METHODS FOR PREPARING NEW TAXOIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: Methods of preparing methylthionemethoxy taxoids of formula (XXXIV) from baccatin and β-lactam are presented. These new taxoids display noteworthy anti-tumor and anti-leukemic properties.
METHODS FOR PREPARING NEW TAXOIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

CROSS-REFERENCE TO RELATED APPLICATIONS


[002] U.S. Patent Application Serial No. 09/528,448, filed March 17, 2000, in turn is also a continuation-in-part of U.S. Patent Application Serial No. 09/516,019, filed February 29, 2000, now U.S. Patent No. 6,218,553; which is a divisional of 08/481,205, filed June 7, 1995; now U.S. Patent No. 6,187,916; which is a continuation of 08/383,610, filed February 2, 1995, now
abandoned; which is a continuation of 08/011,922, filed
February 1, 1993, now abandoned. All of these patents
and applications are hereby specifically incorporated
herein by reference in their entirety.

[003] The present invention relates to methods
of preparing new taxoids of general formula:

[004]

\[
\text{(I)}
\]

[005] in which:

[006] \( Z \) represents a hydrogen atom or a radical
of general formula:

[007]

\[
\text{(II)}
\]

[008] in which:

[009] \( R_1 \) represents a benzoyl radical optionally
substituted with one or more identical or different atoms
or radicals chosen from halogen atoms and alkyl radicals
containing 1 to 4 carbon atoms, alkoxy radicals 
containing 1 to 4 carbon atoms or trifluoromethyl 
radicals, a thenoyl or furoyl radical or a radical R₂-O- 
C(=O)- in which 

[010] R₂ represents:

[011] an alkyl radical containing 1 to 8 carbon 
atoms, an alkenyl radical containing 2 to 8 carbon atoms, an 
alkynyl radical containing 3 to 8 carbon atoms, a 
cycloalkyl radical containing 3 to 6 carbon atoms, a 
cycloalkenyl radical containing 4 to 6 carbon atoms, a 
phenyl radical (unsubstituted or substituted with one or 
more atoms or radicals selected from halogen atoms, alkyl 
radicals containing 1 to 4 carbon atoms, and alkoxy 
radicals containing 1 to 4 carbon atoms), cyano radicals, 
carboxyl radicals, and alkoxycarbonyl radicals in which 
the alkyl portion contains 1 to 4 carbon atoms;

[012] a phenyl or an α- or β-naphthyl radical 
radical, which is unsubstituted or substituted with one 
or more atoms or radicals selected from halogen atoms, 
alkyl radicals containing 1 to 4 carbon atoms, alkoxy 
radicals containing 1 to 4 carbon atoms, and a 5-membered 
aromatic heterocyclic radical;

[013] R₃ represents a phenyl radical;
[014] $R_4$ represents an alkanoyloxy radical in which the alkanoyl portion contains 2 to 6 carbon atoms in an unbranched or branched chain, this radical being unsubstituted or substituted with one or more halogen atoms or with an alkoxy radical containing 1 to 4 carbon atoms, or alternatively $R_4$ represents a cycloalkanoyloxy radical in which the cycloalkanoyl portion contains 4 to 8 carbon atoms, or alternatively $R_4$ represents a benzoyloxy radical; and

[015] $R_5$ represents an alkoxy radical containing 1 to 4 carbon atoms in an unbranched or branched chain, substituted by an alkylthio radical containing 1 to 4 carbon atoms.

[016] Preferably, the radical $R_4$ represents an alkanoyloxy radical in which the alkanoyl portion contains 2 to 6 carbon atoms, or a cycloalkanoyloxy radical in which the cycloalkanoyl portion contains 4 to 8 carbon atoms.

[017] More especially, the present invention relates to the products of general formula (I) in which $Z$ represents a hydrogen atom or a radical of general formula (II) in which

[018] $R_1$ represents a benzoyl radical, or a radical $R_2$-O-C(=O)-, in which
[019] \( R_2 \) represents a tert-butyl radical, and
[020] \( R_3 \) represents a phenyl radical, and
[021] \( R_4 \) represents an alkanoyloxy radical in which the alkanoyl portion contains 2 to 4 carbon atoms, and
[022] \( R_5 \) represents an alkoxy group containing 1 to 4 carbon atoms substituted by a methylthio radical.
[023] Still more especially, the present invention relates to the products of general formula (I) in which \( Z \) represents a hydrogen atom or a radical of general formula (II) in which \( R_1 \) represents a benzoyl radical or a radical \( R_2-O-C(=O)- \) in which \( R_2 \) represents a tert-butyl radical and \( R_3 \) represents a phenyl radical, \( R_4 \) represents an acetoxy, or a methoxyacetoxy radical, and \( R_5 \) represents a methylthiomethoxy radical.
[024] The products of general formula (I) in which \( Z \) represents a radical of general formula (II) display noteworthy anti-tumor and anti-leukemic properties.
[025] According to the present invention, the new products of general formula (I) in which \( Z \) represents a radical of general formula (II) may be obtained by esterification of a product of general formula:
[026]

[027] in which R₄ and R₅ are defined as above, by means of an acid of general formula:

[028]

[029] in which R₁ and R₃ are defined as above, and either R₆ represents a hydrogen atom and R₇ represents a group protecting the hydroxyl function, or R₆ and R₇ together form a saturated 5- or 6-membered heterocycle,
or by means of a derivative of this acid, to obtain an ester of general formula:

in which \( R_1, R_3, R_4, R_5, R_6 \) and \( R_7 \) are defined as above, followed by replacement of the protective groups represented by \( R_7 \) and/or \( R_6 \) and \( R_7 \) by hydrogen atoms.

The esterification by means of a product of general formula (XII):

in which \( R'_4 \) is such that \( R'_4-O- \) is identical to \( R_4 \) defined as above but cannot represent a hydrogen atom or a hydroxyl radical, and in which \( X_1 \) represents a hydroxyl radical, may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic
hydrocarbons, aromatic hydrocarbons) at a temperature of between -10 and 90°C.

[036] The esterification may also be carried out using a product of general formula (XII) in which X₁ represents a radical R₄-O-, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of between 0 and 90°C.

[037] The esterification may also be carried out using a product of general formula (XII) in which X₁ represents a halogen atom, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of between 0 and 80°C.

[038] Preferably, R₆ represents a hydrogen atom and R₇ represents a group protecting the hydroxyl function, or alternatively R₆ and R₇ together form a saturated 5- or 6-membered heterocycle.

[039] When R₆ represents a hydrogen atom, R₇ preferably represents a methoxymethyl, 1-ethoxyethyl,
benzyloxyethyl methyl, trimethylsilyl, triethylsilyl, 
β-trimethylsilylethoxymethyl, benzyloxy carbonyl or
tetrahydroxy pyranyl radical.

[040] When R₆ and R₇ together form a heterocycle,
the latter is preferably an oxazolidine ring optionally
monosubstituted or gem-disubstituted at position 2.

[041] Replacement of the protective groups R₇
and/or R₆ and R₇ by hydrogen atoms may be performed,
depending on their nature, in the following manner:

[042] 1) when R₆ represents a hydrogen atom and
R₇ represents a group protecting the hydroxyl function,
replacement of the protective groups by hydrogen atoms is
performed by means of an inorganic acid (hydrochloric
acid, sulfuric acid, hydrofluoric acid) or organic acid
(acetic acid, methanesulfonic acid,
trifluoromethanesulfonic acid, p-toluenesulfonic acid)
used alone or mixed, working in an organic solvent chosen
from alcohols, ethers, esters, aliphatic hydrocarbons,
halogenated aliphatic hydrocarbons, aromatic hydrocarbons
or nitriles at a temperature of between -10 and 60°C,
2) when \( R_6 \) and \( R_7 \) together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula:

\[
\begin{array}{c}
\text{R}_1 - \text{N} - \text{O} \\
\text{R}_8 \quad \text{R}_9
\end{array}
\]

(VI)

in which \( R_1 \) is defined as above and \( R_8 \) and \( R_9 \), which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an arylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively \( R_8 \) represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and \( R_9 \) represents a hydrogen atom, or alternatively \( R_8 \) and \( R_9 \), together with the carbon atom to which they are linked,
form a 4- to 7-membered ring, replacement of the protective group formed by \( R_6 \) and \( R_7 \) by hydrogen atoms may be performed, depending on the meanings of \( R_4 \), \( R_8 \) and \( R_9 \) in the following manner:

[046]  
a) when \( R_4 \) represents a tert-butoxycarbonyl radical and \( R_8 \) and \( R_9 \), which may be identical or different, represent an alkyl radical or an arylalkyl (benzyl) or aryl (phenyl) radical, or alternatively \( R_8 \) represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and \( R_9 \) represents a hydrogen atom, or alternatively \( R_8 \) and \( R_9 \) together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):

[047]

![Structure](image)

(VII)

[048] in which \( R_3 \), \( R_4 \) and \( R_5 \) are defined as above, which is acylated by means of benzoyl chloride in
which the phenyl ring is optionally substituted or by means of thienoyl chloride, of furoyl chloride or of a product of general formula (VIII):

\[ R_2-O-C(=O)-X \]  \hspace{1cm} (VIII)

in which \( R_2 \) is defined as above and \( X \) represents a halogen atom (fluorine, chlorine) or a residue \(-O-R_2\) or \(-O-C(=O)-O-R_2\), to obtain a product of general formula (I) in which \( Z \) represents a radical of general formula (II).

[051] Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20°C to yield the product of general formula (VII).

[052] Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thienoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is
performed at a temperature of between 0 and 50°C, and preferably in the region of 20°C.

[053] b) when R₁ represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R₂O-C(=O)⁻ in which R₂ is defined as above, R₈ represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R₉ represents a hydrogen atom, replacement of the protective group formed by R₆ and R₇ by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulfuric acid) or organic acid (acetic acid, methanesulfonic acid, trifluoromethane-sulfonic acid, p-toluenesulfonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of between -10 and 60°C, and preferably between 15 and 30°C.

[054] According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom
and $R_4$ and $R_5$ are defined as above, may be obtained from 10-deacetyl-baccatin III of formula (IX):

[055]

![Chemical Structure](image)

(IX)

[056] It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula (X):

[057] \((R)_3\text{-Si-Hal}\) (X)

[058] in which the symbols $R$, which may be identical or different, represent an alkyl radical containing 1 to 4 carbon atoms, optionally substituted with a phenyl radical, or a phenyl radical, on 10-deacetyl-baccatin III, to obtain a product of general formula (XI):
[060] in which R is defined as above, followed by the action of a product of general formula (XII):

\[ R'_4-X_1 \]  \hspace{1cm} (XII)

[062] in which \( R'_4 \) is such that \( R'_4-O^- \) is identical to \( R_4 \) defined as above but cannot represent a hydrogen atom or a hydroxyl radical, and \( X_1 \) represents a halogen atom, to obtain a product of general formula (XIII):

\[ \]  \hspace{1cm} (XIII)
in which $R$ and $R_4$ are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):

![Diagram of molecule XIV]

in which $R_4$ is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

$$R'_5-X_2$$ (XV)

in which $R'_5$ is such that $R'_5-O^-$ is identical to $R_5$ defined as above and $X_2$ represents a halogen atom or a sulfuric or sulfonic ester residue, to give the product of general formula (III).

Generally, the action of a silyl derivative of general formula (X) on 10-deacetyl-baccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or
xylenes, at a temperature between 0°C and the refluxing
temperature of the reaction mixture.

[070] Generally, the action of a product of
general formula (XII) on a product of general formula
(XI) is performed, after metalation of the hydroxyl
function at position 10 by means of an alkali metal
hydride such as sodium hydride, an alkali metal amide
such as lithium amide or an alkali metal alkylide such as
butyllithium, working in an organic solvent such as
dimethylformamide or tetrahydrofuran at a temperature of
between 0 and 50°C.

[071] Generally, the replacement of the silyl
protective groups of the product of general formula
(XIII) by hydrogen atoms is performed by means of an acid
such as hydrofluoric acid or trifluoroacetic acid in the
presence of a base such as triethylamine or pyridine
optionally substituted with one or more alkyl radicals
containing 1 to 4 carbon atoms, the base optionally being
combined with an inert organic solvent such as a nitrile,
for instance acetonitrile, or a halogenated aliphatic
hydrocarbon such as dichloromethane at a temperature of
between 0 and 80°C.

[072] Generally, the action of a product of
general formula (XV) on a product of general formula
(XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

[073] According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), and R₄ and R₅ are defined as above may be obtained from a product of general formula (XVI):

![Chemical Structure Image]

(XVI)

[074] in which R₁, R₃, R₆ and R₇ are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):

![Chemical Structure Image]

(XVII)
[077] in which R, R₁, R₃, R₆ and R₇ are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):

[078]

![Diagram](XVIII)

[079] in which R, R₁, R₃, R₄, R₆ and R₇ are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):

[080]

![Diagram](XIX)
which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0 336 841 and International Applications PCT WO 92/09589 and WO 94/07878, or from the products of general formula (XX):

\[ \text{(XX)} \]
in which \( R_1 \) and \( R_3 \) are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which \( Z \) represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms, on a product of general formula (XXI):

![Chemical Structure](image)

in which \( R_4 \) is defined as above and \( R' \) and \( R'' \), which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a
cycloalkenyl radical containing 3 to 6 carbon atoms, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z₁ represents a hydrogen atom or a radical of general formula (XXII):

\[ \text{(XXII)} \]

[088]

\[ \text{[089]} \]

in which R₁ and R₃ are defined as above, and either R₆ represents a hydrogen atom and R₇ represents a group protecting the hydroxyl function, or R₆ and R₇ together form a saturated 5- or 6-membered heterocycle, and R₄ is defined as above, to obtain a product of general formula (XXIII):

\[ \text{(XXIII)} \]

[090]
in which $R_1$, $R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ are defined as above, followed, when $Z_1$ represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by $R_6$ and/or $R_6$ and $R_7$ by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of the aliphatic alcohol is performed at a temperature of between -10 and 60°C.

According to the invention, the product of general formula (XXI) in which $Z_1$ and $R_4$ are defined as above may be obtained by the action of a dialkyl sulfoxide of general formula (XXIV):

![Diagram of general formula (XXIV)]

in which $R'$ and $R''$ are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulfoxide of general formula (XXIV), preferably dimethyl sulfoxide, with the product of general formula (XIX) is performed in
the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of between 0 and 50°C, and preferably in the region of 25°C.

[097] According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by the action of a product of general formula (XII) on a product of general formula (XXV):

[098]

[099] in which R₁, R₃, R₅, R₆ and R₇ are defined as above, working under the conditions described for the action of a product of general formula (XII) on a product of general formula (XI), followed by replacement of the protective groups represented by R₇, or R₆ and R₇, by hydrogen atoms under the conditions described above.

[0100] The product of general formula (XXV) may be obtained by the action of a zinc halide such as zinc
iodide or hydrazine on a product of general formula (XXVI):

\[
\text{(XXVI)}
\]

[0101] in which R1, R3, R5, R6 and R7 are defined as above.

[0102] Generally, the reaction is performed working in an aliphatic alcohol containing 1 to 4 carbon atoms, such as methanol or ethanol, at a temperature of between 0 and 50°C.

[0103] The product of general formula (XXVI) may be obtained by the action of activated Raney nickel in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms on a product of general formula (XXVII):
[0105] in which $R_1$, $R_3$, $R_6$, $R_7$, $R'$ and $R''$ are defined as above, working under the conditions described above for the preparation of a product of general formula (I) from a product of general formula (XXI).

[0107] The product of general formula (XXVII) may be obtained by the action of a sulfoxide of general formula (XXIV) on a product of general formula (XXVII):

[0109] in which $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above, working under the conditions described above for
the action of a sulfoxide of general formula (XXIV) on a
product of general formula (XIX).

[0110] The product of general formula (XXVIII)
may be obtained from a product of general formula (XXIX):

[0111]

\[
\begin{align*}
R_1 & \quad \text{CH}_3\text{O}\text{CH}_2\text{COO} \\
R_3 & \quad \text{O}\text{Si}(R)_3 \\
R_6 & \quad \text{O}\text{COCH}_3 \\
R_7 & \quad \text{OCOC}_6\text{H}_5
\end{align*}
\]

(XXIX)

[0112] in which \( R_1, R_3, R_6 \) and \( R_7 \) are defined as above, working under the conditions described above for
replacing the silyl groups of the product of general
formula (XIII) by hydrogen atoms.

[0113] The product of general formula (XXIX) may
be prepared under the conditions described in
International Application PCT WO 95/11241.

[0114] The new products of general formula (I)
obtained by carrying out the processes according to the
invention may be purified according to known methods such
as crystallization or chromatography.
[0115] The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

[0116] In vitro measurement of the biological activity was performed on tubulin extracted from pig's brain by the method of M.L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765-768 (1973). Study of the depolymerization of microtubules to tubulin was performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293(7): series II, 501-503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as TAXOL® (paclitaxel) and TAXOTERE® (docetaxel).

[0117] In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of between 1 and 10 mg/kg administered intraperitoneally, as well as on other liquid or solid tumors.

[0118] The new products have anti-tumor properties, and more especially activity against tumors which are resistant to TAXOL® (paclitaxel) or to TAXOTERE® (docetaxel). Such tumors comprise colon tumors.
which have a high expression of the \textit{mdrl} gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumor to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumors such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses \textit{mdrl}.

\textbf{Brief Description of the Drawings:}

[0119] Figure 1 illustrates a method for synthesizing methylthiomethyl taxoids via an oxazolidine coupling method.

[0120] Figure 2 illustrates a method for synthesizing methylthiomethyl-paclitaxel derivatives via a \(\beta\)-lactam synthon method.

[0121] Figure 3 illustrates another method for synthesizing methylthiomethyl-paclitaxel derivatives via a \(\beta\)-lactam synthon method.

[0122] The examples which follow illustrate the present invention.

\textbf{EXAMPLE 1}

[0123] 243 mg of \(4\alpha\)-acetoxy-\(2\alpha\)-benzoyloxy-\(5\beta,20\)-epoxy-\(1\beta\)-hydroxy-\(7\beta\)-methoxy-\(9\)-oxo-\(10\beta\)-(3-
pyridylcarbonyl)oxy-11-taxen-13α-yl (2R,4S,5R)-3-tert-
butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-
oxazolidine-5-carboxylate were dissolved in 4.5 cm³ of a
0.1 N ethanolic solution of hydrochloric acid containing
1% of water. The solution thereby obtained was stirred
for 3 hours at a temperature in the region of 20°C and
25 cm³ of dichloromethane were then added. The organic
phase was separated after settling has taken place and
washed successively two times with 10 cm³ of saturated
aqueous sodium hydrogen carbonate solution, dried over
magnesium sulfate, filtered and concentrated to dryness
under reduced pressure (2.7 kPa) at 40°C. 290 mg of a
white foam were obtained, which were purified by
chromatography on silica gel deposited on plates (gel
thickness 1 mm, plates 20 × 20 cm, eluent:
dichloromethane/methanol, 95:5 by volume) in 80-mg
fractions (4 plates). After localization with UV of the
zone corresponding to the adsorbed product sought, this
zone was scraped off and the silica collected was washed
on sintered glass ten times with 10 cm³ of ethyl acetate.
The filtrates were combined and concentrated to dryness
under reduced pressure (2.7 kPa) at 20°C. A white foam
was obtained, which was repurified according to the same
technique (2 plates: 20 × 20 × 1 mm; eluent:
dichloromethane/methanol, 95:5 by volume). 132 mg of 4α-acetoxyl-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-10β-(3-pyridylcarbonyl)oxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which are as follows:

[0124] - optical rotation: $[\alpha] = -34$ (c = 0.5; methanol).

[0125] - 1H NMR spectrum (300 MHz; CDCl3):
chemical shift $\delta$ in ppm; coupling constants $J$ in Hz):
1.30 (s, 3H: $-\text{CH}_3$ at position 16 or 17); 1.35 (s, 12H: $-\text{C(CH}_3)_3$ and $-\text{CH}_3$ at position 16 or 170; 1.75 (s, 3H: $-\text{CH}_3$); 1.82 and 2.77 (2 mts, 1H each: $-\text{CH}_2-$ at position 6); 1.97 (s, 3H: $-\text{CH}_3$); 2.35 (d, $J = 9$, 2H: $-\text{CH}_2-$ at position 14); 2.39 (s, 3H: $-\text{COCH}_3$); 3.38 (d, $J = 5$, 1H: $-\text{OH}$ at position 2'); 3.42 (s, 3H: $-\text{OCH}_3$); 3.88 (d, $J = 7.5$, 1H: $-\text{H}$ at position 3); 3.96 (dd, $J = 11$ and 7.5, 1H: $-\text{H}$ at position 7); 4.18 and 4.32 (2d, $D J = 8.5$, 1H each: $-\text{CH}_2-$ at position 20); 4.64 (mt, 1H: $-\text{H}$ at position 2'); 4.98 (broad d, $J = 10$, 1H: $-\text{H}$ at position 5); 5.28 (broad d, $J = 10$, 1H: $-\text{H}$ at position 3'); 5.39 (d, $J = 10$, 1H: $-\text{CONH}$-); 5.70 (d, $J = 7.5$, 1H: $-\text{H}$ at position 2); 6.22 (broad t, $J = 9$, 1H: $-\text{H}$ at position 13); 6.69 (s, 1H: $-\text{H}$ at position 10); from 7.25 to 7.45 (mt, 5H: $-\text{C}_6\text{H}_5$).
at position 3'); 7.44 [(dd, J = 8.5 and 6, 1H:
-OCOC₆H₄N(-H at position 5)]; 7.50 [(dd, J = 7.5, 2H:
-OCOC₆H₅(-H at position 3 and H at position 5)]; 7.62 [(t, 
J = 7.5, 1H: -OCOC₆H₅(-H at position 4)]; 8.12 [(d, J = 
7.5, 2H: -OCOC₆H₅(-H at position 2 and -H at position 6)];
8.35 [(dt, J = 8.5 and 1, 1H: -OCOC₆H₄N(-H at position 
4)]; 8.82 (dd, J = 6 and 1, 1H: -OCOC₆H₄N(-H at position 
6)]; 9.32 (d, J = 1, 1H: -OCOC₆H₄N(-H at position 2)].

[0126] 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-10β-(3-pyridylcarbonyloxy-11-ta
taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-
methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was 
prepared in the following manner:

[0127] 290 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-
epoxy-1β,10β-dihydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl 
(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-
phenyl-1,3-oxazolidine-5-carboxylate, 18.5 mg of 
4-(dimethylamino)-pyridine, 0.5 g of 4 Å molecular sieve 
and 112 mg of N,N'-dicyclohexylcarbodiimide were added at 
a temperature in the region of 20°C to a solution, kept 
stirring under an argon atmosphere, of 46 mg of 
3-pyridinecarboxylic acid in 25 cm³ of anhydrous ethyl 
acetate. The reaction mixture was kept stirring for
16 hours at a temperature in the region of 20°C, 46 mg of
2-pyridinecarboxylic acid, 18.5 mg of
4-(dimethylamino)pyridine, 0.5 g of 4 Å molecular sieve
and 112 mg of N,N'-dicyclohexylcarbodiimide were then
added and the mixture was again kept stirring for
24 hours, this cycle then being repeated twice more. The
reaction mixture was filtered through sintered glass
lined with Celite. The sintered glass was washed two
times with 50 cm³ of ethyl acetate, and the filtrates were
combined, washed successively two times with 10 cm³ of
saturated aqueous sodium hydrogen carbonate solution and
six times with 20 cm³ of distilled water, dried over
magnesium sulfate, filtered and concentrated to dryness
under reduced pressure (2.7 kPa) at 40°C. 298 mg of 4α-
acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-
9-oxo-10β-(3-pyridylcarbonyl)oxy-11-taxen-13α-yl
(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-
phenyl-1,3-oxazolidine-5-carboxylate were thereby
obtained in the form of a white foam.

[0128] 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-
1β,10β-dihydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl
(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-
phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

[0129] 0.263 cm$^3$ of hydrazine monohydrate were added dropwise and at a temperature in the region of 20°C to a solution, kept stirring under an argon atmosphere, of 150 mg of 4α-acetoxyl-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetoxyl-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 4 cm$^3$ of anhydrous ethanol. The reaction medium was kept stirring for 1 hour at a temperature in the region of 20°C and then poured into a mixture of 100 cm$^3$ of ethyl acetate and 50 cm$^3$ of distilled water. The organic phase was separated after settling has taken place and the aqueous phase was re-extracted two times with 50 cm$^3$ of ethyl acetate. The organic phases were combined, washed four times with 50 cm$^3$ of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 180 mg of a white foam were obtained, which was purified by chromatography on silica gel deposited on plates [(gel thickness 1 mm, plates 20 × 20 cm, eluent: dichloromethane/methanol (90:10 by volume)] in 90 mg fractions (2 plates). After localization with UV rays of the zone corresponding to
the adsorbed product sought, this zone was scraped off and the silica collected was washed on sintered glass ten times with 10 cm³ of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 113 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

[0130] 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

[0131] 100 cm³ of an ethanolic suspension of activated nickel prepared by Raney's method (obtained from 80 cm³ of the approximately 50% commercial aqueous suspension, by successive washing fifteen times with 100 cm³ of distilled water and four times with 150 cm³ of ethanol to a pH in the region of 7) were added at a temperature in the region of 20°C to a solution, kept stirring under an argon atmosphere, of 1.041 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-
methoxyacetoxyl-7β-methylthiomethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 cm$^3$ of anhydrous ethanol. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20°C and was then filtered through sintered glass. The sintered glass was washed three times with 100 cm$^3$ of ethanol and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 821 mg of a white foam were obtained, which was purified by chromatography on 75 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter (eluent: dichloromethane/ethyl acetate, 90:10 by volume), collecting 5-cm$^3$ fractions. The fractions containing only the product sought were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 228 mg of 4α-acetoxyl-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetoxyl-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

[0132] 4α-Acetoxyl-2β-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxyl-7β-methylthiomethoxy-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-
methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was
prepared in the following manner:

[0133] 3.35 cm\(^3\) of acetic acid and 11.5 cm\(^3\) of
acetic anhydride were added at a temperature in the
region of 20°C to a solution, kept stirring under an argon
atmosphere, of 5 g of 4α-acetoxy-2β-benzoyloxy-5β,20-
epoxy-1β,7β-dihydroxy-10β-methoxyacetoxy-9-oxo-11-taxen-
13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-
methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in
165 cm\(^3\) of anhydrous dimethyl sulfoxide. The reaction
mixture was kept stirring for 3 days at a temperature in
the region of 20°C and was then poured into 500 cm\(^3\) of
dichloromethane. 100 cm\(^3\) of saturated aqueous potassium
carbonate solution were then added with efficient
stirring to a pH in the region of 7. After stirring for
10 minutes, the organic phase was separated after
settling has taken place and the aqueous phase was re-
extracted two times with 250 cm\(^3\) of dichloromethane. The
organic phases were combined, washed with 3 times 100 cm\(^3\)
of distilled water, dried over magnesium sulfate,
filtered and concentrated to dryness under reduced
pressure (2.7 kPa) at 40°C. 9.5 g of a pale yellow oil
were obtained, which was purified by chromatography on
250 g of silica (0.063-0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50 cm³ fractions. The fractions containing only the product sought were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 3.01 g of 4-acetoxy-2β-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7β-methylthiomethoxy-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

[0134] 4α-Acetoxy-2β-benzoyloxy-5β,20-epoxy-1β,7β-dihydroxy-10β-methoxyacetoxy-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

[0135] 220 cm³ of triethylamine/hydrofluoric acid (mole ratio 1:3) complex were added dropwise at a temperature in the region of 0°C to a solution, kept stirring under an argon atmosphere, of 20 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-7β-triethylsilyloxy-1β-hydroxy-10β-methoxyacetoxy-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 200 cm³ of
anhydrous dichloromethane. The reaction mixture was then warmed to a temperature in the region of 20°C, maintained for 3 hours at this temperature and poured into 4 liters of saturated aqueous sodium hydrogen carbonate solution. The pH of the reaction medium thus being brought to around 7. After stirring for 10 minutes, the organic phase was separated after settling has taken place and the aqueous phase was extracted two times with 100 cm³ of dichloromethane. The organic phases were combined, washed with 100 cm³ of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 17.4 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β-dihydroxy-10β-methoxyacetoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

[0136] 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-7β-triethylsilyloxy-1β-hydroxy-10β-methoxyacetoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in International Application PCT WO 95/11241.
EXAMPLE 2:

[0137] Working as in Example 1, but starting from 210 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-
hydroxy-7β-methoxy-9-oxo-10β-(2-pyridylcarbonyl)oxy-11-
taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-
methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate,
145 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-
hydroxy-7β-methoxy-9-oxo-10β-(2-pyridylcarbonyl)oxy-11-
taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-
hydroxy-3-phenylpropionate were obtained in the form of a
white foam, the characteristics of which are as follows:

[0138] - optical rotation: \( [\alpha]^D_{20} = -52 \) (c = 0.5;
methanol).

[0139] - \(^1\)H NMR spectrum (400 MHZ: CDCl\(_3\));
chemical shifts \( \delta \) in ppm; coupling constants \( J \) in Hz):
1.31 (s, 3H: -CH\(_3\) at position 16 or 17); 1.37 [(s, 12H:
-CH\(_3\)_3 and -CH\(_3\) at position 16 or 17]; 1.74 (s, 1H: -OH
at position 1); 1.78 (s, 3H: -CH\(_3\)); 1.82 and 2.78 (2 mts,
1H each: -CH\(_2\)- at position 6); 1.97 (s, 3H: -CH\(_3\)); 2.35
(d, \( J = 9 \), 2H: -CH\(_2\)- at position 14); 2.40 (s, 3H:
-COCH\(_3\)); 3.40 (d, \( J = 4.5 \), 1H: -OH at position 2'); 3.43
(s, 3H: -OCH\(_3\)); 3.92 (d, \( J = 7.5 \), 1H: -H at position 3);
3.98 (dd, \( J = 11 \) and 7, 1H: -H at position 7); 4.20 and
4.32 (2 d, J = 8.5, 1H each: -CH₂- at position 20); 4.64 (mt, 1H: -H at position 2'); 5.00 (broad d, J = 10, 1H: -H at position 5); 5.28 (broad d, J = 10, 1H: -H at position 3'); 5.43 (d, J = 10, 1H: -CONH-); 5.73 (d, J = 7.5, 1H: -H at position 2); 6.22 (broad t, J = 9, 1H: -H at 13); 6.67 (s, 1H: -H at position 10); from 7.25 to 7.45 (mt, 5H: -C₆H₅ at position 3'); 7.51 [(mt, 3H: -OCOC₆H₅(-H at position 3 and H at position 5) and
-OCOC₅H₄N(-H at position 5)]; 7.61 [(t, J = 7.5, 1H: -OCOC₆H₅(-H at position 4)]; 7.88 [(split t, J = 8 and 1, 1H: -OCOC₅H₄N(-H at position 4)]; 8.12 [(d, J = 7.5, 2H: -OCOC₆H₅(-H at position 2 and -H at position 6)]; 8.20 (broad d, J = 8, 1H: -OCOC₅H₄N(-H at position 3)]; 8.82 (broad dd J = 5 and 1, 1H: -OCOC₅H₄N(-H at position 6)].

[0140] Working as in Example 1, but starting from 300 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7β-methoxy-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate, 230 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-10β-(2-pyridylcarbonyloxy-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam.
EXAMPLE 3:

[0141] Working as in Example 1, but starting from 300 mg of 4α-acetoxy-2α-benzoyloxy-10β-
cyclopentylcarbonyloxy-5β, 20-epoxy-1β-hydroxy-7β-methoxy-
9-oxo-11-taxen-13α-y1 (2R, 4S, 5R)-3-tert-butoxycarbonyl-2-
(4-methoxyphenyl)-4-phenyl-1, 3-oxazolidine-5-carboxylate,
96 mg of 4α-acetoxy-2α-benzoyloxy-10β-
cyclopentylcarbonyloxy-5β, 20-epoxy-1β-hydroxy-7β-methoxy-
9-oxo-11-taxen-13α-y1 (2R, 3S)-3-tert-butoxycarbonylamino-
2-hydroxy-3-phenylpropionate were obtained in the form of
a white foam, the characteristics of which are as
follows:

[0142] - optical rotation: \([\alpha]D^{20} = -66\) (c = 0.5;
methanol).

[0143] - \(^1\)H NMR spectrum (400 MHz; CDCl\(_3\); chemical
shifts \(\delta\) in ppm; coupling constants \(J\) in Hz): 1.25 (s,
6H: \(-\text{CH}_3\) at positions 16 and 17); 1.39 [s, 9H: \(-\text{C(\text{CH}_3)}_3\)];
from 1.55 to 1.80 and from 1.90 to 2.10 (2 mts, 4H each:
\(-\text{CH}_2\) of the cyclopentyl); 1.71 (s, 1H: \(-\text{OH}\) at position
1); 1.75 (s, 3H: \(-\text{CH}_3\)); 1.82 and 2.75 (2 mts, 1H each:
\(-\text{CH}_2\) at position 6); 1.93 (s, 3H: \(-\text{CH}_3\)); 2.33 (d, \(J =
9\) Hz, 2H: \(-\text{CH}_2\) at position 14); 2.39 (s, 3H: \(-\text{COCH}_3\));
2.95 (mt, 1H: \(-\text{CH}\) of the cyclopentyl); 3.38 (s, 3H:

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-OCH₃); 3.40 (d, J = 5, 1H: -OH at position 2'); 3.88 (d, J = 7.5, 1H: -H at position 3); 3.91 (dd, J = 11 and 7.5, 1H: -H at position 7); 4.19 and 4.32 (2 d, J = 8.5, 1H each: -CH₂ at position 20); 4.65 (mt, 1H: -H at position 2'); 4.98 (broad d, J = 10, 1H: -H at position 5); 5.28 (broad d, J = 10, 1H: -H at position 3'); 5.41 (d, J = 10, 1H: -CONH-); 5.68 (d, J = 7.5, 1H: -H at position 2); 6.21 (broad t, J = 9, 1H: -H at position 13); 6.45 (s, 1H: -H at position 10); from 7.25 to 7.45 (mt, 5H: -C₆H₅ at position 3'); 7.51 (t, J = 7.5, 2H: -OCOC₆H₅ (-H at position 3 and H at position 5); 7.63 (t, J = 7.5, 1H: -OCOC₆H₅ (-H at position 4)); 8.12 (d, J = 7.5, 2H: -OCOC₆H₅ (-H at position 2 and -H at position 6)).

[0144] Working as in Example 1, but starting from 300 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate, 410 mg of 4α-acetoxy-2α-benzoyl oxy-10β-cyclopentylcarbonyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam.
EXAMPLE 4:

[0145] Working as in Example 1, but starting from 
300 mg of 4α-acetoxy-2α-benzoyloxy-10β-cyclopropyl-
carbonyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-11-
taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-
methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate,
130 mg of 4α-acetoxy-2α-benzoyloxy-10β-
cyclopropylcarbonyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-
9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-
2-hydroxy-3-phenylpropionate were obtained in the form of 
a white foam, the characteristics of which are as 
follows:

[0146] - optical rotation: $[\alpha]_D^{20} = -71$ (c = 0.5;
methanol).

[0147] - $^1$H NMR spectrum (400 MHz; CDCl$_3$, chemical 
shifts $\delta$ in ppm; coupling constants $J$ in Hz): 1.00 and 
1.19 (2 mts, 2H each: $-\text{CH}_2-$ of the cyclopropyl); 1.25 (s, 
3H: $-\text{CH}_3$ at position 16 or 17); 1.27 (s, 3H: $-\text{CH}_3$ at 
position 16 or 17); 1.39 [s, 9H: $-\text{C}($CH$_3)_3$]; 1.71 (s, 1H: 
$-\text{OH}$ at position 1); 1.75 (s, 3H: $-\text{CH}_3$); from 1.70 to 1.90 
(mt, 1H: $=\text{CH}$- of the cyclopropyl); 1.82 and 2.75 (2 mts, 
1H each: $-\text{CH}_2-$ at position 6); 1.93 (s, 3H: $-\text{CH}_3$); 2.33 
(d, $J = 9$, 2H: $-\text{CH}_2-$ at position 14); 2.40 (s, 3H: 

-COCH₃); 3.35 (s, 3H: -OCH₃); 3.40 (d, J = 5, 1H: -OH at position 2'); 3.88 (d, J = 7.5, 1H: -H at position 3); 3.89 (dd, J = 11 and 7.5, 1H: -H at position 7); 4.19 and 4.32 (2 d, J = 8.5, 1H each: -CH₂- at position 20); 4.65 (mt, 1H: -H at position 2'); 5.00 (broad d, J = 10, 1H: -H at position 5); 5.28 (broad d, J = 10, 1H: -H at position 3'); 5.42 (d, J = 10, 1H: -CONH-); 5.68 (d, J = 7.5, 1H: -H at position 2); 6.21 (broad t, J = 9, 1H: -H at position 13); 6.48 (s, 1H: -H at position 10); from 7.25 to 7.45 (mt, 5H: -C₆H₅ at position 3'); 7.52 (t, J = 7.5, 2H: -OCOC₆H₅ (-H at position 3 and H at position 5)); 7.64 (t, J = 7.5, 1H: -OCOC₆H₅ (-H at position 4)); 8.12 (d, J = 7.5, 2H: -OCOC₆H₅ (-H at position 2 and -H at position 6)).

[0148] Working as in Example 1, but starting from 300 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10-dihydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate, 435 mg of 4α-acetoxy-2α-benzoyloxy-10β-cyclopropylcarboxyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam.
EXAMPLE 5:

[0149] Working as in Example 1, but starting from 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetox-9-oxo-11-taxon-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate, 164 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetox-9-oxo-11-taxon-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of a white foam, the characteristics of which are as follows:

[0150] optical rotation: $[\alpha]^D_{20} = -48$ (c = 0.5; methanol)

[0151] $^1$H NMR spectrum (300 MHz; CDCl$_3$; $\delta$ in ppm; coupling constants J in Hz): 1.17 (s, 3H: -H$_3$); 1.22 (s, 3H: -CH$_3$); 1.35 (s, 9H: -C(CH$_3$)$_3$; 1.75 (s, 3H: -CH$_3$); 1.80 and 2.75 (2 mts, 1 H each: -CH$_2$- 6); 1.90 (s, 3H: -CH$_3$); 2.30 (d, J = 9, 2H: -CH$_2$- 14); 2.37 (s, 3H: -COCH$_3$); 3.35 and 3.55 (2 s, 3H each: -OCH$_3$); 3.40 (d, J = 5, 1H: -OH 2'); 3.85 (d, J = 7, 1H: -H 3); 3.88 (dd, J = 11 and 7, 1H: -H 7); 4.17 and 4.32 (2 d, J = 8.5, 1H each: -CH$_2$- 20); 4.19 and 4.27 (2 d, J = 15, 1H each: -OOC$_2$H$_5$OCH$_3$); 4.65 (mt, 1H: -H 2'); 4.97 (broad d, J = 10,
1H: -H 5); 5.25 (broad d, J = 10, 1H: -H 3'); 5.42 (d, J = 10, 1H: -CONH-); 5.66 (d, J = 7, 1H: -H 2); 6.18 (broad t, J = 9, 1H: -H 13); 6.52 (s, 1H: -H 10); from 7.30 to 7.50 (mt, 5H: -C₆H₅ 3'); 7.51 ((t, J = 7.5, 2H: -OCOC₆H₅(-H 3 and H 5)); 7.63 ((t, J = 7.5, 1H: -OCOC₆H₅(-H 4)); 8.12 (d, J = 7.5, 2H: -OCOC₆H₅(-H 2 and H 6)).

EXAMPLE 6:

[0152] Working as in example 1, but starting from 4α-acetoxy-2β-benzoyloxy-5β,20 epoxy-1β-hydroxy-10β-methoxyacetoxy-7β-methylthiomethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate, 98 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methylthiomethoxy-9-oxo-10β-methoxyacetoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenyl propionate of the following structure was obtained:

[0153]
NMR spectrum: $^1$H (400 MHz, CDCl$_3$, δ ppm):
1.25 (s: 6H); 1.38 (s: 9H); 1.71 (s: 1H); 1.78 (s: 3H); 1.88 (mt: 1H); 2.03 (s: 3H); 2.16 (s: 3H); 2.34 (d, J = 9 Hz: 2H); 2.42 (s: 3H); 2.85 (mt: 1H); 3.38 (d, J = 5 Hz: 1H); 3.53 (s: 3H); 3.89 (d, J = 7.5 Hz: 1H); 4.15 (d, J = 16 Hz: 1H); 4.20 (d, J = 8.5 Hz: 1H); 4.27 (d, J = 16 Hz: 1H); from 4.30 to 4.40 (mt: 1H); 4.32 (d, J = 8.5 Hz: 1H); 4.65 (mt: 1H); 4.71 (AB pattern, J=12 Hz: 2H); 4.98 (d large, J = 10 Hz: 1H); 5.28 (d large, J=10Hz: 1H); 5.40 (d, J = 10 Hz: 1H); 5.72 (d, J = 7.5 Hz: 1H); 6.22 (t large, J = 9 Hz: 1H); 6.67 (s: 1H); from 7.25 to 7.45 (mt: 5H); 7.52 (t, J = 7.5 Hz: 2H); 7.64 (t, J = 7.5 Hz: 1H); 8.12 (d, J=7.5Hz: 2H).

EXAMPLE 7:

The intermediate
[0157] when treated with HCl/EtOH by the method of Example 1 can generate 4α-acetoxy-2α-benzoyloxy-5β,20-
epoxy-1β hydroxy-7β-methylthiomethoxy-9-oxo-10β-acetyl-
11-taxon-13α-y1 (2R,3S)-3-tert-butoxycarbonylamino-2-
hydroxy-3-phenyl propionate.

EXAMPLE 8:

[0158] Process for Preparing 7-Alkylthioalkyl-
Paclitaxel Derivatives: Coupling of Taxenes with Phenyloxazolididine Carboxylic Acids (Figure 1)

[0159] A solution of 52g of 4,10β-diacetoxy-2α-
benzoyloxy-5β,20-epoxy,13α-dihydroxy-7β-triethylsiloxy-
9-oxo-tax-11-ene (SIBAC (XXX))

[0160]

\[\text{(SIBAC)}\]

[0161] in 850ml ethyl acetate was dehydrated by distillation under 70mmHg of pressure until a volume of
360ml of distillate was obtained. The resulting solution
was chilled to 0°C. 44.6g (2R,4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylic acid (XXXa)

[0162]

[0163] was added to this solution, followed by rinsing with 20ml ethyl acetate. 22.4g dicyclohexylcarbodiimide and 1.77g 4-dimethylamino-pyridine were then successively added to the solution, followed by an additional rinse with 30ml ethyl acetate. The reaction medium was maintained for about 4 hours at 5°C, whereupon the DCU (dicyclohexylurea) that was formed was filtered off. After the DCU was washed three times (each time with 270ml ethyl acetate), the washing organic phases and the filtrate were recombined and washed twice at room temperature, each time with 815ml of a 5% sodium bicarbonate solution. The organic phase was then dried with 136g of MgSO₄ and evaporated to dryness at 35°C under reduced pressure. The extract was taken up with 200ml of
methanol and then evaporated again to dryness. The dry extract was crystallized at about 30°C in about 350ml of methanol. The resulting suspension was chilled to 0°C over a period of two hours and then kept at this temperature for 30 minutes. The product was then filtered, washed three times (each time with 40ml frozen methanol), and then dried under 5mmHg of pressure at room temperature. 75.5g of the coupled ester (XXXI),

\[\text{Coupled Ester (XXXI)}\]

\[
\text{(2R,4S,5R)-3-benzyol-2-((4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate of 4,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-7β-triethylsiloxy-9-oxo-tax-11-ene were obtained.}
\]

\[\text{Preparation of the Desilylated Product (XXXII)}\]
[0167] Starting with a solution of 72g of (2R,4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate of 4,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-7β-triethylsiloxy-9-oxo-tax-11-ene in 360ml methylene chloride, 74.8g of 3HF.TEA (hydrofluoric acid triethylamine) was added over 15 minutes and at room temperature. This was then left under agitation for approximately 16.5 hours. After the addition of 5.4ml of 3HF.TEA and three hours of additional agitation to complete the reaction, the reaction mixture was washed with 300ml of water and the aqueous phase was counter-extracted with 325ml methylene chloride. The organic phases were recombined, and then washed, in succession, with 360ml water, with a solution of 15g sodium bicarbonate in 360ml water, and then with 360ml water. The organic phase was then concentrated to dryness under reduced pressure at 40°C, whereupon the product was left to dry at 30°C under 5mmHg of pressure.

Yield: 66.6g of (2R,4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate of 4,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,13α-trihydroxy-9-oxo-tax-11-ene.
[0169] Preparation of the Methylthiomethyl-Paclitaxel Derivative (XXXIII) via a Pummerer Reaction

[0170] Starting with a solution of 60g of (2R,4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate of 4,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,13α-trihydroxy-9-oxo-tax-11-ene in 1,500ml of DMSO (pre-dried on a molecular sieve), 1,200ml of acetic acid was poured, over a period of 30 minutes, followed by 321ml acetic anhydride over a period of 10 minutes. The reaction mixture was then left under agitation for about 21 hours at room temperature. Following the addition of 3,600ml of ethyl acetate, the organic phase was washed with 2,335g of sodium bicarbonate in 28 liters of water (800ml of ethyl acetate are added during the operations), then again twice, each
time with 1,800ml water, and then washed once more with 900ml water. The organic phase was then concentrated to dryness under reduced pressure at 40°C. Yield: 84g of 

(2R,4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylate of 4,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-7β-methylthiomethyloxy-9-oxo-tax-11-ene

[0171]

![Chemical Structure Image]

(XXXIII)

[0172] in oil form. The product was taken up in 154g of ethyl acetate for further manipulation.

[0173] Obtaining the Final Product (XXXIV)

[0174] 80g of ethyl acetate and 4.5ml of HCl were added to 230g of the preceding solution. After agitation at room temperature for 30 minutes, the organic phase was washed four times, each time with 140ml of a 17% sodium chloride aqueous solution, then dried with 50g of MgSO₄
and concentrated to dryness under reduced pressure at 35°C. 70.8g of raw product were obtained and were dissolved in 70g ethyl acetate. The product was purified by chromatography on silica gel using ethyl acetate/cyclohexane (45/55 v/v). Thus, from 92g of solution, 30g of pure (2R,3S)-3-benzoylamino-2-hydroxy-3-phenyl propionate of 4,10β-diacetoxyl-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-7β-methylthiomethoxy-9-oxo-tax-11-ene

[0175]

[0176] were obtained after concentration of the fractions to dryness and further drying of the dry extract under a pressure of 5mmHg at room temperature.

[0177] General Methods for Experimental:

[0178] The following general methods were used for Examples 9 and 10. $^1$H and $^{13}$C NMR spectra were measured on a Varian 300 NMR spectrometer using
tetramethyldisilane as the internal standard. Thin layer chromatography (TLC) was performed on Merck DC-alufolien with Kieselgel 60F-254, and column chromatography was carried out on silica gel 60 (Merck; 230-400 mesh ASTM). The chemicals were purchased from Aldrich Co. and Sigma and purified before use by standard methods. Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. 10-Deacetyl-baccatin III (10-DAB) was donated by Indena, SpA, Italy.

**EXAMPLE 9:**

[0179] Process for Preparing 7-Alkylthioalkyl-Paclitaxel Derivatives: Coupling of Alkylthioalkyl-Baccatin III Derivatives with β-lactams (Figure 2)

[0180] Compounds of formula (XXXIV) were made using β-lactam synthetic methods. The present invention developed new methods which achieved coupling of β-lactams in the synthesis of alkoxythioalkyl-paclitaxel.

[0181] In this example, β-lactams comprised β-lactams of the following formula:
[0182] 

\[
\begin{array}{c}
G_1 O \quad R_3'' \\
\text{O} \quad \text{N} \quad R_2'' \\
\text{Y}
\end{array}
\]

[0183] wherein

[0184] Y is oxygen;

[0185] \(G_1\) is an hydroxyl protecting group, such as ethoxyethyl ("EE");

[0186] \(R_2''\) is phenyl; and

[0187] \(R_3''\) is phenyl.

[0188] The \(\beta\)-lactams were coupled with at least one baccatin III compound as described below.

[0189] Generally speaking, 10-deacetyl-baccatin III (10-DAB) was protected sequentially with triethylsilyl and acetyl, in order to generate SIBAC (7-TESS-baccatin III). The 7-position triethylsilyl group may be removed with, for example, a solution of 3HF.TEA (hydrofluoric acid. triethylamine).

[0190] Alternatively, 10-DAB was directly acetylated with acetic anhydride in THF with CeCl₃ according to the methods of Holton et al. (Tetrahedron Lett. 39: 2883-2886 (1998). This procedure gave a 93% yield of baccatin III.
[0191] The resulting free 7-position hydroxyl was reacted in a Pummerer reaction to generate a 7-methylthiomethyl-baccatin III derivative. Under these conditions, the 13-position was oxidized to form a carbonyl group. One of ordinary skill would realize that this position could then be reduced, using standard methods, regenerating the 13-position hydroxyl group.

[0192] The coupling reaction of the 7-methylthiomethyl-baccatin III derivative and the β-lactam may be carried out via any alkali metal or alkaline earth metal alkoxide of the 7-methylthiomethyl-baccatin III derivative at the C-13 hydroxyl group. The corresponding alkoxide is readily generated by reacting the 7-methylthiomethyl-baccatin III derivative with the desired alkali metal or alkaline earth metal base, such as at least one of sodium hexamethyl-disilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS), lithium hexamethyldisilazide (LiHMDS), potassium diisopropylamide (KDA), lithium diisopropylamide (LDA), sodium hydride (NaH), potassium hydride (KH), lithium hydride (LiH), calcium hydride (CaH₂), magnesium hydride (MgH₂), or n-butyllLi in a dry nonprotic organic solvent such as tetrahydrofuran (THF), dioxane, ether, dimethoxyethane (DME), diglyme, dimethylformamide (DMF), mixtures of
these solvents with hexane, toluene, and xylene, in a preferred temperature range from about -100°C to about 50°C, more preferably at about -78°C to about 25°C.

[0193] This reaction may optionally be carried out under inert atmosphere, such as nitrogen and/or argon. The amount of the base used for the reaction is optionally approximately equivalent to the amount of the 7-methylthio-methyl-baccatin III derivative when soluble bases such as sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, sodium diisopropylamide, potassium diisopropylamide or lithium diisopropylamide are used. The use of a slight excess of the base does not adversely affect the reaction. When heterogeneous bases are used, 5-10 equivalents of the base (to the amount of the 7-methylthiomethyl-baccatin III) are preferably employed.

[0194] The coupling reaction of the metal alkoxide of the 7-methylthiomethyl-baccatin III thus generated with the β-lactam is typically carried out by adding the solution of the β-lactam in a dry organic solvent exemplified above in a preferred temperature range from about -100°C to about 50°C, more preferably at about -35°C to about 25°C. The mixture of reactants is
stirred for 15 minutes to 24 hours and the progress and the completion of the reaction is monitored, for example, by thin layer chromatography (TLC). When the limiting reactant is completely consumed, the reaction is quenched by addition of a brine.

[0195] The crude reaction mixture is worked up using the standard isolation procedures which are generally known to those skilled in the art to give the corresponding protected taxoid. The proportion of the \( \beta \)-lactam and the protected baccatin III is in a range from 2:1 to 1:2, more preferably approximately 1:1 for purposes of economy and efficiency, but the ratio is not critical for the reaction.

[0196] Coupling the resulting metalized baccatin derivative with a protected \( \beta \)-lactam as described above resulted in the desired 7-thioalkoxytaxane with a protected 13-position side chain according to the \( \beta \)-lactam synthon methodology (Ojima, I. et al., *Tetrahedron*, 48: 6985-7012 (1992); Ojima, I. et al., *Tetrahedron Letters*, 34(26):4149-4152 (1993)).

[0197] Suitable protecting groups for the \( \beta \)-lactam include standard hydroxyl protecting groups known in the art, e.g., methoxymethyl (MOM), \( \beta \)-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl
(trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), f-MOC, TROC, etc. The protecting group(s) are removed by using standard procedures which are generally known to those skilled in the art to give the desired taxoid derivatives (T.W. Green, Protective Groups in Organic Synthesis, Chapter 2, pages 10-69 (1981)).

[0198] For example, ethoxyethoxy (EE) and triethylsilyl groups can be removed with 0.5N HCl at room temperature for 36 hours, and Troc group can be removed with zinc and acetic acid in methanol at 60°C for 1 hour without disturbing the other functional groups and the skeleton of the taxoid. The deprotected taxoid may be optionally further purified and/or crystallized as necessary. The detailed experimental protocol was as follows.

Baccatin III, Option A:

[0199] A solution of SIBAC (XXX) (103 mg, 0.147 mmol) in 1 mL of 0.1N HCl in EtOH was stirred at 0 °C for 2 h, then treated with saturated NaHCO₃ and extracted with EtOAc.

[0200] The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to give a yellow residue which was chromatographed (hexane:EtOAc = 2:3) to give 79 mg (92%) of baccatin III.
as a colorless solid: $^1$H NMR (CDCl$_3$) 1.13 (s, 6H), 1.70 (s, 3H), 2.27 (s, 3H), 2.31 (s, 3H), 2.78 (m, 1H), 3.90 (d, $J = 6.9$ Hz, 1H), 4.18 (d, $J = 8.1$ Hz, 1H), 4.33 (d, $J = 8.1$ Hz, 1H), 4.50 (m, 1H), 4.91 (m, 1H), 5.01 (d, $J = 8.1$ Hz, 1H), 5.65 (d, $J = 6.9$ Hz, 1H), 6.35 (s, 1H), 7.51 (t, $J = 7.5$ Hz, 2H), 7.64 (m, 1H), 8.13 (d, $J = 7.5$ Hz, 2H).

**Baccatin III, Option B:**

[0201] To a solution of 10-deacetyl-baccatin III (100 mg, 0.184 mmol) in 2 mL of THF was added Ac$_2$O (0.02 mL, 0.2 mmol) and 7 mg of CeCl$_3$·7H$_2$O. The resulting mixture was stirred at rt for 3 h, treated with saturated NaHCO$_3$ and extracted with EtOAc.

[0202] The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and evaporated to give a white residue which was chromatographed (hexane:EtOAc = 2:3) to give 100 mg (93%) of baccatin III as a colorless solid.

**7-Methylthiomethyl-13-oxo-baccatin III:**

[0203] To a solution of baccatin III (90 mg, 0.154 mmol) in 1 mL of DMSO was added 0.40 mL of Ac$_2$O and 0.11 mL of AcOH. The resulting mixture was heated at 50 °C
overnight, then diluted with EtOAc, washed with saturated NaHCO₃ and water.

[0204] The organic layer was dried over MgSO₄, filtered and evaporated to give a yellow residue which was chromatographed (hexane:EtOAc = 3:2) to give 8 mg of the desilylated taxoid and 67.5 mg (75% based on conversion) of 7-methylthiomethyl-13-oxo-baccatin as a colorless solid: ¹H NMR (CDCl₃) 1.23 (s, 3H), 1.30 (s, 3H), 1.77 (s, 3H), 2.18 (s, 3H), 2.24 (s, 3H), 2.71 (d, J = 19.8 Hz, 1 H), 2.84 (m, 1H), 2.99 (d, J = 19.8 Hz, 1 H), 4.01 (d, J = 6.9 Hz, 1H), 4.17 (d, J = 8.7 Hz, 1H), 4.39 (m, 2H), 4.69 (m, 2H), 4.99 (d, J = 9.0 Hz, 1H), 5.73 (d, J = 6.9 Hz, 1H), 6.75 (s, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.68 (m, 1H), 8.11 (d, J = 7.2 Hz, 2H).

7-Methylthiomethyl-baccatin III:

[0205] To a solution of 7-methylthiomethyl-13-oxo-baccatin (67 mg, 0.10 mmol) in 3 mL of EtOH was added 130 mg of NaBH₄ at 0 °C. After 30 min, saturated NH₄Cl was added and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to give a yellow residue which was chromatographed (hexane:EtOAc = 3:2) to give 29 mg of starting material and 34 mg (88% based on conversion) of methylthiomethyl-baccatin III
derivative as a colorless solid: ^1^H NMR (CDCl\textsubscript{3}) 1.09 (s, 3H), 1.23 (s, 3H), 1.79 (s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 2.33 (s, 3H), 2.86 (m, 1H), 3.98 (d, J = 6.9 Hz, 1H), 4.19 (d, J = 8.7 Hz, 1H), 4.37 (m, 2H), 4.72 (m, 2H), 4.89 (m, 1H), 5.01 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 6.9 Hz, 1H), 6.61 (s, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 8.14 (d, J = 7.2 Hz, 2H).

2'-{(1-Ethoxyethyl)-7-methylthiomethyl-paclitaxel:}

[0206] To a solution of methylthiomethyl ether-baccatin derivative (17 mg, 0.026 mmol) and a EE protected β-lactam (20 mg, 0.058 mmol) in 1 mL dry THF was added a 1.0 M LiHMDS in THF (0.10 mL, 0.10 mmol) dropwise at -40 °C, and the solution was stirred at -40 °C for 2 h. The reaction was quenched with aqueous saturated NH\textsubscript{4}Cl solution, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubcript{2}. The combined extracts were then dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo.

[0207] ^1^H NMR (CDCl\textsubscript{3}) 1.05-1.12 (m, 3H), 1.26 (s, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 2.83 (m, 1H), 3.07-3.52 (m, 2H), 3.92 (m, 1H), 4.25 (m, 1H), 4.34 (m, 2H), [4.60 (q, J = 5.4 Hz), 4.84 (q, J = 5.4 Hz)] (1H), 4.69 (m, 3H), 5.00 (t, J = 7.5 Hz, 1H), 5.77 (m, 2H), 6.28 (t, J = 9.0 Hz, 1H), 6.59 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H),
7.36-7.49 (m, 7H), 7.52-7.58 (m, 3H), 7.63-7.70 (m, 1H),
7.83 (m, 2H), 8.15 (m, 2H).

7-Methylthiomethyl-paclitaxel:

[0208] A solution of protected methylthiomethyl ether-baccatin derivative (15 mg, 0.015 mmol) in 1 mL of
0.2 N HCl in EtOH was stirred at 0 °C for 1 h, then
treated with saturated NaHCO₃ and extracted with EtOAc.
The combined organic layers were washed with brine, dried
over MgSO₄, filtered and evaporated to give a yellow
residue which was chromatographed (hexane:EtOAc = 1:1) to
give 12.5 mg (90%) of the target compound as a colorless
solid.

[0209] The proton NMR of the target was as
follows: ¹H NMR (CDCl₃) 1.22 (s, 3H), 1.26 (s, 3H), 1.80
(s, 3H), 2.16 (s, 3H), 2.23 (s, 3H), 2.43 (s, 3H), 2.85
(m, 1H), 3.90 (d, J = 6.9 Hz, 1H), 4.23 (d, J = 8.7 Hz,
1H), 4.34 (m, 2H), 4.71 (m, 2H), 4.84 (d, J = 2.4 Hz,
1H), 4.98 (d, J = 7.8 Hz, 1H), 5.73 (d, J = 6.9 Hz, 1H),
5.84 (dd, J = 2.4 Hz, 9.0 Hz, 1H), 6.23 (m, 1H), 6.56 (s,
1H), 7.09 (d, J = 9.0 Hz, 1H), 7.37-7.49 (m, 5H), 7.52-
7.57 (m, 5H), 7.63-7.68 (m, 1H), 7.80 (m, 2H), 8.16 (m,
2H).
EXAMPLE 10:

[0210] Process for Preparing 7-Alkylthioalkyl-Paclitaxel Derivatives: Coupling of Baccatins with β-Lactams followed by Pummerer Reaction (Figure 3)

[0211] Generally, 10-DAB was protected sequentially with triethylsilyl and acetyl, in order to generate SIBAC (7-TES-baccatin III). SIBAC was metalized to form an alkaline metal or alkaline earth metal salt at position 13 as detailed below. The metalization may be accomplished with, for example, at least one of sodium hexamethyldisilazide (NaHMDS), KHMDS, LiHMDS, LDA, n-butylLi, or NaH.


[0213] The 7-position trialkylsilyl group may be removed with, for example, a solution of 3HF.TEA (hydrofluoric acid.triethylamine); the resulting free 7-position hydroxyl is reacted in a Pummerer reaction to generate a 7-methylthio-methyl-paclitaxel with an optionally protected 2'-hydroxyl. One of skill in the
art would understand that depending on the reaction conditions, the protecting group may be or may not be removed by the conditions of the Pummerer reaction.

[0214] If required, the 2’ protecting group was optionally removed by standard methods. The deprotected paclitaxel was optionally further purified and/or crystallized as necessary. The detailed experimental protocol was as follows.

7-Triethysilyl-10-deacetyl-baccatin III:

[0215] To a solution of 10-deacetyl-baccatin III (300 mg, 0.555 mmol) and imidazole (150 mg, 2.22 mmol) in 14 mL of N,N-dimethylformamide (DMF) was added chlorotriethylsilane (0.37 ml, 2.21 mmol) dropwise via syringe at 0°C, and the reaction mixture was stired for 2 h at 0°C and diluted with EtOAc. The mixture was then washed with H$_2$O, brine, dried over MgSO$_4$ and concentrated.

[0216] The crude product was chromatographed (hexane:EtOAc = 1:1) to give 347 mg (95%) of 7-triethysilyl-10-deacetyl-baccatin III as a white solid:

$^1$H NMR (CDCl$_3$) δ 0.56 (m, 6 H), 0.94 (m, 9H), 1.08 (s, 6H), 1.59 (d, J = 2.5 Hz, 1H), 1.73 (s, 3H), 1.90 (m, 1 H), 2.05 (d, J = 4.8 Hz, 1H), 2.08 (s, 3H), 2.24 (s, 1H), 2.28 (s, 3H), 2.48 (m, 1 H), 3.95 (d, J = 7.1 Hz, 1H), 4.16 (d, J = 8.3 Hz, 1H), 4.25 (s, 1H), 4.31 (d, J = 8.3 Hz, 1H).
Hz, 1H), 4.40 (dd, J = 6.4, 10.5 Hz, 1H), 4.85 (t, J = 7.8 Hz, 1H), 4.95 (d, J = 8.0 Hz, 1H), 5.17 (s, 1H), 5.60 (d, J = 7.0 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 8.10 (d, J = 7.3 Hz, 2H); $^{13}$C NMR (CDCl$_3$) 5.1, 6.7, 9.9, 15.1, 19.5, 22.6, 26.8, 37.2, 38.6, 42.7, 47.0, 57.9, 67.9, 72.9, 74.6, 74.8, 76.5, 78.8, 80.7, 84.2, 87.6, 128.6, 129.4, 130.0, 133.6, 135.1, 141.8, 167.0, 170.7, 210.3.

7-Triethylsilyl-baccatin III:

[0217] To a solution of 7-TES-10-DAB III (345.0 mg, 0.524 mmol) in 30 mL of dry THF was added 1.0 M LiHMDS in THF (0.53 mL, 0.530 mmol) dropwise via syringe at -40°C. The mixture was stirred at -40°C for 5 min, then acetyl chloride (65 µl, 0.706 mmol) was added dropwise. After 90 min, the reaction was quenched with aqueous saturated NH$_4$Cl, extracted with CH$_2$Cl$_2$, and the combined extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo.

[0218] The crude product was purified on a silica gel column (hexane:EtOAc = 7:3 followed by 1:1) to afford 355 mg (93%) of SIBAC (XXX) as a white solid: $^1$H NMR (CDCl$_3$) 0.55 (m, 6 H), 0.90 (m, 9 H), 1.03 (s, 3 H), 1.10 (s, 3H), 1.71 (s, 3H), 2.21 (s, 3 H), 2.32 (s, 3H), 3.90
(d, J = 6.9 Hz, 1H), 4.16 (d, J = 7.8 Hz, 1H), 4.33 (d, J = 7.8 Hz, 1H), 4.51 (dd, J = 6.9, 10.5 Hz, 1H), 4.86 (t, J = 7.8 Hz, 1H), 4.98 (d, J = 9.6 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H) (H2), 6.49 (s, 1H), 7.53 (t, J = 7.4 Hz, 2H), 7.66 (m, 1H), 8.13 (d, J = 7.2 Hz, 2H).

2'-{(1-Ethoxyethyl)-7-triethylsilyl-paclitaxel:

[0219] To a solution of 7-TES-baccatin III (SIBAC XXX) (20 mg, 0.028 mmol) and ethoxyethyl protected β-lactam (20 mg, 0.058 mmol) in 1 mL dry THF was added a 1.0 M LiHMDS in THF (0.10 mL, 0.10 mmol) dropwise at -40°C, and the mixture was stirred at -40°C for 2 h. The reaction was quenched with aqueous saturated NH₄Cl solution, and the aqueous layer was extracted with CH₂Cl₂. The combined extracts were dried over MgSO₄, filtered, and concentrated in vacuo.

[0220] The residue was chromatographed (hexane:EtOAc = 4:1) to give 5 mg of SIBAC and 17 mg of 2'-{(1-ethoxyethyl)-7-triethylsilyl-paclitaxel (77% based on conversion) as a colorless solid: ¹H NMR (CDCl₃) 0.55 (m, 6 H), 0.90 (m, 9 H), 1.70 (s, 3 H), 2.05 (s, 3 H), 2.21 (s, 3H), 3.08-3.44 (m, 2H), 3.86 (m, 1 H), 4.23 (dd, J = 5.7 Hz, 8.7 Hz, 1H), 4.36 (m, 1 H), 4.50 (m, 1H), [4.58 (q, J = 5.4 Hz), 4.84 (q, J = 5.4 Hz)] (1H), [4.68 (d, J = 2.4 Hz), 4.84 (d, J = 3.6 Hz)] (1H), 5.76 (m,
2H), 6.28 (m, 1H), 6.48 (s, 1H), 7.14 (d, \_J = 8.7\ Hz, 1H), 7.31-7.55 (m, 10H), 7.64 (m, 1H), 7.82 (d, \_J = 7.5 Hz, 2H), 8.16 (m, 2 H).

2′-(1-Ethoxyethyl)-paclitaxel:

[0221] To a solution of 2′-(1-ethoxyethyl)-7-triethyloxysilyl-paclitaxel (9 mg, 0.009 mmol) in 0.5 mL pyridine and 0.1 mL of CH₂CN at 0°C was added 0.1 mL of HF/pyridine solution. The resulting mixture was allowed to warm up to room temperature, was stirred overnight, and was then diluted with saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with saturated CuSO₄ and water, dried over MgSO₄, filtered, and evaporated to give a yellow residue.

[0222] The residue was chromatographed (hexane:EtOAc = 2:3) to give 6 mg (67%) of the desilylated taxoid as a colorless solid: \(^1\text{H NMR (CDCl}_3\text{)}\ 0.55 (m, 6H), 0.90 (m, 9H), 1.70 (s, 3H), 2.05 (s, 3H), 2.21 (s, 3H), 3.08-3.44 (m, 2H), 3.86 (m, 1H), 4.23 (dd, \_J = 5.7 Hz, 8.7 Hz, 1H), 4.36 (m, 1 H), 4.50 (m, 1H), [4.58 (q, \_J = 5.4 Hz), 4.84 (q, \_J = 5.4 Hz)] (1H), [4.68 (d, \_J = 2.4 Hz), 4.84 (d, \_J = 3.6 Hz)] (1H), 5.76 (m, 2H), 6.28 (m, 1H), 6.48 (s, 1H), 7.14 (d, \_J = 8.7 Hz, 2H).
1H), 7.31-7.55 (m, 10H), 7.64 (m, 1H), 7.82 (d, J = 7.5 Hz, 2H), 8.16 (m, 2 H).

2′-(1-Ethoxyethyl)-7-methylthiomethyl-paclitaxel
(Protected Methylthiomethyl-Paclitaxel Derivative):

[0223] To a solution of the desilylated taxoid (5 mg, 0.005 mmol), in 0.05 mL of DMSO, was added 0.02 mL of Ac₂O and 5 μL of AcOH. The resulting mixture was heated at 50 °C for 5 h, then diluted with EtOAc, washed with saturated NaHCO₃ and water. The organic layer was dried over MgSO₄, filtered and evaporated to give a yellow residue.

[0224] The residue was chromatographed (hexane:EtOAc = 3:2) to give 4 mg (80%) of the protected 7-methylthiomethyl-paclitaxel derivative as a colorless solid: ¹H NMR (CDCl₃) 1.05-1.12 (m, 3H), 1.26 (s, 3H), 2.16 (s, 3H), 2.22 (s, 3H), 2.83 (m, 1H), 3.07-3.52 (m, 2H), 3.92 (m, 1H), 4.25 (m, 1H), 4.34 (m, 2H), [4.60 (q, J = 5.4 Hz), 4.84 (q, J = 5.4 Hz)] (1H), 4.69 (m, 3H), 5.00 (t, J = 7.5 Hz, 1H), 5.77 (m, 2H), 6.28 (t, J = 9.0 Hz, 1H), 6.59 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.36-7.49 (m, 7H), 7.52-7.58 (m, 3H), 7.63-7.70 (m, 1H), 7.83 (m, 2H), 8.15 (m, 2H).

[0225] The 7-methylthiomethyl-paclitaxel was obtained by the deprotection of 2′-(ethoxyethyl)-7-
methylthiomethyl-paclitaxel in the same manner as that described in Example 9.

EXAMPLE 11:

[0226] Process for Preparing 7-Alkylthioalkyl-Paclitaxel Derivatives: Coupling of Alkylthioalkyl-Baccatins with β-lactams

[0227] The process of Example 9 is followed, with the exception that instead of reacting the 10-acetyl-baccatin derivative in a Pummerer reaction, the 10-acetyl-baccatin derivative is reacted by conversion of the free 7-position hydroxy to a methylthiomethyl ether by using methyl sulfide and benzoyl peroxide. An exemplary procedure was described, for example, in Medina, J.C., and Kyler, K.S., Tetrahedron Letters, 29(31): 3773-3776 (1988).

EXAMPLE 12:

[0228] Process for Preparing 7-Alkylthioalkyl-Paclitaxel Derivatives: Coupling of Baccatins with β-lactams Followed by Conversion of the Alcohol

[0229] The process of Example 10 is followed, with the exception that the Pummerer reaction is replaced by conversion of the alcohol to a methylthiomethyl ether using methyl sulfide and benzoyl peroxide. This

Biological Activity:

[0230] The new products of general formula (I) in which Z represents a radical of general formula (II), and other inventive compounds disclosed herein, manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation.

[0231] Such pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands.

[0232] These pathological conditions can also include psoriasis, solid tumors, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumor, Hodgkin's
disease, melanoma, multiple myeloma, chronic lymphocytic leukemia and acute or chronic granulocytic lymphoma.

[0233] The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

[0234] The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which was preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration was more especially preferred.

[0235] The present invention also comprises preparing pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The preparations of these compositions may be accomplished according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include
diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colorings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

[0236] The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

[0237] For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any
other means which does not adversely affect the composition.

[0238] It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

[0239] The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

[0240] The therapeutic treatment may be performed concurrently with other therapeutic treatments including anti-neoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

[0241] Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as
mechlorethamine, cyclophosphamide, melphalan and
chlorambucil, alkyl sulfonates such as busulfan,
nitrosoureas such as carmustine, lomustine, semustine and
streptozocin, triazenes such as dacarbazine,
antimetabolites such as folic acid analogues, for
instance methotrexate, pyrimidine analogues such as
fluorouracil and cytarabine, purine analogues such as
mercaptopurine and thioguanine, natural products, for
instance Vinca alkaloids such as vinblastine, vincristine
and vindesine, epipodophyllotoxins such as etoposide and
teniposide, antibiotics such as dactinomycin,
daunorubicin, doxorubicin, bleomycin, plicamycin and
mitomycin, enzymes such as L-asparaginase, various agents
such as coordination complexes of platinum, for instance
cisplatin, substituted ureas such as hydroxyurea,
methylhydrazine derivatives such as procarbazine,
adrenocortical suppressants such as mitotane and
aminogluthethimide, hormones and antagonists such as
adrenocorticosteroids such as prednisone, progestins such
as hydroxyprogesterone caproate, methoxyprogesterone
acetate and megestrol acetate, oestrogens such as
diethylstilboestrol and ethynylestradiol, anti-oestrogens
such as tamoxifen, and androgens such as testosterone
propionate and fluoxymesterone.
[0242] The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated.

[0243] In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation. The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect.

[0244] Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained. For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

[0245] In man, the doses are generally between 0.01 and 200 mg/kg. For intraperitoneal administration,
the doses will generally be between 0.1 and 100 mg/kg, preferably between 0.5 and 50 mg/kg and still more specifically between 1 and 10 mg/kg. For intravenous administration, the doses are generally between 0.1 and 50 mg/kg, preferably between 0.1 and 5 mg/kg and still more specifically between 1 and 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

[0246] The example which follows illustrates a composition according to the invention.

PHARMACOLOGICAL EXAMPLE

[0247] 40 mg of the product obtained in Example 1 are dissolved in 1 cm³ of EMULPHOR® EL 620 (Stepan Canada, Inc.) and 1 cm³ of ethanol, and the solution is then diluted by adding 18 cm³ of physiological saline.

[0248] The composition is administered by perfusion over 1 hour by introduction in physiological solution.

[0249] The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are
to be considered in all respects as illustrative only and not restrictive.

[0250] The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.
We claim:

1. A method of preparing \((2R,3S)-3\text{-benzoylamino-2-hydroxy-3-phenylpropionate of 4,10\beta-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-7β-methylthiomethyl-}
loxy-9-oxo-tax-11\text{-ene, formula (XXXIV)},

 \[
\text{(XXXV)}
\]

comprising:

silylating a baccatin of formula (IX)

\[
\text{(IX)}
\]

to obtain a silylated baccatin, wherein the silylation occurs at position 7;

acetylationg said silylated baccatin to obtain a silylated baccatin III of formula (XXX);
removing the silyl group to obtain baccatin III with a 7-hydroxy group;

or, alternatively, directly acetylating the baccatin of formula (IX) to obtain baccatin III with a 7-hydroxy group;

reacting said baccatin III with a 7-hydroxy group, wherein said reacting may include more than one reaction step, including an optional reduction reaction, to generate a compound of formula (A):

wherein R is hydrogen;
performing a metalation of said compound of formula (A) with an alkali metal or alkaline earth metal base, to produce a metalized methylthiomethyl-baccatin III derivative of formula (A), wherein R is an alkali metal or alkaline earth metal;

coupling said metalized methylthiomethyl-baccatin III derivative of formula (A) with a protected β-lactam, wherein said protected β-lactam comprises a β-lactam of formula

\[
\begin{align*}
\text{G}_1 \text{O} & \quad \text{R}_3'' \\
\text{O} & \quad \text{N} \\
\text{Y} & \quad \text{R}_2'' \\
\end{align*}
\]

wherein

Y is oxygen;
G₁ is an hydroxyl protecting group;
R₂'' is phenyl; and
R₃'' is phenyl;

to produce a 2'-protected 7-methylthiomethyl-paclitaxel derivative;
and deprotecting said 2'-protected 7-methylthiomethyl-paclitaxel derivative by removing G$_1$ to produce a compound of formula (XXXIV).

2. The method according to claim 1, wherein said baccatin III with a 7-hydroxy group is subjected to Pummerer reaction conditions to obtain said compound of formula (A).

3. The method according to claim 1, wherein said baccatin III with a 7-hydroxy group is reacted with dimethyl sulfide and benzoyl peroxide to obtain said compound of formula (A).

4. The method according to claim 2, wherein the alkali metal or alkaline earth metal base is at least one compound selected from sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS), lithium
hexamethyldisilazide (LiHMDS), potassium diisopropylamide (KDA), lithium diisopropylamide (LDA), sodium hydride (NaH), potassium hydride (KH), lithium hydride (LiH), calcium hydride (CaH₂), magnesium hydride (MgH₂), and n-butyli Li.

5. The method according to claim 4, wherein said at least one compound is a hexamethyldisilazide.

6. The method according to claim 5, wherein said hexamethyldisilazide is sodium hexamethyldisilazide, and R is Na.

7. The method according to claim 6, wherein G₁ is selected from methoxymethyl (MOM), β-methoxyethoxymethyl (MEM),trialklylsilyl, triphenylmethyl (trityl), TIPSO, tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

8. The method according to claim 7, wherein G₁ is ethoxyethyl.
9. The method according to claim 5, wherein said hexamethyldisilazide is lithium hexamethyldisilazide, and R is Li.

10. The method according to claim 9, wherein G₁ is selected from methoxymethyl (MOM), β-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

11. The method according to claim 10, wherein G₁ is ethoxyethyl.

12. The method according to claim 3, wherein the alkali metal or alkaline earth metal base is at least one compound selected from sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDs), lithium hexamethyldisilazide (LiHMDS), potassium diisopropylamide (KDA), lithium diisopropylamide (LDA), sodium hydride (NaH), potassium hydride (KH), lithium hydride (LiH), calcium hydride (CaH₂), magnesium hydride (MgH₂), and n-butyl Li.
13. The method according to claim 12, wherein said at least one compound is a hexamethyldisilazide.

14. The method according to claim 13, wherein said hexamethyldisilazide is sodium hexamethyldisilazide, and R is Na.

15. The method according to claim 14, wherein $G_1$ is selected from methoxymethyl (MOM), $\beta$-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

16. The method according to claim 15, wherein $G_1$ is ethoxyethyl.

17. The method according to claim 13, wherein said hexamethyldisilazide is lithium hexamethyldisilazide, and R is Li.

18. The method according to claim 17, wherein $G_1$ is selected from methoxymethyl (MOM), $\beta$-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-
butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

19. The method according to claim 18, wherein $G_1$ is ethoxyethyl.


![Chemical Structure](image)

comprising:

silylating a deacetylbaccatin III of formula (IX)
to obtain a silylated deacetyl baccatin III derivative, wherein the silylation occurs at position 7; acetyling said silylated deacetyl baccatin III derivative to obtain a silylated baccatin III of formula (XXX);

performing a metalation of said silylated baccatin III of formula (XXX) with an alkali metal or alkaline earth metal base to produce a metalized silylated baccatin III derivative, in which 13-hydroxy becomes 13-RG, where R is an alkali metal or alkaline earth metal;
coupling said metalized silylated baccatin III derivative with a β-lactam, wherein said β-lactam comprises a lactam of formula

\[
\begin{array}{c}
\text{G}_1\text{O} \\
\text{N} \\
\text{R}_2'' \\
\text{Y} \\
\text{R}_3''
\end{array}
\]

wherein

Y is oxygen;

G₁ is an hydroxyl protecting group;

R₂'' is phenyl; and

R₃'' is phenyl;

to generate a 2'-protected 7-silylated paclitaxel derivative;

removing the 7-silyl group to obtain a 2'-protected paclitaxel derivative with a 7-hydroxy group;

reacting said 2'-protected paclitaxel derivative with a 7-hydroxy group to obtain a 7-methylthiomethyl-paclitaxel derivative, wherein G₁ is optionally replaced by H; and

optionally deprotecting said 7-methylthiomethyl-paclitaxel derivative by removing G₁ to produce a compound of formula (XXXIV).
21. The method according to claim 20, wherein said 2’-protected paclitaxel derivative with a 7-hydroxy group is subjected to Pummerer reaction conditions to obtain said 7-methylthiomethyl-paclitaxel derivative.

22. The method according to claim 20, wherein said 2’-protected paclitaxel derivative with a 7-hydroxy group is reacted with dimethyl sulfide and benzoyl peroxide to obtain said 7-methylthiomethyl-paclitaxel derivative.

23. The method according to claim 20, wherein the alkali metal or alkaline earth metal base is at least one compound selected from sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDSD), lithium hexamethyldisilazide (LiHMDS), potassium diisopropylamide (KDA), lithium diisopropylamide (LDA), sodium hydride (NaH), potassium hydride (KH), lithium hydride (LiH), calcium hydride (CaH₂), magnesium hydride (MgH₂), and n-butyl Li.

24. The method according to claim 23, wherein said at least one compound is a hexamethyldisilazide.
25. The method according to claim 24, wherein said hexamethyldisilazide is sodium hexamethyldisilazide, and R is Na.

26. The method according to claim 20, wherein $G_1$ is selected from methoxymethyl (MOM), β-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

27. The method according to claim 26, wherein $G_1$ is ethoxyethyl.

28. The method according to claim 24, wherein said hexamethyldisilazide is lithium hexamethyldisilazide, and R is Li.

29. The method according to claim 28, wherein $G_1$ is selected from methoxymethyl (MOM), β-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.
30. The method according to claim 29, wherein $G_1$ is ethoxyethyl.

31. The method according to claim 21, wherein the alkali metal or alkaline earth metal base is at least one compound selected from sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS), lithium hexamethyldisilazide (LiHMDS), potassium diisopropylamide (KDA), lithium diisopropylamide (LDA), sodium hydride (NaH), potassium hydride (KH), lithium hydride (LiH), calcium hydride (CaH$_2$), magnesium hydride (MgH$_2$), and n-butyl Li.

32. The method according to claim 31, wherein said at least one compound is a hexamethyldisilazide.

33. The method according to claim 32, wherein said hexamethyldisilazide is sodium hexamethyldisilazide, and R is Na.

34. The method according to claim 33, wherein $G_1$ is selected from methoxymethyl (MOM), $\beta$-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-
butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

35. The method according to claim 34, wherein G₁ is ethoxyethyl.

36. The method according to claim 32, wherein said hexamethyldisilazide is lithium hexamethyldisilazide, and R is Li.

37. The method according to claim 36, wherein G₁ is selected from methoxymethyl (MOM), β-methoxyethoxymethyl (MEM), trialkylsilyl, triphenylmethyl (trityl), tert-butoxycarbonyl (t-BOC), ethoxyethyl (EE), F-MOC, and TROC.

38. The method according to claim 37, wherein G₁ is ethoxyethyl.

39. A method of preparing a 7-methyliothiomethyl-paclitaxel derivative, comprising:

performing a metalation of a 7-methyliothiomethoxy-baccatin III derivative with an alkali metal or alkaline
earth metal base, to produce a metalized 7-methylthiomethyl-baccatin III derivative of formula (A),

wherein R is an alkali metal or alkaline earth metal;

coupling the metalized 7-methylthiomethyl-baccatin III derivative of formula (A) with a β-lactam, wherein said β-lactam comprises a lactam of formula

wherein

Y is oxygen;

G₁ is an hydroxyl protecting group;

R₂" is phenyl; and

R₃" is phenyl;
producing a 2'-protected 7-methylthiomethyl-paclitaxel derivative; and optionally deprotecting said 2'-protected 7-methylthiomethyl-paclitaxel derivative to yield the 7-methylthiomethyl-paclitaxel derivative.

40. A 2'-protected methylthiomethyl-paclitaxel derivative having the structure:

![Chemical structure](image)

or a salt thereof, wherein $G_1$ is a hydroxyl protecting group.
41. A composition comprising at least one 2′-protected methylthiomethyl-paclitaxel derivative having the structure:

wherein $G_1$ is a hydroxyl protecting group;

in which the at least one 2′-protected methylthiomethyl-paclitaxel derivative is present in free form, in at least one salt form, or in a mixture of these forms,

and is present in an amount effective for inhibiting or preventing abnormal cell proliferation in a patient in need of such inhibition or prevention.
FIG. 2
EXAMPLE 9

PROTECTED 7'-METHYLBENZYL BACCATIN DERIVATIVE
A) R=H
B) R=M, ALKALI OR ALKALINE EARTH METAL
**FIG. 3**

**EXAMPLE 10**

PROTECTED METHYLTHIOMETHYL PACLITAXEL DERIVATIVE

DESILYLATED PACLITAXEL DERIVATIVE
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC  | C07D305/14 | A61K31/335 | A61P35/00 |

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| IPC  | C07D |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>GOLIK J ET AL: &quot;Synthesis and antitumor evaluation of paclitaxel phosphonooxymethyl ethers: a novel class of water soluble paclitaxel pro-drugs&quot; BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 15, 6 August 1996 (1996-08-06), pages 1837-1842, XP004135612 ISSN: 0960-894X</td>
<td>40,41</td>
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<td>* see p.1839, ex. 14, p.1840, exs. 12-14 * the whole document ___</td>
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<td>X</td>
<td>EP 0 694 539 A (SQUIBB BRISTOL MYERS CO) 31 January 1996 (1996-01-31)</td>
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<tr>
<td>Y</td>
<td>* see p. 6, scheme IIb, ex. (II), claim 1, definition of R1 * the whole document ___</td>
<td>1-39</td>
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</table>

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

Date of the actual completion of the international search 24 July 2002

Date of mailing of the international search report 27/08/2002

Name and mailing address of the ISA

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Authorized officer

Stellmach, J
<table>
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<tr>
<td></td>
<td>* see claim 37; see p.3, formula B' and examples 12-19 *</td>
<td>1-39</td>
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<td>the whole document</td>
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<tr>
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<td>WO 96 00724 A (UPJOHN CO ; KELLY ROBERT C (US); GEBHARD ILSE (US)) 11 January 1996 (1996-01-11)</td>
<td>40,41</td>
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<tr>
<td></td>
<td>* see claim 1, definition of R7 *</td>
<td>1-39</td>
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<td>X</td>
<td>EP 0 604 910 A (SQUIBB BRISTOL MYERS CO) 6 July 1994 (1994-07-06)</td>
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