein (PrP^{Sc}) from a normal cellular protein.¹ In prions, the change is of sufficient significance that the PrP^{Sc} form is proposed to cause Creutzfeldt–Jakob disease, kuru, and Gerstmann–Sträussler syndrome.² Work with lipases has further demonstrated that even minor changes in conformation can result in modified bioactivity.³ Lipases trapped in a range of conformations through a rapid freeze-drying process were retained in solution in the selected conformation by placing the dried lipase into water-restricted environments. Lipase trapped in a near-inactive form reacted preferentially with short-chain (4–8 carbons) triglyceride substrates, while those trapped in conformations closer to the active form were capable of reacting with triglycerides up to 16 carbons long. Such conformational changes are also important in smaller bioactive molecules where investigation often focuses on sets of computer-generated conformational isomers to assess their docking ability with known binding sites.⁴

The investigation of potentially important conformations in both proteins and smaller molecules by computational methods

allows a large number of conformations to be rapidly characterized in terms of energy and molecular shape. However, the structures obtained suffer from being theoretical constructs that, at times, fail to accurately reproduce the experimental evidence. The modeling approach is also less useful in cases where the structure of the binding sites is not known. An alternative and complementary approach to conformational investigations involves the preparation and characterization of a variety of solid polymorphs of a given molecule. The distinct lattices of the different forms may differ significantly and can involve the inclusion or omission of solvent molecules. Such studies thus simulate the effect of different environments and provide experimental data regarding energetically favorable conformations of the molecule. X-ray diffraction analyses of such polymorphs are often infeasible due to the inability to grow suitable crystals of all lattice forms. However, solid-state NMR is capable of analyzing such materials even when the resulting solid includes a mixture of several lattice types⁵ or consists of amorphous material.⁶ Solid-state NMR thus provides a complementary technique for the characterization of polymorphic solids.

In the work described here, ¹³C solid-state NMR is used to characterize two polymorphs of 10-deacetyl baccatin III (Figure 1), a molecule containing 29 carbons that forms the major portion of the anticancer drug paclitaxel (Taxol). These polymorphs include a dimethyl sulfoxide (DMSO) solvate previously described by X-ray crystallography⁷ and a second solid form

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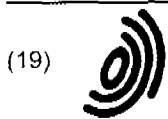
(2) (a) Gajdosik, D. C. *Science* **1977**, *197*, 943; (b) Masters, C. L.; Gajdosik, D. C.; Gibbs, C. J., Jr. *Brain* **1981**, *104*, 535.

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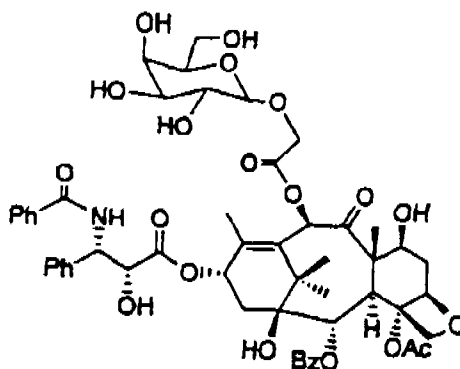
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(54) **TAXOID DERIVATIVES AND PROCESS FOR PRODUCING THE SAME**

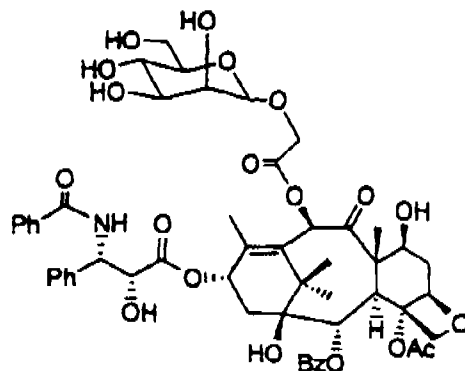
(57) An object of the invention is to develop galactose or mannose derivatives of docetaxel, etc. having improved solubility and physiological activity, to alleviate burden imposed on patients and to provide effective therapeutic drug for tumors.

The present invention provides taxoid derivatives comprising any of paclitaxel, docetaxel and 10-deacetyl-baccatin III to which galactose or mannose is linked through a spacer, and methods for producing taxoid derivatives comprising reacting paclitaxel, docetaxel or 10-deacetyl-baccatin III with tetrabenzyl acetyloxylactoside or tetrabenzyl acetyloxymannoside, subjecting the product to debenzylation reaction, and optionally to triethoxysilylation reaction.

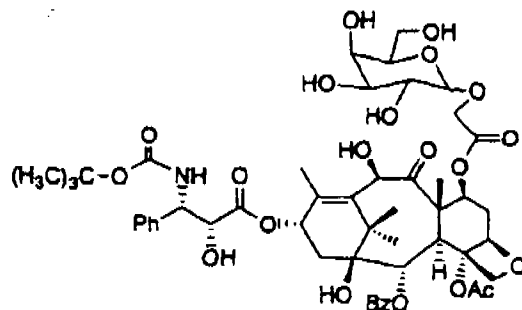
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[0018] Mannosyloxyacetyl-10-paclitaxel (hereinafter, abbreviated as "10-MAG-PT") of the following formula,



[0019] Galactosyloxyacetyl-7-docetaxel (hereinafter, abbreviated as "7-GAG-DT") of the following formula,



[0020] Mannosyloxyacetyl-7-docetaxel (hereinafter, abbreviated as "7-MAG-DT") of the following formula,

Reaction Scheme II

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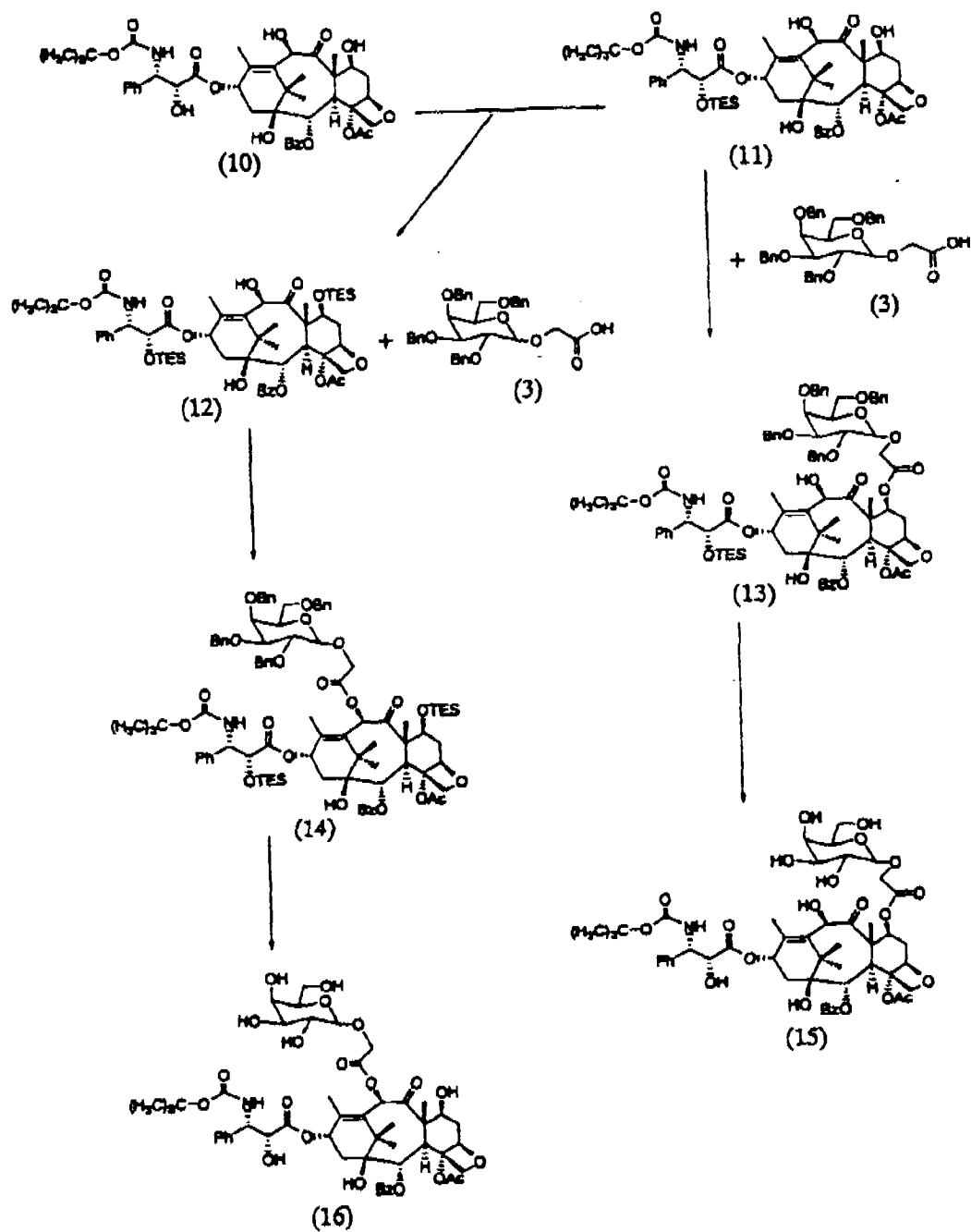
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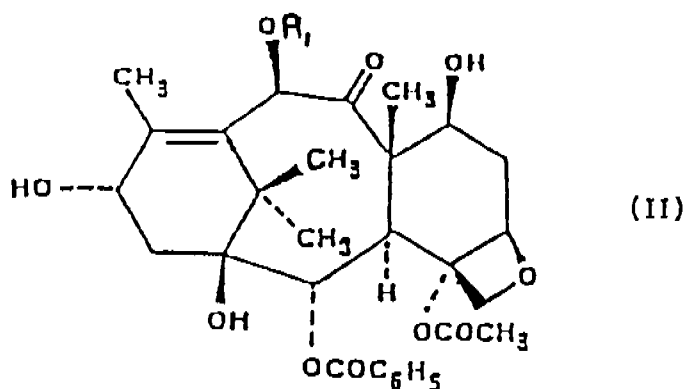
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(21) International Application Number: PCT/US93/07706 (22) International Filing Date: 16 August 1993 (16.08.93) (30) Priority data: 07/930,840 14 August 1992 (14.08.92) US 07/986,852 4 December 1992 (04.12.92) US (71) Applicant: NAPRO BIOTHERAPEUTICS, INC. [US/ US]; 2885 Wilderness Place, Boulder, CO 80301 (US). (72) Inventors: CARVER, David, R. ; 4620 Starboard Drive, Boulder, CO 80301 (US). PROUT, Timothy, R. ; 2227 Canyon Blvd., #158, Boulder, CO 80302 (US). EWALD, Hernita, A. ; 300 E. 17th Avenue, #920, Denver, CO 80203 (US). HENDERSON, Donia, L. ; 4500 19th Street, #595, Boulder, CO 80304 (US).		(74) Agents: REWOLDT, Dana, S. et al.; 44 Union Blvd., Suite 620, Lakewood, CO 80228 (US). (81) Designated States: AU, CA, FI, HU, JP, KR, NO, NZ, Eu- ropean patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i>

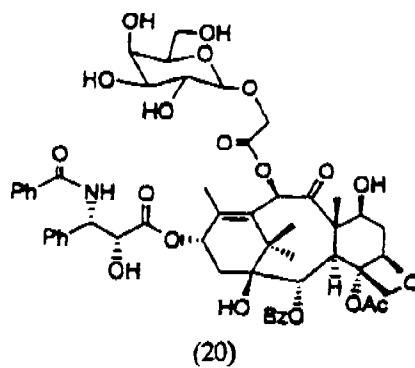
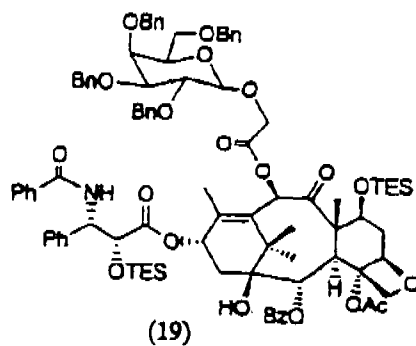
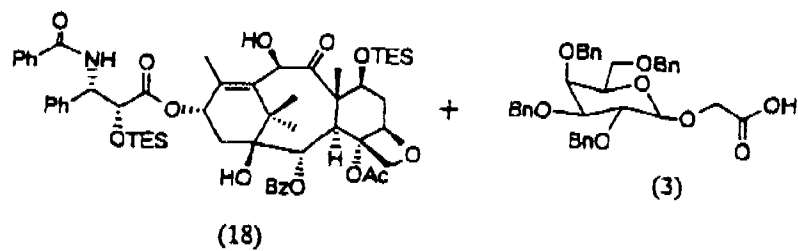
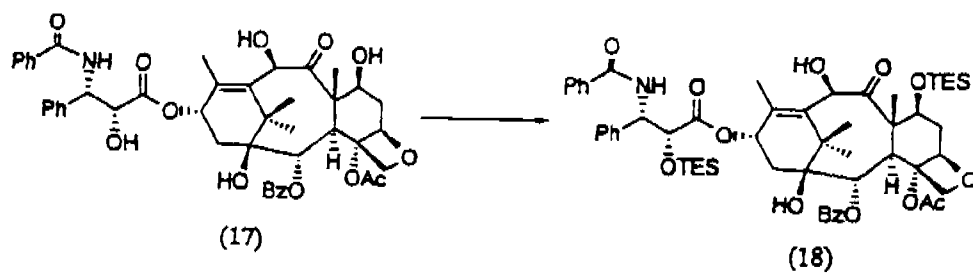
(54) Title: PROCESS OF CONVERTING TAXANES INTO BACCATIN III AND 10-DEACETYLBACCATIN III



(57) Abstract

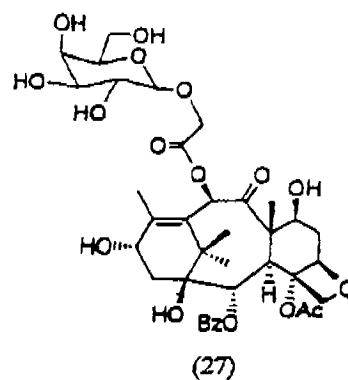
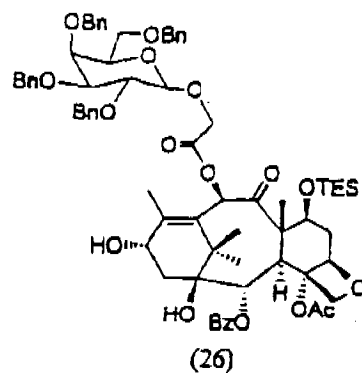
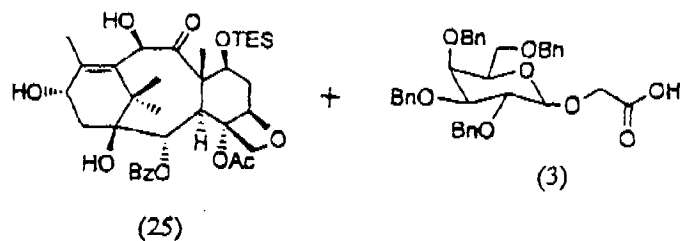
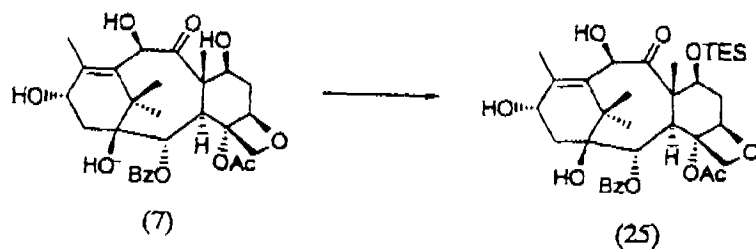
A process for the preparation of a compound of formula (II) where $R_1 = H$ or $R_1 = COCH_3$, comprising contacting a mixture containing at least one taxane compound having an ester linkage at the C-13 position with at least one borohydride reducing salt in a reaction solvent in the presence of a Lewis acid.

Reaction Scheme III



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Reaction Scheme V

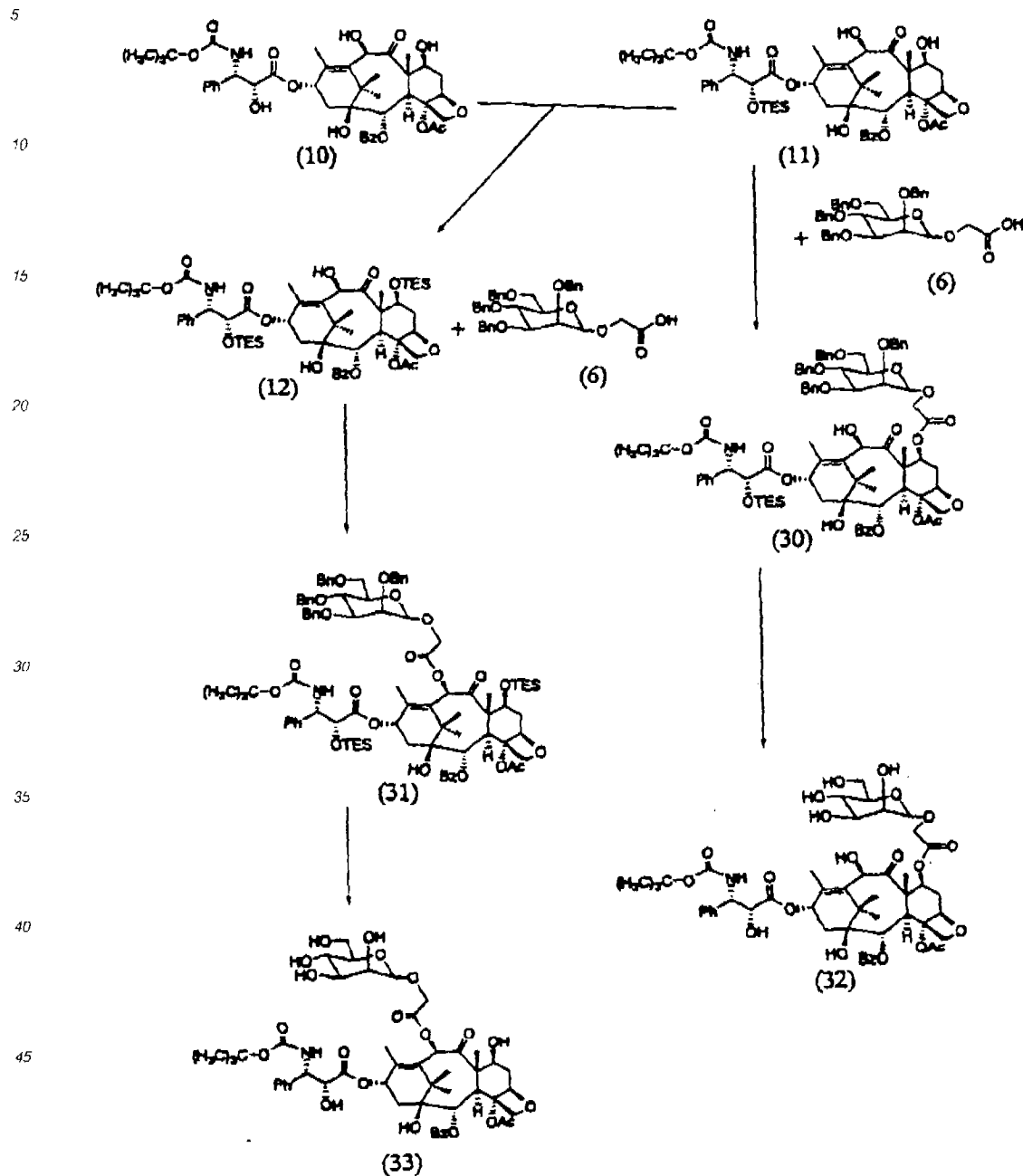


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[0036] The method illustrated in Reaction Scheme (I) is to react 10-deacetyl-baccatin III (7) with tetrabenzyl acetyloxygalactoside (3) and then debenzylate the product and by this method 7-GAG-baccatin III (9) represented by the above formula can be obtained.

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Reaction Scheme VII

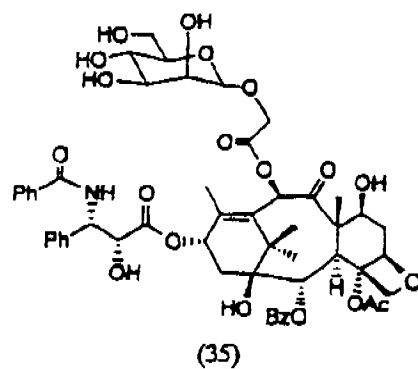
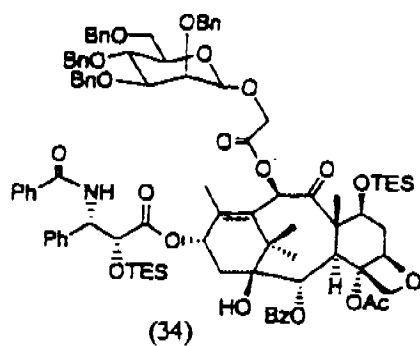
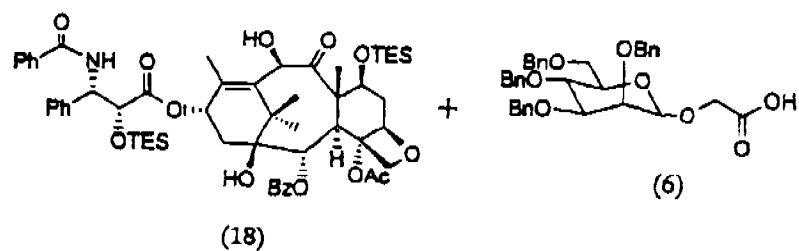
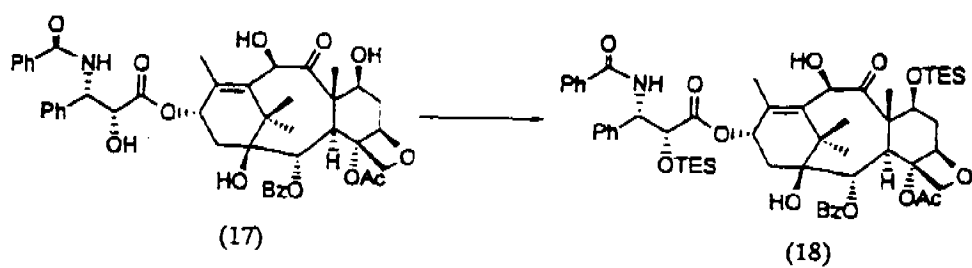


Example 5

[0066] Using 10-deacetyl-paclitaxel (17) instead of docetaxel, compound (18) was obtained in the same manner as in Example 3 above by protecting the 2'- and 7-positions of 10-deacetyl-paclitaxel with TES groups. Thereafter, the

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Reaction Scheme VIII



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Reaction Scheme X

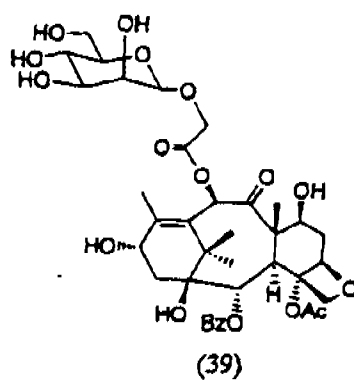
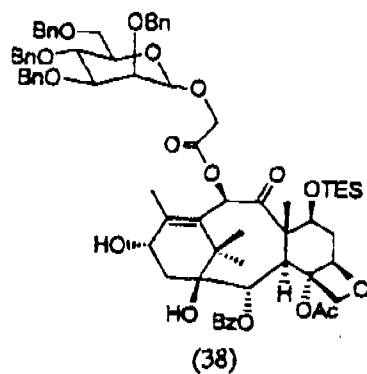
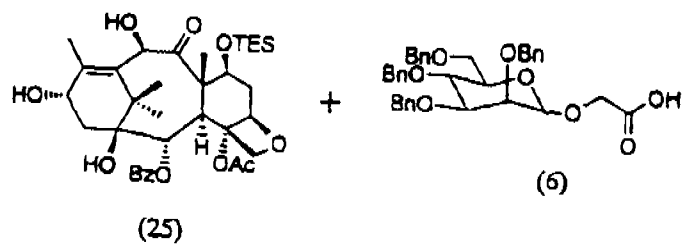
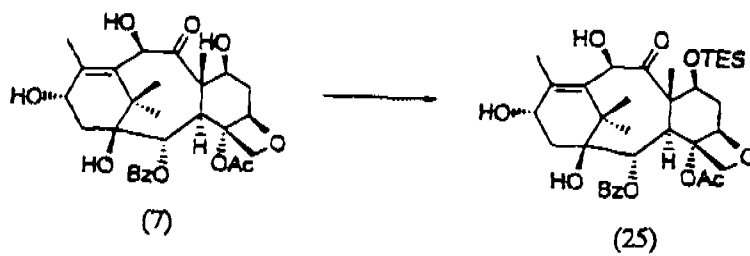


Table 2

Treatment	Number of Animals	Survival Day by Individual	Median of Survival Days	%T/C ^{a)}
No treatment control	10	7 7 7 7 7 7 7 7 10	7	-
Paclitaxel solvent control	10	7 7 7 7 7 7 7 7 7	7	100
Paclitaxel 20 mg/kg	9	9 9 10 10 10 10 11 11 12	10	143
Paclitaxel derivative solvent control	10	7 7 7 7 7 7 7 7 7	7	100
10-MAG-DT (α -anomer) 20 mg/kg	10	8 9 9 9 9 9 10 11 15	9	129
10-GAG-DT (α -anomer) 20 mg/kg	10	10 11 11 11 12 12 12 12 13 14	12	171
10-GAG-DT (β -anomer) 20 mg/kg	10	11 11 11 11 12 12 12 12 13 20	12	171

^{a)}Median of survival days of each treated group (day) X 100 / Median of survival days of control group (day)

[0081] From the table, it is apparent that the median of survival days was 7 days for the control group while it was 10 days for paclitaxel group, 9 days for 10-MAG-DT (α -anomer) group, 12 days 10-GAG-DT (α -anomer) group, and 12 days for 10-GAG-DT (β -anomer) group. From this it follows that the taxoid derivatives have antitumor activity equivalent to or higher than that of paclitaxel. In particular, 10-GAG-DT has excellent antitumor activity.

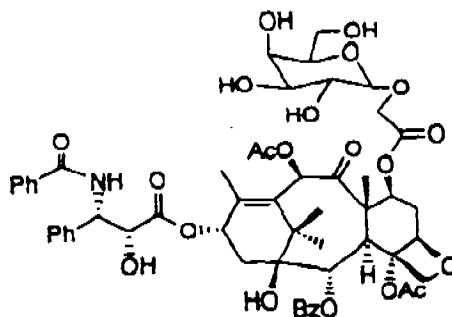
[0082] Furthermore, as will be apparent from the figure, the paclitaxel group showed an abrupt decrease in body weight after the administration in contrast to the taxoid derivatives, which showed substantially no change in body weight, so that the latter are also excellent in safety.

Industrial Applicability

[0083] The present invention provides taxoid derivatives having increased solubility in water and improved physiological activity and production method therefor. The taxoid derivatives alleviate burden imposed on patients and their utilization as an effective therapeutic drug can be expected.

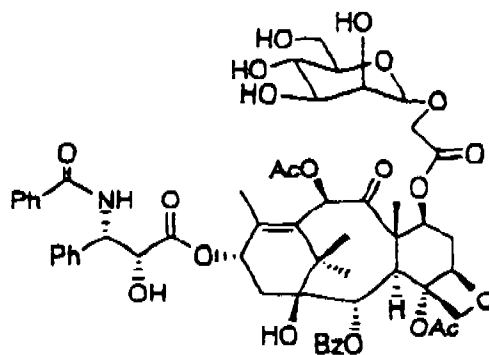
Claims

1. A taxoid derivative comprising any one of paclitaxel, docetaxel and 10-deacetyl-baccatin III to which galactose or mannose is linked through a spacer.
2. The taxoid derivative as claimed in claim 1, wherein the spacer is a glycolate.
3. Galactosyloxyacetyl-7-paclitaxel represented by the following formula.

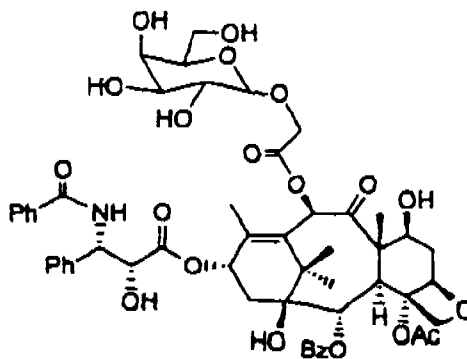


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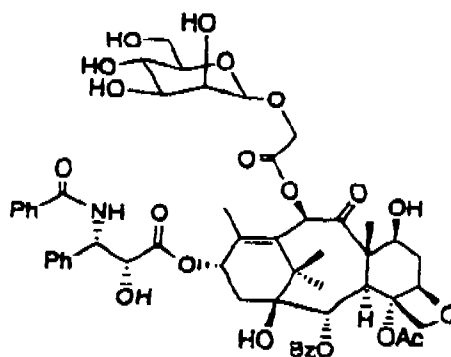
4. Mannosyloxyacetyl-7-paclitaxel represented by the following formula.



5. Galactosyloxyacetyl-10-paclitaxel represented by the following formula.



6. Mannosyloxyacetyl-10-paclitaxel represented by the following formula.



7. Galactosyloxyacetyl-7-docetaxel represented by the following formula.



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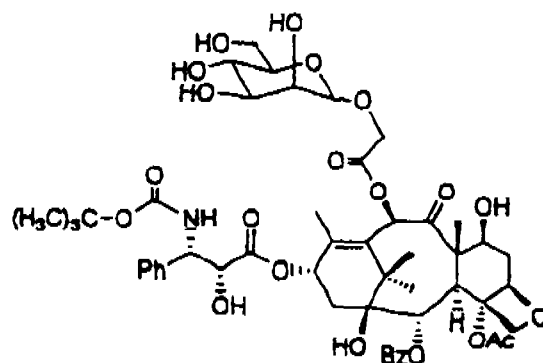
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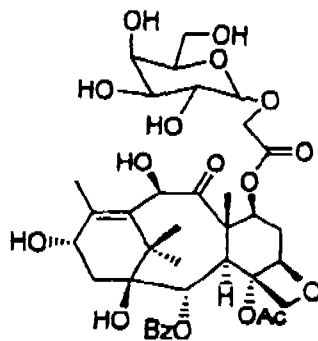
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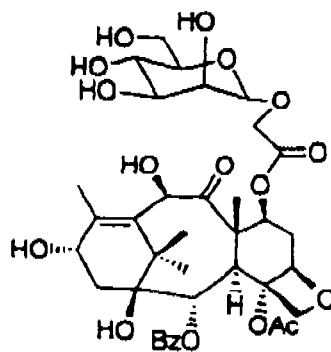
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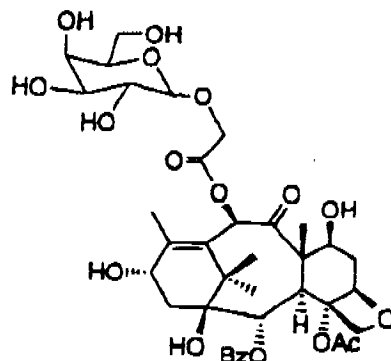
11. Galactosyloxyacetyl-7-baccatin III represented by the following formula.



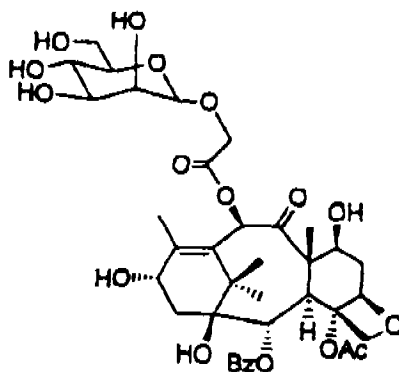
12. Mannosyloxyacetyl-7-baccatin III represented by the following formula.



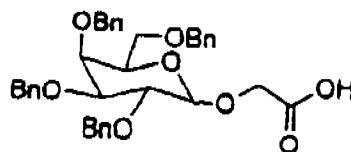
13. Galactosyloxyacetyl-10-baccatin III represented by the following formula.

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14. Mannosyloxyacetyl-10-baccatin III represented by the following formula.

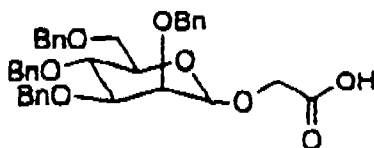


15. A method for producing the taxoid derivative of claim 3 or 7, comprising after protecting a hydroxyl group at the 2'-position of paclitaxel or docetaxel with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxygalactoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.

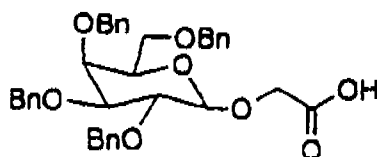


16. A method for producing the taxoid derivative of claim 4 or 8, comprising after protecting a hydroxyl group at the 2'-position of paclitaxel or docetaxel with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.

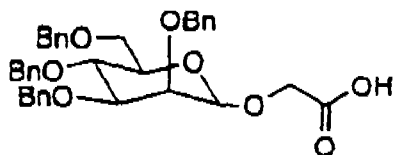
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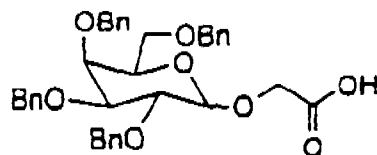
17. A method for producing the taxoid derivative of claim 5 or 9, comprising after protecting hydroxyl groups at the 2'- and 7-positions of 10-deacetyl-paclitaxel or docetaxel, respectively, with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.



18. A method for producing the taxoid derivative of claim 6 or 10, comprising after protecting hydroxyl groups at the 2'- and 7-positions of 10-deacetyl-paclitaxel or docetaxel, respectively, with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.

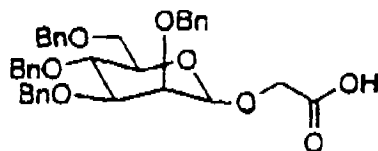


19. A method for producing the taxoid derivative of claim 13, comprising after protecting a hydroxyl group at the 7-position of 10-deacetyl-baccatin III with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.

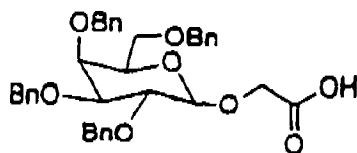


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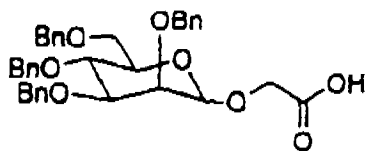
20. A method for producing the taxoid derivative of claim 14, comprising after protecting a hydroxyl group at the 7-position of 10-deacetyl-baccatin III with chlorotriethylsilane, reacting the product with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation or detriethylsilylation reaction.



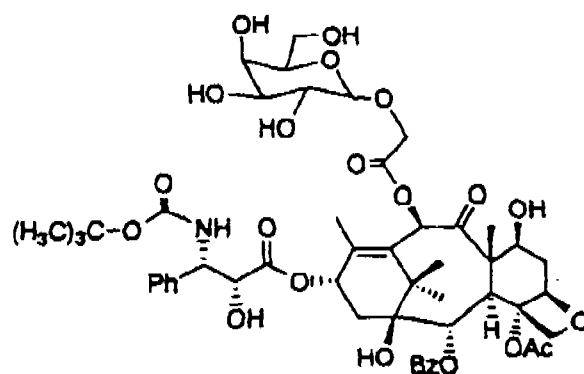
21. A method for producing the taxoid derivative of claim 11, comprising reacting 10-deacetyl-baccatin III with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation reaction.



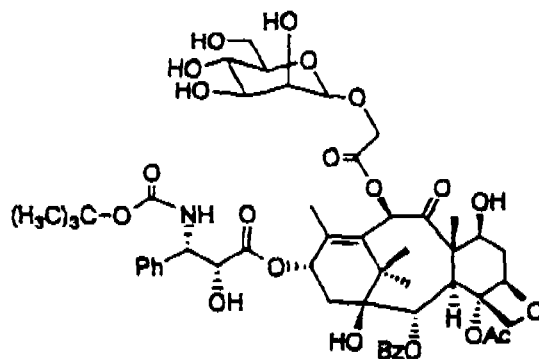
22. A method for producing the taxoid derivative of claim 12, comprising reacting 10-deacetyl-baccatin III with tetrabenzyl acetyloxymannoside represented by the following formula, and then subjecting the product to debenzylation reaction.



23. An antitumor agent comprising galactosyloxyacetyl-10-docetaxel as an active ingredient.



24. An antitumor agent comprising mannosyloxyacetyl-10-docetaxel as an active ingredient.





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(12) **United States Patent**
Holton et al.

(10) **Patent No.:** **US 6,706,896 B1**
(45) **Date of Patent:** **Mar. 16, 2004**

(54) **PROCESS FOR SELECTIVE
DERIVATIZATION OF TAXANES**

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(US)

(73) **Assignee:** **Florida State University**, Tallahassee,
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(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 249 days.

(21) **Appl. No.:** **09/672,270**

(22) **Filed:** **Sep. 28, 2000**

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(62) Division of application No. 09/063,477, filed on Apr. 20,
1998.

(60) Provisional application No. 60/081,265, filed on Apr. 9,
1998, now abandoned, and provisional application No.
60/056,000, filed on Aug. 18, 1997, now abandoned.

(51) **Int. Cl.** **C07D 305/14**

(52) **U.S. Cl.** **549/214; 549/510; 549/511**

(58) **Field of Search** **549/510, 511,
549/214**

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(List continued on next page.)

Primary Examiner Ba K. Trinh

(74) *Attorney, Agent, or Firm*—Senniger, Powers, Leavitt
& Roedel

(57) **ABSTRACT**

Processes for the preparation of taxol and other taxanes
through selective derivatization of the C(7) and C(10)
hydroxyl groups of 10-DAB, particularly a novel process
using a new strategy in which the C(10) hydroxyl group is
protected or derivatized prior to the C(7) hydroxyl group,
and the provision of C(7) and C(10) derivatized 10-DAB
compounds.

10 Claims, No Drawings

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PROCESS FOR SELECTIVE DERIVATIZATION OF TAXANES

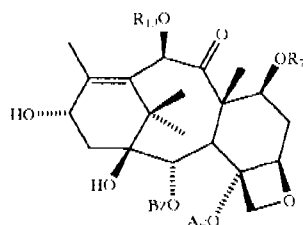
This application is a divisional of U.S. patent application Ser. No. 09/063,477, filed Apr. 20, 1998 pending; which is based on provisional application Serial No. 60/056,000, filed Aug. 18, 1997, now abandoned, and No. 60/081,265, filed Apr. 9, 1998, now abandoned.

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

BACKGROUND OF THE INVENTION

The present invention is directed, in general, to a process for the preparation of taxol and other taxanes, and in particular, to such a process in which the C(7) or C(10) hydroxyl group of a taxane is selectively derivatized.

10-DAB (1), which is extracted from the needles of *taxus baccata* L., the English yew, has become a key starting material in the production of taxol and Taxotere, both of which are potent anticancer agents. Conversion of 10-DAB to taxol, Taxotere® and other taxanes having antitumor activity requires protection or derivatization of the C(7) and C(10) hydroxyl groups followed by esterification of the C(13) hydroxyl group to attach an appropriate side chain at that position.



1 R₁₀ = R₇ = H
2 R₁₀ = H, R₇ = TFS

Until now, strategies for the preparation of taxol and taxol analogs were based upon the observation of Senilh et al. (*C.R. Acad. Sci. Paris, II*, 1981, 293, 501) that the relative reactivity of the four hydroxyl groups of 10-DAB toward acetic anhydride in pyridine is C(7)-OH > C(10)-OH > C(13)-OH > C(1)-OH. Denis, et. al. reported (*J. Am. Chem. Soc.*, 1988, 110, 5917) selective silylation of the C(7) hydroxyl group of 10-DAB with triethylsilyl chloride in pyridine to give 7-triethylsilyl-10-deacetyl baccatin (III) (2) in 85% yield. Based upon these reports, in those processes in which differentiation of the C(7) and C(10) hydroxyl groups is required (e.g., preparation of taxol from 10-DAB), the C(7) hydroxyl group must be protected (or derivatized) before the C(10) hydroxyl group is protected or derivatized. For example, taxol may be prepared by treating 10-DAB with triethylsilyl chloride to protect the C(7) hydroxyl group, acetylating the C(10) hydroxyl group, attaching the side chain by esterification of the C(13) hydroxyl group, and, finally, removal of protecting groups.

It is known that taxanes having various substituents bonded to either the C(10) or the C(7) oxygens show anticancer activity. To provide for more efficient synthesis of these materials, it would be useful to have methods which permit more efficient and more highly selective protection or derivatization of the C(10) and the C(7) hydroxyl groups.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of highly efficient processes for the preparation

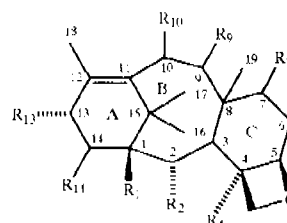
of taxol and other taxanes through selective derivatization of the C(7) group or the C(10) hydroxyl group of 10-DAB and other taxanes, particularly a process in which the C(10) hydroxyl group is protected or derivatized prior to the C(7) hydroxyl group; and the provision of C(7) or C(10) derivatized taxanes.

Briefly, therefore, the present invention is directed to a process for the acylation of the C(10) hydroxy group of a taxane. The process comprises forming a reaction mixture containing the taxane and an acylating agent which contains less than one equivalent of an amine base for each equivalent of taxane, and allowing the taxane to react with the acylating agent to form a C(10) acylated taxane.

The present invention is further directed to a process for the silylation of the C(10) hydroxy group of a taxane having a C(10) hydroxy group. The process comprises treating the taxane with a silylamide or a bisilylamide to form a C(10) silylated taxane.

The present invention is further directed to a process for converting the C(7) hydroxy group of a 10-acyloxy-7-hydroxytaxane to an acetal or ketal. The process comprises treating the 10-acyloxy-7-hydroxytaxane with a ketalizing agent in the presence of an acid catalyst to form a C(10) ketalized taxane.

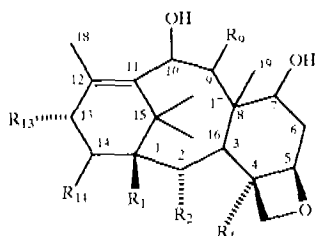
The present invention is further directed to a taxane having the structure:



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taxane without first protecting the C(7) hydroxyl group. Stated another way, it has been discovered that the reactivities previously reported for the C(7) and C(10) hydroxyl groups can be reversed, that is, the reactivity of the C(10) hydroxyl group becomes greater than the reactivity of the C(7) hydroxyl group under certain conditions.

Although the present invention may be used to selectively derivatize a taxane having a hydroxy group at C(7) or C(10), it offers particular advantages in the selective derivatization of taxanes having hydroxy groups at C(7) and C(10), i.e., 7,10-dihydroxy taxanes. In general, 7,10-dihydroxytaxanes which may be selectively derivatized in accordance with the present invention correspond to the following structure:



wherein

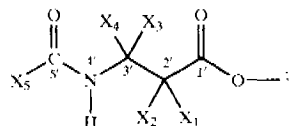
R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_{14} or R_2 forms a carbonate;

R_2 is keto, $-\text{OT}_2$, acyloxy, or together with R_1 forms a carbonate;

R_4 is $-\text{OT}_4$ or acyloxy;

R_6 is hydrogen, keto, $-\text{OT}_6$, or acyloxy;

R_{13} is hydroxy, protected hydroxy, keto, or



R_{14} is hydrogen, $-\text{OT}_{14}$, acyloxy or together with R_1 forms a carbonate;

T_2 , T_4 , T_6 , and T_{14} are independently hydrogen or hydroxy protecting group;

X_1 is $-\text{OX}_6$, $-\text{SX}_7$, or $-\text{NX}_8\text{X}_9$;

X_2 is hydrogen, hydrocarbyl, substituted hydrocarbyl, or heteroaryl;

X_3 and X_4 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heteroaryl;

X_5 is $-\text{X}_{10}$, $-\text{OX}_{10}$, $-\text{SX}_{10}$, $-\text{NX}_8\text{X}_{10}$, or $-\text{SO}_2\text{X}_{11}$;

X_6 is hydrocarbyl, substituted hydrocarbyl, heteroaryl, hydroxy protecting group or a functional group which increases the water solubility of the taxane derivative;

X_7 is hydrocarbyl, substituted hydrocarbyl, heteroaryl, or sulphydryl protecting group;

X_8 is hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_9 is an amino protecting group;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heteroaryl;

X_{11} is hydrocarbyl, substituted hydrocarbyl, heteroaryl, $-\text{OX}_{10}$, or $-\text{NX}_8\text{X}_{14}$; and

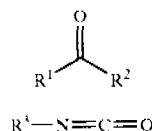
X_{14} is hydrogen, hydrocarbyl, substituted hydrocarbyl, or heteroaryl.

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Selective C(10) Derivatization

In accordance with the process of the present invention, it has been discovered that the C(10) hydroxyl group of a taxane can be selectively acylated in the absence of an amine base. Preferably, therefore, amine bases such as pyridine, triethylamine, dimethylaminopyridine and 2,6-lutidine, if present at all, are present in the reaction mixture in relatively low concentration. Stated another way, if an amine base is present in the reaction mixture, the molar ratio of the amine base to the taxane is preferably less than 1:1, more preferably less than 10:1, and most preferably less than 100:1.

Acylating agents which may be used for the selective acylation of the C(10) hydroxyl group of a taxane include anhydrides, dicarbonates, thiodicarbonates, and isocyanates. In general, the anhydrides, dicarbonates, and thiodicarbonates correspond to structure 4 and the isocyanates correspond to structure 5:



wherein R^1 is $-\text{OR}^a$, $-\text{SR}^a$, or R^a ; R^2 is $-\text{OC}(\text{O})\text{R}^b$, $-\text{OC}(\text{O})\text{OR}^b$, $-\text{OC}(\text{O})\text{SR}^b$, $-\text{OPOR}^b\text{R}^c$, or $-\text{OS}(\text{O})_2\text{R}^b$; R^3 is hydrocarbyl, substituted hydrocarbyl, or heteroaryl; and R^a , R^b , R^c are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl. For example, suitable carboxylic acid anhydride acylating agents include acetic anhydride, chloroacetic anhydride, propionic anhydride, benzoic anhydride, and other carboxylic acid anhydrides containing substituted or unsubstituted hydrocarbyl or heteroaryl moieties; suitable dicarbonate acylating reagents include dibenzyl dicarbonate, diallyl dicarbonate, dipropyl dicarbonate, and other dicarbonates containing substituted or unsubstituted hydrocarbyl or heteroaryl moieties; and suitable isocyanate acylating agents include phenyl isocyanate, and other isocyanates containing substituted or unsubstituted hydrocarbyl or heteroaryl moieties. In addition, although the anhydrides, dicarbonates, and thiodicarbonates used as acylating agents may be mixed, it is generally preferred that they be symmetrical; that is, R^1 and R^2 are selected such that the molecule is symmetrical (e.g., if R^1 is R^a , R^2 is $-\text{OC}(\text{O})\text{R}^b$ with R^a being the same as R^b).

While the acylation of the C(10) hydroxy group of the taxane will proceed at an adequate rate for many acylating agents, it has been discovered that the reaction rate may be increased by including a Lewis acid in the reaction mixture. The concentration of the Lewis acid appears not to be narrowly critical; experimental evidence obtained to date suggests it may be present in either a stoichiometric or a catalytic amount. In general, Lewis acids which may be used include triflates and halides of elements of groups IB, IIB, IIIB, IVB, VB, VIB, VIIB, VIII, IIIA, IVA, lanthanides, and actinides of the Periodic Table (American Chemical Society format). Preferred Lewis acids include zinc chloride, stannic chloride, cerium trichloride, cuprous chloride, lanthanum trichloride, dysprosium trichloride, and ytterbium trichloride. Zinc chloride or cerium trichloride is particularly preferred when the acylating agent is an anhydride or dicarbonate. Cuprous chloride is particularly preferred when the acylating agent is an isocyanate.

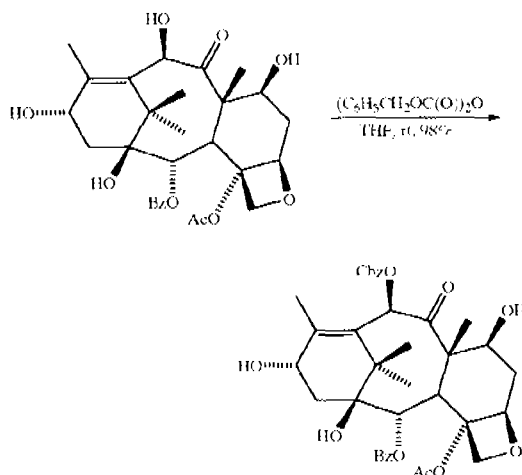
The solvent for the selective acylation is preferably an ethereal solvent such as tetrahydrofuran. Alternatively, however, other solvents such as ether or dimethoxyethane may be used.

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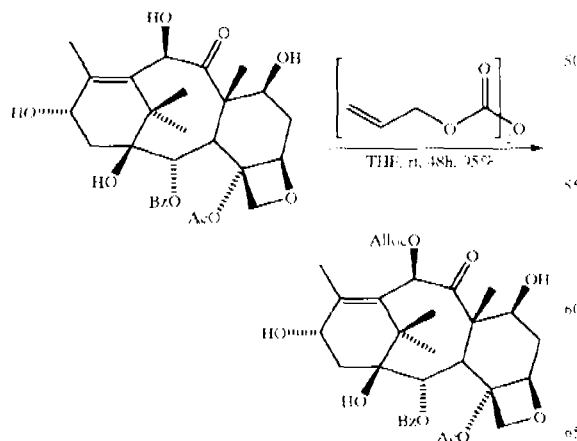
The temperature at which the C(10) selective acylation is carried out is not narrowly critical. In general, however, it is preferably carried out at room temperature or higher in order for the reaction to proceed at a sufficiently high rate.

For purposes of illustration, acylating reactions involving dibenzyl dicarbonate, diallyl dicarbonate, acetic anhydride, chloroacetic anhydride and phenyl isocyanate are illustrated in Reaction Schemes 1 through 5 below. In this series of reaction schemes, the taxane which is selectively acylated at the C(10) position is 10-deacetylbaccatin III. It should be understood, however, that these reaction schemes are merely illustrative and that other taxanes having a C(10) hydroxy group, in general, and other 7,10-dihydroxytaxanes, in particular, may be selectively acylated with these and other acylating agents in accordance with the present invention.

Scheme 1

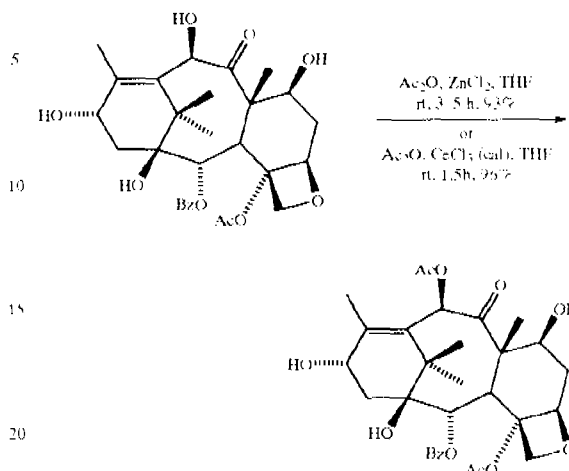


Scheme 2

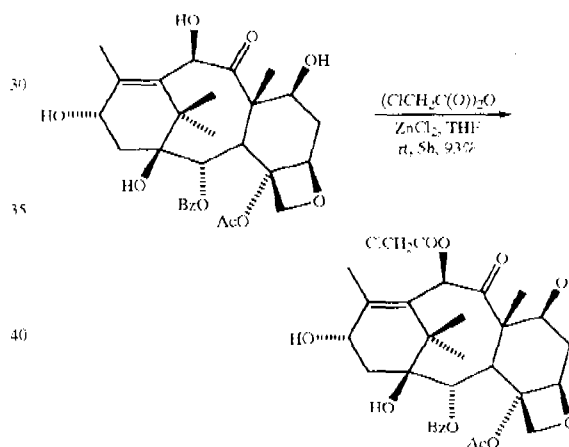


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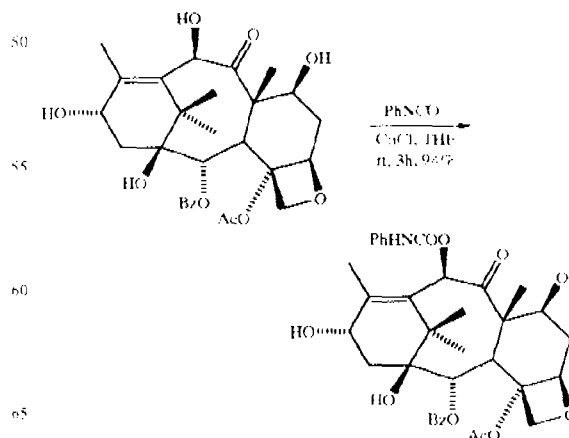
Scheme 3



Scheme 4

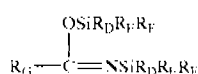
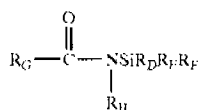


Scheme 5



7

In another aspect of the present invention, the C(10) hydroxyl group of a taxane may be selectively silylated. In general, the silylating agent is selected from the group consisting of silylamides and bissilylamides. Preferred silylamides and bissilylamides correspond to structures 6 and 7, respectively:



wherein R_D , R_E , R_F , R_G , and R_H are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl. Preferably, the silylating agents are selected from the group consisting of tri(hydrocarbyl)silyl-trifluoromethylacetamides and bis tri(hydrocarbyl)-silyltrifluoromethylacetamides, with the hydrocarbyl moiety being substituted or unsubstituted alkyl or aryl. For example, the preferred silylamides and bissilylamides include N,O-bis-(trimethylsilyl)trifluoroacetamide, N,O-bis-(triethylsilyl)trifluoroacetamide, N-methyl-N-triethylsilyltrifluoroacetamide, and N,O-bis-(t-butyltrimethylsilyl)trifluoroacetamide.

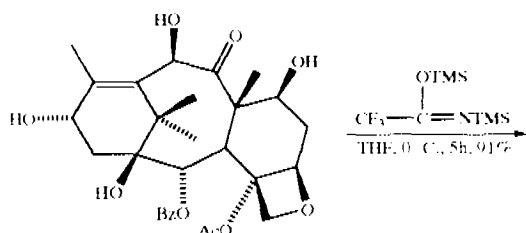
The silylating agents may be used either alone or in combination with a catalytic amount of a base such as an alkali metal base. Alkali metal amides, such as lithium amide catalysts, in general, and lithium hexamethyldisilazide, in particular, are preferred.

The solvent for the selective silylation reaction is preferably an ethereal solvent such as tetrahydrofuran. Alternatively, however, other solvents such as ether or dimethoxyethane may be used.

The temperature at which the C(10) selective silylation is carried out is not narrowly critical. In general, however, it is carried out at 0° C. or greater.

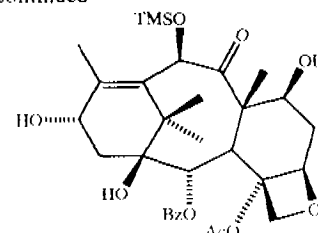
Selective C(10) silylation reactions involving N,O-bis(trimethylsilyl)trifluoroacetamide and N,O-bis(triethylsilyl)trifluoroacetamide are illustrated in Reaction Schemes 6 and 7 below. In these reaction schemes, the taxane which is selectively silylated at the C(10) position is 10-deacetylbaccatin III. It should be understood, however, that these reaction schemes are merely illustrative and that other taxanes, having a C(10) hydroxy group, in general, and other 7,10-dihydroxytaxanes, in particular, may be selectively silylated with these and other silylating agents in accordance with the present invention.

Scheme 6

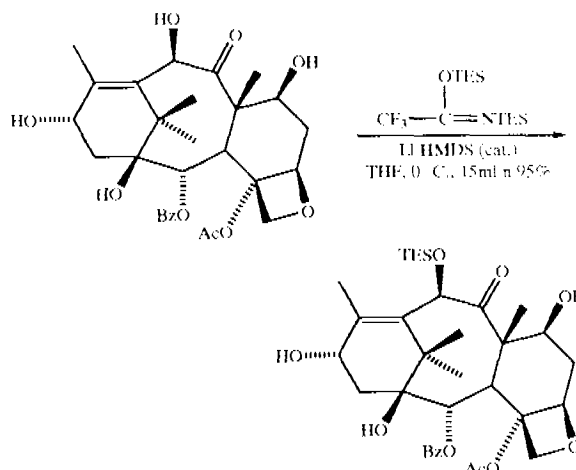


8

-continued



Scheme 7



After the C(10) hydroxyl group of a 7,10-dihydroxytaxane has been derivatized as described herein, the C(7) hydroxyl group can readily be protected or otherwise derivatized selectively in the presence of the C(1) and C(13) hydroxyl groups (and a C(14) hydroxy group, if present).

Selective C(7) Derivatization

Selective acylation of the C(7) hydroxyl group of a C(10) acylated or silylated taxane can be achieved using any of a variety of common acylating agents including, but not limited to, substituted and unsubstituted carboxylic acid derivatives, e.g., carboxylic acid halides, anhydrides, dicarbonates, isocyanates and haloformates. For example, the C(7) hydroxyl group of baccatin III, 10-acyl-10-deacetylbaccatin III or 10-trihydrocarbylsilyl-10-deacetylbaccatin III can be selectively acylated with dibenzyl dicarbonate, diallyl dicarbonate, 2,2,2-trichloroethyl chloroformate, benzyl chloroformate or another common acylating agent.

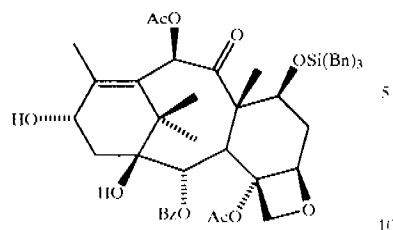
In general, acylation of the C(7) hydroxy group of a C(10) acylated or silylated taxane are more efficient and more selective than are C(7) acylations of a 7,10-dihydroxy taxane such as 10-DAB, i.e., once the C(10) hydroxyl group has been acylated or silylated, there is a significant difference in the reactivity of the remaining C(7), C(13), and C(1) hydroxyl groups (and the C(14) hydroxyl group, if present). These acylation reactions may optionally be carried out in the presence or absence of an amine base.

Examples of selective C(7) acylation of a taxane having an acylated or silylated C(10) hydroxy group are shown in Reaction Schemes 8 through 11. In these reaction schemes, the taxane which is selectively acylated at the C(7) position is baccatin III or 10-triethylsilyl-10-deacetylbaccatin III. It should be understood, however, that these reaction schemes

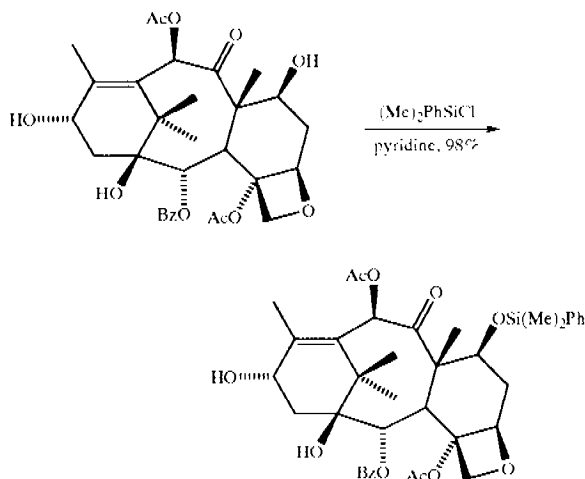
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145 746

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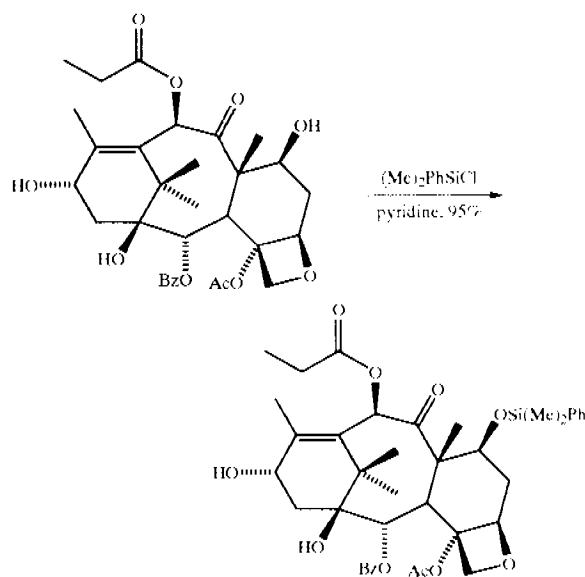
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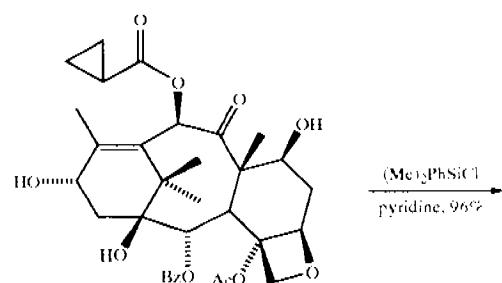
Scheme 13



Scheme 14

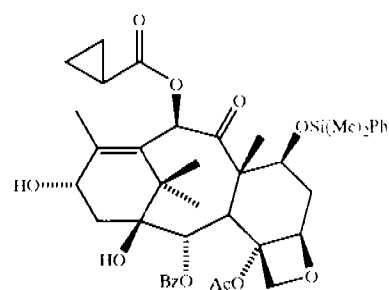


Scheme 15



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-continued

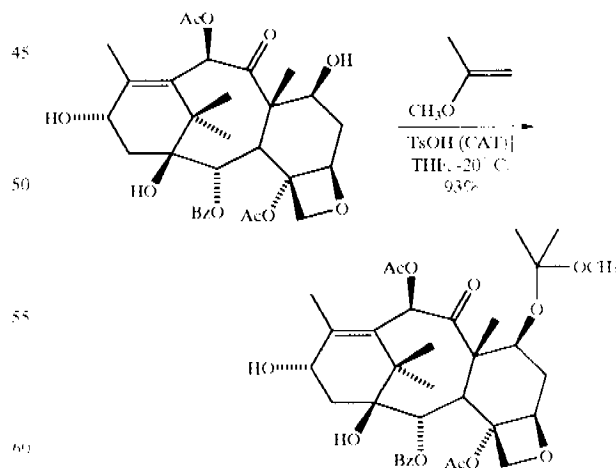


Alternatively, the C(7) hydroxyl group of C(10) acylated taxanes can be selectively protected using any of a variety of common reagents including, but not limited to, simple acetals, ketals and vinyl ethers, in the presence of an acid catalyst. These reagents (whether acetal, ketal, vinyl ether or otherwise) are referred to herein as "ketalizing agents" and are described in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981. The acid catalyst used may be an organic or inorganic acid, such as toluenesulfonic acid or camphorsulfonic acid, in at least a catalytic amount. For example, the C(7) hydroxyl group of baccatin III can be selectively ketalized using 2-methoxy propene. Other suitable reagents for the preparation of acetals and ketals include methyl vinyl ether, ethyl vinyl ether, tetrahydropyran, and the like.

Selective ketalization of the C(7) substituent of a C(10) acylated taxane is more efficient and more selective than it is with 10-DAB, i.e., once the C(10) hydroxyl group has been acylated, there is a large difference in the reactivity of the remaining C(7), C(13), and C(1) hydroxyl groups (and the C(14) hydroxyl group, if present).

An example of selective formation of a C(7) ketal from baccatin III is illustrated in Reaction Scheme 16. It should be understood, however, that this reaction scheme is merely illustrative and that other taxanes may be selectively ketalized with this and other ketalizing agents in accordance with the present invention.

Scheme 16



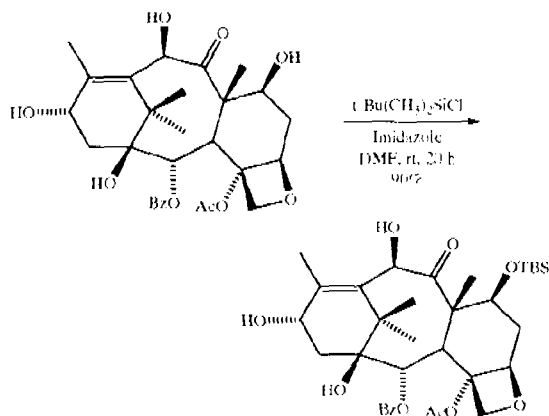
Under appropriate conditions, the C(7) hydroxyl group of a taxane further comprising a C(10) hydroxyl group can be selectively silylated. Advantageously, these silylations are not limited to silyl groups bearing alkyl substituents having three carbons or less.

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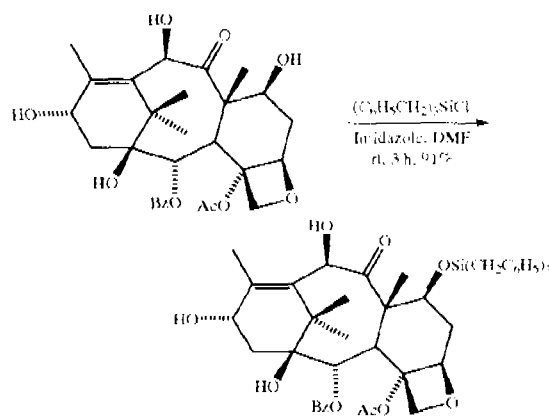
In general, the C(7) hydroxyl group of a taxane can be selectively silylated with a silylating agent which includes the $-\text{SiR}_j\text{R}_k\text{R}_l$ moiety wherein R_j , R_k and R_l are independently substituted or unsubstituted hydrocarbyl or heteroaryl, provided that any substituents are other than hydroxyl. In one embodiment of the present invention, if each of R_j , R_k and R_l is alkyl, then at least one of R_j , R_k , and R_l comprises a carbon skeleton (i.e., carbon chain or ring(s)) having at least four carbon atoms. Suitable silylating agents include silyl halides and silyl triflates, for example, tri(hydrocarbyl)silyl halides and tri(hydrocarbyl)silyl triflates. The hydrocarbyl substituents of these silylating agents may be substituted or unsubstituted and preferably are substituted or unsubstituted alkyl or aryl.

The selective silylation of the C(7) hydroxy group may be carried out in a solvent, such as dimethyl formamide ("DMF") or pyridine and in the presence of an amine base, such as imidazole or pyridine. Reaction Schemes 17-20 illustrate the silylation of the C(7) hydroxy group of 10-DAB in high yield by treating 10-DAB with t-butyltrimethylsilyl chloride, tribenzylsilyl chloride, dimethyl-isopropylsilyl chloride, and dimethylphenylsilyl chloride, respectively. Silylation under these conditions was surprising in view of the report by Denis, et. al. (*J. Am. Chem. Soc.*, 1988, 110, 5917) that selective formation of 7-TBS-10-DAB was not possible.

Scheme 17



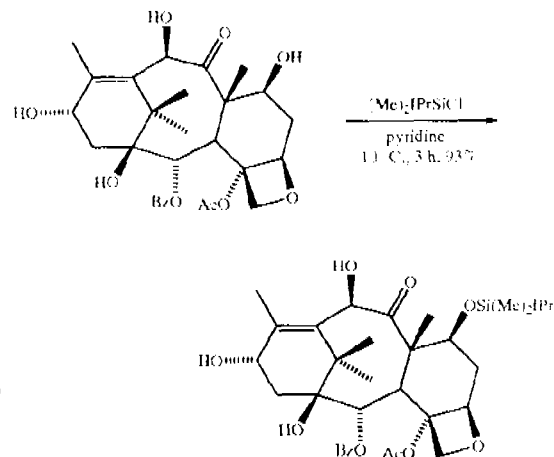
Scheme 18



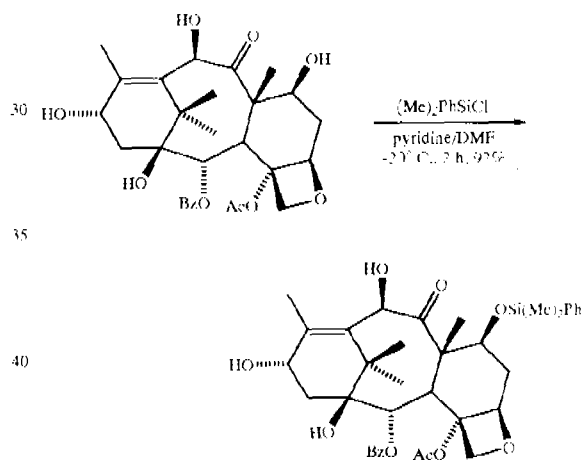
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Scheme 19



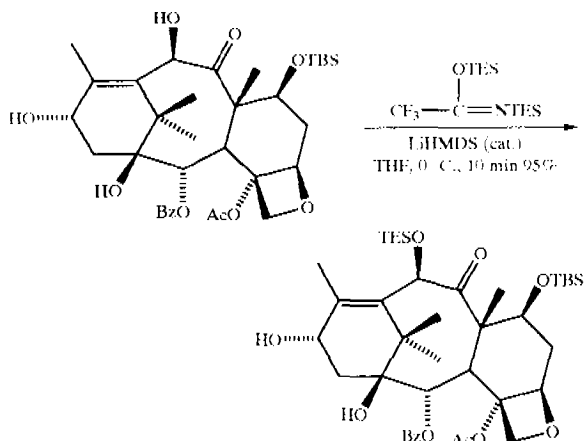
Scheme 20



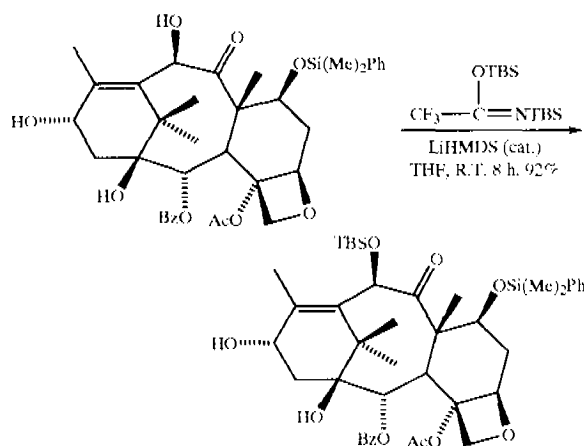
The process of the present invention can also be used to protect the C(7) and C(10) hydroxy groups of a 7,10-dihydroxytaxane with different silyl protecting groups. By selecting groups which can be removed under different conditions, the C(7) and C(10) hydroxy groups can be separately accessed for derivatization. These reactions, therefore, increase the flexibility of the overall process and, enable a higher yield for many of the individual protecting reactions relative to the yield obtained using currently available processes. For example, the triethylsilyl protecting group is more readily removed from C(10) than is the t-butyltrimethylsilyl protecting group from C(7) and the dimethylphenylsilyl protecting group is more readily removed from C(7) than is the t-butyltrimethylsilyl protecting group from C(10). The preparation of 7-t-butyltrimethylsilyl-10-triethylsilyl-10-DAB and 7-dimethylphenylsilyl-10-t-butyltrimethylsilyl-10-DAB are illustrated in Reaction Schemes 21 and 22.

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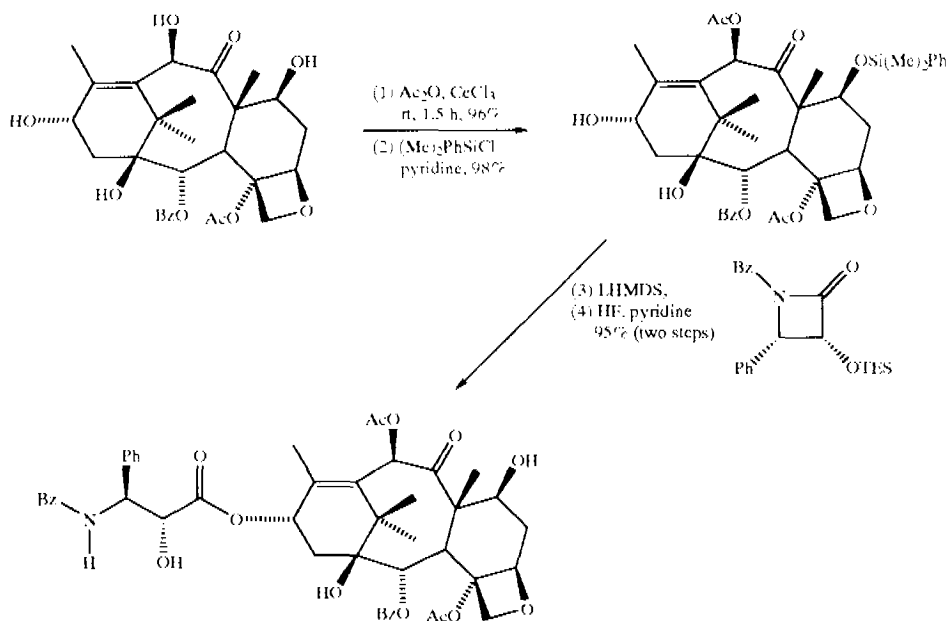
Scheme 21



Scheme 22



Scheme 23



Taxol (89% overall).

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The methods disclosed herein may be used in connection with a large number of different taxanes obtained from natural or synthetic sources to prepare a wide variety of taxane intermediates which may then be further derivatized. For example, the methods of the present invention may be effectively used to protect the C(7) and/or C(10) hydroxy functional group prior to the coupling reaction between a C(13) side chain precursor and a taxane to introduce a C(13) β -amido ester side chain, and also prior to the reactions for preparing taxanes having alternative substituents at various locations on the taxane nucleus.

The attachment of a C(13) side chain precursor to a taxane may be carried out by various known techniques. For example, a side chain precursor such as an appropriately substituted β -lactam, oxazoline, oxazolidine carboxylic acid, oxazolidine carboxylic acid anhydride, or isoserine derivative may be reacted with a tricyclic or tetracyclic taxane having a C(13) hydroxy, metallic oxide or ammonium oxide substituent to form compounds having a β -amido ester substituent at C(13) as described, for example, *Taxol: Science and Applications*, M. Suffness, editor, CRC Press (Boca Raton, Fla.) 1995, Chapter V, pages 97-121. For example, the synthesis of taxol from 10-DAB is illustrated in reaction scheme 23. It should be noted that while a β -lactam and 10-DAB are used in this reaction scheme, other side chain precursors and other taxanes could be substituted therefor without departing from the present invention.

the filtrate in vacuo and followed by flash chromatography (hexane:EtOAc, 4:1) gave 7-Dimethyl-phenylsilyl-10-cyclopropane-carbonyl-10-DAB (816 mg, ~100%). ¹H NMR (CDCl₃, 500 MHz), 80.32, 0.43(2 s, 6 H, Me₂Si), 0.91, 1.00, 1.17(3 m, 5 H, cyclopropyl), 1.07(s, 3 H, Me17), 1.21(s, 3 H, Me16), 1.75(s, 3 H, Me19), 1.74(s, 1 H, 1-OH), 1.78(ddd, J=14.4, 10.5, 2.1 Hz, 1 H, H6b), 2.04(m, 1 H, 13-OH), 2.05(d, J=1.5 Hz, 3 H, Me18), 2.24(s, 3 H, 4-Ac), 2.26(m, 2 H, H14a, H14b), 2.34(ddd, J=14.4, 9.5, 6.7 Hz, 1 H, H6a), 3.87(d, J=7.0 Hz, 1 H, H3), 4.15(d, J=8.2 Hz, 1 H, H20b), 4.26(d, J=8.2 Hz, 1 H, H20a), 4.46(dd, J=10.5, 6.7 Hz, 1 H, H7), 4.82(m, 1 H, H13), 4.85(dd, J=9.5, 2.1 Hz, 1 H, H5), 5.65(d, J=7.0 Hz, 1 H, H2), 6.44(s, 1 H, H10), 7.32-7.36, 7.55-7.57(2 m, 5 H, PhSi), 7.46(m, 2 H, benzoate, m), 7.59(m, 1 H, benzoate, p), 8.10(d, J=8.0 Hz, 2 H, benzoate, o) ppm.

EXAMPLE 8

7-p-Nitrobenzyloxycarbonyl-10-DAB.

To a THF solution (1 mL) of 10-alloc-7-p-nitrobenzyloxycarbonyl-10-DAB (34 mg, 0.048 mmol) at room temperature was added a THF solution (1 mL) of formic acid (19 mL, 0.48 mmol, 10 equiv) and butylamine (47 mL, 0.48 mmol, 10 equiv), followed by the addition of Pd(PPh₃)₄ under N₂. The reaction mixture was stirred at room temperature for 0.5 h. EtOAc (10 mL) was added, and the solution was quickly filtered through a short column of silica gel. The silica gel was washed with EtOAc (100 mL), and the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography using EtOAc:hexanes (1:2) as the eluent and dried in vacuo to give 7-p-nitrobenzyloxycarbonyl-10-DAB as a colorless solid; yield, 28 mg (93%). [α]_D²⁵ -38° (CHCl₃, c=0.48); ¹H NMR (400 MHz, CDCl₃) 81.06(s, 3 H, Me16), 1.09(s, 3 H, Me17), 1.55(s, 1 H, 1-OH), 1.86(s, 3 H, Me19), 2.01(ddd, J=14.4, 10.7, 2.0 Hz, 1 H, H6b), 2.03(d, J=5.1 Hz, 1 H, 13-OH), 2.09(d, J=1.3, 3 H, Me18), 2.28(m, 2 H, H14a, H14b), 2.30(s, 3 H, 4-Ac), 2.62(ddd, J=14.4, 9.5, 7.3 Hz, 1 H, H6a), 3.89(d, J=2.0 Hz, 1 H, 10-OH), 4.08(d, J=6.9 Hz, 1 H, H3), 4.20(d, J=8.4 Hz, 1 H, H20b), 4.34(d, J=8.4 Hz, 1 H, H20a), 4.88(m, 1 H, H13), 4.96(dd, J=9.5, 2.0 Hz, 1 H, H5), 5.19(d, J=13.3, 1 H, CHHOC(O)), 5.26(d, J=13.3, 1 H, CHHOC(O)), 5.36(dd, J=10.7, 7.3 Hz, 1 H, H7), 5.40(d, J=2.0 Hz, 1 H, H10), 5.64(d, J=6.9 Hz, 1 H, H2), 7.48(dd, J=8.1, 7.5 Hz, 2 H, benzoate, m), 7.52(d, J=8.7, 2 H, NO₂C₆H₄), 7.61(t, J=7.5, 1.3 Hz, 1 H, benzoate, p), 8.10(d, J=8.1, 1.3 Hz, 2 H, benzoate, o), 8.26(d, J=8.7, 2 H, NO₂C₆H₄) ppm. ¹³C NMR (75 MHz, CDCl₃) 81.05(Me (19)), 14.6(Me(18)), 19.4(4-Ac), 22.2, 26.4(Me16, Me17), 33.2(C(6)), 38.7(C(14)), 42.4(C(15)), 46.5(C(3)), 56.5(C (8)), 67.9, 68.3(C(13), OCH₂Ph-NO₂-p), 74.7, 75.2, 76.8(C (7), C(2), C(10), C(20)), 78.8(C(1)), 80.4(C(4)), 83.6(C(5)), 124.1, 128.4, 128.9, 130.3, 133.9 (OCH₂Ph-NO₂-p, benzoate), 135.0(C(11)), 142.4, 143.0 (OCH₂Ph-NO₂-p, C(12)), 154.2(OC(O)O), 167.3(benzoate), 171.1(4-Ac), 211.6(C(9)) ppm.

EXAMPLE 9

Selective Esterification of the C-10 Hydroxyl of 10-DAB using the catalytic DyCl₃ reaction:

A solution of butyric anhydride (0.55 mmol) in THF (1.32 ml) was added, under a nitrogen atmosphere, to a solid mixture of 10-DAB (30 mg, 0.055 mmol) and DyCl₃ (1.3 mg, 10 mol. % wrt 10-DAB). The resulting suspension was stirred at room temperature until judged complete by TLC (2:1 EtOAc/Hexane). The reaction was diluted with EtOAc

and washed three times with saturated NaHCO₃ solution. The combined bicarbonate washings were extracted three times with EtOAc, these combined organics were dried (Na₂SO₄) and the solvent evaporated. The crude product was triturated with hexanes and the mother liquors decanted away. Crystallization from EtOAc/hexanes yielded 10-butyryl-10-DAB identical to that isolated from the CeCl₃ catalysed reaction.

EXAMPLE 10

Selective Esterification of the C-10 Hydroxyl of 10-DAB using the catalytic YbCl₃ reaction:

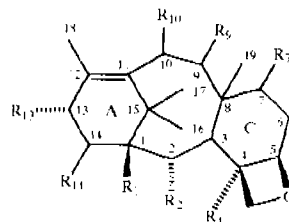
A solution of butyric anhydride (0.55 mmol) in THF (1.32 ml) was added, under a nitrogen atmosphere, to a solid mixture of 10-DAB (30 mg, 0.055 mmol) and YbCl₃ (1.3 mg, 10 mol. % wrt 10-DAB). The resulting suspension was stirred at room temperature until judged complete by TLC (2:1 EtOAc/Hexane). The reaction was diluted with EtOAc and washed three times with saturated NaHCO₃ solution. The combined bicarbonate washings were extracted three times with EtOAc, these combined organics were dried (Na₂SO₄) and the solvent evaporated. The crude product was triturated with hexanes and the mother liquors decanted away. Crystallization from EtOAc/hexanes yielded 10-butyryl-10-DAB identical to that isolated from the CeCl₃ catalysed reaction.

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

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

What is claimed is:

1. A taxane having the structure:



wherein

M is a metal or comprises ammonium;

R₁ is hydrogen, hydroxy, protected hydroxy, or together with R₁₄ or R₂ forms a carbonate;

R₂ is keto, —OT₂, acyloxy, or together with R₁ forms a carbonate;

R₃ is —OT₄ or acyloxy;

R₇ is —OSiR₇R₈R₉;

R₅ is hydrogen, keto, —OT₆, or acyloxy;

R₁₃ is hydrogen, keto, —OT₁₀, or acyloxy;

R₁₄ is hydroxy, protected hydroxy, keto, or MO—;

R₁₄ is hydrogen, —OT₁₄, acyloxy, or together with R₁ forms a carbonate;

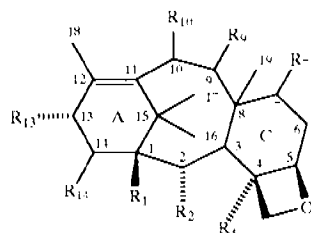
R₇, R₈, R₉ are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl, provided, however, if each of R₇, R₈ and R₉ are alkyl, at least one of R₇, R₈ and R₉ comprises a carbon skeleton having at least four carbon atoms; and

T₂, T₄, T₆, T₁₀, and T₁₄ are independently hydrogen or hydroxy protecting group.

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2. The taxane of claim 1 wherein R_{10} is $-\text{OT}_{10}$, T_{10} is $\text{SiR}_D\text{R}_E\text{R}_F$, and R_D , R_E , R_F are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl.

3. A taxane having the structure:



wherein

M is a metal or comprises ammonium;

R_1 is hydroxy or together with R_{14} or R_2 forms a carbonate;

R_2 is $-\text{OCOZ}_2$, $-\text{OCOOZ}_2$, or together with R_1 forms a carbonate;

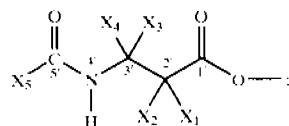
R_4 is $-\text{OCOZ}_4$;

R_7 is $-\text{OSiR}_D\text{R}_E\text{R}_F$;

R_9 is hydrogen or keto;

R_{10} is hydrogen, keto, $-\text{OT}_{10}$, or acyloxy;

R_{13} is hydroxy, protected hydroxy, $\text{MO}-$ or



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

R_D , R_E , R_F are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl, provided, however, if each of R_D , R_E and R_F are alkyl, at least one of R_D , R_E and R_F comprises a carbon skeleton having at least four carbon atoms;

T_{10} is hydrogen or hydroxy protecting group;

X_1 is $-\text{OX}_6$ or $-\text{NX}_8\text{X}_9$;

X_2 is hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_3 and X_4 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heteroaryl;

X_5 is $-\text{X}_{10}$, $-\text{OX}_{10}$, or $-\text{NX}_8\text{X}_{10}$;

X_6 is a hydroxy protecting group;

X_8 is hydrogen, hydrocarbyl, or substituted hydrocarbyl;

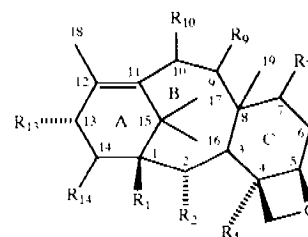
X_9 is an amino protecting group;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heteroaryl; and

Z_2 and Z_4 are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl.

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4. A taxane having the structure:



wherein

M is a metal or comprises ammonium;

R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_{14} or R_2 forms a carbonate;

R_2 is keto, $-\text{OT}_2$, acyloxy, or together with R_1 forms a carbonate;

R_4 is $-\text{OT}_4$ or acyloxy;

R_7 is acyloxy;

R_9 is hydrogen, keto, $-\text{OT}_9$, or acyloxy;

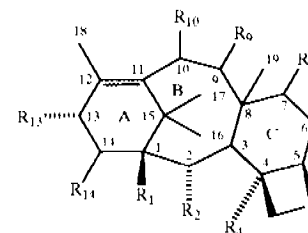
R_{10} is acyloxy provided, however, R_{10} is other than acetoxy and R_7 and R_{10} are different;

R_{13} is hydroxy, protected hydroxy, keto, or $\text{MO}-$;

R_{14} is hydrogen, $-\text{OT}_{14}$, acyloxy, or together with R_1 forms a carbonate; and

T_2 , T_4 , T_9 , and T_{14} are independently hydrogen or hydroxy protecting group.

5. A taxane having the structure:



wherein

M is a metal or comprises ammonium;

R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_{14} or R_2 forms a carbonate;

R_2 is keto, $-\text{OT}_2$, acyloxy, or together with R_1 forms a carbonate;

R_4 is $-\text{OT}_4$ or acyloxy;

R_7 is hydrogen, halogen, hydroxy or acyloxy;

R_9 is hydrogen, keto, $-\text{OT}_9$, or acyloxy;

R_{10} is $-\text{OSiR}_D\text{R}_E\text{R}_F$;

R_{13} is hydroxy, protected hydroxy, keto, or $\text{MO}-$;

R_{14} is hydrogen, $-\text{OT}_{14}$ or together with R_1 forms a carbonate;

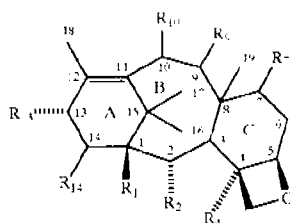
R_D , R_E , R_F are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl; and

T_2 , T_4 , T_9 and T_{14} are independently hydrogen or hydroxy protecting group.

6. The taxane of claim 5 wherein R_7 is acyloxy.

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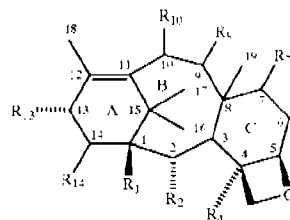
7. A taxane having the structure:



wherein

- M is a metal or comprises ammonium;
 R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_{14} or R_2 forms a carbonate;
 R_2 is keto, $-\text{OT}_2$, acyloxy, or together with R_1 forms a carbonate;
 R_4 is $-\text{OT}_4$ or acyloxy;
 R_7 is acyloxy;
 R_3 is hydrogen, keto, $-\text{OT}_3$, or acyloxy;
 R_{10} is hydrogen, keto, $-\text{OT}_{10}$, or acyloxy, provided, when R_{10} is acyloxy, R_7 and R_{10} are different;
 R_{13} is hydroxy, protected hydroxy, keto, or $\text{MO}-$;
 R_{14} is hydrogen, $-\text{OT}_{14}$, acyloxy or together with R_1 forms a carbonate; and
 T_2 , T_4 , T_6 , T_{10} and T_{14} are independently hydrogen or hydroxy protecting group.

8. A taxane having the structure:

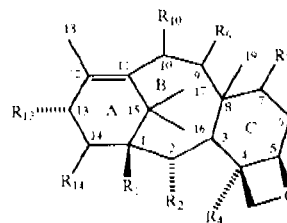


wherein

- M is a metal or comprises ammonium;
 R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_{14} or R_2 forms a carbonate;
 R_2 is keto, $-\text{OT}_2$, acyloxy, or together with R_1 forms a carbonate;
 R_4 is $-\text{OT}_4$ or acyloxy;
 R_7 is $-\text{OT}_7$;
 R_3 is hydrogen, keto, hydroxy or acyloxy;
 R_{10} is hydrogen, keto, $-\text{OT}_{10}$, or acyloxy;
 R_{13} is hydroxy, protected hydroxy, keto, or $\text{MO}-$;
 R_{14} is hydrogen, $-\text{OT}_{14}$, acyloxy, or together with R_1 forms a carbonate;
 T_7 is a ketal or an acetal radical;
 T_2 , T_4 , T_{10} , and T_{14} are independently hydrogen or hydroxy protecting group.

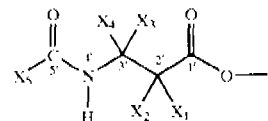
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9. A taxane having the structure:



wherein

- M is a metal or comprises ammonium;
 R_1 is hydroxy or together with R_{14} or R_2 forms a carbonate;
 R_2 is $-\text{OCOZ}_2$, $-\text{OCOOZ}_2$, or together with R_1 forms a carbonate;
 R_4 is $-\text{OCOZ}_4$;
 R_7 is $-\text{OT}_7$;
 R_3 is hydrogen or keto;
 R_{10} is hydrogen, keto, $-\text{OT}_{10}$, or acyloxy;
 R_{13} is hydroxy, protected hydroxy, $\text{MO}-$ or



- R_{13} is hydrogen, hydroxy, protected hydroxy, or together with R_1 forms a carbonate;
 T_7 is a ketal or an acetal radical;
 T_{10} is hydrogen or hydroxy protecting group;
 X_1 is $-\text{OX}_6$ or $-\text{NX}_8\text{X}_{10}$;
 X_2 is hydrogen, hydrocarbyl, or substituted hydrocarbyl;
 X_3 and X_4 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heteroaryl;
 X_5 is X_{10} , OX_{10} , or NX_8X_{10} ;
 X_6 is a hydroxy protecting group;
 X_8 is hydrogen, hydrocarbyl, or substituted hydrocarbyl;
 X_{10} is an amino protecting group;
 X_{10} is hydrocarbyl, substituted hydrocarbyl, or heteroaryl; and
 Z_2 and Z_4 are independently hydrocarbyl, substituted hydrocarbyl, or heteroaryl.

10. The taxane of claim 7 wherein

- R_1 is hydroxy;
 R_2 is benzoyloxy
 R_4 is acetoxy;
 R_3 is oxo; and
 R_{13} is hydroxy.

* * * * *

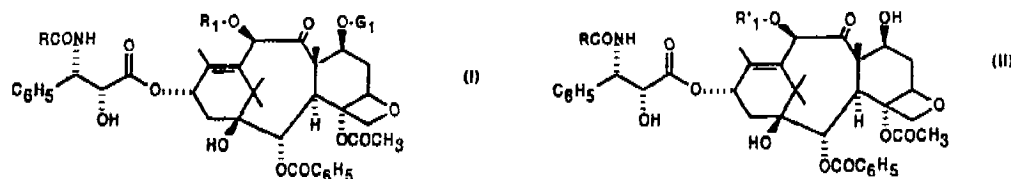

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(54) Title: PROCESS FOR THE PREPARATION OF BACCATIN III AND 10-DEACETYL BACCATIN III DERIVATIVES

(54) Titre: PROCÉDE DE PREPARATION DE DERIVES DE LA BACCATINE III ET DE LA DESACETYL-10 BACCATINE III



(57) Abstract

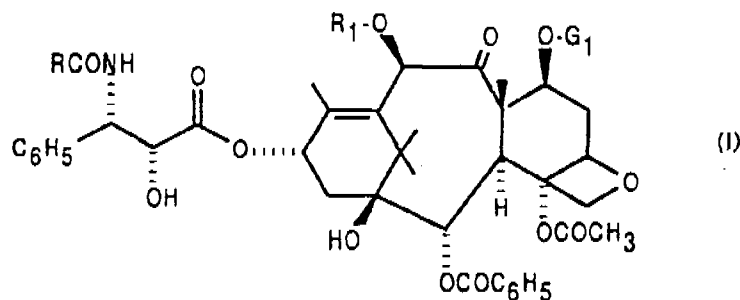
Process for the preparation of a taxane derivative of general formula (I) and use of the product obtained for the preparation of taxane derivatives of general formula (II). In the general formula (I), R_1 is an acetyl radical or a protective grouping, G_1 is a protective grouping and R is a t.butoxy or phenyl radical. In the general formula (II), R is a t.butoxy or phenyl radical and R'_1 is a hydrogen atom or an acetyl radical.

(57) Abrégé

Procédé de préparation d'un dérivé du taxane de formule générale (I) et utilisation du produit obtenu pour la préparation de dérivés du taxane de formule générale (II). Dans la formule générale (I), R_1 représente un radical acétyle ou un groupement protecteur, G_1 représente un groupement protecteur et R représente un radical t.butoxy ou phényle. Dans la formule générale (II), R représente un radical t.butoxy ou phényle et R'_1 représente un atome d'hydrogène ou un radical acétyle.

PROCEDE DE PREPARATION DE DERIVES DE LA
BACCATINE III ET DE LA DESACETYL-10 BACCATINE III

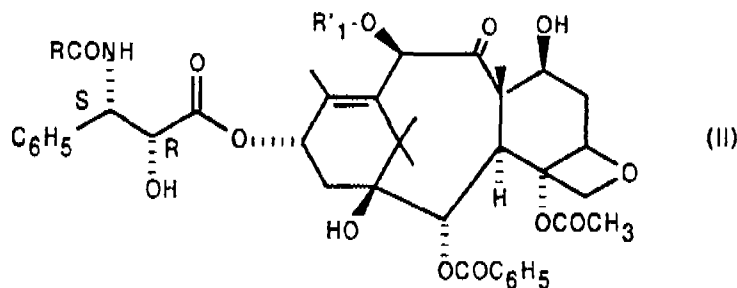
La présente invention concerne un procédé de préparation de dérivés de la baccatine III et de la désacétyl-10 baccatine III de formule générale :



dans laquelle R représente un radical t.butoxy ou phényle, R₁ représente un radical acétyle ou un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate et G₁ représente un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate sous forme 2'R,3'S ou 2'S,3'S.

Plus particulièrement la présente invention concerne un procédé de préparation d'un produit de formule générale (I) dans laquelle R représente un radical t.butoxy ou phényle, R₁ représente un radical acétyle ou trichloro-2,2,2 éthoxycarbonyle et G₁ représente un radical trichloro-2,2,2 éthoxycarbonyle sous forme 2'R,3'S ou 2'S,3'S.

Les produits de formule générale (I) sont particulièrement utiles dans la synthèse des produits de formule générale :



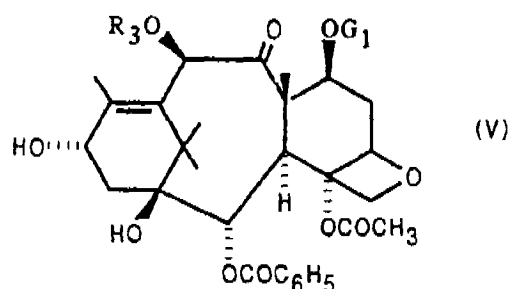
dans laquelle R est défini comme précédemment et R'₁ représente un atome d'hydrogène ou un radical acétyle.

Les produits de formule générale (II) dans laquelle R représente un radical phényle correspondent au taxol et au désacétyl-10 taxol et les produits de formule

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dans laquelle R est défini comme précédemment et R₂ représente un groupement protecteur de la fonction hydroxy choisi notamment parmi les radicaux méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle, (β-triméthylsilyléthoxy)méthyle, tétrahydropyrannyle ou trichloro-2,2,2 éthoxycarbonyle, sur un dérivé de la baccatine III ou

5 de la désacétyl-10 baccatine III de formule générale :



dans laquelle R₃ représente un radical acétyle ou un groupement protecteur de la fonction hydroxy choisi parmi les radicaux trichloro-2,2,2 éthoxycarbonyle ou trialkylsilyle dont chaque partie alcoyle contient 1 à 3 atomes de carbone et G₁ représente

10 un groupement protecteur de la fonction hydroxy choisi parmi les radicaux trichloro-2,2,2 éthoxycarbonyle ou trialkylsilyle dont chaque partie alkyle contient 1 à 3 atomes de carbone, suivie du remplacement des groupements protecteurs des fonctions hydroxy par des atomes d'hydrogène.

Selon la nature des groupements protecteurs, ce remplacement peut être

15 effectué au moyen de zinc en présence d'acide acétique ou d'un acide minéral ou organique tel que l'acide chlorhydrique ou l'acide acétique en solution dans un alcool aliphatique contenant 1 à 3 atomes de carbone en présence de zinc lorsque les groupements protecteurs représentent au moins un radical trichloro-2,2,2 éthoxycarbonyle, soit au moyen d'un acide tel que l'acide chlorhydrique dans un alcool aliphatique contenant 1 à 3 atomes de carbone à une température voisine de 0°C lorsque les

20 groupements protecteurs représentent au moins un radical trialkylsilyle.

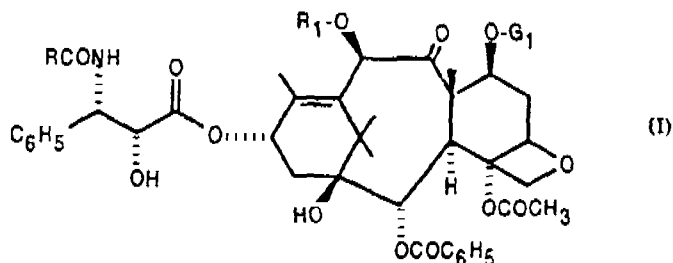
Les produits de formule générale (II) obtenus par la mise en oeuvre de ces procédés antérieurement connus doivent être purifiés, généralement par chromatographie ou par cristallisation, afin, plus particulièrement, de séparer les formes épimères

25 2'R,3'S et 2'S,3'S. Cette séparation est industriellement de mise en oeuvre délicate du fait de la cytotoxicité des produits de formule générale (II).

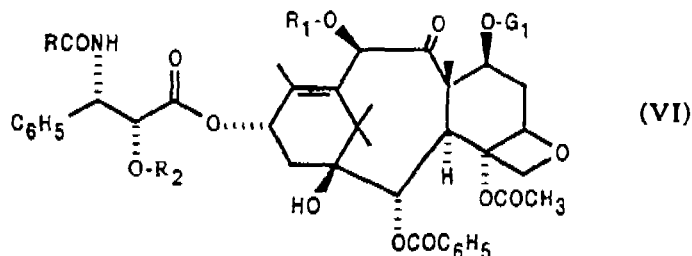
Il a maintenant été trouvé que les produits de formule générale (II) pratiquement purs peuvent être obtenus en purifiant préalablement un produit de formule

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S
15AREVENDICATIONS

1 - Procédé de préparation d'un dérivé de la baccatine III ou de la désacétyl-10 baccatine III de formule générale :



- 5 dans laquelle R représente un radical t.butoxy ou phényle, R₁ représente un radical acétyle ou un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate et G₁ représente un groupement protecteur de la fonction hydroxy sous forme d'un éther, d'un ester ou d'un carbonate sous forme 2'R,3'S ou 2'S,3'S, caractérisé en ce que l'on traite en milieu acide un dérivé du taxane de formule générale :
- 10



- dans laquelle R₁ et G₁ sont définis comme ci-dessus et R₂ représente un groupement protecteur de la fonction hydroxy choisi parmi les radicaux méthoxyméthyle, éthoxy-1 éthyle, benzyloxyméthyle, (β-triméthylsilyléthoxy) méthyle ou tétrahydropyrannyle.
- 15

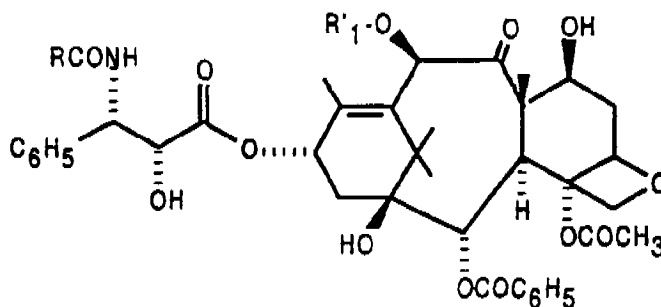
- 2 - Procédé de préparation selon la revendication 1 d'un dérivé de la baccatine III ou de la désacétyl-10 baccatine III de formule générale (I) dans laquelle R représente un radical t.butoxy ou phényle et R₁ représente un radical acétyle ou trichloro-2,2,2 éthoxycarbonyle et G₁ représente un radical trichloro-2,2,2 éthoxycarbonyle sous forme 2'R,3'S ou 2'S,3'S
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3 - Procédé selon la revendication 1 caractérisé en ce que le traitement en milieu acide est effectué au moyen d'une solution alcoolique d'un acide minéral fort.

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4 - Procédé selon la revendication 1 caractérisé en ce que l'on utilise une solution éthanolique d'acide chlorhydrique.

5 - Utilisation d'un dérivé du taxane obtenu par le procédé de l'une des revendications 1 à 4 pour la préparation d'un dérivé du taxane de formule générale :



5 dans laquelle R représente un radical t.butoxy ou phényle et R'₁ représente un atome d'hydrogène ou un radical acétyle caractérisé en ce que l'on traite un dérivé du taxane obtenu par le procédé de l'une des revendications 1 à 3, éventuellement purifié par chromatographie ou cristallisation, par toute méthode connue pour éliminer un groupement protecteur.

10

6 - Utilisation d'un produit obtenu par le procédé de la revendication 2 pour la préparation d'un dérivé du taxane tel que défini dans la revendication 5 caractérisé en ce que l'on traite un dérivé du taxane obtenu par le procédé de la revendication 2, éventuellement purifié par chromatographie ou cristallisation par le zinc dans l'acide acétique en milieu alcoolique à une température comprise entre 20°C et la température de reflux du mélange réactionnel et isole le produit obtenu.

15

Diastereoselective 14 β -Hydroxylation of Baccatin III Derivatives

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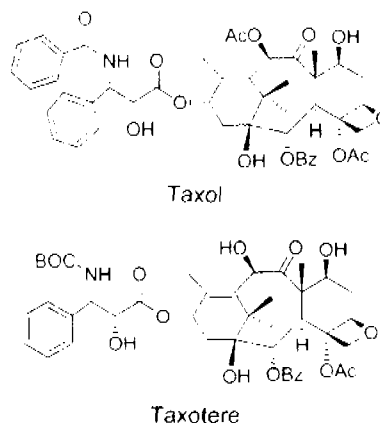
Received May 26, 2003

14 β -Hydroxybaccatin III, a compound with limited availability by natural sources, is the starting material for the synthesis of the second-generation anticancer taxoid oritaxel. The 7-tert-butoxycarbonyl (**1a**) and 7-triethylsilyl (**1b**) derivatives of 14 β -hydroxybaccatin III 1,14-carbonate were synthesized from 10-deacetylbaccatin III (**3**). The crucial steps were (a) the C₁₃ β -hydroxylation of the corresponding 13-oxobaccatin III derivatives by oxaziridine-mediated electrophilic oxidation and (b) the reduction of the C₁₃ carbonyl group with sodium or alkylammonium borohydrides. This protocol provides a practical way for the semisynthesis of oritaxel from 10-deacetylbaccatin III, a compound readily available from various yews.

Introduction

The clinical efficacy¹ and the chemistry² of the natural diterpenoid Taxol[®] (paclitaxel) and its semisynthetic analogue Taxotere[®] (docetaxel) (Chart 1) have been extensively reported. While the taxoids have potent antitumor activity against solid tumors and unique mechanism of action, they also have numerous undesirable side effects and poor activity against certain tumors. Since these drugs are sparingly soluble in water, they must be co-administered with a cosolvent (cremophor EL, Tween 80) which can induce adverse effects.³ The development of resistance, due primarily to multiple drug resistance (MDR)^{4,5} mechanisms, prompts initia-

CHART 1. Taxol and Taxotere



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[§] Università di Milano

(1) (a) George, G. L.; Chen, T. T.; Ojima, I.; Yeas, D. M. *Lovine Anticancer Agents: Basic Science and Current Status*; ACS Symposium Series 553; American Chemical Society: Washington, DC, 1995. (b) Suffness, M. Taxol. In *Annual Report in Medicinal Chemistry*; Eistat, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, Chapter 32, pp 305–311. (c) *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995.

(2) See, for example: (a) *The Chemistry in Pharmacology of Taxol and Related Compounds*; Farnham, V., Ed.; Elsevier: New York, 1995. (b) Nagules, E.; Wolf, S.; Downing, K. H. *Nature* **1998**, *391*, 199–203. (c) Nishino, K. C.; Dai, W.-M.; Gay, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.

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tives to develop novel anticancer taxoids effective against paclitaxel-resistant cancer cell lines.

Recently, a new series of analogues derived from 14 β -hydroxy 10-deacetylbaccatin III (14 β -OH-DAB) were reported (Chart 2).^{6,7} The new derivatives, which bear a

(7) (a) Gupta, R. S. *Cancer Treat. Rep.* **1985**, *69*, 515–522. (b) Schiller, M. J.; Cabral, F. J. *Cell Biol.* **1986**, *102*, 1322–1331. (c) Roy, S. N.; Horwitz, S. B. *Cancer Res.* **1985**, *45*, 3855–3863.

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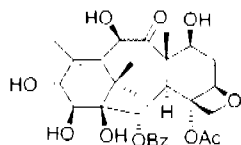
CHART 2. 14 β -OH DAB

CHART 3. Ortataxel

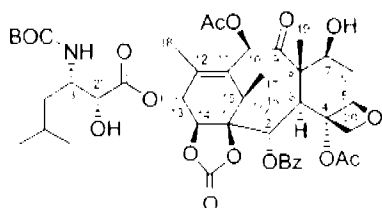
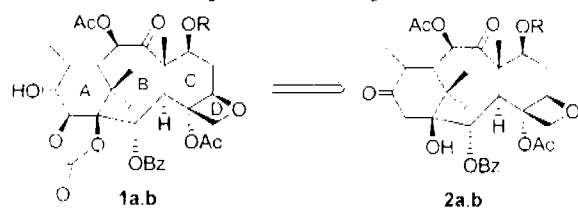
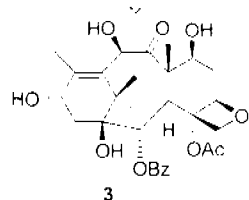


CHART 4. Retrosynthetic Analysis of 1a and 1b



1a 2a: R = BOC;
1b 2b: R = TES



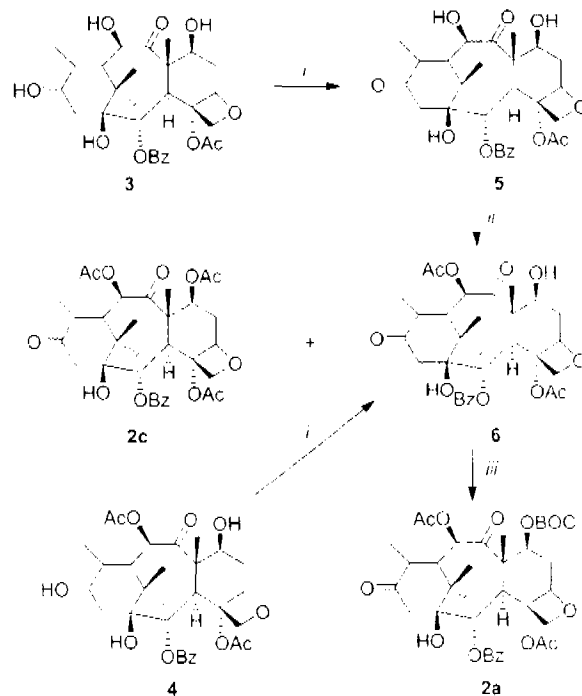
1,14-carbonate moiety, exhibit improved clinical properties such as oral bioavailability and a broader spectrum of antitumor activity.

One of these new taxanes, ortataxel (IDN5109, Bay 55-8862)¹⁰ (Chart 3), was selected for preclinical development. The limited availability of 14 β -OH-DAB¹¹ from Himalayan yew, *Taxus wallichiana* Zucc., prompted us to develop a research program aimed at the semisynthesis of orthogonally protected 14 β -OH-baccatin III from 10-deacetyl-baccatin III (10-DAB) (**3** of Chart 4), a readily available compound.

Such an intermediate would allow direct coupling with the appropriate C₁₃ side chain. This would require protection of C₇-OH as either the 7-*tert*-butoxycarbonyl (7-BOC) or 7-trimethylsilyl (7-TES) derivatives of 14 β -OH-baccatin III 1,14-carbonate (**1a** and **1b**, respectively).

(10) A comparative efficacy study of IDN5109 and paclitaxel was performed using a large panel of human tumor xenografts, characterized by intrinsic or acquired resistance to cisplatin or doxorubicin. IDN5109 is characterized by an improved preclinical profile in terms of efficacy and tolerability. See: (a) Nicoletti, M. L.; Colombo, L.; Rossi, C.; Monardo, C.; Stara, S.; Zuccheri, M.; Riva, A.; Monazzoni, P.; Donati, M. B.; Bombardelli, F.; D'Incalci, M.; Giacuzzi, R. *Clin. Oncol. Res.* **2000**, *6*, 842–846. (b) Polizzi, D.; Preates, G.; Monestavoli, S.; Tortoreto, M.; Zunino, F.; Bombardelli, F.; Riva, A.; Monazzoni, P.; Colombo, L.; D'Incalci, M.; Zuccheri, M. *Clin. Cancer Research* **2000**, *6*, 2070–2074. (c) Polizzi, D.; Preates, G.; Tortoreto, M.; Supino, R.; Riva, A.; Bombardelli, F.; Zunino, F. *Cancer Res.* **1999**, *59*, 1036–1040.

(11) Appendino, G.; Saribodi, P.; Gaberla, B.; Pace, R.; Bombardelli, F.; Vitello, D. *J. Chem. Soc., Perkins Trans. 1* **1992**, 2925–2929.

SCHEME 1. Synthesis of 2a from 3 or 4^a

^a Reagents and conditions: (i) O₃, CH₂Cl₂/MeOH, 78 °C; (ii) Yb(OTf)₃, Ac₂O, THF; (iii) 1-methylimidazole, (BOC)₂O, CCl₄.

Insertion of the C₁₃-OH moiety would require enolization of the C₁₃ carbonyl moiety, eventually leading to 7-protected 13-oxo derivatives of baccatin III (**2**) as starting materials.

Results and Discussion

The formation of the 13-oxo-7-TES-baccatin III (**2b**) from 10-DAB **3** was previously reported, by sequential transformation of **3** via selective silylation and acetylation of the C₇ and C₁₀ hydroxy groups¹² followed by MnO₂ oxidation to give **2b**.¹³ However, a protocol for preparation of the 7-BOC analogue **2a** was not available; thus, we studied two different routes to obtain it (Scheme 1). In the initial approach, 10-DAB **3** was oxidized in very high yields (92%) to 13-oxo-DAB **5** with ozone on a multigram scale. The acylation of the C₁₀ hydroxyl group of **5** with Ac₂O at 25 °C, to give 13-oxo-baccatin III (**6**), was facilitated by Lewis acid lanthanide triflate catalysts following a literature protocol.¹⁴ A proper choice of the lanthanide was crucial to minimize competitive acylation of the C₇ hydroxyl group and/or formation of 7,10-bis-acetylated byproduct **2c**. Acylation of **5** in the presence of cerium or scandium triflates gave **6** in moderate amounts (62% and 33%, respectively). Notably, ytterbium triflate [Yb(OTf)₃] afforded **6** in 91% yields, with trace amounts of 7,10-bis-acetyl-13-oxo-DAB **2c** (5%). This material was identical to a sample of **6** made by ozonolysis of baccatin III **4** (62% yields).

(12) Greene, D. J.; N. Guenard, D.; Gueritte-Vogelstein, V.; Mengesha, L.; Pavia, P. *J. Am. Chem. Soc.* **1988**, *110*, 5017–5019.

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TABLE 1. Effect of the Type of Base,^a Solvent,^{b,c} and Oxidant on the Hydroxylation of Compounds 2a,b

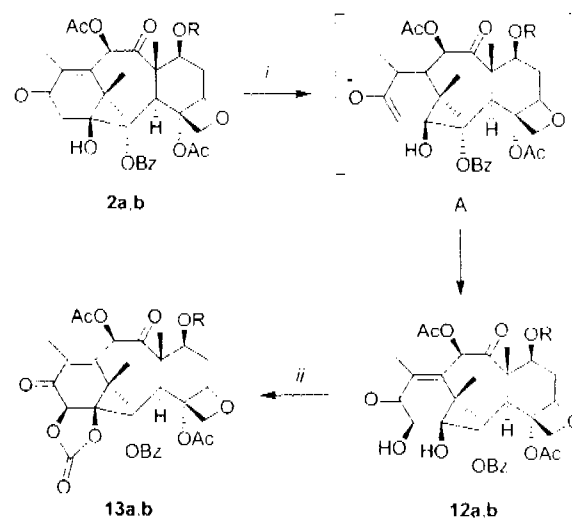
entry	reagents	base	solvent	yield ^d (%)	entry	reagents	base	solvent	yield ^d (%)
1	2a + 7	KHMDS	THF	30	8	2b + 7	KHMDS	A	74
2	2a + 7	KHMDS	CH ₂ Cl ₂	45	9	2b + 8	KHMDS	A	74
3	2a + 9	NaHMDS	B	15	10	2b + 9	KHMDS	A	71
4	2a + 9	KHMDS	B	62	11	2b + 10	KHMDS	A	70
5	2a + 9	LDEA	B	74	12	2b + 11	KHMDS	A	71
6	2a + 9	^t BuOK	B	88	13	2b + 10	^t BuOK	B	83
7	2b + 7	^t BuOK	B	90 ^e	14	2b + 11	^t BuOK	B	83

^a LDEA: lithium diethylamide, KHMDS: potassium hexamethyldisilazane, NaHMDS: sodium hexamethyldisilazane, ^tBuOK: potassium *tert*-butoxide. ^b HMPA: hexamethylphosphoramide, DMPU: 2,2-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, THF: tetrahydrofuran. ^c A: THF/HMPA (83:17), B: THF/DMPU (83:17). ^d Isolated yield. ^e Yield based on HPLC analysis.

Treatment of **6** with BOC-pyrocabonate (BOC₂O) in CH₂Cl₂ at 20 °C, in the presence of either acylation catalysts 4-(dimethylamino)pyridine (DMAP) or 1-methylimidazole (MEIM), afforded 7-BOC-13-oxobaccatin III (**2a**). When DMAP (10–20 mol %) was employed, yields of **2a** were moderate, with two byproducts whose structural assignments are still under investigation. However, with MEIM and excess BOC₂O (2.5 equiv), 7-BOC-13-oxobaccatin III (**2a**) was obtained in very high yields (95%) when the reaction was carried out in the apolar solvent CCl₄. Minor amounts of contaminants were formed when the polar solvent MeCN was used. Notably, we observed that MEIM also catalyzed the hydrolysis of excess BOC₂O to *tert*-butyl alcohol, when water was added to the crude reaction mixture. This facilitates the in situ crystallization of **2a** which was used without additional purification.

The α -hydroxylation of aliphatic ketones by either the oxidation of silyl enol ethers with peracids¹⁵ or the direct oxidation of the enolates with oxaziridines¹⁶ is a versatile procedure. A four-step synthesis of 7-TES-13-oxo-14 β -OH-baccatin III (**12b**), via a silyl-enol ether route, starting from compound **2b** was recently reported.¹⁷ The treatment of **2b** with trimethylsilyl chloride (TMS-Cl) and DBU gave a mixture of 7-TES-13-TMS-enol ether and 7-TES-1,13-bis-TMS-enol ether derivatives of **2b**. The latter compound was selectively desilylated with 1.0 M HCl to give the enol ether that was converted into **12b** by sequential oxidation with *m*-CPBA and desilylation. The laborious nature of this procedure prompted us to examine functionalization of an enolate to afford targets **12a,b** directly.

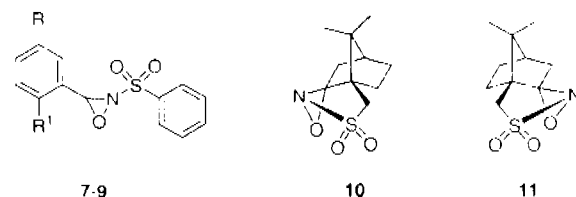
Significant efforts were expended to develop an efficient protocol to convert intermediates **2a,b** to 14-OH-13-oxobaccatin III derivatives **12a,b**. This was accomplished by treatment of the appropriate enolates with *N*-(sulfonyl)oxaziridines (**7–11**)¹⁸ (Scheme 2). Various bases (LDEA, ^tBuOK, KHMDS, and NaHMDS), solvents (THF, THF/HMPA, 85:15, and THF/DMPU, 80:20) and oxaziridines [2-benzenesulfonyl-3-phenyloxaziridine (**7**), 2-benzenesulfonyl-3-(2-chloro-5-nitrophenyl)oxaziridine

SCHEME 2. Conversion of 2a,b to 12a,b^a

12a, 13a: R = BOC; **12b, 13b:** R = TES

^a Reagents and conditions: (i) **2a, 2b** (see Table 1); (ii) **13a:** carbonyldiimidazole, toluene; **13b:** COCl₂/pyridine, CH₂Cl₂, 0 °C.

CHART 5. Oxaziridines 7–11



7: R = R¹ = H; **8:** R = NO₂, R¹ = Cl; **9:** R = NO₂, R¹ = H

(**8**), 2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine (**9**), (1*S*)-(1*S*)-camphorsulfonyloxaziridine (**10**), and (1*S*)-enantiomer (**11**) were studied (Table 1 and Chart 5). No appreciable differences were noticed with the type of substituent at the C-1 hydroxy group. Our first attempts to carry out the hydroxylation in THF or CH₂Cl₂ (entries 1 and 2) gave moderate amounts of the target product. However, yields increased significantly when the reactions were performed in THF, in the presence of 15–20% HMPA or DMPU.

A series of reactions performed on compound **2a**, in THF/DMPU (83:17), with 2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine (**9**) clearly showed that the nature of the base was an important factor for yields (entries 3–6). The reactivity order was ^tBuOK > LDEA > KHMDS > NaHMDS. The greater efficiency of ^tBuOK with respect

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(16) For an exhaustive review on oxidation adjacent to C=C bonds by hydroxylation methods, see: Jones, B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. A.; Liu, S. V., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, Chapter 2, pp 151–181.

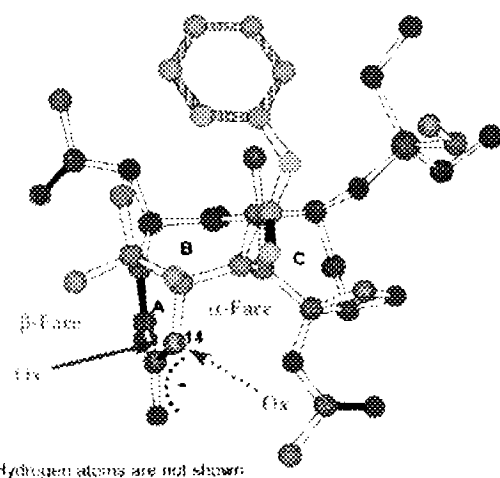
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TABLE 2. Synthesis of Compounds **1a** and **1b** (α -Epimers) and **14a** and **14b** (β -Epimers) by Reduction of Compounds **13a,b**

entry	reagent	reductant	solvent	T (°C)	time (min)	OY ^a (%)	1/14 ^b	1 yield ^c (%)
1	13b	Ca ⁺ BH ₄	EtOH	26	730	54	1.1	26
2	13a	Ca ⁺ BH ₄	EtOH	26	400	22	1.0	15
3	13b	Na ⁺ BH ₄	EtOH	+15	180	82	1.8	52
4	13a	Na ⁺ BH ₄	EtOH	+10	300	46	1.2	25
5	13b	Na ⁺ BH ₄	EtOH	+20	20	80	1.0	40
6	13b	Na ⁺ BH ₄	DME ^d	+15	180	78	1.0	39
7	13a	Na ⁺ BH ₄	THF	+20	180	62	1.5	37
8	13b	Na ⁺ BH ₄	MeOH	15	50	80	3.0	60
9	13a	Na ⁺ BH ₄	MeOH	+25	180	52	2.8	38
10	13b	<i>n</i> Bu ₃ N ⁺ BH ₄ ⁻	MeOH	0	20	83	3.8	66
11	13b	<i>n</i> Bu ₃ N ⁺ BH ₄ ⁻	MeOH	15	30	95	4.6	76
12	13b	<i>n</i> Bu ₃ N ⁺ BH ₄ ⁻	DME ^d	+20	30	80	1.0	46
13	13a	<i>n</i> Bu ₃ N ⁺ BH ₄ ⁻	MeOH	25	80	81	3.2	62
14	13a	Et ₃ N ⁺ BH ₄ ⁻	A ^e	-40	240	89	3.0	67
15	13a	Et ₃ N ⁺ BH ₄ ⁻	A ^e	55	360	87	3.6	68
16	13a	Me ₃ N ⁺ DH ₄ ⁻	A ^e	30	400	84	2.8	62
17	13a	Na ⁺ BH ₄ ^f	THF	+20	30	69	0.15	8
18	13a	<i>n</i> Bu ₃ N ⁺ BH ₄ ^f	THF	+20	20	60	0.13	7

^a Overall yields. ^b By ¹H NMR. ^c Isolated yields. ^d DME: dimethoxyethane. ^e A: MeOH/THF (2:1). ^f In the presence of Amberlyst 15.

FIGURE 1. Chem 3D view of the enolate of **2b**.

to KHMDS was also confirmed for the analogue **2b** when oxaziridine **7** was the oxidant (entries 7 and 8). The stereo- and electronic effects of the enolate oxidation of **2b** were explored (entries 8–10). The reaction yields were only slightly affected by the electrophilicity of the oxidant with a range of 70–74% yields of compound **12b**. Notably, yields of products were not affected by the chirality of the oxidant when either enantiomer of camphorsulfonyl oxaziridine were used (entries 11–14). However, steric demand of these oxidants impeded conversion of the enolate, with recovery of variable amounts of starting materials (ca. 10%; see entries 13 and 14). The diastereoselectivity of the hydroxylation can be rationalized by a folded conformation of the terpenoid skeleton of the enolates, which precludes attack of the sterically demanding oxaziridines from the more hindered α -face of the A ring system, thus promoting formation of the 14/ β -O1 epimers (Figure 1).

The formation of trace amounts of contaminants, whose structure and relative amounts depended on the type of reaction, was also observed. For instance, HPLC–MS showed at least five isomeric compounds of **12a,b**, ranging between 1 and 4%. A major problem related to the

use of oxaziridines **7–9** was the purification of compounds **12a,b** which required multiple column chromatography and fractional crystallization due to the presence of unreacted oxaziridine, imine, and imine hydrolysis products. Thus, traces of unseparable byproducts were often detected after the purification process. When camphorsulfonyloxaziridines **10** and **11** were used, higher purities of **12a,b** were obtained.

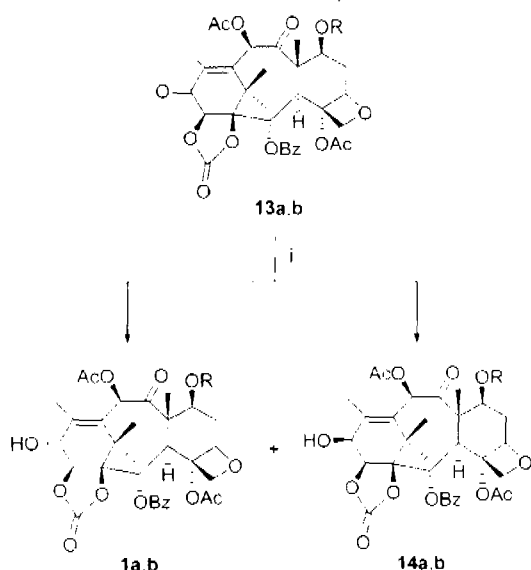
To minimize losses of valuable taxoid intermediates **12a,b**, the crude products were converted to the carbonates **13a,b** by one of two protocols: (i) phosgene in pyridine¹⁹ or (ii) carbonyldiimidazole (Scheme 2). Compound **13a** was obtained from crude **12a** with carbonyldiimidazole in 84% yield (entry 6), while compound **13b** was obtained from crude **12b** in 75–80% yields (entry 7 and 14).

Reduction of the 13-keto group of **13a,b** consistently afforded the α -epimers **1a,b** (major products) with the β -epimers **14a,b** (Table 2, Scheme 3). Higher-order borohydrides, with substituents linked directly to the boron atom, such as (*R*)-Alpine hydride, (*S*)-Selectride, lithium triethylborohydride, and Ipc₂BCl, failed to reduce the 13-oxo group. The diastereoselectivity of the ketone reduction is dependent on a balance of steric demands of the ketone moiety and the reductant. The folded structure of the taxane skeleton, associated by the presence of the C₁₄ hydrogen atom in the α -face, favors hydride approach from the β -face, while the 1,14-carbonate moiety shields the β -face which inhibits reduction (Figure 2).²⁰ Thus, remarkable ratios of the α/β -epimers were obtained from the reduction.

Compounds (**1b**, **14b**) were usually obtained in higher yields vs **1a**, **14a** when metalated borohydrides were used (entries 1–4 and 8–9). NaBH₄ is more efficient than

(19) Attempted phosgenation with bis(trichloromethyl)carbonate (triphosgene) gave only moderate amounts (30–60%) of compounds **13a**.

(20) The importance of the bulkiness of the 1,14-carbonate moiety on the selectivity is indirectly documented in the literature. In fact, the Na⁺BH₄-induced reduction of a series of C₁₄ analogues of 7-TPS-13-oxobaccatin III in MeOH stereoselectively led to the corresponding 13- β -hydroxyl derivatives. See: Nicolini, R. C.; Conduccion, C. E.; Kontner, P. G.; Reiland, J.; Gay, R. K.; Wradislo, W. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1581–1582.

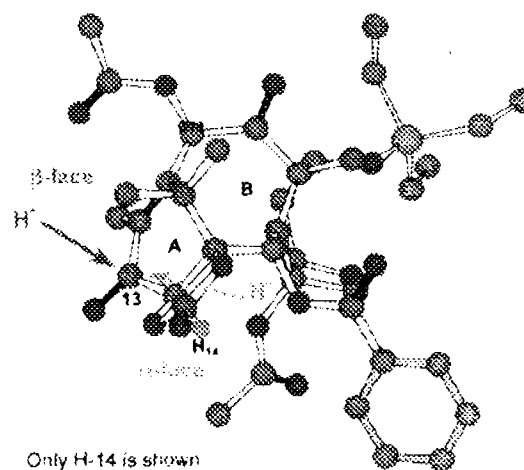
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160SCHEME 3. Reduction of Compounds **13a,b**^a

1a, 14a: R = BOC 1b, 14b: R = TES

^a Reagents and conditions: see Table 2.

$\text{Ca}(\text{BH})_2$ while no reaction was observed with the more sterically demanding $\text{Zn}(\text{BH})_2$. The reaction yields were significantly reduced due to partial hydrolysis of the C₁₃-acetoxy moiety which occurred to a greater extent with compounds **1a** and **14a** versus **1b** and **14b**. Best results were obtained with alkylammonium borohydrides which required shorter reaction times (entries 8, 11 and 9, 13), with minimal deacetylation.

The observed diastereoselectivity is dependent on solvent, hydride, and temperature. Aprotic solvent dimethoxyethane (DME), which does not solvate the borohydride, was completely unselective (entries 6 and 12). Protic solvents such as MeOH and EtOH which solvate the borohydride ion²¹ increased the bulkiness of the reductant, allowing partial diastereoselection. The best results were found when **13a,b** were reduced with a combination of NaBH_4 in MeOH (entries 8 and 9). This solvent appears more efficient than ethanol, confirming literature data.²² Alkylammonium borohydrides increased the α -diastereoselectivity with respect to metalated borohydrides (entries 8, 11 and 9, 13). This can be rationalized by a steric approach control model.²³ Accordingly, in an early transition state for reduction of hindered ketones, the transition state energy is controlled by such factors as ease of approach of the hydride. We postulate that better solvation of the hydride increases the bulkiness of the reductant. So steric considerations are relevant in protic solvents and for the more dissociated ammonium salts versus the metalated reducing agents. As a consequence, better diastereoselection has been observed with the $\text{MeOH}/\text{R}_4\text{N}^+\text{BH}_4^-$ couple. On the basis of these results, the transition state corresponding to the attack of the

FIGURE 2. Chem 3D view of carbonate **13b**.

hydride to the β -face has lower energy than that the α -face. Confirmatory of this hypothesis, diastereoselection was improved at lower temperatures (entries 10, 11 and 14, 15).

Other reduction methods were attempted, such as acid induced hydroboration and transfer hydrogenation. NaBH_4 -induced reduction of **13a,b**, in the presence of the sterically demanding CeCl_3 Lewis acid catalyst, failed to improve diastereoselectivity. However, proton-induced catalysis, using Amberlyst 15, caused an inversion of the α/β ratio regardless of the size of the alkylammonium borohydride (entries 17 and 18). The adverse effect of the Lewis acid catalysts could be rationalized by the formation of a sterically congested five membered ring chelate between the catalyst, the C₁₃-carbonyl, and the C₁₇-oxygen atom.²⁴ Finally, transfer hydrogenation of **13a** with Pd/C in methanol, in the presence of ammonium formate, resulted in nucleophilic substitution of C₁₇-oxygen atom by the hydride ion with the formation of **2a**.

Spectral data of **1b** was compared with those reported in the literature. The α -stereochemistry of the C₁₃-OH group of **1a** and **14a** were confirmed by qualitative homonuclear NOE difference spectra. Irradiation of the C₂-H signal at 6.08 ppm of **1a** showed consistent enhancement (4%) of the C₁₃-H proton at 5.37 ppm, suggesting that both protons are located in the β -face of the taxane skeleton. Consistently, the irradiation of the C₂-H signal did not show any NOE-effect on the C₁₇-H proton at 4.81 ppm. The C₁₃-epimer **14a** showed an enhancement of the C₁₃-H proton at 5.31 ppm (6%) upon irradiation of the C₂-H signal at 4.18 ppm.

Conclusions

An efficient six-step protocol of preparation of **1a,b**, key intermediates for the synthesis of ortataxel and related taxoids, has been developed starting from the readily available 10-DAB III (**3**). Each step of the synthesis proceeds with high yields, which minimizes the require-

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(23) These results could be in line with the observation that sodium and alkylboron hydrides failed to reduce compound **12a** (see ref 21). In this case, the reductant probably combines with the C₁₃ carbonyl and the C₁₇-OH of the substrate to form a sterically hindered five-membered ring intermediate.

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ment for chromatography purification in many steps. These results provide an efficient industrial synthesis of this class of taxoids.

Experimental Section

13-Oxo-10-deacetylbaaccatin III (13-Oxo DAB) (5). Ozonolysis was passed through a solution of compound **3** (2.0 g, 3.67 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (200 mL, 5:1) at -78°C for 35 min. The reaction mixture was left at -78°C for 1 h. The excess of O_3 was destroyed by addition of an excess of Me_2S and pyridine. The temperature was raised to 20°C and the solvent evaporated. The residue was treated twice with CCl_4 to yield 2.0 g of solid which was chromatographed (SiO_2 , *n*-pentane/ $\text{Et}_2\text{O}/\text{EtOAc}$, 2:1:1) to give 13-oxo-DAB **5** (1.83 g, 3.37 mmol, 92%).

13-Oxobaaccatin III (6). $\text{Yb}(\text{O}i\text{Pr})_3$ (0.21 g, 0.30 mmol) and Ac_2O (0.79 mL, 8.36 mmol) were added to a stirred solution of **5** (2.2 g, 4.06 mmol) in THF (20.0 mL) at 25°C . EtOAc was added after 4 h, the solution washed with saturated NH_4Cl and dried, and the solvent was evaporated. Chromatography (SiO_2 , *n*-hexane/ EtOAc , 1.5:1) gave compound **6** (2.16 g, 3.69 mmol, 91%).

13-Oxo-7-BOC-baaccatin III (2a). 13-Oxobaaccatin III **6** (1.10 g, 1.9 mmol) in CH_2Cl_2 (0.5 mL) was added to CCl_4 (14.0 mL) at 20°C . 1-Methylimidazole (25 μL , 0.28 mmol) and (BOC) $_2\text{O}$ (1.03 g, 4.7 mmol) were added under stirring. 1-Methylimidazole (16.0 μL , 0.20 mmol) was added after 8 h. The solution was left at 20°C for 24 h. The solvent was evaporated, and the residue was dissolved in a mixture of acetone/ Et_2O (10.0 mL, 1:1) and left at 20°C for 16 h. The precipitate was filtered to yield **2a** (1.12 g, 1.63 mmol, 86%). The residue was chromatographed to yield an additional amount of **2a** (0.12 g, 9%). mp = $192\text{--}193^\circ\text{C}$; $[\alpha]_D^{25} = -35.6$ ($c = 1.05$, CHCl_3); IR (CDCl_3) ν_{max} 3483, 1731, 1676, 1571, 1274; ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, 2H), 7.61–7.54 (m, 1H), 7.44–7.50 (m, 2H), 6.57 (s, 1H), 5.67 (d, 1H, $J = 6.8$ Hz), 5.39 (m, 1H, $J_1 = 10.4$ Hz, $J_2 = 7.2$ Hz), 4.94 (d, 1H, $J_1 = 9.5$ Hz, $J_2 = 2.0$ Hz), 4.32 (d, 1H, $J = 9.0$ Hz), 4.09 (d, 1H, $J = 9.0$ Hz), 4.02 (d, 1H, $J = 6.8$ Hz), 2.94 (d, 1H, $J = 19.6$ Hz), 2.66 (d, 1H, $J = 19.6$ Hz), 2.64 (m, 1H, $J_1 = 7.2$ Hz, $J_2 = 14.8$ Hz, $J_3 = 9.5$ Hz), 2.20 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.92 (s, 3H), 1.91 (m, 1H, $J_1 = 10.4$ Hz, $J_2 = 14.8$ Hz, $J_3 = 2.0$ Hz), 1.76 (s, 3H), 1.47 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 260.5, 198.4, 170.3, 168.3, 167.0, 152.5, 152.4, 141.0, 134.5, 130.3, 129.0, 128.9, 84.0, 83.4, 80.3, 78.7, 77.4, 76.5, 76.3, 74.7, 72.8, 57.3, 46.7, 42.7, 35.6, 33.1, 27.9, 21.9, 21.0, 18.4, 14.0, 10.7; MS m/z 684.49 (M $^+$), calcd for $\text{C}_{30}\text{H}_{40}\text{O}_{13}$ 684.73; Anal. Calcd for $\text{C}_{30}\text{H}_{40}\text{O}_{13}$: C, 63.15; H, 6.48; Found: C, 63.39; H, 6.80.

13-Oxo-7-BOC-14 β -hydroxybaaccatin III (12a). 13-Oxo-7-BOC-baaccatin III **2a** (0.65 g, 0.95 mmol), dissolved in THF/DMPU (11.0 mL, 8:3), was added under stirring to a THF (10 mL) solution of BuOK (0.43 g, 3.79 mmol) at -65°C . After 15 min, oxaziridine **9** (0.804 g, 2.63 mmol), dissolved in THF/DMPU (10.0 mL, 9:1), was added, and the temperature was raised to -55°C . An additional amount of BuOK (0.10 g, 0.89 mmol) was added. After 30 min, acetic acid (0.2 mL) and aqueous NH_4Cl (10%, 25.0 mL) were sequentially added. The organic layer was extracted with water, dried, and evaporated. The residue was chromatographed, giving **12a** with minor impurities. The mixture was treated with H_2O and filtered. After the solvent was evaporated, the residue was chromatographed to yield **12a** (0.60 g, 0.84 mmol, 88%).

13-Oxo-7-TES-14 β -hydroxybaaccatin III (12b). A solution of BuOK (2.2 mL of 1.0 M in THF) was added, at -65°C , to a solution of 13-oxo-7-TES-baaccatin III **2b** (0.60 g, 0.86 mmol) in THF/DMPU (11.0 mL, 8:3). Then a solution of oxaziridine **11** (0.80 g, 1.29 mmol) in THF (2.0 mL) was added. The reaction mixture was quenched at -60°C with acetic acid (0.2 mL, 40% in THF) and warmed to room temperature. After

dilution with brine (10.0 mL), the mixture was extracted with EtOAc (2 $\times$ 10 mL). The organic layer was dried and evaporated. Workup of the residue as described above gave **12b** (0.52 g, 0.73 mmol, 85%); mp $189\text{--}190^\circ\text{C}$ ($\text{EtOAc}/\text{hexane}$); $[\alpha]_D^{25} = +26.0$ ($c = 1.0$, CHCl_3); IR (Nujol) ν_{max} 3395, 2921, 2853, 1749, 1726, 1690, 1463, 1375, 1273, 1242; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, 2H), 7.46–7.66 (m, 3H), 6.53 (s, 1H), 5.89 (d, 1H, $J = 7.0$ Hz), 4.93 (d, 1H, $J = 7.3$ Hz), 4.49 (dd, 1H, $J_1 = 10.7$, $J_2 = 6.6$ Hz), 4.31 (s, 2H), 4.11 (d, 1H, $J = 1.8$ Hz), 3.87 (d, 1H, $J = 6.9$ Hz), 3.73 (d, 1H, $J = 1.8$ Hz), 3.64 (s, 1H), 2.46–2.61 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 1.83–2.05 (m, 1H), 1.75 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 0.91–0.99 (t, 9H, $J = 8.7$ Hz), 0.58–0.66 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.8, 200.1, 170.4, 169.3, 166.0, 153.5, 137.4, 133.9, 130.3, 129.8, 129.0, 84.3, 81.4, 76.4, 75.4, 74.4, 73.1, 72.9, 72.5, 59.4, 45.4, 43.5, 37.4, 33.2, 22.9, 22.0, 21.1, 14.0, 10.2, 7.1, 5.6; MS m/z 714.59 (M $^+$), calcd for $\text{C}_{31}\text{H}_{40}\text{O}_{13}\text{Si}$ 714.87; Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{O}_{13}\text{Si}$: C, 62.16; H, 7.05; Found: C, 62.19; H, 6.98.

13-Oxo-7-BOC-14 β -hydroxybaaccatin III 1,14-Carbonate (13a). Compound **12a** was prepared according to the synthetic procedure reported before from **2a** (2.0 g, 2.9 mmol) and **9** (1.65 g, 5.40 mmol). After removal of the solvent, the crude reaction mixture was dissolved in toluene (25.0 mL), and carbonyldiimidazole (2.0 g, 12.0 mmol) was added at 20°C . The solution was stirred under argon for 50 min at 75°C . After the solution was cooled at 20°C , HCl (15.0 mL, 0.2 N) and AcOH (15.0 mL) were added. The organic phase was separated, washed with water, and dried, and the solvent was evaporated. Chromatography of the residue (SiO_2 , *n*-pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 14:3:5:2:5) gave 13-oxo-7-BOC-14 β -OH-1,14-carbonate baaccatin III **13a** (1.77 g, 2.43 mmol, 84%).

13-Oxo-7-TES-14 β -hydroxybaaccatin III 1,14-Carbonate (13b). (a) A solution of phosgene (20%) (4.3 mL, 8.6 mmol, 20% in toluene) and pyridine (1.4 mL, 17.2 mmol) was added to CH_2Cl_2 (15.0 mL) at 0°C . A solution of **12b** (0.47 g, 0.76 mmol) in CH_2Cl_2 (5.0 mL) was added. The reaction was quenched after 20 min with methanol (1.0 mL) and diluted with CH_2Cl_2 (10.0 mL). The mixture was washed with aqueous NaHCO_3 (15.0 mL), dried, and evaporated. Chromatography (SiO_2 , $\text{EtOAc}/\text{cyclohexane}$, 15:85) gave **13b** (0.48 g, 0.65 mmol, 85%). (b) Compound **12b** (crude reaction mixture prepared as reported above) was dissolved in CH_2Cl_2 (7.0 mL) and added dropwise to a stirred solution of phosgene (4.26 mL, 20% in toluene, 8.6 mmol) and pyridine (1.36 mL, 17.2 mmol) in CH_2Cl_2 (15 mL) at 0°C . After 20 min, the reaction was quenched, washed, evaporated, and purified as described in method a to give **13b** (using oxidant **11**: 75% using oxidant **7**: 80%); mp $190\text{--}191^\circ\text{C}$; $[\alpha]_D^{25} = +17.0$ ($c = 1.0$, CHCl_3); IR (Nujol) ν_{max} 2953, 1828, 1754, 1731, 1459, 1376, 1240, 1224; ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dd, 2H, $J = 7.0$ Hz), 7.62–7.70 (m, 1H), 7.51 (t, 2H), 6.54 (s, 1H), 6.15 (d, 1H, $J = 7.0$ Hz), 4.95 (d, 1H, $J = 7.3$ Hz), 4.81 (s, 1H), 4.49 (dd, 1H, $J_1 = 11.0$, $J_2 = 7.0$ Hz), 4.30 (m, 2H), 3.83 (d, 1H, $J = 7.0$ Hz), 2.48–2.63 (m, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 1.89–2.13 (m, 1H), 1.75 (s, 3H), 1.39 (s, 3H), 1.21 (s, 3H), 0.91–0.99 (t, 9H, $J = 8.7$ Hz), 0.58–0.66 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.0, 190.0, 170.3, 168.7, 164.5, 151.3, 151.2, 139.4, 134.5, 129.9, 129.1, 127.7, 86.4, 83.9, 80.6, 75.9, 74.7, 72.0, 68.3, 59.3, 45.5, 41.7, 37.0, 32.7, 21.8, 20.7, 19.5, 14.0, 9.9, 6.7, 5.3; MS m/z 740.69 (M $^+$), calcd for $\text{C}_{31}\text{H}_{40}\text{O}_{13}\text{Si}$ 740.86; Anal. Calcd for $\text{C}_{31}\text{H}_{40}\text{O}_{13}\text{Si}$: C, 61.60; H, 6.53; Found: C, 61.61; H, 6.65.

7-BOC-14 β -hydroxybaaccatin III 1,14-Carbonates (1a) and (14a). (a) Compound **13a** (0.71 g, 0.98 mmol) in THF (3.0 mL) was added at -55°C to a MeOH solution (11.0 mL) of $\text{Bu}_4\text{N}^+\text{BF}_4^-$ (1.23 g, 9.0 mmol). The reaction was quenched after 6 h with solid citric acid (0.6 g) and then with saturated aqueous citric acid (10.0 mL). The reaction was extracted with AcOEt and dried, and the solvent was evaporated. The crude material was chromatographed (SiO_2 , *n*-hexane/ethyl acetate, 1:4:1) to yield **1a** (0.49 g, 0.67 mmol, 68.0%) and **14a** (0.12 g, 0.18 mmol, 19.0%).

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7-TES-14- β -hydroxybaccatin III 1,14-Carbonates (1b) and (14b). To a solution of **13b** (0.14 g, 0.2 mmol) in MeOH (8.0 mL) was added $\text{Bu}_4\text{N}^+\text{BF}_4^-$ (0.12 g, 0.49 mmol) at -15°C . Citric acid (0.1 g) and water (10.0 mL) were sequentially added after 40 min, and the reaction mixture was extracted with EtOAc, dried, and evaporated. The crude material was chromatographed (SiO_2 , cyclohexane/EtOAc, 80:20–70:30) to yield **1b** (0.11 g, 0.15 mmol, 76%) and **14b** (0.027 g, 0.037 mmol, 19%). **1b**: mp 216–218°C; $[\alpha]_D^{25} = -54.0$ ($c = 1.0$, CHCl_3); IR (Nujo) ν_{max} 3448, 2929, 2852, 1815, 1731, 1454, 1376, 1238; ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, 2H, $J = 7.0$ Hz), 7.60–7.68 (m, 1H), 7.50 (t, 2H), 6.45 (s, 1H), 6.11 (d, 1H, $J = 7.4$ Hz), 5.00–5.03 (m, 1H), 4.99 (d, 1H, $J = 7.3$ Hz), 4.82 (d, 1H), 4.49 (dd, 1H, $J_1 = 10.3$ Hz, $J_2 = 6.6$ Hz), 4.12–4.35 (m, 2H), 3.74 (d, 1H, $J = 7.4$ Hz), 2.47–2.65 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H), 1.85–2.14 (m, 1H, 6-H), 1.74 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H), 0.91–0.99 (t, 9H, $J = 8.7$ Hz), 0.58–0.66 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 260.9, 170.5, 169.2, 164.9, 153.0, 142.2, 134.2, 132.9, 129.9, 123.9, 128.2, 88.5, 84.2, 84.0, 80.4, 76.0, 75.1, 71.9, 71.8, 69.5, 58.8, 46.7, 41.5, 37.0, 25.9, 22.3, 21.7, 20.8, 14.8, 10.1, 6.8, 5.3; MS m/z 742.96 (M^+ , calcd for $\text{C}_{38}\text{H}_{50}\text{O}_{12}\text{Si}$ 742.88); Anal. Calcd for $\text{C}_{38}\text{H}_{50}\text{O}_{12}\text{Si}$: C, 61.44; H, 6.78. Found: C, 61.68; H, 6.87. **14b**: mp 234–236°C; $[\alpha]_D^{25} = -10.0$ ($c = 0.7$, CHCl_3); IR

(Nujo) ν_{max} 3457, 2955, 2920, 2852, 1814, 1736, 1731, 1455, 1375, 1240; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, 2H, $J = 7.0$ Hz), 7.61–7.68 (m, 1H), 7.49 (t, 2H), 6.45 (s, 1H), 6.14 (d, 1H, $J = 7.3$ Hz), 4.92 (d, 1H, $J = 7.7$ Hz), 4.83 (d, 1H, $J = 8.0$ Hz), 4.41 (m, 2H, 13-H), 4.28 (m, 2H), 3.70 (d, 1H, $J = 7.0$ Hz), 2.46–2.65 (m, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.85–2.10 (m, 1H), 1.73 (s, 3H), 1.44 (s, 3H), 1.18 (s, 3H), 0.91–0.98 (t, 9H, $J = 8.7$ Hz), 0.58–0.66 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.4, 170.1, 169.2, 164.7, 152.6, 139.8, 139.0, 134.2, 129.8, 128.9, 128.2, 92.3, 84.0, 81.0, 76.0, 75.0, 74.8, 71.9, 69.5, 68.7, 59.2, 46.2, 40.8, 37.1, 30.5, 22.1, 21.4, 20.8, 20.0, 10.0, 6.8, 5.3; MS m/z 742.64 (M^+ , calcd for $\text{C}_{38}\text{H}_{50}\text{O}_{12}\text{Si}$ 742.88); Anal. Calcd for $\text{C}_{38}\text{H}_{50}\text{O}_{12}\text{Si}$: C, 61.44; H, 6.78. Found: C, 61.33; H, 6.71.

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Supporting Information Available: General techniques and spectroscopic and analytical data for compounds **1a**, **5**, **6**, **12a**, **13a**, and **14a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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263Synthetic Studies with
13-Deoxybaccatin IIIYu Mi Ahn, David G. Vander Velde, and
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Abstract: An efficient synthesis of 13-*epi*-7-*O*-(triethylsilyl)-baccatin III from 13-deoxybaccatin III is described. Oxidation of 13-deoxy-7-*O*-(triethylsilyl)baccatin III with *tert*-butyl peroxide, followed by reduction with SnI_2 , produced 13-*epi*-7-*O*-(triethylsilyl)baccatin III in good overall yield. The preparation of 13-oxo-7-*O*-(triethylsilyl)baccatin III from 13-*epi*-7-*O*-(triethylsilyl)baccatin III using tetrapropylammonium perphthalate and *N*-methylmorpholine *N*-oxide is also reported.

Paclitaxel (**1**, Figure 1), a complex diterpene isolated from the bark of *Taxus brevifolia* (Pacific Yew),^{1,2} is a chemotherapeutic agent with impressive antitumor activity.^{3,4} Paclitaxel is available only in small quantities from natural sources;^{1,2} however, semisynthetic approaches toward paclitaxel synthesis and analogue development have been developed, utilizing 10-deacetyl-baccatin III, a more readily available paclitaxel-related natural product.^{5–7} A major advantage of using 10-deacetyl-baccatin III is that it can be obtained from a regenerable source, the needles of *Taxus baccata*.⁸ As paclitaxel becomes widely used for the treatment of several types of cancers, plant cell culture represents an alternative method for paclitaxel production. The major goal of plant cell culture is to produce paclitaxel in high yield, minimizing the formation of other taxane diterpenes.⁹ However, certain byproducts can become useful if appropriate synthetic routes can be developed to convert these intermediates to paclitaxel or its derivatives. We now report on the chemistry of such a byproduct, 13-deoxybaccatin III (**2**, Figure 1), which is produced in high quantity from plant cell cultures.⁹

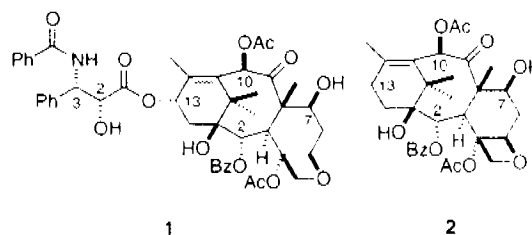
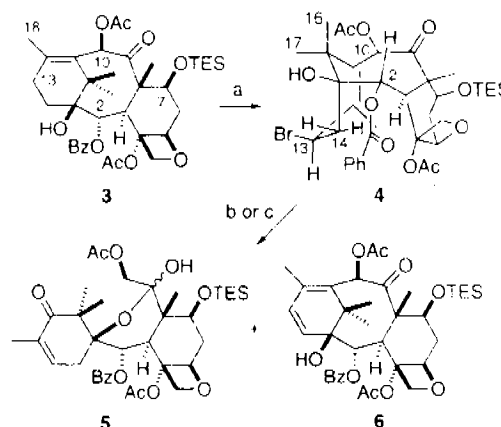


FIGURE 1. Structures of paclitaxel (**1**) and 13-deoxybaccatin III (**2**).

SCHEME 1^a

^a Conditions: (a) NBS, benzoyl peroxide, CCl_4 , reflux, 8 h, 94%; (b) NaBH_4 , DMF, 40 °C, 7 h, 79% (**5:6** = 1:1); (c) AgOAc , DMF, 40 °C, 7 h, 85% (**5:6** = 2:1).

The 7-hydroxy group of 13-deoxybaccatin III was protected with triethylsilyl chloride (TES-Cl) to provide 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**)^{10,11} in 95% yield. Then, 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**) was treated with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide producing the corresponding 13 β -bromo derivative **4** in 94% yield (Scheme 1). Bromo compound **4** was found to be unstable on silica gel and was therefore not subjected to purification via column chromatography. The stereochemistry at C13 of **4** was determined through NOE experiments. Irradiation of H16 (δ 1.14) strongly enhanced H12, but not H13, and irradiation of H17 (δ 1.24) significantly enhanced H14 β , but not H15. Therefore, the stereochemistry of the 13-bromo group was assigned as 13 β . This bromide is unsuitable for further elaboration into bioactive compounds. When reacted with sodium azide and silver acetate, the bromide produced a mixture of 10,11-*seco* derivative **5**¹² and diene **6** (Scheme 1).¹³

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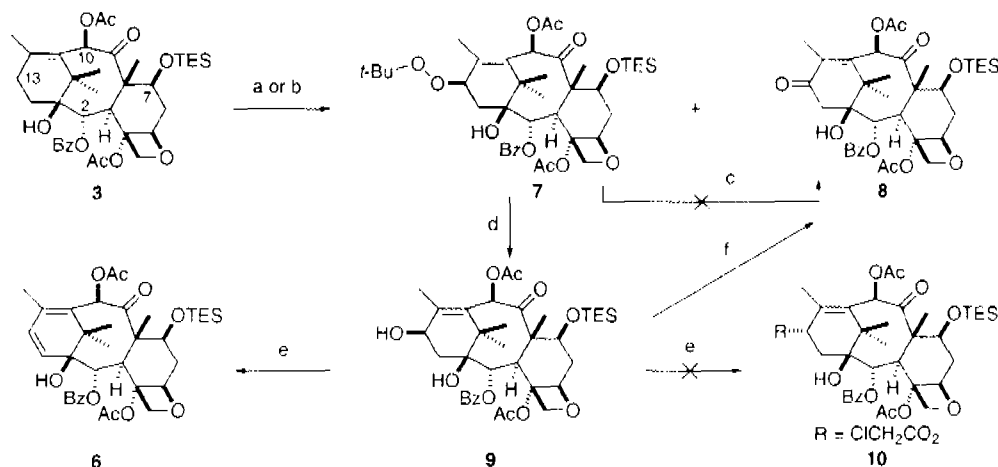
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SCHEME 2^a

^a Conditions: (a) *tert* BuOOH, benzene, 60 °C, 7 h, 78% for product **7**; (b) oxidants, *tert* BuOOH, benzene, rt, 22–26 h, gave **7** and **8**, 0–31% for product **7**; (c) PDC, CuBr, or CuCl, *tert* BuOOH, benzene, 50–55 °C, 18–23 h; (d) SmI₂, THF, rt, 3.5 h, 86%; (e) DFAD, Me₃P, ClCH₂CO₂H, toluene, from 0 to 90 °C, 24 h, 43% for product **6**; (f) TPAP, NMO, CH₂Cl₂, rt, 2 h, 81%.

TABLE 1. Oxidation of **3** with Various Oxidants in the Presence of *tert*-Butyl Hydroperoxide in Benzene

entry	substrate	reagents ^b	time (h)	T (°C)	relative product ratio (%) ^a (isolated yield, %)		
					3	7	8
1	3	PDC/ <i>t</i> BuOOH	20	25	18	43(31)	37
2	3	CrO ₃ / <i>t</i> BuOOH	23	25	5	31(14)	64
3	3	SeO ₂ / <i>t</i> BuOOH	25	25	100	0	0
4	3	PCC/ <i>t</i> BuOOH	23	25	25	30(23)	45
5	3	CuBr/ <i>t</i> BuOOH ^c	22	55	37	63(43)	0
6	3	CuCl/ <i>t</i> BuOOH ^c	26	50	0	100(72)	0
7	3	<i>t</i> BuOOH	22	25	19	55(34)	26
8	3	<i>t</i> BuOOH	7	60	0	100(78)	0
9	7	PDC/ <i>t</i> BuOOH	23	50	0	100(>95) ^d	0
10	7	CuBr/ <i>t</i> BuOOH ^c	18	55	0	100(>95) ^d	0
11	7	CuCl/ <i>t</i> BuOOH ^c	20	55	0	100(>95) ^d	0

^a Obtained from integration of signals in the ¹H NMR of unpurified reaction products. ^b Ratio of **3**:oxidants:*t* BuOOH = 1:10:10. ^c CuBr and CuCl were used as catalysts. ^d Starting material **7** was recovered quantitatively.

We also carried out allylic oxidation reactions with compound **3**¹¹ using various oxidants (Scheme 2 and Table 1) in the presence of *tert*-butyl hydroperoxide. Thus, 7-protected 13-deoxybaccatin III **3** was subjected to oxidants (PCC, PDC, MnO₂, CrO₃, and SeO₂) in the presence of *tert*-butyl hydroperoxide in order to obtain ketone **8**. However, the oxidations gave a mixture of starting material **3**, *tert*-butylperoxy product **7**, and 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) (Scheme 2, Table 1, entries 1–4). When CuCl and CuBr were used as catalysts in the *tert*-butyl hydroperoxide oxidation reac-

tions,^{15,16} none of the ketone **8** was obtained (Table 1, entries 5 and 6). Furthermore, treatment of **3** with only *tert*-butyl hydroperoxide in benzene at 60 °C resulted in the formation of the *tert*-butylperoxy derivative **7** in good yield (78%) as the exclusive product (Scheme 2 and Table 1, entry 8).

The *tert*-butylperoxy compound **7** could be a potential intermediate in the pathway leading to the ketone **8**. Thus, the *tert*-butylperoxy compound **7** was further reacted with *tert*-butyl hydroperoxide and PDC,¹⁷ CuBr, and CuCl^{15,16} in order to produce 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**); however, none of the desired product was formed, and the *tert*-butylperoxy compound **7** was recovered in all cases (Scheme 2 and Table 1, entries 9–11).

The stereochemistry at C13 of the *tert*-butylperoxy compound **7** was determined through NOE studies as described above for bromo compound **4**. Since the same results were obtained, the stereochemistry of the 13-*tert*-butylperoxy group was assigned as 13 β .

(11) The structure of diene **6** was confirmed by HMQC and HMBC NMR experiments. The protons at C13 and C14 resonate as doublets at 5.00 and 5.60 ppm, respectively ($J_{\text{H13,H14}} = 9.1$ Hz). In an HMQC experiment, H13 and H14 have correlations with carbon signals at 132.6 and 133.0 ppm, respectively. Therefore, we assigned the signal at 132.6 ppm to C13 and the 133.0 ppm signal to C14. In an HMBC experiment, we found that the proton at C13 showed three bond couplings to the carbons at C12 and C14 and a long-range coupling to C18. The proton at C14 showed three bond couplings to the carbons at C1 and C18. The diene **6** was subjected to epoxidation and dihydroxylation reagents such as *m*CPBA, oxone, OsO₄, and VO(acac)₃. However, starting material was recovered in all cases.

(12) Nicolaou and co-workers reported that compound **3** can also be converted to ketone **8** by oxidation using excess of pyridiniumchlorochromate (30 equiv) in refluxing benzene (75% yield). See also refs 10 and 11.

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To effect the reductive cleavage of the oxygen–oxygen bond in *tert*-butylperoxy compound **7** to form 13-*epi*-baccatin III **9**, a variety of hydride delivering reagents were used, including LiAlH_4 , NaBH_4 , LiBH_4 , and 1-Selectride. However, none of these reagents provided the desired product. The results of these reactions included multiple ester cleavage products or recovery of the starting taxane diterpene. Dimethyl sulfide, triphenylphosphine, and trimethoxyphosphine were also unsuccessfully employed in the attempted reductive cleavage of the oxygen–oxygen bond of peroxide **7**.¹⁸ Therefore, we turned our attention to SmI_2 ,¹⁹ as a reducing reagent, which cleanly reacted with **7** to generate the desired product, 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**) in excellent yield (86%, Scheme 2). The coupling constants between H13 and both H14 α and H14 β of 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**) show 9.7 and 3.5 Hz, respectively, which are similar to those reported before for 13-*epi*-paclitaxel.²⁰

In 1995, the syntheses of 13-*epi*-paclitaxel and 4-deacetyl-13-*epi*-baccatin III via removal of the 4-acetyl group of a 13-ketobaccatin III derivative were published.²⁰ The free 4-hydroxy group assisted in the transannular delivery of a hydride [$\text{Me}_4\text{NBH}(\text{OAc})_3$] to the 13-ketone moiety yielding the corresponding 4-deacetyl-13-*epi*-baccatin III. The new two-step preparation of 13-*epi*-baccatin III from 13-deoxy-7-*O*-(triethylsilyl)baccatin III by *tert*-butyl hydroperoxide oxidation followed by SmI_2 reduction avoids the deacetylation and reacetylation at C4.

Mitsunobu conditions were then utilized in an attempt to invert the C13 stereochemistry of 13-*epi*-baccatin III **9**; however, starting material was recovered in all cases investigated.²¹ These results are in agreement with the observation that the cup-shaped conformation of the taxane diterpene ring disfavors reactions at C13 from the concave side of the molecule.^{10,11}

13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**) was treated with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) to obtain 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) in 81% yield (Scheme 2). The structure of **8** was identical in all respects to the compound described in the literature.^{10,11} Compound **8** can be converted regio- and stereoselectively to 7-*O*-(triethylsilyl)baccatin III by reduction with NaBH_4 .^{10,11}

In conclusion, an efficient synthetic pathway has been developed to prepare 13-*epi*-baccatin III by oxidation of 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**) with *tert*-butyl peroxide, followed by reduction with SmI_2 . 13-*epi*-7-*O*-

(triethylsilyl)baccatin III (**9**) was oxidized to 13-oxo-7-*O*-(triethylsilyl)baccatin III (**8**) using TPAP/NMO conditions.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on a VG instrument ZAB double-focusing mass spectrometer. Column chromatography was carried out employing silica gel (EM-9385-9, 230–400 mesh). Analytical thin layer chromatography (TLC) was performed on a silica gel 60F₂₅₄ plate (EM-5717, Merck). SmI_2 was freshly prepared from samarium metal and 1,2-dichloroethane using the procedure described by Kagan.²² THF and CH_2Cl_2 were distilled before use, and anhydrous solvents were purchased commercially.

13-Deoxy-7-*O*-(triethylsilyl)baccatin III (3). To a solution of 13-deoxybaccatin III (**2**, 102 mg, 0.18 mmol) in DMF (3 mL) were added TESC (300 μL , 10 equiv) and 4-(dimethylamino)pyridine (catalytic amount). The reaction mixture was stirred at room temperature for 17 h and then poured into ice water (10 mL) and extracted with CH_2Cl_2 . The organic phase was washed with 10% HCl, saturated NaHCO_3 , and brine solution. The organic phase was dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (2:1 EtOAc/hexane) to give **3** (137 mg, 95%) as a white solid; mp 208–209 °C; R_f 0.74 (1:1 EtOAc/hexane); $[\alpha]_D^{25}$ –6.32 (c 0.590, CHCl_3). The structure of **3** was identical in all respects to the compound described in the literature.^{10,11}

13-Deoxy-13 β -*tert*-butylperoxy-7-*O*-(triethylsilyl)baccatin III (7). To a solution of 13-deoxy-7-*O*-(triethylsilyl)baccatin III (**3**, 80 mg, 0.12 mmol) in benzene (5 mL) in an ice–water bath was added *tert*-butyl hydroperoxide (400 μL , 70 wt % in water). The reaction mixture was heated at 60 °C for 7 h; the reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , and then the solvent was evaporated. The residue was purified by flash silica gel column chromatography (1:4 EtOAc/hexane) to give **7** (72 mg, 78%) as a white solid; mp 169–170 °C; R_f 0.54 (1:2 EtOAc/hexane); IR (KBr) ν 3500 (br), 2960, 2875, 1745, 1724, 1716, 1370, 1236, 1102 cm^{-1} ; ^1H NMR δ 8.13 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 6.49 (s, 1H), 5.65 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.47 (dd, J = 6.9, 10.0 Hz, 1H), 4.34 (A of AB, d, J = 8.4 Hz, 1H), 4.29 (dd, J = 3.0, 9.0 Hz, 1H), 4.18 (B of AB, d, J = 8.4 Hz, 1H), 3.60 (d, J = 6.8 Hz, 1H), 2.63 (dd, J = 9.6, 16.0 Hz, 1H), 2.55 (m, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 2.16 (dd, J = 2.5, 16.0 Hz, 1H), 1.89 (m, 1H), 1.69 (s, 3H), 1.28 (s, 9H), 1.25 (s, 3H), 1.19 (s, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.59 (dq, J = 2.2, 7.9 Hz, 6H); ^{13}C NMR δ 202.0, 170.6, 169.9, 167.2, 140.5, 138.2, 134.0, 130.5, 129.7, 129.0, 84.3, 83.6, 81.7, 81.0, 80.5, 76.7, 76.4, 73.4, 72.8, 59.5, 47.3, 42.6, 37.8, 33.9, 32.0, 27.1, 22.5, 21.4, 19.4, 10.1, 7.2, 5.7. HRMS (FAB) m/z calcd for $\text{C}_{41}\text{H}_{64}\text{O}_{12}\text{Si}$ [M + NH_4]⁺ 790.4198, found 790.4215; $[\alpha]_D^{25}$ –3.64 (c 0.560, CHCl_3).

13-Oxo-7-*O*-(triethylsilyl)baccatin III (8). To a solution of 13-*epi*-7-*O*-(triethylsilyl)baccatin III (**9**, 1 mg, 0.0014 mmol) in CH_2Cl_2 (0.3 mL) were added TPAP (catalytic amount) and NMO (2 mg). The reaction mixture was stirred at room temperature for 2 h. The solution was purified by filtration over silica gel (1:3 EtOAc/hexane) to give **8** (0.8 mg, 81%) as a white solid; R_f 0.36 (1:1 EtOAc/hexane). The structure of **8** was identical in all respects to the compound described in the literature.^{10,11}

13-*epi*-7-*O*-(triethylsilyl)baccatin III (9). To a solution of **7** (20 mg, 0.026 mmol) in dry THF (2 mL) under argon was added SmI_2 (0.1 M solution in THF) until the color of the reaction

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(21) Treatment of **9** with diethyl azodicarboxylate (DEAD), trimethoxyphosphine, and chloroacetic acid for *p*-nitrobenzoic acid in toluene at 90 °C resulted in the formation of elimination product **6** instead of providing baccatin III **10** (Scheme 2). Other conditions for the Mitsunobu reaction of **9** were investigated (a) triphenylphosphine, *p*-nitrobenzoic acid, DEAD, at room temperature in THF; (b) triphenylphosphine, *p*-nitrobenzoic acid, DEAD, at 90 °C in toluene; (c) trimethylphosphine, *p*-nitrobenzoic acid, DEAD, at room temperature in THF.

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2020
Bogotá, D.C.,

Doctor:
Humberto Rubio Camacho
Apoderado

Oficio N°:
4341

ASUNTO:

Radicación PCT N°	06-108806
Trámite	011
Evento	379
Actuación	440
Folios	087

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

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