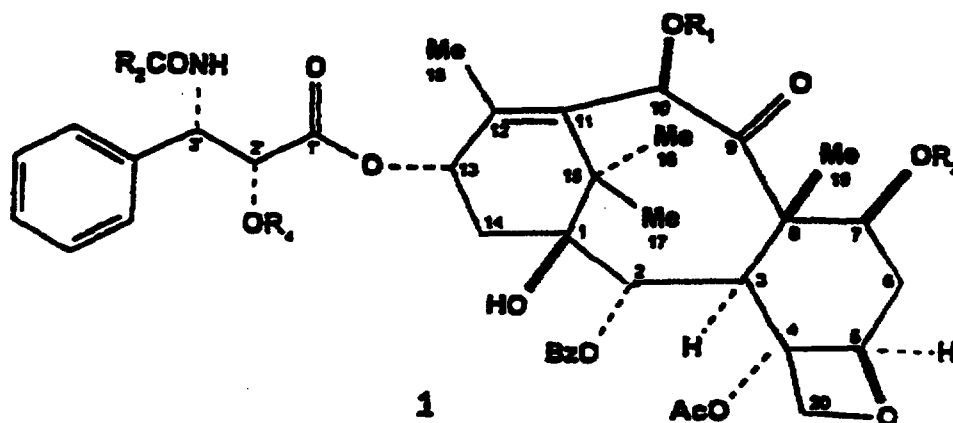
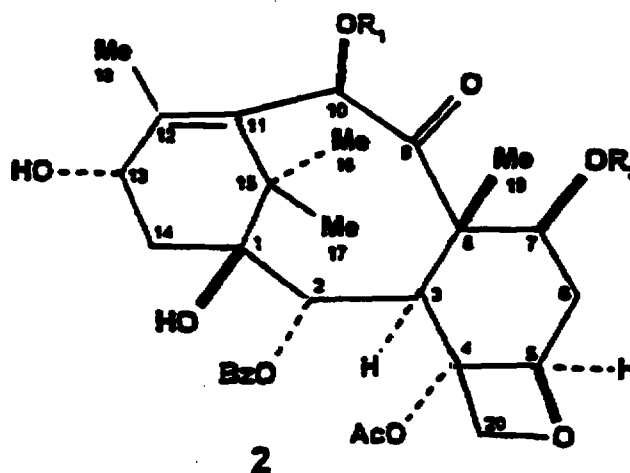


**INTERMEDIATES FOR THE HEMISYNTHESIS OF TAXANES AND
THEIR PROCESSES OF PREPARATION**

The present invention relates to novel intermediates for the hemisynthesis of taxanes and to
5 their processes of preparation.

Taxanes, natural substances with a diterpene skeleton which is generally esterified by a β -amino acid side chain derived from N-alkyl- or N-aroylphenylisoserine, are known as anticancer agents.
10 Several dozen taxanes have been isolated from Taxaceae of the genus *Taxus*, such as, for example, paclitaxel ($R_1 = \text{Ac}$, $R_2 = \text{Ph}$, $R_3 = R_4 = \text{H}$), cephalomannine, their derivatives deacetylated in the 10 position, or baccatins (derivatives without side chain) represented
15 by the formulae 1 and 2 below.





Because of concern not to rapidly exhaust its original source, *Taxus brevifolia*, French researchers have sought to isolate paclitaxel from renewable parts (leaves) of *T. baccata*, the European yew. They have thus demonstrated the probable biogenetic precursor of taxanes, 10-deacetylbaccatin III, the springboard of choice for the hemisynthesis because of its relative abundance in leaf extracts.

The hemisynthesis of taxanes, such as paclitaxel or docetaxel ($R_1 = Ac$, $R_2 = t$ -butyloxy, $R_3 = R_4 = H$), thus consists in esterifying the 13-hydroxyl of a protected derivative of baccatin or of 10-deacetylbaccatin III with a β -amino acid derivative.

Various processes for the hemisynthesis of paclitaxel or of docetaxel are described in the state of the art (EP-0 253 738, EP-0 336 840, EP-0 336 841, EP-0 495 718, WO 92/09589, WO 94/07877, WO 94/07878, WO 94/07879, WO 94/10169, WO 94/12482, EP-0 400 971,

EP-0 428 376, WO 94/14787). Two recent works [I. Georg, T.T. Chen, I Ojima, and D.M. Vyas, "Taxane Anticancer Agents, Basic Science and Current Status", ACS Symposium Series 583, Washington (1995)] and especially
5 [Matthew Suffness, "Taxol® Science and Applications" CRC Press (1995) and 1500 references cited] comprise exhaustive compilations of hemisyntheses of taxanes.

The β -amino acid side chains derived from N-alkyl- or N-aroylphenylisoserine of paclitaxel or
10 docetaxel are of (2R,3S) configuration and one of the main difficulties in the hemisynthesis of taxanes is to obtain an enantiomerically pure product. The first problem consists in obtaining a pure enantiomer of the phenylisoserine derivatives employed in the
15 hemisynthesis of taxanes. The second problem consists in retaining this enantiomeric purity during the esterification of the baccatin derivative and the subsequent treatments of the products obtained (deprotection of the hydroxyls, and the like).

20 Many studies on asymmetric synthesis involving derivatives of β -amino acids have focused on the chemistry of isoserine and of its derivatives, β -amino acids for which a dehydrated cyclic form is a β -lactam (EP-0 525 589). The majority of the various
25 syntheses of phenylisoserine derivatives useful as precursors of taxane side chains focus on a common intermediate, (2R,3R)-cis- β -phenylglycidic acid, which is subsequently converted to β -phenylisoserine by

reaction with ammonia (EP-0 495 718) or a nucleophile (Gou et al., *J. Org. Chem.*, 1983, 58, 1287-89). These various processes require a large number of stages in order to produce β -phenylisoserine of (2R,3S) configuration, necessarily with a stage of racemic resolution by conventional selective crystallization techniques, either for cis- β -phenylglycidic acid or for β -phenylisoserine, or subsequently, after conversion. Furthermore, in order to retain the enantiomeric purity of taxane side chain precursors during the esterification of the baccatin derivative, various means have been provided, in particular by using cyclic intermediates of blocked configuration, which remove the risks of isomerization during esterification reactions under severe reaction conditions. In particular, they involve β -lactam (EP-0 400 971), oxazolidine (WO 92/09589, WO 94/07877, WO 94/07878, WO 94/07879, WO 94/10169, WO 94/12482), oxazinone (EP-0 428 376) or oxazoline (WO 94/14787) derivatives. These cyclic precursors are prepared from the corresponding β -phenylisoserine derivative. As for the latter, the processes provided involve a large number of stages and a necessary racemic resolution in order to obtain the desired taxane side chain precursor. It was thus important to develop a novel route for the improved synthesis of intermediates which are taxane side chain precursors, in particular of enantiomers of cis- β -phenylglycidic acid, of β -phenylisoserine and of

their cyclic derivatives.

Finally, for the hemisynthesis of taxanes and in particular of paclitaxel, the sole appropriate baccatin derivative used until now is that for which the 7-hydroxy radical is protected by a trialkylsilyl (EP-0 336 840, WO 94/14787), the deprotection of which is carried out exclusively in acidic medium. It was thus also important to employ novel protective groups for the hydroxyl functional group which in particular make possible selective protection of the 7-hydroxy radical and in addition allow a wider choice of operating conditions for the deprotection stage.

The present invention relates first of all to an improved process for the preparation of taxane side chain precursors.

The process according to the invention consists in converting a cis- β -arylglycidate derivative of general formula I



in which

Ar represents an aryl, in particular phenyl, and R represents a hydrocarbon radical, preferably a linear or branched alkyl or a cycloalkyl optionally substituted by one or more alkyl groups,

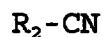
so as to regio- and stereospecifically introduce the

β -N-alkylamide and the α -hydroxyl or their cyclic precursors in a single stage by a Ritter reaction. Depending on the reaction mixture, two types of Ritter reaction are thus distinguished: one with opening of the oxetane, resulting in a linear form of the chain which is directly and completely functionalized, the other resulting in the direct formation of an oxazoline. The "*" symbol indicates the presence of an asymmetric carbon, with an R or S configuration. In both cases, the Ritter reaction is stereospecific, with retention of C-2 configuration and inversion of C-3 configuration. The process according to the invention is advantageously carried out on one of the enantiomers of the cis- β -arylglycidate derivative of general formula I, so as to obtain the corresponding enantiomer of the linear chain or of the oxazoline obtained, without subsequently requiring a racemic resolution. According to the method of preparation of the cis- β -arylglycidate derivative of general formula I described subsequently, R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical, advantageously a cycloalkyl substituted by one or more alkyl groups, in particular a cyclohexyl. R will then preferably be one of the enantiomers of the menthyl radical, in particular (+) menthyl.

1. Direct synthesis of the linear chain

The direct synthesis of the linear chain by

the Ritter reaction consists in reacting a
 cis- β -arylglycidate derivative of general formula I
 defined above with a nitrile of formula

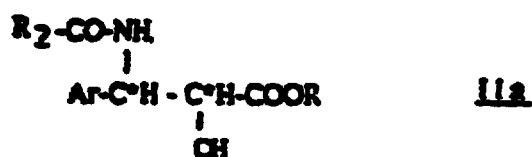


5 in which

R_2 represents an aryl radical, preferably a
 phenyl,

in the presence of a proton acid, such as sulphuric
 acid, perchloric acid, tetrafluoroboric acid, and the
 10 like, and of water.

A β -arylisoserine derivative of general
 formula IIa



in which Ar, R and R_2 are defined above,
 is then obtained.

15 The reaction is carried out with inversion of
 the configuration of the C-3 of the
 cis- β -phenylglycidate derivative. Thus, starting from a
 (2R,3R)-cis- β -phenylglycidate derivative, the
 corresponding β -arylisoserine derivative of (2R,3S)
 20 configuration is obtained.

The Ritter reaction is carried out in an
 appropriate solvent, at a temperature of between -75
 and +25°C.

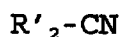
The appropriate solvent can be the nitrile

itself, when it is liquid at the reaction temperature,
 or alternatively the acid itself (sulphuric ac.,
 perchloric ac. or tetrafluoroboric ac.), or a solvent,
 such as, for example, methylene chloride or ethyl
 5 ether. The proton acids conventionally used can contain
 the water necessary for the hydrolysis.

When benzonitrile (R_2 = phenyl) is employed
 with the cis- β -arylglycidate of general formula I of
 (2R,3R) configuration for which Ar represents a phenyl,
 10 then the corresponding β -arylisoserine derivative of
 general formula IIa of (2R,3S) configuration for which
 Ar and R_2 represent a phenyl is directly obtained,
 which product is none other than the precursor of the
 side chain of paclitaxel.

15 2. Direct synthesis of the cyclic chain

For this second possibility, a Ritter
 reaction is also carried out with a nitrile of formula



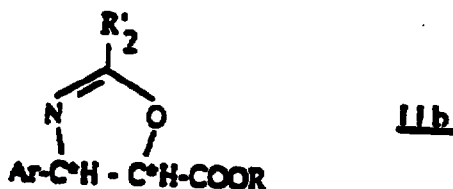
in which

20 R'_2 represents R_2 defined above or a lower alkyl or
 lower perhaloalkyl radical, such as
 trichloromethyl,
 in the presence of a Lewis acid, in particular the
 boron trifluoride acetic acid complex, boron
 25 trifluoride etherate, antimony pentachloride, tin
 tetrachloride, titanium tetrachloride, and the like, or
 of a proton acid, such as, for example,
 tetrafluoroboric acid, the reaction being carried out

in anhydrous medium.

As for the synthesis of the linear chain, the solvent can be the nitrile itself, when it is liquid at the reaction temperature, or alternatively an
 5 appropriate solvent, such as, for example, methylene chloride or ethyl ether. The reaction temperature is also between -75 and $+25^{\circ}\text{C}$.

In the absence of water, an intramolecular Ritter reaction is carried out and the oxazoline of
 10 general formula IIb



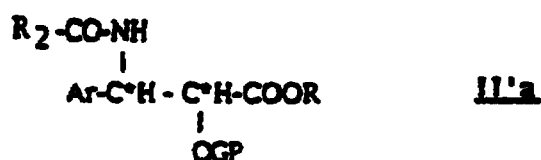
in which Ar, R and R'_2 are as defined above,
 is obtained.

As in the Ritter reaction in the presence of water, the reaction is carried out with inversion of
 15 the configuration of the C-3 of the cis- β -phenylglycidate derivative. Thus, starting from a (2R,3R)-cis- β -phenylglycidate derivative, the corresponding oxazoline of (2R, 3S) configuration is obtained.

20 For both Ritter reactions, in order to avoid the formation of a free carbocation which is the cause of many potential side reactions, the reactants are preferably added in the following order: i) the complex between the nitrile and the acid is first formed, then

ii) the acid catalyst is added to the mixture composed of the oxirane and the nitrile.

The products obtained by this first stage, which are β -arylisoserine derivatives of general formula IIa or oxazoline derivatives of general formula IIb, can be further converted in a second optional stage described hereinbelow or then converted to acids by controlled saponification, before being coupled to a protected baccatin derivative for the hemisynthesis of taxanes, in particular of paclitaxel and its 10-deacetylated derivatives or of docetaxel. In the case of β -arylisoserine derivatives of general formula IIa, the saponification can be preceded by a conventional stage of protection of the hydroxyl by an appropriate protective group. A derivative of general formula II'a



in which

Ar, R and R₂ are defined above, and GP represents a protective group for the hydroxyl functional group which is appropriate for the synthesis of taxanes, in particular chosen from alkoxy ether, aralkoxy ether, aryloxy ether or haloalkoxycarbonyl radicals, such as, for example, methoxymethyl, 1-ethoxyethyl, benzyloxymethyl or

(β -trimethylsilylethoxy)methyl groups, tetrahydropyranyl or β -alkoxycarbonyl (TrOC) radicals, β -halogenated or alkylsilyl ethers or alkoxyacetyl, aryloxyacetyl, haloacetyl or formyl radicals, is then obtained.

3. Possible conversion of the derivatives of formula IIa or IIb

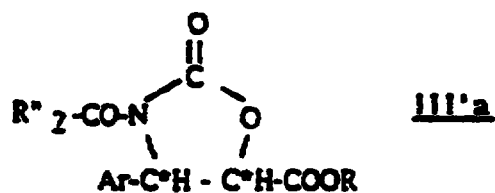
The derivatives of general formula IIa or IIb obtained above can optionally be converted into novel intermediates which are side chain precursors in the hemisynthesis of taxanes. These conversions take place with retention of the configuration of the C-2 and C-3 positions. The novel intermediates obtained will thus have the same stereochemistry as the derivatives of formula IIa or IIb from which they derive. The products obtained in this second stage are subsequently converted into acids by controlled saponification, before being coupled with a protected baccatin derivative for the hemisynthesis of taxane, in particular of paclitaxel or of docetaxel.

3.1 Cyclization of the derivatives of general formula IIa

The derivatives of general formula IIa can subsequently be converted into oxazolines of formula IIb according to conventional methods of the state of the art (WO 94/14787).

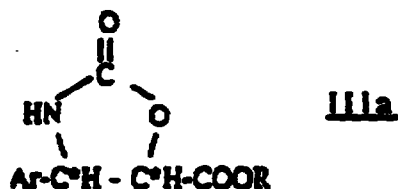
The β -arylisoserine derivatives of general formula IIa can also be converted into novel

oxazolidinone cyclic intermediates of general formula
III'a



in which Ar and R are defined above and R''₂ represents
R'₂, defined above, an alkoxy radical, preferably a
5 t-butoxy radical, or a linear or branched alkyl radical
comprising at least one unsaturation, for example a
1-methyl-1-propylene radical, and the corresponding
dialkyl acetals.

The oxazolidinones of general formula III'a
10 are obtained first of all by reacting a β-arylisoserine
derivative of general formula IIa with a
haloalkoxycarbonyl ester, in particular 2,2,2-
trichloroethoxycarbonyl (TrOC), and then by cyclization
in the presence of a strong organic base, such as
15 diazabicycloundecene (DBU). An oxazolidinone derivative
of general formula IIIa



in which Ar and R are defined above,
is then obtained.

The derivatives of general formula IIIa can
20 also be obtained by direct synthesis, by reacting the

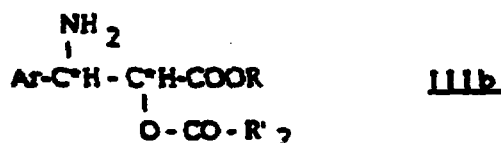
β -arylglycidate derivatives of formula II'a with urea.

The acylated derivatives of general formula III'a are obtained by introducing the R''_2 -CO- radical according to the usual acylation techniques, in the presence of an appropriate acylating agent, for example an acyl halide of formula R''_2 -CO-X, in which R''_2 is defined above and X represents a halogen, or an anhydride of the corresponding acid.

The dialkyl acetals are obtained according to the usual techniques for the formation of acetals.

3.2 Opening of the oxazoline of general formula IIb

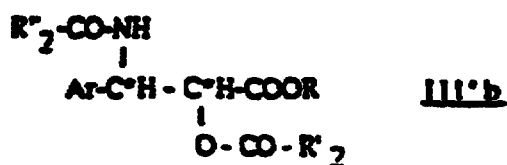
The β -arylisoserine derivative of general formula IIIb



in which Ar, R and R'_2 are defined above, is obtained by hydrolysis of the oxazoline of general formula IIb in acidic medium.

Advantageously, when R'_2 represents a lower perhaloalkyl, such as trichloromethyl, the R'_2 -CO- radical constitutes a protective group for the hydroxyl functional group.

This taxane side chain precursor can then be converted into amides of general formula III'b



in which

Ar, R, R'₂ and R''₂ are defined above.

The precursor of the side chain of paclitaxel (R''₂ = phenyl) or of docetaxel (R''₂ = t-butoxy) can thus
 5 be obtained without distinction.

4. Preparation of the cis-β-arylglycidic acid derivative of formula I

The cis-β-arylglycidic acid derivative of formula I can be prepared according to conventional
 10 processes of the state of the art or by simple esterification of cis-β-arylglycidic acid with the corresponding alcohol R-OH. In order to improve the overall yield in the synthesis of taxane chain precursors, a cis-β-arylglycidate derivative of general
 15 formula I



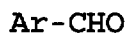
in which

Ar is defined above and

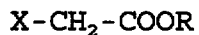
R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon
 20 radical,

is prepared in the process according to the invention

by reacting the aldehyde of formula



with the haloacetate of formula



- 5 Ar and R being defined above and
 X representing a halogen, in particular a chlorine
 or a bromine.

Advantageously, the optically pure enantiomer
of a highly sterically hindered chiral hydrocarbon
10 radical is a cycloalkyl substituted by one or more
alkyl groups, in particular a cyclohexyl.

It concerns a Darzens' reaction through which
a mixture of the two diastereoisomers, ester of
(2R,3R)-cis- β -arylglycidic acid and (2S,3S)-cis- β -
15 arylglycidic acid and of an optically pure enantiomer
of the chiral alcohol R-OH, is obtained, since the
Darzens' reaction, carried out with a highly sterically
hindered haloacetate, results essentially in the cis
form of the β -arylglycidate. Advantageously, the highly
20 sterically hindered chiral hydrocarbon radical will be
chosen so that it allows the physical separation of the
two diastereoisomers from the reaction mixture, for
example by selective crystallization, without requiring
a stereospecific separation of the desired enantiomer
25 at the end of the reaction by conventional
crystallization or chiral column chromatography
methods.

Advantageously, R-OH represents menthol, one

of the rare highly sterically hindered chiral alcohols which is economic and commercially available in both its enantiomeric forms.

In the process for the synthesis of a precursor of the taxane side chain, the goal is to prepare a cis- β -phenylglycidate of (2R,3R) configuration. In this case, the highly sterically hindered chiral hydrocarbon radical R will be selected so that the diastereoisomer of the cis- β -phenylglycidate of (2R,3R) configuration crystallizes first from the reaction mixture. When R-OH is menthol, (+)-menthol is advantageously employed.

The asymmetric Darzens' reaction is carried out in the presence of a base, particularly an alkali metal alkoxide, such as potassium tert-butoxide, or an amide, such as lithium bistrimethylsilylamide, in an appropriate solvent, in particular an ether, such as ethyl ether, at a temperature of between -78°C and 25°C. The reaction results in a diastereoisomeric mixture composed virtually exclusively of the cis-glycidates, which can reach a yield of greater than 95%, in the region of 97%. Treatment of the isolated product in an appropriate solvent, in particular a methanol/water mixture, makes it possible readily to obtain physical separation of the required diastereoisomers.

By fractional crystallization (2 stages), rapid enrichment in the desired diastereoisomer is

obtained, with a diastereoisomeric purity of greater than 99%.

The latter point is particularly important because it conditions the isomeric purity of the final taxane, the undesirable diastereoisomers exhibiting
5 their own biological activity which is different from that of the desired taxane.

It is remarkable to observe that the selective use of the two enantiomers of the menthyl
10 ester makes it possible to access, using the same process, the 2 precursor diastereoisomers of the two enantiomers of glycidic acid.

In addition to a fairly high yield of pure isolated diastereoisomer (up to 45%), the
15 diastereoisomeric purity of the major product of the reaction, the ease of implementation of the reaction, the simplicity and the speed of the purification, and the low cost of the reactants and catalysts make the industrial synthesis of this key intermediate in the
20 asymmetric synthesis of β -amino acids easy and economical to access.

When a derivative of general formula I obtained by an asymmetric Darzens' reaction is used in the process according to the invention, the derivatives
25 of general formulae IIa, II'a, IIb, IIIa, IIIb and III'b defined above are then obtained for which R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical, such as

a cycloalkyl substituted by one or more alkyl groups, in particular a cyclohexyl, preferably menthyl, advantageously (+)-menthyl.

The present invention also relates to these
5 derivatives, which are of use as intermediates in the synthesis of taxane side chains.

It should be noted that the present process constitutes a very rapid access to the substituted chiral oxazolines already described in the literature
10 (WO 94/14787), in 3 stages from commercially available products instead of 6 to 8.

5. Controlled saponification

A controlled saponification of the derivatives of general formulae IIa, II'a, IIb, IIIa, IIIb and III'b is carried out under mild conditions, so
15 as to release the acidic functional group while retaining the structure of the said derivatives, for example in the presence of an alkali metal carbonate in a methanol/water mixture.

20 After controlled saponification, the derivatives of general formulae IIa, II'a, IIb, IIIa, IIIb and III'b defined above for which R represents a hydrogen atom are obtained, which derivatives can be employed directly in the hemisynthesis of taxanes by
25 coupling with an appropriate baccatin III derivative.

6. Hemisynthesis of taxanes

6.1 Esterification

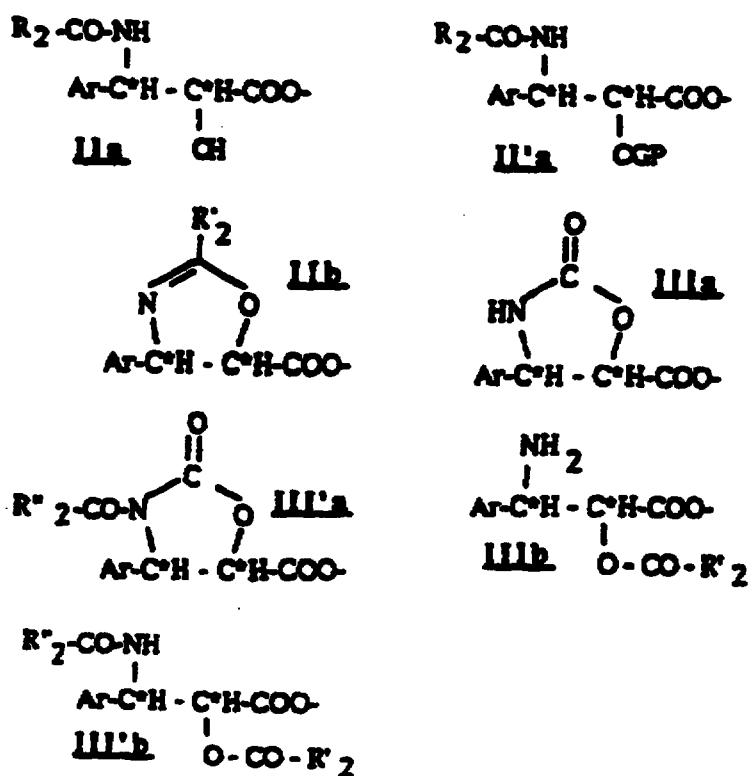
The present invention thus also relates to a

process for the hemisynthesis of taxanes of general formula IV,

C-B IV

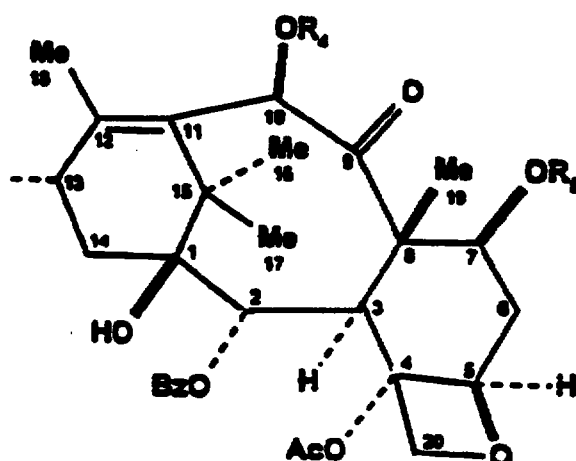
in which

- 5 C represents a side chain chosen from the radicals of following formulae:



in which Ar, R₂, R'₂, R''₂, R₃ and GP are defined above,
and

- 10 B represents a radical derived from baccatin III of general formula V



in which

Ac represents the acetyl radical,

Bz represents the benzoyl radical,

Me represents the methyl radical,

- 5 R_4 represents an acetyl radical or a protective group for the hydroxyl functional group GP1, and
 R_5 represents a protective group for the hydroxyl functional group GP2,

by esterification of an appropriate baccatin III
 10 derivative of general formula V, carrying a C-13 hydroxyl functional group, with one of the derivatives of general formulae IIa, II'a, IIb, IIIa, III'a, IIIb and III'b defined above, for which R represents a hydrogen atom, under conventional conditions for the
 15 preparation of taxanes as defined in the state of the art (in particular: EP-0 253 738, EP-0 336 840, EP-0 336 841, EP-0 495 718, WO 92/09589, WO 94/07877, WO 94/07878, WO 94/07879, WO 94/10169, WO 94/12482, EP-0 400 971, EP-0 428 376, WO 94/14787).

The GP1 and GP2 protective groups are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as trialkylsilyls (EP-0 336 840) or TrOC (EP-0 336 841).

5 GP1 and GP2 also represent, independently of one another, linear or branched hindered haloalkoxycarbonyl radicals comprising at least one halogen atom. They are advantageously radicals in which the alkyl residue comprises between 1 and 4 carbon
10 atoms and 3 or 4 halogen atoms, preferably chosen from 2,2,2-tribromoethoxycarbonyl, 2,2,2,1-tetrachloroethoxycarbonyl, 2,2,2-trichloro-t-butoxycarbonic and trichloromethoxycarbonyl radicals, radicals which are all more hindered than the haloalkoxycarbonyl (TrOC)
15 used until now to protect taxanes in the 7 position.

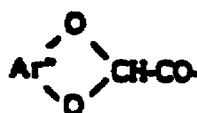
GP1 and GP2 also represent, independently of one another, acyl radicals in which the carbon α to the carbonyl functional group carries at least one oxygen atom.

20 These acyl radicals are described in particular in Patent Application EP-0 445 021. They are advantageously alkoxy- or aryloxyacetyl radicals of formula



25 in which R_6 represents a sterically hindered alkyl radical, a cycloalkyl radical or an aryl radical, or arylidenedioxyacetyl radicals of formula

in which Ar"



represents an

arylidene radical.

Sterically hindered alkyl is preferably
 5 understood to mean a linear or branched C₁-C₆ alkyl
 radical substituted by one or more bulky substituents
 chosen from halogens or linear or branched C₁-C₆ alkyl,
 linear or branched C₁-C₆ alkoxy or C₃-C₆ cycloalkyl or
 aryl radicals. It will be, for example, a tert-butyl or
 10 triphenylmethyl radical.

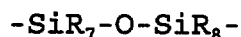
Cycloalkyl is preferably understood to mean a
 C₃-C₆ cycloalkyl radical optionally substituted by one
 or more bulky substituents chosen from halogens or
 linear or branched C₁-C₆ alkyl, linear or branched C₁-C₆
 15 alkoxy or aryl radicals. Advantageously, it is a
 cyclohexyl radical substituted by one or more linear or
 branched C₁-C₆ alkyl radicals, such as, for example,
 menthyl, its racemate or its enantiomers and their
 mixtures in all proportions.

20 Aryl is preferably understood to mean a
 phenyl, naphthyl, anthryl or phenantryl radical
 optionally substituted by one or more bulky
 substituents chosen from halogens or linear or branched
 C₁-C₆ alkyl, linear or branched C₁-C₆ alkoxy or aryl
 25 radicals, in particular the phenyl radical. It is
 preferably a phenyl radical optionally substituted by
 one or two above bulky substituents ortho- and ortho'-

to the ether bond.

Finally, arylidene is preferably understood to mean a phenylene, naphthylene, anthrylene or phenanthrylene radical optionally substituted by one or
5 more bulky substituents chosen from halogens or linear or branched C₁-C₆ alkyl, linear or branched C₁-C₆ alkoxy or aryl radicals, in particular the phenyl radical.

GP1 and GP2 also represent, independently of one another, a trialkylgermyl radical or together
10 form a divalent radical of formula

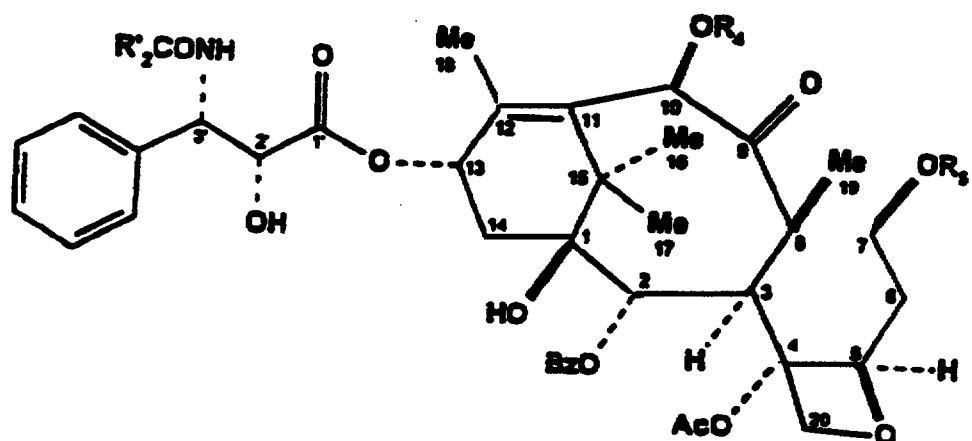


in which

R₇ and R₈, independently of one another, represent a sterically hindered alkyl radical as defined above; in
15 particular, R₇ and R₈ each represent an isopropyl radical.

6.2 Optional opening

When C represents a radical of formula IIb or IIIa, the oxazoline ring is opened in order to obtain a
20 taxane derivative of formula VI



in which

Ac, Bz, Me, Ar, R₂, R₄ and R₅ are defined above.

The IIb, IIIa and III'a radicals are generally opened by hydrolysis in acidic or basic medium. The radical of formula IIb can be opened according to the methods described in the state of the art (in particular WO 94/14787), by hydrolysis in acidic medium, followed by treatment in basic medium, in order to obtain the derivative of general formula VI.

6.3 Deprotection

Finally, the hydroxyls of the derivatives of general formula V or VI are deprotected by replacing the protective groups for the hydroxyl functional group, GP (when C represents the II'a radical), GP1 (when R₄ is other than an acetyl) and GP2, by a hydrogen atom according to the usual techniques.

For the derivatives of general formula V in which C represents a radical of formula IIb or IIIa and

GP1 and/or GP2 are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as trialkylsilyls, the deprotection is carried out simultaneously with the opening described
5 above.

When GP1 and/or GP2 are bulky haloalkoxycarbonyl radicals, deprotection is carried out according to the usual techniques described for TrOC, by the action of zinc or of zinc doped with heavy
10 metals, such as copper, in an organic solvent, in particular in acetic acid, tetrahydrofuran or ethyl alcohol, with or without water.

When GP1 and/or GP2 are acyl radicals in which the carbon α to the carbonyl functional group
15 carries at least one oxygen atom, deprotection is carried out in basic medium by saponification in methanol at low temperature, advantageously with ammonia in methanol at a temperature of less than 10°C, preferably in the region of 0°C.

20 For the case where C represents a radical of formula IIb, opening of the oxazoline is carried out simultaneously with deprotection in basic medium, in order to result, in one stage, in the corresponding taxane derivative of general formula VI in which R₄
25 represents an acetyl radical or a hydrogen atom and R₅ represents a hydrogen atom, in contrast to the opening in acidic medium described in the state of the art,

which requires a second stage in basic medium.

The known protective groups are removed using known methods and the oxazoline chain, when it was present, opened out by hydrolysis, giving taxanes in every respect identical to the reference taxanes. By way of example, and in order to show the validity of the invention without, however, limiting the scope thereof, paclitaxel, 10-deacetyltaxol, cephalomarine and docetaxel can be obtained from the corresponding protected derivatives.

The deblocking of the acyls in which the carbon α to the carbonyl functional group carries at least one oxygen atom was first attempted under the conventional conditions regarded as the mildest, that is to say zinc acetate in methanolic medium at reflux. In this case, the reaction being complete in a few hours (against a few days for acetates), we constantly isolated, in addition to the desired product, its C-7 epimer resulting from the conventional retroaldolization equilibrium. It being presumed that, even under the neutral, indeed slightly acidic, conditions, the main agents responsible were methanol and especially the temperature, we returned to the standard conditions for deblocking acyls described by early writers, by saponification in basic medium in ethanol at low temperature. Under these conditions, no significant epimerization was observed. By way of example, we obtained paclitaxel, 10-deacetyltaxol,

cephalomanine and docetaxel, in every respect identical to the reference taxanes, from the corresponding alkoxy- or aryloxyacetylated derivatives.

Finally, it should be noted that all the methods described previously, which are nevertheless targeted at improving the overall yield of the hemisynthesis, consist in synthesizing the phenylisoserine chain beforehand, for the purpose of converting it into one of the cyclic structures mentioned above (β -lactams, oxazolidines or oxazolines). Thus, paradoxically, the apparent better performances in the coupling of these cyclic structures only compensates for the fall in overall yield caused by the addition of ring creation stages to the synthetic sequence for the linear chain (i.e. a total of 9 stages). For the general process for the synthesis of taxanes according to the invention, a product such as paclitaxel is obtained in only 5 stages:

- (1S,2R,5S) - (+) -menthyl (2R,3R) -3-phenylglycidate
- (1S,2R,5S) - (+) -menthyl (4S,5R) -2,4-diphenyl-4,5-dihydroxazole-5-carboxylate
- saponification
- hemisynthesis (esterification)
- opening and deprotection.

Finally, the present invention relates to the synthetic intermediates of general formulae IV, V and VI described above which are of use in the general synthesis of taxanes, a subject of the present

invention.

Generally, hydroxycarbon radical is preferably understood to mean according to the invention a saturated or unsaturated hydrocarbon radical which can comprise one or more unsaturations, such as an optionally unsaturated linear or branched alkyl, an optionally unsaturated cycloalkyl, an aralkyl or an aryl, it being possible for each optionally to be substituted by one or more substituents, in particular alkyl substituents.

Linear or branched alkyl is preferably understood to mean according to the invention a C_1 - C_6 alkyl, in particular chosen from the methyl radical, ethyl radical, propyl radical, isopropyl radical, butyl radical and its various branched isomers, such as, for example, tert-butyl, pentyl radical and hexyl radical and their various branched isomers. This definition also applies to the alkyl residues of the alkoxy or aralkoxy radicals.

Cycloalkyl is preferably understood to mean according to the invention a C_3 - C_6 cycloalkyl, in particular chosen from the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl radicals.

Aryl is preferably understood to mean according to the invention an aromatic or heteroaromatic radical, in particular chosen from the phenyl, naphthyl, anthryl, phenantryl, pyridyl or pyrimidyl radicals and the like.

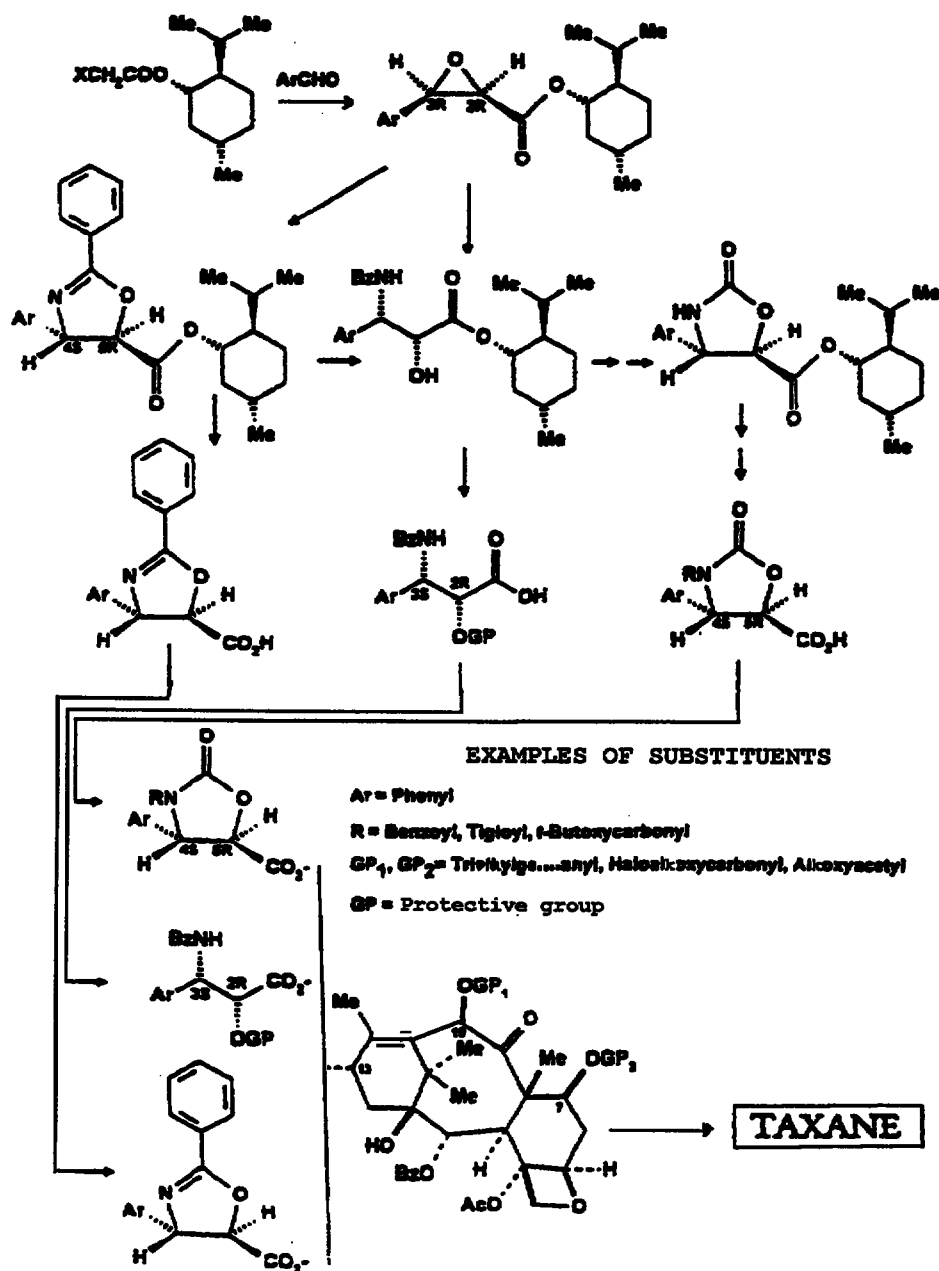
Finally, halogen is preferably understood to mean chlorine, bromine or iodine. The haloalkoxy-carbonyl radicals are preferably radicals in which the alkyl residue comprises between 1 and 4 carbon atoms
5 and 3 or 4 halogen atoms.

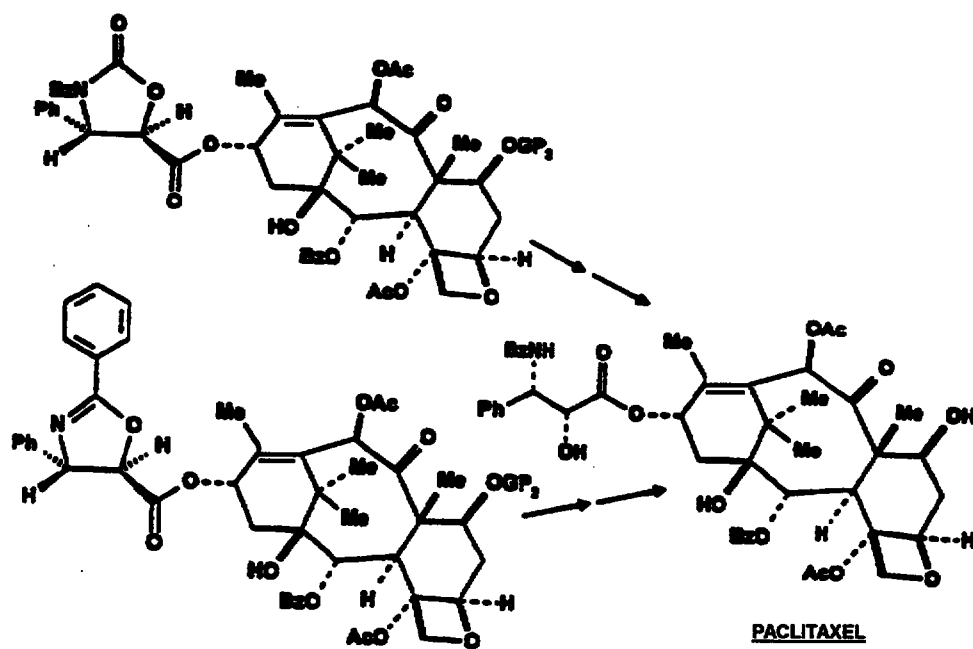
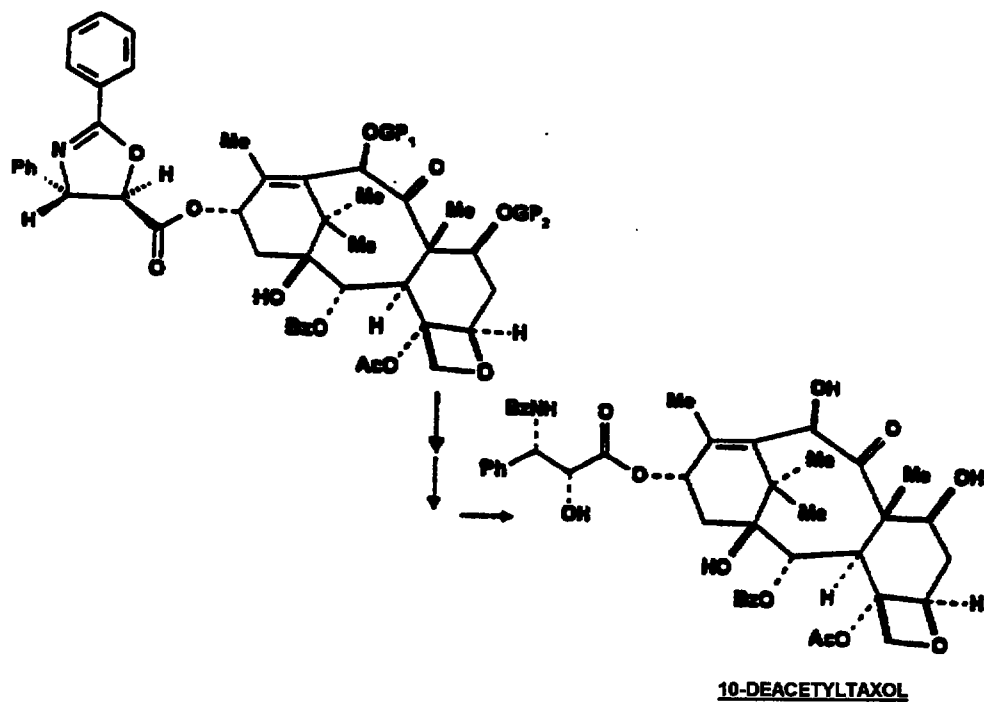
The general process for the synthesis of taxanes according to the invention is repeated in Scheme 1 below, for R representing (+)-menthyl and R₂ or R'₂ representing phenyl.

10 The final stage in the hemisynthesis of taxanes by the process according to the invention is summarized in Schemes 2 and 3 below. Scheme 2 summarizes the synthesis of paclitaxel from derivatives of formula IV defined above in which C represents a
15 radical of formulae IIb or III'a. Scheme 3 summarizes the synthesis of 10-deacetyltaxol from a derivative of formula IV in which C represents a radical of formula IIb.

Of course, the same synthetic schemes can be
20 used for the other definitions of the substituents.

SCHEME 1



SCHEME 2SCHEME 3

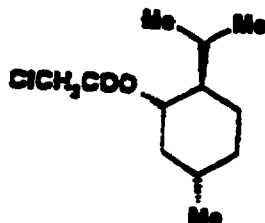
GP_1, GP_2 = triethylgermanium, 2,2,2-trichloro-*t*-butoxycarbonyl

EXPERIMENTAL PART

I. Taxane side chain precursors

Example 1:

(1S,2R,5S) - (+) -Menthyl chloroacetate



5 57 mL (0.704 mol) of anhydrous pyridine are added to a stirred solution at room temperature of 100 g (0.640 mol) of (1S,2R,5S) - (+) -menthol in 1 L of dry dichloromethane. After stirring for a few minutes, 56 mL (0.704 mol) of chloroacetyl chloride are

10 subsequently added and the reaction is allowed to continue for 30 min. After monitoring by T.L.C., 50 g of crushed ice are added and the reaction mixture is left vigorously stirring for 1 h. After diluting with 100 mL of dichloromethane, the organic phase is washed

15 several times with a saturated aqueous sodium chloride solution (200 mL), dried over MgSO_4 and then concentrated under reduced pressure. After purifying the crude product thus obtained by silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 20/1), 146 g of (1S,2R,5S) - (+) -menthyl

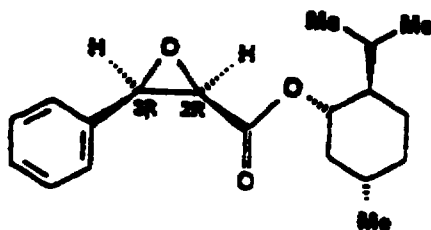
20 chloroacetate are obtained in the form of a syrup.

The compound obtained exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 4.77 (1H, dt), 4.06 and 4.02 (2H, 2d, $J = 13.6$ Hz), 2.02 (1H, m, $J = 11.8$ Hz), 1.87 (1H, m, $J = 7$ and 2.6 Hz), 1.69 (2H, m), 1.50 (1H, m), 1.43 (1H, m, $J = 11.7$ and 3 Hz), 1.07 (1H, m), 1.02 (1H, q, $J = 11.8$ Hz), 0.92 and 0.90 (6H, 2d, $J = 6.4$ Hz), 0.89 (1H, m), 0.77 (3H, d, $J = 7$ Hz).

Example 2:

(1S,2R,5S)-(+)-Menthyl (2R,3R)-3-phenyl-glycidate



69 mL (0.686 mol) of benzaldehyde are added to a stirred solution at room temperature of 152 g (0.653 mol) of (1S,2R,5S)-(+)-menthyl chloroacetate in 600 mL of anhydrous ethyl ether. After stirring for a few minutes, the solution is cooled to -78°C under an inert atmosphere, a suspension of 85 g (0.718 mol) of potassium *tert*-butoxide in 400 mL of anhydrous ethyl ether is subsequently added over 2 h and the reaction mixture is allowed to return to room temperature. After monitoring by T.L.C., the organic part is diluted with 200 mL of dichloromethane, washed several times with a saturated sodium chloride solution, dried over MgSO_4 and concentrated under reduced pressure. 200 g of a crude product are thus obtained in the form of a syrup

containing four diastereoisomers (of which two are *cis* and two are *trans*), which is subjected as is to a fractional crystallization.

In a first step, the solution of the crude
5 product in 2 L of methanol brought to 60°C, to which
700 mL of osmosed water are gradually added, is left
for 16 h at room temperature without being subjected to
vibrations. A yellow-coloured lower solid phase rich in
trans isomers is discarded and the white crystals of
10 the upper phase, which are rich in *cis* isomers, are
separated by filtration. The crystals thus obtained are
redissolved in 2 L of methanol brought to 60°C, 500 mL
of osmosed water are added, until a persistent
cloudiness is obtained, and the mixture is left for
15 16 h at room temperature. Three additional
crystallizations, carried out according to the same
process but with reduced volumes of methanol (1 L) and
water (200 mL), are necessary to obtain 23 g of
(1*S*,2*R*,5*S*)-(+) -menthyl (2*R*,3*R*)-3-phenylglycidate in the
20 crystalline state with an HPLC purity > 99% (Yd = 12%).

The compound obtained exhibits the following characteristics:

- M.p. = 104°C
- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 7.40 (2H, dd,
25 J = 7.8 Hz and 1.7 Hz), 7.32 (3H, m), 4.58 (1H, dt,
J = 10.9 Hz and 4.2 Hz), 4.26 (1H, d, J = 4.6 Hz), 3.83
(1H, d, J = 4.8 Hz), 1.6 to 0.85 (9H, m), 0.78 (3H, d,
J = 7 Hz), 0.75 (3H, d, J = 6.4 Hz), 0.62 (3H, d,

$J = 6.9 \text{ Hz}$).

X-ray diffraction of a (1S,2R,5S) - (+) -menthyl (2R,3R) - 3-phenylglycidate single crystal for the purpose of the indirect determination of the absolute configuration:

5 The single crystal was obtained from a crystalline suspension resulting from the addition, while hot, of the non-solvent (water) to a semi-saturated solution of the glycidate in methanol. On slow cooling, fine needles with a purity of 99.95%
10 (HPLC) were deposited by this solution, which needles were stored under moist conditions until the final selection.

 The selected sample (fine needle with dimensions $0.12 \times 0.12 \times 0.40 \text{ mm}$) was studied on a CAD4
15 Enraf-Nonius automatic diffractometer (molybdenum radiation with graphite monochromator). The unit-cell parameters were obtained by refinement of a set of 25 reflections with a high theta angle. Data collection ($2\theta_{\text{max}} = 50^\circ$, scanning $\omega/2\theta = 1$, $t_{\text{max}} = 60 \text{ s}$, HKL domain:
20 H 0.6 K 0.14 L 0.28, intensity controls without significant drift (0.1%)) provided 1888 reflections, 1037 of which with $I > 1.5\sigma(I)$.

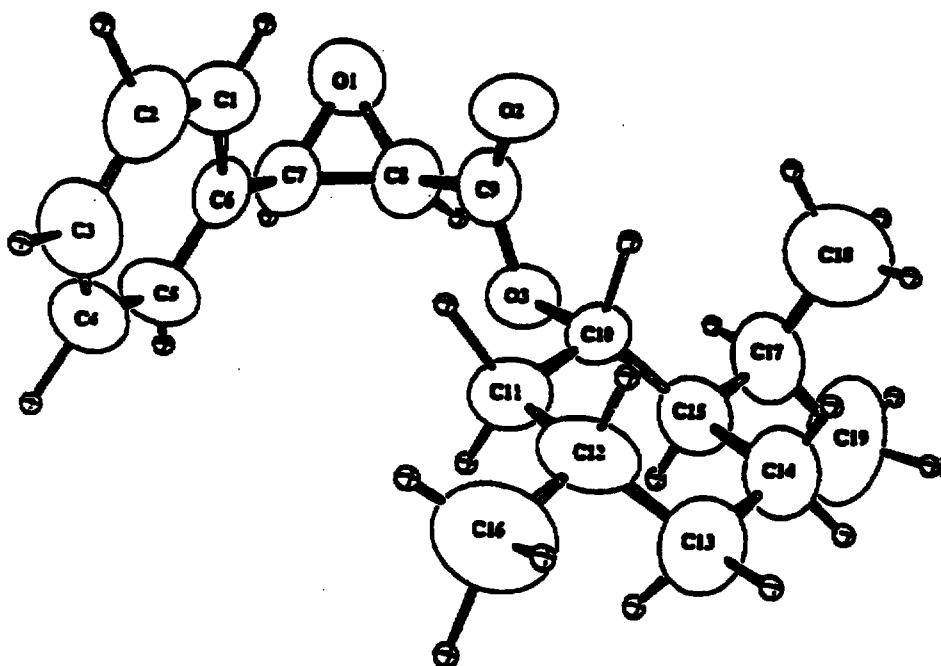
$\text{C}_{19}\text{H}_{26}\text{O}_3$: Mr = 302.42, orthorhombic, $P2_12_12_1$,
 $a = 5.709(11)$, $b = 12.908(4)$, $c = 24.433(8) \text{ \AA}$,
25 $V = 1801(5) \text{ \AA}^3$, $Z = 4$, $D_x = 1.116 \text{ Mg.m}^{-3}$, $\lambda(\text{MoK}\alpha) = 0.70926 \text{ \AA}$, $\mu = 0.69 \text{ cm}^{-1}$, $F(000) = 656$, $T = 294 \text{ K}$,
final $R = 0.072$ for 1037 observations.

After Lorenz corrections and polarization

corrections, the structure was solved using Direct Methods which make it possible to locate the majority of the nonhydrogen atoms of the molecule, the remaining atoms being located by Fourier differences and successive scaling operations. After isotropic refinement ($R = 0.125$) and then anisotropic refinement ($R = 0.095$), most of the hydrogen atoms are located using a Fourier difference (between 0.39 and 0.14 $\text{e}\text{\AA}^{-3}$), the others being positioned by calculation. The complete structure was refined by whole matrix (x , y , z , β_{ij} for C and O, x , y , z for H; 200 variables and 1037 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) resulting in $R = 0.080$, $R_w = 0.072$ and $S_w = 1.521$ (residue $\Delta\rho \leq 0.21 \text{ e}\text{\AA}^{-3}$).

The scattering factors are taken from the International Tables of crystallography [International Tables for X-ray Crystallography (1974), Vol. IV, Birmingham: Kynoch Press (Current distributor D. Reidel, Dordrecht)]. The calculations were carried out on a Hewlett-Packard 9000-710 for the determination of the structure [Sheldrick, G.M. (1985), Crystallographic Computing 3: Data Collection, Structure Determination, Proteins and Databases, edited by G.M. Sheldrick, C. Krüger and R. Goddard, Oxford, Clarendon Press] and on a Digital MicroVax 3100 for the other calculations with the MOLEN suite of programs [Fair, C.K. (1990), MOLEN: An Interactive Intelligent System for Crystal Structure Analysis, Enraf-Nonius,

[Johnson, C.K. (1965), ORTEP, Report ORNL-3794,
Oak Ridge National Laboratory, Tennessee, USA]

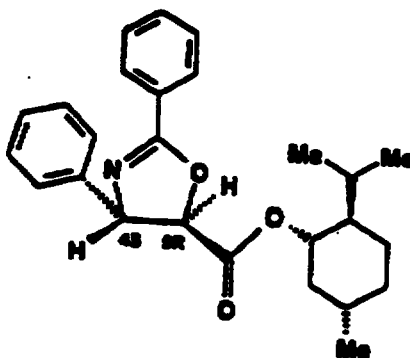


10 • $[\alpha]_D^{28} = +12$ (c = 1.15, chloroform)

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 7.40 (2H, d, J = 8 Hz), 7.32 (3H, m), 4.26 (1H, d, J = 4.6 Hz), 3.84 (1H, d, J = 4.6 Hz), 3.55 (3H, s).

Example 3:

(1S,2R,5S) - (+) -Menthyl (4S,5R) -2,4-diphenyl-4,5-dihydrooxazole-5-carboxylate



15 mL (0.109 mol) of a 54% solution of
 5 tetrafluoroboric acid in ether are added over 10 min to
 a stirred solution, under an inert atmosphere at -65°C ,
 of 30 g (0.0993 mol) of (1S,2R,5S) - (+) -menthyl (2R,3R) -
 3-phenylglycidate and 305 mL (2.98 mol) of benzonitrile
 in 1.5 L of anhydrous dichloromethane. The reaction is
 10 allowed to continue at -65°C for 1 h and, after
 monitoring by T.L.C., 300 mL of a saturated aqueous
 sodium hydrogencarbonate solution are added and the
 reaction mixture is allowed to return to room
 temperature with stirring. After extracting the aqueous
 15 phase with dichloromethane (2 $\times$ 200 mL), the combined
 organic phases are washed with a saturated sodium
 chloride solution (200 mL) and with water (50 mL) and
 dried over MgSO_4 . After concentrating under reduced
 pressure and removing the residual benzonitrile under
 20 high vacuum at 50°C , the crude product obtained is
 purified by silica gel chromatography (15-40 μm)

(eluent: cyclohexane/ethyl acetate, 20/1).

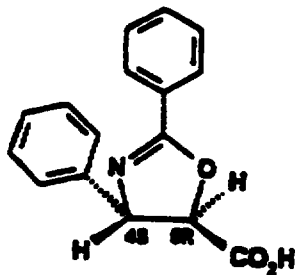
32 g of (1S,2R,5R)-(+)-menthyl (4S,5R)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylate are thus isolated in the form of a colourless syrup (Yd = 80%)

5 which exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.10 (2H, d, $J = 7.1$ Hz), 7.54 (1H, t, $J = 7.4$ Hz), 7.46 (2H, t, $J = 7.4$ Hz), 7.34 (5H, m), 5.40 (1H, d, $J = 6.4$ Hz), 4.88 (1H, d, $J = 6.4$ Hz), 4.85 (1H, dt, $J = 10.9$ and 4.4 Hz), 2.09 (1H, m), 1.84 (1H, m, $J = 7$ and 2.7 Hz), 1.71 (1H, m), 1.69 (1H, m), 0.94 (3H, d, $J = 6.5$ Hz), 0.9 (1H, m), 0.85 (3H, d, $J = 7$ Hz), 0.77 (3H, d, $J = 7$ Hz).

Example 4:

15 (4S,5R)-2,4-Diphenyl-4,5-dihydrooxazole-5-carboxylic acid



25 mL of a solution of 6 g (43.2 mmol) of potassium carbonate in osmosed water are added to a stirred solution at room temperature of 3.5 g (8.64 mmol) of (1S,2R,5S)-(+)-menthyl (4S,5R)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylate in methanol (70 mL) and the reaction is left to continue for 16 h at room temperature. After monitoring by T.L.C., the

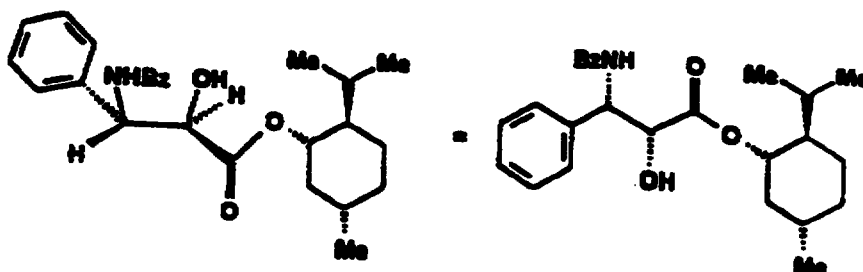
reaction mixture is concentrated under reduced pressure. The aqueous phase thus obtained is washed with dichloromethane (3 × 100 mL), acidified to pH 2 by slow addition of 20 mL of a 1M aqueous HCl solution and
 5 extracted with ethyl acetate (3 × 100 mL). The combined organic extraction phases are dried (MgSO₄) and concentrated under reduced pressure.

2.26 g of (4S,5R)-2,4-diphenyl-4,5-dihydrooxazole-5-carboxylic acid are thus obtained in
 10 the form of a white powder (Yd = 98%) which exhibits the following characteristics:

- $[\alpha]_D^{22} = +27.7$ (c = 0.99, CH₂Cl₂/MeOH, 1/1)
- F = 201-202°C
- 400 MHz ¹H NMR (d₆-DMSO) (δ ppm): 7.99 (2H, d, J = 7.3 Hz), 7.64 (1H, t, J = 7.4 Hz), 7.55 (2H, t, J = 7.7 Hz), 7.36 (5H, m), 5.40 (1H, d, J = 6.3 Hz), 4.99 (1H, d, J = 6.4 Hz).

Example 5:

(1S,2R,5S) - (+) -Menthyl (2R,3S) -N-benzoyl-3-phenylisoserinate
 20 phenylisoserinate



15 mL of a 1M aqueous HCl solution are added to a stirred solution at room temperature of 1 g (2.47 mmol) of (1S,2R,5S) - (+) -menthyl (4S,5R) -2,4-

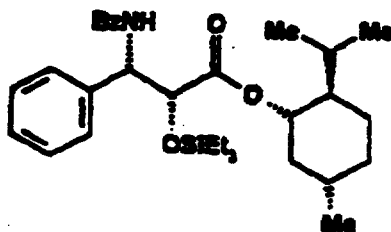
diphenyl-4,5-dihydrooxazole-5-carboxylate in a mixture of methanol (15 mL) and tetrahydrofuran (15 mL). The reaction mixture is brought for 1 h to reflux and, after monitoring by T.L.C. and returning to room temperature, a saturated aqueous sodium hydrogencarbonate solution (45 mL) is gradually added until a basic pH is obtained. After stirring for 48 h at room temperature, the aqueous phase obtained after concentrating under reduced pressure is extracted with dichloromethane (100 mL). The aqueous phase is washed with a saturated sodium chloride solution (2 × 50 mL), dried over MgSO₄ and concentrated under reduced pressure and the residue obtained is chromatographed on silica gel (15-40 μm) (eluent: dichloromethane/methanol, 95/05).

0.835 g of (1S,2R,5S)-(+) -menthyl (2R,3S)-*N*-benzoyl-3-phenylisoserinate is thus isolated in the form of a white solid (Yd = 80%) which exhibits the following characteristics:

• 400 MHz ¹H NMR (CDCl₃) (δ ppm): 7.77 (2H, d, J = 7.2 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.45 (4H, m), 7.36 (2H, t, J = 7.2 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.04 (1H, d, J = 9.2 Hz), 5.78 (1H, dd, J = 9.2 and 2.1 Hz), 4.79 (1H, dt, J = 10.9 and 4.4 Hz), 4.63 (1H, broad s), 3.35 (1H, broad s), 1.81 (2H, m), 1.67 (3H, m), 1.5 to 1.36 (2H, m), 1.09 to 0.91 (2H, m), 0.89 (3H, d, J = 6.9 Hz), 0.77 (3H, d, J = 6.5 Hz), 0.74 (3H, d, J = 6.9 Hz).

Example 6:

(1S,2R,5S) - (+) -Menthyl (2R,3S) -N-benzoyl-O-triethylsilyl-3-phenylisoserinate



0.255 g (2.08 mmol) of 4-dimethylamino-
 5 pyridine is added to a solution of 0.8 g (1.89 mmol) of
 (1S,2R,5S) - (+) -menthyl (2R,3S) -N-benzoyl-3-
 phenylisoserinate in 10 mL of anhydrous
 dichloromethane. After stirring for a few minutes at
 room temperature, 477 μ L (2.84 mmol) of triethylsilyl
 10 chloride are added over 5 min. After stirring for 1 h
 at room temperature and monitoring by T.L.C., the
 reaction mixture is diluted with 100 mL of
 dichloromethane. The organic phase is washed with a
 saturated aqueous sodium hydrogencarbonate solution
 15 (2 $\times$ 20 mL) and with a saturated sodium chloride
 solution (50 mL), dried over MgSO_4 and concentrated
 under reduced pressure. After purifying the residue
 obtained by silica gel chromatography (15-40 μ m)
 (eluent: cyclohexane/ethyl acetate, 10/1), 0.74 g of
 20 (1S,2R,5S) - (+) -menthyl (2R,3S) -N-benzoyl-O-
 triethylsilyl-3-phenylisoserinate is obtained in the
 form of a colourless syrup (Yd = 75%).

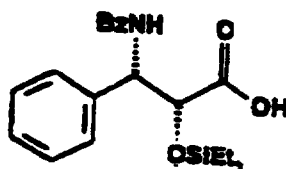
The compound obtained exhibits the following

characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 7.82 (2H, d, $J = 7$ Hz), 7.52 (1H, t, $J = 7.4$ Hz), 7.45 (2H, t, $J = 7$ Hz), 7.37 (2H, d, $J = 7.2$ Hz), 7.32 (2H, t, $J = 7.2$ Hz), 7.26 (2H, m), 5.60 (1H, dd), 4.73 (1H, dt, $J = 11$ and 4.3 Hz), 1.88 to 1.67 (m), 1.44 (2H, m), 1.06 and 0.87 (m), 0.80 (m), 0.67 (3H, d, $J = 7$ Hz), 0.62 to 0.34 (m).

Example 7:

- 10 **(2R,3S)-N-Benzoyl-O-triethylsilyl-3-phenylisoserine**



- A solution of 0.644 g (4.655 mmol) of sodium carbonate in 10 mL of osmosed water is added to a stirred solution at room temperature of 0.5 g (0.931 mmol) of (1S,2R,5S)-(+)-menthyl (2R,3S)-N-benzoyl-O-triethylsilyl-3-phenylisoserinate in 15 mL of methanol. After stirring for 16 h at room temperature and monitoring by T.L.C., the reaction mixture is concentrated under reduced pressure and the residual aqueous phase is washed with dichloromethane (3 x 50 mL) and then acidified to pH 2 by slow addition of a 1M aqueous HCl solution (10 mL). The aqueous phase is extracted with ethyl acetate (3 x 50 mL) and the combined organic phases are dried over MgSO_4 and

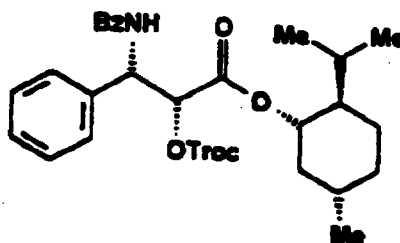
concentrated under reduced pressure.

0.320 g of (2R,3S)-N-benzoyl-O-triethylsilyl-3-phenylisoserine is obtained in the form of a white powder (Yd = 90%) which exhibits the following characteristics:

- 400 MHz ^1H NMR (d_6 -DMSO) (δ ppm): 8.46 (1H, d, J = 9.3 Hz), 7.82 (2H, d, J = 7.1 Hz), 7.54 (1H, t, J = 7.2 Hz), 7.47 (4H, m), 7.32 (2H, t), 7.36 (1H, t), 5.44 (1H, dd, J = 9.2 and 5.5 Hz), 4.64 (1H, d, J = 5.6 Hz), 0.77 (9H, m), 0.45 (6H, m).

Example 8:

(1S,2R,5S)-(+)-Menthyl (2R,3S)-N-benzoyl-O-(2,2,2-trichloroethoxy)carbonyl-3-phenylisoserinate



480 mg (3.96 mmol) of 4-dimethylaminopyridine are added to a stirred solution at room temperature under an inert atmosphere of 1.38 g (3.3 mmol) of (1S,2R,5S)-(+)-menthyl (2R,3S)-N-benzoyl-3-phenylisoserinate in 30 mL of anhydrous dichloromethane. After stirring for 10 min, 540 μL (3.96 mmol) of 2,2,2-trichloroethoxycarbonyl chloride are added over 5 min. After stirring for 2 h at room temperature and monitoring by T.L.C., the organic phase is washed with a saturated sodium hydrogencarbonate

solution (2 x 10 mL) and with a saturated sodium chloride solution (10 mL), dried over MgSO₄ and concentrated under reduced pressure. After purifying the residue obtained by silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 5/1), 1.60 g of (1S,2R,5S) - (+) -menthyl (2R,3S) -N-benzoyl-O-(2,2,2-trichloroethoxy)carbonyl-3-phenylisoserinate are obtained in the form of a colourless syrup (Yd = 82%).

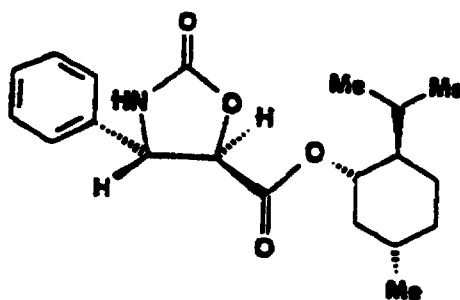
The compound obtained exhibits the following characteristics:

• 400 MHz ¹H NMR (CDCl₃) (δ ppm): 7.82 (2H, d, J = 7.4 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.44 (4H, m), 7.35 (2H, t, J = 7 Hz), 7.29 (1H, t, J = 7 Hz), 7.09 (1H, d, J = 9.3 Hz), 6.0 (1H, dd, J = 9.3 and 2.5 Hz), 5.45 (1H, d, J = 2.6 Hz), 4.78 and 4.72 (2H, 2d, J = 11.9 Hz), 4.77 (1H, m), 1.85 (1H, m), 1.79 (1H, m), 1.65 (2H, m), 1.43 (1H, m), 1.02 (1H, m), 0.96 (1H, m), 0.86 (1H, m), 0.83 (3H, d, J = 7 Hz), 0.78 (3H, d, J = 6.5 Hz), 0.68 (3H, d, J = 6.9 Hz).

20

Example 9:

(1S,2R,5S) - (+) -Menthyl (4S,5R) -4-phenyloxazolidin-2-one-5-carboxylate



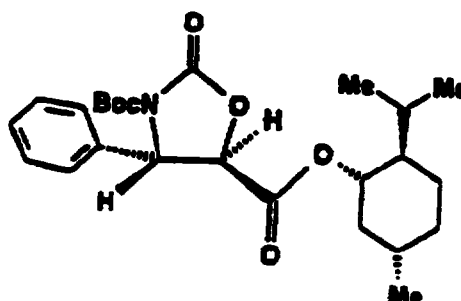
1 mL (7.28 mmol) of 1,8-diazabicyclo[5,4,0]-undec-7-ene is added to a stirred solution at room temperature under an inert atmosphere of 3.96 g (6.62 mmol) of (1S,2R,5S)-(+)-menthyl (2R,3S)-N-benzoyl-O-(2,2,2-trichloroethoxy)carbonyl-3-phenylisoserinate in 30 mL of anhydrous dichloromethane. After stirring for 30 min at room temperature, the organic phase is washed with 10 mL of a saturated sodium chloride solution, dried over MgSO₄ and concentrated under reduced pressure. After purifying the residue by silica gel chromatography (15-40 μ m) (eluent: cyclohexane/ethyl acetate, 7/3), 2.18 g of the compound cited in the title are obtained in the form of a yellow syrup (Yd = 95%).

15 The compound obtained exhibits the following characteristics:

- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 7.40 (5H, m), 6.09 (1H, s), 4.93 (1H, d, J = 5.3 Hz), 4.86 (1H, dt, J = 11 and 4.4 Hz), 4.73 (1H, d, J = 5.4 Hz), 2.05 (1H, m), 1.81 (1H, m), 1.71 (2H, m), 1.54 to 1.41 (3H, m), 1.07 (2H, m), 0.94 (3H, d, J = 6.5 Hz), 0.88 (3H, d, J = 7 Hz), 0.77 (3H, d, J = 7 Hz).

Example 10:

(1S,2R,5S) - (+) -Menthyl (4S,5R) -N-t-butoxycarbonic-4-phenyloxazolidin-2-one-5-carboxylate



3.8 mL (6.07 mmol) of a 1.6M solution of
 5 n-butyllithium in hexane are added to a stirred
 solution at -40°C under an inert atmosphere of 1.91 g
 (5.52 mmol) of (1S,2R,5S) - (+) -menthyl (4S,5R) -4-
 phenyloxazolidin-3-one-5-carboxylate in 20 mL of
 anhydrous tetrahydrofuran. After stirring for 10 min at
 10 -40°C, a solution of 1.81 g (8.28 mmol) of
 t-butoxycarbonic anhydride in solution in 5 mL of
 tetrahydrofuran is added and the reaction mixture is
 allowed to return to room temperature over 15 min.
 After diluting with 50 mL of dichloromethane and
 15 washing with a 2% aqueous HCl solution until a pH = 5
 is obtained, the organic phase is dried (MgSO₄) and
 concentrated under reduced pressure. After purifying
 the crude product by silica gel chromatography
 (15-40 μm) (eluent: cyclohexane/ethyl acetate, 5/1),
 20 2.12 g of the compound cited in the title are obtained
 in the form of a colourless syrup (Yd = 86%).

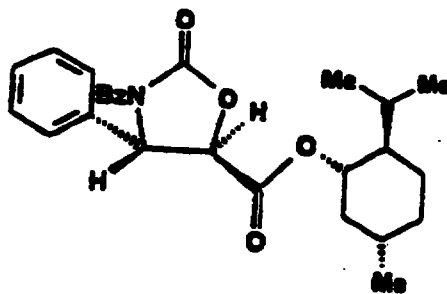
The compound thus obtained exhibits the

following characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 7.45 to 7.26 (5H, m), 5.19 (1H, d, $J = 3.7$ Hz), 4.86 (1H, dt, $J = 10.9$ and 4.5 Hz), 4.66 (1H, d, $J = 3.7$ Hz), 2.05 (1H, m), 1.79 (1H, m), 1.73 (2H, m), 1.62 to 1.24 (3H, m), 1.33 (9H, s), 1.11 (2H, m), 0.94 (3H, d, $J = 6.5$ Hz) and (1H, m), 0.89 (3H, d, $J = 7$ Hz), 0.77 (3H, d, $J = 7$ Hz).

Example 11:

(1S,2R,5S) - (+) -Menthyl (4S,5R) -3-*N*-benzoyl-4-phenyloxazolidin-3-one-5-carboxylate



0.25 mL (2.17 mmol) of benzoyl chloride is added to a stirred solution at room temperature under an inert atmosphere of 500 mg (1.45 mmol) of (1S,2R,5S) - (+) -menthyl (4S,5R) -4-phenyloxazolidin-3-one-5-carboxylate and 176 mg (1.16 mmol) of 4-pyrrolidinopyridine in 7 mL of anhydrous dichloromethane. After stirring for 3 h at 50°C, the reaction mixture is brought back to room temperature and diluted with 20 mL of dichloromethane. The organic phase is washed with 10 mL of a saturated sodium chloride solution, dried over MgSO_4 and concentrated under reduced pressure. After purifying the crude

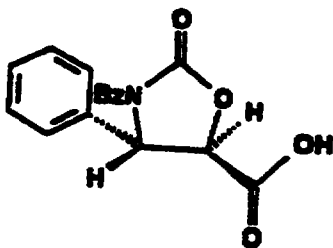
product by silica gel chromatography (15-40 μ m)
(eluent: cyclohexane/ethyl acetate, 5/1), 300 mg of the
compound cited in the title are obtained in the form of
a colourless syrup (Yd = 46%).

5 The compound thus obtained exhibits the
following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.16 (2H, d,
J = 7.1 Hz), 7.68 (1H, t), 7.53 (4H, m), 7.43 (3H, m),
5.57 (1H, d, J = 4.4 Hz), 4.90 (1H, dt, J = 10.9 and
10 4.4 Hz), 4.85 (1H, d, J = 4.3 Hz), 2.07 (1H, m), 1.80
(1H, m), 1.72 (2H, m), 1.47 (3H, m), 1.09 (2H, m), 0.95
(3H, d, J = 6.5 Hz), 0.88 (3H, d, J = 7 Hz), 0.78 (3H,
d, J = 7 Hz).

Example 12:

15 **(4S,5R)-3-N-Benzoyl-4-phenyloxazolidin-3-one-5-carboxylic acid**



A solution of 75 mg (0.543 mmol) of potassium
carbonate in 1 mL of water is added to a stirred
mixture at room temperature of 120 mg (0.266 mmol) of
20 (1S,2R,5S)-(+)-menthyl (4S,5R)-3-N-benzoyl-4-
phenyloxazolidin-3-one-5-carboxylate in 2 mL of
methanol. After stirring for 30 min, the reaction
mixture is diluted with 10 mL of water and the aqueous

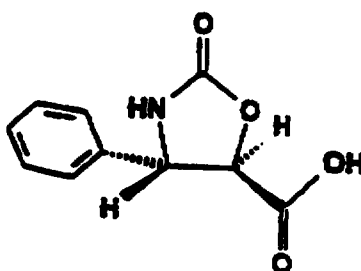
phase is washed with 5 mL of dichloromethane. After acidifying to pH = 4 by means of 1M HCl, the residual aqueous phase is extracted with ethyl acetate (3 × 10 mL). The combined organic phases are washed with 5 mL of a saturated sodium chloride solution, dried over MgSO₄ and concentrated under reduced pressure.

40 mg of (4S,5R)-3-*N*-benzoyl-4-phenyloxazolidin-3-one-5-carboxylic acid are obtained in the form of a white powder (Yd = 52%) which exhibits the following characteristics:

• 400 MHz ¹H NMR (d₆-DMSO) (δ ppm): 12.98 (1H, broad s), 7.95 (2H, d, J = 7.1 Hz), 7.63 (1H, t, J = 7.4 Hz), 7.50 (2H, t, J = 7.5 Hz), 7.42 (2H, m), 7.37 (3H, m), 4.90 (1H, d, J = 5 Hz), 4.77 (1H, d, J = 5 Hz).

Example 13:

(4S,5R)-4-Phenyloxazolidin-3-one-5-carboxylic acid



10 mL of a homogeneous solution of 360 mg (8.67 mmol) of NaOH, 3 mL of methanol and 0.5 mL of water in pyridine are rapidly added to a stirred solution at 0°C under an inert atmosphere of 300 mg (0.867 mmol) of (1S,2R,5S)-(+)-menthyl (4S,5R)-4-

phenyloxazolidin-2-one-5-carboxylate, 3 mL of methanol and then 0.5 mL of water in 6.5 mL of pyridine. After stirring for 20 min at 0°C, the reaction mixture is diluted with water (30 mL) and washed with
 5 dichloromethane (30 mL). After acidifying to a pH = 1, the residual aqueous phase is extracted with ethyl acetate (3 x 20 mL) and the combined organic phases are dried (MgSO₄) and concentrated under reduced pressure.

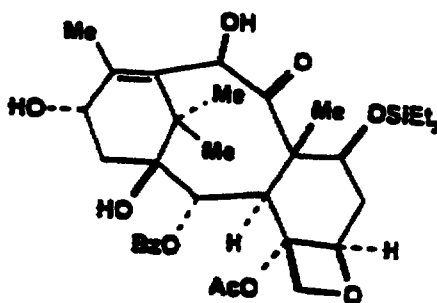
86 mg of (4S,5R)-4-phenyloxazolidin-3-one-5-carboxylic acid are thus obtained in the form of a
 10 yellow syrup (Yd = 53%) which exhibits the following characteristics:

- 400 MHz ¹H NMR (d₆-DMSO) (δ ppm): 13.33 (1H, broad s), 8.46 (1H, s), 7.38 (5H, m), 4.89 (1H, d, J = 5 Hz),
 15 4.75 (1H, d, J = 5 Hz).

II. Baccatin III derivatives

Example 14:

7-O-Triethylsilyl-10-deacetylbaccatin III



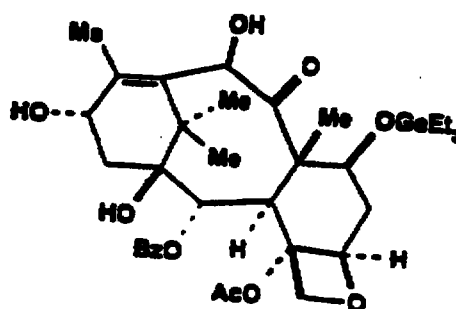
6.2 mL (36.6 mmol) of triethylsilyl chloride
 20 are added over 10 min to a stirred solution, at room temperature and under an inert atmosphere, of 10 g (18.3 mmol) of 10-deacetylbaccatin III and 8.17 g

(54.9 mmol) of 4-pyrrolidinopyridine in 500 mL of anhydrous dichloromethane. After reacting for 3 h at room temperature, 10 g of crushed ice are added and the mixture is left stirring vigorously for 10 min. The
5 residual organic phase is washed with water (200 mL), dried over MgSO_4 and concentrated under reduced pressure.

After treating the crude product obtained with the minimum amount of ethyl acetate, 11.2 g of
10 7-O-triethylsilyl-10-deacetylbaccatin III are obtained in the crystalline state (Yd = 92.3%).

The product thus obtained exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.10 (2H, d, $J = 7.4$ Hz), 7.60 (1H, t, $J = 7.5$ Hz), 7.47 (2H, t, $J = 7.6$ Hz), 5.60 (1H, d, $J = 7$ Hz), 5.17 (1H, d, $J = 1.9$ Hz), 4.96 (1H, d, $J = 8$ Hz), 4.86 (1H, m), 4.41 (1H, dd, $J = 10.6$ and 6.6 Hz), 4.31 and 4.16 (2H, 2d, $J = 8.4$ Hz), 4.26 (1H, d, $J = 1.9$ Hz), 3.95 (1H, d, $J = 6.9$ Hz), 2.48 (1H, ddd, $J = 14.5$, 9.7 and 6.7 Hz),
15 2.29 (3H, s), 2.27 (2H, m), 2.08 (3H, s), 1.90 (1H, m), 1.73 (3H, s), 1.62 (1H, s), 1.08 (6H, s), 0.94 (9H, t, $J = 8$ Hz), 0.56 (6H, m).

Example 15:**7-O-Triethylgermanyl-10-deacetylbaccatin III**

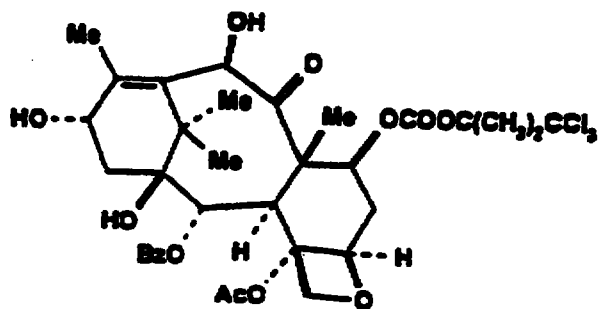
80 μ L (0.476 mmol) of triethylgermanyl chloride are added over 10 min to a stirred solution, at room temperature and under an inert atmosphere, of 100 mg (0.183 mmol) of 10-deacetylbaccatin III and 41 mg (0.275 mmol) of 4-pyrrolidinopyridine in 4 ml of anhydrous dichloromethane and the mixture is stirred at 50°C for 13 h. After cooling the reaction mixture and diluting with 15 mL of dichloromethane, 1 g of crushed ice is added and the mixture is left stirring vigorously for 10 min. The residual organic phase is washed with a saturated sodium hydrogencarbonate solution (5 mL) and a saturated sodium chloride solution (5 mL), dried over MgSO_4 and concentrated under reduced pressure. After chromatographing the crude product on silica gel (15-40 μ m) (eluent: cyclohexane/ethyl acetate, 25/75), 67 mg of 7-O-triethylgermanyl-10-deacetylbaccatin III are obtained in the form of a colourless syrup.

The product thus obtained exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.09 (2H, d, $J = 7.1$ Hz), 7.60 (1H, t, $J = 7.4$ Hz), 7.48 (2H, t, $J = 7.6$ Hz), 5.63 (1H, d, $J = 7.1$ Hz), 5.24 (1H, s), 4.99 (1H, d, $J = 8$ Hz), 4.78 (1H, t), 4.32 (1H, d, $J = 8.3$), 4.28 (1H, m), 4.17 (2H, m), 3.97 (1H, d, $J = 7$ Hz), 2.59 (1H, m), 2.30 (3H, s), 2.24 (1H, m), 2.10 (1H, m), 2.03 (3H, s), 1.82 (1H, m), 1.73 (3H, s), 1.11 (9H, m), 1.0 (6H, t, $J = 7.7$ Hz).

Example 16:

10 **7-*O*-(2,2,2-Trichloro-*t*-butoxycarbonyl)-10-deacetylbaecatin III**



3.3 g (13.8 mmol) of 2,2,2-trichloro-*t*-butoxycarbonyl chloride are added over 2 h to a stirred solution at 40°C under an inert atmosphere of 5 g (9.19 mmol) of 10-deacetylbaecatin III and 1.1 mL of anhydrous pyridine in 250 mL of dry dichloromethane. After reacting for an additional 30 min and returning to room temperature, the organic solution is washed with a 2% aqueous HCl solution (30 mL), washed with osmosed water (2 × 100 mL), dried over MgSO_4 and concentrated under reduced pressure ($\text{Yd} = 55\%$). After chromatographing the crude product on silica gel

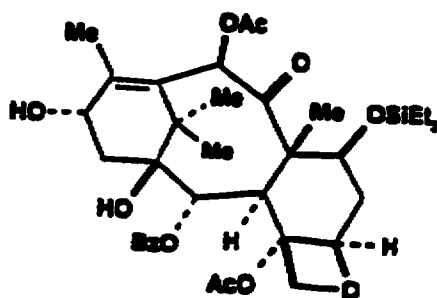
(15-40 μ m) (eluent: cyclohexane/ethyl acetate, 60/40),
7-O-(2,2,2-trichloro-*t*-butoxycarbonyl)-10-
deacetylbaecatin III is obtained in the form of a white
powder.

5 The product obtained exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.10 (2H, d, $J = 7$ Hz), 7.62 (1H, t, $J = 7.4$ Hz), 7.49 (2H, t, $J = 7.6$ Hz), 5.65 (1H, d, $J = 6.9$ Hz), 5.44 (1H, dd, $J = 10.8$ and 7.3 Hz), 5.39 (1H, d, $J = 7.5$ Hz), 4.89 (1H, m), 4.35 and 4.20 (2H, 2d, $J = 8.4$ Hz), 4.10 (1H, d, $J = 7$ Hz), 4.01 (1H, d, $J = 1.8$ Hz), 2.64 (1H, m), 2.31 (3H, s), 2.29 (1H, m), 2.11 (3H, d), 2.05 (2H, m), 1.89 (3H, s), 1.09 (3H, s), 1.07 (3H, s).

Example 17:

a) 7-O-Triethylsilylbaccatin III

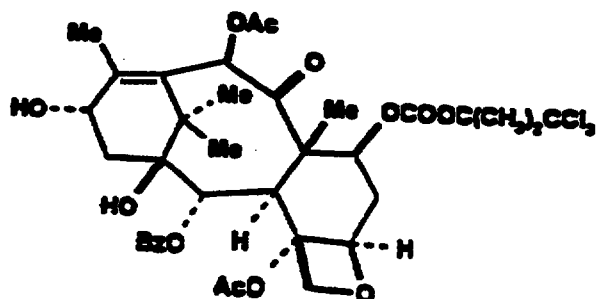


0.54 mL (7.5 mmol) of acetyl chloride is added over 10 min to a stirred solution at room temperature under an inert atmosphere of 1 g (1.5 mmol) of 7-O-triethylsilyl-10-deacetylbaccatin III and 1.25 mL (15 mmol) of pyridine in 15 mL of dry

dichloromethane. After reacting for 2 h at room temperature and monitoring by T.L.C., 1 g of crushed ice is added and the mixture is left stirring vigorously for 10 min. The residual organic phase is washed with water (2 x 10 mL), dried over MgSO₄ and concentrated under reduced pressure. After silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 60/40), 0.756 g of 7-O-triethylsilylbaccatin III is obtained in the form of a white powder (Yd = 70%).

The compound obtained exhibits the following characteristics:

- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 8.11 (2H, d, J = 7.1 Hz), 7.6 (1H, t, J = 7.4 Hz), 7.48 (2H, t, J = 7.7 Hz), 6.46 (1H, s), 5.63 (1H, d, J = 7 Hz), 4.96 (1H, d, J = 8.1 Hz), 4.83 (1H, m), 4.49 (1H, dd, J = 10.4 and 6.7 Hz), 4.31 and 4.15 (2H, 2d, J = 8.3 Hz), 3.88 (1H, d, J = 7 Hz), 2.53 (1H, m), 2.29 (3H, s), 2.27 (2H, m), 2.19 (3H, d, J = 0.8 Hz), 2.18 (3H, s), 2.12 (1H, d), 1.88 (1H, m), 1.68 (3H, s), 1.65 (1H, s), 1.2 (3H, s), 1.04 (3H, s), 0.92 (9H, t), 0.59 (6H, m).

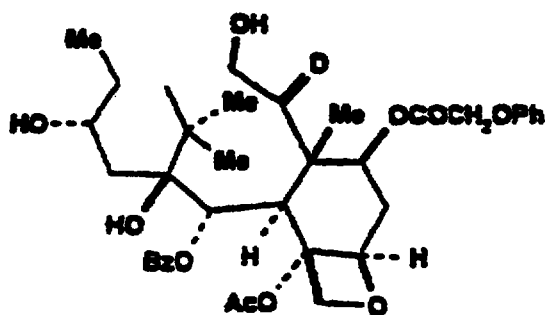
Example 18:**7-O-(2,2,2-Trichloro-t-butoxycarbonyl)-
baccatin III**

50 μ L (0.695 mmol) of acetyl chloride are
 5 added to a stirred solution at room temperature under
 an inert atmosphere of 260 mg of 7-O-(2,2,2-trichloro-
 t-butoxycarbonyl-10-deacetylbaccatin III and 127.5 mg
 (1.04 mmol) of 4-dimethylaminopyridine in 2.5 mL of dry
 dichloromethane. After reacting for 1 h at room
 10 temperature, the organic phase is washed with a 2%
 aqueous HCl solution until a pH = 6 is obtained, dried
 over MgSO_4 and concentrated under reduced pressure.
 After chromatographing the residue obtained on silica
 gel (15-40 μ m) (eluent: cyclohexane/ethyl acetate,
 15 6/4), 0.23 g of 7-O-(2,2,2-trichloro-t-
 butoxycarbonyl)baccatin III is obtained in the solid
 state (Yd = 83%).

The compound obtained exhibits the following
 characteristics:

20 • 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.11 (2H, d,
 J = 7.1 Hz), 7.62 (1H, t, J = 7.4 Hz), 7.49 (2H, t,
 J = 7.6 Hz), 6.39 (1H, s), 5.64 (1H, d, J = 6.9 Hz),

5.61 (1H, dd, $J = 10.7$ and 7.2 Hz), 4.99 (1H, d, $J = 8.2$ Hz), 4.87 (1H, m), 4.33 and 4.16 (2H, 2d, $J = 8.4$ Hz), 4.02 (1H, d, $J = 6.9$ Hz), 2.64 (1H, ddd, $J = 14.4$, 9.5 and 7.2 Hz), 2.30 (3H, s) and (2H, m),
 5 2.17 (3H, s), 2.13 (3H, d, $J = 0.8$ Hz), 2.04 (1H, m),
 1.83 (3H, s), 1.63 (1H, s), 1.14 (3H, s), 1.09 (3H, s).

Example 19:**7-O-Phenoxyacetyl-10-deacetylbaaccatin III**

1.05 mL (7.5 mmol) of phenoxyacetyl chloride
 10 are added over 10 min to a stirred solution, at room
 temperature and under an inert atmosphere, of 1.03 g
 (1.88 mmol) of 10-deacetylbaaccatin III and 0.6 mL
 (7.5 mmol) of anhydrous pyridine in 100 mL of dry
 dichloromethane. After reacting for 30 min at room
 15 temperature and monitoring by T.L.C., the organic
 solution is washed with a 2% aqueous HCl solution until
 a pH = 2 is obtained, washed with osmosed water
 (2 x 50 mL), dried over MgSO_4 and concentrated under
 reduced pressure (Yd = 70.5%). After chromatographing
 20 the crude product on silica gel (15-40 μm) (eluent:
 cyclohexane/ethyl acetate, 60/40), 7-O-phenoxyacetyl-
 10-deacetylbaaccatin III is obtained in the form of a

white powder.

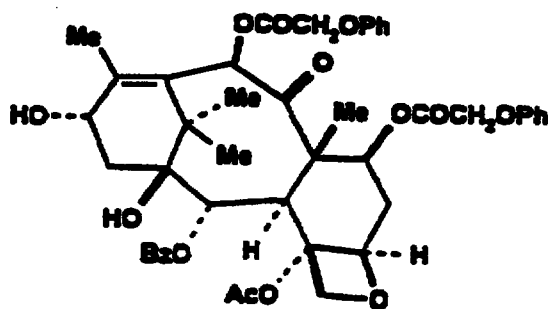
The product obtained exhibits the following characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.09 (2H, d, $J = 7.3$ Hz), 7.61 (1H, t, $J = 7.4$ Hz), 7.48 (2H, t, $J = 7.6$ Hz), 7.31 (2H, t, $J = 7.7$ Hz), 6.99 (3H, m), 6.42 (1H, s), 5.61 (1H, d, $J = 7$ Hz), 4.97 (1H, d, $J = 7.8$ Hz), 4.86 (3H, m), 4.44 (1H, dd, $J = 10.6$ and 6.8 Hz), 4.30 and 4.15 (2H, 2d, $J = 8.4$ Hz), 3.86 (1H, d, $J = 7$ Hz), 2.56 (1H, m), 2.27 (3H, s), 2.27 (2H, m), 2.05 (3H, s), 1.86 (1H, m), 1.68 (3H, s), 1.01 (3H, s), 0.98 (3H, s).

Example 20:

7,10-O-Di(phenoxyacetyl)-10-deacetylbaccatin

15 **III**



- 0.5 mL (3.68 mmol) of phenoxyacetyl chloride is added over 10 min to a stirred solution, at room temperature and under an inert atmosphere, of 500 mg (0.92 mmol) of 10-deacetylbaccatin III and 0.6 mL (7.36 mmol) of anhydrous pyridine in 50 mL of dry dichloromethane. After reacting for 6 h at room temperature and monitoring by T.L.C., the solution is

washed with a 2% aqueous HCl solution until a pH = 2 is obtained, washed with osmosed water (2 x 20 mL), dried over MgSO₄ and concentrated under reduced pressure.

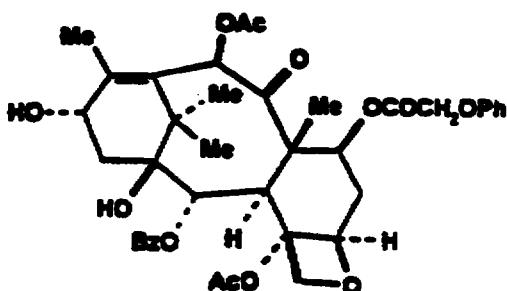
After chromatographing the crude product on silica gel
5 (15-40 μm) (eluent: cyclohexane/ethyl acetate, 6/4),
0.55 g of 7-10-O-bis(phenoxyacetyl)-10-deacetylbaccatin
III is obtained in the form of a white powder
(Yd = 74%).

The product obtained exhibits the following
10 characteristics:

- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 8.09 (2H, d,
J = 7.1 Hz), 7.61 (1H, t, J = 7.4 Hz), 7.48 (2H, t,
J = 7.6 Hz), 7.29 (2H, t, J = 6.8 Hz), 7.22 (2H, t,
J = 7.5 Hz), 6.96 (4H, m), 6.84 (2H, d, J = 7.9 Hz),
15 6.42 (1H, s), 5.69 (1H, dd, J = 10.5 and 7.1 Hz), 5.60
(1H, d, J = 6.9 Hz), 4.96 (1H, d, J = 8.2 Hz), 4.84
(1H, t, J = 7.4 Hz), 4.8 (2H, s), 4.65 and 4.41 (2H,
2d, J = 15.8 Hz), 4.32 and 4.14 (2H, 2d, J = 8.4 Hz),
3.98 (1H, d, J = 6.8 Hz), 2.65 (1H, m), 2.28 (3H, s),
20 2.26 (2H, m), 2.09 (3H, s), 1.80 (3H, s) and (1H, m),
0.98 (6H, s).

Example 21:

7-O-Phenoxyacetylbaccatin III



0.233 mL (3.27 mmol) of acetyl chloride is added over 10 min to a stirred solution, at room temperature and under an inert atmosphere, of 1.11 g (1.64 mmol) of 7-O-phenoxyacetyl-10-deacetylbaccatin III in 40 mL of anhydrous pyridine. After reacting for 16 h at room temperature and monitoring by T.L.C., the reaction mixture is diluted with 50 mL of osmosed water and the aqueous phase is extracted with ethyl acetate (3 × 30 mL). The combined organic phases are washed with water (2 × 20 mL), dried over MgSO₄ and concentrated under reduced pressure (Yd = 84.5%). After silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 60/40), 7-O-phenoxyacetyl-baccatin III is obtained in the crystalline state.

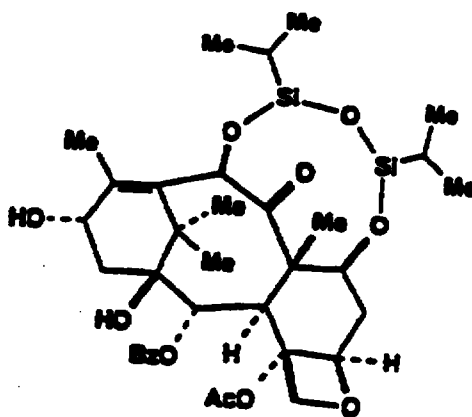
The product obtained exhibits the following characteristics:

- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 8.10 (2H, d, J = 7.1 Hz), 7.61 (1H, t, J = 7.4 Hz), 7.48 (2H, t, J = 7.7 Hz), 7.27 (2H, t, J = 8 Hz), 6.95 (3H, m), 6.26 (1H, s), 5.71 (1H, dd, J = 10.4 and 7.2 Hz), 5.62 (1H,

d, $J = 6.9$ Hz), 4.96 (1H, d, $J = 8.3$ Hz), 4.80 (1H, m),
 4.81 and 4.53 (2H, 2d, $J = 16$ Hz), 4.32 and 4.14 (2H,
 2d, $J = 8.5$ Hz), 4.0 (1H, d, $J = 6.9$ Hz), 2.64 (1H, m),
 2.29 (2H, m), 2.28 (3H, s), 2.24 (1H, d, $J = 5$ Hz),
 5 2.16 (3H, s), 2.09 (3H, d, $J = 0.7$ Hz), 1.81 (1H, m),
 1.78 (3H, s), 1.13 (3H, s), 1.08 (3H, s).

Example 22;

**7-10-0-(1,1,3,3-Tetraisopropyl-1,3-
 disiloxanediyl)-10-deacetylbaecatin III**



10 1.28 ml (2.05 mmol) of *n*-butyllithium as a
 1.6M solution in hexane are added over 10 min to a
 stirred solution, at -40°C and under an inert
 atmosphere, of 500 mg (0.93 mmol) of 10-deacetyl-
 baecatin III in 20 mL of anhydrous tetrahydrofuran.
 15 After stirring for 5 min, 350 μL (1.12 mmol) of 1,3-
 dichloro-1,1,3,3-tetraisopropyldisiloxane are added and
 the reaction mixture is allowed to return to room
 temperature over 20 min. After stirring for 1 h at room
 temperature, 225 mg (2.05 mmol) of 4-dimethylamino-
 20 pyridine are added and the reaction mixture is left

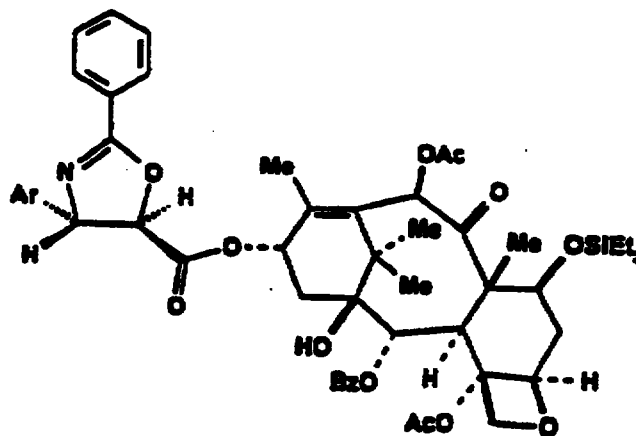
stirring for an additional 1 h. After adding 20 mL of a saturated aqueous sodium chloride solution, the mixture is extracted with dichloromethane (3 x 30 mL). The combined organic phases are washed with a saturated aqueous sodium chloride solution (20 ml), dried over MgSO₄ and concentrated under reduced pressure. After purifying by silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 60/40), 480 mg of 7,10-O-(1,1,3,3-tetraisopropyl-1,3-disyloxanediyl)-10-deacetylbaecatin III are obtained in the amorphous state (Yd = 65%).

The product obtained exhibits the following characteristics:

• 400 MHz ¹H NMR (CDCl₃) (δ ppm): 8.10 (2H, d, J = 7.2 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.47 (2H, t, J = 7.6 Hz), 5.60 (1H, s), 5.59 (1H, d), 4.97 (1H, d, J = 7.9 Hz), 4.87 (1H, m), 4.68 (1H, dd, J = 10.4 and 6.9 Hz), 4.30 and 4.17 (2H, 2d, J = 8.5 Hz), 3.92 (1H, d, J = 7.1 Hz), 2.49 (1H, m), 2.28 (3H, s), 2.27 (1H, m), 2.04 (1H, m), 1.91 (1H, m), 1.67 (3H, s), 1.55 (1H, s), 1.32 to 0.85 (34H, m).

Example 23:

13-O-[[(4S,5R)-2,4-Diphenyl-4,5-dihydroxazol-5-yl]carbonyl]-7-O-triethylsilylbaccatin III



2.06 g (10 mmol) of dicyclohexylcarbodiimide
 5 are added to a stirred solution, at room temperature
 and under an inert atmosphere, of 2.67 g (10 mmol) of
 (4S,5R)-2,4-diphenyl-4,5-dihydroxazol-5-carboxylic acid
 in 55 mL of anhydrous toluene. After stirring for
 5 min, 3.5 g (5 mmol) of 7-O-triethylsilylbaccatin III
 10 and 0.61 g (5 mmol) of 4-dimethylaminopyridine are
 added and the reaction mixture is brought to 70°C for
 1 h. After returning to room temperature and removing
 the insoluble materials by filtration, the organic
 phase is concentrated under reduced pressure. After
 15 purifying the crude product by silica gel
 chromatography (15-25 μ m) (eluent: cyclohexane/ethyl
 acetate, 90/10).

4.62 g of 13-O-[[(4S,5R)-2,4-diphenyl-4,5-
 dihydroxazol-5-yl]carbonyl]-7-O-triethylsilylbaccatin
 20 III are obtained in the crystalline state (Yd = 97%).

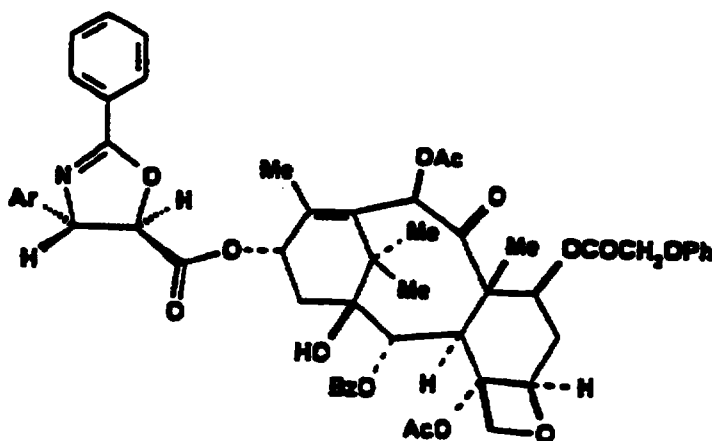
The compound thus obtained exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.23 (2H, d, $J = 7.2$ Hz), 8.07 (2H, d, $J = 7.3$ Hz), 7.63 (1H, t, $J = 7.4$ Hz), 7.58 (1H, t, $J = 7.4$ Hz), 7.49 (4H, m), 7.38 (5H, m), 6.42 ((1H, s), 6.18 (1H, t, $J = 8.2$ Hz), 5.68 (1H, d, $J = 7.1$ Hz), 5.60 (1H, d, $J = 6.5$ Hz), 4.95 (2H, d), 4.50 (1H, dd, $J = 10.5$ and 6.7 Hz), 4.29 (1H, d, $J = 8.4$ Hz), 4.14 (1H, d, $J = 8.4$ Hz), 3.83 (1H, d, $J = 7.1$ Hz), 2.55 (1H, m), 2.37 (1H, dd, $J = 15.3$ and 9.3 Hz), 2.26 (1H, dd, $J = 15.3$ and 8.6 Hz), 2.16 (3H, s), 2.07 (3H, s), 1.99 (3H, s), 1.89 (1H, m), 1.72 (1H, s), 1.69 (3H, s), 1.23 (3H, s), 1.19 (3H, s), 0.92 (9H, t, $J = 8$ Hz), 0.57 (6H, m).

15

Example 24:

13-O-[[4S,5R)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-phenoxyacetylbaccatin III



380 mg (1.84 mmol) of dicyclohexylcarbodiimide are added to a stirred solution, at room temperature and under an inert atmosphere, of 490 mg

20

(1.83 mmol) of (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid in 10 mL of anhydrous toluene. After stirring for 5 min, 660 mg (0.92 mmol) of 7-O-phenoxyacetylbaaccatin III and 112 mg (0.92 mmol) of 4-dimethylaminopyridine are added and the reaction mixture is brought to 70°C for 2 h.

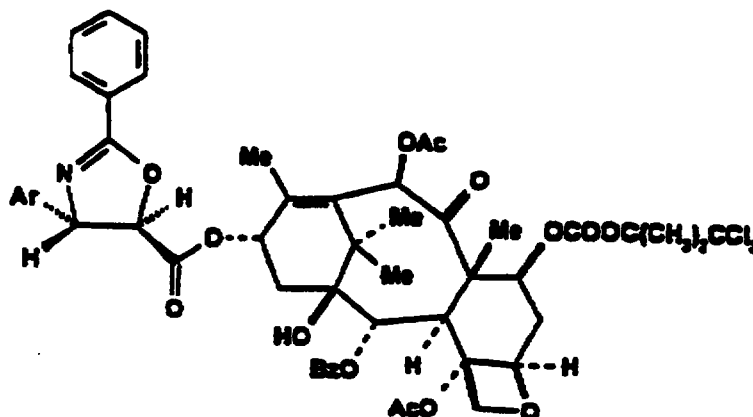
After returning to room temperature and removing the insoluble materials by filtration, the organic phase is concentrated under reduced pressure. After purifying the crude product by silica gel chromatography (15-40 μ m) (eluent: cyclohexane/ethyl acetate, 99/1), 800 mg of 13-O-[[4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-phenoxyacetylbaaccatin III are obtained in the crystalline state (Yd = 90%).

The compound thus obtained exhibits the following characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.18 (2H, d, $J = 7$ Hz), 8.07 (2H, d, $J = 7.3$ Hz), 7.63 (1H, t, $J = 7.4$ Hz), 7.59-7.32 (10H, m), 7.28 (2H, t, $J = 7.5$ Hz), 6.94 (3H, m), 6.23 (1H, s) and (1H, m), 5.70 (1H, dd, $J = 10.4$ and 7.1 Hz), 5.67 (1H, d, $J = 7.3$ Hz), 5.58 (1H, d, $J = 7$ Hz), 4.93 (2H, d), 4.79 and 4.53 (2H, 2d, $J = 15.9$ Hz), 4.30 and 4.13 (2H, 2d, $J = 8.5$ Hz), 3.97 (1H, d, $J = 6.9$ Hz), 2.67 (1H, m), 2.38 (1H, dd, $J = 15.2$ and 9.3 Hz), 2.26 (1H, dd, $J = 15.2$ and 8.4 Hz), 2.15 (3H, s), 2.02 (3H, s), 1.95 (3H, s) and (1H, m), 1.80 (3H, s), 1.74 (1H, s), 1.25 (3H, s), 1.17 (3H, s).

Example 25:

13-O-[[[(4S,5R)-2,4-Diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III



5 27 mg (0.13 mmol) of dicyclohexylcarbodiimide are added to a stirred solution, at room temperature and under an inert atmosphere, of 35 mg of (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid in 3 mL of anhydrous toluene. After stirring for 5 min, 51 mg
10 (0.065 mmol) of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III and 8 mg (0.065 mmol) of 4-dimethylaminopyridine are added and the mixture is brought to 70°C for 1 h. After returning to room temperature and removing the insoluble materials by
15 filtration, the organic phase is concentrated under reduced pressure and the residue obtained is purified by silica gel chromatography (15-40 μ m) (eluent: cyclohexane/ethyl acetate, 9/1).

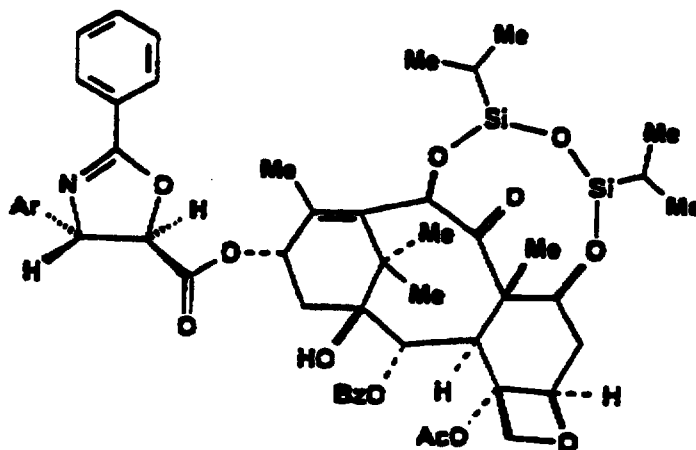
0.99 g of the compound cited in the title is
20 thus obtained in the form of a white solid (Yd = 67%)

which exhibits the following characteristics:

• 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.18 (2H, d, $J = 7.2$ Hz), 8.07 (2H, d, $J = 7.3$ Hz), 7.65 (1H, t, $J = 7.4$ Hz), 7.59 (1H, t, $J = 7.3$ Hz), 7.52 (4H, m),
 5 7.39 (5H, m), 6.35 (1H, s), 6.24 (1H, t, $J = 8.4$ Hz), 5.68 (1H, d, $J = 7.1$ Hz), 5.59 (1H, d, $J = 7$ Hz) and
 (1H, dd), 4.95 (1H, d), 4.94 (1H, d, $J = 7$ Hz), 4.31
 and 4.15 (2H, 2d, $J = 8.4$ Hz), 3.97 (1H, d,
 $J = 6.9$ Hz), 2.64 (1H, m), 2.37 (1H, dd, $J = 15.1$ and
 10 6 Hz), 2.27 (1H, dd, $J = 15.2$ and 8.5 Hz), 2.16 (3H,
 s), 2.01 (3H, s), 1.98 (3H, s), 1.83 (3H, s), 1.72
 (1H, s), 1.25 (3H, s), 1.18 (3H, s).

Example 26:

13-*O*-[[4*S*,5*R*)-2,4-Diphenyl-4,5-dihydrooxazol-
 15 5-yl]carbonyl]-7,10-*O*-(1,1,3,3-tetraisopropyl-1,3-
 disiloxanediyl)-10-deacetylbaccatin III



7 mg (0.06 mmol) of dicyclohexylcarbodiimide
 are added to a stirred solution, at room temperature
 and under an inert atmosphere, of 4 mg (0.015 mmol) of
 20 (4*S*,5*R*)-2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic

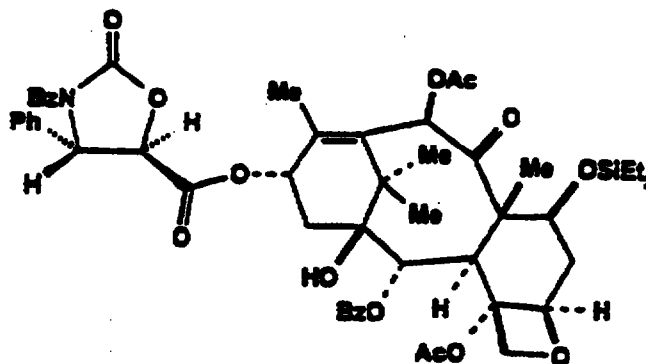
acid in 0.5 mL of anhydrous toluene. After stirring for 5 min, a solution of 5 mg (0.0065 mmol) of 7,10-0-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-10-deacetylbaecatin III and of 1 mg (0.0078 mmol) of 4-dimethylaminopyridine in 1 mL of anhydrous toluene is added. After stirring for 20 min at room temperature, the mixture is brought to 50°C for an additional 20 min. After returning to room temperature, the organic phase is diluted with 5 mL of dichloromethane, washed with 2 mL of a saturated aqueous sodium chloride solution, dried over MgSO₄ and concentrated under reduced pressure. After purifying the crude product by silica gel chromatography (15-25 μ m) (eluent: cyclohexane/ethyl acetate, 7/3), 6 mg of the derivative cited in the title are obtained (Yd = 90%) in the amorphous state.

The compound obtained exhibits the following characteristics:

- 400 MHz ¹H NMR (CDCl₃) (δ ppm): 8.21 (2H, d, J = 7.2 Hz), 8.07 (2H, d, J = 7.6 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.59 (1H, t, J = 7.4 Hz), 7.50 (2H, t, J = 7.4 Hz), 7.39 (5H, m), 6.26 (1H, t), 5.64 (1H, d, J = 7 Hz), 5.59 (1H, d, J = 6.9 Hz), 5.54 (1H, s), 4.93 (1H, d, J = 6.8 Hz) and (1H, m), 4.68 (1H, dd), 4.28 and 4.16 (2H, 2d, J = 8 Hz), 3.84 (1H, d, J = 7.3 Hz), 2.48 (1H, m), 2.35 and 2.25 (2H, 2dd), 2.02 (3H, s), 1.88 (3H, s) and (1H, m), 1.67 (3H, s), 1.63 (1H, s), 1.30 to 0.90 (34H, m).

Example 27:

13-O-[[(4S,5R) -3-N-Benzoyl-4-phenyloxazolidin-3-one-5-yl]carbonyl]-7-O-triethylsilylbaccatin III



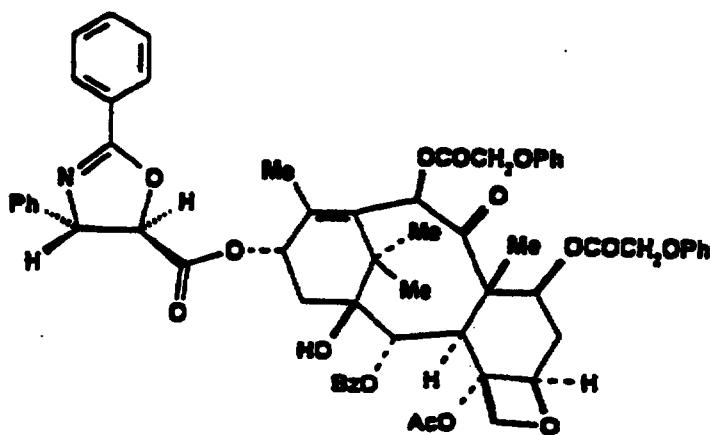
- 5 28 mg (0.136 mmol) of dicyclohexylcarbodiimide are added to a stirred solution at room temperature under an inert atmosphere of 40 mg (0.137 mmol) of (4S,5R)-3-N-benzoyl-4-phenyloxazolidin-3-one-5-carboxylic acid in 2 mL of anhydrous toluene.
- 10 After stirring for 5 min, 30 mg (0.043 mmol) of 7-O-triethylsilylbaccatin III and 8 mg (0.066 mmol) of 4-dimethylaminopyridine are added and the reaction mixture is brought to 60°C for 13 h. After returning to room temperature, the reaction mixture is diluted with
- 15 10 mL of dichloromethane and the organic phase is washed with 5 mL of a saturated sodium chloride solution, dried over MgSO₄ and concentrated under reduced pressure. After purifying by silica gel chromatography (15-14 μm) (eluent: cyclohexane/ethyl
- 20 acetate, 2/1), 13 mg of the derivative cited in the title are obtained in the amorphous state (Yd = 31%).

The compound obtained exhibits the following characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.06 (2H, d, $J = 7.3$ Hz), 7.72 (2H, d, $J = 7$ Hz), 7.63 (1H, t, $J = 7.4$ Hz), 7.58 (1H, t, $J = 7.4$ Hz), 7.54 to 7.44 (8H, m), 7.40 (1H, t), 6.44 (1H, s), 6.33 (1H, t), 5.73 (1H, d, $J = 5.7$ Hz), 5.67 (1H, d, $J = 5.7$ Hz), 4.96 (1H, d, $J = 5.8$ Hz), 4.88 (1H, d, $J = 8.3$ Hz), 4.45 (1H, dd, $J = 10.4$ and 6.6 Hz), 4.27 and 4.12 (2H, 2d, $J = 8.3$ Hz), 3.80 (1H, d, $J = 7$ Hz), 2.50 (1H, m), 2.26 (2H, m), 2.19 (3H, s), 2.07 (3H, s), 1.98 (3H, s), 1.85 (1H, m), 1.76 (1H, s), 1.67 (3H, s), 1.24 (3H, s), 1.23 (3H, s), 0.91 (9H, t, $J = 7.9$ Hz), 0.56 (6H, m).

Example 28:

- 15 13-O-[[**(4S,5R)**-4-Phenyloxazolidin-3-one-5-yl]carbonyl]-7,10-O-di(phenoxyacetyl)-10-deacetylbaccatin III



- 65 mg (0.315 mmol) of dicyclohexylcarbodiimide are added to a stirred solution, at room temperature and under an inert atmosphere, of 78 mg
- 20

(0.293 mmol) of (4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-carboxylic acid in 3 mL of anhydrous toluene. After stirring for 5 min, a solution of 237 mg (0.293 mmol) of 7,10-O-bis(phenoxyacetyl)-10-deacetylbaecatin III and 36 mg (0.295 mmol) of 4-dimethylaminopyridine in 3 mL of toluene is added and the reaction mixture is brought to 60°C for 1 h. After returning to room temperature and removing the insoluble materials by filtration, the organic phase is concentrated under reduced pressure and the crude product obtained is purified by silica gel chromatography (15-40 μ m) (eluent: cyclohexane/ethyl acetate, 1/1).

280 mg of the compound cited in the title are thus obtained in the amorphous state (Yd = 90%), which compound exhibits the following characteristics:

- 400 MHz ^1H NMR (CDCl_3) (δ ppm): 8.18 (2H, d, J = 7 Hz), 8.06 (2H, d, J = 7.1 Hz), 7.64 (1H, t, J = 7.4 Hz), 7.58 (1H, t, J = 7.3 Hz), 7.51 (4H, m), 7.39 (5H, m), 7.25 (4H, m), 6.96 (4H, m), 6.85 (2H, d, J = 8 Hz), 6.33 (1H, s), 6.19 (1H, t, J = 9 Hz), 5.68 (1H, dd, J = 10.5 and 7.1 Hz), 5.65 (1H, d, J = 6.9 Hz), 5.59 (1H, d, J = 7 Hz), 4.93 (2H, d, J = 7.1 Hz), 4.79 (2H, s), 4.63 and 4.40 (2H, 2d, J = 15.9 Hz), 4.30 and 4.13 (2H, 2d, J = 8.4 Hz), 3.94 (1H, d, J = 6.9 Hz), 2.68 (1H, m), 2.37 (1H, dd, J = 15.3 and 9.3 Hz), 2.24 (1H, dd, J = 15.3 and 8.7 Hz), 2.02 (3H, s), 1.95 (3H, s), 1.80 (3H, s) and (1H, m), 1.69 (1H, s), 1.12 (3H, s), 1.01 (3H, s).

III. Hemisynthesis

Example 29:

Preparation of paclitaxel

a) From 13-O-[[**(4S,5R)**-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-triethylsilylbaccatin
5 **III**

0.6 L (0.6 mol) of a 1M aqueous HCl solution is added to a stirred solution, at room temperature and under an inert atmosphere, of 90 g (0.095 mol) of 13-O-
10 [[**(4S,5R)**-2,4-diphenyl-4,5-dihydrooxazol-5-yl]-carbonyl]-7-O-triethylsilylbaccatin **III** in a mixture of tetrahydrofuran (1.2 L) and methanol (1.2 L) and the reaction mixture is stirred at room temperature for 4 h 30. After adding 3.5 L of a saturated aqueous
15 sodium hydrogencarbonate solution, the solution is kept homogeneous by addition of 6 L of tetrahydrofuran and 6 L of water and the reaction mixture is stirred for an additional 1 h 30. After adding 15 L of ethyl acetate and 15 L of osmosed water, the residual aqueous phase
20 is extracted with ethyl acetate (15 L). The organic phase is dried over MgSO₄ and concentrated under reduced pressure and the crude product thus obtained is purified by silica gel chromatography (15-40 μm) (eluent: cyclohexane/ethyl acetate, 1/1).

25 75 g of taxol are thus isolated in the crystalline state (Yd = 95%), the characteristics of which are in every respect in accordance with the literature data.

b) From 13-O-[[[(4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III

90 μ L (0.09 mmol) of a 1M aqueous HCl solution are added to a stirred solution, at room temperature and under an inert atmosphere, of 15 mg (0.0148 mmol) of 13-O-[[[(4S,5R)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]-7-O-(2,2,2-trichloro-t-butoxycarbonyl)baccatin III in a mixture of 10 tetrahydrofuran (0.18 mL) and methanol (0.18 mL) and the reaction mixture is stirred at room temperature for 8 h. After adding 0.6 mL of a saturated aqueous sodium hydrogencarbonate solution, the solution is kept homogeneous by addition of 1 mL of tetrahydrofuran and 15 1 mL of water and the reaction mixture is stirred for an additional 1 h 30. After adding 2.5 mL of ethyl acetate and 2.5 mL of osmosed water, the residual aqueous phase is extracted with ethyl acetate (2.5 mL). The combined organic phases are dried over MgSO_4 and 20 concentrated under reduced pressure.

14 mg of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)taxol are thus obtained in the crude state (Yd = 93%), which product is used without additional purification in the following stage.

25 30 μ L (0.525 mmol) of acetic acid and 22.5 mg (0.344 mmol) of zinc powder are added to a stirred solution at room temperature of 13 mg (0.0128 mmol) of 7-O-(2,2,2-trichloro-t-butoxycarbonyl)taxol in 2 mL of

ethyl acetate. After stirring for 2 h 30 at room temperature and monitoring by T.L.C., and after diluting the reaction mixture with 3 mL of ethyl acetate, the organic phase is washed with osmosed water (1 mL), with a saturated aqueous sodium hydrogencarbonate solution (1 mL) and again with water, dried over MgSO_4 and concentrated under reduced pressure.

After chromatographing the crude product on silica gel (15-40 μm) (eluent: cyclohexane/ethyl acetate, 6/4), 9.5 mg of taxol are thus isolated in the crystalline state ($\text{Yd} = 89\%$).



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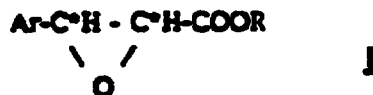
WO 97/15562

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PCT/FR96/01676

CLAIMS

1. Process for the preparation of taxane side chain precursors in which a cis- β -arylglycidate derivative of general formula I



5 in which

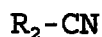
Ar represents an aryl radical and

R represents a hydrocarbon radical, preferably a linear or branched alkyl or a cycloalkyl optionally substituted by one or more alkyl

10 groups,

is converted, so as to regio- and stereospecifically introduce the β -N-alkylamide and the α -hydroxyl or their cyclic precursors in a single stage by a Ritter reaction, which consists either:

15 a of the direct synthesis of a linear chain by reacting a cis- β -arylglycidate derivative of general formula I defined above with a nitrile of formula



20 in which

R2 represents an aryl radical, in the presence of a protonic acid and of water, in order to obtain a β -arylisoserine derivative of general formula IIa,

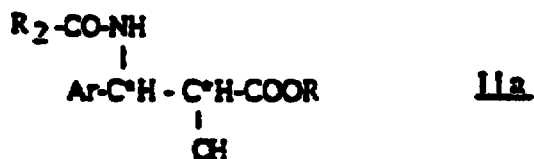
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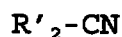
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in which Ar, R and R_2 are defined above; or

b of the direct synthesis of a cyclic chain by reacting a cis- β -arylglycidate derivative of general formula I defined above with a nitrile of formula



in which

R'_2 represents R_2 defined above or a lower alkyl or lower perhaloalkyl radical, such as trichloromethyl,

in the presence of a Lewis acid or of a protonic acid, in anhydrous medium, in order to obtain the oxazoline of general formula IIb



in which Ar, R and R'_2 are defined above.

2. Process according to claim 1, characterized in that R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical, advantageously a cycloalkyl substituted by one or more alkyl groups, in particular a cyclohexyl.

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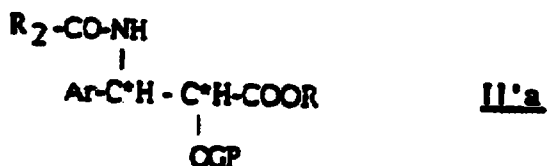
3. Process according to claim 2,
characterized in that R is one of the enantiomers of
the menthyl radical, in particular (+)-menthyl.

4. Process according to one of claims 1 to
5 3, characterized in that the cis- β -phenylglycidate
derivative of general formula I is of (2R,3R)
configuration and the derivatives of general formulae
IIa and IIb obtained are of (2R,3S) configuration.

5. Process according to one of claims 1 to
10 4, characterized in that Ar and R₂ represent a phenyl.

6. Process according to one of claims 1 to
5, characterized in that the protonic acid in the stage a
a is chosen from sulphuric acid, perchloric acid or
tetrafluoroboric acid, the Lewis acid in the stage b is
15 chosen from the boron trifluoride acetic acid complex,
boron trifluoride etherate, antimony pentachloride, tin
tetrachloride or titanium tetrachloride and the
protonic acid in the stage b is tetrafluoroboric acid.

7. Process according to one of claims 1 to
20 6, characterized in that the β -arylisoserine derivative
of general formula IIa is converted by protection of
the hydroxyl by an appropriate protective group (GP),
in order to obtain a derivative of general formula II'a



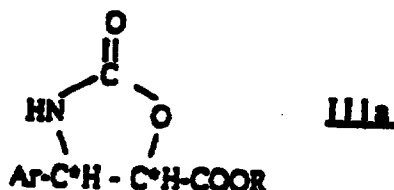
in which





Ar, R and R₂ are defined above and
GP represents a protective group for the hydroxyl
functional group which is appropriate for the synthesis
of taxanes, in particular chosen from alkoxy ether,
5 aralkoxy ether, aryloxy ether or haloalkoxycarbonyl
radicals, such as, for example, methoxymethyl,
1-ethoxyethyl, benzyloxymethyl or (β -trimethyl-
silylethoxy)methyl groups, tetrahydropyranyl or
 β -alkoxycarbonyl radicals, β -halogenated or alkylsilyl
10 ethers, or alkoxyacetyl, aryloxyacetyl, haloacetyl or
formyl radicals.

8. Process according to one of claims 1 to
6, characterized in that the β -arylisoserine derivative
of general formula IIa is converted into novel
15 oxazolidinone cyclic intermediates of general formula
IIIa

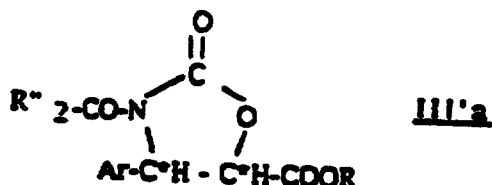


in which Ar and R are defined above
by reacting a β -arylisoserine derivative of general
formula IIa according to one of claims 1 to 5 with a
20 haloalkoxycarbonyl ester, in particular 2,2,2-
trichloroethoxycarbonyl (TrOC), and then by cyclization
in the presence of a strong organic base, such as
diazabicycloundecene (DBU),
optionally converted subsequently into the



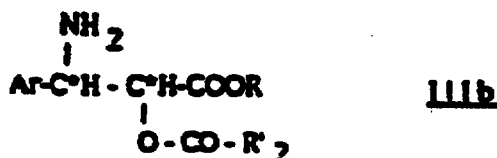


corresponding amide of general formula III'a

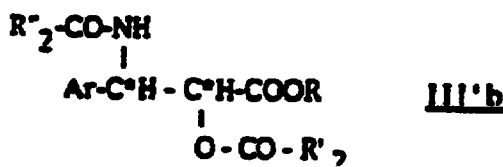


in which Ar and R are defined above and R''₂ represents
R'₂ defined above, an alkoxy radical or a linear or
5 branched alkyl radical comprising at least one
unsaturation.

9. Process according to one of claims 1 to
6, characterized in that the oxazoline of general
formula IIb is hydrolysed in acidic medium in order to
obtain the β-arylisoserine derivative of general
10 formula IIIb,



in which Ar, R and R'₂ are defined above,
optionally converted subsequently into the
corresponding amide of general formula III'b



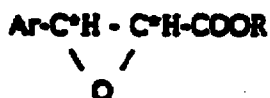
in which Ar, R, R'₂ and R''₂ are defined above.

15 10. Process according to one of claims 1 to
9, characterized in that the cis-β-arylglycidate





derivative of general formula I

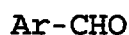


in which

Ar is defined above and

5 R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical,

is prepared by reacting the aldehyde of formula



with the haloacetate of formula



Ar and R being defined above and

X representing a halogen, in particular a chlorine or a bromine.

11. Process according to one of claims 1 to
15 10, characterized in that the derivatives of formulae IIa, II'a, IIb, IIIa, III'a, IIIb and III'b defined above in which R represents a hydrogen atom are obtained by controlled saponification.

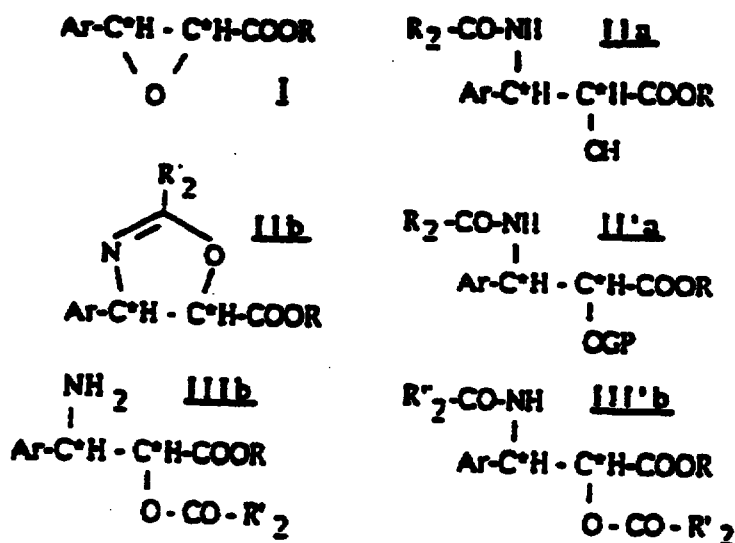
12. Precursor compounds of taxane side
20 chains, characterized in that they are selected from the derivatives of following general formulae I, IIa, IIb, II'a, IIIb and III'b:





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in which

Ar, R₂, R'₂, R''₂ and GP are defined in one of claims 1 to 3 and 5, and

R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical.

13. Compounds according to claim 12, characterized in that R is one of the enantiomers of the menthyl radical, in particular (+)-menthyl.

10 14. Compounds according to either of claims 12 and 13, characterized in that the cis-β-phenylglycidate derivative of general formula I is of (2R,3R) configuration and the derivatives of general formulae IIa, IIb, IIIb and III'b are of (2R,3S) configuration.

15 15. Precursor compounds of taxane side chains, characterized in that they are selected from the derivatives of following general formulae IIIa and

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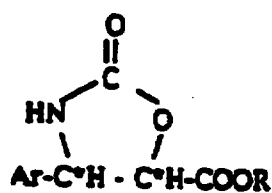




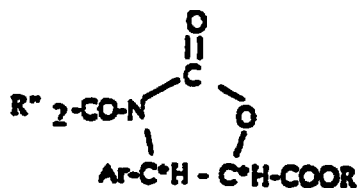
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III'a:



IIIa



III'a

in which

Ar, R and R''2 are defined above or R represents a hydrogen atom.

5 16. Compounds according to claim 15,
characterized in that they are of (2R,3S)
configuration.

17. Process for the preparation of taxanes
of general formula IV,

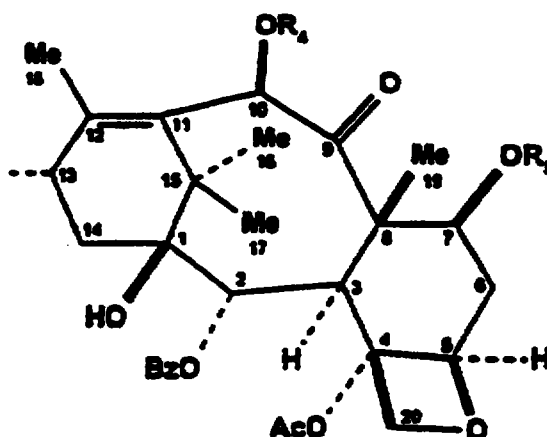
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C-B

IV

in which

B represents a radical of general formula V



in which

Ac represents the acetyl radical,

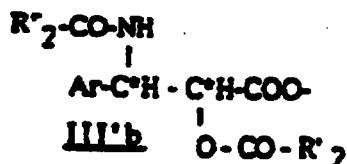
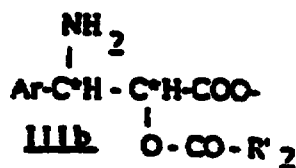
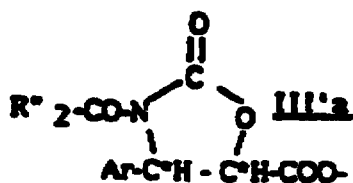
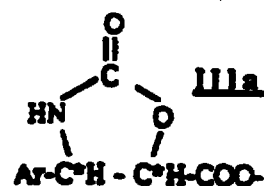
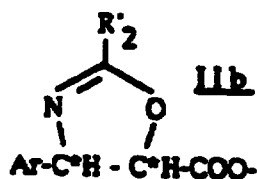
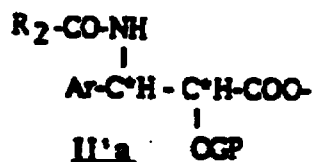
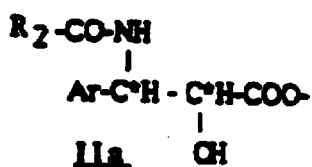
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Bz represents the benzyl radical,
 Me represents the methyl radical,
 R_4 represents an acetyl radical or a protective
 group for the hydroxyl functional group GP1, and
 5 R_5 represents a protective group for the hydroxyl
 functional group GP2, and
 C represents a side chain chosen from the radicals
 of following formulae IIa, II'a, IIb, IIIa, III'a,
 IIIb and III'b:



10 in which Ar, R_2 , R'_2 , R''_2 and GP are defined above,
 by esterification of an appropriate baccatin III
 derivative of general formula V, carrying a C-13

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hydroxyl functional group, with one of the derivatives of formulae IIa, II'a, IIb, IIIa, III'a, IIIb and III'b, for which R represents a hydrogen atom, obtained by the process according to claim 11.

- 5 18. Process according to claim 17, characterized in that the GP1 and GP2 protective groups are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as
- 10 trialkylsilyls or TROC, or linear or branched bulky haloalkoxycarbonyl radicals comprising at least one halogen atom, acyl radicals in which the carbon α to the carbonyl functional group carries at least one oxygen atom, or a trialkylgermanyl radical or GP1 and GP2 together form a divalent radical of formula



in which

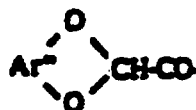
R₇ and R₈, independently of one another, represent a sterically hindered alkyl radical.

19. Process according to either of claims 17
- 20 and 18, characterized in that the acyl radicals in which the carbon α to the carbonyl functional group carries at least one oxygen atom are chosen from
- alkoxy- or aryloxyacetyl radicals of formula



- 25 in which R₆ represents a sterically hindered alkyl radical, a cycloalkyl radical or an aryl radical,
- or arylidenedioxyacetyl radicals of formula





in which Ar["] represents an aryldiene radical.

20. Process according to claim 19,
characterized in that:

the sterically hindered alkyl radical is a
5 linear or branched C₁-C₆ alkyl radical substituted by
one or more bulky substituents chosen from halogens or
linear or branched C₁-C₆ alkyl, linear or branched C₁-C₆
alkoxy or C₃-C₆ cycloalkyl or aryl radicals,

the cycloalkyl radical is a C₃-C₆ cycloalkyl
10 radical optionally substituted by one or more bulky
substituents chosen from halogens or linear or branched
C₁-C₆ alkyl, linear or branched C₁-C₆ alkoxy or aryl
radicals, preferably a cyclohexyl radical substituted
by one or more linear or branched C₁-C₆ alkyl radicals,
15 for example menthyl, its racemate or its enantiomers
and their mixtures in all proportions,

the aryl radical is a phenyl, naphthyl,
anthryl or phenantryl radical optionally substituted by
one or more bulky substituents chosen from halogens or
20 linear or branched C₁-C₆ alkyl, linear or branched C₁-C₆
alkoxy or aryl radicals, in particular the phenyl
radical, preferably a phenyl radical optionally
substituted by one or two above bulky substituents
ortho- and ortho'- to the ether bond, and

25 the aryldiene radical is a phenylene,

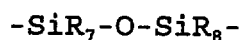




naphthylene, anthrylene or phenanthrylene radical optionally substituted by one or more bulky substituents chosen from halogens or linear or branched C₁-C₆ alkyl, linear or branched C₁-C₆ alkoxy or aryl radicals, in particular the phenyl radical.

21. Process according to either of claims 17 and 18, characterized in that R₄ represents an acetyl radical and GP2 represents a trialkylsilyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2,2,2,1-tetrachloroethoxycarbonyl, 2,2,2-trichloro-t-butoxycarbonyl, trichloromethoxycarbonyl, phenoxyacetyl or trialkylgermanyl radical.

22. Process according to either of claims 17 and 18, characterized in that R₄ represents a GP1 group and GP1 and GP2 represent a 2,2,2-trichloroethoxycarbonyl or phenoxyacetyl radical or together form a divalent radical of formula



in which R₇ and R₈ each represent an isopropyl radical.

23. Process according to one of claims 17 to 21, characterized in that

C represents a radical of formula IIa with Ar and

R₂ representing a phenyl and

R₄ represents an acetyl radical.

24. Process according to one of claims 17 to 23, characterized in that, subsequently, the hydroxyls of the derivatives of general formula IV are

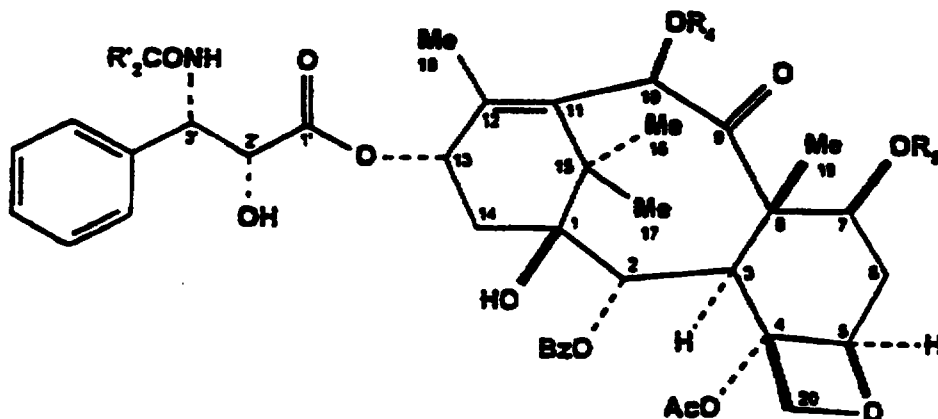
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deprotected and, if appropriate, simultaneously or separately, the oxazoline ring of the radicals of formula IIb or IIIa is opened, in order to produce a taxane derivative of general formula VI



5 in which

Ac, Bz, Me and R'₂ are defined in one of the preceding claims,

R₄ represents a hydrogen atom or an acetyl radical, and

10 R₅ represents a hydrogen atom.

25. Taxane derivatives of general formula IV

C-B IV

in which C and B are defined in one of claims 17 to 23, with the exception of the derivatives in which C
15 represents a radical of formula IIa, II'a, IIb, IIIb or III'b, and GP1 and/or GP2 are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as trialkylsilyls or TroC.

20 26. Baccatin III derivatives which are of

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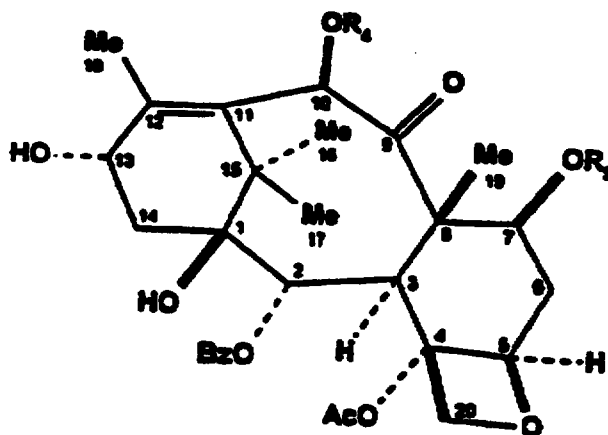




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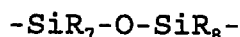
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use in the hemisynthesis of taxanes, characterized in that they are chosen from the derivatives of general formula V



in which

- 5 Ac represents the acetyl radical,
 Bz represents the benzyl radical,
 Me represents the methyl radical,
 R₄ represents an acetyl radical or a protective
 group for the hydroxyl functional group GP1,
10 R₅ represents a protective group for the hydroxyl
 functional group GP2, and
 GP1 and GP2 are, independently of one another,
 bulky haloalkoxycarbonyl radicals, with the
 exception of TrOC, acyl radicals in which the
15 carbon α to the carbonyl functional group carries
 at least one oxygen atom, or trialkylgermanyl
 radicals or GP1 and GP2 together form a divalent
 radical of formula



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in which

R_7 and R_8 , independently of one another, represent a
sterically hindered alkyl radical.

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