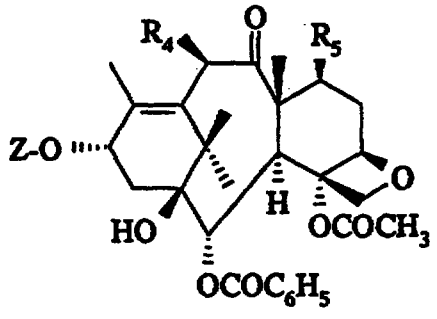
NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

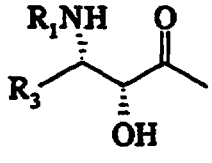
The present invention relates to new taxoids of general formula:



(I)

in which:

Z represents a hydrogen atom or a radical of general formula:



(II)

in which:

R_1 represents a benzoyl radical 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 R_2-O-CO- in which R_2 represents:

- 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 or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from halogen atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino or morpholino radicals, 1-piperazinyl radicals (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms), cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals (optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms), cyano or carboxyl radicals or alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms, or a 5-membered aromatic heterocyclic radical preferably chosen from furyl and thienyl radicals,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms chosen from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents chosen from halogen atoms and alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or alkoxycarbonyl radicals, on the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and

the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and that the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkanoyloxy radical in which the alkanoyl portion contains 2 to 6 carbon atoms in an unbranched or branched chain, with the exception of an acetyl radical, an alkenoyloxy radical in which the alkenoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain or an alkynoyloxy radical in which the alkynoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, these radicals being optionally substituted with one or more halogen atoms or with an alkoxy radical containing 1 to 4 carbon atoms or an alkylthio radical containing 1 to 4 carbon atoms or with a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano or carbamoyl radical or an N-alkylcarbamoyl or N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom chosen from oxygen, sulphur or nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms or a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 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 a cycloalkenoyloxy radical in which the cyccloalkenoyl portion contains 4 to 8 carbon atoms, or alternatively R_4 represents a benzoyloxy radical or a heterocycle-carbonyloxy radical in which the heterocyclic portion represents a 5- or 6-membered aromatic heterocycle containing one or more hetero atoms chosen from oxygen, sulphur or nitrogen atoms,

R_5 represents an alkoxy radical containing 1 to 6 atoms this carbon an unbranched or branched chain, optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with one or more halogen atoms or with an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano or carbamoyl radical or an N-alkylcarbamoyl or N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom chosen from

oxygen, sulphur or nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms or a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals chosen from halogen atoms (fluorine, chlorine, bromine, iodine) and alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms chosen from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents chosen from halogen atoms (fluorine, chlorine, bromine, iodine) and alkyl

radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano, carboxyl or carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms or alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

Preferably, the radicals R_4 represents an alkyloxyacetoxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a cycloalkanoyloxy radical in which the cycloalkanoyl portion contains 4 to 8 carbon atoms, a cycloalkenoyloxy radical in which the cycloalkenoyl portion contains 4 to 8 carbon atoms, a benzoyloxy radical or a heterocycle-carbonyloxy radical in which the heterocyclic portion represents a 5- or 6-membered aromatic heterocycle containing one or more hetero atoms chosen from oxygen, sulphur or

nitrogen atoms, and R_5 represents an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, methylthio, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

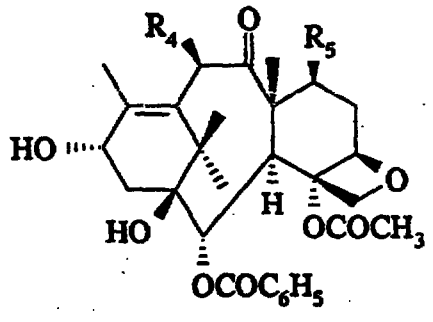
More especially, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms (fluorine, chlorine) and alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino) or trifluoromethyl radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and R_4 represents an alkyloxyacetoxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a cycloalkanoyloxy radical in which the cycloalkanoyl portion contains 4 to 6 carbon atoms or a

pyridylcarbonyloxy radical, and R_5 represents an unbranched or branched alkyloxy radical containing 1 to 6 carbon atoms.

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-CO- in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, R_4 represents a methoxyacetoxy, cyclopropylcarbonyloxy, cyclopentylcarbonyloxy, 2-pyridylcarbonyloxy or 3-pyridylcarbonyloxy radical and R_5 represents a methoxy radical.

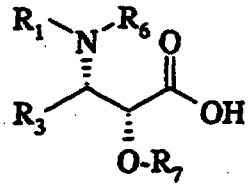
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

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:



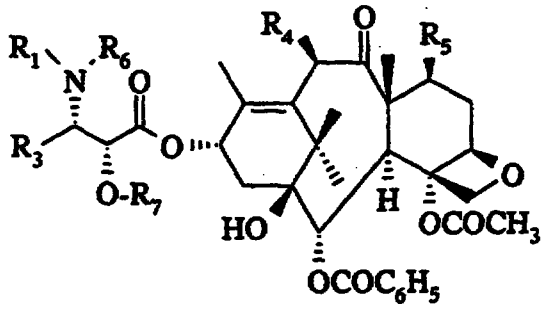
(III)

in which R_4 and R_5 are defined as above, by means of an acid of general formula:



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 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:



(V)

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 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.

The esterification may also be carried out using a product of general formula (XII) in which X_1 represents a radical R_4-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.

The esterification may also be carried out using a product of general formula (XII) in which X_1 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.

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

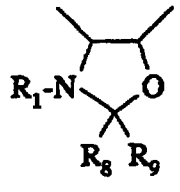
When R_6 and R_7 together form a heterocycle,

the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the following manner:

1) when R_6 represents a hydrogen atom and R_7 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, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic 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:

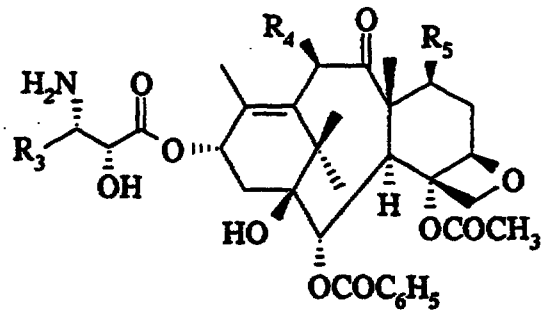


(VI)

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 aralkyl 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_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl (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)

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 thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

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

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).

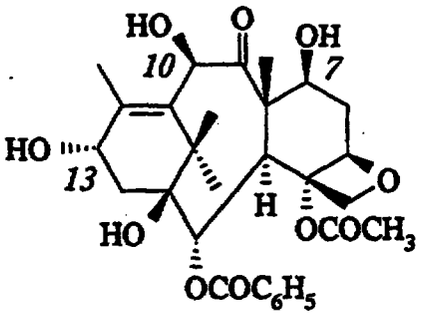
Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent chosen from esters 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.

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 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 R_9 represents a hydrogen atom, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic 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.

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-deacetylbaccatin III of formula:

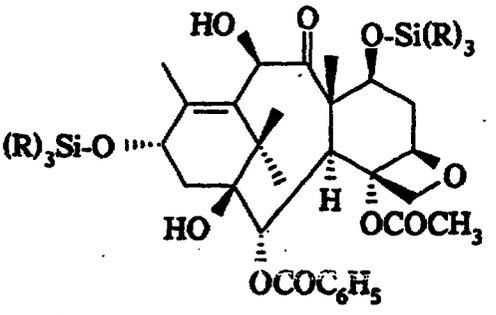


(IX)

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:

$$(R)_3\text{-Si-Hal} \qquad (X)$$

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-deacetylbaccatin III, to obtain a product of general formula:

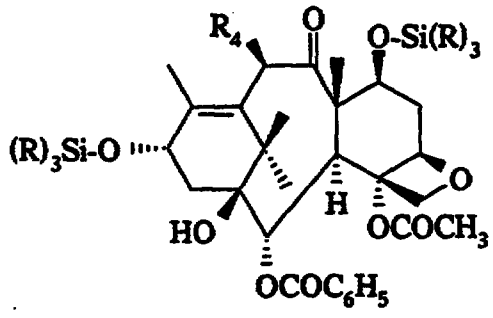


(XI)

in which R is defined as above, followed by the action of a product of general formula:

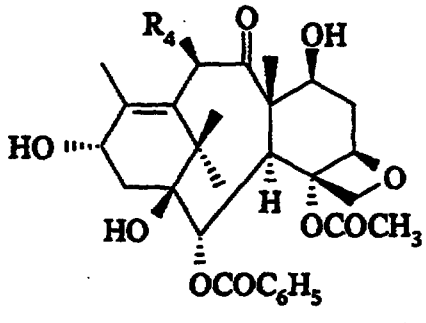
$$R'_4\text{-}X_1 \qquad (XII)$$

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 X_1 represents a halogen atom, to obtain a product of general formula:



(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)

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

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

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

Generally, the action of a silyl derivative

of general formula (X) on 10-deacetylbaccatin 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.

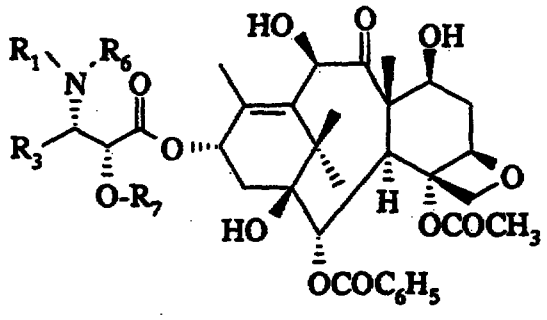
Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride such as sodium hydride, an alkali metal amide such as lithium amide or an alkali metal alkylide such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

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.

Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is

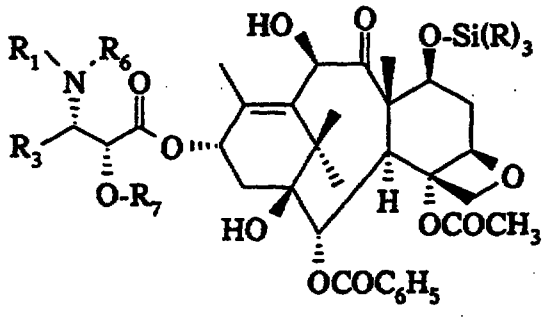
performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), and R_4 and R_5 are defined as above may be obtained from a product of general formula:



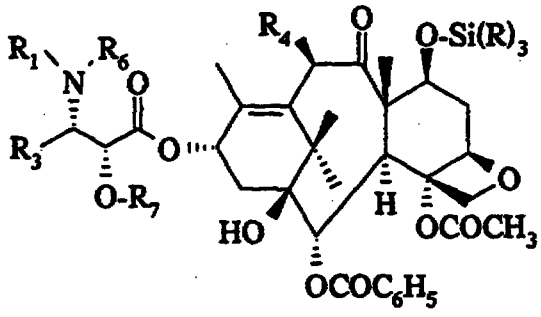
(XVI)

in which R_1, R_3, R_6 and R_7 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:



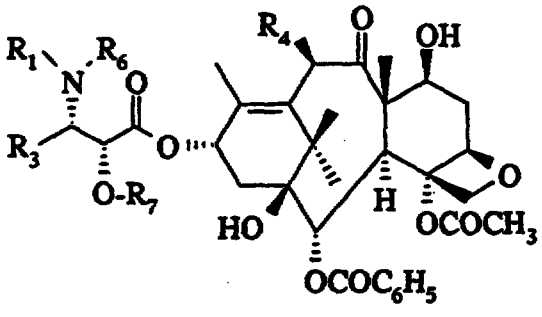
(XVII)

in which R, R_1, R_3, R_6 and R_7 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)

in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula:



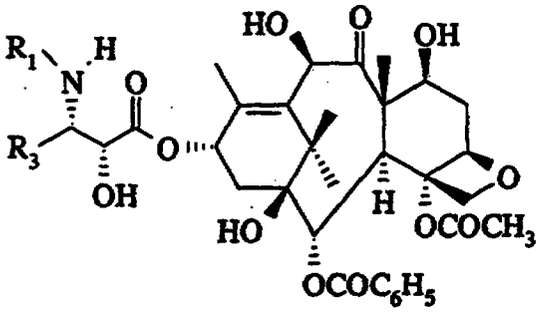
(XIX)

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

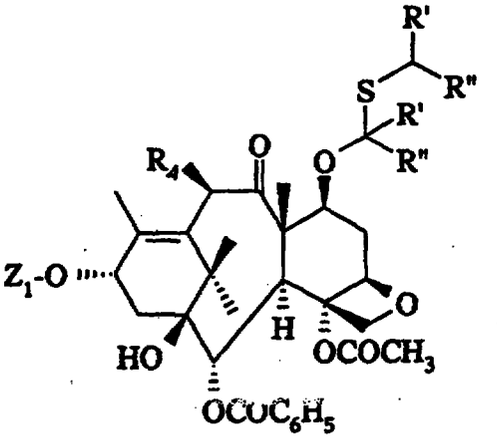
of general formula:



(XX)

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.

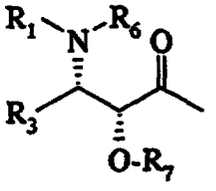
According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms, on a product of general formula:



(XXI)

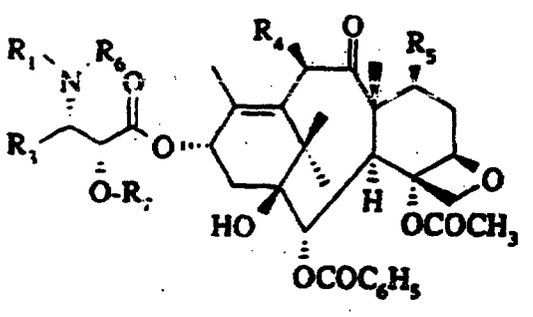
in which R_4 is defined as above and R' and R", which may be identical or different, represent a hydrogen

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 cycloakyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and Z_1 represents a hydrogen atom or a radical of general formula:



(XXII)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, and R_4 is defined as above, to obtain a product of general formula:

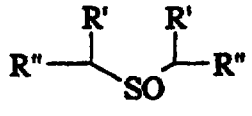


(XXIII)

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 sulphoxide of general formula:



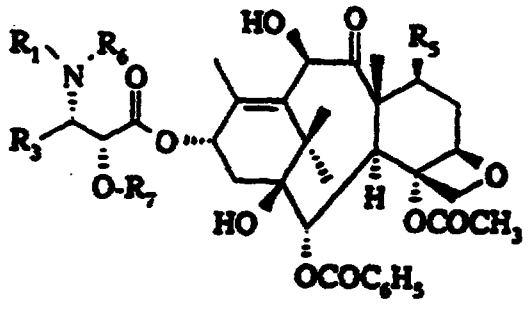
(XXIV)

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

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, 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.

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

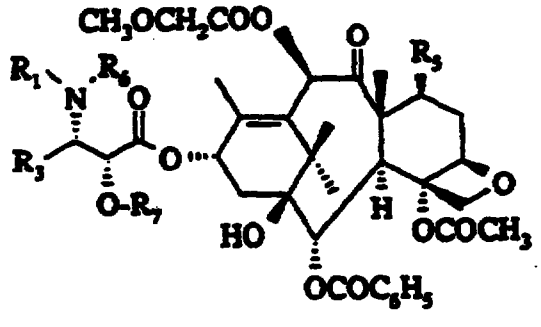
product of general formula (XII) on a product of general formula:



(XXV)

in which R_1, R_3, R_5, R_6 and R_7 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 R_7 or R_6 and R_7 by hydrogen atoms under the conditions described above.

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:

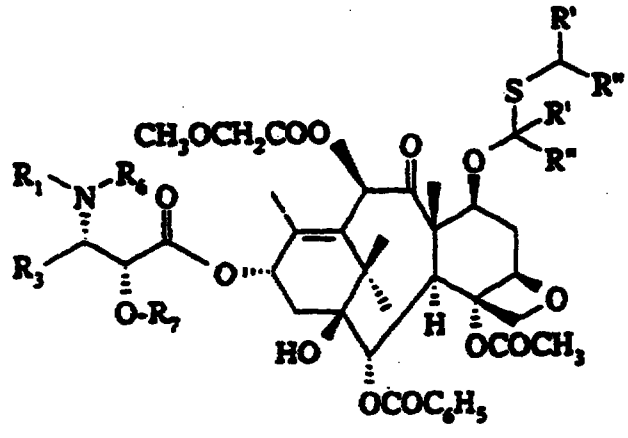


(XXVI)

in which R_1, R_3, R_5, R_6 and R_7 are defined as above.

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.

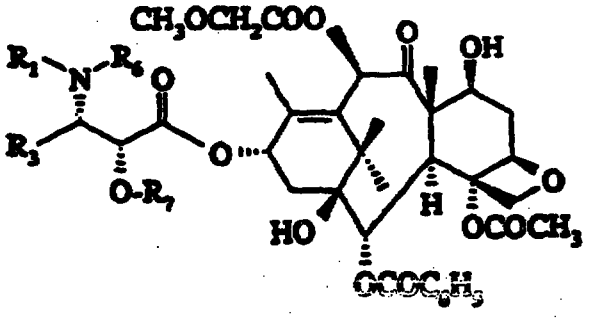
The product of general formula (XXVI) may be obtained by the action of activated Raney nickel in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms on a product of general formula:



(XXVII)

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).

The product of general formula (XXVII) may be obtained by the action of a sulphoxide of general formula (XXIV) on a product of general formula:

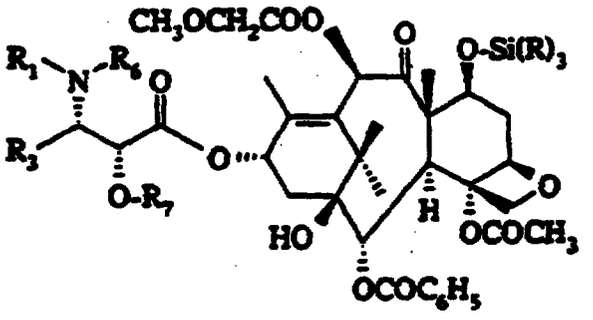


(XXVIII)

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 sulphoxide of general formula (XXIV) on a product of

general formula (XIX).

The product of general formula (XXVIII) may be obtained from a product of general formula:



(XXIX)

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

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

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.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is 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 is

performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, 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 and Taxotere.

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 tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

EXAMPLE 1

243 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 are dissolved in 4.5 cm^3 of a 0.1 N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained is stirred for 3 hours at a temperature in the region of 20°C and 25 cm^3 of dichloromethane are then added. The organic phase is separated after settling has taken place and washed successively with 2 × 10 cm^3 of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 290 mg of a white foam are obtained, which is 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 rays of the zone corresponding to the adsorbed product sought, this zone is scraped off and the silica collected is washed on sintered glass with 10 × 10 cm^3 of ethyl acetate. The filtrates are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. A white foam is obtained, which is repurified according to the same technique [(2 plates: 20 × 20 × 1 mm; eluent: dichloromethane/methanol (95:5 by volume)]. 132 mg of 4α-acetoxy-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 are thereby obtained in the form of a white foam, the characteristics of which are as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -34 (c = 0.5; methanol).
- ^{1}H NMR spectrum (300 MHz; $CDCl_3$: chemical shifts δ in ppm; coupling constants J in Hz): 1.30 (s, 3H: $-CH_3$ at position 16 or 17); 1.35 [(s, 12H: $-C(CH_3)_3$ and $-CH_3$ at position 16 or 17]; 1.75 (s, 3H: $-CH_3$); 1.82 and 2.77 (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); 2.39 (s, 3H: $-COCH_3$); 3.38 (d, J = 5, 1H: -OH at position 2'); 3.42 (s, 3H: $-OCH_3$); 3.88 (d, J = 7.5, 1H: -H at position 3); 3.96 (dd, J = 11 and 7.5, 1H: -H at position 7); 4.18 and 4.32 (2d, J = 8.5, 1H each: $-CH_2-$ at position 20); 4.64 (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'); 5.39 (d, J = 10, 1H: -CONH-); 5.70 (d, J = 7.5, 1H: -H at position 2); 6.22 (broad t, J = 9, 1H: -H at position 13); 6.69 (s, 1H: -H at position 10); from 7.25 to 7.45 (mt, 5H: $-C_6H_5$ at position 3'); 7.44 [(dd, J = 8.5 and 6, 1H: $-OCOC_5H_4N$(-H at position 5)]; 7.50 [(dd, J = 7.5, 2H: $-OCOC_6H_5$(-H at position 3 and H at position 5)]; 7.62 [(t, J = 7.5, 1H: $-OCOC_6H_5$(-H at position 4)]; 8.12 [(d, J = 7.5, 2H: $-OCOC_6H_5$(-H at position 2 and -H at position 6)]; 8.35 [(dt, J = 8.5 and 1, 1H: $-OCOC_5H_4N$(-H at position 4)]; 8.82 (dd, J = 6 and 1, 1H: $-OCOC_5H_4N$(-H at position 6)];

9.32 (d, J = 1, 1H: -OCOC$_5$H$_4$N(-H at position 2)].

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 may be prepared in the following manner:

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-butyoxycarbonyl-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 are 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 cm^3 of anhydrous ethyl acetate. The reaction mixture is 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 are then added and the mixture is again kept stirring for 24 hours, this cycle then being repeated twice more. The reaction mixture is filtered through sintered glass lined with Celite. The sintered glass is washed with 2 times 50 cm^3 of ethyl acetate, and the filtrates are combined, washed successively with 2 times 10 cm^3 of saturated aqueous sodium hydrogen carbonate solution and with 6 times 20 cm^3 of distilled water, dried over

magnesium sulphate, 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 are thereby obtained in the form of a white foam.

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

0.263 cm^3 of hydrazine monohydrate is 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-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 in 4 cm^3 of anhydrous ethanol. The reaction medium is 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 is separated after settling has taken place and the aqueous phase is re-extracted with 2 times 50 cm^3 of ethyl acetate. The organic phases are combined, washed with 4 times 50 cm^3 of distilled water, dried over magnesium sulphate, filtered and

concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 180 mg of a white foam are obtained, which is purified by chromatography on silica gel deposited on plates [(gel thickness 1 mm, plates 20 x 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 is scraped off and the silica collected is washed on sintered glass with 10 times 10 cm^3 of ethyl acetate. The filtrates are 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 are thereby obtained in the form of a white foam.

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 may be prepared in the following manner:

100 cm^3 of an ethanolic suspension of activated nickel prepared by Raney's method (obtained from 80 cm^3 of the approximately 50% commercial aqueous suspension, by successive washing to a pH in the region of 7 with 15 times 100 cm^3 of distilled water and with 4 times 150 cm^3 of ethanol) are 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-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 in 100 cm^3 of anhydrous ethanol. The reaction mixture is kept stirring for 7 days at a temperature in the region of 20°C and is then filtered through sintered glass. The sintered glass is washed with 3 times 100 cm^3 of ethanol and the filtrates are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 821 mg of a white foam are obtained, which is 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 are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 228 mg of 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 are thereby obtained in the form of a white foam.

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

may be prepared in the following manner:

3.35 cm^3 of acetic acid and 11.5 cm^3 of acetic anhydride are 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 sulphoxide. The reaction mixture is kept stirring for 3 days at a temperature in the region of 20°C and is then poured into 500 cm^3 of dichloromethane. 100 cm^3 of saturated aqueous potassium carbonate solution are then added with efficient stirring to a pH in the region of 7. After stirring for 10 minutes, the organic phase is separated after settling has taken place and the aqueous phase is re-extracted with 2 times 250 cm^3 of dichloromethane. The organic phases are combined, washed with 3 times 100 cm^3 of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 9.5 g of a pale yellow oil are obtained, which is 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-cm^3 fractions. The fractions containing only the product sought are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 3.01 g of

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 are thereby obtained in the form of a white foam.

4α-Acetoxy-2β-benxoyloxy-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 may be prepared in the following manner:

220 cm^3 of triethylamine/hydrofluoric acid (mole ratio 1:3) complex are 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-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 200 cm^3 of anhydrous dichloromethane. The reaction mixture is then warmed to a temperature in the region of 20°C, maintained for 3 hours at this temperature and poured into 4 litres 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 is separated after settling has taken place and the aqueous phase is extracted with 2 times 100 cm^3 of dichloromethane. The organic phases are combined, washed with 100 cm^3 of

distilled water, dried over magnesium sulphate, 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 are thereby obtained in the form of a white foam.

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 may be prepared under the conditions described in International Application PCT WO 95/11241.

EXAMPLE 2

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 are obtained in the form of a white foam, the characteristics of which are as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -52 (c = 0.5; methanol).
- ^{1}H NMR spectrum (400 MHz: $CDCl_3$); chemical shifts δ in

pp,; coupling constants J in Hz): 1.31 (s, 3H: $-CH_3$ at postion 16 or 17); 1.37 [(s, 12H: $-C(CH_3)_3$ 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: $-CH_2-$ 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: $-C_6H_5$ at position 3'); 7.51 [(mt, 3H: $-OCOC_6H_5$(-H at position 3 and H at position 5) and $-OCOC_5H_4N$(-H at position 5)]; 7.61 [(t, J = 7.5, 1H: $-OCOC_6H_5$(-H at position 4)]; 7.88 [(split t, J = 8 and 1, 1H: $-OCOC_5H_4N$(-H at position 4)]; 8.12 [(d, J = 7.5, 2H: $-OCOC_6H_5$(-H at position 2 and -H at position 6)]; 8.20 (broad d, J = 8, 1H: $-OCOC_5H_4N$(-H at position 3)]; 8.82 (broad dd J = 5 and 1, 1H: $-OCOC_5H_4N$(-H at position 6)].

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, 230 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 are obtained in the form of a white foam.

EXAMPLE 3

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-yl (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-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -66 (c = 0.5; methanol).
- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz); 1.25 (s, 6H: -C$\underline{H}_3$ at positions 16 and 17); 1.39 [s, 9H; -C(C$\underline{H}_3$)$_3$]; from 1.55 to 1.80 and from 1.90 to 2.10 (2 mts, 4H each: -C$\underline{H}_2$- of the cyclopentyl); 1.71 (s, 1H: -O$\underline{H}$ at position 1); 1.75 (s, 3H: -C$\underline{H}_3$); 1.82 and 2.75 (2 mts, 1H each: -C$\underline{H}_2$- at position 6); 1.93 (s, 3H: -C$\underline{H}_3$); 2.33 (d, J = 9 Hz, 2H: -C$\underline{H}_2$- at position 14); 2.39 (s, 3H: -COC$\underline{H}_3$); 2.95 (mt, 1H: =C$\underline{H}$- of the cyclopentyl); 3.38 (s, 3H: -OC$\underline{H}_3$); 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: $-CH_2$ 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: $-C_6H_5$ at position 3'); 7.51 [t, J = 7.5, 2H: $-OCOC_6H_5$ (-H at position 3 and H at position 5)]; 7.63 [t, J = 7.5, 1H: $-OCOC_6H_5$ (-H at position 4)]; 8.12 [d, J = 7.5, 2H: $-OCOC_6H_5$ (-H at position 2 and -H at position 6)].

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-benzoyloxy-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 are obtained in the form of a white foam.

EXAMPLE 4

Working as in Example 1, but starting from 300 mg of 4α-acetoxy-2α-benzoyloxy-10β-cyclopropylcarbonyloxy-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 are obtained in the form of a white foam, the characteristics of which are as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -71 (c = 0.5; methanol).
- ^{1}H NMR spectrum (400 MHz; $CDCl_3$, chemical shifts δ in ppm; coupling constants J in Hz): 1.00 and 1.19 (2 mts, 2H each: -C<u>H</u>$_2$- of the cyclopropyl); 1.25 (s, 3H: -C<u>H</u>$_3$ at position 16 or 17); 1.27 (s, 3H: -C<u>H</u>$_3$ at position 16 or 17; 1.39 [s, 9H: -C(C<u>H</u>$_3$)$_3$]; 1.71 (s, 1H: -O<u>H</u> at position 1); 1.75 (s, 3H: -C<u>H</u>$_3$); from 1.70 to 1.90 (mt, 1H: =C<u>H</u>- of the cyclopropyl); 1.82 and 2.75 (2 mts, 1H each: -C<u>H</u>$_2$- at position 6); 1.93 (s, 3H: -C<u>H</u>$_3$); 2.33 (d, J = 9, 2H: -C<u>H</u>$_2$- at position 14); 2.40 (s, 3H: -COC<u>H</u>$_3$); 3.35 (s, 3H: -OC<u>H</u>$_3$); 3.40 (d, J = 5, 1H: -O<u>H</u> at position 2'); 3.88 (d, J = 7.5, 1H: -<u>H</u> at position 3); 3.89 (dd, J = 11 and 7.5, 1H: -<u>H</u> at position 7); 4.19 and 4.32 (2 d, J = 8.5, 1H each: -C<u>H</u>$_2$- at position 20); 4.65 (mt, 1H: -<u>H</u> at position 2'); 5.00 (broad d, J = 10, 1H: -<u>H</u> at position 5); 5.28 (broad d, J = 10, 1H: -<u>H</u> at position 3'); 5.42 (d, J = 10, 1H: -CON<u>H</u>-); 5.68 (d, J = 7.5, 1H: -<u>H</u> at position 2); 6.21 (broad t, J = 9, 1H: -<u>H</u> at position 13); 6.48 (s, 1H: -<u>H</u> at position 10); from 7.25 to 7.45 (mt, 5H: -C$_6$<u>H</u>$_5$ at position 3'); 7.52 [t, J = 7.5, 2H: -OCOC$_6$H$_5$ (-<u>H</u> at position 3 and <u>H</u> at

position 5)]; 7.64 [t, J = 7.5, 1H: $-OCOC_6\underline{H}_5$ (-H at position 4)]; 8.12 [d, J = 7.5, 2H: $-OCOC_6\underline{H}_5$ (-H at position 2 and -H at position 6)].

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-13a-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-cyclopropylcarbonyloxy-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 are obtained in the form of a white foam.

EXAMPLE 5

Working as in Example 1, but starting from 430 mg of 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, 164 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- optical rotation: $[\alpha]_{20}^{D}$ = -48 (c = 0.5; methanol)
- ^1H NMR spectrum (300 MHz: $CDCl_3$; δ in ppm; coupling constants J in Hz): 1.17 (s, 3H: $-\underline{H}_3$); 1.22 (s, 3H: $-C\underline{H}_3$); 1.35 (s, 9H: $-C(C\underline{H}_3)_3$; 1.75 (s, 3H: $-C\underline{H}_3$); 1.80

and 2.75 (2 mts, 1 H each: -C<u>H</u>$_2$- 6); 1.90 (s, 3H: -C<u>H</u>$_3$); 2.30 (d, J = 9, 2H: -C<u>H</u>$_2$- 14); 2.37 (s, 3H: -COC<u>H</u>$_3$); 3.35 and 3.55 (2 s, 3H each): -OC<u>H</u>$_3$); 3.40 (d, J = 5, 1H: -O<u>H</u> 2'); 3.85 (d, J = 7, 1H: -<u>H</u> 3); 3.88 (dd, J = 11 and 7, 1H: -<u>H</u> 7); 4.17 and 4.32 (2 d, J = 8.5, 1H each: -C<u>H</u>$_2$- 20); 4.19 and 4.27 (2 d, J = 15, 1H each: -OCOC<u>H</u>$_2$OCH$_3$); 4.65 (mt, 1H: -<u>H</u> 2'); 4.97 (broad d, J = 10, 1H: -<u>H</u> 5); 5.25 (broad d, J = 10, 1H: -<u>H</u> 3'); 5.42 (d, J = 10, 1H: -CON<u>H</u>-); 5.66 (d, J = 7, 1H: -<u>H</u> 2); 6.18 (broad t, J = 9, 1H: -<u>H</u> 13); 6.52 (s, 1H: -<u>H</u> 10); from 7.30 to 7.50 (mt, 5H: -C$_6$<u>H</u>$_5$ 3'); 7.51 [(t, J = 7.5, 2H: -OCOC$_6$H$_5$(-<u>H</u> 3 and <u>H</u> 5)]; 7.63 [(t, J = 7.5, 1H: -OCOC$_6$H$_5$(-<u>H</u> 4)]; 8.12 (d, J = 7.5, 2H: -OCOC$_6$H$_5$(-<u>H</u> 2 and <u>H</u> 6)].

The new products of general formula (I) in which Z represents a radical of general formula (II) 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. The 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. These pathological conditions can also

include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma. 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.

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

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared 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, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

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.

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.

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.

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.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic 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. 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 mechloretamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates 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 aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

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. 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. 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.

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.

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

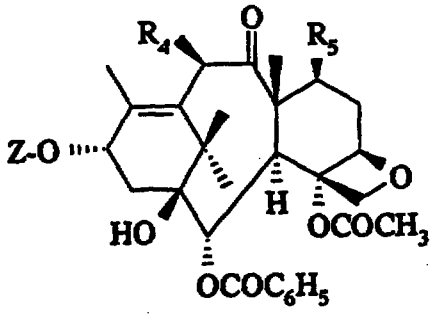
EXAMPLE

40 mg of the product obtained in Example 1 are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline.

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

CLAIMS

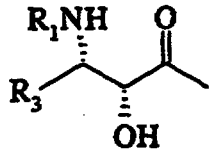
1. New taxoids of general formula:



(I)

in which:

Z represents a hydrogen atom or a radical of general formula:



(II)

in which:

R_1 represents a benzoyl radical 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 R_2-O-CO- in which R_2 represents:

- 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 or

a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from halogen atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino or morpholino radicals, 1-piperazinyl radicals (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms), cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals (optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms), cyano or carboxyl radicals or alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms, or a 5-membered aromatic heterocyclic radical preferably chosen from furyl and thienyl radicals,

- or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more

alkyl radicals containing 1 to 4 carbon atoms,

R_3 represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms chosen from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents chosen from halogen atoms and alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or alkoxycarbonyl radicals, on the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and that the alkenyl and alkynyl radicals

contain 2 to 8 carbon atoms, and that the aryl radicals are phenyl or α- or β-naphthyl radicals,

R_4 represents an alkanoyloxy radical in which the alkanoyl portion contains 2 to 6 carbon atoms in an unbranched or branched chain, with the exception of an acetyl radical, an alkenoyloxy radical in which the alkenoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain or an alkynoyloxy radical in which the alkynoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, these radicals being optionally substituted with one or more halogen atoms or with an alkoxy radical containing 1 to 4 carbon atoms or an alkylthio radical containing 1 to 4 carbon atoms or with a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano or carbamoyl radical or an N-alkylcarbamoyl or N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom chosen from oxygen, sulphur or nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4 carbon atoms or a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 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 a

cycloalkenoyloxy radical in which the cycloalkenoyl portion contains 4 to 8 carbon atoms, or alternatively R_4 represents a benzoyloxy radical or a heterocycle-carbonyloxy radical in which the heterocyclic portion represents a 5- or 6-membered aromatic heterocycle containing one or more hetero atoms chosen from oxygen, sulphur or nitrogen atoms,

R_5 represents an alkoxy radical containing 1 to 6 atoms this carbon in an unbranched or branched chain, optionally substituted with an alkoxy radical containing 1 to 4 carbon atoms, an alkenyloxy radical containing 3 to 6 carbon atoms, an alkynyloxy radical containing 3 to 6 carbon atoms, a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 3 to 6 carbon atoms, these radicals being optionally substituted with one or more halogen atoms or with an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano or carbamoyl radical or an N-alkylcarbamoyl or N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom chosen from oxygen, sulphur or nitrogen atoms, optionally substituted with an alkyl radical containing 1 to 4

* C L M S *

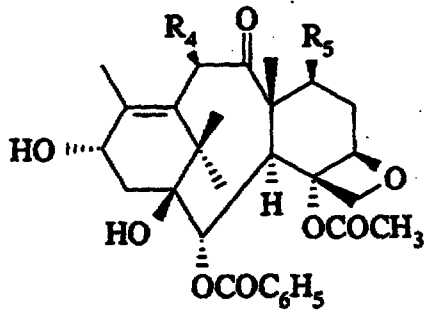
carbon atoms or a phenyl radical or a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

2. New taxoids according to claim 1 for 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-CO- in which R_2 represents a tert-butyl radical and R_3 represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms and alkyl, alkoxy, dialkylamino, acylamino, alkoxycarbonylamino or trifluoromethyl radical, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and R_4 represents an alkyloxyacetoxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a cycloalkanoyloxy radical in which the cycloalkanoyl portion contains 4 to 8 carbon atoms or a pyridylcarbonyloxy radical, and R_5 represents an unbranched or branched alkyloxy radical containing 1 to 6 carbon atoms.

3. New taxoids according to claim 1 for 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-CO- in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl,

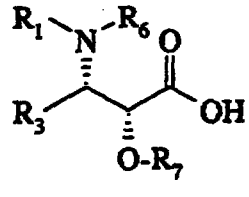
isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, R_4 represents a methoxyacetoxy, cyclopropylcarbonyloxy, cyclopentylcarbonyloxy, 2-pyridylcarbonyloxy or 3-pyridylcarbonyloxy radical, and R_5 represents a methoxy radical.

4. Process for preparing the taxoids according to one of claims 1, 2 and 3 for which Z represents a radical of general formula (II), characterized in that a product of general formula:



(III)

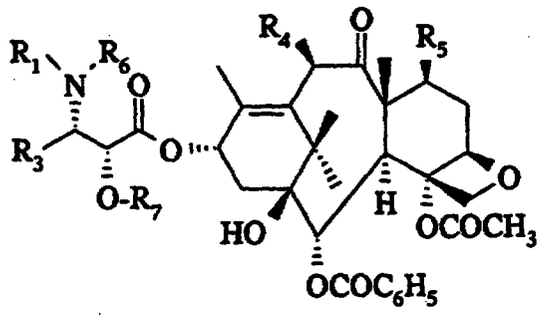
in which R_4 and R_5 are defined as in one of claims 1, 2 and 3, is esterified by means of an acid of general formula:



(IV)

in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 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:



(V)

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

5. Process according to claim 4, characterized in that the esterification is performed by means of an acid of general formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of between -10 and 90°C.

6. Process according to claim 4, characterized in that the esterification is performed by means of an acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent in an organic solvent at a temperature of between 0 and 90°C.

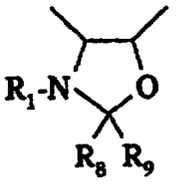
7. Process according to claim 4, characterized in that the esterification is performed using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, working in an organic solvent at a

temperature of between 0 and 80°C.

8. Process according to claim 4, characterized in that the protective groups R_7 and/or R_6 and R_7 are replaced by hydrogen atoms, working, depending on their nature, in the following manner:

1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, the protective groups are replaced by hydrogen atoms by means of an inorganic or organic 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 of general formula:

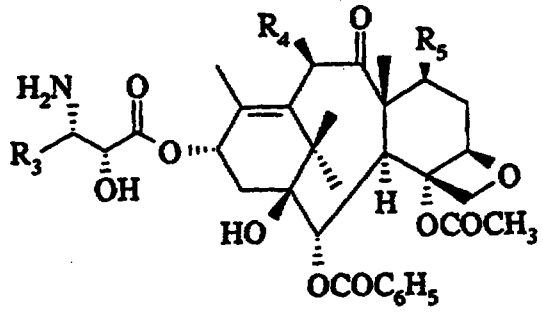


(VI)

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 aralkyl 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, the protective group formed by R_6 and R_7 is replaced by hydrogen atoms, working, depending on the meanings of R_1, R_8 and R_9, in the following manner:

a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9, which may be identical or different, represent an alkyl radical or an aralkyl or aryl 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, the ester of general formula (V) is treated with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, to obtain the product of general formula:



(VII)

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 thenoyl chloride, of furoyl chloride or of a product of general formula:

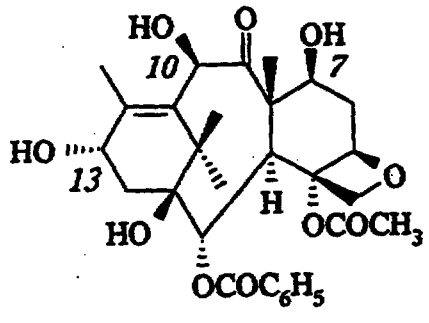
$$R_2\text{-O-CO-X} \qquad \text{(VIII)}$$

in which R_2 is defined as above and X represents a halogen atom or a residue $-O-R_2$ or $-O-CO-O-R_2$, to obtain a product of general formula (I) in which Z represents a radical of general formula (II),

b) when R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical R_2O-CO- in which R_2 is defined as above, R_8 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 R_9 represents a hydrogen atom, the protective group formed by R_6 and R_7 is replaced by hydrogen atoms, in the presence of an inorganic or organic 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.

9. Process for preparing a new taxoid according to one of claims 1, 2 and 3 for which Z represents a hydrogen atom, R_4 is defined as in one of claims 1, 2 and 3 and R_5 is defined as in one of claims 1, 2 and 3, characterized in that 10-deacetylbaccatin III of formula:

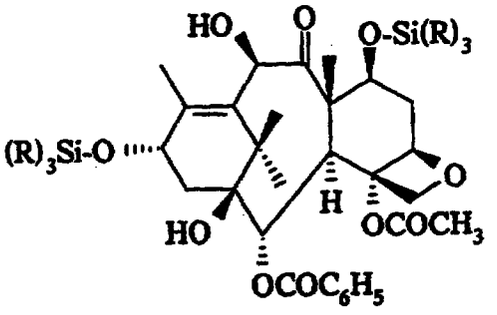


(IX)

is treated with a silyl halide of general formula:

$$(R)_3\text{-Si-Hal} \qquad (X)$$

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, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of general formula:

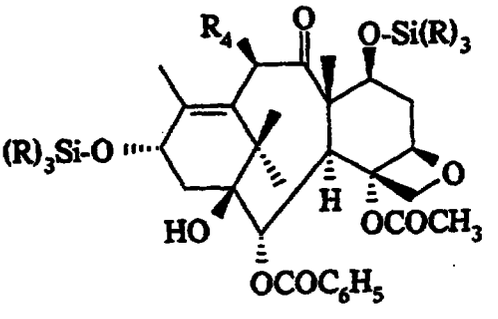


(XI)

in which R is defined as above, which is treated with a product of general formula:

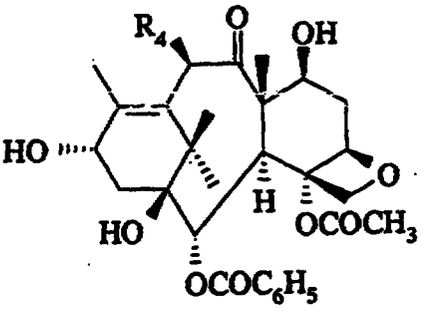
$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

in which R'_4 is such that R'_4-O- is identical to R_4 defined as in one of claims 1, 2 and 3 and X_1 represents a halogen atom, to obtain a product of general formula:



(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:



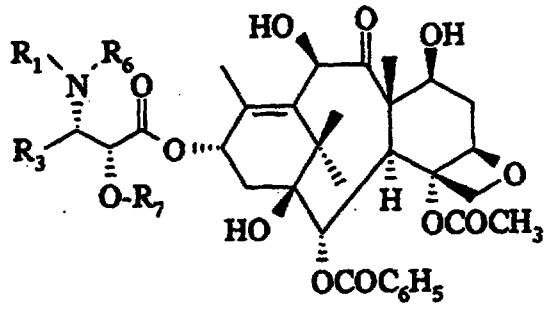
(XIV)

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

$$R'_5\text{-}X_2 \qquad \text{(XV)}$$

in which R'_5 is such that R'_5-O- is identical to R_5 defined as in one of claims 1, 2 and 3 and X_2 represents a reactive ester residue or a halogen atom, to give the product of general formula (I) in which Z represents a hydrogen atom.

10. Process for preparing a product according to one of claims 1, 2 and 3 for which Z represents a radical of general formula (II), R_4 is defined as in one of claims 1, 2 and 3 and R_5 is defined as in one of claims 1, 2 and 3, characterized in that a product of general formula:



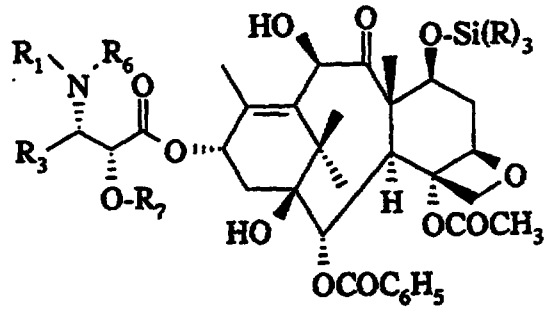
(XVI)

in which R_1, R_3, R_6 and R_7 are defined as in one of claims 1, 2, 3 and 4, is treated by means of a product of general formula:

$$(R)_3Si\text{-}Hal \qquad \text{(X)}$$

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 cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of general formula:

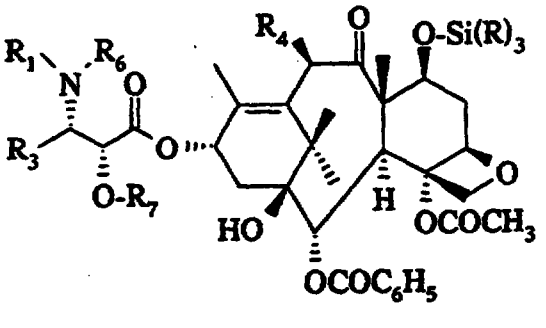


(XVII)

in which R, R_1, R_3, R_6 and R_7 are defined as above, which is functionalized at position 10 by means of a product of general formula:

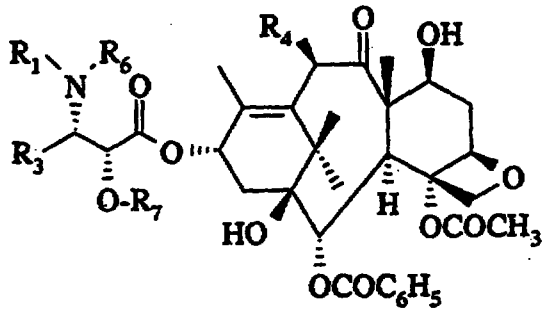
$$R'_4\text{-}X_1 \qquad \text{(XII)}$$

in which R_4 is such that R'_4-O- is identical to R_4 defined as in one of claims 1, 2 and 3 and X_1 represents a halogen atom or a reactive ester residue, to give a product of general formula:



(XVIII)

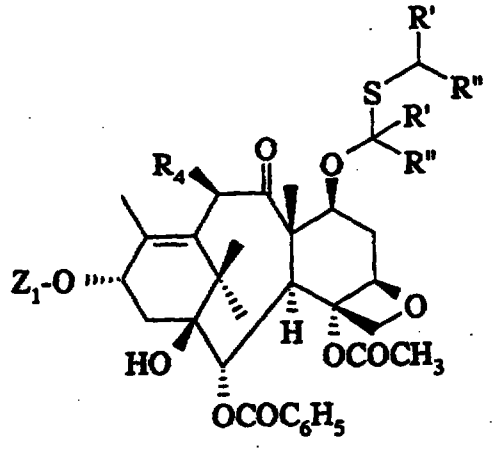
in which R, R_1, R_3, R_4, R_6 and R_7 are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula:



(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).

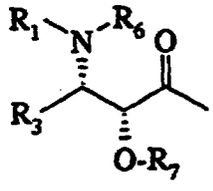
11. Process for preparing a product according to one of claims 1, 2 and 3, characterized in that activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, is reacted with a product of general formula:



(XXI)

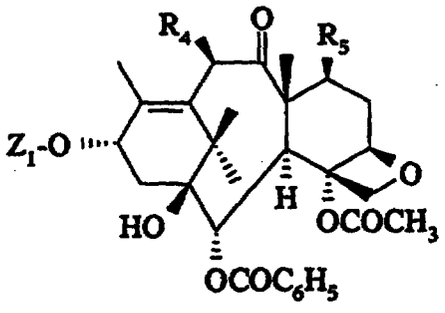
in which R_4 is defined as in one of claims 1, 2 and 3 and R' and R", which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical

containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 2 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, 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 Z_1 represents a hydrogen atom or a radical of general formula:



(XXII)

in which R_1 and R_3 are defined as in one of claims 1 to 3 and R_6 and R_7 are defined as in claim 4, to obtain a product of general formula:



(XXIII)

followed, when Z_1 represents a radical of general formula (XXII), by replacement of the protective groups represented by R_6 and/or R_6 and R_7 by hydrogen atoms under the conditions of claim 8.

12. Preparation process according to claim 11, characterized in that it is carried out at a temperature of between -10 and 60°C.

13. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-10β-methoxyacetoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

14. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-cyclopropylcarbonyloxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

15. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-cyclopentylcarbonyloxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

16. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-(2-pyridyl)carbonyloxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

17. 4α-Acetoxy-2α-benzoyloxy-1β-hydroxy-5β,20-epoxy-7β-methoxy-10β-(3-pyridyl)carbonyloxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

18. Pharmaceutical composition, characterized in that it contains at least one product according to one of claims 1, 2 and 3 for which Z represents a radical of general formula (II), in combination with one or more pharmaceutically

acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

19. Pharmaceutical composition, characterized in that it contains at least the product according to claim 13 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

20. Pharmaceutical composition, characterized in that it contains at least the product according to claim 14 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

21. Pharmaceutical composition, characterized in that it contains at least the product according to claim 15 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

22. Pharmaceutical composition, characterized in that it contains at least the product according to claim 16 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

23. Pharmaceutical composition, characterized in that it contains at least the product

* C L M S *

according to claim 17 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.