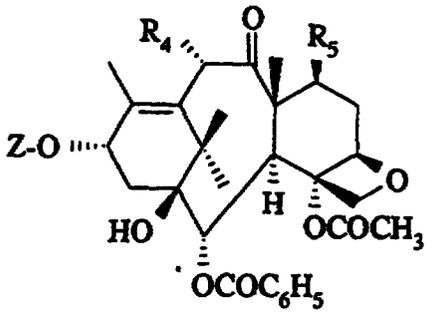
TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

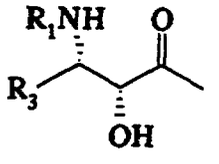
The present invention relates to new taxoids of general formula:



(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, thenoyl or furoyl radicals 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 the 4-position 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 a hydroxyl radical or an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms, a cycloalkenyloxy radical containing 3 to 6 carbon atoms, an alkanoyloxy radical in which the alkanoyl portion contains 2 to 6 carbon atoms in an unbranched or branched chain, an alkenoyloxy radical in which the alkenoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, an alkynoyloxy radical in which the alkynoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, an alkoxyacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms in an unbranched or branched chain, an alkylthioacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms in an unbranched or branched chain or an alkyloxycarbonyloxy radical in which the alkyl portion contains 1 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, 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 and 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 carbamoyloxy radical or an N-alkylcarbamoyloxy radical in which the alkyl portion contains 1 to 4 carbon atoms, an N,N-dialkylcarbamoyloxy radical in which each alkyl portion contains 1 to 4 carbon atoms or a benzoyloxy radical or a heterocyclylcarbonyloxy radical in which radical the heterocyclic portion represents a 5- or 6-membered aromatic heterocycle containing one or more hetero atoms chosen from oxygen, sulphur and nitrogen atoms,

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms 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, 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 and 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 radical R_4 represents a hydroxyl radical or an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms or an alkanoyloxy radical containing 2 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 and R_5 represents an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

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) and trifluoromethyl radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and R_4 represents a hydroxyl radical or an unbranched or branched alkyloxy radical containing 1 to 6 carbon atoms or an alkanoyloxy radical containing 2 to 6 carbon atoms 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 hydroxyl radical or a methoxy, ethoxy or propoxy 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.

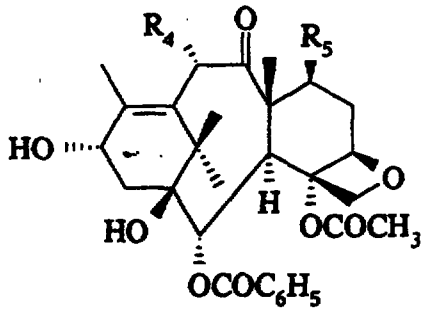
According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula:

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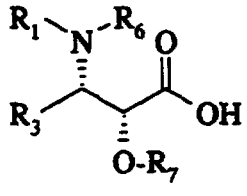
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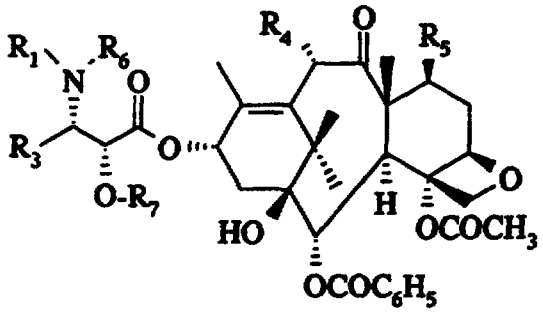
(III)

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 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 the replacement of the protective groups represented by R_7 and/or R_6 and R_7 with hydrogen atoms.

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To obtain a product of general formula (I) in which R_4 represents a hydroxyl radical, it is advantageous to protect the hydroxyl function at the 10-position of the product of general formula (III), prior to the esterification, in the form, for example, of an alkoxyacetoxy radical and then to replace the protective group at the 10-position with a hydroxyl radical by means, for example, of hydrazine hydrate and the protective groups R_7 and/or R_6 and R_7 with hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be carried out in the presence of a condensing agent (reactive carbonate, carbodiimide) and of 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 performed using the acid of general formula (IV) in the form of a symmetric anhydride, 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 performed using the acid of general formula (IV) in the form of a

halide or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, 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 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, benzoyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzoyloxycarbonyl or tetrahydropyranyl radical.

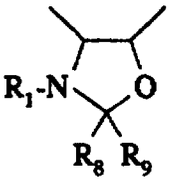
When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally mono-substituted or gem-disubstituted at the 2-position.

The replacement of the protective groups R_7 and/or R_6 and R_7 with hydrogen atoms may be carried out, depending on their nature, in the following manner:

1) When R_6 represents a hydrogen atom and R7 represents a group protecting the hydroxyl function, the replacement of the protective groups with hydrogen atoms is carried out by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid)

or an organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid), used alone or in the form of a mixture, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitriles, at a temperature of between -10 and 60°C, or by means of a source of fluoride ions such as a hydrofluoric acid-triethylamine complex or by catalytic hydrogenation,

2) When R_6 and R_7 together form a saturated 5- or 6-membered heterocycle and more particularly an oxazolidine ring of general formula:

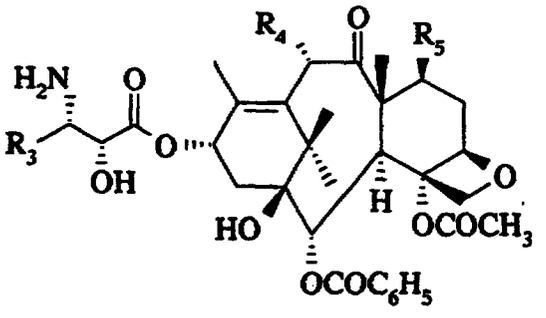


(VI)

in which R_1 is defined as above, R_8 and R_9, which are 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, either 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 R_8 and R_9 together form, with the carbon atom to which they are linked, a ring having 4 to 7 members, the replacement of the protective group formed by R_6 and R_7 with hydrogen atoms may be carried out, according to the meanings of R_1, R_8 and R_9, in the following manner:

a) When R_1 represents a tert-butoxycarbonyl radical, R_8 and R_9, which are identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, either R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical, and R_9 represents a hydrogen atom, or R_8 and R_9 together form a 4- to 7-membered ring, the treatment of the ester of general formula (V) with an inorganic or organic acid, optionally in an organic solvent such as an alcohol, gives 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, thenoyl

chloride, furoyl chloride or 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 give the product of general formula (VII).

Preferably, the acylation of the product of general formula (VII) by means of benzoyl chloride in which the phenyl radical is optionally substituted, thenoyl chloride or furoyl chloride or a product of general formula (VIII) is carried out in an inert organic solvent chosen from esters such as ethyl acetate, isopropyl acetate or n-butylacetate 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 carried out at a temperature of between 0 and 50°C, preferably in the region of 20°C.

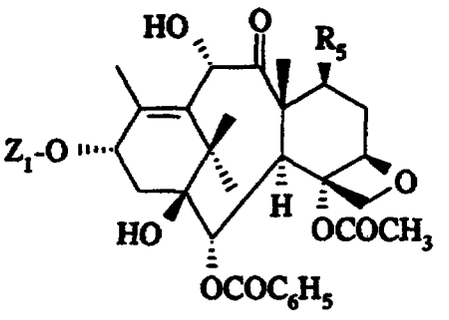
b) When R_1 represents an optionally substituted benzoyl radical, a thenoyl or furoyl

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, the replacement of the protective group formed by R_6 and R_7 with hydrogen atoms is carried out in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or an organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid), used alone or in the form of a mixture, in a stoichiometric or catalytic quantity, 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, preferably between 15 and 30°C.

According to the invention, the products of general formula (I) in which R_4 and R_5 are defined as above, R4 not being capable of represents a hydroxyl radical and Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of a product of general formula:

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

in which R'_4 is such that R'_4-O is identical to R_4 defined as above and X_1 represents a halogen atom, on a product of general formula:



(X)

in which R_5 is defined as above and Z_1 represents a hydrogen atom or a group protecting the hydroxyl function or a radical of general formula:



(XI)

in which R_1, R_3, R_6 and R_7 are defined as above, optionally followed by the replacement of the protective groups with hydrogen atoms.

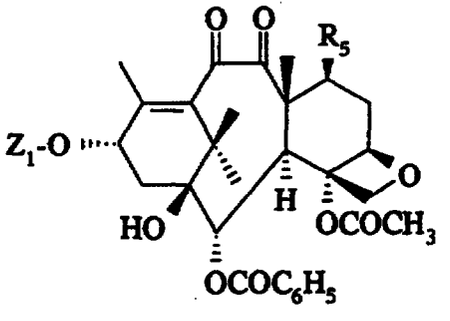
Generally, the action of the product of general formula (IX) on a product of general formula (X) is carried out, after metalation of the hydroxyl function at the 10-position by means of an alkali metal hydride such as sodium hydride, an alkali metal amide such as lithium amide or an alkali metal alkylide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

When Z_1 represents a group protecting the hydroxyl function, this group is preferably a silylated radical, such as a trialkylsilyl radical, whose

replacement with a hydrogen atom is carried out 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, optionally combined with an inert organic solvent such as a nitrile such as acetonitrile or a halogenated aliphatic hydrocarbon such as dichloromethane, at a temperature of between 0 and 80°C.

When Z_1 represents a radical of general formula (XI), the replacement of the protective groups R_6 and/or R_6 and R_7 with hydrogen atoms is carried out under the conditions described above for the replacement of the protective groups of the product of general formula (V).

The product of general formula (X) may be obtained by reduction of a product of general formula:



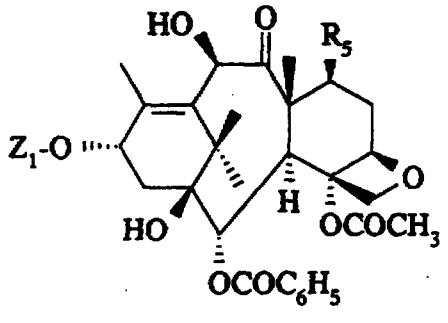
(XII)

in which R_5 and Z_1 are defined as above.

Generally, the reducing agent is chosen from aluminohydrides or borohydrides such as alkali or alkaline-earth metal borohydrides such as sodium

borohydride, in the presence of an aliphatic alcohol containing 1 to 4 carbon atoms such as methanol, the reduction being performed at a temperature of between 0 and 50°C, preferably in the region of 20°C.

The product of general formula (XII) may be obtained by the action of an oxidizing agent on a product of general formula:

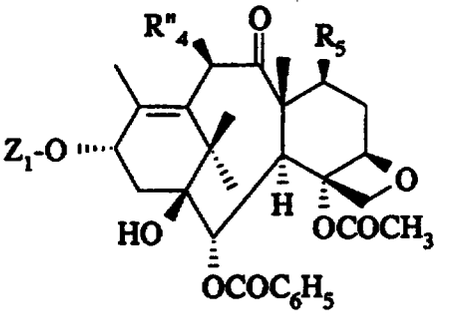


(XIII)

in which R_5 and Z_1 are defined as above.

Generally, the oxidizing agent is chosen from agents which make it possible to oxidize the secondary alcohol function without affecting the rest of the molecule, such as for example oxygen, ammonium perruthenate, manganese dioxide, copper acetate or pyridinium chlorochromate, working in an organic solvent such as optionally halogenated aliphatic hydrocarbons such as dichloromethane, at a temperature of between 0 and 50°C, preferably in the region of 25°C.

The product of general formula (XIII) may be obtained by the action of hydrazine, preferably in hydrate form, on a product of general formula:

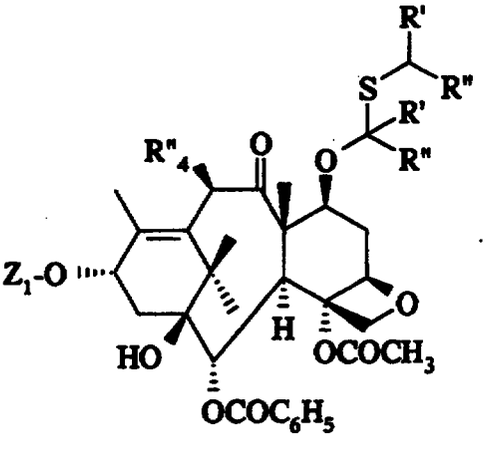


(XIV)

in which Z_1 and R_5 are defined as above and R''_4 represents an alkoxyacetoxy or alkylthioacetoxy radical in which the alkyl portion contains 1 to 4 carbon atoms.

Generally, the reaction is carried out working in an aliphatic alcohol containing 1 to 4 carbon atoms such as ethanol, at a temperature of between 0 and 50°C.

The product of general formula (XIV) 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:



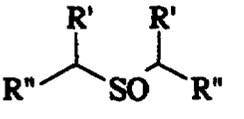
(XV)

in which Z_1 and R''_4 are defined as above, R' and R", which are 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 R′ and R" together form, with the carbon atom to which they are linked, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms.

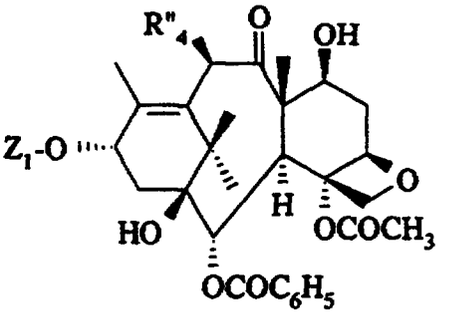
Generally, the action of the activated Raney nickel in the presence of the aliphatic alcohol is carried out at a temperature of between -10 and 60°C.

The product of general formula (XV) may be obtained by the action of a dialkyl sulphoxide of general formula:



(XVI)

in which R′ and R" are defined as above, on a product of general formula:



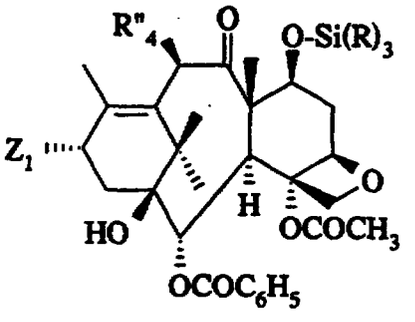
(XVII)

in which Z_1 and $R"_4$ are defined as above.

Generally, the reaction of the sulphoxide of

general formula (XVI), preferably dimethyl sulphoxide, on the product of general formula (XVII) is carried out in the presence of a mixture of acetic acid and acetic anhydride or of a derivative of acetic acid such as a haloacetic acid, at a temperature of between 0 and 50°C, preferably in the region of 25°C.

The product of general formula (XVII) may be obtained by the action, for example, of a triethylamine-hydrofluoric acid complex, on a product of general formula:



(XVIII)

in which Z_1 and $R"_4$ are defined as above.

Generally, the reaction is carried out working in an organic solvent such as an optionally halogenated aliphatic hydrocarbon, at a temperature of between -25 and 25°C.

The product of general formula (XVIII) may be obtained under the conditions described in international patent 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 into 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 example which follows illustrates the present invention.

EXAMPLE 1

35 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10α-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 dissolved in 0.74 cm^3 of a 0.1 N hydrochloric acid ethanolic solution containing 1 % of water. The solution thus obtained is stirred for 2 hours at a temperature in the region of 20°C and then supplemented with 1 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and 3 cm^3 of dichloromethane. The mixture is stirred for 5 minutes at a temperature in the region of 20°C and separated by decantation of the organic phase. The aqueous phase is reextracted with twice 3 cm^3 of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 34 mg of a white foam are obtained which are purified by chromatography on silica gel plates [(gel 1 mm thick, 1 plate of 20 × 20 cm, eluent, dichloromethane/methanol (95-5 by volume)]. After locating, using UV rays, the zone

corresponding to the desired product adsorbed, this zone is scraped off and the silica recovered is washed on sintered glass with 10 times 2 cm^3 of ethyl acetate. The filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. 22 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10α-dihydroxy-7β-methoxy-9-oxo-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:

- ^1H NMR spectrum (400 MHz ; $CDCl_3$; chemical shifts δ in ppm ; coupling constants J in Hz) : 1.13 (s, 3H : $-CH_3$ at position 16 or 17) ; 1.27 (s, 3H : $-CH_3$ at position 16 or 17) ; 1.38 [s, 9H : $-C(CH_3)_3$] ; 1.72 (s, 3H : $-CH_3$) ; 1.76 (s, 1H : OH at position 1) ; 1.82 and 2.75 (2 mts, 1H each : $-CH_2-$ at position 6); 2.08 (s, 3H : $-CH_3$) ; 2.28 and 2.35 (2 dd, J = 16 and 9, 1H each : $-CH_2-$ at position 14 ; 2.40 (s, 3H : $-COCH_3$) ; 2.71 (d, J = 2, 1H : -OH at position 10) ; 3.30 (s, 3H : $-OCH_3$) ; 3.42 (broad s, 1H : -OH at position 2') ; 4.20 and 4.32 (2 d, J = 8.5, 1H each : $-CH_2-$ at position 20) ; 4.27 (d, J = 7.5, 1H : -H at position 3) ; 4.31 (mt, 1H : -H at position 7) ; 4.64 (mt, 1H : -H at position 2') ; 5.02 (broad d, J = 10, 1H : -H at position 5) ; 5.21 (mt, 1H : -H at position 10) ; 5.32 (broad d, J = 10, 1H : -H at position 3') ; 5.48 (d, J = 10, 1H : -CONH-); 5.65 (d, J = 7.5, 1H : -H at position 2) ; 6.18 (broad t, J = 9, 1H : -H at position

13) ; from 7.25 to 7.45 (mt, 5H : $-C_6\underline{H}_5$ at position 3') ; 7.52 [t, J = 7.5, 2H : $-OCOC_6H_5$ ($-\underline{H}$ at position 3 and $\underline{H}$ at position 5)] ; 7.63 [t, J = 7.5, 1H : $-OCOC_6H_5$ ($-\underline{H}$ at position 4)] ; 8.13 [d, J = 7.5, 2H : $-OCOC_6H_5$ ($-\underline{H}$ at position 2 and $\underline{H}$ at position 6)].

4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10α-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 may be prepared in the following manner:

9 mg of sodium tetrahydruroborate are added, at a temperature in the region of 20°C, to a solution of 45 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9,10-dioxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 2 cm^3 of anhydrous ethanol, maintained under an argon atmosphere and with stirring, and the reaction mixture is maintained stirring for 1 hour at a temperature in the region of 20°C and then 1 cm^3 of distilled water is added and the mixture is stirred for 5 minutes at 20°C. 3 cm^3 of dichloromethane are added and the organic phase is separated by decantation. The aqueous phase is reextracted with twice 3 cm^3 of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered on sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. A white foam is obtained which is purified by

chromatography on a silica gel plate [(gel 1 mm thick, 1 plate of 20 × 20 cm, eluent: dichloromethane/methanol (95-5 by volume)]. After locating, using UV rays, the zone corresponding to the desired product adsorbed, this zone is scraped off and the silica recovered is washed on sintered glass with 10 times 2 cm^3 of ethyl acetate. The filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. 22.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10α-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-9,10-dioxo-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:

500 mg of a 4Å molecular sieve powder and 43 mg of pyridinium chlorochromate are successively added, at a temperature in the region of 20°C, to a solution of 100 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 in 5 cm^3 of dichloromethane, maintained under an argon atmosphere and with stirring. The suspension obtained is stirred for 21 hours at a temperature in the region of 20°C and

then filtered on sintered glass coated with celite. The sintered glass is washed with 3 times 5 cm^3 of dichloromethane. The filtrates are pooled and supplemented with powdered animal charcoal and then filtered on sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. A yellow foam is thereby obtained which is purified by chromatography on a silica gel plate [(gel 1 mm thick, 1 plate of 20 × 20 cm, eluent: dichloromethane/methanol (95-5 by volume)]. After locating, using UV rays, the zone corresponding to the desired product adsorbed, this zone is scraped off and the silica recovered is washed on sintered glass with 10 times 5 cm^3 of ethyl acetate. The filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. 47 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β-methoxy-9,10-dioxo-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 light beige foam.

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 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 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, maintained under an argon atmosphere and with stirring. The reaction medium is maintained 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 by decantation and the aqueous phase is reextracted with twice 50 cm^3 of ethyl acetate. The organic phases are pooled, 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 are purified by chromatography on silica gel plates [gel 1 mm thick, 20 × 20 cm plates, eluent: dichloromethane/ethanol (90-10 by volume)] in 90-mg fractions (2 plates). After locating, using UV rays, the zone corresponding to the desired product adsorbed, this zone is scraped off and the silica recovered is washed on sintered glass with 10 times 10 cm^3 of ethyl acetate. The filtrates are pooled 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 Raney nickel (obtained from 80 cm^3 of an aqueous commercial suspension at about 50%, by successive washes, up 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 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, maintained under an argon atmosphere and with stirring. The reaction medium is maintained stirring for 7 days at a temperature in the region of 20°C and then filtered on sintered glass. The sintered glass is washed with 3 times 100 cm^3 of ethanol, the filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 821 mg of a white foam are obtained which are 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 desired product 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-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 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 of 5 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 in 165 cm^3 of anhydrous dimethyl sulphoxide, maintained under an argon atmosphere and with stirring. The reaction medium is maintained stirring for 3 days at a temperature in the region of 20°C and then poured into 500 cm^3 of dichloromethane. 100 cm^3 of a saturated aqueous potassium carbonate solution are then added, with vigorous stirring, until a pH in the region of 7 is obtained. After stirring for

10 minutes, the organic phase is separated by decantation and the aqueous phase is reextracted with twice 250 cm^3 of dichloromethane. The organic phases are pooled, 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 are 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 desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 3.01 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 are thereby obtained in the form of a white foam.

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 may be prepared in the following manner:

220 cm^3 of the triethylamine-hydrofluoric acid complex (1-3 by mol) are added dropwise, at a temperature in the region of 0°C, to a solution 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, maintained under an argon atmosphere and with stirring. The reaction medium is then heated up to a temperature in the region of 20°C, maintained for 3 hours at this temperature and poured into 4 litres of an aqueous saturated sodium hydrogen carbonate solution. The pH of the reaction medium is thus brought to about 7. After stirring for 10 minutes, the organic phase is separated by decantation and the aqueous phase is extracted with twice 100 cm^3 of dichloromethane. The organic phases are pooled, 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

A solution of 40 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10α-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 cm^3 of a 0.1 N hydrochloric acid ethanolic solution containing 1% water is stirred for 2 hours at a temperature in the region of 20°C and then supplemented with 1 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and with 2 cm^3 of dichloromethane. The mixture is stirred for 5 minutes at a temperature in the region of 20°C and the organic phase is separated by decantation. The aqueous phase is reextracted with twice 2 cm^3 of dichloromethane. The organic phases are pooled, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 38 mg of a white foam are obtained which are purified by chromatography on a silica gel plate [gel 1 mm thick, 1 plate of 20 × 20 cm, eluent: dichloromethane/methanol (95-5 by volume)]. After locating, using UV rays, the zone corresponding to the desired product adsorbed, this zone is scraped off and the silica recovered is washed on sintered glass with 10 times 2 cm^3 of ethyl acetate. The filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. 14 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10α-dimethoxy-9-oxo-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:

- ^{1}H NMR spectrum (400 MHz ; $CDCl_3$; chemical shifts δ in ppm ; coupling constants J in Hz) : 1.13 (s, 3H : $-C\underline{H}_3$ at position 16 or 1 at position 7) ; 1.27 (s, 3H : $-C\underline{H}_3$ at position 16 or 17) ; 1.39 [s, 9H : $-C(C\underline{H}_3)_3$] ; 1.72 (s, 3H : $-C\underline{H}_3$) ; 1.76 (s, 1H : $-O\underline{H}$ at position 1) ; 1.78 and 2.78 (2 mts, 1H each : $-C\underline{H}_2-$ at position 6) ; 2.03 (s, 3H : $-C\underline{H}_3$) ; 2.27 and 2.37 (2dd, J = 16 and 9, 1H each : $-C\underline{H}_2-$ at position 14) ; 2.38 (s, 3H : $-COC\underline{H}_3$) ; 3.28 (s, 3H : $-OC\underline{H}_3$) ; 3.42 (broad s, 1H : $-O\underline{H}$ at position 2') ; 3.47 (s, 3H : $-OC\underline{H}_3$) ; from 4.15 to 4.25 (mt, 2H: $-\underline{H}$ at position 3 and $-\underline{H}$ at position 7); 4.18 and 4.32 (2 d, J = 8.5, 1H each : $-C\underline{H}_2-$ at position 20) ; 4.52 (broad s, 1H : $-\underline{H}$ at position 10); 4.64 (mt, 1H : $-\underline{H}$ at position 2') ; 5.01 (broad d, J = 10, 1H : $-\underline{H}$ at position 5) ; 5.30 (broad d, J = 10, 1H : $-\underline{H}$ at position 3') ; 5.45 (d, J = 10, 1H : $-CON\underline{H}-$) ; 5.65 (d, J = 7.5, 1H : $-\underline{H}$ at position 2) ; 6.15 (broad t, J = 9, 1H : $-\underline{H}$ at position 13) ; from 7.25 to 7.45 (mt, 5H : $-C_6\underline{H}_5$ at position 3') ; 7.51 [t, J = 7.5, 2H : $-OCOC_6H_5$($-\underline{H}$ at position 3 and $\underline{H}$ at position 5)]; 7.62 [t, J = 7.5, 1H : $-OCOC_6H_5$($-\underline{H}$ at position 4)] ; 8.12 [d, J = 7.5, 2H : $-OCOC_6H_5$($-\underline{H}$ at position 2 and $\underline{H}$ at position 6)].

4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10α-dimethoxy-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:

0.5 cm^3 of methyl iodide and 3.6 mg of a dispersion at 50 % by weight of sodium hydride in mineral oil are added, at a temperature in the region of 0°C, to a solution of 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10α-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 in 0.5 cm^3 of anhydrous dimethylformamide, maintained under an argon atmosphere and with stirring. The reaction medium is maintained stirring for 30 minutes at a temperature in the region of 0°C and then 10 cm^3 of ethyl acetate and 5 cm^3 of an aqueous saturated ammonium chloride solution are added. After stirring for 5 minutes, the organic phase is separated by decantation and the aqueous phase is reextracted with twice 5 cm^3 of ethyl acetate. The organic phases are pooled, washed with twice 10 cm^3 of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. A white foam is obtained which is purified by chromatography on a silica gel plate [gel 1 mm thick, 1 plate of 20 × 20 cm, eluent: dichloromethane/methanol (95-5 by volume)]. After locating, using UV rays, the zone corresponding to the desired product adsorbed, this zone is scraped off and

the silica recovered is washed on sintered glass with 10 times 2 cm^3 of ethyl acetate. The filtrates are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 20°C. 26 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10α-dimethoxy-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.

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 may also be provided in the

form of tablets, pills, powders or granules which can be administered via the oral route.

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 mechlorethamine, 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 the 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 the factors which may influence the efficacy of the treatment.

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

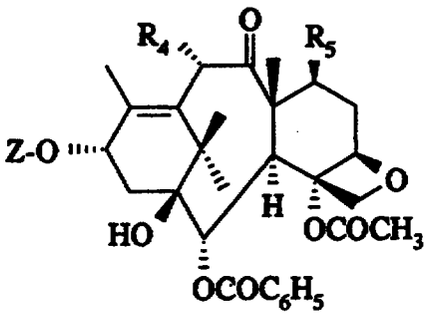
EXAMPLE

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:

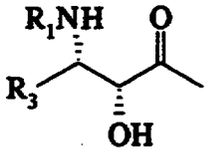


(I)

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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, thenoyl or furoyl radicals 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

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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 the 4-position 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

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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

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

R_4 represents a hydroxyl radical or an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms, a cycloalkenyloxy radical containing 3 to 6 carbon atoms, an alkanoyloxy radical in which the alkanoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, an alkenoyloxy radical in which the alkenoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, an alkynoyloxy radical in which the alkynoyl portion contains 3 to 6 carbon atoms in an unbranched or branched chain, an alkoxyacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms in an unbranched or branched chain, an alkylthioacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms in an unbranched or branched chain or an alkyloxycarbonyloxy radical in which the alkyl portion contains 1 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, an alkylthio radical containing 1 to 4 carbon atoms or a carboxyl radical, an alkyloxycarbonyl

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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 and 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 benzoyloxy radical or a heterocyclylcarbonyloxy radical in which radical the heterocyclic portion represents a 5- or 6-membered aromatic heterocycle containing one or more hetero atoms chosen from oxygen, sulphur and nitrogen atoms,

R_5 represents an alkoxy radical containing 1 to 6 carbon atoms 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, 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

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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 and 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.

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 and trifluoromethyl radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and R_4 represents a hydroxyl radical or an unbranched or branched alkyloxy radical containing 1 to

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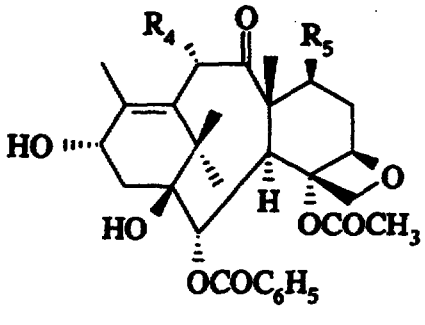
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6 carbon atoms and R_5 represents an unbranched or branched alkyloxy radical containing 1 to 6 carbon atoms.

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 hydroxyl radical or a methoxy radical and R_5 represents a methoxy radical.

4. Process for the preparation of a product 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:



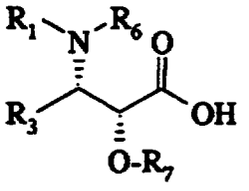
(III)

in which R_4 and R_5 are defined as in one of claims 1, 2 and 3, it being possible for R_4, in addition, to represent a group protecting the hydroxyl function chosen from alkoxyacetyl radicals, is esterified by means of an acid of general formula:

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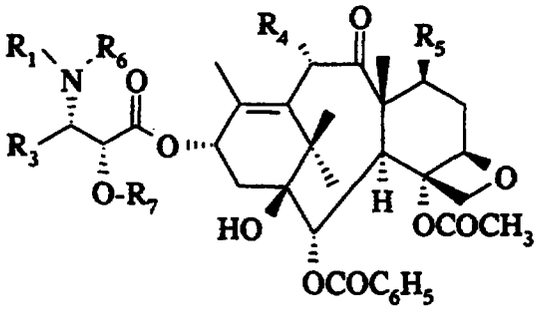
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(IV)

in which R_1 and R_3 are defined as in one of claims 1, 2 and 3, 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 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, and then the protective groups represented by R_7 and/or R_6 and R_7 are replaced with hydrogen atoms and, optionally, the R_4 radical with a hydroxyl radical.

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

6. Process according to claim 4,

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characterized in that the esterification is carried out by means of an acid of general formula (IV) in the form of a symmetric 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 carried out using the acid of general formula (IV) in the form of a halide 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 with hydrogen atoms, working, according to their nature, in the following manner:

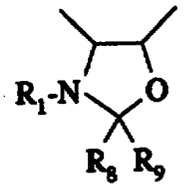
1) When R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, the replacement of the protective groups with hydrogen atoms is carried out by means of an inorganic acid or an organic acid, used alone or in the form of a mixture, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and 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:

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(VI)

in which R_1 is defined as above, R_8 and R_9, which are 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 represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, either R_8 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or R_8 and R_9 together form, with the carbon atom to which they are linked, a ring having 4 to 7 members, the replacement of the protective group formed by R_6 and R_7 with hydrogen atoms is carried out, according to the meanings of R_1, R_8 and R_9, working in the following manner:

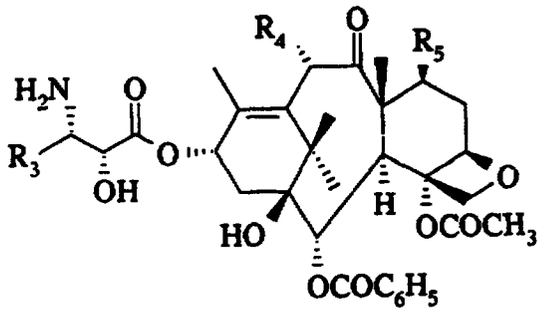
a) When R_1 represents a tert-butoxycarbonyl radical, R_8 and R_9, which are identical or different, represent an alkyl radical or an aralkyl or aryl radical, either R_8 represents a trihalomethyl radical

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or a phenyl radical substituted with a trihalomethyl radical, and R_9 represents a hydrogen atom, or 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, optionally in an organic solvent such as an alcohol, to give 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, thenoyl chloride, furoyl chloride or 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 according to one of claims 1, 2 and 3 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

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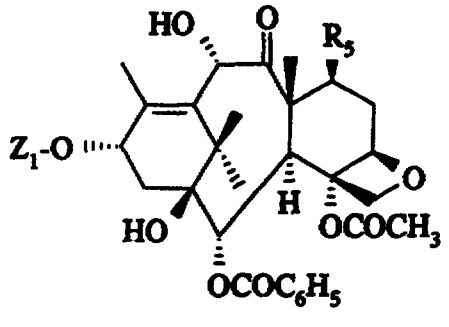
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carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and R_9 represents a hydrogen atom, the protective group formed by R_6 and R_7 is replaced with hydrogen atoms is carried out in the presence of an inorganic acid or an organic acid, used alone or in the form of a mixture, in a stoichiometric or catalytic quantity, 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 the preparation of a product according to one of claims 1, 2 or 3, in which Z represents a hydrogen atom or a radical of general formula (II), characterized in that a product of general formula:

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

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, is reacted with a product of general formula:



(X)

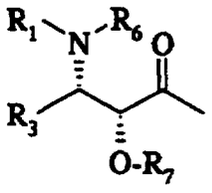
in which R_5 is defined as in one of claims 1, 2 and 3

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and Z_1 represents a hydrogen atom or a group protecting the hydroxyl function or a radical of general formula:



(XI)

in which R_1 and R_3 are defined as in one of claims 1, 2 and 3, 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 then the protective groups represented or carried by Z_1 are optionally replaced under the conditions described in claim 8.

10. Process according to claim 9, characterized in that the product of general formula (IX) is reacted with the product of general formula (X), after metalation of the hydroxyl function at the 10-position by means of an alkali metal hydride, an alkali metal amide or an alkali metal alkylide, working in an organic solvent chosen from dimethylformamide or tetrahydrofuran, at a temperature of between 0 and 50°C.

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

12. 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10α-dimethoxy-9-oxo-11-taxen-13α-yl

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(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

13. 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.

14. Pharmaceutical composition characterized in that it contains at least one product claim 11 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

15. Pharmaceutical composition characterized in that it contains at least one product according to claim 12 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

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