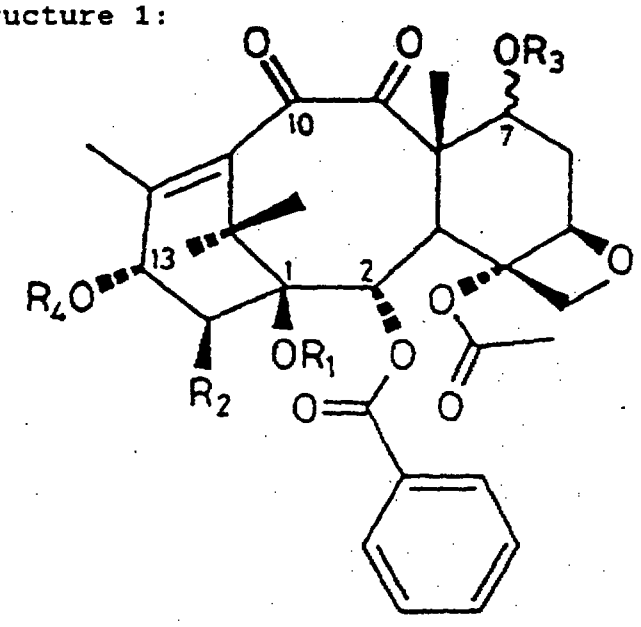
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10-DEACETYLBACCATINE III AND 10-DEACETYL 14β-HYDROXYBACCATINE III DERIVATIVES, A PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

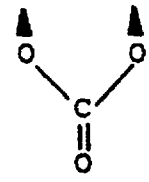
Paclitaxel (taxol), as it is already well-known, is a diterpenoid extracted from plants of the Taxus genus having anticancerogenic activity on different forms of human tumours. Its clinical use still involves some drawbacks due to the poor water solubility, which makes its administration complex, as well as to the onset of serious side-effects. Moreover, paclitaxel induces resistance quickly. Due to these reasons, researches have been in progress for some years aiming at synthesizing novel paclitaxel analogues which cause less adverse effects compared with the parent molecule. The present invention relates to novel derivatives with taxane skeleton endowed with a marked anti-tumoural activity. The novel derivatives have the general structure 1:



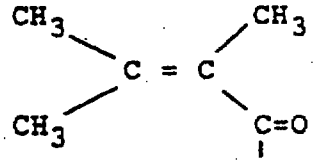
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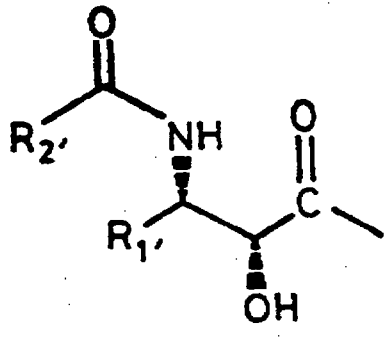
wherein R_1 and R_2 are hydrogen atoms, or R_1 is an hydrogen atom and R_2 is an hydroxyl or an acetyloxy group, or OR_1 and R_2 together form a cyclic carbonate group of formula:



R_3, which can be α- o β-oriented, is an hydrogen atom or an alkylsilyl group, preferably triethylsilyl (TES); R_4 is hydrogen, or the residue



or an isoserine residue of formula A:

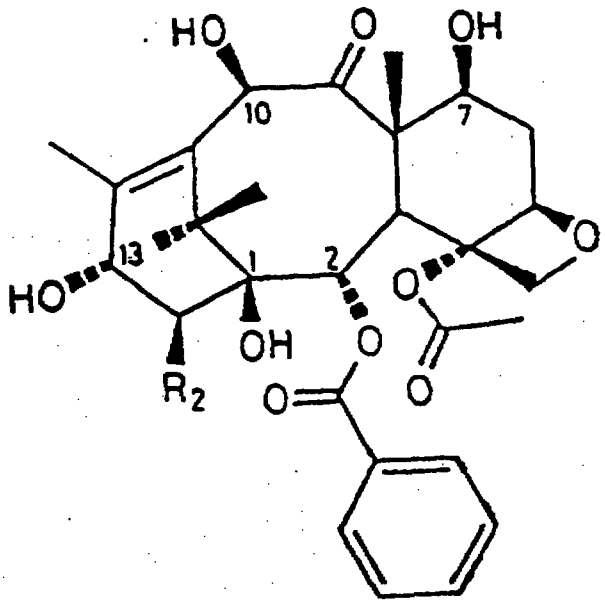


(A)

wherein R_1' is a straight or branched alkyl or alkenyl group, containing one to five carbon atoms, or an aryl residue; R_2' is a straight or branched alkyl or alkenyl group, containing one to five carbon atoms, or an aryl residue, or a tert-butoxy group.

The novel derivatives of general formula (1) are prepared by semisynthesis, starting from the natural syntons 10-deacetylbaccatine III (2) and 10-deacetyl-14β-hydroxybaccatine III (3). For this purpose, they are

selectively oxidized in position 10 and then esterified in position 13 with a suitable acylating agent which allows to introduce the group R_4.



2 R_2=H

3 R_2=OH

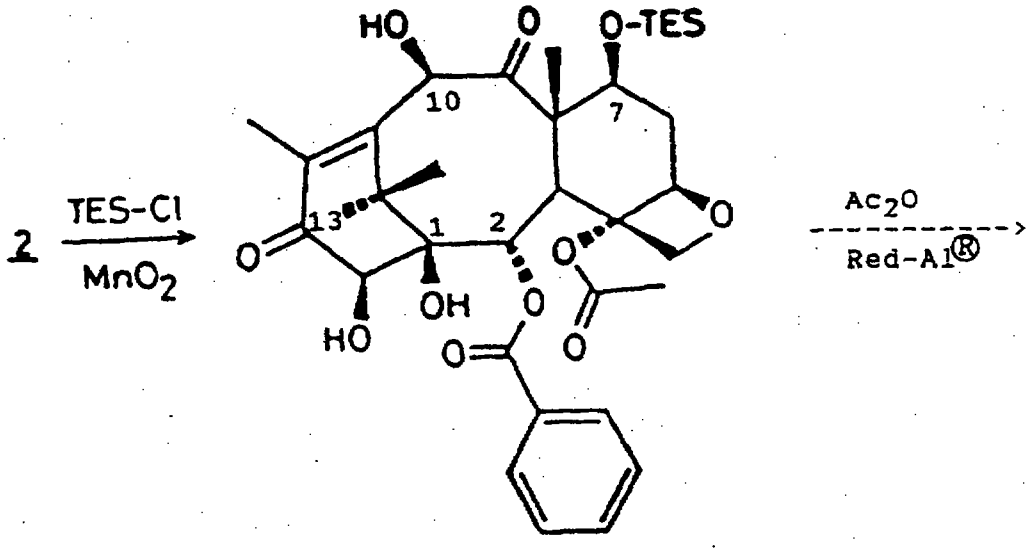
When taxanes of natural or synthetic origin already containing the desired isoserine chain in position 13, the molecules of structure 1 can be obtained from said taxanes by selective oxidation in position 10. As it will be described hereinafter, the selective oxidation in position 10 of 2, 3 and of the taxanes already containing the isoserine chain in position 13, can be obtained by treatment with copper (II) salts.

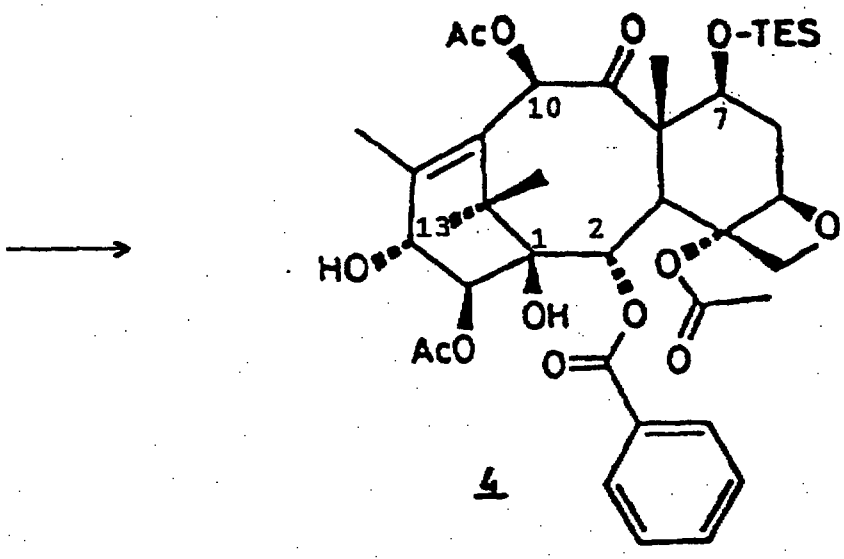
10-Deacetylbaccatine III (2) and its 14β-hydroxy (3) analogous can be recovered from suitably selected vegetable material (see. Indena Patent US-5,269,591).

However, and it is one of the objects of the present invention, it is possible to synthesize taxane syntons containing an oxygenated function in position

14, which are therefore useful for the preparation of compounds of structure 1, containing an oxygenated function in position 14, starting from 10-deacetylbaccatine III (2). In fact, it has surprisingly been found that, after protecting the hydroxyl in position 7 of compound 2 as a silyl ether, the oxidation to ketone of the carbon in 13 and the introduction of a β-oriented alcohol function on the carbon in 14 take place by treatment with manganese dioxide. After protection of the hydroxyls in 10 and 14, for example as acetates, by treatment with hydrides, the 13-keto function is reduced to 13α-hydroxy.

The process, which is schematized below, leads to the formation of synton 4, useful for the preparation of compounds with structure 1.



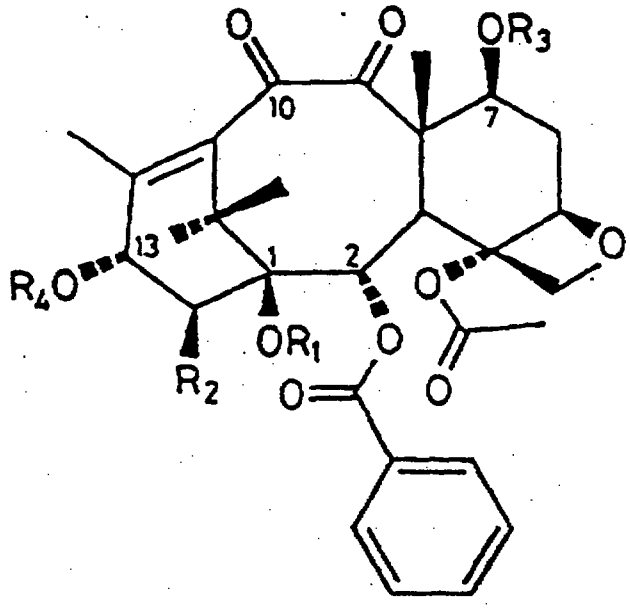


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From synton 4, after removing the protective groups with known methods described in literature, for example using hydrochloric acid to remove the silyl group and a base to remove the acetate groups, 10-deacetyl-14β-hydroxybaccatine III (3) is obtained. Therefore, as mentioned, in order to prepare compounds of formula 1, 10-deacetylbaccatine III (2), 10-deacetyl-14β-hydroxybaccatine III (3), natural or semisynthetic, or other taxanes having an hydroxyl function at 10 and already containing in position 13 the isoserine chain represented by the group R_4, must be available.

It has surprisingly been found that all these syntons, by treatment with copper (II) salts, preferably copper acetate, undergo a selective oxidation in position 10, without need for the protection of the other hydroxyl functions. For example, 10-deacetylbaccatine III (2), 10-deacetyl-14β-hydroxybaccatine III (3) and the natural taxane 10-deacetyl-cephalomannine give the respective 10-keto

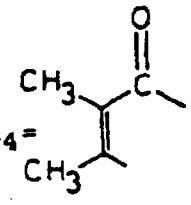
derivatives 5-7 in yields from 75 to 85%. The oxidation generally requires protracted times (100-140 hours) and an oxidizer excess, and it is carried out at room temperature and in alcoholic solvent.



5 $R_1=R_2=R_3=R_4=H$

6 $R_1=R_3=R_4=H; R_2=OH$

8 $R_1,R_2=-CO-O; R_3=R_4=H$



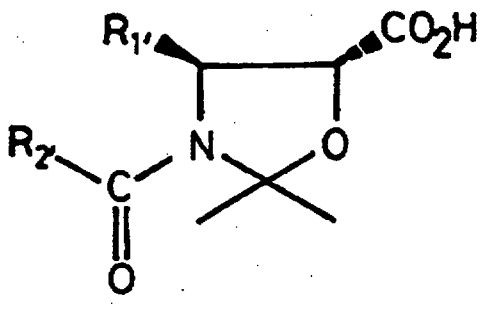
7 $R_1=R_2=R_3=H; R_4=$

When, in the compound of formula 1 to prepare, the presence of a cyclic carbonate group between the positions 1 and 14 is required, synton 3 is previously treated with phosgene in pyridine and the resulting carbonate is then oxidized in position 10 with copper (II) acetate, to give carbonate synton 8.

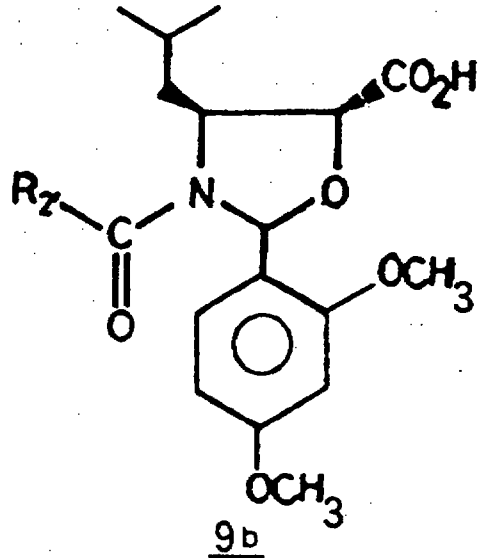
By treatment with bases, diketones 5-8 undergo an inversion in position 7, i.e. the hydroxyl in position 7 becomes α-oriented. Syntons 5, 6 and 8 or optionally their epimers in position 7, are therefore used for the preparation of taxanes of structure 1, after protection of the alcoholic functions present. The alcohol function in 13, contrary to the other hydroxyalcohol functions,

is poorly reactive to silylation and therefore does not undergo derivatization.

For the esterification in position 13, the suitably activated isoserine chains are used, according to what reported in literature for the semisynthesis of paclitaxel and of its analogues (see. for example Eur. Pat. Appl. 400971, 1992; Fr. Dem. 86, 10400; E. Didier et al., Tetrahedron letters 35, 2349, 1994; E. Didier et al.; ibid 35, 3063, 1994). Preferably, isoserin chains are used in the activated forms of oxazolidinecarboxylic acids 9a and 9b.



9a



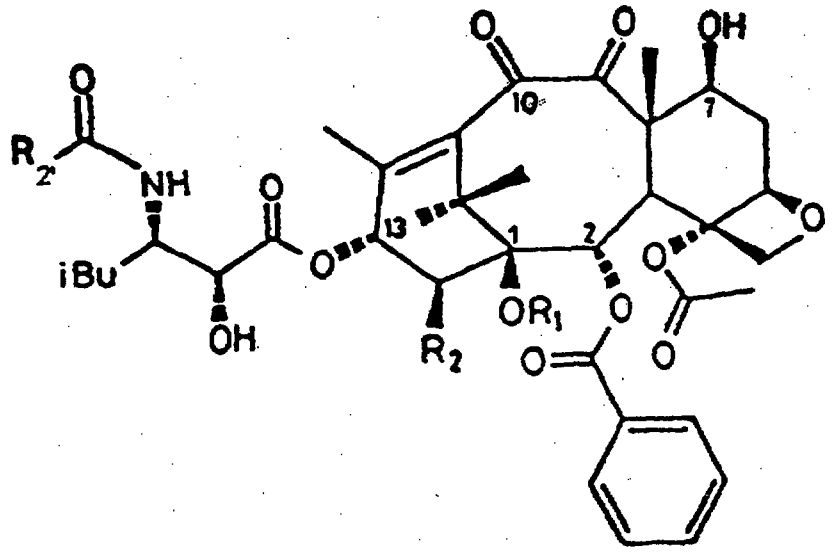
9b

In formulae 9a and 9b, R_1'and R_2' have the meaning described above. The esterification of the oxazolidinecarboxylic acids with the taxane syntons and the subsequent elimination of the protective groups are carried out as described in literature for the synthesis of paclitaxel and the analogues thereof.

Among the compounds of formula 1, compounds 10, 11

and 12 turned out to be particularly active. Compound 10 is 13-[(2R,3S)-3-ter-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]-10-deacetyl-10-dehydro-baccatine III. Therefore, referring to general formula 1, compound 10 has: $R_1 = R_2 = H$, $OR_3 = \beta$-OH, $R_1' =$ iso-But, $R_2' =$ t-BuO. Compound 11 is 13-[(2R,3S)-3-ter-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]-10-dehydro-10-deacetyl-14β-hydroxy-baccatine III 1,14-carbonate. Therefore 11, referring to general formula 1, has R_1, R_2 = -CO-O, $OR_3 = \beta$-OH, $R_1' =$ iso-But, $R_2' =$ t-BuO.

Compound 12 is 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutyl-propanoyl]-10-dehydro-10-deacetyl-14β-hydroxy-baccatine III 1,14-carbonate. Therefore 12, referring to general formula 1, has R_1, R_2 = -CO-O, $OR_3 = B$-OH, $R_1' =$ iso-But, $R_2' = C_5H_{11}$.



10 $R_1 = R_2 = H$, $R_2' =$ t-butoxy

11 R_1, R_2 = CO-O, $R_2' =$ t-butoxy

12 R_1, R_2 = CO-O, $R_2' = C_5H_{11}$

The cytotoxicity data of the compounds 10 and 11 compared with those of paclitaxel are reported in the following Table.

Table - IC_{50}s of compounds 10, 11 and paclitaxel on 6 human tumour cell lines.

Cell line	Exposition time (h)	IC_{50} (nM) Paclitaxel	10	11
L1210 (murine leukemia)	48	7.0 ± 3.0	0.6 ± 0.1	2.0 ± 0.1
A121 (human ovarian)	72	3.7 ± 0.3	0.8 ± 0.3	1.6 ± 0.2
A549 (human NSCLC)	72	5.4 ± 0.5	1.9 ± 0.3	2.1 ± 0.3
HT-29 (human colon)	72	6.0 ± 0.6	0.4 ± 0.1	0.6 ± 0.4
MCF7 (human breast)	72	4.3 ± 0.1	1.2 ± 0.2	0.8 ± 0.2
MCF7-ADR (resistant)	72	395 ± 8.7	13 ± 2.2	28 ± 6.2

Standard conditions : basal medium = RPMI 1640 + 20 mM HEPES + 2 mM L-Glutamine.

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Compounds of formula 1 show surprising advantages compared with paclitaxel on cell lines resistant to other anti-tumoural substances, such as adriamycin or cis-platinum. The differences between paclitaxel and these products are even more evident in in vivo models, such as athymic nude mouse with human tumour implant. Moreover, it has been found that the compounds of the invention in which R'_2 is an alkyl or alkenyl group are surprisingly devoid of cardiotoxic activity, contrary to taxol and the known derivatives thereof, and therefore they can advantageously be used in the treatment of tumours in cardiopathic patients who cannot be treated with taxol and its known derivatives.

The products object of the invention can be incorporated in suitable pharmaceutical formulations for the administration of the products both parenterally and orally. For the intravenous administration, mixtures of Chremoform L and ethanol, polysorbates or liposomial preparations prepared with natural or synthetic phosphatidylcholine or mixtures of natural phospholipids in the presence of cholesterol are mainly used.

The following examples further illustrate the invention.

Example 1 - Preparation of 10-deacetyl-10-dehydrobaccatine III (5).

10 g of 10-deacetylbaccatine III (2), (isolated as described by G. Chauviere et al., C.R. Acad. Sci. Ser. II 293. 591. 1981) are suspended in 350 ml of methanol and added with 65 g of $Cu(OAc)_2$. The suspension is stirred at room temperature for 120 h. The salts are filtered off and the solution is chromatographed on 100

g of silica gel eluting with a hexane/ethyl acetate 6:4 mixture. Upon crystallization from ligroin, 9.5 g of (5) are obtained, M^+a m/z 542.

Example 2 - Preparation of 10-deacetyl-10-dehydro-14β-hydroxybaccatine III 1,14-carbonate (8).

10 g of 10-deacetyl-14β-hydroxybaccatine III (3), isolated as described by G. Appendino et al., J. Chem. Soc. Perkin Trans I, 2925. 1992, are dissolved in 50 ml of anhydrous pyridine and treated for one hour with 1.5 eq. of 5% phosgene in toluene at -10°C. The reaction mixture is poured onto ice and the aqueous suspension is extracted with ethyl acetate, washing thoroughly the organic phase with diluted HCl. After drying over Na_2SO_4, the organic phase is concentrated to dryness. 9 g of 1,14-carbonate are obtained, which are suspended in 350 ml of methanol and treated with 50 g of $Cu(OAc)_2$ under stirring at room temperature for 120 h. The suspension is filtered and the solution is evaporated to dryness. The residue is chromatographed on 100 g of silica gel eluting with a hexane/ethyl acetate 1:1 mixture. 8 g of (8) are obtained, M^+a m/z 584.

Example 3 - Preparation of 13-[(2R,3S)-3-ter-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]10-deacetyl-10-dehydrobaccatine III (10)

A solution of 300 mg (1.84 mmol) of 7-O-triethylsilyl-10-deacetyl-10-dehydrobaccatine III, obtained from compound (5) (Example 1) by silylatio in position 7 with the method described by J. Denis et al., J. am. Chem. Soc. 100. 5917. 1988. in 60 ml of toluene is added with 500 mg of (4S, 5R)-N-(ter-butoxy-carbonyl)-2.2-dimethyl-4-isobutyl-5-oxazolidineecar-

boxylic acid, 240 mg of dicyclohexylcarbodiimide (1.2 eq.) and 24 mg of N,N-dimethylaminopyridine (0.2 eq). The reaction mixture is kept at 80°C for 2 hours, then is filtered and washed with water; the organic phase is concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel eluting with acetone/hexane 4:6. 350 mg of (10) are obtained. M^+a m/z 785.

Example 4 - Preparation of 13-[(2R,3S)-3-tert-butoxycarbonyl-amino-2-hydroxy-3-isobutyl-propanoyl]10-deacetyl-10-dehydro-14β-hydroxybaccatine III 1,14-carbonate (11).

0.5 g of 7-O-triethylsilyl-10-deacetyl-10-dehydro-14β-hydroxybaccatine III 1,14-carbonate, obtained from compound (8) (Example 2) by silylation in position 7 according to what reported by J. Denis et al., J. Am. Soc. 100. 5917. 1988. are dissolved in 60 ml of toluene. The solution is added with 800 mg of (4S,5R)-N-(tert-butoxycarbonyl)-2.2-dimethyl-4-isobutyl-5-oxazolidineecarboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours, then is filtered and washed with water and the organic phase is concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness

and the residue is chromatographed on silica gel, eluting with acetone/hexane 4:6. 580 mg of (11) are obtained, M^+a m/z 827.

Example 5 - Preparation of 10-deacetyl-10-dehydro-14β-hydroxybaccatine III (6).

10 g of 10-deacetyl-14β-hydroxybaccatine III (3) are suspended in 350 ml of methanol and added with 65 g of $Cu(OAc)_2$. The suspension is kept under stirring at room temperature for 120 h. The salts are filtered off, the solution is evaporated to dryness and the residue is chromatographed on 100 g of silica gel eluting with a hexane/ethyl acetate 6:4 mixture. Upon crystallization from ligroin, 9.3 g of (6) are obtained, M^+a m/z 558.

Example 6 - Preparation of 10-deacetyl-10-dehydro-cephalomannine (7).

0.4 g of 10-deacetylcephalomannine (J. L. Laughlin et al., J. Nat. Prod. 44. 312. 1981) are dissolved in 5 ml of MeOH and added with 600 mg of $Cu(OAc)_2$. The reaction mixture is left under stirring for 54 hours at room temperature. After eliminazione of the salts for filtration, the solution The salts are filtered off, the solution is evaporated to dryness and chromatographed on silica gel (10 g) using a hexane-acetate d'ethyl 1:1 mixture as eluent. 220 mg of (7) are obtained. M^+a m/z 829.

Example 7 - Preparation of 7-triethylsilyl-14β-hydroxybaccatine III (4)

500 mg of 7-triethylsilyl-10-deacetylbaccatine III, prepared according to the method by J. Denis et al., J. Am. Chem. Soc. 100. 5917. 1988 are dissolved in 15 ml of a ethyl acetate-methylene chloride 9:1 mixture. The

solution is added with 10 g of MnO_2 leaving the suspension at room temperature under stirring for 24 hours. After filtration, the solution is evaporated to dryness and the residue is chromatographed on silica gel (20 g) eluting with a hexane-ethyl acetate 8:2 mixture. 310 mg of 7-triethylsilyl-10-deacetyl-13-dehydro-14β-hydroxybaccatine III are obtained (M^+a m/z 672).

300 mg of this product are dissolved in 2 ml of pyridine. The solution is added with 910 mg of Ac_2O. After 16 hours the reaction mixture is poured onto ice and then extracted with ethyl acetate. The organic phase is washed with diluted HCl and then with water to neutrality. After evaporation of the solvent, the residue is crystallized from ether (220 mg, M^+a m/z 756). The solid is dissolved in 10 ml of anhydrous THF; the solution is added with 160 µl of sodium bis(2-methoxy-ethoxy)aluminium hydride (65% solution). After about 10 minutes, 10 ml of a NH_4Cl saturated solution are added, extracting then with ethyl acetate. The organic phase is evaporated to dryness. The residue is purified on silica gel (15 g) eluting with a hexane-ethyl acetate 7:3 mixture. 80 mg of (4) are obtained. M^+a 716.

Example 8 - Preparation of (4S,5R)-N-caproyl-2-(2.4-dimethoxyphenyl)-4-isobutyl-5-oxazolidinee carboxylic acid methyl ester.

5 g of N-caproyl-β-isobutyl-isoserine methyl ester are dissolved in 200 ml of a mixture of anhydrous THF and benzene and the solution is treated with 2 equivalents of 2.4-dimethoxy benzaldehyde dimethyl acetale in the presence of 120 mg of pyridinium p-

toluenesulfonate. The solution is refluxed for 1 hour. The solvent is distilled and the residue is chromatographed on silica gel eluting the main compound with a ethyl acetate/hexane 8:2 mixture. After removing under vacuum the solvent from the fractions containing the desidered isomer, the residue is crystallized from hexane/isopropyl ether. 2.5 g of a compound having m.p. 98°C are obtained.

Example 9 - Preparation of (4S,5R)-N-caproyl-2-(2.4-dimethoxyphenyl)-4-isobutyl-5-oxazolidinee carboxylic acid

2 g of the compound of Example 8 are suspended in 50 ml of a mixture of methanol aqueous (8:2) containing 5 g of K_2CO_3. The reaction mixture is left under stirring until complete dissolution of the isoserine derivative. The reaction mixture is carefully acidified to pH 5. with stirring, in the presence of ethyl acetate. The aqueous phase is discarded, whereas the organic one is dried over sodium sulfate and concentrated to dryness at low temperature under vacuum. The residue is dissolved in a toluene/methylene chloride mixture and it is ready for the reaction with the selected taxanes.

Example 10 - Preparation of 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutyl-propanoyl]-10-dehydro-10-deacetyl-14β-hydroxy-baccatine III 1,14-carbonate (12)

5 g of 1,14-carbonate-7-TES-10-dehydro-baccatine III are dissolved in 100 ml of a mixture of toluene and methylene chloride in a 8.2 ratio, together with 6 g of (4S,5R)-N-caproyl-2-(2.4-dimethoxyphenyl)-4-isobutyl-5-oxazolidinee carboxylic acid. The reaction mixture is

added with 500 mg of 4-dimethylaminopyridine and 2.5 g of 1.3-dicyclohexylcarbodiimide, then heated for 2 hours under mild reflux until the reagents disappear. The compounds insoluble in the medium are filtered off and the solution is concentrated to dryness. The residue is taken up with 50 ml of methanol/HCl (0.01%) and the reaction mixture is left at room temperature for 1 hour. The solution is alkalinized to pH 5 and concentrated to dryness in the vacuum. The residue is chromatographed on a silica gel column eluting with a methylene chloride/methanol 98:2 mixture. Upon crystallization from ethyl acetate, 1.2 g of compound (12) are obtained.

Example 11 - Solution of compound (10) for the parenteral administration

Compound 10		2 mg
Cremophor EL		175 mg
Absolute alcohol	q.s. to	0.4 ml.

Example 12 - Solution of compound (11) for the parenteral administration

Compound 11		2 mg
Cremophor EL		175 mg
Absolute alcohol	q.s. to	0.4 ml.

Example 13 - Tablets containing compound (10)

Compound 10	10 mg
Cross-linked sodium carboxymethyl cellulose	15 mg
Lactose (spray dried)	41.5 mg
Microcrystalline cellulose	40 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1 mg.

Example 14 - Tablets containing compound (11)

Compound 11	10 mg

Cross-linked sodium carboxymethyl cellulose	15	mg
Lactose (spray dried)	41.5	mg
Microcrystalline cellulose	40	mg
Colloidal silicon dioxide	0.5	mg
Magnesium stearate	1	mg.

Example 15 - Capsules containing compound (10)

Compound 10	10	mg
Lactose (spray dried)	30	mg
Microcystalline cellulose	48.5	mg
Pre-gelatinized starch	10	mg
Magnesium stearate	1	mg
Colloidal silicon dioxide	0.5	mg.

Example 16 - Capsules containing compound (11)

Compound 11	10	mg
Lactose (spray dried)	30	mg
Microcrystalline cellulose	48.5	mg
Pre-gelatinized starch	10	mg
Magnesium stearate	1	mg
Colloidal silicon dioxide	0.5	mg.

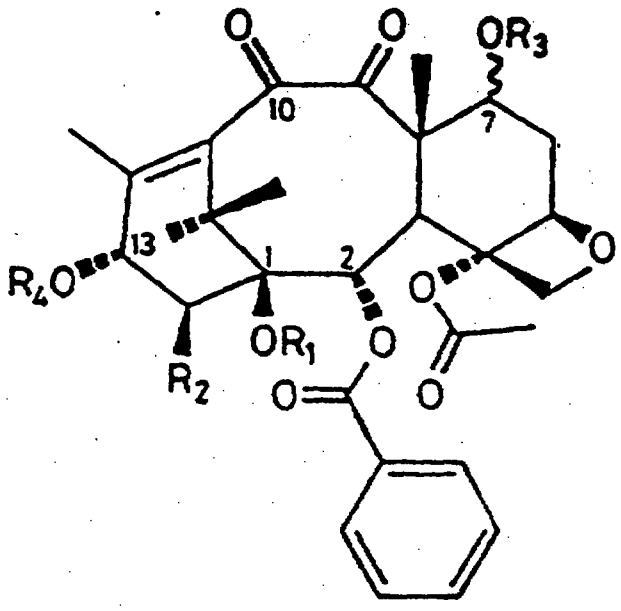
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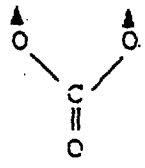
CLAIMS

1. 10-Deacetylbaccatine III and 10-deacetyl-14β-hydroxybaccatine III derivatives of formula (1)

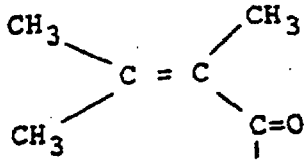


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wherein R_1 and R_2 are hydrogen atoms, or R_1 is an hydrogen atom and R_2 is an hydroxyl or an acetyloxy group, or OR_1 and R_2 together form a cyclic carbonate group of formula:



R_3, which can be α- o β-oriented, is an hydrogen atom or an alkylsilyl group, preferably triethylsilyl (TES); R_4 is hydrogen, or the residue

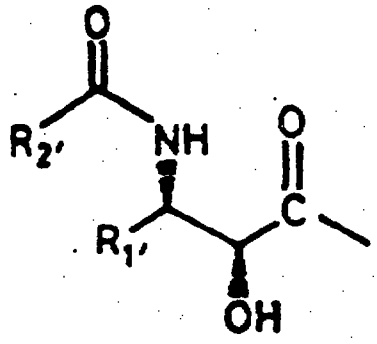


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or an isoserine residue of formula A:



(A)

wherein R_1' is a straight or branched alkyl or alkenyl group, containing one to five carbon atoms, or an aryl residue; R_2' is a straight or branched alkyl or alkenyl group, containing one to five carbon atoms, or an aryl residue, or a tert-butoxy group.

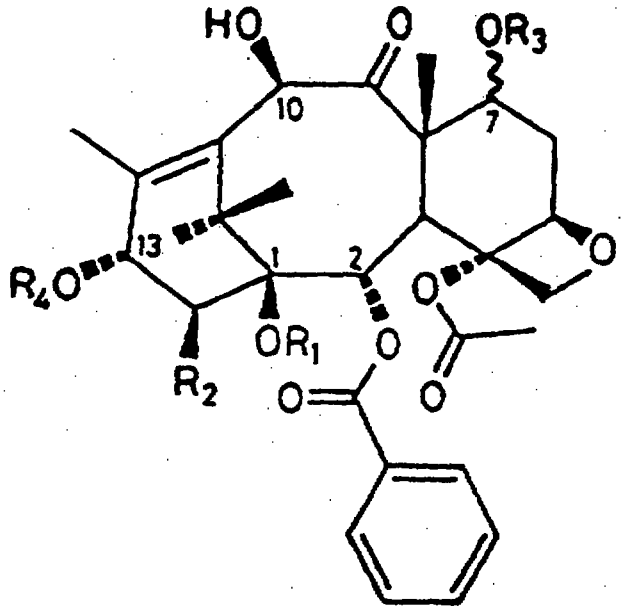
2. A compound according to claim 1, selected from the group consisting:

- 10-deacetyl-10-dehydrobaccatine III;
- 10-deacetyl-10-dehydro-14β-hydroxybaccatine III;
- 10-deacetyl-10-dehydrocephalomannine;
- 10-deacetyl-10-dehydro-14β-hydroxybaccatine III 1,14-carbonate;
- 13-[(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]10-deacetyl-10-dehydrobaccatine III;
- 13-[(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]10-deacetyl-10-dehydro-14β-hydroxybaccatine III 1,14-carbonate;
- 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutyl-propanoyl]-10-dehydro-10-deacetyl-14β-hydroxy-baccatine III 1,14-carbonate.

3. A process for the preparation of 10-deacetylbaccatine III and 10-deacetyl-14β-hydroxybaccatine III derivatives according to claim 1,

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characterized in that syntons of formula B:



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(B)

wherein R_1, R_2, R_3 and R_4 have the meanings defined above,

a) when R_2 = H or OH, or OR_1 and R_2 are together a carbonate group, and $R_4 \neq H$, are oxidized in position 10 by treatment with copper(II) salts; and optionally deprotected in position 7;

b) when $R_2 = R_4 = H$, are oxidized in position 10 by treatment with copper(II) salts and optionally (previous silylation in 7 when R_3 = H) esterified in position 13 with acylating agents which allow to introduce the group $R_4 \neq H$.

4. A process for the preparation of syntons of formula B according to claim 3, wherein R_2 = OH and R_4 = H, characterized in that a 7-trialkylsilyl-10-deacetylbaccatine III (or the 7-epimer) thereof is subjected to a selective oxidation in position 13 and a simoultaneous β-hydroxylation in position 14 by treatment with manganese dioxide, the resulting 7-

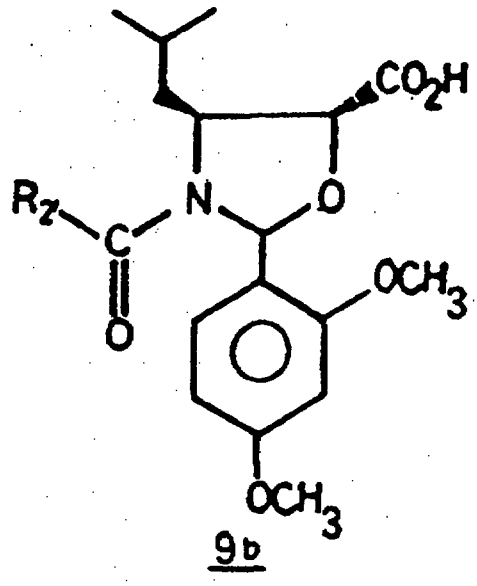
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trialkylsilyl-10-deacetyl-13-dehydro-14β-hydroxybaccatine III (or the 7-epimer thereof) is acetylated in 10 and in 14 and the 7-trialkylsilyl-13-dehydro-14β-hydroxy-14-acetylbaccatine III (or the 7-epimer thereof) is subjected to a reduction with hydrides, to obtain the corresponding 13β-hydroxyderivative.

5. Syntons of formula B according to claim 3.

6. Intermediates of formula 9b:



9b

wherein R_2' has the meaning described above.

7. Pharmaceutical compositions containing as the active ingredient one or more compounds of formula 1 according to claim 1, with R_3 = H.

8. Pharmaceutical compositions according to claim 7, which can be administered parenterally or orally.

9. Compounds of claims 1-2 as anti-tumoural agents.

10. The use of taxanes of claim 1, wherein R'_2 is an alkyl or alkenyl group, for the preparation of medicaments useful for the treatment of tumours in cardiopathic patients.

* C L M S *