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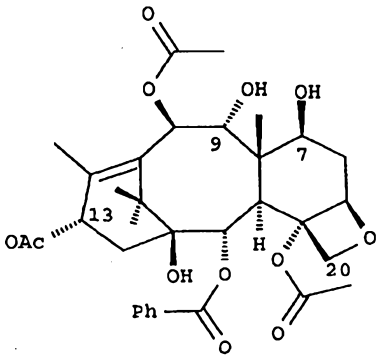

(X)

(57) Abstract

This invention provides a process for the preparation of Baccatin III from a compound of formula (X) which comprises the steps of: (i) protecting the hydroxy group on a compound of Formula (X) at the 7-position or C9, or both C7 and C9 sequentially; (ii) oxidizing the resulting group at the C9 position; (iii) either: (a) sequentially deacylating the esters at positions C13 and C7 or, (b) simultaneously deacylating the esters at positions C13 and C7.

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THE SEMI-SYNTHESIS OF BACCATIN III

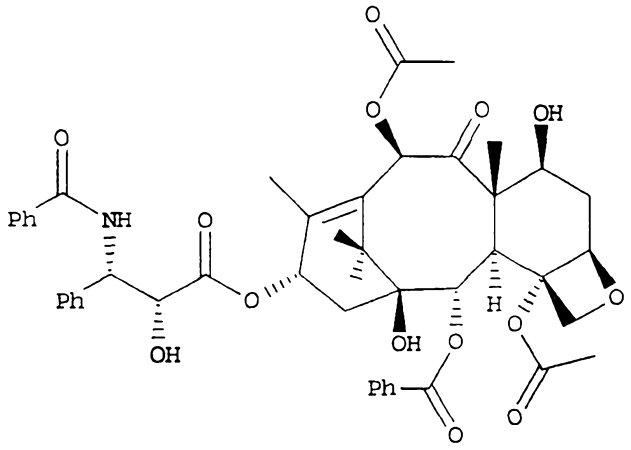
FIELD OF THE INVENTION

The present invention relates to a semi-synthetic process to convert a naturally occurring taxane into a suitable starting material for the synthesis of paclitaxel and related compounds. Specifically, the present invention relates to a process for the conversion of 9-dihydro-13-acetylbaccatin III into baccatin III which can then be used as starting material for the synthesis of taxane derivatives such as paclitaxel, docetaxel, cephalomannine and other taxanes structurally related to baccatin III. The method as described uses a preparative scale technique which is amenable to commercial scale-up.

BACKGROUND OF THE INVENTION

The taxane family of terpenes is considered to be an exceptionally promising group of cancer chemotherapeutic agents. Many taxane derivatives, including paclitaxel, docetaxel, taxcultine canadensol are highly cytotoxic and possess strong *in vivo* activities in a number of leukemic and other tumor systems. Paclitaxel, and a number of its derivatives, have been shown to be effective against advanced breast and ovarian cancers in clinical trials (W.P. MacGuire et al., *Annals of Internal Medicine,* vol 111, pg. 273, 1989). They have also exhibited promising activity against a number of other tumor types in preliminary investigations. Paclitaxel has recently been approved in the U.S. and Canada for the treatment of ovarian cancers (Rose *et al.*, in "The Alkaloids", A. Brossi, Ed., Academic Press, New York, Paclitaxel: A Review of its preclinical *in vivo* Antitumor Activity. Anti-Cancer Drugs **3**, 311-321 1992; and Suffness, M., Paclitaxel: from discovery to therapeutic use. Ann. Rep. In Med. Chem., **28**, 305-314, 1993). Taxanes are believed to exert their antiproliferative effect by inducing tubulin polymerization, which forms extremely stable and nonfunctional microtubules (Schiff, *et al.*, Promotion of Microtubule Assembly *in vitro* by Paclitaxel. Nature, 277, 665-667, 1979). However, a major problem with the clinical studies is the limited availability of paclitaxel and its derivatives.

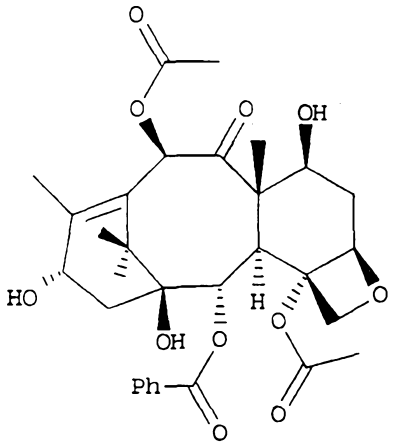
Taxanes are natural products which can be isolated from yew trees. The first taxane to be characterized was paclitaxel (also known as taxol™) which was isolated and purified from the bark of the Pacific yew in 1971. The only available natural source of paclitaxel to date are several species of a slow growing yew (genus *Taxus*), wherein paclitaxel is found in very low concentrations (less than 400 parts per million) in these trees. Furthermore the extraction is difficult, the process is expensive and the yield of paclitaxel is low (Huang *et al*, J. Nat. Prod. 49 665, 1986, reported a yield of 0.00025% of a crude paclitaxel fraction from *Taxus brevifolia* bark).



Paclitaxel

Paclitaxel can be isolated from the bark of *Taxus brevifolia*, the pacific yew tree, or from *Taxus baccata*, its European relative. Since removal of the bark destroys the trees and endangers the species, isolation of taxanes from the stems and needles of various *Taxus* species offers hope that the supply of taxanes, in particular paclitaxel, would become more abundant.

The preparation of paclitaxel derivatives, some of which have been reported to demonstrate enhanced chemotherapeutic activity, ultimately depends upon the supply of the parent compound - baccatin III. The structure of baccatin III has the basic diterpenoid structure of paclitaxel without the side chain at the C-13 position.



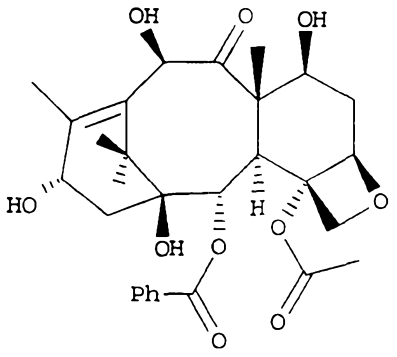
Baccatin III

Baccatin III is an important starting material in paclitaxel semi-synthesis. Therefore the significance of baccatin III will likely increase as more clinical studies are performed using paclitaxel. One such reason is that it appears that water soluble paclitaxel-like compounds with slightly modified C-13 side chains may be more desirable as cancer chemotherapeutic agents than the naturally occurring less water soluble paclitaxel. This increases the urgent need for baccatin III as a starting material to synthesize both paclitaxel and second or third generation paclitaxel-like compounds. There is, therefore, a need for an improved method of isolating and/or synthesizing Baccatin III.

The majority of research to date has been concerned with the development of techniques to increase the availability of either paclitaxel or baccatin III. These techniques have included improvements to the isolation and purification processes (U.S. Patent 5,407,674 and U.S. Patent 5,380,916), to the total synthesis (U.S. Patent No. 5,405,972) and partial synthesis (from more abundant paclitaxel precursors) and also isolation from a variety of cell culture systems (U.S. Pat No.5,019,504). In Addition, an endophytic fungi isolated form bald cypress (*Taxodium distichum*) was reported to produce very small amounts of paclitaxel (Strobel, R. *et al.*, Microbiology, **142**, 2223-2226, 1996)

Because of the structural complexity of paclitaxel, partial synthesis is a far more viable approach to providing adequate supplies of paclitaxel and paclitaxel precursors than total

synthesis. The first successful semi-synthesis of paclitaxel was developed by Denis *et al*, (U.S. Pat No. 4,924,011 re-issued as 34,277), using the starting material 10-deacetylbaccatin III which can be extracted in relatively high yield from the needles of specific species.



10-deacetylbaccatin III

In fact, most of the research to date regarding the semi-synthesis of paclitaxel has involved 10-deacetylbaccatin III. The conversion of 10-deacetylbaccatin III into paclitaxel is typically achieved by protecting the hydroxy at C-7, attachment of an acetyl group at the C-10 position, attachment of a C-13 β-amido ester side chain at the C-13 position through esterification of the C-13 alcohol with the β-lactam moiety, and deprotecting C-7. Since the supply of 10-deacetylbaccatin III is limited, other sources should be pursued.

Research has recently centred on semi-synthesis of paclitaxel from 10-deacetylbaccatin III because it is the major metabolite obtained from specific species of the European Yew *(Taxus baccata)*. However to date, the yields of 10-deacetylbaccatin III have been unsatisfactory, ranging from 50-165 mg taxane per kilogram of starting material (*i.e.* providing yields of between 0.005 to 0.017%). Hence there is an urgent need for novel semi-synthetic techniques to produce higher yields of paclitaxel precursors, such as baccatin III, for subsequent use in the production of paclitaxel derivatives. The present invention provides such a method, describing the conversion of a known taxane (9-dihydro-13-acetylbaccatin III), which is produced as a major metabolite in a certain species of taxus, into a paclitaxel precursor which produces relatively large amounts of a 7-protected baccatin III. Depending on the collection sites, the yield of 9-dihydro-13-acetylbaccatin III can vary from 2.0 to 2.5g per kilogram of dry plant and this taxane can be chemically transformed, by the present invention, into 7-

protected baccatin III in 20% yield.

SUMMARY OF THE INVENTION

The present invention is directed towards a new method of producing baccatin III, from a naturally occuring taxane (9-dihydro-13-acetylbaccatin III) which is produced in high yields in *Taxus canadensis*. The baccatin III can be used as a starting material for the synthesis of paclitaxel and paclitaxel derivatives.

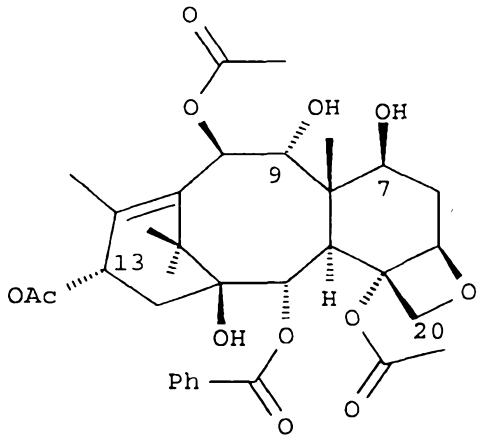
Accordingly, it is an object of this invention to provide a reproducible method for the semi-synthesis of baccatin III from the naturally occurring compound, 9-dihydro-13-acetylbaccatin III, isolated from plant matter derived from the *Taxus* genus of plants.

It is a further object of this invention to provide a method for the semi-synthesis of baccatin III, and other protected intermediates, that proceeds with higher yields than currently known methods.

Still a further object is to provide a simple, inexpensive method of preparing baccatin III that proceeds at room temperature.

It is also an object of this invention to provide a method for the semi-synthesis of baccatin III, from plant matter that is on a preparative scale which is amenable to commercial scale-up processes.

The present invention provides a process for the preparation of Baccatin III from a compound of formula (X)



X

which comprises the steps of:

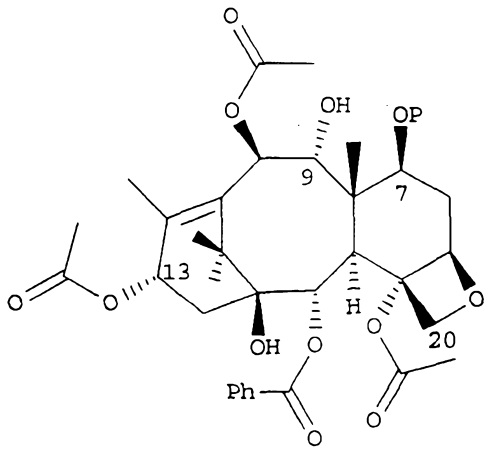
(i) protecting the hydroxy group on a compound of Formula X at the 7-position or C9 , or both C7 and C9 sequentially;

(ii) oxidizing the resulting group at the C9 position;

(iii) either: (a) sequentially deacylating the esters at positions C13 and C7 or,

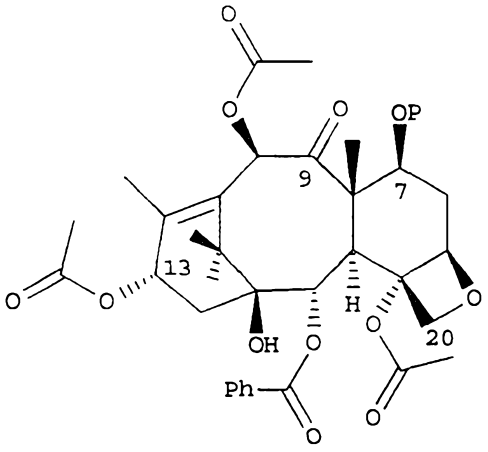
(b) simultaneously deacylating the esters at position C13 and C7.

The present invention provides a process for the preparation of a 7-protected-9-dihydro-13-acetylbaccatin of formula I.

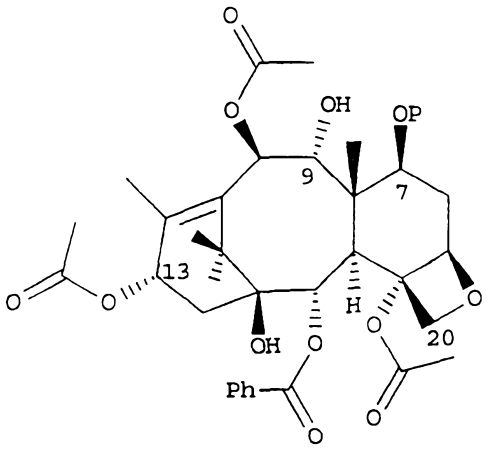


wherein P is a hydroxy protecting group, which comprises the step of reacting 9-dihydro-13-acetylbaccatin III with a hydroxy protecting group to form a compound of formula I.

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



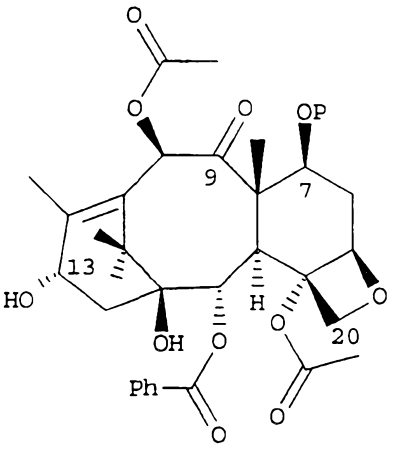
II



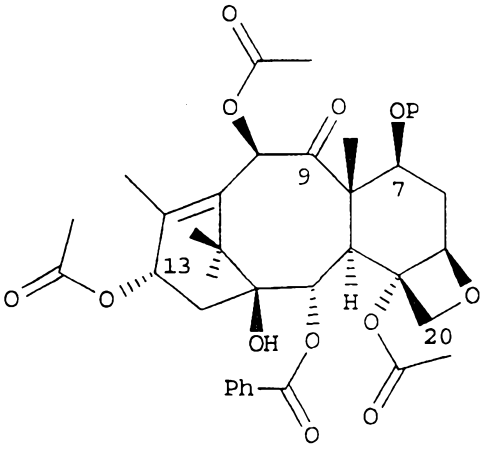
I

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

The present invention further provides aprocess for the preparation of a compound of formula III from a compound of formula II



III



II

wherein P is a hydroxy protecting group, which comprises converting a 13-acetyl group to 13-hydroxyl group of a compound of compound of formula II.

In a preferred embodiment 7-protected-9-dihydro-13-acetylbaccatin is formed by reacting 9-dihydro-13-acetylbaccatin III with a silylhalide, benzylhalide or alkylhalide, the halide is selected from Cl, Br, or I. Preferred protecting reagents are *t*-butyldiphenylsilylchloride, *t*-butyldimethylsilylchloride, triethylsilylchloride or triisopropylsilylchloride.

In a preferred embodiment the oxidation is facilitated by Jones' reagent, pyridinium dichromate, a Swern oxidation, a permanganate ion or Sarret's reagent.

In a preferred embodiment deacylation is facilitated by reaction with an alkylalkalimetal or arylalkalimetal reagent. Most preferred regent for deacylation is *n*-butyllithium.

These and other objects, as well as the nature, scope and utilization of this invention, will become readily apparent to those skilled in the art from the following description, the drawings and the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

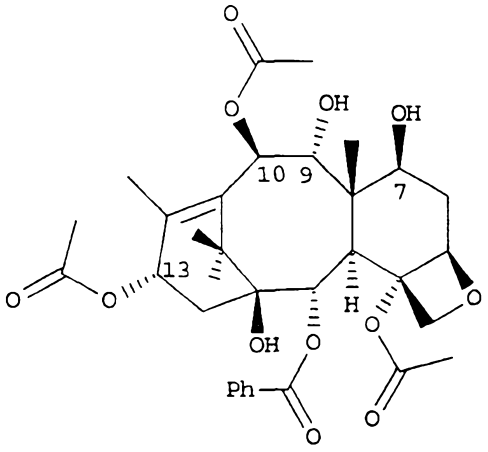
The present invention is disclosed in connection with the appended drawings, in which: figure 1 shows NMR spectra of an example of Compound 2, 9-dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III; figure 2 shows NMR spectra of an example of Compound 3,

13-acetyl-7-t-butyldiphenyl-silyl-baccatin III; and figure 3, shows NMR spectra of an example of Compound 4, 7-tert-butyldiphenylsilylbaccatin III.

DETAILED DESCRIPTION OF INVENTION

The present invention relates to a high yield process for converting 9-dihydro-13-acetylbaccatin III (an abundant taxane found in *T. canadensis* needles), into a 7-protected baccatin III, and baccatin III itself, which can subsequently be used as starting material for the synthesis of paclitaxel and related compounds.

The starting material for use in this invention is vegetal material, selected from a group of plants commonly referred to as taxads. The most suitable plants of this group are the species Taxus. Amongst the Taxus species, *Taxus canadensis* is a preferred source for use in the semi-synthetic method claimed in the present invention and differs from other yews both in its physical appearance (it is a small ramping evergreen bush), and in the composition of some of its taxanes. Paclitaxel, cephalomannine and 10-deacetylbaccatin III can be isolated from *Taxus canadensis* which are also found in most if not all other yews. *Taxus canadensis* is, however, the only yew presently known which accumulates a significant quantity of 9-dihydro-13-acetyl baccatin III in its needles, wherein it is found in concentrations 3 - 7 times greater than paclitaxel (Zamir L. O. *et al.* Tetrahedron Letters 33 5173, 1992).



9-dihydro-13-acetylbaccatin III

The methods disclosed herein are equally effective when using the roots or bark of the Taxus bushes but the preferred source is the needles which are in abundant supply and one of the most renewable parts of the plant.

A number of different methods have described the isolation and purification of 9-dihydro-13-acetylbaccatin III (Gunawardana G. P. *et al.*, J. Nat. Prod. **55**, 1686, 1992 and Zamir *et al.* Can. J. Chem. **73**, 655, 1995). One particular advantage of using 9-dihydro-13-acetylbaccatin III as starting material is that it can be isolated by simple recrystallisations instead of the numerous silica gel column and HPLC techniques commonly used. Hence 9-dihydro-13-acetylbaccatin III can be obtained in relatively high yield, rendering it an ideal starting material for many semi-synthetic pathways.

SCHEME I

The conversion of 9-dihydro-13-acetylbaccatin III into baccatin III involves the oxidation of the hydroxyl group at C-9 into a carbonyl group and deacetylation at C-13. The key step: the oxidation at C-9 was the main hurdle.

One major difficulty that had to be overcome was how to achieve these synthetic conversions while maintaining the integrity of the other hydroxyl groups in baccatin III, particularly the hydroxyl group at C-7. For example, direct oxidation of the hydroxyl group at C-9 on 9-dihydro-13-acetylbaccatin III into a carbonyl group using the Jones' reagent (chromium trioxide and sulphuric acid) resulted in the oxidation of both C-7 and C-9 positions. In another instance, the use of pyridinium dichromate, a milder oxidizing agent than the Jones' reagent, also resulted in oxidation of the C-7 hydroxyl group with opening of the oxetane ring.

A number of different protecting groups were investigated, to prevent unwanted oxidative reactions, some of the more successful attempts included the use of certain silyl chlorides. The present invention has largely overcome this problem with the method described by the steps illustrated in Scheme I which can be summarised as follows:

Step A:

Compound 1, 9-dihydro-13-acetylbaccatin III, is reacted with a suitable protecting group. It is necessary to protect the hydroxyl group at position 7 of 9-dihydro-13-acetylbaccatin III, to prevent oxidation. This can be achieved through the use of silyl chlorides (eg. triethyl, tri-isopropyl, t-butyldimethyl or t-butyldiphenyl) or alkyl chlorides (eg. benzyl chloride,

methoxy-methyl chloride, allyl chloride or methoxy-ethyl chloride) or by the use of dihydrofuran. When t-butyldiphenyl silyl chloride is used, the above reaction yields Compound 2, 9-dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III, a 7-protected intermediate.

Step B:

Compound 2, the 7-protected intermediate, is then oxidized by the use of reagents such as Jones' reagent (chromium trioxide and sulphuric acid), pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), Swern oxidation ($C_2O_2Cl_2$/DMSO), potassium permanganate ($KMnO_4$) or Sarret's agent (CrO_3/pyridine). The above oxidation procedure generates Compound 3, which contains a carbonyl moiety at C-9.

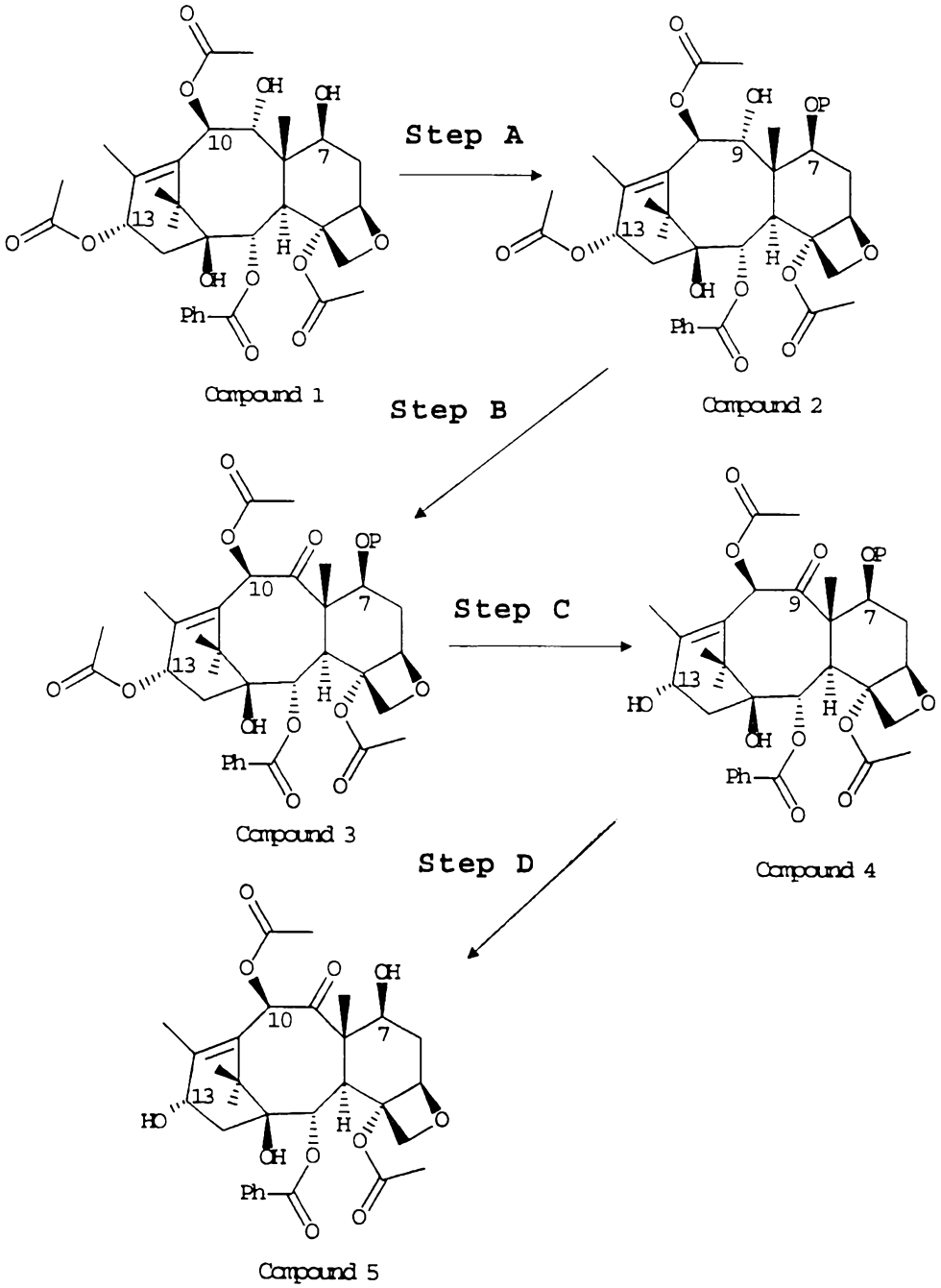
Step C:

The acetyl group at C-13 is then removed in the presence of THF and an alkyl lithium such as methyl lithium or butyl lithium to yield Compound 4, which is a 7-protected baccatin III

Step D:

Compound 4, the 7-protected baccatin III can then be used as starting material for the semi-synthesis of known and novel taxanes by derivatization at C-13. This can be achieved by the use of a range of side chains (Ojima, I. *et al.*, Tetrahedron, **48**, 6985-7012, 1992; and Ojima, I. *et al.*, Tetrahedron Letters, **34**, 4149-4152, 1992).

Scheme I


Step A
Step B
Step C
Step D
Compound 1
Compound 2
Compound 3
Compound 4
Compound 5

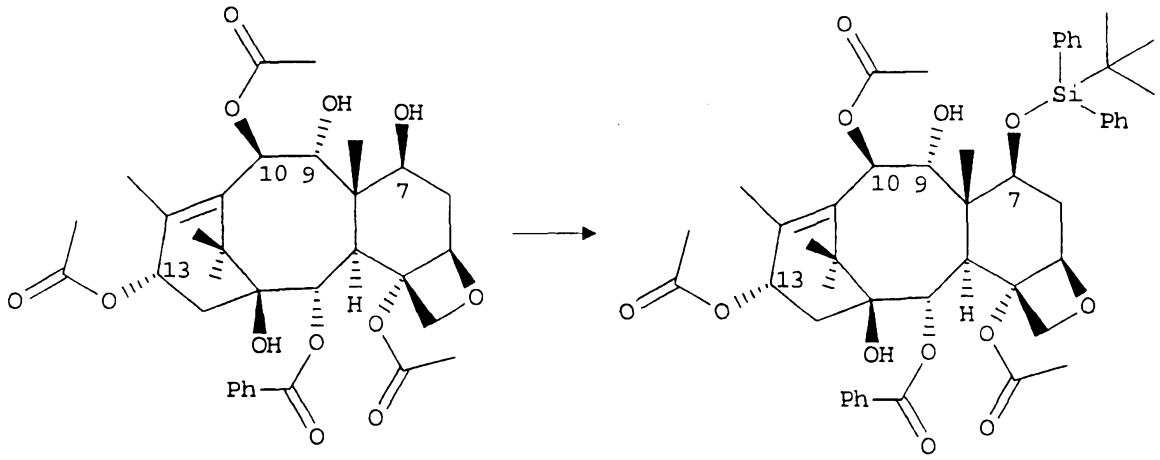
The success of the current invention is largely dependent upon an abundant supply of 9-dihydro-13-acetylbaccatin III which is one of the major metabolites produced by *T. canadensis*. Typically, 1.0 kg of dry needles will afford 1.0 to 2.5 g of pure 9-dihydro-13-acetylbaccatin III, making it one of the highest yielding taxanes from any taxus species known to date. The following examples therefore describe the chemical transformation of this baccatin III precursor into baccatin III derivatives which in turn can be transformed into paclitaxel and other biologically active taxanes. For a review of hydroxy protective groups the reader is directed to: T. W. Green and P.G. M. Wuts. Protective Groups In Organic Synthesis 2nd Ed.; J. Wiley and Sons, 1991, the disclosure of which is incorporated herein by reference.

Further, to assist in understanding the current invention, the following non-limiting examples are provided. The following examples should not be construed as specifically limiting the present invention, variations presently known or later developed, which would be in the understanding of one skilled in the art and considered to fall within the scope of the present invention as described herein.

EXAMPLE 1: Preparation of Compounds of Formula II

(a) Preparation of 9-Dihydro-13-Acetyl-7-t-Butyl-Diphenylsilyl-Baccatin III

In one procedure for making Compounds of Formula II, 9-dihydro-13-acetylbaccatin III, (63 mg; 0.1 mmol, 1 eq) was dissolved in 1 mL of dimethylformamide, to which imidazole (107 mg; 1.57 mmol; 15.7 eq) was added and the solution was stirred. t-Butyldiphenylsilylchloride (350 uL; 1.35 mmol) was added to this reaction mixture dropwise, with stirring. After being stirred for 18 hours, and the work up consisted of adding ethyl acetate, washing the organic layer with water and brine, dring over anhydrous sodium sulphate, and evaporation. The residue was subjected to silica gel chromatography with hexane and dichloromethane to obtain a 60% yield of Compound 2; 9-dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III.

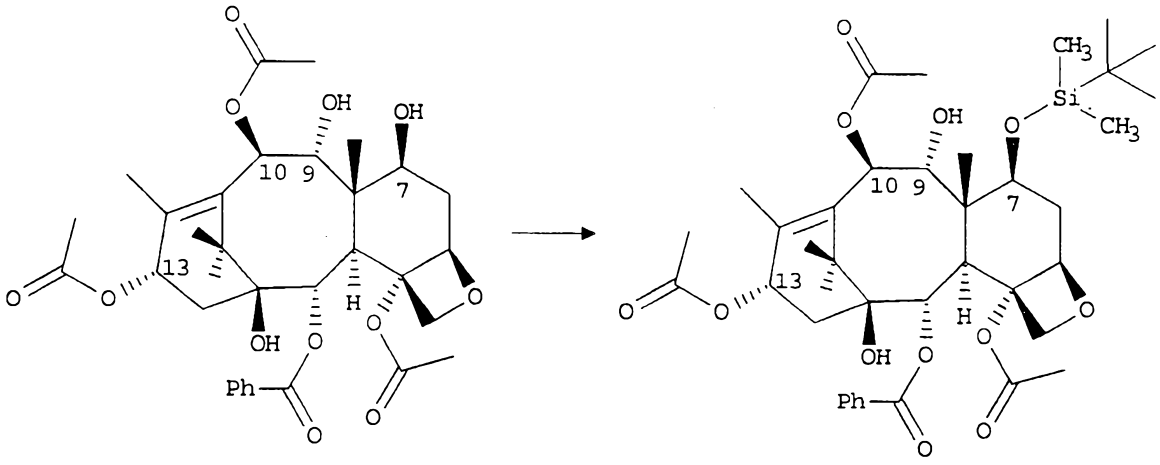


(1)
9-Dihydro-13-acetylbaccatin III

(2a)
9-Dihydro-13-Acetyl-7-t-Butyl-Diphenylsilyl-Baccatin III

(b) Preparation of 9-Dihydro-13-Acetyl-7-t-Butyl-Dimethylsilyl-Baccatin III

A solution of 9-dihydro-13-acetylbaccatin III (20 mg; 0.032 mmol), t-butyldimethyl-silylchloride (70 mg; 0.46 mmol) and imidazole (60 mg; 1.13 mmol) was stirred in anhydrous dimethylformamide (1.0 mL) at room temperature for 18 hours. Ethyl acetate (10 mL) was added, the solution was washed with water (3 x 2 mL) and dried over anhydrous magnesium sulphate. The residue was placed on a silica gel column and eluted with a gradient of ethyl acetate (33 to 50%) in hexane, affording 9-dihydro-13-acetyl-7-t-butyldimethylsilyl-baccatin III (Compound 2b) as a white solid (20 mg; 0.027 mmol; 85% yield; Rf = 0.66 eluting with ethyl acetate). The structure was determined by a ^{1}H-NMR at 500 MHz in $CDCl_3$.



(1)

9-Dihydro-13-acetylbaccatin III

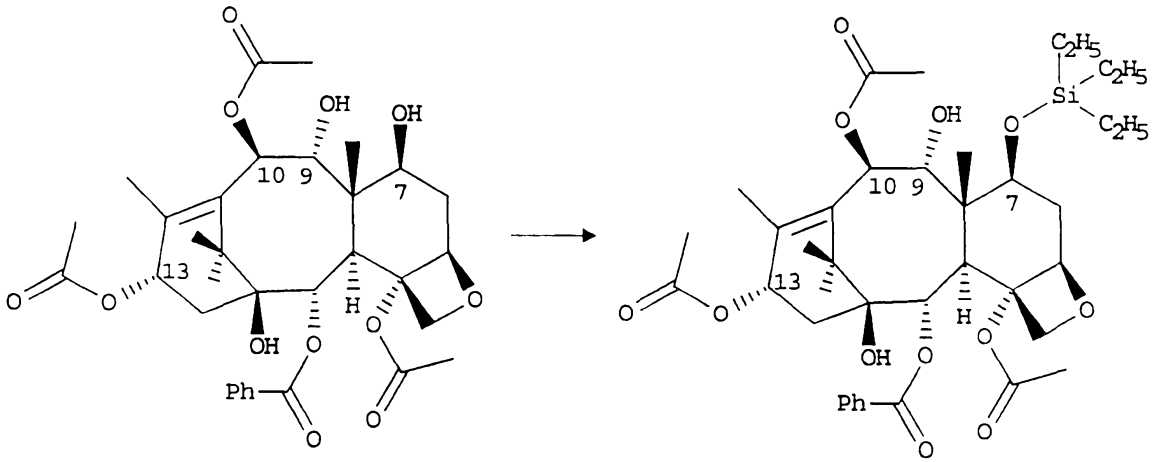
(2b)

9-Dihydro-13-Acetyl-7-t-Butyl-Dimethylsilyl-Baccatin III

(c) Preparation of 9-dihydro-13-acetyl-7-triethylsilyl-baccatin III

9-dihydro-13-acetyl-7-triethylsilyl-baccatin III was prepared in the same manner as the other silyl derivatives just using triethylsilylchloride as reagent.

A solution of 9-dihydro-13-acetylbaccatin III (20 mg; 0.032 mmol) triethylsilychloride (50 µL; 44.9 mg; 0.30 mmol) and imidazole (60mg; 1.13 mmol) was stirred in anhydrous dimethylformamide (1.0 mL) at room temperature for 18 hours. Ethyl acetate (10mL) was added, the solution was washed with water (3 X 2mL) and dried over anhdydrous magnesium suphast. The residue was placed on a silica gel column and eluted with a gradient of ethyl acetate (33 to 50%) in hexane, affording 9-dihydro-13-acetyl-7-triethylsily-baccatin III (Compound 2c) as a white solid (17mg; 0.023 mmol; 72% yield). The stucture was determined by ^{1}H-NMR at 500 MHz in $CDCl_3$.



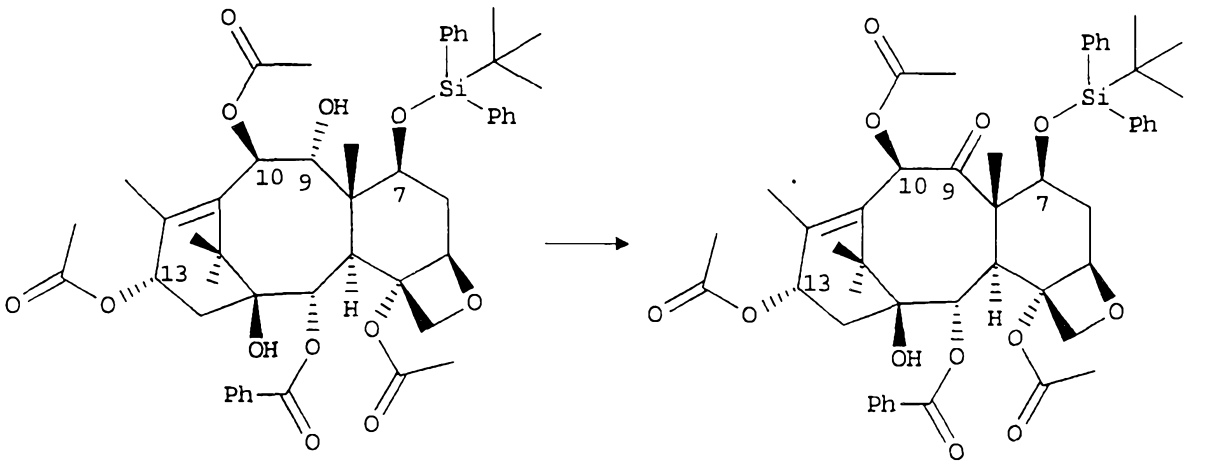
(1)
9-Dihydro-13-acetylbaccatin III

(2c)
9-Dihydro-13-Acetyl-7-triethylsilyl-Baccatin III

Example 2: Preparation of Compounds of Formula 3

(a) Preparation of 13-acetyl-7-t-butyldiphenylsilyl-baccatin III

One compound of Formula II, 9-dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III (6.0 mg) was dissolved in acetone (1.0 mL) and stirred at room temperature. To this was added 50 µL of Jones' reagent, prepared by adding 200 mg of chromium trioxide in a mixture of conc. H_2SO_4 and water (1 mL; 3:7 v/v), and stirred at room temperature for 30 mins. The resulting solution was worked-up by treating the reaction mixture with potassium bicarbonate and anhydrous magnesum sulphate. The crude material was then chromatographed on silica gel to obtain 5.0 mg of 13-acetyl-7-t-butyldiphenyl-silyl-baccatin III, depicted as Compound 3.



(2b)
9-Dihydro-13-Acetyl-7-t-Butyl-Diphenylsilyl-Baccatin III

(3)
13-acetyl-7-t-butyldiphenylsilyl-baccatin III

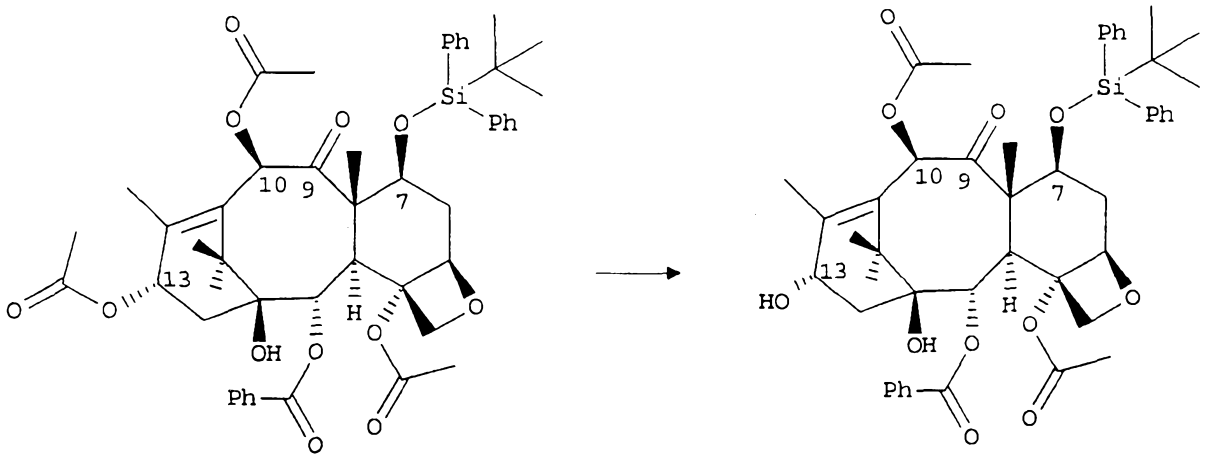
(b) *Preparation of 13-acetyl-7-t-butyldiphenylsilyl-baccatin III*

9-Dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III (0.095 g; 0.109 mmol) was dissolved in acetone (16 ml) and was stirred at 25°C. To this was added 0.79 ml of Jones' reagent, prepared by adding 200 mg of chromium trioxide in a mixture of concentrated sulfuric acid and water (1 ml; 3:7 v/v), and stirred at 25°C for 30 min. The reaction mixture was diluted in ethyl acetate and washed with a saturated solution of $NaHCO_3$ and with brine to neutrality. The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was flash chromatographed on silica gel with hexane:ethyl acetate (60:40) to obtain 0.073 g (77% yield) of the desired ketone.

Example 3: Preparation of Compounds of Formula 4

(a) Preparation of 7-tert-butyldiphenylsilylbaccatin III

One of the Compounds of Formula III, 13-acetyl-7-t-butyldiphenyl-silyl-baccatin III (5.0 mg) was dissolved in a polar donor solvent such as tetrahydrofuran (500 µL). After cooling the reaction mixture to -78°C, 50 µL of 1.4 M methyl lithium in ether was added and the solution stirred for 1.5 hours. The reaction mixture was then quenched with aqueous sodium acetate and worked-up with ethyl acetate. The crude reaction mixture was subjected to HPLC and three compounds were isolated. The desired product, 7-tert-butyldiphenylsilylbaccatin III, depicted as Compound 4, was purified using preparative HPLC (RP-18 column) gradient (100 min; 25% MeCN to 100% MeCN) with a retention time of 81 min.



(3)

13-acetyl-7-t-butyldiphenylsilyl-baccatin III

(4)

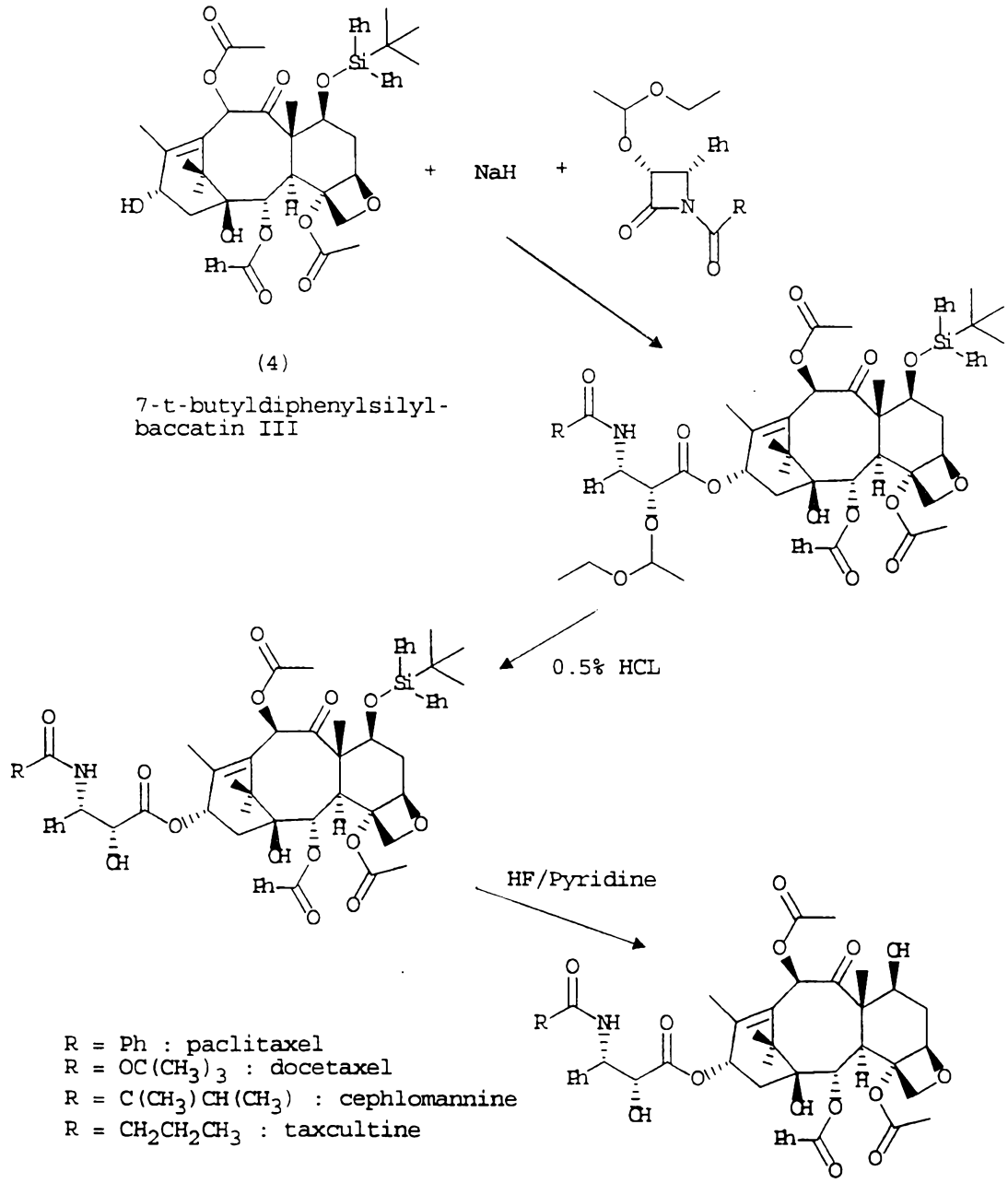
7-t-butyldiphenylsilyl-baccatin III

(b) *Preparation of 7-t-butyldiphenylsilyl-baccatin III*

13-Acetyl-7-t-butyldiphenylsilyl-baccatin III (0.080 g; 0.092 mmol) was dissolved in tetrahydrofuran (18 ml) and cooled to -44°C. To this was added a 2.5 M solution of n-BuLi in hexanes (0.115 ml; 0.288 mmol), and stirred for 1 h at -44°C. n-BuLi (0.120 ml) was added again and the reaction was stirred for an additional 1.5 h. The reaction was then quenched with brine and extracted with ethyl acetate which was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was flash chromatographed on silica gel with hexane:ethyl acetate (gradient of 60:40 to 50:50) to obtain 0.022 g (46% yield based on recovered starting material).

Example 4: Conversion of a Compound of Formula 4 into a Taxane

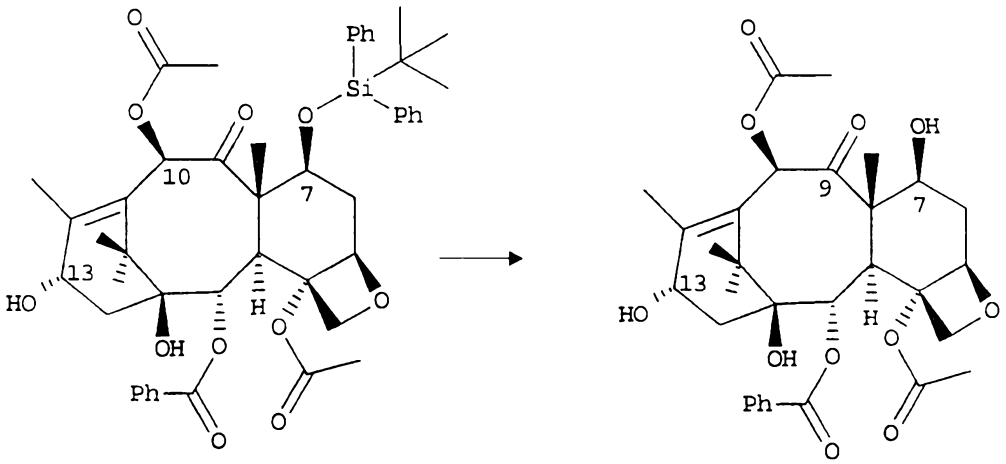
Conversion of the 7-protected baccatin III into paclitaxel, docetaxol or canadensol is conducted according to the references of Ojima *et al.*, (previously cited) and following the steps described below.



Example 5: Deprotection of a 7-hydroxy group

Preparation of Baccatin III

7-*t*-Butyldiphenylsilyl-baccatin III (0.010 g; 0.012 mmol) was dissolved in 1.5 ml 95% ethanol and was treated with concentrated HCl (0.040 ml; 0.3 M HCl in ethanol). After stirring at 25°C. for 24 h, the mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate which was dried ($MgSO_4$), filtered and evaporated *in vacuo*.



7-t-Butyldiphenylsily-baccatin III

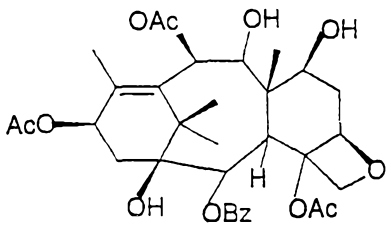
Baccatin III

Example 6: SCHEME II

Conversion of the major taxane from *Taxus canadensis* to baccatin III

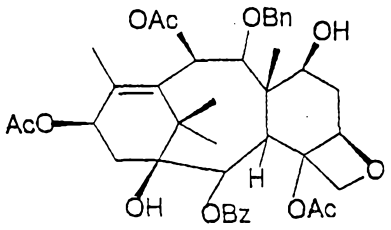
One skilled in the art will appreciate how to choose a suitable protecting group at position 7 that is not removed by the acidic conditions necessary for the oxidation step.

The first step consists of benzylating 13-Acetyl-9(R)-dihydrobaccatin III. This results in a major product (47% yield) of a benzyl adduct at position 9 (designated as compound 1) and two minor products. Compound 2 (10% yield) has the benzyl also at position 9 but the acetyl group at position C-10 has been removed while compound 3 (6% yield) has the benzyl attached at position C-7. Compound 4 (90% yield) is produced when compound 1 is acetylated to protect the C-7 position. The further removal of the benzyl group at the C-9 position, followed by the oxidation of compound 4 leads to compound 5. Butyl lithium is then used to remove the acetyl group at position C-13 resulting in compound 6 (36% yield). Finally, by treating this compound with CF_3COOH followed by $NaBH_4$, the 7-acetyl-baccatin III is converted to baccatin III (approximately 100% yield).



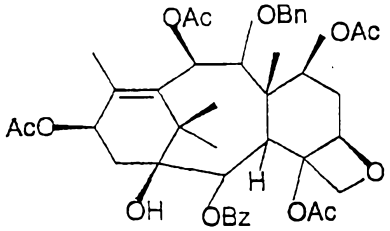
13-Acetyl-9(R)-Dihydrobaccatin III

Benzyl bromide/Ag_2O/DMF



compound 1

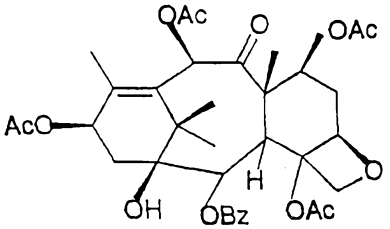
Ac_2O/pyr/4-DMAP



compound 4

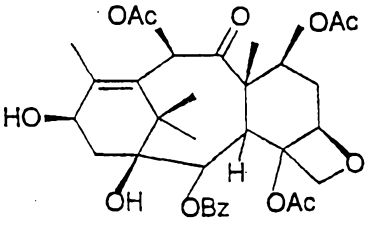
H_2/Pd/C

$CrO_3/H_2SO_4/H_2O$



compound 5

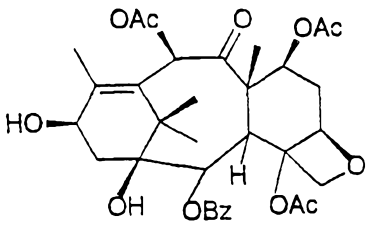
n-BuLi/THF/-44C



compound 6

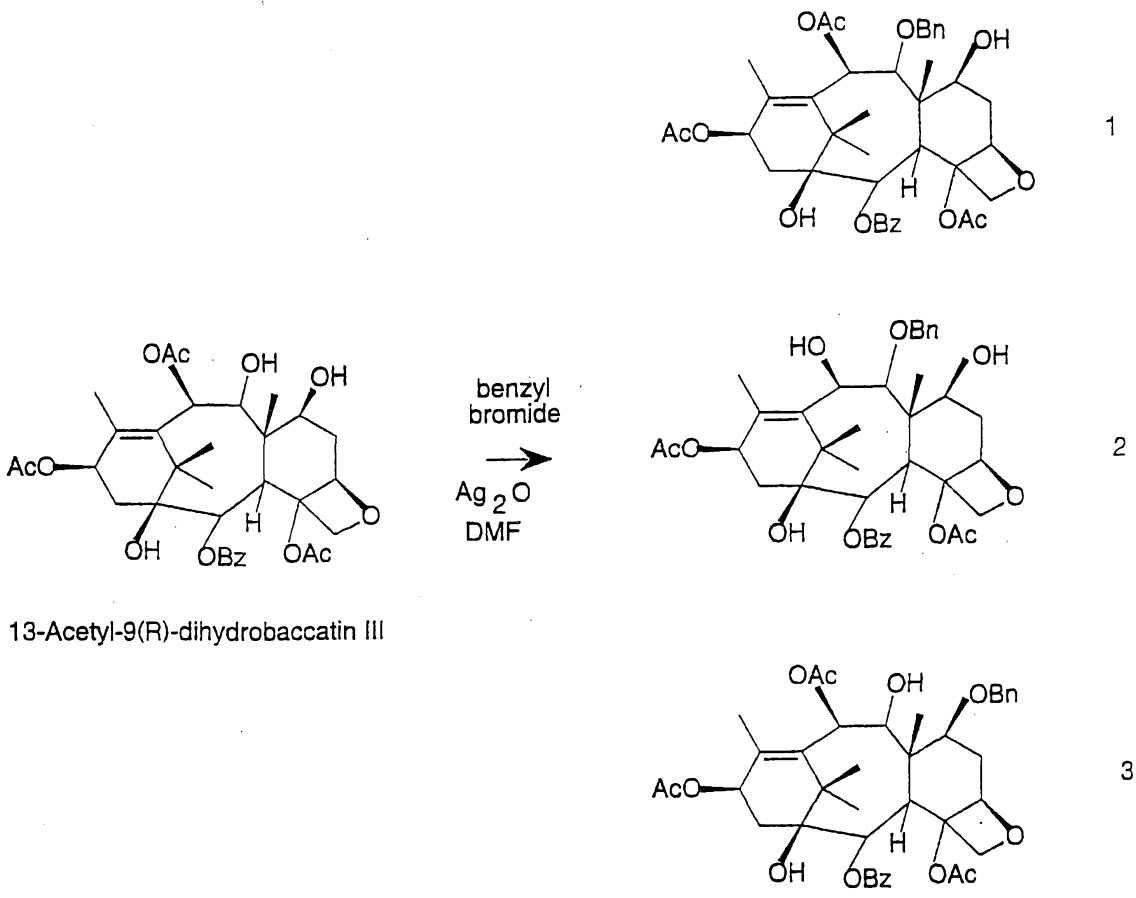
CF_3COOH

$NaBH_4$



baccatin III

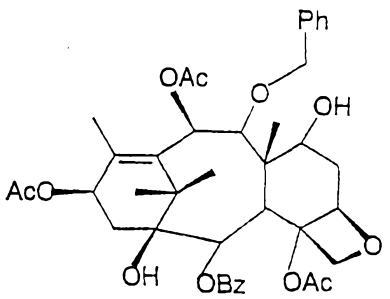
Scheme II



13-Acetyl-9(R)-dihydrobaccatin III

A solution of 13-acetyl-9 (R)-dihydrobaccatin III (0.150g; 0.238 mmol) in 9 ml DMF is treated with freshly prepared Ag_2O (0.083 g; 0.357 mmol). After the solution is cooled to O°C, a solution of benzyl bromide (0.030 ml; 0.252mmol) is added. This mixture is stirred for 18 hours at 25°C. The slurry is then filtered through a bed of dry silica gel, rinsing with ethyl acetate. The filtrate is washed with brine, dried over $MgSO_4$ and evaporated. The resulting residue is chromatographed through silica gel using a gradient of hexane:ethyl acetate (40:60 - 25:75). This results in compound1 (0.80 g; 47%), compound 2 (0.016 g; 10%) and compound 3 (0.011 g; 6%). HRMS: 1:M+Na^+ required $C_{40}H_{48}O_{12}Na$ = 743.30435; found: 743.30410; 2: M+H^+ required $C_{38}H_{47}O_{11}$ = 679.31184; found: 679.31182; 3: M+Na^+ required $C_{40}H_{48}O_{12}Na$ = 743.30435; found: 743.30422.

(AN-1614-14-17) Compound 1: Detailed NMR Characterization

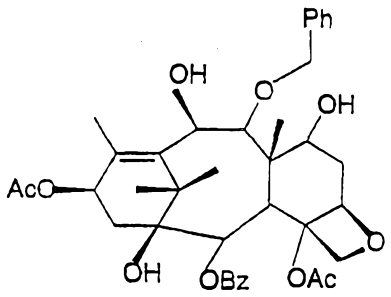


Compound 1

Position	δH - muκ	J(Hz)	δC	HMBC	NOESY
1 OH-1	- 1.736 (s)		78.51	 C1, C14	 H2, *Me16*
2	5.819 (d)	5.6	73.53	1314167.2	H3,H9, Me17/19, H20b
3	3.026 (d)	5.8	46.47	1, 2, 7, 8, 19, 20	H2,H7,H10,**H14,Me18**
4	-		81.82		
5	4.952 (d)	8.8	84.21		H6a, H7/20a, H9
6a 6b	2.612 (dt) 1.83 (o.m)	15.1, 8.5, 8.5	37.15	578	**H5, H6b, H7**
7 OH-7	4.32 (o.m) 5.225 (s)		72.18	 678	 **H7**, H10, **Me19**
8	-		46.82		
9	4.535 (d)	11	86.42	3/8, 7,10,19,78.8	
10	6.324 (d)	11	73.46	9111215169.26	H3, H7, Me18, OH7
11	-		133.6		
12	-		140.56		
13	6.160 (t)	8.8	69.55	111214170.5	H14, Me16
14	2.22 (o.m)		35.46	121315	
15	-		42.91		

16	1.267 (s)		28.18	1111517	**H13**, H14, **OH1**
17	1.789 (s)		22.66	1111516	
18	1.983 (s)		14.84	111213	H3,**H7**,**H10**,H13
19	1.778 (s)		12.88	3, 7, 9	
20a	4.324 (o.d)	8.3	76.34	345	
20b	4.134 (d)	8.3			H2, **Me19**?, **H20a**
O-CH_2	4.983 (d)	10.7	78.42	C9, 136.9, 126.9	
	4.848 (d)	10.8		C9, 136.9, 126.9	**H9**, **Me19**
Ph	7.42-7.28		136.86		
o	(m)		126.86		
m			128.67		
p			128.15		
OAc	2.266 (s)		22.83	169.03	
	2.190 (s)	Ac-13	21.21	170.45	
	1.957 (s)	Ac-10	21.07	169.26	
OBz			129.09	167.06	
o	8.101 (d)	7.1	130.08		
m	7.489 (t)	7.8	128.75		
p	7.622 (t)	7.3	133.81		

(AN-1593) Compound 2: Detailed NMR Characterization



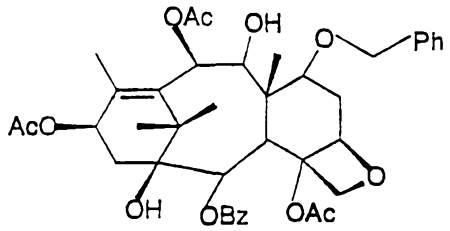
Compound 2

There is a CH_2-Ph group at position 9 or 7. HMBC will determine the position.

Position	δH - mux	J(Hz)	δC	HMBC	NOESY
1	-- 1.66 (s)		78.65		
2	5.814 (d)	5.9	73.65	1, 8. 14, 167.2	3, 9, 14, 20b, 17/19, OH1
3	3.034 (d)	5.4	46.63	1, 2, 7, 8, 19, 20	
4	-		81.91		
5	4.950 (o.d.)	7.8	84.24	3, 4, 7	
6a 6b	2.578 (ddd) 1.867 (dd)	8.5, 8.5, 15.7 10.0, 16.0	37.22	78	H5 (or Bnz), H7, H6b
7	4.234 (t)	8.5	72.33	3, 19	H3, H6b, H10, OH7
8			46.41		
9			88.93	7, 8, 10, 19, CH_2 (Bz)	H2, Me17/19, CH, Bnz
10 OH-10	5.080 (br.d) 2.328 (br.s)	10.2	70.85	9, 11, 12, 15	3, OH-10, Me18, 7, OH7 H10
11	-		136.54		
12	-		137.89		

13	6.200 (br.t)	8.6	69.79	11. 12. 14. 170.7	**H14, H16**. H18
14	2.22 (o.m)		35.34	1. 2. 12. 13	H3. H13. **o-Bz**
15	–		42.76		
16	1.340 (s)		28.48	C1. C11. C15. C17	13. 14 (2.207). 1.807 (18)
17	1.826 (s)		22.68		
18	1.807 (d)	0.7	14.92		
19	1.818 (s)		12.99		
20a 20b	4.318 (d) 4.150 (d)	8.0 8.1	76.47	C4. C3 C5. C3	**H5, H20b, Bz-o** **H2**. *H3*. **Me19, H20a**
O-CH_2	5.008 (d) 4.936 (o.d)	10.5 10.2	79.16	C9. 136.5. 127.9	**Hb, H9, Me(1.8),** Ph
Ph	7.41-7.34		136.5. 128.64. 127.90		
OAc-4 OAc-13	2.272 (s) 2.186 (s)		22.89 21.27	169.16 170.56	
OBz o m p	 8.101 (d) 7.488 (t) 7.619 (t)	 8.3 7.5 7.6	129.19 130.08 128.98 133.73	167.12	
OH-7	5.337 (s)			6. 7. 8	

(AN-1625-47-56) Compound 3

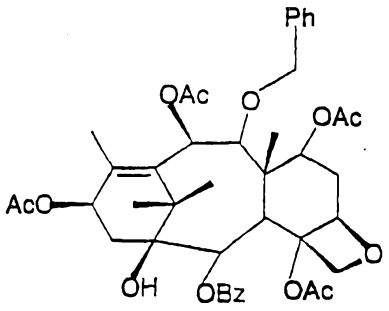


Compound 3

Position	δH - muκ	J(Hz)	δC	HMBC	NOESY
1			78.8		
2	5.741 (d)	5.9	73.32	C1, C3, C8, C14, C15, 167.0	**H9/20a**, H20b, **Me17**, **Me19**
3	3.069 (d)	5.9	47.77		H2, **H7**, H10, **H14, Me18**
4	–				
5	4.978 (d)	9	83.68		**H6a**, H6b, H20a
6a 6b	2.752 (ddd) 1.970 (dd)	14.6, 9.2, 7.0 14.2, 11.2	33.86		**H5, H6b, H7, CH_2-Ph-B** *H5*, **H6a**, Me19
7	4.222 (dd)	10.0, 7.1	82.04	C3, C8, 71.4, C19	**H3, H6a, H10, Me18, CH_2-Ph-A**
8	–		45.24		
9 OH-9	4.297 (o.t.) 5.152 (d)	 10.2	76.32	 C9, C8	H2, Me17, Me19 H9, H10, Me19, *Ph (7.41)*
10	6.205 (d)	11	72.46	C9, C11, C12, C15, 170.5	H3, **H7, Me18, OH9**, CH_2-Ph-A
11	–		135.72		
12	–		138.46		

13	6.156 (t)	8.5	68.77		H9/20a, **H14**, **Me16**, Me18
14	2.18 (o.m.)		35.22		
15	–		43.06		
16	1.251 (s)		28.3		**H13**, H14, **Me17**
17	1.700 (s)		22.5		**H2**, **H9**, **Me16**
18	1.829 (s)		14.79		*H3*, H7, **H10**
19	1.854 (s)		13.05		**H2**, **H9**, **H20b**, **OH9**
20a 20b	4.311 (o.d) 4.174 (d)	8.0 8.3	76.59		H2, **Me19**, **H20a**
O-CH_2	4.688 (d) 4.629 (d)	10.7 10.5	71.54	C7. 136.4. Ph-o	**Ph (7.41), H6a, H7, H10, Hb** Ph (7.41), **H6a**, **H7**, Ha
Ph o m p	7.41 (=d) 7.38 (=t) 7.33 (=t)		136.28 128.7 128.6 128.38		
OAc	2.282 (s) 2.190 (s) 2.145 (s)		22.86 21.37 21.26	169.4 170.5 170.5	
OBz o m p	 8.080 (d) 7.471 (t) 7.602 (t)	 7.3 7.6 7.6	167.0 130.05 128.5 133.66	162.00?? 	

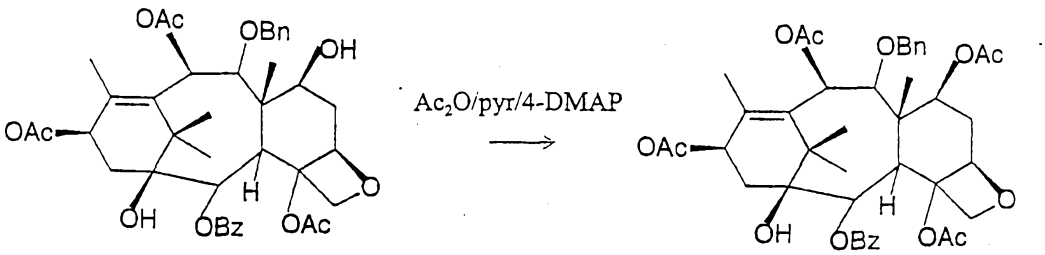
(AN-1628) Compound 4



Compound 4

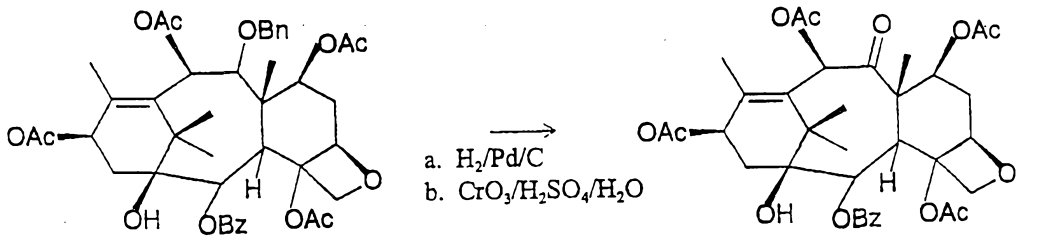
Position	δH - mux	J(Hz)	δC	HMBC	NOESY
1 OH-1	– 1.718 (s)		78.59		H2, H14, Me17, Me16
2	5.840 (d)	5.6	73.34	166.98	H3, H9, Me17, Me19, H20a, OH1
3	3.125 (d)	5.6	47.03		H2, H7, H10, H14, Me18
4	–		81.53		
5	4.975 (d)	8.8	83.98		H3, H6a, H6b, H20b
6a 6b	2.467 (dt) 1.890 (o.dd)	14.9, 8.5, 8.5, 9.6, 14.9	34.63		H5, H6b, H7
7	5.473 (t)	8.5	71.11	170.5	H3, H10, H6b
8	–		47.41		
9	4.298 (d)	11	83.58	77.6 (Bz)	H2, Me19, Me17, Bn-CH_2 (AB)
10	6.371 (d)	11	73.56	169.1	H3, H7, Me18
11	–		134.04		
12	–		140.23		
13	6.160 (t)	9.2	69.6	170.5	Me16
14	2.21 (o.m.)		35.5		H3, H13, Me16
15	–		42.9		

16	1.253 (s)		28.19		H13, H14, Me17
17	1.800 (s)		22.59		H2, H9, Me16
18	2.065 (s)		14.92		H3, H7, H10
19	1.870 (s)		13.32		H2, H9, H20b, Bn (4.65)
20a	4.338 (d)	8.3	76.44		H5, H20b, Bz-o
20b	4.171 (d)	8.3			H2, H20a, Me19
O-CH_2	4.914 (d)	10.2	77.77	C9	HB, H9, Me17
	4.660 (d)	10.2			HA, H9, Me19
Ph	7.36-7.26		138.24		
			128.31		
			127.72		
			127.46		
OAc	2.271		22.75	168.9	
	2.189		20.22	170.5	
	1.988		20.22	169.1	
	1.642		20.22	170.5	
OBz			167.07		
o	8.106 (d)	7.5	130.08		
m	7.492 (t)	7.5	128.67		
p	7.622 (t)	7.3	133.78		



1 4

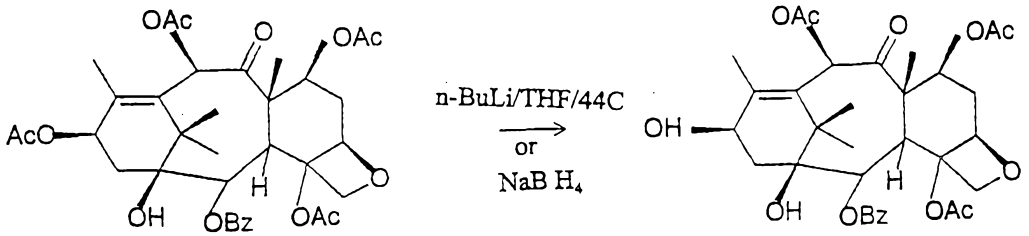
To a solution of 13-acetyl-9-O-benzyl-dihydrobaccatin III I (0.080 g; 0.111 mmol) in 4 ml pyridine were added 4-(dimethylamino)pyridine (0.007 g; 0.0573 mmol) and acetic anhydride (0.40ml; 4.24 mmol). The reaction mixture was stirred at 25°C for 18 h, diluted with ethyl acetate, washed with potassium phosphate buffer, pH 7.0, and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel using hexane:ethyl acetate (45:55) to give 4 (0.076 g; 90%). HRMS: $M+Na^+$ required $C_{42}H_{50}O_{13}Na$ = 785.31491; found: 785.31462



4 5

A mixture of 7,13-diacetyl-9-O-benzyl-dihydrobaccatin III 4 (0.071 g; 0.093 mmol) dissolved in 15ml methanol and 200mg of 10% palladium on activated carbon was bubbled with hydrogen at 25°C for 48 h. The suspension was filtered, evaporated and the residue was dissolved as such in 7.5 ml acetone. The solution was cooled to 0°C and treated with 200:1 of Jones reagent prepared by dissolving 0.2 g CrO_3 in 1 ml of a mixture of concentrated H_2SO_4:water (3:7). The reaction as monitored by TLC was instantaneous. The solution was diluted with ethyl acetate, washed with a saturated solution of $NaHCO_3$ and brine to neutrality, dried over $MgSO_4$ filtered and evaporated. The mixture was purified by preparative HPLC on one Mag 20 reverse phase column using a gradient of 25% acetonitrile in water to 100%

acetonitrile over70 min at 18 ml/min. This gave **5** (0.011 g; 19% overall yield based on recovered starting material **4** (0.006g)). HRMS: M+Na$^+$ required $C_{35}H_{42}O_{13}Na$ = 693.25231; found: 693.25261. Compounds **5** and **6** were also compared with a sample of baccatin III acetylated. The product of treatment of compound **6** with CF_3COOH and Na BH_4 was identical to standard baccatin III.



5 6

There are two possibilities of converting compound 5 to compound 6: either treatment with butyl lithium or reductive cleavage of C-13 with $NaBH_4$:

n-BuLi hydrolysis at C-13.

A solution of 7,13-diacetylbaccatin III **5** (0.025 g; 0.037 mmol) is dissolved in 2 ml THF and cooled to -44°C. This is then treated with a 2.5 M solution of n-butyl lithium in hexane (0.090 ml; 0.225 mmol). After a period of 30 minutes at -44°C, the reaction is quenched with a potassium phosphate buffer (pH 7.0). This solution is diluted with ethyl acetate, and washed with brine to reach neutrality. The resulting organic phase is dried over $MgSO_4$, filtered and evaporated. The residue is purified by preparative HPLC on one Mag 20 reverse phase column using a gradient of 25% acetonitrile in water to 100% acetonitrile over 70 min at 18ml/min. This gives compound 6 (0.007 g; 36% overall yield based on recovered starting material **5** (0.004 g)).

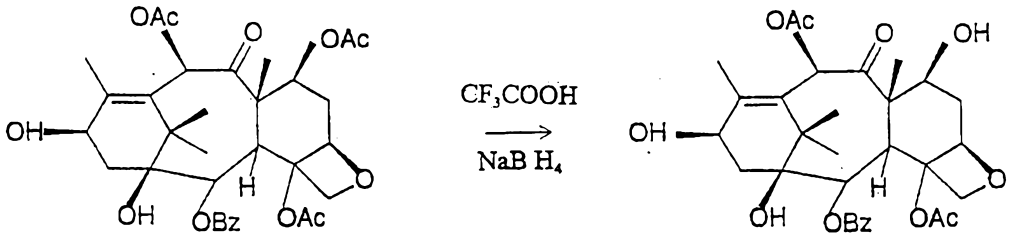
$NaBH_4$ reductive cleavage of C-13.

The compound 7,13-Diacetylbaccatin III **5** (0.020 g; 0.0298 mmol) is dissolved in 0.90 ml THF: potassium phosphate buffer, pH 7.0 (2:1) resulting in a slightly turbid solution. Upon

treatment with $NaBH_4$ (4.5 mg; 0.118 mmol) gas evolution is observed. This reaction is monitored by HPLC. Three more subsequent additions of $NaBH_4$ over a 24 h period gives a compound with the same retention time on the HPLC as compound 6. The reaction is quenched with acetone, diluted with ethyl acetate, and finally washed with brine. The resulting organic phase is dried over $MgSO_4$, filtered and evaporated.

Hydrolysis of 7-acetylbaccatin III 6.

The compound 7-Acetylbaccatin III 6 is dissolved in 0.60 ml THF. This is then treated with 0.60ml of 50% aqueous CF_3COOH, followed by a solution of $NaBH_4$ (4.5 mg; 0.118 mmol). Two more subsequent additions of the $NaBH_4$ over a 24 h period produced the completed conversion of 7 acetylbaccatin III to baccatin III, which is monitored by HPLC.



6 Baccatin III

Example 7: SCHEME III

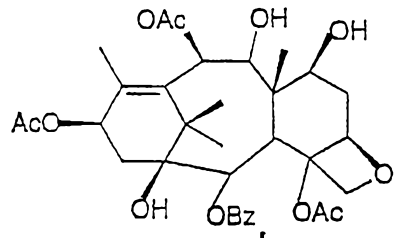
This method entails using a protecting group which will react only with the hydroxyl group at the C7 position and not at the C9 position. The C7 protecting group will be stable to acid conditions during the subsequent oxidation step, and can be easily removed.

13-acetyl-9 (R)-dihydrobaccatin III is acetylated at the C-7 position. A successful method for acetylating 13-acetyl-9 (R)-dihydrobaccatin II is achieved by adding this compound dropwise to the acetylating mixture. After approximately 4 hours reaction time, one can obtain 30% of an acetylated product and recover almost 70% of the starting material. The mixture is oxidized to generate two compounds: the major one corresponding to a rearranged diketone (which can be obtained from oxidation of the starting material) and another compound which is found to correspond to compound 5 (Scheme I) following high performance liquid chromatography.

The yield of the acetylated product can be improved by leaving the reaction mixture overnight at room temperature, after which two major compounds can be obtained. Preparative thin layer chromatography can be employed to separate the two compounds, which can improves the yield to approximately 60% monoacetylated product and 40% recovered starting material. The monoacetylated product can be analysed by NMR to demonstrate pure compound 1' (scheme II) with no trace of acetylated product at C-9, the stereochemistry at C-9 unchanged. This yield can also be optimized. One advantage to this procedure is that the only other product is the recovered starting material which can be recycled.

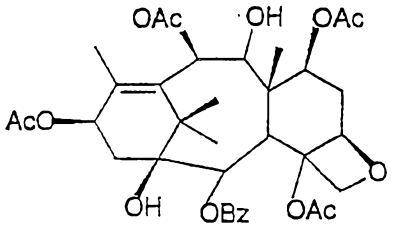
Oxidation of this compound quantitatively yields compound 2' (scheme II). Removal of C-13 and C-7 acetate are performed sequentially with $NaBH_4$ in buffer and CF_3 COOH, respectively. Both steps on are followed by thin layer chromotography and can be reacted to completion by adding more $NaBH_4$.

Therefore scheme III entails few steps and provides excellent yields in the conversion of 13-acetyl-9(R)-dihydrobaccatin III to baccatin III and therefore to paclitaxel and other bioactive taxanes.



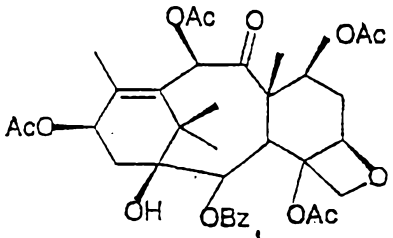
13-Acetyl-9(R)-Dihydrobaccatin III

Acetylation (overnight)



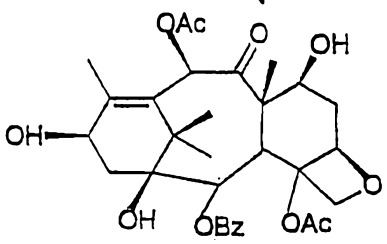
compound 1'

Oxidation



compound 2'

1. $NaBH_4$ in buffer (pH 7.0)
2. CF_3COOH / $NaBH_4$



baccatin III

Scheme III

Acetylation of 13-acetyl-9(R)-dihydrobaccatin III:

1.0 mL of pyridine and 13.35 μL (0.1425 mmoles) of acetic anhydride are added to a scintillation vial adapted with a magnetic stirrer and a rubber septum. A mixture containing 1.5 mL of pyridine and 30 mg (0.0475 mmoles) of 13-acetyl-9(R)-dihydrobaccatin III are added to this mixture, dropwise using a syringe over a period of half an hour. The reaction mixture is left to stir at room temperature for 4 hours. The reaction mixture is worked up by diluting it in 30 mL of ethyl acetate, washing the organic phase with 3 x 20 mL of brine, drying the organic layer over magnesium sulfate and then evaporation of organic phase. Thin layer chromatography of the residue shows some product formation (~30%) while ~70% is unreacted starting material. Since the reaction of 13-acetyl-9(R)-dihydrobaccatin III with Jones oxidation (a rearranged diketone) has been previously identified and the properties of the desired ketone are known (compound 5 of scheme II), the mixture can be taken as is for Jones oxidation.

Jones oxidation

In a scintillation vial adapted with a magnetic stirrer, the entire residue is dissolved in 4 mL of acetone. Jones reagent is prepared by mixing 300 μL of concentrated sulfuric acid and 700 μL of water, afterwhich 200 μL of Jones reagent is added and the reaction is left to stir for 15 minutes.

The reaction is instantaneous monitored by thin layer chromatography to reveal the formation of products. After 15 minutes, the reaction mixture is worked up by diluting it in 30 mL of ethyl acetate, which is then washed to neutrality with saturated sodium bicarbonate, then brine, then dried over magnesium sulfate and evaporated. The residue is purified by preparative thin layer chromatography in 65% ethylacetate in hexane. Two major bands are isolated. The compounds in the two major bands are run on analytical HPLC (gradient 25% CH_3CN : 75% H_2O, finish with 100% CH_3CN over 50 minutes). The more polar of the two compounds has an HPLC retention time of 36.18 minutes, which matches the rearranged diketone obtained from Jones oxidation of 13-acetyl-9 (R) - dihydrobaccatin III. The second major compound (compound 2', Scheme II) showed a retention time of 40.95 minutes which was identical to

compound 5, scheme II.

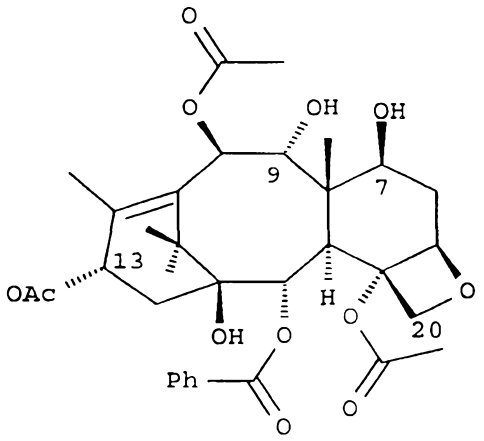
Acetylation of 13-acetyl-9(R)-dihydrobaccatin III

1.0 mL of pyridine and 13.35 μL (0.1425 mmoles) of acetic anhydride are added to a scintillation vial adapted with a magnetic stirrer and a rubber septum. A mixture containing 1.5 mL of pyridine and 30 mg (0.0475 mmoles) of 13-acetyl-9(R)-dihydrobaccatin III are added to this mixture, dropwise using a syringe over a period of half an hour. The reaction mixture is left to stir at room temperature for 17.5 hours. The reaction mixture is then worked up by diluting it in 30 mL of ethyl acetate, washing the organic phase with 3 x 20 mL of brine, drying the organic layer over magnesium sulfate and then evaporating the organic phase. Thin layer chromatography in 65% ethyl acetate shows two major bands with an rf:0.14 corresponding to unreacted 13-acetyl-9(R)-dihydrobaccatin III and another band with an rf:0.28 corresponding to monoacetylated 13-acetyl-9(R)-dihydrobaccatin III. Preparative thin layer chromatography is performed and the corresponding bands eluted with ethyl acetate, evaporated, weighed and a portion analysed using NMR. The yield is 60% monoacetylated product and 40% recovered 13-acetyl-9(R)-dihydrobaccatin III.

It is to be understood that the examples described above are not meant to limit the scope of the present invention. It is expected that numerous variants will be obvious to the person skilled in the art to which the present invention pertains, without any departure from the spirit of the present invention. The appended claims, properly construed, form the only limitation upon the scope of the present invention.

THE EMBODIMENTS IN WHICH AN EXCLUSIVE PROPERTY AND PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of Baccatin III from a compound of formula (X)



X

which comprises the steps of:

(i) protecting the hydroxy group on a compound of Formula X at the 7-position or C9 , or both C7 and C9 sequentially;

(ii) oxidizing the resulting group at the C9 position;

(iii) either: (a) sequentially deacylating the esters at positions C13 and C7 or,

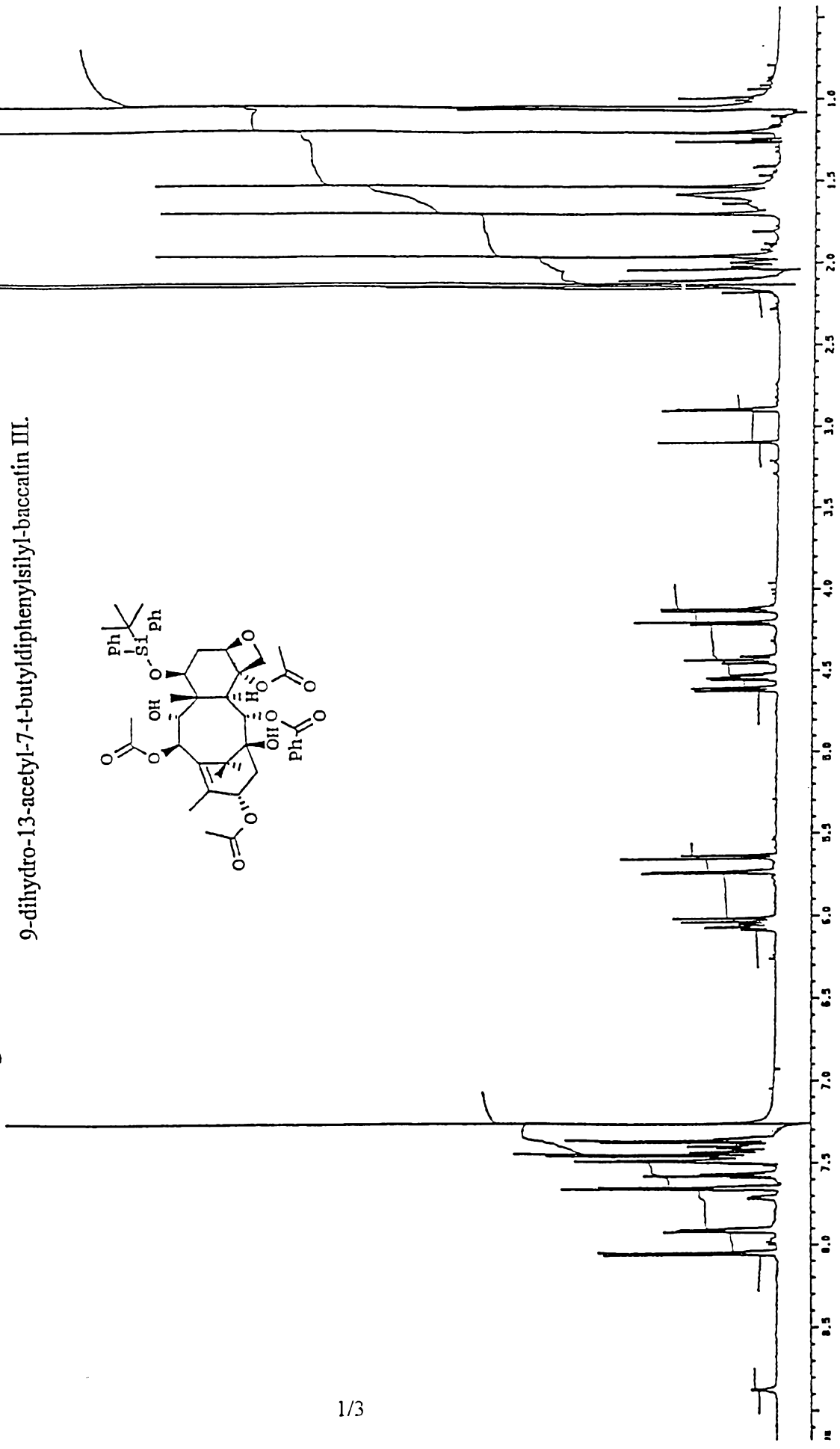
(b) simultaneously deacylating the esters at position C13 and C7.

2. A process according to claim 1, wherein the sequential protection at C9 and C7 is benzyl and acetyl.

3. A process according to claim 1, wherein the protecting group at C7 is acetyl.

4. A process according to claim 1, wherein the protecting group at C7 is benzyl.

Figure 1; shows NMR spectra of an example of Compound 2, 9-dihydro-13-acetyl-7-t-butyldiphenylsilyl-baccatin III.



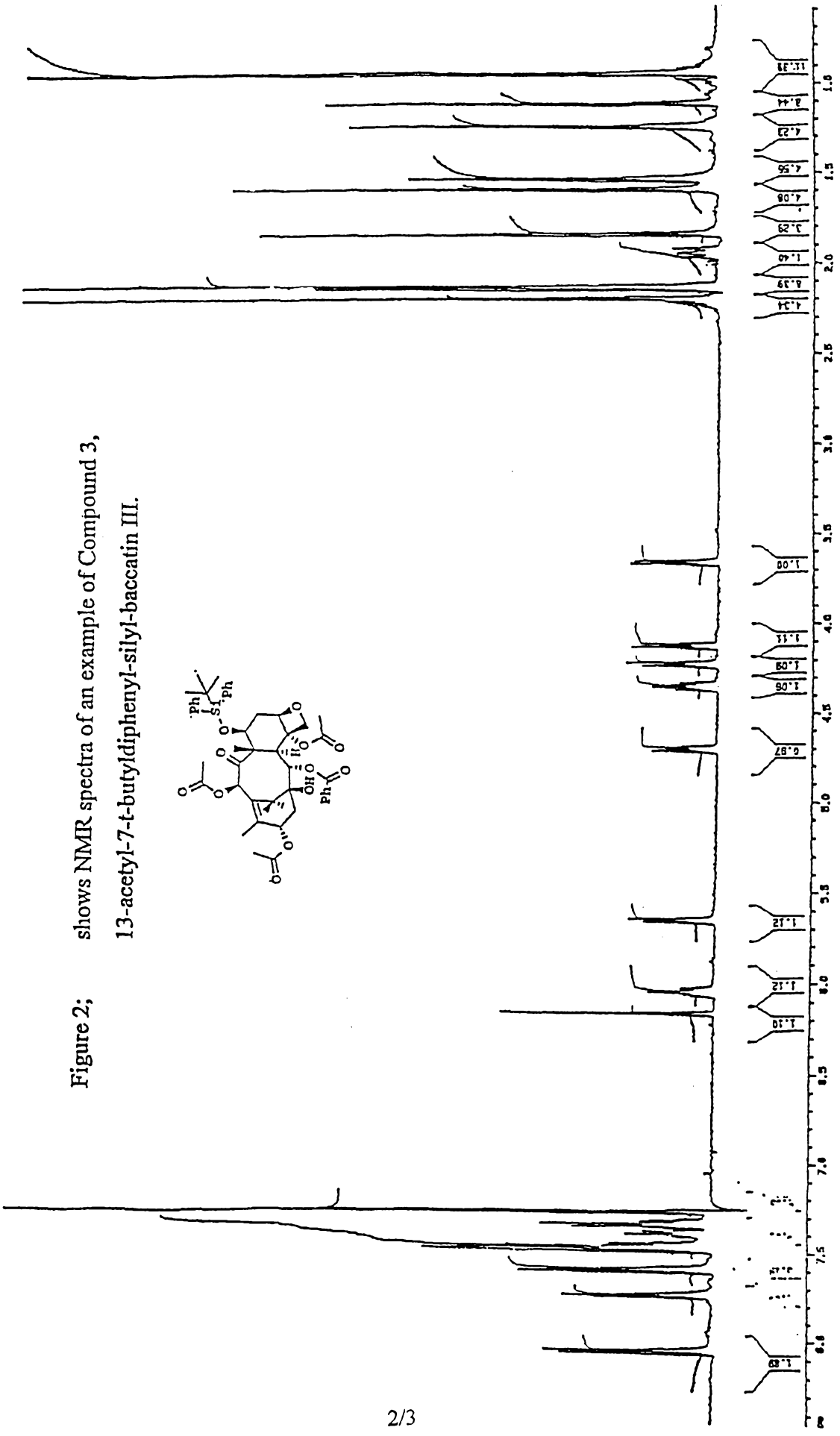


Figure 2; shows NMR spectra of an example of Compound 3, 13-acetyl-7-t-butyldiphenyl-silyl-baccatin III.

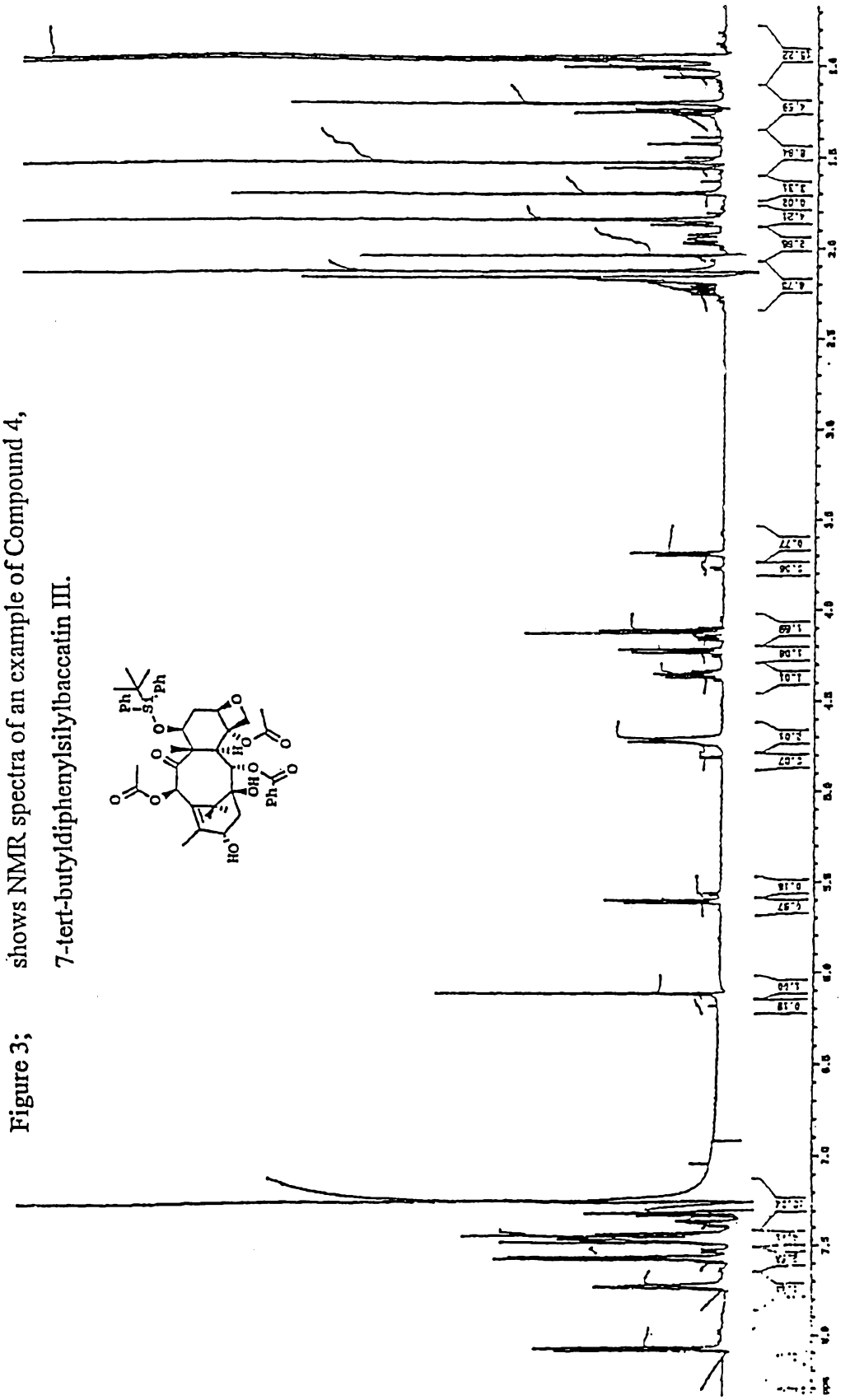


Figure 3; shows NMR spectra of an example of Compound 4, 7-tert-butyldiphenylsilylbaccatin III.