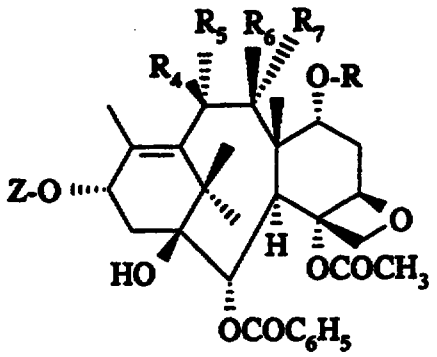
NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

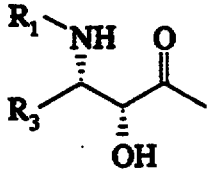
The present invention relates to new taxoids of general formula:



(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, cycloalkenyl radicals containing 4 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,

either R_4 represents a hydrogen atom,

and R_6 and R_7 together form a ketone function,

and and R and R_5 together form a bond,

or R_4 represents a hydrogen atom or 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 1 to 6 carbon atoms in an unbranched or branched chain, an aroyloxy radical in which the aryl portion contains 6 to 10 carbon atoms, 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, a cycloalkanoyloxy radical containing 3 to 6 carbon atoms, 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 or alkylcarbamoyloxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a 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,

and R_5 represents a hydrogen atom

or R_4 and R_5 together form a ketone function,

and R_6 represents a hydrogen atom, and

R and R_7 together form a bond.

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.

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

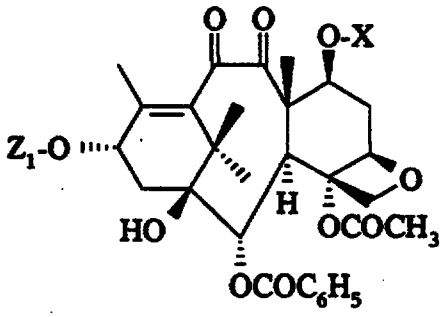
different atoms or radicals chosen from halogen atoms (fluorine, chlorine) and alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino) or trifluoromethyl radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and either R_4 represents a hydrogen atom, and R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a hydroxyl radical or an alkoxy radical containing 1 to 6 carbon atoms, an alkanoyloxy radical containing 1 to 6 carbon atoms or an alkoxyacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms, R_5 represents a hydrogen atom, and R_6 represents a hydrogen atom and R and R_7 together form a bond, or R_4 and R_5 together form a ketone function, and R_6 represents a hydrogen atom, and R and R_7 together form a bond.

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, either R_4 represents a hydrogen atom, and R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a

hydroxyl radical or a methoxy, acetoxy, propanoyloxy or methoxyacetoxy radical, and R_5 represents a hydrogen atom, and R_6 represents a hydrogen atom and R and R_7 together form a bond.

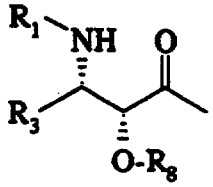
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the invention, the products of general formula (I) in which either R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond may be obtained by the action of a reducing agent on a product of general formula



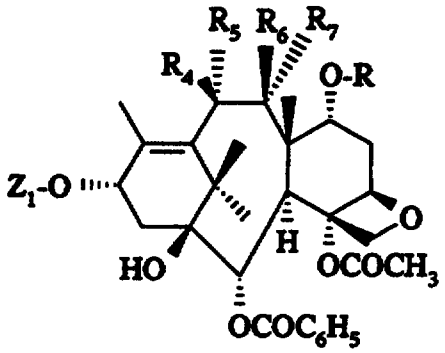
(III)

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



(IV)

in which R_8 represents a group protecting the hydroxyl function, and X represents, with the oxygen atom to which it is linked, a leaving group chosen from alkylsulphonyl radicals containing 1 to 4 carbon atoms optionally substituted with one or more halogen atoms, or arylsulphonyl radicals in which the aryl portion is a phenyl 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, or nitro or trifluoromethyl radicals, to obtain a product of general formula:



(V)

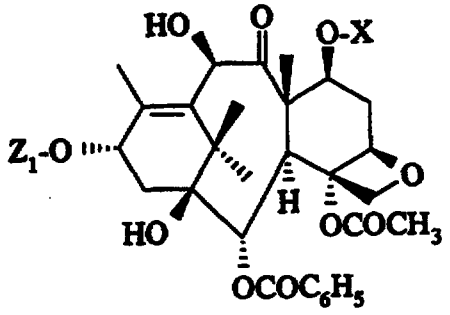
in which Z_1, R, R_4, R_5, R_6 and R_7 are defined as above, followed by the replacement of the protective group represented by Z_1 or R_8 by a hydrogen atom.

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 ethanol, the reaction being carried out at a temperature of between 0 and 50°C, preferably in the region of 20°C.

Preferably, the protective group represented by R_8 is chosen from groups which can be easily introduced and easily removed without affecting the rest of the molecule, such as silylated radicals such as the triethylsilyl radical. The replacement of the protective group by a hydrogen atom, when it represents a silylated radical, is generally performed by means of an inorganic acid such as hydrochloric acid in an aliphatic alcohol containing 1 to 4 carbon atoms, at a temperature of between -10 and 20°C, preferably in the region of 0°C, or in the presence of a source of fluoride ions such as a hydrofluoric acid-triethylamine complex, working in an inert organic solvent such as a halogenated aliphatic hydrocarbon such as dichloromethane at a temperature of between 0 and 50°C, preferably in the region of 20°C.

The carrying out of the process generally leads to a mixture of a product of general formula (I) in which R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function, and R and R_5 together form a bond, and of a product of general formula (I) in which R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, which are separated by the usual methods such as chromatography.

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

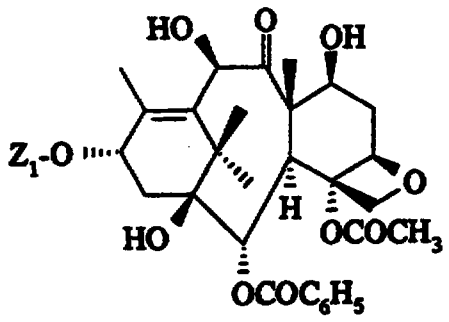


(VI)

in which Z_1 and X 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 peruthenate, manganese dioxide, copper acetate or pyridinium chlorochromate. Preferably, pyridinium chlorochromate is used, 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 (VI) in which Z_1 and X are defined as above may be obtained by the action of a sulphonyl halide on a product of general formula:

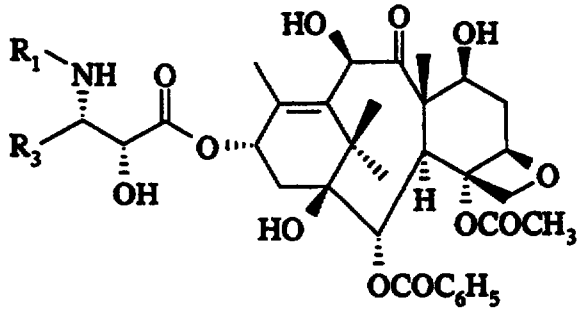


(VII)

in which Z_1 is defined as above.

The product of general formula (VI) in which X preferably represents a trifluoromethylsulphonyl radical may be obtained by the action of a derivative of trifluoromethanesulphonic acid such as the anhydride or N-phenyl trifluoromethanesulphonimide in an inert organic solvent such as an optionally halogenated aliphatic hydrocarbon such as dichloromethane, working in the presence of an organic base such as pyridine or a tertiary aliphatic amine such as triethylamine, at a temperature of between -50 and 20°C, on a product of general formula (VII).

The product of general formula (VII) in which Z_1 represents a radical of general formula (IV), in which R_8 is defined as above, may be obtained by the action of a silylating agent on a product of general formula:



(VIII)

in which R_1 and R_3 are defined as above.

Generally, a trialkylsilyl halide such as triethylsilyl chloride is used, working in an optionally halogenated hydrocarbon such as dichloromethane, in the presence of an organic base such as pyridine or a tertiary aliphatic amine such as

triethylamine.

The product of general formula (VIII) for which R_3 represents a phenyl radical and R_1 represents a tert-butyl radical is known by the name of docetaxel. The docetaxel derivatives which correspond to the general formula (VIII) may be obtained under the conditions described in International Applications PCT WO 92/09589, WO 93/16060 and WO 94/12484.

The product of general formula (VII) in which Z_1 represents a hydrogen atom is 10-deactylbaccatin III which is extracted in a known manner from yew (Taxus baccata) leaves.

According to the invention, the products of general formula (I) in which Z is defined as above, R_4 represents 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 1 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, a cycloalkanoyloxy

radical containing 1 to 6 carbon atoms, 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 or alkylcarbamoyloxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a dialkylcarbamoyloxy radical in which each alkyl portion contains 1 to 4 carbon atoms or a benzoyloxy radical or

a heterocyclic radical attached to a carbonyloxy group 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 a hydrogen atom, R_6 represents a hydrogen atom, and R and R_7 together form a bond, may be obtained by the action of a product of general formula:

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

in which R'_4 is such that R'_4-O- is identical to R_4 defined as above and Y represents a leaving group such as a halogen atom, on the product of general formula (V) in which Z_1 is defined as above, R_4 represents a hydroxyl radical, R_6 represents a hydrogen atom and R and R_7 together form a bond.

Generally, the action of a product of general formula (IX) on the product of general formula (V) defined above is performed, after optional metalation of the hydroxyl function at position 10 by means of an alkali or alkaline-earth metal hydride such as sodium hydride, an alkali metal amide such as lithium diisopropylamide or an alkali metal alkylide such as n-butyllithium, working in an organic solvent such as dimethylformamide or tetrahydrofuran or pyridine, at a temperature of between 0 and 50°C, optionally followed by the replacement of the group protecting the hydroxyl function Z_1 or R_8 under the conditions described above.

When Z_1 is different from a radical of

general formula (IV), it is particularly advantageous to perform the reaction on a product of general formula (V) in which Z_1 represents a group protecting the hydroxyl function which is preferably a triethylsilyl radical. In this case, the protective group is introduced by the action of a trialkylsilyl halide, preferably triethylsilyl chloride, on a product of general formula (VI) in which Z_1 represents a hydrogen atom.

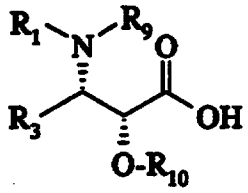
According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4 and R_5 together form a ketone function, R_6 represents a hydrogen atom, and R and R_7 together form a bond, may be obtained by oxidation of a product of general formula (V) in which Z_1 is defined as above, R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, optionally followed by the replacement of the protective group represented by Z_1 or R_8 by a hydrogen atom under the conditions described above.

Generally, the oxidation is performed under the conditions described above for the oxidation of a product of general formula (VI).

According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), R_4, R_5 and R_6 each represent a hydrogen atom and R and R_7 together form a bond, may be

obtained from a product of general formula (V) in which Z_1 is defined as above, R_4 represents a hydroxyl radical, R_5 and R_6 each represent a hydrogen atom and R and R_7 together form a bond, after conversion of the hydroxyl radical represented by R_4 to a dithiocarbonate followed by the reduction of the product obtained by means of a trialkyltin hydride such as tributyltin hydride, optionally followed by the replacement of the protective group represented by Z_1 or R_8 by a hydrogen atom under the conditions described above.

According to the invention, the products of general formula (I) may also be obtained by esterification of a product of general formula (I) in which Z represents a hydrogen atom by means of an acid of general formula:



(X)

in which, either R_9 represents a hydrogen atom and R_{10} represents a group protecting the hydroxyl function, or R_9 and R_{10} together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, followed by the replacement of the protective groups by hydrogen atoms.

The conditions for esterification and replacement of the protective groups are identical to

those which are described, for example, in International Applications PCT WO 92/09589, WO 93/16060 and WO 94/12484.

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

117 mg of sodium borohydride are added to a solution of 0.65 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate in 6.5 cm^3 of absolute ethanol maintained under an argon atmosphere at a temperature in the region of 20°C. After 5 minutes at a temperature in the region of 20°C, the reaction mixture is diluted with 50 cm^3 of ethyl acetate. The organic phase is washed with 3 times 10 cm^3 of distilled water and then with twice 10 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered

glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 600 mg of a white foam are thereby obtained which are combined with 313 mg of an identical crude mixture obtained from 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate under the same conditions. The purification is performed by chromatography at atmospheric pressure on 100 g of silica (0.063-0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane mixture (elution gradient from 2-98 to 15-85 by volume), collecting 20-cm^3 fractions. The fractions containing only the desired products are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 153 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,10α-epoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are thereby obtained in the form of a white foam and 384 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxy-propionate in the form of a white foam.

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

propionate displays the following characteristics:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 0.34 and 0.41 (2 mts, 6H: CH_2 of the triethylsilyl at position 2'); 0.77 (t, J = 7.5, 9 H: CH_3 of the triethylsilyl at position 2'); 1.23 (s, 3H: CH_3); 1.38 (s, 3H: CH_3); 1.40 (s, 9H: $C(CH_3)_3$; 1.82 (s, 3H: CH_3); 1.90 (s, 3H: CH_3); 1.93 (s, 1H: OH at position 1); from 2.15 to 2.40 (mt, 2H: CH_2 at position 14); from 2.15 to 2.40 and 2.48 (2 mts, 1H each: CH_2 in position 6); 2.48 (s, 3H: $COCH_3$); 3.70 (d, J = 8, 1H: H at position 7); 4.25 and 4.32 (2 d, J = 8, 1H each: CH_2 at position 20); 4.58 (d, J = 7, 1H: H at position 3); 4.59 (broad s, 1H: H at position 2'); 4.86 (mt, 1H: H at position 10); 5.11 (d, J = 5, 1H: H at position 5); 5.32 (broad d, J = 10, 1H: H at position 3'); 5.56 (d, J = 10, 1H: CONH); 5.62 (d, J = 7, 1H: H at position 2); 6.34 (broad t, J = 9, 1H: H [lacuna]; from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.13 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate displays the following characteristics:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 0.33 and 0.40 (2 mts, 6H: CH_2 of

the triethylsilyl at position 2'); 0.75 (t, J = 7.5, 9H: CH_3 of the triethylsilyl at position 2'); 1.13 (s, 3H: CH_3); 1.27 (s, 3H: CH_3); 1.37 (s, 9H: $C(CH_3)_3$); 1.75 (s, 3H: CH_3); 1.85 (s, 1H: OH at position 1); 2.04 (s, 3H: CH_3); 2.23 and from 2.30 to 2.50 (dd and mt respectively, J = 15 and 8, 1H each: CH_2 at position 14); from 2.30 to 2.50 (mt, 2H: CH_2 at position 6); 2.48 (s, 3H: $COCH_3$); 2.55 (d, J = 7, 1H: OH at position 10); 4.05 and 4.29 (2 d, J = 7.5, 1H each: CH_2 at position 20); 4.17 (d, J = 6, 1H: H at position 3); 4.60 (broad s, 1H: H at position 2'); from 4.75 to 4.90 (mt, 3H: H at position 7 - H at position 9 and H at position 10); 4.97 (broad s, 1H: H at position 5); 5.33 (broad d, J = 10, 1H: H at position 3'); 5.54 (d, J = 10, 1H: CONH); 5.80 (d, J = 6, 1H: H at position 2); 6.18 (broad t, J = 8, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.49 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.15 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate in 1.7 cm^3 of 0.1N ethanolic solution of hydrogen chloride is stirred, under an argon atmosphere, at a temperature in the region of 0°C, for 1 hour. The reaction mixture is then diluted with 20 cm^3 of dichloromethane. The organic

phase is washed with twice 5 cm^3 of distilled water and then with twice 5 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 130 mg of an ivory-coloured foam are thereby obtained, which product is purified by preparative thin-layer chromatography [12 Merck preparative silica gel $60F_{254}$ plates: 20 × 20 cm; thickness 0.25 mm; application in solution in dichloromethane], eluting twice with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvent under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 22.6 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; at a temperature of 333°K, δ in ppm; coupling constants J in Hz): 1.14 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.40 (s, 9H: $C(CH_3)_3$); 1.74 (s, 3H: CH_3); 1.86 (s, 1H: OH at position 1); 1.95 (s, 3H: CH_3); from 2.15 to 2.45 (mt, 4H: CH_2 at position 14 and CH_2 at position 6); 2.33 (s, 3H: $COCH_3$); 2.50

(unres. comp., 1H: OH at position 10); 3.67 (unres. comp., 1H: OH at position 2'); 4.06 and 4.27 (2 d, J = 7.5, 1H each: CH_2 at position 20); 4.17 (d, J = 6, 1H: H at position 3); 4.65 (mt, 1H: H at position 2'); from 4.75 to 4.90 (mt, 3H: H at position 7 - H at position 9 and H at position 10); 4.93 (broad s, 1H: H at position 5); 5.30 (broad d, J = 10, 1H: H at position 3'); 5.50 (d, J = 10, 1H: CONH); 5.79 (d, J = 6, 1H: H at position 2); 6.06 (broad t, J = 9, 1H: H at position 13); 7.30 (t, J = 7.5, 1H: H at the para position of the aromatic at position 3'); 7.38 (t, J = 7.5, 2H: H at the meta position of the aromatic at position 3'); 7.44 (d, J = 7, 2H: H at the ortho position of the aromatic at position 3'); 7.49 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.13 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate may be prepared in the following manner:

1.91 g of pyridinium chlorochromate are rapidly added to a suspension of 1.87 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate and 4 g of activated 4 Å molecular sieve

in 10 cm^3 of anhydrous dichloromethane maintained under an argon atmosphere at a temperature in the region of 20°C. The reaction mixture is stirred for 20 hours at a temperature in the region of 20°C and then purified directly by applying to a chromatography column at atmospheric pressure containing 200 g of silica (0.063-0.2 mm; column 3.5 cm in diameter), eluting with dichloromethane alone and then with a methanol/dichloromethane (0.5-99.5 by volume) mixture, collecting 15-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 for 2 hours. 1.16 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are thereby obtained in the form of a pale yellow foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 0.42 (mt, 6H: CH_2 from triethylsilyl at position 2'); 0.81 (t, J = 7.5, 9H: CH_3 from triethylsilyl at position 2'); 1.26 (s, 3H: CH_3); 1.35 (s, 3H: CH_3); 1.37 (s, 9H: $C(CH_3)_3$); 1.93 (s, 3H: CH_3); 2.01 (s, 3H: CH_3); 2.23 and 2.43 (2 dd, J = 15 and 9, 1H each: CH_2 at position 14); 2.36 and 2.89 (2 mt, 1H each: CH_2 at position 6); 2.57 (s, 3H: $COCH_3$); 3.82 (d, J = 7, 1H: H at position 3); 4.23 and 4.42 (2d, J = 8.5, 1H each: CH_2 at position 20); 4.58 (broad

s, 1H: H at position 2'); 4.95 (broad d, J = 9.5, 1H: H at position 5); 5.28 (dd, J = 10 and 7.5, 1H: H at position 7); 5.30 (broad d, J = 10, 1H: H at position 3'); 5.52 (d, J = 10, 1H: CONH); 5.87 (d, J = 7, 1H: H at position 2); 6.28 (broad t, J = 9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.55 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.67 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.13 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate may be prepared in the following manner:

A solution of 3.2 cm^3 of trifluoromethanesulphonic anhydride in 3 cm^3 of anhydrous dichloromethane is added dropwise to a suspension of 8.85 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate and 2 g of activated 4 Å molecular sieve in 50 cm^3 of anhydrous dichloromethane and 3.9 cm^3 of anhydrous pyridine maintained under an argon atmosphere at a temperature in the region of -30°C. The reaction mixture is stirred for 5 minutes at -35°C and then for 1 hour at a temperature in the region of 0°C. After cooling to a temperature in the

region of -10°C, 6 cm^3 of distilled water are added. After filtration through a sintered glass lined with Celite, rinsing of the sintered glass with 20 cm^3 of an ethyl acetate/dichloromethane (50-50 by volume) mixture and decantation, the organic phase is washed with twice 10 cm^3 of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 11.3 g of an orange-coloured foam are thereby obtained, which product is purified by chromatography at atmospheric pressure on 800 g of silica (0.063-0.2 mm) contained in a column 7 cm in diameter, eluting with a methanol/dichloromethane (1-99 and then 2-98 by volume) mixture, collecting 60-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 for 2 hours. 9.55 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are thereby obtained in the form of a mixture. This mixture is purified by chromatography at atmospheric pressure on 700 g of silica (0.063-0.2 mm) contained in a column 6 cm in diameter, eluting with dichloromethane alone and then with an ethyl acetate/dichloromethane (5-95 by volume) mixture, collecting 60-cm^3 fractions. The fractions containing only the desired product are

pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40°C for 2 hours. 4.09 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are thereby obtained in the form of a pale yellow foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (300 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 0.38 (mt, 6H: CH_2 of the triethylsilyl at position 2'); 0.79 (t, J = 7.5, 9 H: CH_3 of the triethylsilyl at position 2'); 1.14 (s, 3H: CH_3); 1.28 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$); 1.74 (s, 1H: OH at position 1); 1.94 (s, 3H: CH_3); 1.98 (s, 3H: CH_3); 2.20 and 2.37 (2 dd, J = 16 and 9, 1H each: CH_2 at position 14); from 2.25 to 2.40 and 2.84 (2 mt, 1H each: CH_2 at position 6); 2.55 (s, 3H: $COCH_3$); 4.02 (broad s, 1H: OH at position 10); 4.04 (d, J = 7 Hz, 1H: H at position 3); 4.24 and 4.38 (2d, J = 8.5, 1H each: CH_2 at position 20); 4.54 (broad s, 1H: H at position 2'); 4.96 (broad d, J = 9.5, 1H: H at position 5); 5.28 (broad d, J = 10, 1H: H at position 3'); 5.38 (broad s, 1H: H at position 10); 5.44 (dd, J = 10 and 7.5, 1H: H at position 7); 5.52 (d, J = 10, 1H: CONH); 5.74 (d, J = 7, 1H: H at position 2); 6.34 (broad t, J = 9, 1H: H at position 13); from 7.25 to 7.40 (mt, 5H: aromatic H at position 3'); 7.50 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J = 7.5, 1H:

$OCOC_6H_5$ H at the para position); 8.12 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxy-propionate may be prepared in the following manner:

8.05 cm^3 of triethylsilyl chloride are added dropwise to a solution of 8.6 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate in 40 cm^3 of anhydrous dichloromethane and 8.6 cm^3 of anhydrous pyridine at a temperature in the region of 20°C under an inert argon atmosphere. The reaction mixture is stirred at a temperature in the region of 20°C for 2 hours and then 300 cm^3 of dichloromethane are added. The organic phase is washed with twice 50 cm^3 of distilled water, 50 cm^3 of a 0.1N aqueous hydrochloric acid solution, 50 cm^3 of distilled water, and then 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 14.2 g of a white foam are thereby obtained, which product is purified by chromatography at atmospheric pressure on 800 g of silica (0.063-0.2 mm) contained in a column 7 cm in diameter, eluting with a methanol/dichloromethane (2-98 by volume) mixture, collecting 30-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 for 2 hours. 8.85 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are thereby obtained in the form of a white foam.

EXAMPLE 2

0.0125 cm^3 of acetic anhydride and then 13.5 mg of N,N'-dimethylamino-4-pyridine are added to a solution of 200 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate in 2 cm^3 of anhydrous pyridine maintained under an argon atmosphere at a temperature in the region of 20°C. After 30 minutes at a temperature in the region of 20°C, the reaction mixture is diluted with 40 cm^3 of ethyl acetate. The organic phase is washed with twice 6 cm^3 of distilled water and then 6 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 237.4 mg of a pale yellow foam are thereby obtained, which product is purified by chromatography at atmospheric pressure on 20 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in

diameter, eluting with an ethyl acetate/dichloromethane (elution gradient from 2-98 to 10-90 by volume) mixture, collecting 10-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 for 2 hours. 184.8 mg of 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxy-propionate are thereby obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 0.34 and 0.40 (2 mt, 6H: CH_2 of the triethylsilyl at position 2'); 0.76 (t, J = 7.5, 9 H: CH_3 of the triethylsilyl at position 2'); 1.26 (s, 3H: CH_3); 1.28 (s, 3H: CH_3); 1.38 (s, 9H: $C(CH_3)_3$); 1.72 (s, 3H: CH_3); 1.88 (s, 1H: OH at position 1); 2.01 (s, 3H: CH_3); 2.14 (s, 3H: $COCH_3$); 2.23 and from 2.30 to 2.45 (dd and mt respectively, J = 15 and 9, 1H each: CH_2 at position 14); 2.39 (mt, 2H: CH_2 at position 6); 2.48 (s, 3H: $COCH_3$): 4.05 and 4.30 (2 d, J = 7.5, 1H each: CH_2 at position 20); 4.13 (d, J = 6, 1H: H at position 3); 4.62 (broad s, 1H: H at position 2'); 4.80 (t, J = 7.5, 1H: H at position 7); 4.88 (d, J = 6, 1H: H at position 9); 4.98 (broad s, 1H: H at position 5); 5.34 (broad d, J = 10, 1H: H at position 3'); 5.54 (d, J = 10, 1H: CONH); 5.71 (d, J = 6, 1H: H at position 10); 5.83 (d, J = 6, 1H: H at position 2); 6.10 (broad t, J

= 9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.48 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.15 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

0.93 cm^3 of a hydrofluoric acid/triethylamine ($3HF/Et_3N$) complex is added dropwise to a solution of 180 mg of 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxy-propionate in 1 cm^3 of anhydrous dichloromethane maintained under an argon atmosphere at a temperature in the region of 20°C. After 7.5 hours at a temperature in the region of 20°C, the reaction mixture is diluted with 30 cm^3 of ethyl acetate and 8 cm^3 of a saturated aqueous sodium hydrogen carbonate solution. After decantation, the organic phase is washed with twice 8 cm^3 of distilled water and then 8 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 167.5 mg of a white foam are thereby obtained, which product is purified by preparative thin-layer chromatography on silica [9 Merck preparative silica gel $60F_{254}$ plates; 20 × 20 cm; thickness 0.5 mm; application in solution in dichloromethane], eluting with a methanol/dichloromethane (4-96 by volume) mixture. After elution

of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 143.6 mg of 4α,10β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm; coupling constants J in Hz): 1.24 (s, 3H: CH_3); 1.32 (s, 3H: CH_3); 1.41 (s, 9H: $C(CH_3)_3$); 1.68 (s, 3H: CH_3); 1.91 (s, 1H: OH at position 1); 1.92 (s, 3H: CH_3); 2.12 (s, 3H: $COCH_3$); 2.21 and from 2.25 to 2.55 (dd and mt respectively, J = 15 and 8, 1H each: CH_2 at position 14); from 2.25 to 2.55 (mt, 2H: CH_2 6); 2.31 (s, 3H: $COCH_3$); 3.43 (unres. comp., 1H: OH at position 2'); 4.03 and 4.30 (2 d, J = 8, 1 H each: CH_2 at position 20); 4.13 (d, J = 6, 1H: H at position 3); 4.65 (mt, 1H: H at position 2'); 4.82 (dd, J = 8.5 and 5.5, 1H: H at position 7); 4.86 (d, J = 6, 1H: H at position 9); 4.93 (broad s, 1H: H at position 5); 5.34 (broad d, J = 10, 1H: H at position 3'); 5.54 (d, J = 10, 1H: CONH); 5.65 (d, J = 6, 1H: H at position 10); 5.83 (d, J = 6, 1H: H at position 2); 6.03 (broad t, J = 8, 1H: H at position 13); 7.30 (t, J = 7.5, 1H: H at the para position of the aromatic at position 3'); 7.38 (t, J =

7.5, 2H: H at the meta position of the aromatic at position 3'); 7.43 (d, J = 7.5, 2H: H at the ortho position of the aromatic at position 3'); 7.50 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.13 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 3

0.805 cm^3 of hydrofluoric acid/triethylamine ($3HF/Et_3N$) complex is added dropwise to a solution of 149 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,10α-epoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate, obtained in Example 1, in 1.5 cm^3 of anhydrous dichloromethane, maintained under an argon atmosphere at a temperature in the region of 20°C. After 1 hour at a temperature in the region of 20°C, the reaction mixture is diluted with 50 cm^3 of dichloromethane, 5 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and 5 cm^3 of distilled water. After decantation, the organic phase is washed with 3 times 8 cm^3 of distilled water and then 8 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 133.2 mg of a pale yellow foam are thereby obtained, which product is purified by preparative thin-layer chromatography on

silica [10 Merck preparative silica gel $60F_{254}$ plates; 20 × 20 cm; thickness 0.5 mm; application in solution in dichloromethane), eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 114.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,10α-epoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, which product is purified by preparative thin-layer chromatography on silica [8 Merck preparative silica gel $60F_{254}$ plates; 20 × 20 cm; thickness 0.5 mm; application in solution in dichloromethane], eluting with a methanol/dichloromethane (2-98 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 92.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,10α-epoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; at a temperature of 333°K, δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: CH_3); 1.33 (s, 3H: CH_3); 1.41 (s, 9H: $C(CH_3)_3$); 1.78 (s, 3H: CH_3); 1.83 (s, 3H: CH_3); 1.88 (s, 1H: OH at position 1); 2.12 and 2.35 (2 dd, J = 15 and 8, 1H each: CH_2 at position 14); 2.28 (s, 3H: $COCH_3$); 2.33 and 2.43 (2 dd, H at position 7); 3.85 (unres. comp., 1H: OH at position 2'); 4.28 (limiting AB, J = 8, 2H: CH_2 at position 20); 4.52 (d, J = 6.5, 1H: H at position 3); 4.63 (mt, 1H: H at position 2'); 4.83 (mt, 1H: H at position 10); 5.06 (d, J = 5, 1H: H at position 5); 5.30 (broad d, J = 10, 1H: H at position 3'); 5.53 (d, J = 10, 1H: CONH); 5.59 (d, J = 6.5, 1H: H at position 2); 6.22 (broad t, J = 8, 1H: H at position 13); 7.30 (t, J = 7.5, 1H: H at the para position of the aromatic at position 3'); 7.37 (t, J = 7.5, 2H: H at the meta position of the aromatic at position 3'); 7.44 (d, J = 7.5, 2H: H at the ortho position of the aromatic at position 3'); 7.50 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 4

1 mg of sodium hydride at 50 % in oil is added to a solution of 10 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-

phenyl-2-triethylsilyloxypropionate in 0.1 cm^3 of methyl iodide and 0.01 cm^3 of anhydrous dimethylformamide under an argon atmosphere at a temperature in the region of 20°C. After 12 minutes at a temperature in the region of 20°C, the crude reaction mixture is purified by preparative thin-layer chromatography on silica [1 Merck preparative silica gel $60F_{254}$ plate; 20×20 cm; thickness 0.5 mm; application of the crude reaction mixture], eluting with a methanol/dichloromethane (3-97 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through cotton and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 4.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate are obtained in the form of a white lacquer.

0.01 cm^3 of hydrofluoric acid/triethylamine ($3HF/Et_3N$) complex is added dropwise to a solution of 4 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-triethylsilyloxypropionate in 0.1 cm^3 of anhydrous dichloromethane maintained under an argon atmosphere at a temperature in the region of 20°C. After 35 minutes

at a temperature in the region of 20°C, the crude reaction mixture is purified by preparative thin-layer chromatography on silica [1 Merck preparative silica gel $60F_{254}$ plate; 20 × 20 cm; thickness 0.5 mm; application of the crude reaction mixture], eluting with a methanol/dichloromethane (4-96 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through cotton and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 3.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-7α,9α-epoxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate are obtained in the form of a white lacquer, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; at a temperature of 333°K, δ in ppm; coupling constants J in Hz): 1.17 (s, 3H: CH_3); 1.22 (s, 3H: CH_3); 1.41 (s, 9H: $C(CH_3)_3$); 1.67 (s, 3H: CH_3); 1.94 (s, 1H: OH at position 1); 2.00 (s, 3H: CH_3); 2.23 and 2.41 (2 dd, respectively J = 15 and 8 and J = 15 and 10, 1H each: CH_2 at position 14); from 2.20 to 2.40 (mt, 2H: CH_2 at position 6); 2.31 (s, 3H: $COCH_3$); 3.33 (s, 3H: OCH_3); 4.03 (unres. comp., 1H: OH at position 2'); 4.03 and 4.31 (2 d, J = 7.5, 1H each: CH_2 at position 20); 4.13 (d, J = 6.5, 1H: H at position 3); 4.29 (d, J = 7, 1H: H at position 9); 4.67 (mt, 1H: H at position 2'); 4.77 (dd, J = 8.5 and 5.5,

1H: H at position 7); 4.90 (d, J = 7, 1H: H at position 10); 4.93 (broad s, 1H: H 5); 5.37 (broad d, J = 10, 1H: H at position 3'); 5.61 (d, J = 10, 1 H: CONH); 5.81 (d, J = 6.5, 1H: H at position 2); 6.06 (mt, 1H: H at position 13); 7.30 (t, J = 7.5, 1H: H at the para position of the aromatic at position 3'); 7.38 (t, J = 7.5, 2H: H at the meta position of the aromatic at position 3'); 7.46 (d, J = 7.5, 2H: H at the ortho position of the aromatic at position 3'); 7.49 (t, J = 7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J = 7.5, 1H: $OCOC_6H_5$ H at the para position); 8.13 (d, J = 7.5, 2H: $OCOC_6H_5$ H at the ortho position).

EXAMPLE 5

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-oxa-10β-propanoyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate may be prepared in the following manner:

0.0053 cm^3 of concentrated hydrochloric acid (36 %, d = 1.18) is added to a solution of 50 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-oxa-10β-propanoyloxy-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 cm^3 of ethyl acetate maintained at a temperature in the region of 20°C. After 2 hours at a temperature in the region of 20°C, the crude reaction mixture is purified by preparative

thin-layer chromatography: 1 Merck preparative silica gel $60F_{254}$ plate, 20 × 20 cm, thickness 1 mm, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 21 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-oxa-10β-propanoyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.18 (t, J = 7.5 Hz, 3H: CH_3 of the ethyl); 1.26 (s, 3H: CH_3); 1.33 (s, 3H: CH_3); 1.41 (s, 9H: $C(CH_3)_3$); 1.69 (s, 3H: CH_3); 1.92 (s, 3H: CH_3); 2.23 and from 2.25 to 2.50 (dd and mt respectively, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.25 to 2.50 (mt, 4H: CH_2 6 and $OCOCH_2$ ethyl); 2.33 (s, 3H: $COCH_3$); 3.97 (broad s, 1H: OH at position 2'); 4.03 and 4.31 (2 d, J = 8 Hz, 1H each: $CH_2$20); 4.13 (d, J = 6 Hz, 1H: H 3); 4.68 (mt, 1H: H 2'); 4.84 (dd, J = 8.5 and 5.5 Hz, 1H: H 7); 4.88 (d, J = 6 Hz, 1H: H 9); 4.96 (broad s, 1H: H 5); 5.35 (broad d, J = 10 Hz, 1H: H 3'); 5.58 (d, J = 10 Hz, 1H: CONH); 5.69 and 5.85 (2 d, J = 6 Hz, 1H each: H 2 and H 10); 6.05 (broad t, J = 8 Hz, 1H: H 13); 7.31 (t, J = 7.5 Hz, 1H: H at the para position of the aromatic at position 3'); 7.39 (t, J =

7.5 Hz, 2H: H at the meta position of the aromatic at position 3'); 7.46 (d, J = 7.5 Hz, 2H: H at the ortho position of the aromatic at position 3'); 7.50 (t, J = 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.53 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.13 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-oxa-10β-propanoyloxy-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate may be prepared in the following manner:

20 mg of 4-(N,N'-dimethylamino)pyridine and then 0.042 cm^3 of propionic anhydride are added successively to a solution of 100 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 1 cm^3 of anhydrous pyridine maintained under an argon atmosphere at a temperature in the region of 20°C. After 2 hours at a temperature in the region of 20°C, the reaction mixture is diluted with 5 cm^3 of dichloromethane and 2 cm^3 of distilled water. After decantation, the organic phase is dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. A colourless oil is thereby obtained which is purified by preparative thin-layer chromatography: 3 Merck preparative silica gel

$60F_{254}$ plates, 20×20 cm, thickness 1 mm, application in solution in a minimum volume of dichloromethane, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 51 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7α,9α-oxa-10β-propanoyloxy-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.04 (t, J = 7.5 Hz, 3H: CH_3 of the ethyl); 1.05 (s, 9H: $C(CH_3)_3$); 1.24 (s, 6H: CH_3); 1.63 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.80 (s, 3H: $COCH_3$); 2.10 and from 2.15 to 2.55 (dd and mt respectively, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.15 to 2.55 (mt, 4H: CH_2 6 and $OCOCH_2$ ethyl); 3.80 (s, 3H: $ArOCH_3$); 3.92 and 4.22 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.02 (d, J = 6 Hz, 1H: H 3); 4.62 (d, J = 5 Hz, 1H: H 2'); 4.73 (dd, J = 8 and 7.5 Hz, 1H: H 7); 4.78 (d, J = 6 Hz, 1H: H 9); 4.88 (broad s, 1H: H 5); 5.35 (broad d, J = 5 Hz, 1H: H 3'); 5.63 and 5.75 (2 d, J = 6 Hz, 1H each: H 2 and H 10); 5.93 (broad t, J = 8 Hz, 1H: H 13); 6.30 (broad s, 1H:

H 5'); 6.89 (d, J = 8.5 Hz, 2H: aromatic H at the ortho position of the OCH_3); from 7.25 to 7.50 (mt, 9H: aromatic H at position 3' - aromatic H at the meta position of the OCH_3 and $OCOC_6H_5$ H meta); 7.58 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.03 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

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

60 mg of sodium borohydride are added to a solution of 1.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonate-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 30 cm^3 of absolute ethanol maintained under an argon atmosphere at a temperature in the region of 0°C. After one hour at a temperature in the region of 0°C, the reaction mixture is diluted with 100 cm^3 of ethyl acetate. The organic phase is washed with 50 cm^3 of distilled water and then twice 25 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 1.04 g of a pale yellow foam is thereby obtained, which product is purified by chromatography at atmospheric

pressure on 50 g of silica (0.063-0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2-98 by volume) mixture, collecting 20-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 for 2 hours. 230 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate are thereby obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.05 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: CH_3); 1.25 (s, 3H: CH_3); 1.58 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.85 (broad s, 3H: $COCH_3$); 2.10 and 2.22 (2 dd, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.25 to 2.45 (mt, 2H: CH_2 6); 3.82 (s, 3H: $ArOCH_3$); 3.93 and 4.23 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.08 (d, J = 6 Hz, 1H: H 3); 4.62 (d, J = 5 Hz, 1H: H 2'); from 4.70 to 4.80 (mt, 2H: H 9 and H 10); 4.80 (dd, J = 8.5 and 6 Hz, 1H: H 7); 4.88 (broad s, 1H: H5); 5.36 (unres. comp., 1H: H 3'); 5.75 (d, J = 6 Hz, 1H: H 2); 6.02 (broad t, J = 8 Hz, 1H: H 13); 6.37 (broad unres. comp., 1H: H 5'); 6.95 (d, J = 8.5 Hz, 2H: aromatic H at the ortho position of the OCH_3); from 7.25 to 7.55 (mt, 9H: aromatic H at position 3' - aromatic H at the meta position of the OCH_3 and $OCOC_6H_5$ H meta); 7.65 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.07

(d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonate-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate may be prepared in the following manner:

1.8 g of pyridinium chlorochromate are rapidly added to a suspension of 2.2 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonate-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate and 4.5 g of activated 4 Å molecular sieve in 10 cm^3 of anhydrous dichloromethane maintained under an argon atmosphere at a temperature in the region of 20°C. The reaction mixture is stirred for 17 hours at a temperature in the region of 20°C and then filtered through Clarcel. The solid residue is rinsed with dichloromethane and then the filtrate is concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. A brown foam is thereby obtained which is purified by chromatography at atmospheric pressure on 200 g of silica (0.063-0.2 mm) contained in a column 4 cm in diameter, eluting with a methanol/dichloromethane (0.5-99.5 by volume) mixture, collecting 20-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 for 2 h. 1.5 g of

4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9,10-dioxo-7β-trifluoromethanesulphonate-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate are thereby obtained in the form of a yellow foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.07 (s, 9H: $C(CH_3)_3$); 1.20 (s, 3H: CH_3); 1.27 (s, 3H: CH_3); 1.58 (s, 3H: CH_3); 1.85 (s, 3H: CH_3); 1.94 (unres. comp., 3H: $COCH_3$); 2.13 and 2.27 (2 dd, J = 16 and 8 Hz, 1H each: CH_2 14); 2.13 and 2.82 (2 mts, 1H each: CH_2 6); 366 (d, J = 6.5 Hz, 1H: H 3); 3.84 (s, 3H: $ArOCH_3$); 4.11 and 4.31 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.58 (d, J = 5 Hz, 1H: H 2'); 4.81 (broad d, J = 10 Hz, 1H: H 5); 5.18 (dd, J = 10 and 7.5 Hz, 1H: H 7); 5.44 (unres. comp., 1H: H 3'); 5.77 (d, J = 6.5 Hz, 1H: H 2); 6.11 (broad t, J = 8 Hz, 1H: H 13); 6.40 (unres. comp., 1H: H 5'); 6.91 (d, J = 8.5 Hz, 2H: aromatic H at the ortho position of the OCH_3); from 7.30 to 7.50 (mt, 7H: aromatic H at position 3' - aromatic H at the meta position of the OCH_3); 7.51 (t, J = 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.66 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.02 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

The preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β-trifluoromethanesulphonate-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate may be carried out, for

example, according to the procedure described in Patent FR 9,408,198 (first filing of 04/07/94).

EXAMPLE 6

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7α,9α-oxa-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate may be prepared in the following manner:

0.0053 cm^3 of concentrated hydrochloric acid (36 %, d = 1.18) is added to a solution of 30 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 1 cm^3 of ethyl acetate maintained at a temperature in the region of 20°C. After 45 minutes at a temperature in the region of 20°C, 0.002 cm^3 of concentrated hydrochloric acid is added. After 2 hours at a temperature in the region of 20°C, the crude reaction mixture is purified by applying to preparative thin-layer chromatography: 1 Merck preparative silica gel $60F_{254}$ plate, 20×20 cm, thickness 0.5 mm, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a

temperature in the region of 40°C, 13 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7α,9α-oxa-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.24 (s, 3H: CH_3); 1.31 (s, 3H: CH_3); 1.40 (s, 9H: $C(CH_3)_3$); 1.67 (s, 3H: CH_3); 1.86 (s, 3H: CH_3); 1.99 (s, 1H: OH at position 1); 2.20 and from 2.25 to 2.50 (dd and mt respectively, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.25 to 2.50 (mt, 2H: CH_2 6); 2.31 (s, 3H: $COCH_3$); 3.44 (s, 3H: OCH_3); 3.87 (broad s, 1H: OH at position 2'); 4.01 and 4.18 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.04 and 4.11 (2 d, J = 16.5 Hz, 1H each: $OCOCH_2O$); 4.10 (d, J = 6 Hz, 1H: H 3); 4.64 (mt, 1H: H 2'); 4.80 (dd, J = 8.5 and 5.5 Hz, 1H: H 7); 4.86 (d, J = 6 Hz, 1H: H 9); 4.92 (broad s, 1H: H 5); 5.30 (broad d, J = 10 Hz, 1H: H 3'); 5.53 (d, J = 10 Hz, 1H: CONH); 5.74 and 5.80 (2 d, J = 6 Hz, 1H each: H 2 and H 10); 6.01 (broad t, J = 8 Hz, 1H: H 13); 7.30 (t, J = 7.5 Hz, 1H: H at the para position of the aromatic at position 3'); 7.36 (t, J = 7.5 Hz, 2H: H at the meta position of the aromatic at position 3'); 7.42 (d, J = 7.5 Hz, 2H: H at the ortho position of the aromatic at position 3'); 7.47 (t, J = 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.61 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.11 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate may be prepared in the following manner:

0.093 cm^3 of n-butyllithium (in 1.6M solution in hexane) and then 8 minutes later 0.023 cm^3 of methoxyacetyl chloride are added to a solution of 90 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 2 cm^3 of anhydrous tetrahydrofuran maintained under an argon atmosphere at a temperature in the region of -78°C. The cooling bath is removed and then the crude reaction mixture, after returning to a temperature in the region of 20°C, is purified by applying to preparative thin-layer chromatography: 2 Merck preparative silica gel $60F_{254}$ plates, 20×20 cm, thickness 1 mm, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 31 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxyacetoxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-

1,3-oxazolidine-5-carboxylate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.05 (s, 9H: $C(CH_3)_3$); 1.26 (s, 6H: CH_3); 1.64 (s, 3H: CH_3); 1.67 (unres. comp., 3H: CH_3); 1.78 (s, 3H: $COCH_3$); 2.10 and 2.21 (2 dd, J = 16 and 8.5 Hz, 1H each: CH_2 14); 2.29 (mt, 2H: CH_2 6); 3.45 (s, 3H: OCH_3); 3.81 (s, 3H: $ArOCH_3$); 3.92 and 4.24 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.00 (d, J = 6 Hz, 1H: H 3); 4.03 and 4.10 (2 d, J = 16 Hz, 1H each: $OCOCH_2O$); 4.62 (d, J = 5 Hz, 1H: H 2'); 4.75 (dd, J = 8 and 7.5 Hz, 1H: H 7); 4.82 (d, J = 6 Hz, 1H: H 9); 4.85 (broad s, 1H: H 5); 5.34 (unres. comp. 1H: H 3'); 5.68 and 5.75 (2 d, J = 6 Hz, 1H each: H 2 and H 10); 5.95 (mt, 1H: H 13); from 6.30 to 6.45 (very broad unres. comp., 1H: H 5'); 6.92 (d, J = 8.5 Hz, 2H: aromatic H at the ortho position of the OCH_3); from 7.25 to 7.50 (mt, 9H: aromatic H at position 3' - aromatic H at the meta position of the OCH_3 and $OCOC_6H_5$ H meta); 7.62 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.06 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

EXAMPLE 7

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-dimethylaminocarbonyloxy-7α,9α-oxa-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate may be prepared in the

following manner:

0.0043 cm^3 of concentrated hydrochloric acid (36 %, d = 1.18) is added to a solution of 40 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-dimethylaminocarbonyloxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 1 cm^3 of ethyl acetate maintained at a temperature in the region of 20°C. After 1.5 hours at a temperature in the region of 20°C, the crude reaction mixture is purified by applying to preparative thin-layer chromatography: 2 Merck preparative silica gel $60F_{254}$ plates, 20×20 cm, thickness 0.5 mm, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 20 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-dimethylaminocarbonyloxy-7α,9α-oxa-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are obtained in the form of a white foam, the characteristics of which are as follows:

- ^1H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.24 (s, 3H: CH_3); 1.31 (s, 3H: CH_3); 1.40 (s, 9H: $C(CH_3)_3$); 1.69 (s, 3H: CH_3); 1.91 (s, 1H: OH at position 1); 1.97 (s, 3H: CH_3); 2.22 and from 2.25 to 2.50 (dd and mt

respectively, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.25 to 2.50 (mt, 2H: CH_2 6); 2.32 (s, 3H: $COCH_3$); 2.94 and 2.96 (2 s, 3H each: $N(CH_3)_2$); 3.96 (broad s, 1H: OH at position 2'); 4.03 and 4.31 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.13 (d, J = 6 Hz, 1H: H 3); 4.67 (mt, 1H: H 2'); 4.81 (dd, J = 8.5 and 5.5 Hz, 1H: H 7); 4.91 (d, J = 6 Hz, 1H: H 9); 4.95 (broad s, 1H: H 5); 5.24 (broad d, J = 10 Hz, 1H: H 3'); 5.58 (d, J = 10 Hz, 1H: CONH); 5.69 and 5.83 (2 d, J = 6 Hz, 1H each: H 2 and H 10); 6.07 (broad t, J = 8 Hz, 1H: H 13); 7.31 (t, J = 7.5 Hz, 1H: H at the para position of the aromatic at position 3'); 7.39 (t, J = 7.5 Hz, 2H: H at the meta position of the aromatic at position 3'); 7.46 (d, J = 7.5 Hz, 2H: H at the ortho position of the aromatic at position 3'); 7.48 (t, J = 7.5 Hz, 2H: $OCOC_6H_5$ H meta); 7.62 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.13 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-dimethylaminocarbonyloxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate may be prepared in the following manner:

0.103 cm^3 of n-butyllithium (in 1.6M solution in hexane) and then 5 minutes later 0.0253 cm^3 of dimethylaminocarbamoyl chloride are added to a solution of 100 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-

phenyl-1,3-oxazolidine-5-carboxylate in 2 cm^3 of anhydrous tetrahydrofuran maintained under an argon atmosphere at a temperature in the region of -78°C. After 30 minutes at a temperature in the region of -78°C, the cooling bath is removed and then the cooled reaction mixture, after returning to a temperature in the region of 20°C, is diluted with 1 cm^3 of distilled water. After decantation, the aqueous phase is reextracted with 2 cm^3 of ethyl acetate. The pooled organic phases are dried over magnesium sulphate, filtered through sintered glass and concentrated under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 99 mg of a colourless lacquer are thereby obtained, which product is purified by preparative thin-layer chromatography: 2 Merck preparative silica gel $60F_{254}$ plates, 20×20 cm, thickness 1 mm, application in solution in a minimum of dichloromethane, eluting with a methanol/dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product with methanol/dichloromethane (15-85 by volume) mixture, filtration through sintered glass and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40°C, 43 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-dimethylaminocarbonyloxy-7α,9α-oxa-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate

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

- ^{1}H NMR spectrum (400 MHz; $CDCl_3$; δ in ppm): 1.05 (s, 9H: $C(CH_3)_3$); 1.24 (s, 6H: CH_3); 1.61 (s, 3H: CH_3); 1.70 (s, 3H: CH_3); 1.81 (s, 1H: OH at position 1); 1.87 (s, 3H: $COCH_3$); 2.14 and from 2.15 to 2.35 (dd and mt respectively, J = 16 and 8 Hz, 1H each: CH_2 14); from 2.15 to 2.35 (mt, 2H: CH_2 6); 2.92 (s, 6H: $N(CH_3)_2$); 3.80 (s, 3H: $ArOCH_3$); 3.92 and 4.23 (2 d, J = 8 Hz, 1H each: CH_2 20); 4.02 (d, J = 6 Hz, 1H: H 3); 4.62 (d, J = 5 Hz, 1H: H 2'); 4.71 (dd, J = 8 and 7.5 Hz, 1H: H 7); 4.83 (d, J = 6 Hz, 1H: H 9); 4.88 (broad s, 1H: H 5); 5.35 (broad d, J = 5 Hz, 1H: H 3'); 5.68 and 5.77 (2 d, J = 6 Hz, 1H: H 2 and H 10); 6.00 (broad t, J = 8 Hz, 1H: H 13); 6.30 (s, 1H: H 5'); 6.92 (d, J = 8.5 Hz, 2H: aromatic H at the ortho position of the OCH_3); from 7.25 to 7.50 (mt, 9H: aromatic H at position 3' - aromatic H at the meta position of the OCH_3 and $OCOC_6H_5$ H meta); 7.60 (t, J = 7.5 Hz, 1H: $OCOC_6H_5$ H para); 8.05 (d, J = 7.5 Hz, 2H: $OCOC_6H_5$ H ortho).

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 or the oral 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 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.

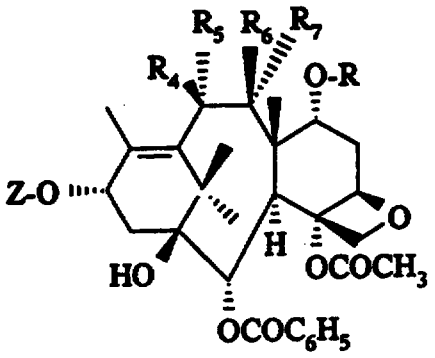
EXAMPLE

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

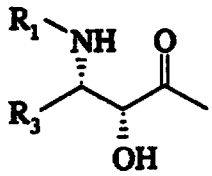
1. New taxoids of general formula:



(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, cycloalkenyl radicals containing 4 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,

either R_4 represents a hydrogen atom,

R_6 and R_7 together form a ketone function, and

R and R_5 together form a bond,

or R_4 represents a hydrogen atom or 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 1 to 6 carbon atoms in an unbranched or branched chain, an aroyloxy radical in which the aryl portion contains 6 to 10 carbon atoms, 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, a cycloalkanoyloxy radical containing 3 to 6 carbon atoms, 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 or alkylcarbamoyloxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a 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,

* C L M S *

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R_5 represents a hydrogen atom

or R_4 and R_5 together form a ketone function,

R_6 represents a hydrogen atom, and

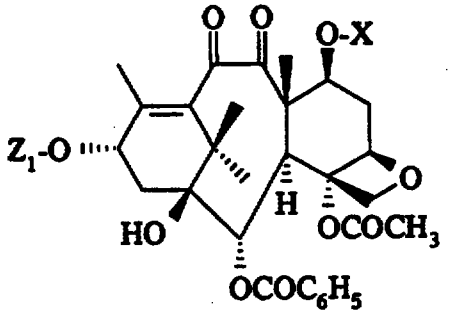
R and R_7 together form a bond.

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 [lacuna] or more identical or different atoms or radicals chosen from atoms and alkyl, alkoxy, dialkylamino, acylamino, alkoxycarbonylamino or trifluoromethyl radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and either R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a hydroxyl radical or an alkoxy radical containing 1 to 6 carbon atoms, an alkanoyloxy radical containing 1 to 6 carbon atoms or an alkoxyacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, or R_4 and R_5 together form a ketone function, R_6 represents a hydrogen atom, R and R_7 together form a bond.

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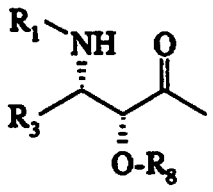
3. New taxoids according to Claim 1, for which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical R_2-O-CO- in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, either R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a hydroxyl radical or a methoxy, acetoxy, propanoyloxy or methoxyacetoxy radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond.

4. Process for the preparation of a product according to one of Claims 1, 2 or 3, in which either R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function and R and R_5 together form a bond, or R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, characterized in that a reducing agent is reacted with a product of general formula:



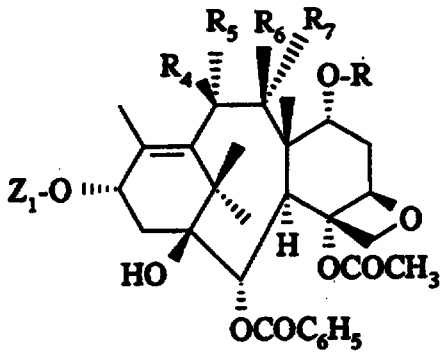
(III)

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



(IV)

in which R_1 and R_3 are defined as in one of Claims 1, 2 or 3 and R_8 represents a group protecting the hydroxyl function, and X represents, with the oxygen atom to which it is linked, a leaving group chosen from alkylsulphonyl radicals containing 1 to 4 carbon atoms optionally substituted with one or more halogen atoms, or arylsulphonyl radicals in which the aryl portion is a phenyl 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, or nitro or trifluoromethyl radicals, to obtain a product of general formula:



(V)

in which Z_1, R, R_4, R_5, R_6 and R_7 are defined as above, in the form of a mixture of a product of general

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formula (I) in which R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function, and R and R_5 together form a bond, and of a product of general formula (I) in which R_4 represents [lacuna] hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom, and R and R_7 together form a bond, which is separated by the usual methods, and then the protective group represented by Z_1 or R_8 is optionally replaced with a hydrogen atom.

5. Process according to Claim 4, characterized in that the reducing agent is chosen from aluminohydrides or borohydrides such as alkali or alkaline-earth metal borohydrides, in the presence of an aliphatic alcohol containing 1 to 4 carbon atoms such as ethanol, the reaction being carried out at a temperature of between 0 and 50°C.

6. Process according to Claim 4, characterized in that when the protective group represents a silylated radical, it is replaced by a hydrogen atom by means of an inorganic acid in an aliphatic alcohol containing 1 to 3 carbon atoms at a temperature of between -10 and 20°C or by means of the hydrofluoric acid/triethylamine complex, working in an inert organic solvent at a temperature of between 0 and 50°C.

7. Process for the preparation of a product according to one of Claims 1, 2 or 3, for which Z is defined as in one of Claims 1, 2 or 3, R_4 represents an

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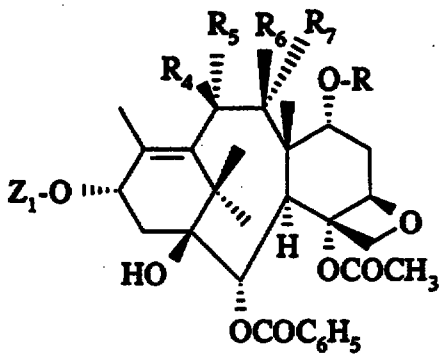
alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain, a cycloalkyloxy radical containing 3 to 6 carbon atoms, a cycloalkenyloxy radical containing 3 to 6 carbon atoms, an alkanoyloxy radical in which the alkanoyl portion contains 1 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, a cycloalkanoyloxy radical containing 1 to 6 carbon atoms, 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 or alkylcarbamoyloxy radical in which the alkyl portion contains 1 to 4 carbon atoms, a 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 a hydrogen atom, R_6 represents a hydrogen atom, and R and R_7 together form a bond, characterized in that a product of general formula:

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

in which R'_4 is such that R'_4-O- is identical to R_4 defined as above and Y represents a leaving group is reacted with a product of general formula:

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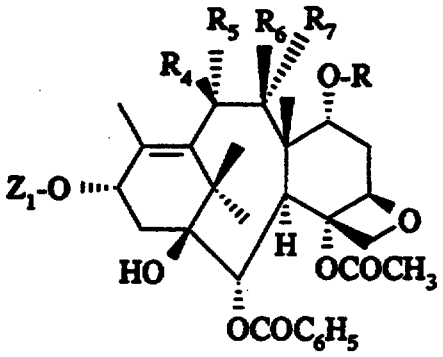
(V)

in which Z_1 is defined as above, R_4 represents a hydroxyl radical, R_6 represents a hydrogen atom and R and R_7 together form a bond, followed by the replacement of the protective group represented by Z_1 or R_8 by a hydrogen atom under the conditions of Claim 6.

8. Process according to Claim 7, characterized in that prior to the action of the product of general formula (IX) the hydroxyl function at position 10 is optionally metalated by means of an alkali metal hydride, amide or alkylide.

9. Process for the preparation of a product according to Claims 1, 2 or 3, for which Z represents a radical of general formula (II), R_4 and R_5 together form a ketone function, R_6 represents a hydrogen atom, and R and R_7 together form a bond, characterized in that a product of general formula:

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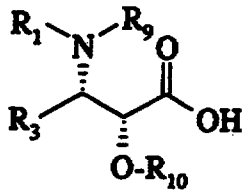
in which Z_1 is defined as in Claim 4, R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, is oxidized and then the protective group represented by Z_1 or R_8 is optionally replaced by a hydrogen atom under the conditions of Claim 6.

10. Process according to Claim 9, characterized in that the oxidation is carried out by means of oxygen, ammonium peruthenate, manganese dioxide, copper acetate or pyridinium chlorochromate.

11. Process for the preparation of a product according to one of Claims 1, 2 or 3, for which Z represents a radical of general formula (II), R_4, R_5 and R_6 each represent a hydrogen atom and R and R_7 together form a bond, may be obtained from a product of general formula (V) in which Z_1 is defined as in Claim 4, R_4 represents a hydroxyl radical, R_5 and R_6 each represent a hydrogen atom and R and R_7 together form a bond, after conversion of the hydroxyl radical represented by R_4 to a dithiocarbonate followed by the reduction of

the product obtained by means of a trialkyltin hydride optionally followed by the replacement of the protective group represented by Z_1 or R_8 by a hydrogen atom under the conditions of Claim 6.

12. Process for the preparation of a product according to one of Claims 1, 2 or 3, characterized in that a product according to one of Claims 1, 2 or 3 is esterified by means of an acid of general formula:



(X)

in which, either R_9 represents a hydrogen atom and R_{10} represents a group protecting the hydroxyl function, or R_9 and R_{10} together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, and the protective groups are then replaced by hydrogen atoms, working under known conditions.

13. Pharmaceutical composition, characterized in that it contains at least one product according to one of Claims 1, 2 or 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.

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R_4 represents a hydrogen atom
or R_4 and R_5 together form a ketone function,
R_6 represents a hydrogen atom, and
R and R_7 together form a bond.

2. 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 radicals, or a 2- or 3-furyl, 2- or 3-thienyl or 2-, 4- or 5-thiazolyl radical, and either R_4 represents a hydrogen atom, R_5 and R_7 together form a ketone function and R and R_6 together form a bond, or R_4 represents a hydroxyl radical or an alkoxy radical containing 1 to 6 carbon atoms, an alkanoyloxy radical containing 1 to 6 carbon atoms or an alkoxyacetyl radical in which the alkyl portion contains 1 to 6 carbon atoms, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom and R and R_7 together form a bond, or R_4 and R_5 together form a ketone function, R_6 represents a hydrogen atom, R and R_7 together form a bond.

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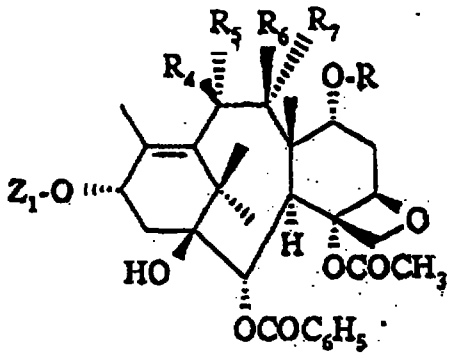
formula (I) in which R_4 represents a hydrogen atom, R_6 and R_7 together form a ketone function, and R and R_5 together form a bond, and of a product of general formula (I) in which R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom, R_6 represents a hydrogen atom, and R and R_7 together form a bond, which is separated by the usual methods, and then the protective group represented by Z_1 or R_8 is optionally replaced with a hydrogen atom.

5. Process according to Claim 4, characterized in that the reducing agent is chosen from aluminohydrides or borohydrides such as alkali or alkaline-earth metal borohydrides, in the presence of an aliphatic alcohol containing 1 to 4 carbon atoms such as ethanol, the reaction being carried out at a temperature of between 0 and 50°C.

6. Process according to Claim 4, characterized in that when the protective group represents a silylated radical, it is replaced by a hydrogen atom by means of an inorganic acid in an aliphatic alcohol containing 1 to 3 carbon atoms at a temperature of between -10 and 20°C or by means of the hydrofluoric acid/triethylamine complex, working in an inert organic solvent at a temperature of between 0 and 50°C.

7. Process for the preparation of a taxoid according to one of Claims 1, 2 or 3, for which Z is defined as in one of Claims 1, 2 or 3, R_4 represents an

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(V)

in which Z_1 is defined as above, R_4 represents a hydroxyl radical, R_5 represents a hydrogen atom and R and R_7 together form a bond, followed by the replacement of the protective group represented by Z_1 or R_4 by a hydrogen atom under the conditions of Claim 6.

8. Process according to Claim 7, characterized in that prior to the action of the product of general formula (IX) the hydroxyl function at position 10 is metalated by means of an alkali metal hydride, amide or alkylide.

9. Process for the preparation of a taxoid according to Claims 1, 2 or 3, for which Z represents a radical of general formula (II), R_4 and R_5 together form a ketone function, R_6 represents a hydrogen atom, and R and R_7 together form a bond, characterized in that a product of general formula:

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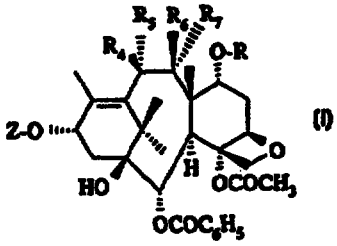
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(54) Title: NOVEL TAXOIDS, PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

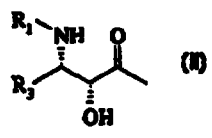
(54) Titre: NOUVEAUX TAXOIDES, LEUR PREPARATION ET LES COMPOSITIONS PHARMACEUTIQUES QUI LES CONTIENNENT

(57) Abstract

Novel taxoids of general formula (I), the preparation thereof and pharmaceutical compositions containing same, are disclosed. In general formula (I), Z is a hydrogen atom or a radical of general formula (II), wherein R_1 is an optionally substituted benzoyl, furoyl or thenoyl radical or a radical R_2-O-CO- where R_2 is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, optionally substituted phenyl or heterocyclyl radical; R_3 is an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, phenyl, naphthyl or aromatic heterocyclic radical; or R_4 is a hydrogen atom, R_6 and R_7 together form a ketone function, and R and R_5 together form a bond; or R_4 is a hydrogen atom or a hydroxy radical or an alkoxy, alkenyloxy, optionally substituted alkynyloxy, alkanoyloxy, aroyloxy, alkenoyloxy, alkynoyloxy, cycloalkanoyloxy, alkoxyacetyl, alkylthioacetyl, alkyloxycarbonyloxy, cycloalkyloxy, cycloalkenyloxy, carbamoyloxy, alkylcarbamoyloxy or dialkylcarbamoyloxy radical; R_5 is a hydrogen atom, or R_4 and R_5 together form a ketone function, R_6 is a hydrogen atom, and R and R_7 together form a bond. The novel products of general formula (I), wherein Z is a radical of general formula (II), have remarkable antitumoral and antileukemic properties.



(I)



(II)

(57) Abrégé

Nouveaux taxoïdes de formule générale (I), leur préparation et les compositions pharmaceutiques qui les contiennent. Dans la formule générale (I), Z représente un atome d'hydrogène ou un radical de formule générale (II), dans laquelle R_1 représente un radical benzoyle éventuellement substitué, furoyle ou thénoyle ou un radical R_2-O-CO- dans lequel R_2 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle, bicycloalcoyle, phényle éventuellement substitué ou hétérocyclyle; R_3 représente un radical alcoyle, alcényle, alcynyle, cycloalcoyle, cycloalcényle, phényle, naphtyle ou hétérocyclique aromatique; ou bien, R_4 représente un atome d'hydrogène; R_6 et R_7 forment ensemble une fonction cétone; et R et R_5 forment ensemble une liaison; ou bien, R_4 représente un atome d'hydrogène ou un radical hydroxy ou un radical alcoxy, alcényloxy, alcynyloxy éventuellement substitué, alcanoyloxy, aroyloxy, alcénoyloxy, alcynoyloxy, cycloalcanoyloxy, alcoxyacétyle, alcoylthioacétyle, alcoyloxycarbonyloxy, cycloalcoyloxy, cycloalcényloxy, carbamoyloxy, alcoylcarbamoyloxy ou dialcoylcarbamoyloxy; R_5 représente un atome d'hydrogène; ou R_4 et R_5 forment ensemble une fonction cétone; R_6 représente un atome d'hydrogène; et R et R_7 forment ensemble une liaison. Les nouveaux produits de formule générale (I) dans laquelle Z représente un radical de formule générale (II) présentent des propriétés antitumorales et antileucémiques remarquables.