682011

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Rhone-Poulenc Rorer S.A.**, the applicant/Nominated Person in respect of Application No. 51149/93 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventors 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.

DATED this NINTH day of MAY 1995

....

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

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METHOD FOR THE STEREOSELECTIVE PREPARATION OF A DERIVATIVE OF BETA -PHENYLISOSERINE AND ITS USE IN THE PREPARATION OF TAXANE DERIVATIVES

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(56) Prior Art Documents
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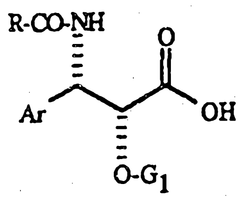
AU 79722/91
EP 414610

(57) Claim

1. Process for the stereoselective preparation of a β-phenylisoserine derivative of general formula:



where appropriate in the form of a salt or ester, in which

Ar represents an aryl radical,

R represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and

.../2

alkoxy radicals containing 1 to 4 carbon atoms, or a radical R_1-O in which R_1 represents:

- an unbranched or branched 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 11 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from halogen atoms and hydroxyl radicals, alkyloxy 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, cyano or carboxyl radicals or alkyloxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,
- or a phenyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkyloxy radicals containing 1 to 4 carbon atoms,
- or a saturated or unsaturated 4- or 6-membered nitrogenous heterocyclic radical optionally substituted

.../3

with one or more alkyl radicals containing 1 to 4 carbon atoms,

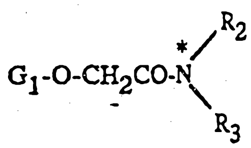
on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals can be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, and

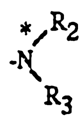
G_1 represents a group protecting the hydroxyl function, chosen from methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, tetrahydrofuryl, tetrahydropyranyl and β-(trimethylsilyl)ethoxymethyl radicals, trialkylsilyl radicals in which the alkyl radicals contain 1 to 4 carbon atoms, or $-CH_2-Ph$ in which Ph represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms,

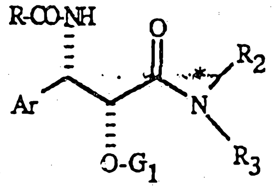
characterized in that an N-carbonylarylimine of general formula:

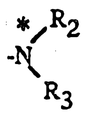
Ar-CH=N-CO-R

in which Ar and R are defined as above, is reacted with a previously anionized optically active amide of a protected hydroxyacetic acid, of general formula:



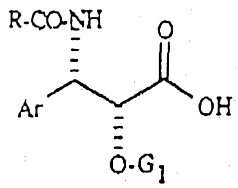
in which G_1 is defined as above and  represents the residue of an optically active organic base, the product obtained, of general formula:



in which R, Ar, G_1 and 

are defined as above, is then hydrolysed, and the product obtained is isolated.

17. The β-phenylisoserine derivatives of general formula:



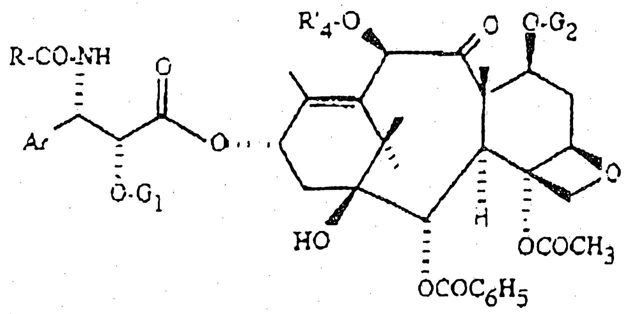
in the form of salts or esters, in which R and Ar are defined as in one of claims 1 to 3 and G_1 represents a $-CH_2$-Ph radical in which Ph represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms.

18. Use of an N-carbonylarylimine of general formula:

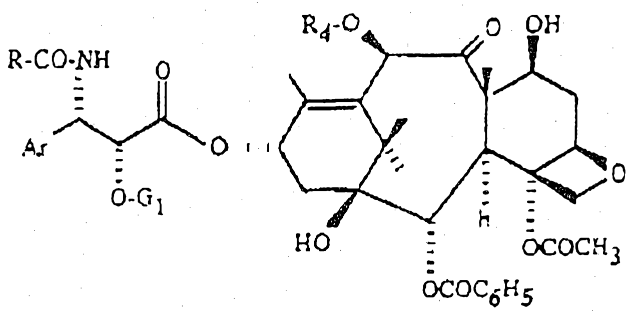
Ar-CH=N-CO-R

in which Ar is as defined in any one of claims 1 to 3 and R represents a t-butoxy radical in a process as claimed in any one of claims 1 to 16 for preparing a ß-phenylisoserine derivative.

19. Use of a product according to claim 17, for the preparation of a taxane derivative of general formula:



in which Ar, R and G_1 are defined as in claim 17 and G_2 and R'_4 are defined as above, the protective groups G_2 and, where appropriate, R'_4 are replaced by hydrogen atoms to obtain a product of general formula:



the protective group G_1 of which is replaced by a hydrogen atom, and the product obtained is isolated.

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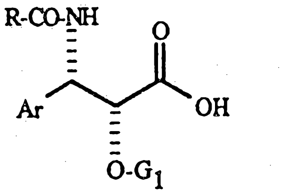
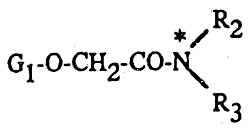
(54) Title: METHOD FOR THE STEREOSELECTIVE PREPARATION OF A DERIVATIVE OF β-PHENYLISOSERINE AND ITS USE IN THE PREPARATION OF TAXANE DERIVATIVES

(54) Titre: PROCEDE DE PREPARATION STEREOSELECTIVE D'UN DERIVE DE LA β-PHENYLISOSERINE ET SON UTILISATION POUR LA PREPARATION DE DERIVES DU TAXANE



(I)

Ar-CH=N-CO-R (II)



(III)

(57) Abstract

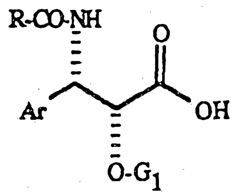
Method of stereoselective preparation of a derivative of β-phenylisoserine of formula (I) by the action of an N-carbonylbenzylimine of formula (II) on an optically active amide of a protected hydroxyacetic acid of formula (III), followed by hydrolysis of the product obtained. In formulae (I), (II) or (III), R is an optionally substituted phenyl radical or R_1-O, Ar is an optionally substituted aryl radical and G_1 is a hydroxy function protection grouping. The product of formula (I) is particularly useful in preparing taxol and Taxotere which have remarkable antitumor properties.

(57) Abrégé

Procédé de préparation stéréosélective d'un dérivé de la β-phénylisosérine de formule (I) par action d'une N-carbonylbenzylimine de formule (II) sur un amide optiquement actif d'un acide hydroxyacétique protégé de formule (III), suivie de l'hydrolyse du produit obtenu. Dans les formules (I), (II) ou (III), R représente un radical phényle éventuellement substitué ou R_1-O, Ar représente un radical aryle éventuellement substitué et G_1 représente un groupement protecteur de la fonction hydroxy. Le produit de formule (I) est particulièrement utile pour la préparation du taxol et du Taxotère qui présentent des propriétés antitumorales remarquables.

PROCESS FOR THE STEREOSELECTIVE PREPARATION OF A β-PHENYLISOSERINE DERIVATIVE AND ITS USE FOR THE PREPARATION OF TAXANE DERIVATIVES

The present invention relates to a process for the stereoselective preparation of a β-phenylisoserine derivative of general formula:



(I)

in which

Ar represents an aryl radical,

R represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms, or a radical R_1-O in which R_1 represents:

- an unbranched or branched 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 11 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from halogen atoms and hydroxyl radicals, alkyloxy 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, cyano or carboxyl radicals or alkyloxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- or a phenyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkyloxy radicals containing 1 to 4 carbon atoms,

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

on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals can be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, and

G_1 represents a group protecting the hydroxyl function, chosen from methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, tetrahydrofuranyl, tetrahydropyranyl and β-(trimethylsilyl)ethoxymethyl radicals, trialkylsilyl radicals in which the alkyl radicals contain 1 to 4 carbon atoms, or $-CH_2-Ph$ in which Ph represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms.

Preferably, Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen (fluorine, chlorine, bromine, iodine) atoms 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 alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 3 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

More especially, Ar represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms and alkyl, alkoxy, amino, alkylamino, dialkylamino, acylamino, alkoxycarbonylamino and trifluoromethyl radicals.

Still more especially, Ar represents a phenyl radical optionally substituted with a chlorine or fluorine atom or with an alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino) or alkoxycarbonylamino (tert-butoxycarbonylamino) radical.

Of even more special importance are the products of general formula (I) in which Ar represents a phenyl radical, R represents a phenyl or tert-butoxy radical and G_1 represents a benzyl or p-methoxybenzyl radical.

The products of general formula (I), and especially those for which G_1 represents $-CH_2-Ph$, which are new products constituting another subject of the present invention, are especially useful for preparing taxol or Taxotere and their analogues, by condensation with a baccatin III or 10-deacetylbaccatin III derivative in which the hydroxyl functions are suitably protected, working under the conditions described, for example, in European Patents EP 0,336,840 or EP 0,336,841.

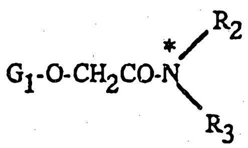
It is known to prepare analogues of the product of general formula (I) from a β-phenylglycidic acid by working, for example, under the conditions described in European Patent EP 0,414,610.

It has now been found that the products of general formula (I) may be obtained directly, with very good enantio- and diastereoselectivity, by carrying out a process which requires far fewer steps to be carried out than according to the previously known processes.

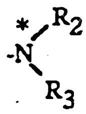
According to the present invention, the products of general formula (I) may be obtained by the action of an N-carbonylarylimine of general formula:

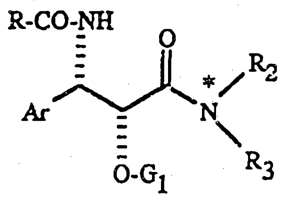
Ar-CH=N-CO-R (II)

in which Ar and R are defined as above, on the anion of an optically active amide of a protected hydroxyacetic acid, of general formula:

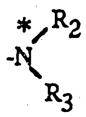


(III)

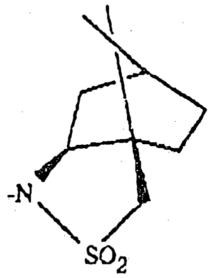
in which G_1 is defined as above and  represents the residue of an optically active organic base, followed by hydrolysis of the product thereby obtained, of general formula:



(IV)

in which R, Ar, G_1 and  are defined as above.

It is especially advantageous to use an amide of general formula (III) in which $-N\langle^{R_2}_{R_3}$ represents an L(+)-2,10-camphorsultam residue of formula:



(V)

The process according to the invention is generally carried out by reacting the N-carbonyl-arylimine of general formula (II), optionally prepared in situ, with the previously anionized amide of the protected hydroxyacetic acid. The anionization is generally effected by means of an alkali metal amide. Amongst suitable amides, there may be mentioned sodium bis(trimethylsilyl)amide (NHMDS), lithium bis(trimethylsilyl)amide (LHMDS) or potassium bis(trimethylsilyl)amide (KHMDS), lithium diisopropylamide (LDA), lithium diethylamide (LDEA), lithium dicyclohexylamide (LDCHA), $(CH_3)_3SiN(R')Li$ (R' = alkyl, cycloalkyl, aryl) and tBuLi. Of very special importance is lithium bis(trimethylsilyl)amide which enables a high yield and excellent stereoselectivity to be obtained.

Typically, the anionisation is carried out at a temperature below -30°C. Generally, the anionization is performed in an inert organic solvent, for instance an ether such as tetrahydrofuran, at a temperature below 0°C and preferably in the region of -78°C.

The action of the product of the general formula (II) on the previously anionized product of general formula (III) is generally performed in the same solvent and at the same temperature.

The product of general formula (IV) is hydrolysed to the product of general formula (I) by means of an inorganic base such as sodium hydroxide, potassium hydroxide or lithium hydroxide in an aqueous or aqueous-organic medium. It is especially advantageous to work in a tetrahydrofuran/water mixture in the presence of hydrogen peroxide. The reaction temperature is generally between -10 and 20°C, and preferably in the region of 0°C.

The N-carbonylarylimine of general formula (II) in which Ar is defined as above and R represents a t-butoxy radical is a new product which constitutes another subject of the present invention.

The N-carbonylarylimine of general formula (II) may be obtained by the action of an optionally substituted benzoyl halide or a reactive derivative of general formula:

$$R_1\text{-O-CO-X} \qquad (VI)$$

in which R_1 is defined as above and X represents a halogen (fluorine, chlorine) atom or a residue $\text{-O-}R_1$ or $\text{-O-CO-O}R_1$, on a product of general formula:

$$\text{Ar-CH=N-Z} \qquad (VII)$$

in which Ar is defined as above and Z represents a reactive group, for instance a trialkylsilyl radical such as a trimethylsilyl radical.

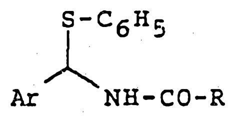
Generally, the action of the optionally substituted benzoyl halide or the product of general formula (VI) on the product of general formula (VII) is performed by heating in an organic solvent, for instance an ester such as ethyl acetate or a halogenated aliphatic hydrocarbon such as dichloromethane or chloroform or an aromatic hydrocarbon such as toluene or benzene.

The imine of general formula (VII) may be obtained from the aldehyde of general formula:

Ar-CHO (VIII)

in which Ar is defined as above, according to known methods. For example, the product of general formula (VII) in which Z represents a trimethylsilyl radical may be obtained according to D.J. Hart et al., J. Org. Chem., 48, 289 (1983), by the action of lithium bis(trimethyldisilyl)amide (LHMDS), optionally prepared in situ by the action of butyllithium on bis(trimethylsilylamine), on the corresponding aldehyde of general formula (VIII).

The N-carbonylarylimine of general formula (II) may also be prepared in situ by the action of a strong base, for instance an amide such as lithium bis(trimethylsilyl)amide, on a thioether of general formula:



(IX)

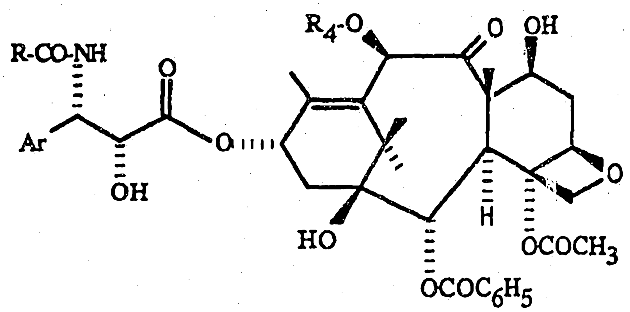
in which Ar and R are defined as above.

The optically active amide of general formula (III) may be obtained by the action of an activated derivative of a protected hydroxyacetic acid of general formula:

$$G_1\text{-O-CH}_2\text{-COOH} \qquad (X)$$

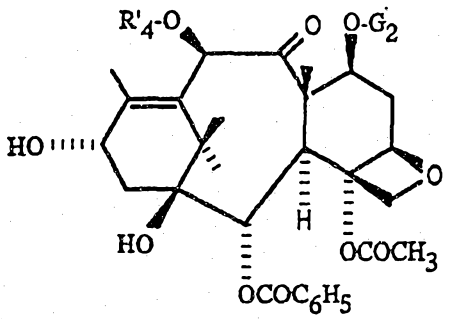
in which G_1 is defined as above, such as the halide or anhydride, on the optionally anionized corresponding chiral base.

The product of general formula (I) may be used to prepare the therapeutically active taxane derivatives of general formula:



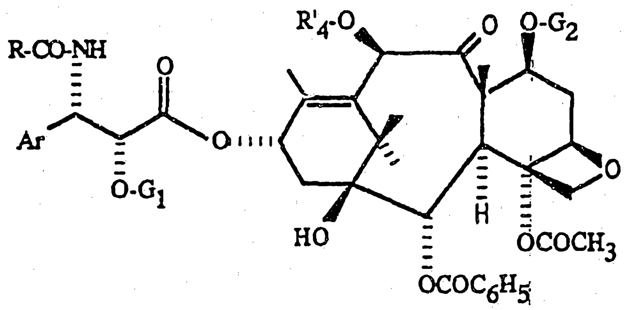
(XI)

in which Ar and R are defined as above and R_4 represents a hydrogen atom or an acetyl radical, in a process which consists in reacting a product of general formula (I) with a baccatin III or 10-deacetylbaccatin III derivative of general formula:



(XII)

in which G_2 represents a group protecting the hydroxyl function, such as a 2,2,2-trichloroethoxycarbonyl or trialkylsilyl radical, and R'_4 represents an acetyl radical or a group protecting the hydroxyl function, such as a 2,2,2-trichloroethoxycarbonyl radical, to obtain a product of general formula:



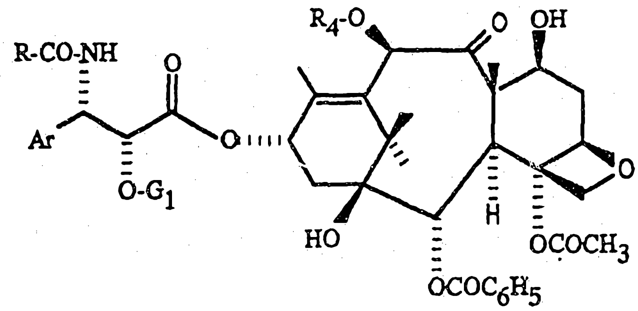
(XIII)

in which R, Ar, G_1, G_2 and R'_4 are defined as above, the protective groups G_1, G_2 and, where appropriate, R'_4 of which are replaced by hydrogen atoms, simultaneously or successively.

Generally, the esterification of a product of general formula (XII) with a product of general formula (I) is performed in the presence of a condensing agent, for instance a carbodiimide such as dicyclohexylcarbodiimide or a reactive carbonate such as 2-pyridyl carbonate, and an activating agent, for instance an aminopyridine such as 4-(dimethylamino)-pyridine or 4-pyrrolidinopyridine, working in an organic solvent such as an aromatic hydrocarbon (benzene, toluene, xylene, ethylbenzene, isopropylbenzene, chlorobenzene), an ether (tetrahydrofuran), a nitrile (acetonitrile) or an ester (ethyl acetate), at a temperature of between 0 and 90°C.

When G_1 represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, 2,2,2-trichloroethoxy-methyl, tetrahydrofuryl, tetrahydropyranyl or β-trimethylsilylethoxymethyl radical or a trialkylsilyl radical in which the alkyl radicals contain 1 to 4 carbon atoms, the replacement of the protective groups G_1, G_2 and, where appropriate, R'_4 of the product of general formula (XIII) is performed either with zinc, optionally in combination with copper, in the presence of acetic acid or by means of an inorganic or organic acid such as hydrochloric acid or acetic acid optionally dissolved in an aliphatic alcohol containing 1 to 3 carbon atoms, in the presence of zinc, optionally in combination with copper, when one of the protective groups represents a 2,2,2-trichloroethoxycarbonyl radical, or by treatment with an inorganic or organic acid such as hydrochloric acid or acetic acid optionally dissolved in an aliphatic alcohol containing 1 to 3 carbon atoms, when one of the protective groups represents a silyl radical.

When G_1 represents a $-CH_2-Ph$ or, where appropriate, a benzyloxymethyl radical, the replacement of the protective groups G_2 and, where appropriate, R'_4 by hydrogen atoms is performed first, under the conditions described above, to obtain the product of general formula:



(XIV)

in which R, Ar and R_4 are defined as above, the $Ph-CH_2-$ or, where appropriate, the benzyloxymethyl group of which is replaced by a hydrogen atom to obtain the product of general formula (XI).

The replacement of the $Ph-CH_2-$ or, where appropriate, the benzyloxymethyl group of the product of general formula (XIV) by a hydrogen atom is generally performed by hydrogenolysis by means of hydrogen in the presence of a catalyst such as palladium black, working in an organic solvent such as acetic acid at a temperature of between 0 and 60°C, and preferably in the region of 40°C. It can be advantageous to work under pressure and optionally in the presence of a catalytic amount of an acid such as perchloric acid. The same replacement is also performed by the action of dichlorodicyanobenzoquinone (DDQ) in an organic solvent such as dichloromethane or acetonitrile.

The taxane derivatives of general formula (XI) thereby obtained may be optionally purified by application of the usual techniques.

The examples which follow illustrate the present invention.

EXAMPLE 1

287 mg (0.79 mmol) of L-N-(benzyloxyacetyl)-2,10-camphorsultam and 3 cm^3 of anhydrous tetrahydrofuran are introduced under an argon atmosphere into a 10-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. The solution is cooled to -78°C, and 0.8 cm^3 (0.8 mmol) of a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran is then added dropwise. The mixture is left to react for 1 hour at -78°C, and 248 mg (1.21 mmol) of N-t-butoxycarbonylbenzylimine dissolved in 1.7 cm^3 of anhydrous tetrahydrofuran are then added. After 15 minutes of reaction at -78°C, the reaction mixture is hydrolysed by adding saturated aqueous ammonium chloride solution. It is extracted twice with dichloromethane. The combined organic phases are washed twice with water, then once with saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulphate. After filtration and removal of the solvents under reduced pressure, a residue (578 mg) is obtained, which is purified by chromatography on silica

gel, eluting with a hexane/ethyl acetate mixture (85:15 by volume). 294 mg (0.52 mmol) of syn-L(+)-N-(2-benzyloxy-3-t-butoxycarbonylamino-3-phenylpropionyl)-2,10-camphorsultam, the characteristics of which are as follows, are thereby obtained in a 66 % yield.

- melting point: 79°C, then 130°C (dichloromethane/hexane)
- optical rotation: $[\alpha]^{25}_D$ = + 53° (c = 0.98; chloroform)
- infrared spectrum (film): main characteristic absorption bands at 3450, 3050, 3020, 2975, 1720, 1500, 1460, 1420, 1395, 1370, 1340, 1280, 1240, 1220, 1170, 1140, 1100, 1070, 1020, 860, 810, 760, 750 and 700 cm^{-1}
- proton NMR spectrum (300 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz):

0.99 (s, 3H); 1.1-1.6 (m, 2H); 1.28 (s, 3H); 1.39 (s, 9H); 1.83-2.25 (m, 5H); 3.51 (AB_q, J_{AB} = 13.7, $\delta_A-\delta_B$ = 21.4, 2H); 3.94-4.03 (m, 1H); 4.36 (AB_q, J_{AB} = 11.4, $\delta_A-\delta_B$ = 120, 2H); 4.86 (broad s, 1H); 5.33 (d, J = 9.8, 1H); 5.60 (d, J = 9.8, 1H); 6.9-7.05 (m, 2H); 7.14-7.4 (m, 8H).

- ^{13}C NMR spectrum (75.47 MHz; $CDCl_3$):

19.97 (CH_3); 20.64 (CH_3); 26.59 (CH_2); 28.24 (CH_3); 32.81 (CH_2); 37.53 (CH_2); 44.49 (CH); 47.92 (C); 48.89 (C); 53.11 (CH_2); 55.70 (CH); 65.07 (CH); 72.47 (CH_2); 79.32 (C); 81.29 (CH); 126.78 (CH); 127.17 (CH); 127.65 (CH); 127.84 (CH); 128.09 (CH); 136.72 (C); 139.54 (C); 154.95 (C); 169.90 (C).

66 mg (0.116 mmol) of the product obtained above and 1 cm^3 of a tetrahydrofuran/water mixture (4:1 by volume) are introduced under an argon atmosphere into a 10 cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. The mixture is cooled to 0°C, and 95 µl (0.93 mmol) of hydrogen peroxide containing 30 % by volume and 20 mg (0.48 mmol) of hydrated lithium hydroxide ($LiOH.H_2O$) are then added. The mixture is left to react for 1 hour at 0°C and then stirred for 15 hours at 20°C. A solution of 117 mg (0.93 mmol) of sodium sulphite in 0.7 cm^3 of water is then added. After evaporation of the tetrahydrofuran, water is added, and the basic aqueous solution obtained is then extracted 3 times with dichloromethane. The basic aqueous phase is acidified to pH 1-2 by adding 2M aqueous hydrochloric acid solution, and is extracted 6 times with ethyl acetate. The combined organic phases are washed with saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulphate. After filtration and removal of the solvent under reduced pressure, 30 mg (0.081 mmol) of (2R,3S)-2-benzyloxy-3-t-butoxy-carbonylamino-3-phenylpropionic acid, the characteristics of which are as follows, are obtained in a 70 % yield:

- infrared spectrum (film): characteristic absorption bands at 3700-2300, 3450, 3300, 3075, 3050, 3025, 2975, 2925, 1720, 1660, 1510, 1500, 1450, 1390, 1370, 1250, 1165, 1110, 1020, 860, 740 and 695 cm^{-1}

- proton NMR spectrum (200 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz):

1.42 (s, 9H); 4.20 (broad s, 1H); 4.52 (AB_q, J_{AB} = 11.6, $\delta_A-\delta_B$ = 65, 2H); 5.30 (distorted d, J = 9.9, 1H); 5.78 (distorted d, J = 9.4, 1H); 6.2 (broad s, 1H); 7.0-7.06 (m, 2H); 7.06-7.44 (m, 8H)

- ^{13}C NMR spectrum (50.3 MHz, $CDCl_3$):

28.24 (CH_3); 55.67 (CH); 72.90 (CH_2); 79.84 (CH); 80.49 (C); 126.60 (CH); 127.50 (CH); 127.95 (CH); 128.30 (CH); 136.40 (C); 139.36 (C); 155.66 (C); 173.08 (C).

- elemental analysis ($C_{21}H_{25}O_5N$)

calculated	C % 67.91	H % 6.78	N % 3.77
found	67.67	6.68	3.87

N-(t-Butoxycarbonyl)benzylimine may be prepared in the following manner:

20 cm^3 (95 mmol) of freshly distilled bis(trimethylsilyl)amine are introduced under an argon atmosphere into a 100-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system, and then cooled to 0°C. 34 cm^3 (85 mmol) of a 2.5M solution of n-butyllithium in hexane are then added dropwise. The temperature is allowed to rise to a value in the region of 20°C and the mixture is then left to react for 10 minutes. It is cooled to 0°C, and 8.63 cm^3 (85 mmol) of freshly distilled benzaldehyde are then added. The mixture is left to react at 0°C for 3 hours 30 minutes. After removal of the solvent under reduced pressure,

the residue is distilled under reduced pressure. 13.8 g (78 mmol) of N-(trimethylsilyl)benzylimine, the characteristics of which are as follows, are thereby obtained in a 92 % yield:

- infrared spectrum (film): main characteristic absorption bands at 3050, 3020, 2950, 2900, 2800, 2700, 1650, 1600, 1580, 1450, 1300, 1250, 1210, 1160, 1070, 1020, 970, 860, 840, 750 and 690 cm^{-1}
- proton NMR spectrum (200 MHz; $CDCl_3$): 0.3 (s, 9H); 7.42-7.56 (m, 3H); 7.77-7.90 (m, 2H); 9.02 (s, 1H).

2.92 g (16.5 mmol) of the imine obtained above and then 50 cm^3 of anhydrous chloroform are introduced under an argon atmosphere into a 100-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. The mixture is cooled to 0°C, and 6.93 g (31.8 mmol) of pure di-t-butyl dicarbonate are then added dropwise. The reaction mixture is heated to reflux for 12 hours.

After removal of the chloroform under reduced pressure, the residue is distilled under reduced pressure (1.3 Pa) at 103-105°C. 1.91 g (9.3 mmol) of N-(t-butoxycarbonyl)benzylimine, the characteristics of which are as follows, are thereby obtained in a 56 % yield:

- infrared spectrum (film): 3050, 2970, 2925, 1730, 1650, 1605, 1590, 1485, 1460, 1320, 1275, 1260, 1220, 1155, 1000, 980, 885, 850, 755, 690 cm^{-1}
- proton NMR spectrum (200 MHz, $CDCl_3$): 1.61 (s, 9H);

7.44-7.60 (m, 3H);

7.9-8.0 (m, 2H); 8.9 (s, 1H).

L-N-(Benzyloxyacetyl)-2,10-camphorsultam may be prepared in the following manner:

181 mg (0.84 mmol) of L(+)-10,2-bornanesultam dissolved in 2 cm^3 of anhydrous toluene are introduced under an argon atmosphere into a 10-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. The mixture is cooled to 0°C, and 50 mg (1.25 mmol) of 60 % sodium hydride dispersed in mineral oil are then added. The mixture is left to react to 30 minutes at 0°C, and 0.17 cm^3 (1.08 mmol) of benzyloxyacetyl chloride is then added. The temperature is allowed to rise to 20°C and the mixture is then left to react for 2 hours. The reaction mixture is diluted by adding dichloromethane, and water is then added slowly. The organic phase, separated after settling has taken place, is washed with water and then with saturated aqueous sodium chloride solution and finally dried over anhydrous magnesium sulphate. After filtration and removal of the solvents under reduced pressure, 511 mg of an oily residue are obtained, which residue is purified by chromatography on a column of silica gel, eluting with a hexane/ethyl acetate mixture (80:20 by volume). 294 mg (0.81 mmol) of L-N-(benzyloxyacetyl)-2,10-camphorsultam, the characteristics of which are as follows, are thereby obtained in a 97 % yield:

- infrared spectrum (film): main characteristic absorption bands at 2980, 2970, 1710, 1460, 1420, 1395, 1340, 1270, 1245, 1225, 1170, 1140, 1115, 1065, 1040, 1030, 985, 950, 870, 800, 780, 750 and 700 cm^{-1}
- proton NMR spectrum (200 MHz; $CDCl_3$): 0.96 (s, 3H); 1.13 (s, 3H); 1.2-1.6 (m, 2H); 1.6-2.3 (m, 5H); 3.3-3.6 (m, 2H); 3.8-4.0 (m, 1H); 4.4-4.75 (m, 4H); 7.1-7.5 (m, 5H).

EXAMPLE 2

42 mg (0.115 mmol) of L-N-(benzyloxyacetyl)-2,10-camphorsultam and 0.4 cm^3 of anhydrous tetrahydrofuran are introduced under an argon atmosphere into a 5-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. The mixture is cooled to -78°C, and 115 µl (0.115 mmol) of a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran are then added. The mixture is left to react for 1 hour at -78°C, and 72 mg (0.23 mmol) of N-t-butoxycarbonyl-α-(phenylthio)benzylamine and 230 µl (0.23 mmol) of a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran are then added. The reaction mixture is left to react for 1 hour 30 minutes at -78°C, and is then hydrolysed by adding saturated aqueous ammonium chloride solution. The temperature is allowed to rise to 20°C and the mixture is then extracted 3 times with ether. The combined organic phases are washed twice with water and then once with saturated aqueous sodium chloride solution

and then dried over anhydrous magnesium sulphate. After filtration and removal of the solvents under reduced pressure, the residue obtained (114 mg) is purified by chromatography on a column of silica gel, eluting with a hexane/ethyl acetate mixture (85:15 by volume).

35 mg (0.062 mmol) of syn-L(+)-N-(2-benzyloxy-3-t-butoxycarbonylamino-3-phenylpropionyl)-2,10-camphorsultam, the characteristics of which are identical to those of the product obtained in Example 1, are thereby obtained in a 54 % yield.

EXAMPLE 3

94 mg (0.253 mmol) of (2R,3S)-2-benzyloxy-3-t-butoxycarbonylamino-3-phenylpropionic acid dissolved in 3.5 cm^3 of anhydrous toluene are introduced under an argon atmosphere into a 10-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. 52.3 mg (0.253 mmol) of distilled dicyclohexylcarbodiimide are then added. The mixture is left to react for 5 minutes at a temperature in the region of 20°C, and a mixture of 7.7 mg (0.063 mmol) of 4-(N,N-dimethylamino)pyridine and 56.3 mg (0.063 mmol) of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,13α-dihydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxene is then added all at once. The mixture is left to react for 20 hours at a temperature in the region of 20°C. The reaction mixture is diluted by adding 40 cm^3 of ethyl acetate. The organic phase is washed once with 5 cm^3 of distilled water, twice with 5 cm^3 of saturated

aqueous sodium hydrogen carbonate solution and then once with 5 cm^3 of saturated aqueous sodium chloride solution and is finally dried over anhydrous sodium sulphate. After filtration and removal of the solvents under reduced pressure, a residue (166 mg) is obtained, which is purified by chromatography on a column of silica gel, eluting with an ether/dichloromethane mixture (1:99 by volume). 73 mg (0.0585 mmol) of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-(benzyloxy)-propionate, the characteristics of which are as follows, are thereby obtained in a 93 % yield:

- optical rotation (repurified product) $[\alpha]^{25}_D = -32°$ (c = 0.86; chloroform)
- infrared spectrum (film): main characteristic absorption bands at 3450, 3050, 2970, 2920, 2900, 1760, 1740, 1720, 1600, 1580, 1490, 1450, 1375, 1242, 1175, 1165, 1100, 1060, 1000, 975, 960, 820, 770, 720 and 700 cm^{-1}
- proton NMR spectrum (200 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz):

1.21 (s, 3H); 1.30 (s, 3H); 1.35 (s, 9H); 1.8-2 (m, 1H); 1.86 (s, 3H); 2.01 (s, 3H); 2-2.2 (m, 2H); 2.26 (s, 3H); 2.57-2.68 (m, 1H); 3.91 (d, J = 7, 1H); 4.24 (s, 1H); 4.25 (AB_q, J_{AB} = 8.7, δ_A-δ_B = 43.8, 2H); 4.50 (AB_q, J_{AB} = 12, δ_A-δ_B = 109, 2H); 4.76 (AB_q, J_{AB} = 11.8, δ_A-δ_B = 91, 2H); 4.78 (AB_q, J_{AB} = 12, δ_A-δ_B = 7.6, 2H);

4.95 (distorted d, J = 10.5, 1H); 5.14-5.36 (m, 1H); 5.4-5.6 (m, 1H); 5.57 (q, J = 7.2 and 10.7, 1H); 5.71 (d, J = 7, 1H); 6.2-6.33 (m, 1H); 6.26 (s, 1H); 7-7.1 (m, 2H aromatic); 7.22-7.86 (m, 11H aromatic); 8.06-8.11 (m, 2H aromatic).

- elemental analysis ($C_{56}H_{61}O_{18}NCl_6$)

calculated	C % 53.86	H % 4.92	N % 1.12
found	53.75	5.15	1.32

58 mg (0.0465 mmol) of the ester obtained above dissolved in 3 cm³ of glacial acetic acid are introduced under an argon atmosphere into a 10-cm³ single-necked round-bottomed flask equipped with a magnetic stirrer system. 3 cm³ of methanol are then added, followed by 260 mg of zinc/copper system (prepared from 20 g of zinc and 3 g of copper sulphate monohydrate). The black heterogeneous medium is heated to 65°C for 30 minutes. After cooling to a temperature in the region of 20°C, the reaction mixture is diluted in 40 cm³ of ethyl acetate. It is filtered through Celite, and the solids are then washed 3 times with 20 cm³ of ethyl acetate. The solvents are removed under reduced pressure. The residue obtained is purified by preparative thin-layer chromatography on silica gel, eluting with a methanol/dichloromethane mixture (5:95 by volume). 38 mg of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-(benzyloxy)propionate, the characteristics of which are

as follows, are obtained in a 91 % yield:

- infrared spectrum (film): characteristic absorption bands at 3430, 3050, 2975, 2910, 2880, 1740, 1725, 1710, 1495, 1450, 1390, 1370, 1350, 1270, 1240, 1160, 1105, 1065 and 980 cm^{-1}

- proton NMR spectrum (200 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz):

1.14 (s, 3H); 1.26 (s, 3H); 1.33 (s, 9H); 1.75 (s, 3H); 1.91 (s, 3H); 1.8-2.3 (m, 3H); 2.24 (s, 3H); 2.46-2.73 (m, 1H); 3.91 (d, J = 7, 1H); 4.12-4.38 (m, 3H); 4.20 (s, 1H); 4.51 (AB_q, J_{AB} = 12, δ_A-δ_B = 71, 2H); 4.94 (d, J = 7.5, 1H); 5.21 (s, 1H); 5.13-5.29 (m, 1H); 5.44-5.6 (m, 1H); 5.69 (d, J = 7, 1H); 6.27 (distorted t, J = 7.3 and 8.8, 1H); 7-7.1 (m, 2H aromatic); 7.19-7.66 (m, 11H aromatic); 8.08-8.12 (m, 2H aromatic).

- elemental analysis ($C_{50}H_{59}O_{14}N$)

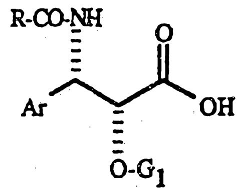
calculated	C % 66.87	H % 6.62	N % 1.56
found	66.65	6.72	1.73

14 mg (0.0156 mmol) of the product obtained above dissolved in 1.6 cm^3 of glacial acetic acid are introduced under an argon atmosphere into 5-cm^3 single-necked round-bottomed flask equipped with a magnetic stirrer system. 5 mg of palladium black are then added, and the mixture is thereafter placed under a hydrogen atmosphere. It is heated and stirred at 40°C and then left to react for 6 hours. After cooling to a temperature in the region of 20°C, the reaction mixture is diluted in 5 cm^3 of ethyl acetate. After filtration

through Celite, the solids are washed with 5 times 5 cm^3 of ethyl acetate. The combined organic phases are washed 3 times with 5 cm^3 of saturated aqueous sodium hydrogen carbonate solution, 3 times with 5 cm^3 of water and once with 5 cm^3 of saturated aqueous sodium chloride solution and are then dried over anhydrous sodium sulphate. After filtration and removal of the solvents under reduced pressure, the residue obtained (14 mg) is purified by preparative thin-layer chromatography on silica, eluting with a methanol/dichloromethane mixture (5:95 by volume). 8.5 mg (0.0105 mmol) of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (or Taxotere), the characteristics of which are identical to those described in the literature, are thereby obtained in a 67 % yield.

CLAIMS

1. Process for the stereoselective preparation of a β-phenylisoserine derivative of general formula:



where appropriate in the form of a salt or ester, in which

Ar represents an aryl radical,

R represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms, or a radical R_1-O in which R_1 represents:

- an unbranched or branched 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 11 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from halogen atoms and hydroxyl radicals, alkyloxy 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, cyano or carboxyl radicals or alkyloxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- or a phenyl radical optionally substituted with one or more atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkyloxy radicals containing 1 to 4 carbon atoms,

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

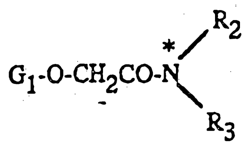
on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals can be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, and

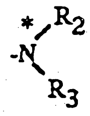
G_1 represents a group protecting the hydroxyl function, chosen from methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, tetrahydrofuryl, tetrahydropyranyl and β-(trimethylsilyl)ethoxymethyl radicals, trialkylsilyl radicals in which the alkyl radicals contain 1 to 4 carbon atoms, or $-CH_2-Ph$ in which Ph represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms,

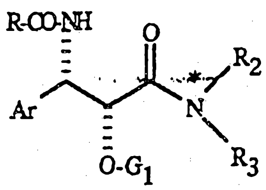
characterized in that an N-carbonylarylimine of general formula:

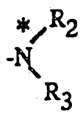
Ar-CH=N-CO-R

in which Ar and R are defined as above, is reacted with a previously anionized optically active amide of a protected hydroxyacetic acid, of general formula:



in which G_1 is defined as above and  represents the residue of an optically active organic base, the product obtained, of general formula:



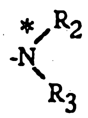
in which R, Ar, G_1 and  are defined as above, is then hydrolysed, and the product obtained is isolated.

2. Process according to claim 1, characterized

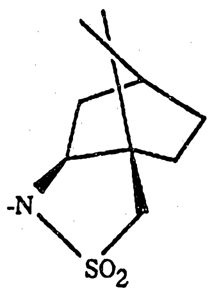
in that, R and G_1 being defined as in claim 1, Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from halogen (fluorine, chlorine, bromine, iodine) atoms and alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, 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 alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 3 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

3. Process according to claim 1, characterized in that, R and G_1 being defined as in claim 1, Ar represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms and alkyl, alkoxy, amino, alkylamino, dialkylamino, acylamino, alkoxycarbonylamino and trifluoromethyl radicals.

4. Process according to one of claims 1 to 3, characterized in that



represents an L(+)-2,10-camphorsultam residue of formula:



5. Process according to one of claims 1 to 4, characterized in that the anionization of the optically active amide of the protected hydroxyacetic acid is effected by means of an alkali metal amide chosen from sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, $(CH_3)_3SiN(R')Li$ with R' representing alkyl, cycloalkyl or aryl, or t-butyllithium.

6. Process according to claim 5, characterized in that the alkali metal amide is lithium bis(trimethylsilyl)amide.

7. Process according to one of claims 5 and 6, characterized in that the anionization is performed working in an inert organic solvent at a temperature below -30°C.

8. Process according to claim 7, characterized in that the solvent is chosen from ethers such as tetrahydrofuran.

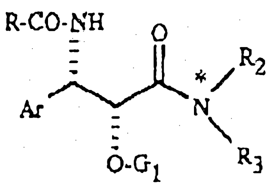
9. Process according to claim 7, characterized in that the anionization is performed at -78°C.

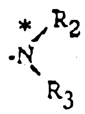
10. Process according to one of claims 1 to 9, characterized in that the action of the N-carbonylarylimine on the anion of the optically active amide of the protected hydroxyacetic acid is performed in an inert organic solvent at a temperature below 0°C.

11. Process according to claim 10, characterized in that the organic solvent is chosen from ethers.

12. Process according to claim 10, characterized in that the reaction is performed at -78°C.

13. Process according to one of claims 1 to 4, characterized in that the hydrolysis of the condensation product of general formula:



in which R, Ar, G_1 and  are defined as in claims 1 to 4, is performed by means of an inorganic base in an aqueous or aqueous-organic medium.

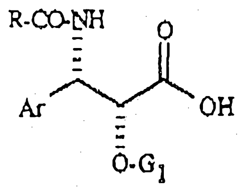
14. Process according to claim 13, characterized in that the hydrolysis is performed, in addition, in

in the presence of hydrogen peroxide.

15. Process according to one of claims 13 and 14, characterized in that the hydrolysis is performed at a temperature of between -10 and 20°C.

16. Process according to one of claims 13 to 15, characterized in that the base is lithium hydroxide.

17. The β-phenylisoserine derivatives of general formula:



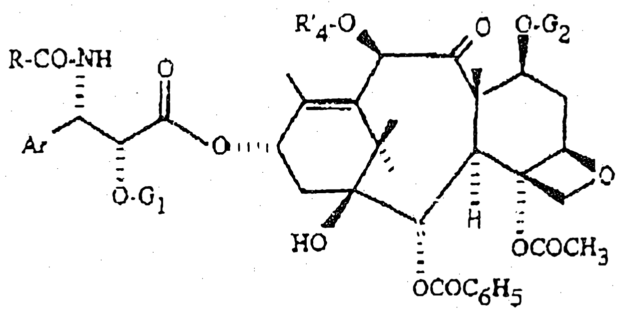
in the form of salts or esters, in which R and Ar are defined as in one of claims 1 to 3 and G_1 represents a $-CH_2-Ph$ radical in which Ph represents a phenyl radical optionally substituted with one or more identical or different atoms or radicals chosen from halogen atoms and alkyl radicals containing 1 to 4 carbon atoms or alkoxy radicals containing 1 to 4 carbon atoms.

18. Use of an N-carbonylarylimine of general formula:

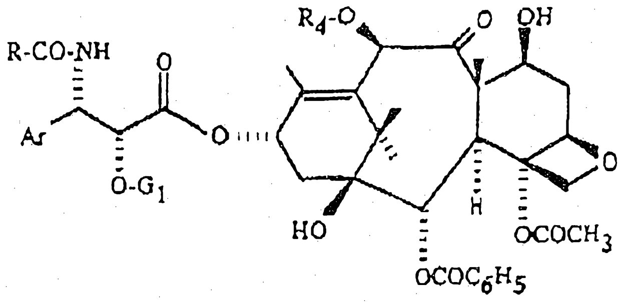
Ar-CH=N-CO-R

in which Ar is as defined in any one of claims 1 to 3 and R represents a t-butoxy radical in a process as claimed in any one of claims 1 to 16 for preparing a ß-phenylisoserine derivative.

19. Use of a product according to claim 17, for the preparation of a taxane derivative of general formula:



in which Ar, R and G_1 are defined as in claim 17 and G_2 and R'_4 are defined as above, the protective groups G_2 and, where appropriate, R'_4 are replaced by hydrogen atoms to obtain a product of general formula:



the protective group G_1 of which is replaced by a hydrogen atom, and the product obtained is isolated.

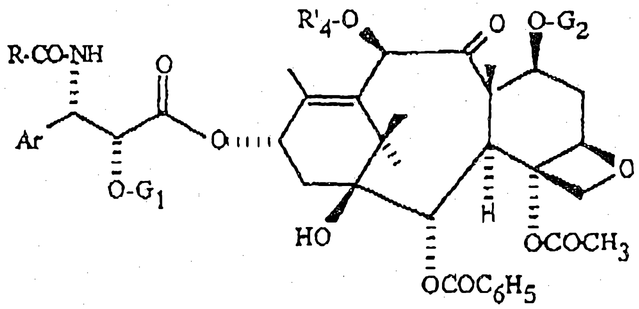
20. Use according to claim 19, characterized in that the esterification is performed in the presence of a condensing agent an activating agent, in an organic solvent chosen from aromatic hydrocarbons, ethers, nitriles and esters, at a temperature of between 0 and 90°C.

21. Use according to claim 19, characterized in that the replacement of the protective groups G_2 and, where appropriate, R'_4 by hydrogen atoms is performed with zinc, optionally in combination with copper, in

the presence of acetic acid or an inorganic or organic acid dissolved in an aliphatic alcohol when G_2 and/or R'_4 represent a 2,2,2-trichloroethoxycarbonyl radical, or by treatment in an acid medium when one of the protective groups represents a silyl radical.

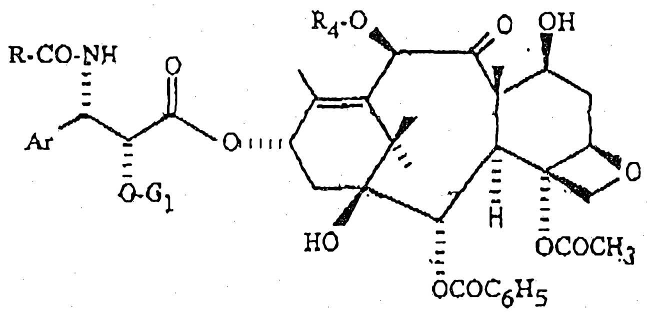
22. Use according to claim 19, characterized in that the replacement of the protective group G_1 by a hydrogen atom is performed by hydrogenolysis by means of hydrogen in the presence of a catalyst, or by the action of dichlorodicyanobenzoquinone (DDQ) in an organic solvent.

23. A taxane derivative of general formula:



in which R, Ar and G_1 are defined as in claim 17 and G_2 and R'_4 are defined as in claim 19, when prepared by use of a ß-phenylisoserine derivative as claimed in any one of claims 19-22.

24. A taxane derivatives of general formula:



in which R, Ar and G_1 are defined as in claim 17 and R_4 represents a hydrogen atom or an acetyl radical, when prepared by use of a ß-phenylisoserine derivative as claimed in any one of claims 19-22.

25. Process according to claim 1 substantially as hereinbefore described.

26. ß-phenylisoserine derivative as defined in claim 1 when prepared by a process claimed in any one of claims 1 to 16 or 25.

27. Use according to claim 19 substantially as hereinbefore described.

28. Taxane derivative as defined in claim 19 when prepared by using a ß-phenylisoserine as claimed in any one of claims 19 to 22.

DATED this THIRTIETH day of JUNE 1997

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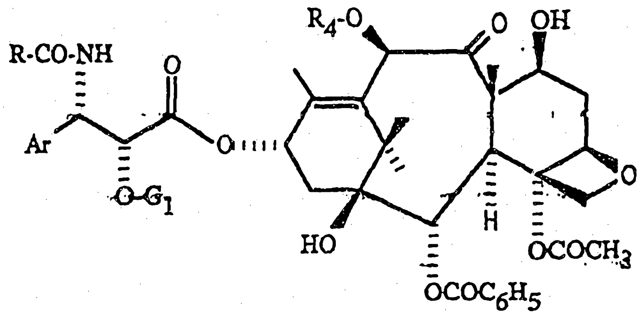
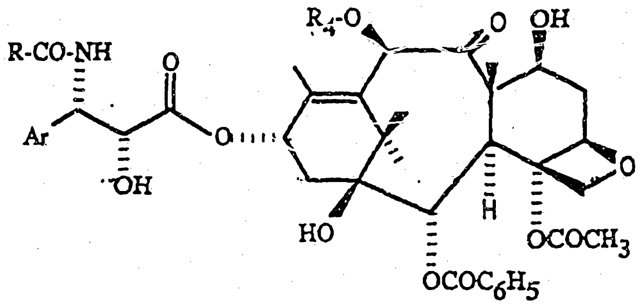
Patent Attorneys for the applicant



in which R, Ar and G_1 are defined as in claim 17 and R_4 represents a hydrogen atom or an acetyl radical.

26. The taxane derivatives of general formula:



in which R and Ar are defined as in one of claims 1 to 3 and R_4 represents a hydrogen atom or an acetyl radical, when they are obtained from a β-phenylisoserine derivative prepared according to the process according to one of claims 1 to 16.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 93/00966

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C271/22 C07D305/14 C07C271/12

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)
IPC 5 C07C 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 practical, 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.
A	EP,A,0 414 610 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 27 February 1991 cited in the application see page 3 - page 4; claims 1,16	1,17,19
A	WO,A,91 17977 (RHONE-POULENC RORER) 28 November 1991 see page 2 - page 3; claims 1,5	1,17,19
A	WO,A,91 17976 (RHONE-POULENC RORER) 28 November 1991 see page 2 - page 3; claims 1,9	1,17,19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 1994	19. 01. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	English, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FR 93/00966

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA-A- 2079314	23-11-91
		EP-A- 0530285	10-03-93