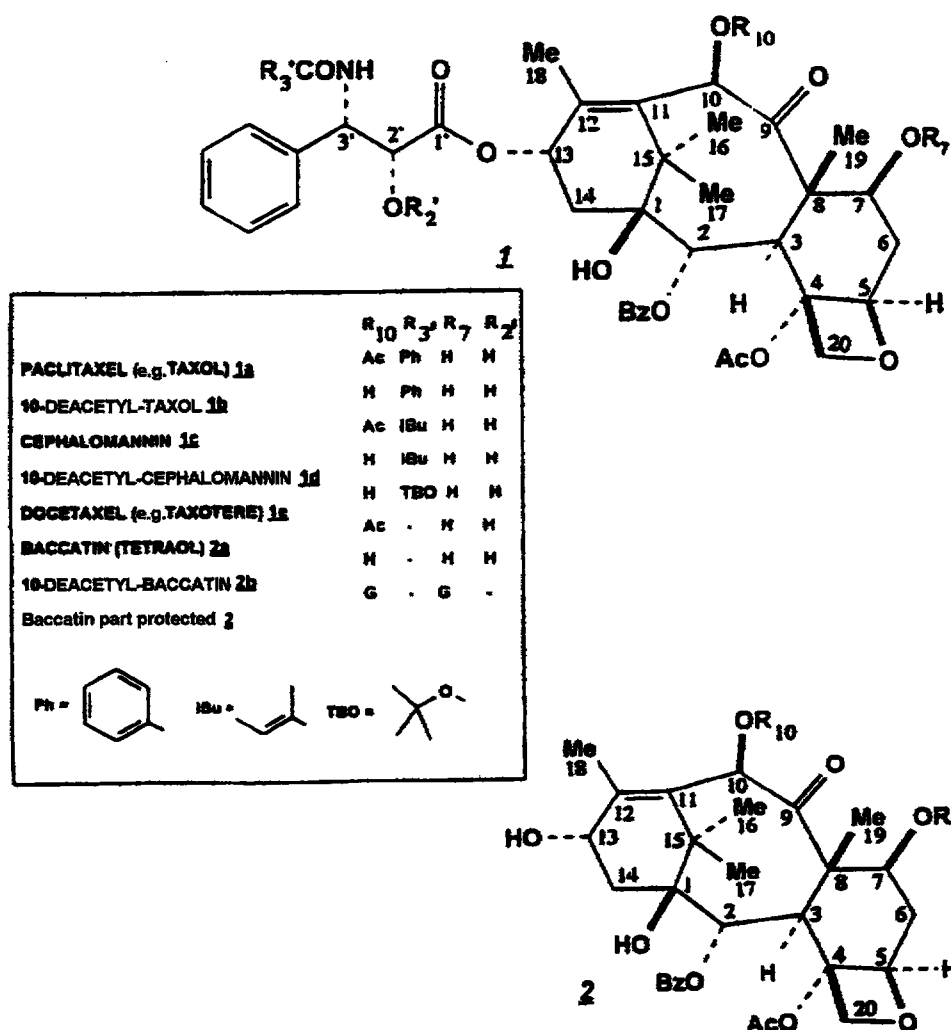


PROCESS FOR THE SELECTIVE PROTECTION OF BACCATIN  
DERIVATIVES AND ITS USE IN THE SYNTHESIS OF TAXANES

The present invention relates to new  
intermediates for the semisynthesis of taxanes and to  
5 the processes for preparing them.

Taxanes, natural substances whose diterpenic  
backbone is generally esterified with a  $\beta$ -amino acid  
side chain derived from N-alkyl- or N-aroyl-phenyl-  
isoserine, are known as anticancer agents. There are  
10 several tens of taxanes isolated from Taxaceae of the  
genus Taxus, such as for example, PACLITAXEL (R1 = Ac,  
R2 = Ph, R3 = R4 = H), cephalomanin, their derivatives  
which are deacetylated at the 10-position, or baccatins  
(derivatives without a side chain) represented by the  
15 formulae 1 and 2 below.



In an effort not to rapidly exhaust its original source, *T. brevifolia*, French researchers have sought to isolate PACLITAXEL from renewable parts (the leaves) of the European yew tree. They have thus

5 identified the probable biogenetic precursor of taxanes, 10-deacetylbaccatin III, an ideal springboard for semisynthesis, because of its relative abundance in the leaf extracts.

The semisynthesis of taxanes, such as

10 PACLITAXEL or DOCETAXEL (R<sub>1</sub> = Ac, R<sub>2</sub> = t.butyloxy, R<sub>3</sub> = R<sub>4</sub> = H), therefore consists in esterifying the hydroxyl

at the 13-position of a protected derivative of baccatin or of 10-deacetylbaccatin III with a  $\beta$ -amino acid derivative.

Various processes for the semisynthesis of  
5 PACLITAXEL or of DOCETAXEL are described in the state of the art (EP-0,253,738, EP-0,336,840, EP-0,336,841, EP-0,495,718, WO 92/09589, WO 94/07877, WO 94/07878, WO 94/07879, WO 94/10169, WO 94/12482, EP-0,400,971, EP-0,428,376, WO 94/14787. Two recent manuals  
10 [I. Georg, T.T. Chen, I Ojima, and D.M. Vyas, "Taxane Anticancer Agents, Basic Science and Current Status", ACS Symposium Series 583, Washington (1995)] and in particular [Matthew Suffness, "TAXOL® Science and Applications" CRC press (1995) and 1500 cited  
15 references] comprise exhaustive compilations of the semisyntheses of taxanes.

The selective monoprotection of taxanes dihydroxylated at the 7- and 10-positions has so far been obtained only with the aid of trialkylsilane ether  
20 groups (EP-A-0,336,840). This protection is of great interest because, on the one hand, of the rarity, for example, of baccatin III, direct precursor of PACLITAXEL and, on the other hand, of the impossibility of manufacturing it under profitable conditions from  
25 its much more easily available homologue, 10-deacetylbaccatin III, without an effective selective protection at the 10-position.

Indeed, the use of common groups such as

acetate groups, or even of slightly hindered haloalkoxycarbonyls such as the conventional trichloroethoxycarbonyl to protect dihydroxytaxanes such as 10-deacetylbaccatin III, has the disadvantage of not at all being selective. On the other hand, they have up until now been widely used in the nonselective deprotection of 7,10-dihydroxytaxanes such as 10-deacetylbaccatin III, to give 7,10-di-(2,2,2-trichloroethoxycarbonyloxy)-10-deacetylbaccatin III, a key intermediate in the synthesis of DOCETAXEL (EP-A-0,336,841).

The use of trialkylsilanes for the protection of the hydroxyl situated at the 7-position of taxanes which are dihydroxylated at the 7- and 10-positions has, because of the relative lability of these protecting groups towards slightly acidic media, a number of major disadvantages which counterbalance their good selectivity.

1/ Subsequent acylation at the 10-position, which justifies prior selective protection at the 7-position, which is going to be the case in the present invention, gives rise to 50 to 60% average yields because of the ease of trialkylsilylated ethers to be substituted by the acylating group present in the reaction medium, this situation being worsened by the greater difficulty of esterifying the 10-position when the 7-position is already occupied by a bulky group. This side reaction could be avoided provided it is

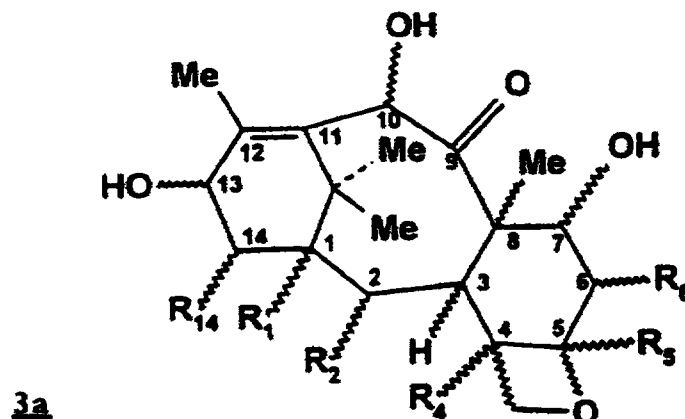
carried out at a very low temperature using an alkali metal alcoholate as intermediate, but would introduce a new double disadvantage for an industrial synthesis as indicated in application WO-A-94/14787.

5                   2/ The sensitivity of the alkylsilylated ethers to acidic conditions limits the possibilities of using acidic reagents in treatments of the subsequent synthetic sequence and therefore makes the field of application of these protecting groups a lot narrower.  
10 Furthermore, it should be noted that higher homologues such as tert-butyldimethylsilyl ether are thought to be more resistant to these conditions, but their introduction is made impossible because of their excessively large steric hindrance.

15                   3/ The well-known sensitivity of alkylsilylated ethers to hydroxylated solvents such as water and alcohols makes the use of these solvents impossible in recrystallizations, systems which are nevertheless valuable because they are highly purifying  
20 in this series of compounds, which is another major disadvantage.

                  4/ The partial decomposition, during industrial chromatographic purifications of intermediates carrying silylated ethers, practically  
25 does not allow this purification technique which is nevertheless valuable for the purpose of producing high value-added pharmaceutical raw materials of high purity.

The taxoids not carrying a side chain of the following formula 3a:



in which

$R_1, R_2, R_4, R_5, R_6, R_{14}$  represent, independently of each other, a radical Q, with:

$Q = R, H, OH, OR, SH, SR, OCOR, OCOOR, HCO, X,$  and

$X = \text{halogen},$  and

R represents, independently of each other, a saturated or unsaturated, linear or branched alkyl radical, a perhaloalkyl radical, a saturated or unsaturated, linear or branched heteroalkyl radical, a saturated or unsaturated cycloalkyl radical, a saturated or unsaturated heterocycloalkyl radical, an aryl radical, an aralkyl radical, it being possible for the radicals to be substituted, in particular with one or more halogens or otherwise, their single multiple combined assemblies, and more generally any combination containing them in the form of single or repeated units,

and in particular the derivatives of general formula 2 such as for example 10-deacetylbaccatin III often have at least four free hydroxyls, one which is tertiary, at the 1-position, highly hindered and only esterifiable under drastic conditions, the other three, which are secondary, at the 7-, 10- and 13-positions, easier to esterify, which can, on the basis of their steric hindrance, be divided into two reactivity groups:

- the first, at the 13-position, is relatively hardly reactive to esterification under standard reaction conditions (including, according to the literature, for the introduction of the side chain);
- the second group, at the 7- and 10-positions, which is of interest to the subject of the present invention, can, in turn, be divided into two levels, which are different in a subtle way, of reactivities towards esterification or carbonation, slightly in favour of the hydroxyl at the 7-position.

It also emerges from our personal work that the two hydroxylation sites present a case of allosteric interaction: the introduction of a hindered ester into one of the 7- or 10-positions modifies the steric availability of the other position.

The present invention therefore relates to a new process for the selective protection at the 7-position of 7,10-dihydroxytaxanes of general formula 3a above, using particular reaction conditions,

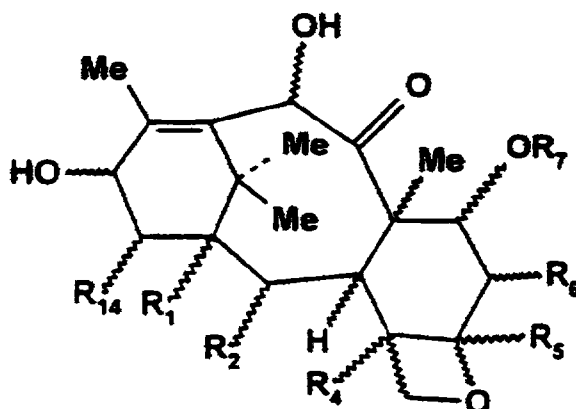
simultaneously with the use of alkoxycarbonyl groups substituted at the 2- (or  $\beta$ -) position which are more hindered than 2,2,2-trichloroethoxycarbonyl (which remains nonselective under our particular reaction conditions), which are capable of being removed by a  $\beta$ -elimination mechanism (*Protecting Groups*, P.J. Kocienski, Thieme Verlag Ed., p. 7 (1994) and cited references), and exhibiting none of the disadvantages of the trialkylsilylated ethers mentioned above.

Patent Application WO-A-94/07877 describes a process for the synthesis of taxanes, for which it is possible to use 2-trichloromethyl-2-propoxycarbonyl as protecting group for hydroxyls 7 and 10 of 10-deacetylbaccatin III. It emerges, however, from the description that this group is not used for the selective protection of the hydroxyl at the 7-position, but for the protection of the two hydroxyls 7 and 10, which is necessary for the preparation of DOCETAXEL, the only product really prepared in the examples, with moreover the only exemplified use of 2,2,2-trichloroethoxycarbonyl as protecting group. The teaching of this patent application therefore tends to lead persons skilled in the art away from the use of  $\beta$ -haloalkoxycarbonyl groups which are even more hindered than 2,2,2-trichloroethoxycarbonyl for the preparation of baccatin III protected at the 7-position, from 10-deacetylbaccatin III.

The invention also relates to the new intermediates resulting therefrom, the process for the selective acylation at the 10-position (in relation to the hydroxyl situated at the 13-position) of taxanes protected at the 7-position and the new 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-acyloxytaxanes resulting therefrom, their use in coupling with side chains in taxanes and the new protected taxane intermediates resulting therefrom.

Finally, the present invention consists in describing the selective removal of the  $\beta$ -substituted-alkoxycarbonyl protecting groups leading to the final taxanes, in particular DOCETAXEL.

The present invention therefore relates, first of all, to a process for the preparation of 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-hydroxytaxane derivatives corresponding to the following formula **3b**:



**3b**

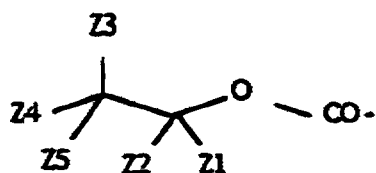
in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_{14}$  are defined above,

R<sub>7</sub> represents an alkoxy carbonyl group substituted at the 2- (or β-) position which is more hindered than 2,2,2-trichloroethoxycarbonyl and which is capable of being removed by a β-elimination mechanism,

by the slow addition, at a temperature greater than room temperature, contrary to the practice commonly used, preferably between 20 and 80°C, of the corresponding alkoxy carbonyl chloride substituted at the 2-position, diluted in an appropriate solvent, to a vigorously stirred solution of the 7-10-dihydroxytaxane of general formula 3a defined above in the presence of pyridine and/or of a hindered substituted pyridine, such as, for example, 4-pyrrolidinopyridine or dimethylaminopyridine.

In particular, R<sub>7</sub> represents an alkoxy carbonyl radical of general formula



in which

Z<sub>1</sub> and Z<sub>2</sub> represent, independently of each other, a hydrogen atom, a radical R defined above or a halogen,

Z<sub>3</sub>, Z<sub>4</sub> and Z<sub>5</sub> represent, independently of each other, a hydrogen atom, a halogen, a radical R, OR, Si(R)<sub>3</sub>, R being defined above, or two of Z<sub>3</sub>, Z<sub>4</sub> and

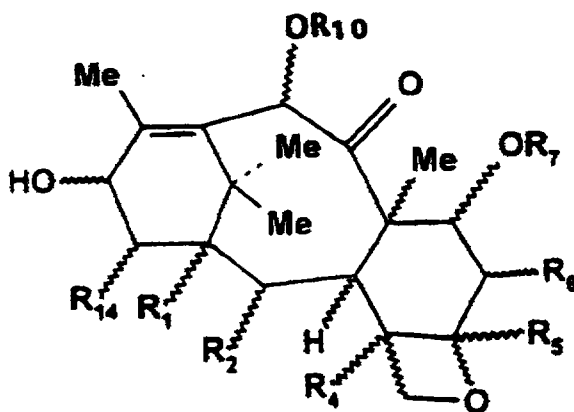
Z5 together form part of a ring which is aromatic or otherwise,

provided that when one of Z3, Z4 or Z5 represents a hydrogen atom, at least one of Z3, Z4 or Z5 represents a radical  $\text{Si}(\text{R})_3$ , and

provided that when one of Z3, Z4 or Z5 represents a halogen, Z3, Z4 and Z5 each represent a halogen chosen from bromine or iodine.

Advantageously, the esterification is carried out with 1 to 1.5 equivalents of chloroformate in relation to the 7-10-dihydroxytaxane of general formula 3a.

The 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-acyloxytaxanes corresponding to the following general formula 3c:



3c

in which

$\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_4$ ,  $\text{R}_5$ ,  $\text{R}_6$ ,  $\text{R}_7$  and  $\text{R}_{14}$  are defined above, and

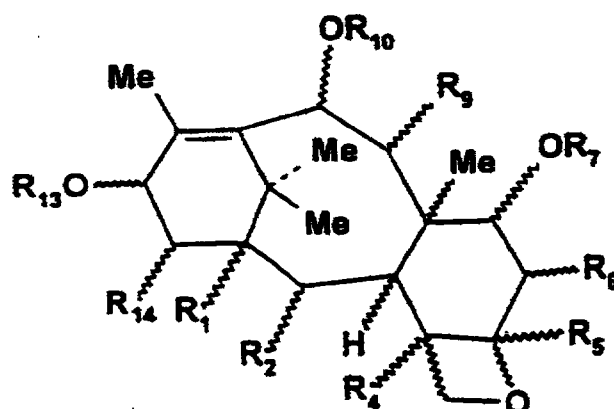
$\text{R}_{10}$  represents an acyl radical of formula

O-CO-R, R being defined above,

are then prepared by the slow addition at room temperature of the corresponding acyl chloride (1 to 1.2 equivalents) diluted in an appropriate solvent to a vigorously stirred solution of the 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-hydroxytaxane derivative obtained above, in the presence of pyridine and/or of a hindered substituted pyridine such as, for example, 4-pyrrolidinopyridine or dimethylaminopyridine.

For these two reactions, the appropriate solvent is a nonhydroxylated solvent, in particular an alkyl halide such as, for example, methylene chloride, chloroform or dichloroethane.

The taxanes 3c protected at the 7-position which are obtained above, can be used for the semisynthesis of taxanes, by esterification of the hydroxyl at the 13-position with an appropriate taxane side chain precursor, in order to obtain a taxane derivative of general formula 3d

3d

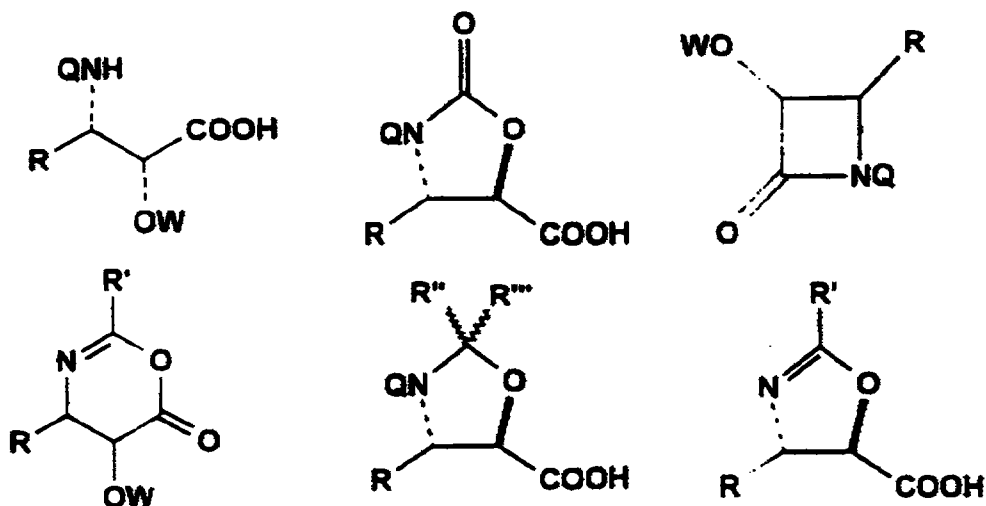
in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$  and  $R_{14}$  are defined above, and

$R_{13}$  represents a radical which is a taxane side chain precursor,  
 5 and then by the selective deprotection of the hydroxyl at the 7-position, optionally accompanied and/or preceded by the opening and/or the conversion and/or the deprotection of the side chain precursor in order  
 10 to obtain the desired taxane.

There will be used in particular the taxane side chain precursors described in the state of the art (EP-0,253,738, EP-0,336,840, EP-0,336,841,  
 EP-0,495,718, WO 92/09589, WO 94/07877, WO 94/07878,  
 15 WO 94/07879, WO 94/10169, WO 94/12482, EP-0,400,971, EP-0,428,376, WO 94/14787) or an oxazolidinone described in Patent Application FR-95 12 735, which is incorporated herein by way of reference. They may be in

particular the following chain precursors:



for which

Q = H, RCO, ROCO,

W = Bz or a group for protecting the hydroxyl

5 functional group PG,

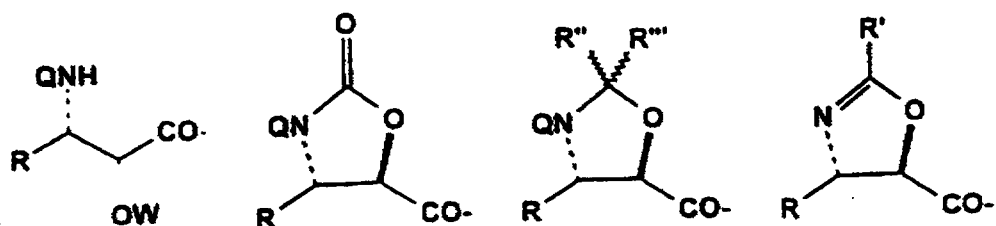
R' = R, OR, SR, X, Si(R)<sub>3</sub>,

R'' and R''' = R,

R being defined above,

combined with the derivative of formula 3c according to  
 10 techniques known in the literature (EP-0,253,738,  
 EP-0,336,840, EP-0,336,841, EP-0,495,718, WO 92/09589,  
 WO 94/07877, WO 94/07878, WO 94/07879, WO 94/10169,  
 WO 94/12482, EP-0,400,971, EP-0,428,376, WO 94/14787 or  
 FR 95 12 735), in order to give the direct precursor of  
 15 corresponding taxanes.

Advantageously, the following taxane side  
 chain precursors will be used:

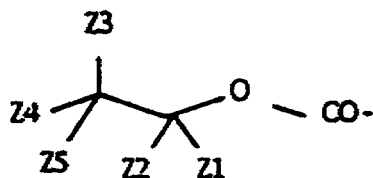


for which Q, R, R', R'', R''' and W are defined above, in particular those for which R and R' represent an aryl, and Q represents an aroyl radical.

If an oxazolidinone described in Patent Application FR 95 12 735 is used, it will be preferably N-benzoyl-4-phenyloxazolidin-2-onecarboxylic acid, in particular the (4S,5R) isomer, advantageously obtained by controlled saponification of the corresponding (+)-menthyl ester.

The deprotection of the hydroxyl at the 7-position of baccatin is carried out by  $\beta$ -elimination, according to the customary techniques [P.J. Kocienski, Protecting Groups, Thieme Verlag Ed., p. 7 (1994) and cited references].

Preferably, the group for protecting the hydroxyl functional group R, represents a radical of formula



in which Z1 and Z2 represent a hydrogen atom.

When Z3, Z4 and Z5 represent a halogen, it is preferably a bromine.

According to another preferred embodiment of the invention, at least one of Z3, Z4 or Z5 represents an alkyl radical, and at least one of the remaining Z3, Z4 and Z5 represents a perhaloalkyl radical.

5           According to another preferred embodiment of the invention, two of Z3, Z4 and Z5 together form part of a fluorenyl ring.

Advantageously, the radical R<sub>7</sub> is chosen from the 2,2,2-tribromoethoxycarbonyl, 2-trichloromethyl-2-propoxycarbonyl, 2-trimethylsilylethoxycarbonyl and  
10           fluorenylmethoxycarbonyl groups.

The process according to the invention is described in a general way for 7,10-dihydroxytaxanes of general formula 3a since it relates to the selective  
15           protection of the hydroxyl at the 7-position, independently of the nature of the substituents R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> or R<sub>14</sub>. Of course, it is particularly appropriate for the protection of the 10-deacetylbaccatin of general formula 2 for which R<sub>7</sub>  
20           and R<sub>10</sub> represent a hydrogen atom, a key intermediate in the semisynthesis of PACLITAXEL.

The present invention therefore also relates to a process for the production of PACLITAXEL, obtained by esterification of the baccatin III derivative of  
25           general formula 2 for which R<sub>7</sub> represents a protecting group as defined above, and R<sub>10</sub> represents an acetyl radical, with an appropriate precursor of the side chain of PACLITAXEL, and then by deprotection of the

hydroxyl at the 7-position according to the technique described above, optionally accompanied and/or preceded by the opening and/or the conversion and/or the deprotection of the PACLITAXEL side chain precursor, in  
5 order to give the said PACLITAXEL side chain.

Linear or branched alkyl is preferably understood to mean according to the invention a  $C_1$ - $C_6$  alkyl, in particular chosen from methyl, ethyl, propyl, isopropyl and butyl radicals and its various branched  
10 isomers such as, for example, tert-butyl, pentyl and hexyl and their various branched isomers. This definition also applies to the alkyl residues of the alkoxy, aralkyl or aralkoxy radicals.

Cycloalkyl is preferably understood to mean  
15 according to the invention a  $C_3$ - $C_6$  cycloalkyl, in particular chosen from the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl radicals.

Aryl is preferably understood to mean according to the invention an aromatic or  
20 heteroaromatic radical, in particular chosen from the phenyl, naphthyl, anthryl, phenanthryl, pyridyl and pyrimidyl radicals, and the like.

Finally, halogen is preferably understood to mean chlorine, bromine or iodine. For the perhaloalkyl  
25 radicals, there will preferably be perchlorinated radicals, in particular the trichloromethyl or pentachloroethyl radicals.

Other characteristics of the processes and

intermediates according to the invention will emerge in the light of the examples below.

#### COMPARATIVE STUDIES WITH THE AID OF HALOALKOXYCARBONYLS

The principal object of this invention being  
5 to demonstrate the determining advantage, in terms of selectivity, of  $\beta$ -substituted alkoxy carbonyl protecting groups, which are more hindered than 2,2,2-trichloroethoxycarbonyl (Troc), already used nonselectively in the nonselective protection of  
10 taxanes having at least two free hydroxyls at the 7- and 10-positions (EP-A-0,336,841), the comparative kinetic study was carried out in relation to it.

By way of comparison, and without limiting the scope of the present invention, we selected as  
15 example 2,2,2-trichloro-tert-butoxycarbonyl (TCBoc) and tribromoethoxycarbonyl (Tbroc), protecting groups which are substantially more hindered than Troc, using as example of substrate 10-deacetyl baccatin III, the usual precursor for the semisynthesis of PACLITAXEL and of  
20 DOCETAXEL.

The reaction conditions used in this example of kinetic study are the following:

- Temperature: 38°C
- Solvent: dichloromethane
- 25 - Chloroformate: 1.1 to 1.5 molar equivalents
- Total duration of the study: 16 hours
- Catalysts: pyridine, 5 molar equivalents,

4-pyrrolidinopyridine, 1.4 molar equivalents

- Procedures: vigorous stirring, slow addition of chloroformate (1 molar equivalent per hour).

Quantitative analytical monitoring was  
5 carried out by high-performance liquid chromatography.

The results of this comparative kinetic study are collated in Table I below.

**TABLE I**

**COMPARATIVE EXAMPLES OF PROTECTION OF**

10 **10-DEACETYLBACCATIN III: COMPARATIVE TABLE**

|  | Cumulative<br>yield % |
|--|-----------------------|
|--|-----------------------|

Protection by Troc, under the usual conditions

|                                            |         |
|--------------------------------------------|---------|
| 7-TROC-10-DAB III (0-25°C, DMAP, pyridine) | 49 - 54 |
| 7-TROC-BACCATIN III                        | 47 - 52 |

Example of protection by Troc, under special conditions

15

|                                            |         |
|--------------------------------------------|---------|
| 7-TROC-10-DAB III (0-25°C, DMAP, pyridine) | 56 - 60 |
| 7-TROC-BACCATIN III                        | 51 - 57 |

Example of protection by TCboc, under special conditions

|                                            |         |
|--------------------------------------------|---------|
| 7-TCBOC-10-DAB III (40-60°C, PP, pyridine) | 78 - 89 |
| 7-TCBOC-BACCATIN III                       | 75 - 87 |

## Protection by TES (comparative)

|                    |         |
|--------------------|---------|
| 7-TES-10-DAB III*  | 90 - 94 |
| 7-TES-BACCATIN III | 57 - 64 |

Abbreviations: TROC = 2,2,2-Trichloroethoxycarbonyl;

5 TCBOC = 2,2,2-Trichloroterbutoxycarbonyl; TES =  
Triethylsilyl; DMAP = Dimethylaminopyridine; PP =  
4-pyrrolidinopyridine; DAB = deacetylbaccatin  
\* 84-86% according to the literature [J.-N. Denis,  
A. Greene, *J. Am. Chem. Soc.*, 5917 (1988)].

10           The results of this comparative study show  
without ambiguity that the new protecting groups  
according to the invention which are used for the  
synthesis of baccatin III protected at the 7-position  
make it possible to obtain 10-deacetylbaccatin III  
15 protected at the 7-position with a selectivity close to  
that of triethylsilyl, the only group used in the state  
of the art.

When the selective acylation of the hydroxyl  
at the 10-position is then carried out, yields are then  
20 obtained which are greater than those obtained with  
7-triethylsilyl-10-deacetylbaccatin III.

An overall yield of synthesis of baccatin III  
protected at the 7-position from 10-deacetylbaccatin is  
therefore obtained which is greater than that obtained  
25 for the state of the art process (75-87% against  
57-64%).

**EXPERIMENTAL PART****EXAMPLE 1****7-O-(2,2,2-Trichloro-t-butoxycarbonyl)-10-deacetylbaecatin III**

5                   A solution of 0.26 g (1.10 mmol) of 2,2,2-trichloro-t-butoxycarbonyl chloride in 2 ml of dichloromethane is added, over 50 min, to a stirred solution, at 40°C under an inert atmosphere, of 500 mg (0.919 mmol) of 10-deacetylbaecatin III and 0.19 g  
10 (1.29 mmol) of 4-pyrrolidinopyridine in 5 ml of dry dichloromethane. After an additional 1 h of reaction, and returning to room temperature, the organic solution is washed with a 2% aqueous solution of HCl (5 ml), washed with osmosed water (2 × 5 ml), dried over MgSO<sub>4</sub>  
15 and concentrated under reduced pressure. After chromatography of the crude product on silica gel (15-40 µm) (eluent: cyclohexane-ethyl acetate, 60/40), 7-O-(2,2,2-trichloro-t-butoxycarbonyl)-10-deacetylbaecatin III is obtained in the form of a white  
20 powder (Y = 89%).

The product obtained has the following characteristics:

- <sup>1</sup>H NMR 400 MHz (CD Cl<sub>3</sub>) (δ ppm): 8.10 (2H, d, J = 7.3 Hz); 7.62 (1H, t, J = 7.3 Hz); 7.49 (2H, t, J = 7.6 Hz); 5.64 (1H, d, J = 6.8 Hz); 5.50 (1H, d); 5.39 (1H, dd, J = 10.6 and 7.3 Hz); 4.97 (1H, d, J = 8.6 Hz); 4.89 (1H, m); 4.34 and 4.20 (2H, 2d, J = 8.4 Hz); 4.09 (1H, d); 4.06 (1H, d); 2.60 (1H, m);

2.31 (3H, s); 2.29 (1H, m); 2.13 (3H, s) and (1H, m);  
2.06 (1H, m); 1.90 (6H, s); 1.85 (3H, s); 1.09 (3H,  
s); 1.06 (3H, s).

## **EXAMPLE 2**

### 5                    **7-O-(2,2,2-Trichloro-t-butoxycarbonyl)-                       baccatin III**

50  $\mu$ l (0.695 mmol) of acetyl chloride are  
added to a stirred solution, at room temperature under  
an inert atmosphere, of 260 mg (0.347 mmol) of 7-O-  
10 (2,2,2-trichloro-t-butoxycarbonyl)-10-deacetylbaccatin  
III and 127.5 mg (1.04 mmol) of 4-dimethylaminopyridine  
in 2.5 ml of dry dichloromethane. After 1 h of reaction  
at room temperature, the organic phase is washed with a  
2% aqueous solution of HCl until pH = 6 is obtained,  
15 dried over MgSO<sub>4</sub> and concentrated under reduced  
pressure. After chromatography of the residue obtained  
on silica gel (15-40  $\mu$ m) (eluent: cyclohexane-ethyl  
acetate, 6/4), 7-O-(2,2,2-trichloro-t-  
butoxycarbonyl)baccatin III is obtained in the solid  
20 state (Y = 96%).

The compound obtained has the following  
characteristics:

- <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>) ( $\delta$  ppm): 8.10 (2H, d, J =  
7.6 Hz); 7.61 (1H, t, J = 7.4 Hz); 7.48 (2H, t, J =  
25 7.7 Hz); 6.52 (1H, s); 5.65 (1H, d, J = 6.9 Hz); 5.39  
(1H, dd, J = 10.4 and 7.3 Hz); 4.96 (1H, d, J =  
8.9 Hz); 4.86 (1H, m); 4.32 and 4.17 (2H, 2d, J =  
8.4 Hz); 4.01 (1H, d, J = 6.9 Hz); 2.69 (1H, m); 2.30

(2H, m); 2.29 (3H, s); 2.16 (3H, s); 2.14 (3H, s);  
2.07 (1H, d,  $J = 4.8$ ); 1.97 (1H, m); 1.95 and 1.91  
(6H, 2s); 1.80 (3H, s); 1.61 (1H, s); 1.15 (3H, s);  
1.07 (3H, s).

5 **EXAMPLE 3 (comparative)**

**7-O-trichloroethoxycarbonyl-10-deacetyl-  
baccatin III**

A solution of 0.152 ml (1.10 mmol) of  
trichloroethoxycarbonyl chloride in 2 ml of  
10 dichloromethane is added, over 40 min, to a stirred  
solution, at 40°C under an inert atmosphere, of 500 mg  
(0.919 mmol) of 10-deacetylbaccatin III and 0.19 g  
(1.29 mmol) of 4-pyrrolidinopyridine in 5 ml of dry  
dichloromethane. After an additional 1 h of reaction  
15 and returning to room temperature, the organic solution  
is washed with a 2% aqueous solution of HCl (5 ml),  
washed with osmosed water (2 × 5 ml), dried over  $\text{MgSO}_4$   
and concentrated under reduced pressure (HPLC yield =  
57%). After chromatography of the crude product on  
20 silica gel (15-40  $\mu\text{m}$ ) (eluent: cyclohexane-ethyl  
acetate, 60/40), 7-O-trichloroethoxycarbonyl-10-  
deacetylbaccatin III is obtained in the form of a white  
powder.

The product obtained has the following  
25 characteristics:

- $^1\text{H}$  NMR 400 MHz ( $\text{CDCl}_3$ ) ( $\delta$  ppm): 8.10 (2H, d,  $J =$   
7 Hz); 7.62 (1H, t,  $J = 7.4$  Hz); 7.49 (2H, t,  $J =$   
7.6 Hz); 5.65 (1H, d,  $J = 6.9$  Hz); 5.44 (1H, dd,  $J =$

10.8 and 7.3 Hz); 5.39 (1H, d); 4.98 (1H, d, J = 7.5 Hz); 4.89 (1H, m); 4.84 and 4.70 (2H, 2d, J = 11.9 Hz); 4.35 and 4.20 (2H, 2d, J = 8.4 Hz); 4.10 (1H, d, J = 7 Hz); 4.01 (1H, d, J = 1.8 Hz); 2.64 (1H, m); 2.31 (3H, s); 2.29 (1H, m); 2.11 (3H, d); 2.05 (2H, m); 1.89 (3H, s); 1.09 (3H, s); 1.07 (3H, s).

#### **EXAMPLE 4**

##### **7-O-trichloroethoxycarbonylbaccatin III**

10 **(comparative)**

0.68 ml (0.695 mmol) of acetyl chloride is added to a stirred solution, at room temperature under an inert atmosphere, of 1.70 g (2.36 mmol) of 7-O-trichloroethoxycarbonyl-10-deacetylbaccatin III and 0.96 ml (12 mmol) of pyridine in 17 ml of dry dichloromethane. After 3 h of reaction at room temperature, the organic phase is washed with water (2 × 20 ml), dried over MgSO<sub>4</sub> and concentrated under reduced pressure. After chromatography of the residue obtained on silica gel (15-40 μm) (eluent: cyclohexane-ethyl acetate, 6/4), 1.38 g of 7-O-trichloroethoxycarbonylbaccatin III are obtained in the solid state (Y = 75%).

25 The compound obtained has the following characteristics:

- <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>) (δ ppm): 8.11 (2H, d, J = 7.1 Hz); 7.62 (1H, t, J = 7.4 Hz); 7.49 (2H, t, J = 7.6 Hz); 6.39 (1H, s); 5.64 (1H, d, J = 6.9 Hz); 5.61

(1H, dd,  $J = 10.7$  and  $7.2$  Hz); 5.04 and 4.65 (2H, 2d,  $J = 12$  Hz); 4.99 (1H, d,  $J = 8.2$  Hz); 4.87 (1H, m); 4.33 and 4.16 (2H, 2d,  $J = 8.4$  Hz); 4.02 (1H, d,  $J = 6.9$  Hz); 2.64 (1H, ddd,  $J = 14.4, 9.5$  and  $7.2$  Hz);  
 5 2.30 (3H, s) and (2H, m); 2.17 (3H, s); 2.13 (3H, d,  $J = 0.8$  Hz); 2.04 (1H, m); 1.83 (3H, s); 1.63 (1H, s); 1.14 (3H, s); 1.09 (3H, s).

**EXAMPLE 5**

10 **13-O-[[ (4S,5R)-2,4-Diphenyl-4,5-dihydro-oxazol-5yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III**

2.61 g (12.7 mmol) of dicyclohexylcarbodiimide are added to a stirred solution, at room temperature and under an inert atmosphere, of 3.38 g (12.7 mmol) of (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid in 60 ml of anhydrous toluene. After stirring for 5 min, 5 g (6.33 mmol) of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III and 0.77 g (6.33 mmol) of 4-dimethylaminopyridine are added, and  
 20 the mixture is stirred at room temperature for 15 min. After removing the insoluble matter by filtration, the organic phase is concentrated under reduced pressure and the residue obtained is purified by chromatography on silica gel (15-40  $\mu$ m) (eluent: cyclohexane-ethyl  
 25 acetate, 9/1).

6.2 g of the compound cited in the title are thus obtained in the form of a white solid ( $Y = 94\%$ ), which compound has the following characteristics:

-  $^1\text{H}$  NMR 400 MHz ( $\text{CDCl}_3$ ) ( $\delta$  ppm): 8.18 (2H, d,  $J$  = 7.2 Hz); 8.07 (2H, d,  $J$  = 7.6 Hz); 7.64 (1H, t,  $J$  = 7.4 Hz); 7.60 (1H, t,  $J$  = 7.3 Hz); 7.52 (4H, m); 7.39 (5H, m); 6.47 (1H, s); 6.24 (1H, t,  $J$  = 8.4 Hz); 5.70 (1H, d,  $J$  = 7 Hz); 5.59 (1H, d,  $J$  = 7.3 Hz); 5.35 (1H, dd,  $J$  = 10.4 and 7.2); 4.93 (2H, d,  $J$  = 7.3 Hz); 4.29 and 4.17 (2H, 2d,  $J$  = 8.5 Hz); 3.96 (1H, d,  $J$  = 6.9 Hz); 2.71 (1H, m); 2.37 (1H, dd,  $J$  = 15.1 and 9.2 Hz); 2.28 (1H, dd,  $J$  = 15.1 and 8.8 Hz); 2.13 (3H, s); 2.01 (6H, s); 1.95 and 1.93 (6H, 2s); 1.80 (3H, s); 1.72 (1H, s); 1.23 (3H, s); 1.18 (3H, s).

#### **EXAMPLE 6**

**13-O-[(2R,3S)-O-Benzoyl-3-phenylisoserin-1-yl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)-baccatin III**

0.2 ml (0.2 mmol) of a 1 M aqueous solution of HCl is added to a stirred solution, at room temperature and under an inert atmosphere, of 100 mg (0.0963 mmol) of 13-O-[[ (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III in a mixture of tetrahydrofuran (1 ml) and methanol (1 ml), and the reaction mixture is stirred at room temperature for 14 h 30 min. After addition of 15 mg (0.2 mmol) of solid sodium hydrogen carbonate followed by stirring for 10 min, the reaction medium is extracted with ethyl acetate (2  $\times$  2 ml), and the organic phase is washed with water, dried over  $\text{MgSO}_4$  and concentrated under

reduced pressure.

102 mg of the compound cited in the title are thus isolated (crude yield = quantitative), which compound will be used as it is in the next step, and which has the following characteristics:

-  $^1\text{H}$  NMR 400 MHz ( $\text{DMSO}-d_6$ ) ( $\delta$  ppm): 8.15 (2H, d,  $J = 7.9$  Hz); 7.97 (2H, d,  $J = 7.7$  Hz); 7.75 (2H, t,  $J = 7.4$  Hz); 7.64 (1H, t,  $J = 7.7$  Hz); 7.59 (1H, t,  $J = 7.7$  Hz); 7.48 (2H, d,  $J = 7.3$  Hz); 7.42 (2H, t,  $J = 7.5$  Hz); 7.42 (2H, t,  $J = 7.5$  Hz); 7.19 (1H, t,  $J = 7$  Hz); 6.34 (1H, s); 5.89 (1H, t,  $J = 8.9$  Hz); 5.47 (1H, d,  $J = 7$  Hz); 5.28 (1H, dd,  $J = 10.5$  and  $7.3$ ); 5.16 (1H, d,  $J = 6.8$  Hz); 4.98 (1H, d,  $J = 9.5$  Hz); 4.80 (1H, s); 4.41 (1H, d,  $J = 6.8$ ); 4.06 (2H, broad s); 3.72 (1H, d,  $J = 7$  Hz); 2.26 (3H, s); 2.07 (3H, s); 2.0 to 1.6 (4H, m); 1.86 (6H, s); 1.83 (3H, s); 1.64 (3H, s); 1.05 (3H, s); 1.01 (3H, s).

#### EXAMPLE 7

##### **7-O-(2,2,2-trichloro-t-butoxycarbonyl)taxol**

0.25 ml of a saturated aqueous solution of sodium hydrogen carbonate is added to a stirred solution, at room temperature and under an inert atmosphere, of 90 mg (0.0852 mmol) of 13-O-[(2R,3S)-O-Benzoyl-3-phenylisoserin-1-yl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III in a mixture of tetrahydrofuran (4 ml) and methanol (4 ml), and the reaction mixture is stirred at room temperature for 48 h. After extraction of the reaction medium with

ethyl acetate (2 x 5 ml), the organic phase separated is washed with water (5 ml), dried over  $\text{MgSO}_4$ , concentrated under reduced pressure and the residue obtained is purified by chromatography on silica gel (15-40  $\mu\text{m}$ ) (eluent: cyclohexane-ethyl acetate, 6/4).

63 mg of the product cited in the title are thus obtained in the form of a white solid (Y = 70%), which compound has the following characteristics:

-  $^1\text{H}$  NMR 400 MHz ( $\text{CDCl}_3$ ) ( $\delta$  ppm): 8.12 (2H, d, J = 7.4 Hz); 7.75 (2H, d, J = 7.3 Hz); 7.61 (1H, t, J = 7.4 Hz); 7.50 (5H, m); 7.38 (5H, m); 7.19 (1H, d, J = 9 Hz); 6.47 (1H, s); 6.18 (1H, t, J = 8.6 Hz); 5.79 (1H, dd, J = 8.9 and 2.2 Hz); 5.70 (1H, d, J = 6.8 Hz); 5.33 (1H, dd, J = 10.3 and 7.2); 4.93 (1H, d, J = 9 Hz); 4.80 (1H, d, J = 2.4 Hz); 4.31 and 4.21 (2H, 2d, J = 8.5 Hz); 3.91 (1H, d, J = 6.8 Hz); 2.66 (1H, m); 2.38 (3H, s); 2.33 (2H, m); 2.13 (3H, s); 1.99 (1H, m); 1.94 (3H, s); 1.90 (6H, s); 1.81 (3H, s); 1.19 (3H, s); 1.18 (3H, s).

#### 20 **EXAMPLE 8**

##### **13-O-[[ (4S,5R)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]baccatin III**

300  $\mu\text{l}$  (5.26 mmol) of acetic acid and 221 mg (3.38 mmol) of zinc powder are added to a stirred solution, at room temperature and under an inert atmosphere, of 390 mg (0.376 mmol) of 13-O-[[ (4S,5R)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III in 10 ml

of ethyl acetate. After stirring for 1 h 15 min at 30°C and checking by TLC, the organic phase after filtration is washed with osmosed water (5 ml), with a saturated aqueous solution of sodium hydrogen carbonate (2 × 5 ml), again with water (2 × 5 ml), dried over MgSO<sub>4</sub> and concentrated under reduced pressure.

314 mg of the compound cited in the title (crude yield = quantitative) are thus isolated, which compound will be used as it is in the next step and which has the following characteristics:

- <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>) (δ ppm): 8.18 (2H, d, J = 7.3 Hz); 8.07 (2H, d, J = 7.4 Hz); 7.64 (1H, t, J = 7.4 Hz); 7.60 (1H, t, J = 7.3 Hz); 7.52 (2H, t, J = 8.1 Hz); 7.50 (2H, t, J = 7.8 Hz); 7.39 (5H, m); 6.27 (1H, s); 6.24 (1H, t, J = 8.5 Hz); 5.67 (1H, d, J = 7.1 Hz); 5.59 (1H, d, J = 6.9 Hz); 4.96 (1H, d); 4.95 (1H, d, J = 6.9 Hz); 4.29 and 4.15 (2H, 2d, J = 8.4 Hz); 3.82 (1H, d, J = 7 Hz); 2.57 (1H, ddd, J = 15.9, 6 and 6.8 Hz); 2.48 (1H, d, J = 4 Hz); 2.38 (1H, dd, J = 15.3 and 9 Hz); 2.27 (1H, dd, J = 15.3 and 8.7 Hz); 2.24 (3H, s); 2.04 (3H, s); 1.89 (3H, s); 1.88 (1H, m); 1.75 (1H, s); 1.67 (3H, s); 1.26 (3H, s); 1.15 (3H, s).

#### **EXAMPLE 9**

**Preparation of paclitaxel**

**a) from 13-O-[[[(4S,SR)-2,4-diphenyl-4,5-dihydro-oxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III**

90  $\mu$ l (0.09 mmol) of a 1 M aqueous solution of HCl are added to a stirred solution, at room temperature and under an inert atmosphere, of 15 mg (0.0148 mmol) of 13-O-[[ (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III in a mixture of tetrahydrofuran (0.18 ml) and methanol (0.18 ml), and the reaction mixture is stirred at room temperature for 8 h. After addition of 0.6 ml of a saturated aqueous solution of sodium hydrogen carbonate, the solution is maintained homogeneous by addition of 1 ml of tetrahydrofuran and 1 ml of water, and the reaction medium is stirred for an additional 1 h 30 min. After addition of 2.5 ml of ethyl acetate and 2.5 ml of osmosed water, the residual aqueous phase is extracted with ethyl acetate (2.5 ml). The combined organic phases are dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

14 mg of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)taxol are thus obtained in the crude state (Y = 93%) which are used without further purification in the next step.

30  $\mu$ l (0.525 mmol) of acetic acid and 22.5 mg (0.344 mmol) of zinc powder are added to a stirred solution, at room temperature, of 13 mg (0.0128 mmol) of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)taxol in 2 ml of ethyl acetate. After stirring for 2 h 30 min at room temperature and checking by TLC, and after dilution of

the reaction medium with 3 ml of ethyl acetate, the organic phase is washed with osmosed water (1 ml), with a saturated aqueous solution of sodium hydrogen carbonate (1 ml), again with water, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

After chromatography of the crude product on silica gel (15-40  $\mu\text{m}$ ) (eluent: cyclohexane-ethyl acetate, 6/4), 9.5 mg of PACLITAXEL are thus isolated in the crystallized state ( $Y = 89\%$ ).

10    **b)            from 13-O-[[ (4S,5R)-2,4-diphenyl-4,5-dihydro-oxazol-5-yl]carbonyl]baccatin III**

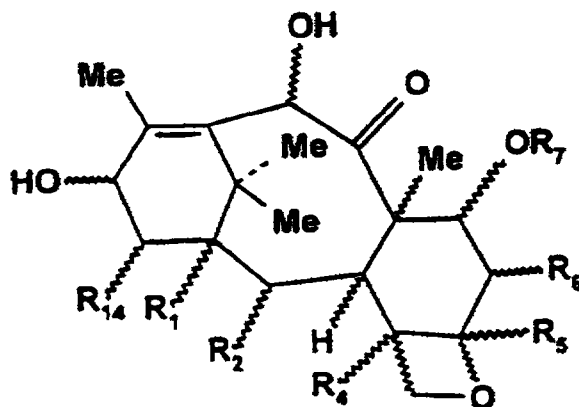
0.7 ml (0.7 mmol) of a 1 M aqueous solution of HCl is added to a stirred solution, at room temperature and under an inert atmosphere, of 290 mg (0.347 mmol) of 13-O-[[ (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]baccatin III in a mixture of tetrahydrofuran (4 ml) and methanol (4 ml), and the reaction mixture is stirred at room temperature for 4 h. After addition of 6 ml of a saturated aqueous solution of sodium hydrogen carbonate, the solution is maintained homogeneous by addition of 10 ml of water, and the reaction medium is stirred for an additional 3 h 30 min. After addition of 20 ml of ethyl acetate and 10 ml of osmosed water, the residual aqueous phase is extracted with ethyl acetate (20 ml). The combined organic phases are dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

After chromatography of the crude product on

silica gel (15-40  $\mu\text{m}$ ) (eluent: cyclohexane-ethyl acetate, 5/5), 270 mg of PACLITAXEL are thus isolated in the crystallized state ( $Y = 93\%$ ).

CLAIMS

1. Process for the preparation of 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-hydroxytaxane derivatives corresponding to the following formula 3b:

3b

5 in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_{14}$  represent,

independently of each other, a radical Q, with:

$Q = H, OH, R, OR, SH, SR, OCOR, OCOOR, HCO,$

X, and

10

X = halogen,

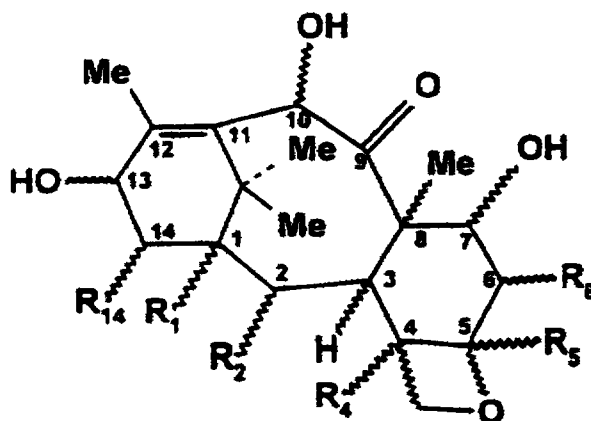
R represents, independently of each other, a saturated or unsaturated, linear or branched alkyl radical, a perhaloalkyl radical, a saturated or unsaturated, linear or branched heteroalkyl radical, a saturated or unsaturated cycloalkyl radical, a saturated or unsaturated heterocycloalkyl radical, an aryl radical, an aralkyl radical, it being possible for the radicals to be substituted, in particular with one



or more halogens, and

$R_7$  represents an alkoxy carbonyl group substituted at the 2-position which is more hindered than 2,2,2-trichloroethoxy carbonyl and which is capable of being removed by a  $\beta$ -elimination mechanism,

by the slow addition, at a temperature greater than room temperature, preferably between 20 and 80°C, of the corresponding alkoxy carbonyl chloride substituted at the 2-position, diluted in an appropriate solvent, to a vigorously stirred solution of the 7-10-dihydroxytaxane of general formula 3a

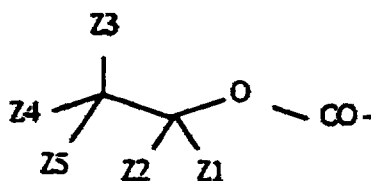


3a

in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_{14}$  are defined above, in the presence of pyridine and/or of a hindered substituted pyridine, such as, for example, 4-pyrrolidinopyridine or dimethylaminopyridine.

2. Process according to claim 1, characterized in that  $R_7$  represents an alkoxy carbonyl radical of general formula



in which

Z1 and Z2 represent, independently of each other, a hydrogen atom, a radical R defined above or a halogen,

5           Z3, Z4 and Z5 represent, independently of each other, a hydrogen atom, a halogen, a radical R, OR,  $\text{Si}(\text{R})_3$ , R being defined above, or two of Z3, Z4 and Z5 together form part of a ring which is aromatic or otherwise,

10           provided that when one of Z3, Z4 or Z5 represents a hydrogen atom, at least one of Z3, Z4 or Z5 represents a radical  $\text{Si}(\text{R})_3$ , or two of Z3, Z4 and Z5 together form part of a ring which is aromatic or otherwise, and

15           provided that when one of Z3, Z4 or Z5 represents a halogen and Z1 and Z2 each represent a hydrogen atom then Z3, Z4 and Z5 each represent a halogen chosen from bromine or iodine.

20           3. Process according to claim 2, characterized in that Z1 and Z2 represent a hydrogen atom or an alkyl radical.

          4. Process according to either of claims 2 and 3, characterized in that Z3, Z4 and Z5 each represent a bromine.

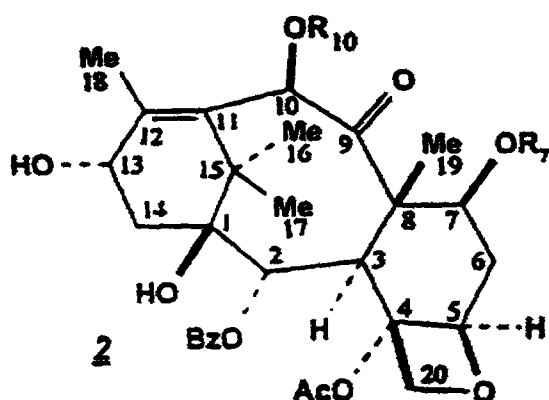


5. Process according to either of claims 2 and 3, characterized in that Z1 and Z2 each represent an alkyl radical, and Z3, Z4 and Z5 each represent a halogen.

5 6. Process according to either of claims 2 and 3, characterized in that two of Z3, Z4 and Z5 together form part of a fluorenyl ring.

7. Process according to either of claims 2 and 3, characterized in that the radical R<sub>7</sub> is chosen  
10 from the 2,2,2-tribromoethoxycarbonyl, 2-trichloromethyl-2-propoxycarbonyl, 2-trimethylsilylethoxycarbonyl and fluorenylmethoxycarbonyl groups.

8. Process according to one of claims 1 to 7, characterized in that the 10-hydroxytaxane of  
15 formula 3a is the 10-deacetylbaccatin of general formula 2



for which R<sub>10</sub> represents a hydrogen atom, and R<sub>7</sub> is defined above.

9. Process according to one of claims 1 to  
20 7, characterized in that the esterification is carried

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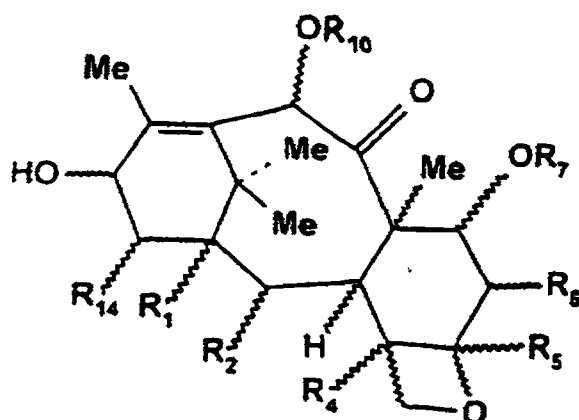


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out with 1 to 1.5 equivalents of alkoxycarbonyl chloride substituted at the 2-position which is more hindered than 2,2,2-trichloroethoxycarbonyl in relation to the 7-10-dihydroxytaxane of general formula 3a.

- 5                    10. Process according to one of claims 1 to 9, characterized in that a 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-acyloxytaxane derivative of the following general formula 3c is then prepared:



3c

in which

- 10                     $R_1, R_2, R_4, R_5, R_6, R_7$  and  $R_{14}$  are defined above, and

$R_{10}$  represents an acyl radical of formula  $O-CO-R$ ,  $R$  being defined above,

- by the slow addition at room temperature of  
15 the corresponding acyl chloride diluted in an appropriate solvent to a vigorously stirred solution of the 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-hydroxytaxane derivative of formula 3b defined in claims 1 to 9, in the presence of pyridine and/or of a



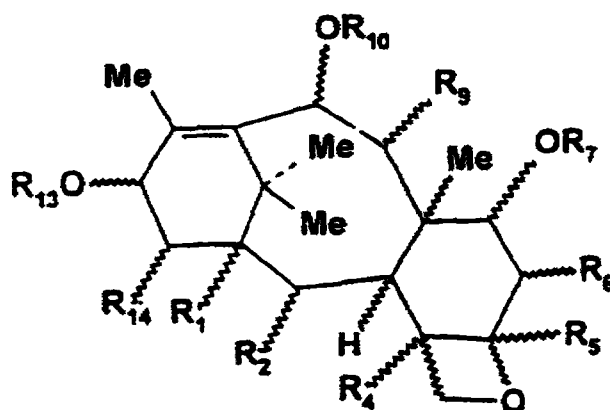


hindered substituted pyridine such as, for example,  
4-pyrrolidinopyridine or dimethylaminopyridine.

11. Process according to claim 10,  
characterized in that R represents an alkyl group, in  
5 particular a methyl.

12. Process according to one of claims 1 to  
11, characterized in that the appropriate solvent is a  
nonhydroxylated solvent, in particular an alkyl halide,  
such as, for example, methylene chloride, chloroform or  
10 dichloroethane.

13. Process according to one of claims 1 to  
12, characterized in that the taxanes of general  
formula 3c defined in claim 10, are then used for the  
semisynthesis of taxanes, by esterification of the  
15 hydroxyl at the 13-position with an appropriate taxane  
side chain precursor, in order to obtain a taxane  
derivative of general formula 3d



3d

in which

R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>10</sub> and R<sub>14</sub> are defined

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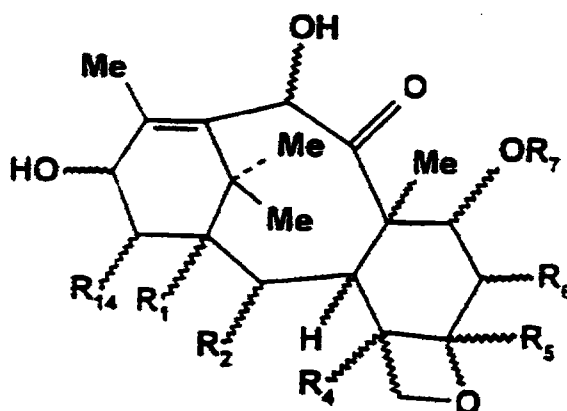
above, and

$R_{13}$  represents a radical which is a taxane side chain precursor, and then by the selective deprotection of the hydroxyl at the 7-position, optionally accompanied and/or preceded by the opening and/or the conversion and/or the deprotection of the side chain precursor in order to obtain the desired taxane.

14. Process according to claim 13, characterized in that  $R_{13}$  is the PACLITAXEL side chain precursor.

15. Process according to either of claims 13 and 14, characterized in that the deprotection of the hydroxyl at the 7-position is carried out by  $\beta$ -elimination.

16. 7-( $\beta$ -substituted-alkoxycarbonyloxy)-10-hydroxytaxane derivatives corresponding to the following formula 3b:



3b

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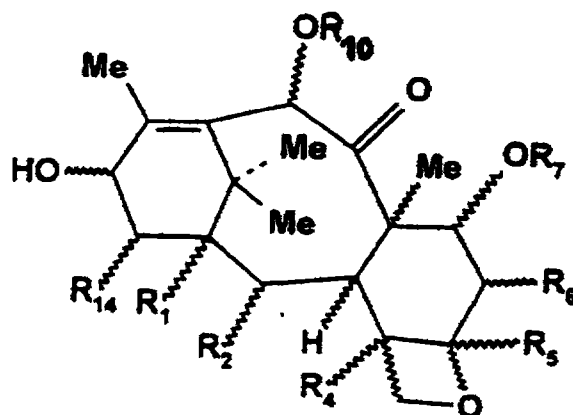
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in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_{14}$  are defined in one of claims 1 to 8.

17. Derivatives of the following general  
5 formula 3c:

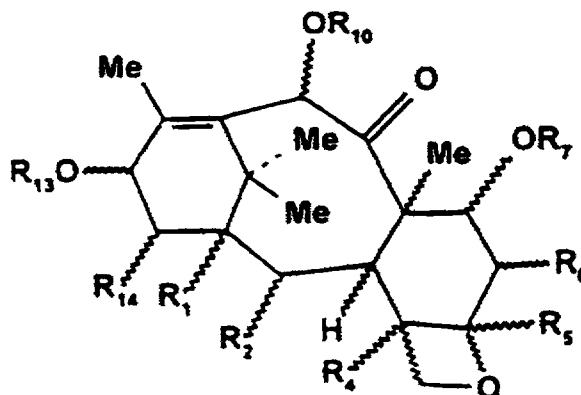


3c

in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_{14}$  are defined in one of claims 1 to 8, and  $R_{10}$  is defined in claim 10.

18. Derivative of the following general  
10 formula 3d:



3d

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in which

$R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{10}$  and  $R_{14}$  are defined in claim 17, and  $R_{13}$  represents a radical which is a taxane side chain precursor.

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