686095

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Rhone-Poulenc Rorer S.A.**, the applicant/Nominated Person in respect of Application No. 35048/93 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventor Elie Fouque, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person derives title to the invention from inventor Jean-Manuel Mas by assignment.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this EIGHTH day of SEPTEMBER 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1682820)

AU9335048

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(54) Title
METHOD FOR PREPARING TAXANE DERIVATIVES

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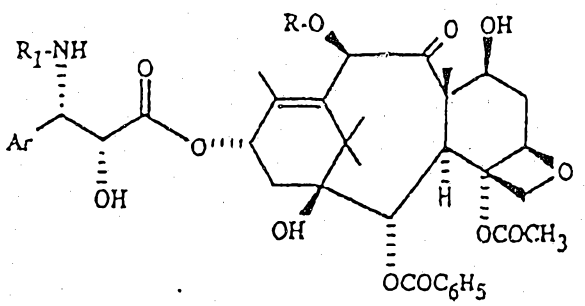
(56) Prior Art Documents
AU 32519/89
AU 32426/89

(57) Claim

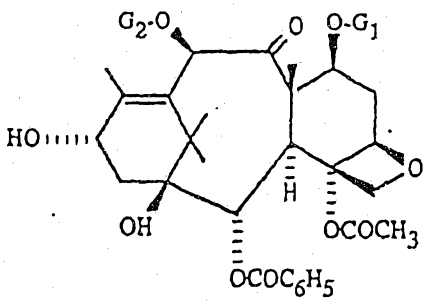
1. Method for preparing taxane derivatives of general formula:



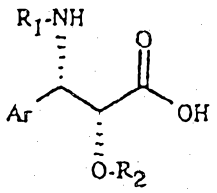
(I)

in which Ar represents an aryl radical, R represents a hydrogen atom or an acetyl radical and R_1 represents a benzoyl or tert-butoxycarbonyl radical, which comprises esterifying in the presence of a condensing agent and an activating agent a derivative of baccatin III or of 10-deacetyl baccatin III of general formula:

.../2



in which G_1 represents a protecting group for the hydroxyl function and G_2 represents an acetyl radical or a protecting group for the hydroxyl function using an acid of general formula:



in which Ar and R_1 are defined as above and R_2 represents a protecting group for the hydroxyl function, followed by replacement, by hydrogen atoms, of the protecting groups G_1, G_2 and R_2 of the product obtained, characterized in that the esterification is carried out at a temperature between -10 and 60°C (60°C not included).

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(81) Etats désignés: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, US, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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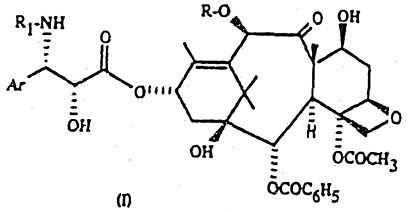
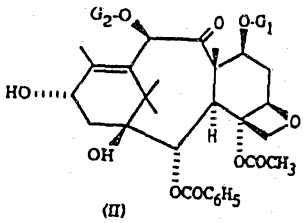
686095

(54) Title: METHOD FOR PREPARING TAXANE DERIVATIVES

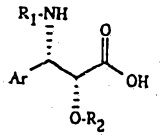
(54) Titre: PROCEDE DE PREPARATION DE DERIVES DU TAXANE



(I)



(II)



(III)

(57) Abstract

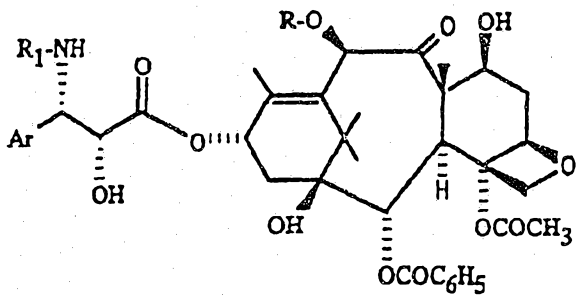
Method for preparing taxane derivatives of general formula (I) by esterification at a temperature between -10 and 60 °C of a derivative of baccatine III or 10-deacetyl baccatine III of general formula (II) by means of an acid of general formula (III), followed by replacement of the protective groupings G_1, G_2 and R_2 of the resulting product by hydrogen atoms. In formulae (I), (II) or (III), Ar stands for an aryl radical; R stands for hydrogen or acetyl; R_1 is benzoyl or tert.butoxycarbonyl; G_1 is a hydroxy function protective grouping, G_2 stands for the acetyl radical or a hydroxy function protective grouping, and R_2 stands for a hydroxy function protective grouping.

(57) Abrégé

Procédé de préparation de dérivés du taxane de formule générale (I) par estérification à une température comprise entre -10 et 60 °C d'un dérivé de la baccatine III ou de la désacétyl-10 baccatine III de formule générale (II) au moyen d'un acide de formule générale (III) suivie du remplacement des groupements protecteurs G_1, G_2 et R_2 du produit obtenu par des atomes d'hydrogène. Dans les formules (I), (II) ou (III): Ar représente un radical aryle; R représente hydrogène ou acétyle; R_1 représente benzoyle ou tert.butoxycarbonyle; G_1 représente un groupement protecteur de la fonction hydroxy, G_2 représente le radical acétyle ou un groupement protecteur de la fonction hydroxy et R_2 représente un groupement protecteur de la fonction hydroxy.

METHOD FOR PREPARING TAXANE DERIVATIVES

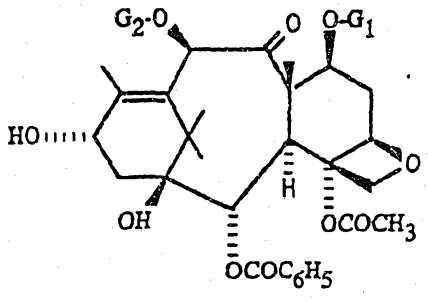
The present invention relates to a new method for preparing taxane derivatives of general formula:



(I)

in which Ar represents an aryl radical, R represents a hydrogen atom or the acetyl radical and R_1 represents a benzoyl or tert-butoxycarbonyl radical, which derivatives display noteworthy antitumour properties.

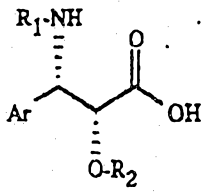
It is known, from American Patents US 4 924 011 and US 4 924 012, to prepare taxane derivatives of general formula (I) by esterification of a derivative of baccatin III or of 10-deacetyl baccatin III of general formula:



(II)

in which G_1 represents a protecting group for the hydroxyl function such as the 2,2,2-trichloroethoxycarbonyl radical or a

trialkylsilyl radical in which each alkyl part contains 1 to 4 carbon atoms and G_2 represents the acetyl radical or a protecting group for the hydroxyl function such as the 2,2,2-trichloroethoxycarbonyl radical, using an acid of general formula:



(III)

in which Ar and R_1 are defined as above and R_2 represents a protecting group for the hydroxyl function such as a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (β-trimethylsilylethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxymethyl or 2,2,2-trichloroethoxycarbonyl radical, followed by replacement, by hydrogen atoms, of the protecting groups G_1, G_2 and R_2 of the product obtained.

The esterification is carried out in the presence of a condensing agent such as a carbodiimide, for instance dicyclohexylcarbodiimide, or a reactive carbonate, for instance 2-dipyridyl carbonate, and an activating agent such as a dialkylaminopyridine, for instance 4-dimethylaminopyridine, working in an organic aromatic solvent such as benzene, toluene, xylenes, ethylbenzene, isopropylbenzene or chlorobenzene at a temperature between 60 and 90°C.

Replacement of the protecting groups by

hydrogen atoms is carried out using zinc in acetic acid or by hydrolysis in an acidic medium.

It has now been found, and this forms the subject of the present invention, that the esterification of the alcohol of general formula (II) using the acid of general formula (III) may be performed at a temperature between -10 and 60°C (60°C not inc), preferably between 20 and 35°C, working in an organic solvent chosen from ethers such as tetrahydrofuran, diisopropyl ether, methyl tert-butyl ether or dioxane, ketones such as methyl isobutyl ketone, nitriles such as acetonitrile, esters such as ethyl acetate, isopropyl acetate or n-butyl acetate, aliphatic hydrocarbons such as pentane, hexane or heptane, chlorinated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane and aromatic hydrocarbons such as benzene, toluene or xylenes. Esters and aromatic hydrocarbons are very particularly advantageous.

The esterification is ~~generally~~ carried out in the presence of a condensing agent such as a carbodiimide, for instance dicyclohexylcarbodiimide, and an activating agent such as an aminopyridine, for instance 4-dimethylaminopyridine or 4-pyrrolidinopyridine.

It is advantageous to perform the esterification using an excess of acid of general formula (III) relative to the alcohol of general

formula (II), but the reaction may also be carried out using a stoichiometric amount of acid of general formula (III) and of alcohol of general formula (II). The condensing agent is generally used in a stoichiometric amount relative to the acid of general formula (III) and the activating agent represents a stoichiometric amount or less relative to the alcohol of general formula (II).

Since the method according to the invention is implemented at a temperature below that of the methods known previously, it allows higher yields of ester to be obtained due to the greater stability of the acid of general formula (III) in the reaction mixture and to the decrease in side reactions.

The examples which follow illustrate the present invention.

EXAMPLE 1

1.0045 g of 96 % 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxene (equivalent to 1.08 mmol), 1.1545 g of 100 % (2R,3S)-2-(1-ethoxyethoxy)-3-tert-butoxycarbonylamino-3-phenylpropionic acid (equivalent to 3.3 mmol), 0.6669 g of 99 % dicyclohexylcarbodiimide (equivalent to 3.2 mmol), 0.0742 g of 98 % 4-pyrrolidinopyridine (equivalent to 0.49 mmol) and 6 cm^3 of anhydrous toluene are introduced into a 20 cm^3 conical flask. The mixture is stirred vigorously for 72 hours while

maintaining the temperature at -10°C.

Assay of the reaction medium by high performance liquid chromatography shows that the medium contains 1.1370 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 0.91 mmol) and 0.1705 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2S,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 0.14 mmol).

The overall yield is 97 % with a degree of epimerization of 12.7 %.

EXAMPLE 2

50.011 g of 96 % 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxene (equivalent to 53.6 mmol), 56.81 g of 100 % (2R,3S)-2-(1-ethoxyethoxy)-3-tert-butoxycarbonylamino-3-phenylpropionic acid (equivalent to 160.7 mmol), 33.54 g of 99 % dicyclohexylcarbodiimide (equivalent to 160.9 mmol), 1.79 g of 98 % 4-pyrrolidinopyridine (equivalent to 11.8 mmol) and 299 cm^3 of anhydrous toluene are introduced into a 500 cm^3 jacketed glass reactor fitted with a nitrogen inlet, a temperature probe and a condenser. The mixture is stirred

vigorously for 12 hours while maintained at a temperature in the region of 25°C.

Assay of the reaction medium by high performance liquid chromatography shows that the medium contains 57.00 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 45.7 mmol) and 8.52 g of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2S,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 6.8 mmol).

The overall yield is 98 % with a degree of epimerization of 13.0 %.

EXAMPLES 3 to 19

250 mg of 96 % 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxene (equivalent to 0.27 mmol), 284 mg of 100 % (2R,3S)-2-(1-ethoxyethoxy)-3-tert-butoxycarbonylamino-3-phenylpropionic acid (equivalent to 0.80 mmol), 190 mg of 99 % dicyclohexylcarbodiimide (equivalent to 0.91 mmol), 9 mg of 98 % 4-dimethylaminopyridine (equivalent to 0.07 mmol) and 3 cm^3 of solvent are introduced into a 10 cm^3 conical flask. The reaction medium is stirred vigorously while maintained at a

temperature in the region of 30°C.

After stirring for 16 to 24 hours, assay of the reaction medium by high performance liquid chromatography allow the yield of esterification and the degree of epimerization to be calculated.

The results which are obtained with various solvents are collated in the following table.

Example	Solvent	Duration of the reaction (hours)	Yield of esterification	Degree of epimerization (%)
3	Tetrahydrofuran	17.0	24.5	7.3
4	Diisopropyl ether	23.5	87.4	14.2
5	Methyl tert-butyl ether	17.0	87.3	12.5
6	Dioxane	16.2	19.6	10.8
7	Acetonitrile	23.5	58.8	46.9
8	Benzene	16.2	96.0	12.6
9	Toluene	23.5	98.0	13.9
10	meta-Xylene	17.0	97.8	14.4
11	Anisole	16.2	94.1	19.2
12	Chlorobenzene	16.2	96.0	17.5
13	Cyclohexane	17.0	61.7	15.8
14	Pentane	16.2	51.0	31.2
15	n-Hexane	23.5	42.1	29.7
16	Heptane	16.2	37.2	21.5
17	1,2-Dichloroethane	17.0	92.8	28.9
18	Dichloromethane	17.0	83.7	26.6
19	Methyl isobutyl ketone	16.2	58.8	17.4
20	Ethyl acetate	8	75	12.7

EXAMPLE 21

503.6 mg of 96 % 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyl-11-taxene (equivalent to 0.54 mmol), 579.0 mg of 99 % (2R,3S)-2-(1-ethoxyethoxy)-3-tert-butoxycarbonylamino-3-phenylpropionic acid (equivalent to 1.62 mmol),

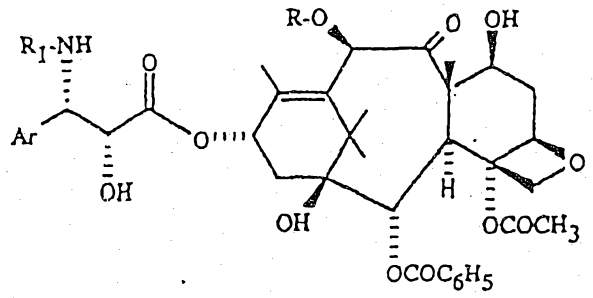
357.8 mg of 99 % dicyclohexylcarbodiimide (equivalent to 1.72 mmol), 45.5 mg of 98 % 4-pyrrolidinopyridine (equivalent to 0.30 mmol) and 3 cm^3 of anhydrous toluene are loaded into a 10 cm^3 conical flask. The mixture is stirred vigorously for 5 hours 20 minutes while maintaining the temperature at 45°C.

Assay of the reaction medium by high performance liquid chromatography shows that the medium contains 559.5 mg of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 0.45 mmol) and 90.8 mg of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy)carbonyloxy-11-taxen-13α-yl (2S,3S)-3-tert-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (equivalent to 0.07 mmol).

The overall yield is 97 % with a degree of epimerization of 13.9 %.

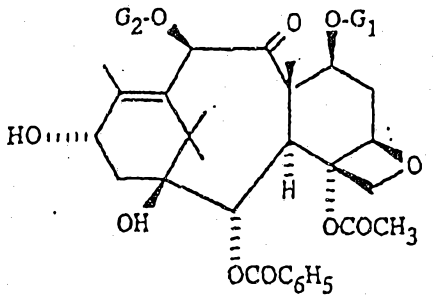
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Method for preparing taxane derivatives of general formula:

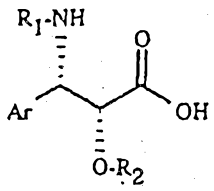


(I)

in which Ar represents an aryl radical, R represents a hydrogen atom or an acetyl radical and R_1 represents a benzoyl or tert-butoxycarbonyl radical, which comprises esterifying in the presence of a condensing agent and an activating agent a derivative of baccatin III or of 10-deacetyl baccatin III of general formula:



in which G_1 represents a protecting group for the hydroxyl function and G_2 represents an acetyl radical or a protecting group for the hydroxyl function using an acid of general formula:



in which Ar and R_1 are defined as above and R_2 represents a protecting group for the hydroxyl function, followed by replacement, by hydrogen atoms, of the protecting groups G_1, G_2 and R_2 of the product obtained, characterized in that the esterification is carried out at a temperature between -10 and 60°C (60°C not included).

2. Method according to claim 1, characterized in that the esterification is carried out in an organic solvent chosen from ethers, ketones, esters, nitriles, aliphatic hydrocarbons, chlorinated aliphatic hydrocarbons and aromatic hydrocarbons.

3. Method according to claim 2, characterized in that the solvent is chosen from esters and aromatic hydrocarbons.

4. Method according to any one of claims 1 to 3, characterized in that the condensing agent is a carbodiimide.

5. Method according to any one of claims 1 to 3, characterized in that the activating agent is an aminopyridine.

6. Method according to claim 4, characterized in that the carbodiimide is

dicyclohexylcarbodiimide.

7. Method according to claim 5, characterized in that the aminopyridine is 4-dimethylaminopyridine or 4-pyrrolidinopyridine.

8. Method according to claim 1 substantially as described in the foregoing Examples.

9. A taxane derivative of general formula (I) as defined in claim 1 when prepared by a method claimed in any one of claims 1 to 8.

DATED this TWENTY-FIRST day of JANUARY 1997
Rhone-Poulenc Rorer S.A.
By DAVIES COLLISON CAVE
Patent Attorneys for the applicant(s)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 93/00110

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.5 C07D305/14

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.5 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 336 840 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 11 October 1989 see page 2, line 54 - page 3, line 33 & US,A,4 924 011 cited in the application	1-8
X	EP,A,0 336 841 (RHONE-POULENC SANTE) 11 October 1989 see page 2, line 43 - page 3, line 27 & US,A,4 924 012 cited in the application	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 May 1993 (07.05.93)	14 May 1993 (14.05.93)
Name and mailing address of the ISA/ European Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

FR 9300110
SA 70260

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0336840	11-10-89	FR-A-	2629818	13-10-89
		AU-A-	3251989	12-10-89
		JP-A-	1305076	08-12-89
		US-A-	4924011	08-05-90
EP-A-0336841	11-10-89	FR-A-	2629819	13-10-89
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		JP-A-	1305077	08-12-89
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