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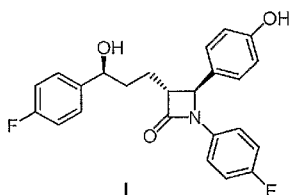
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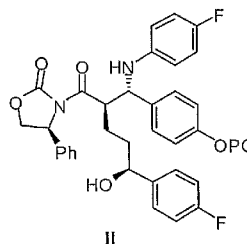
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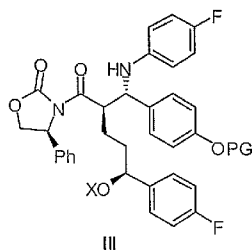
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(54) Title: METHOD OF PRODUCING (3R,4S)-L-(4-FLUOROPHENYL)-3-[(3S)-3-(4-FLUOROPHENYL)- HYDROX-
YPROPYL]-4-(4-HYDROXYPHENYL)-2-AZETIDINONE

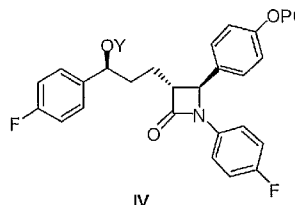
I



II



III



IV

(57) Abstract: Method of producing (3R,4S)-L-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3- hydroxypropyl]-4-(4-hydrox-
yphenyl)-2-azetidinone (ezetimibe) of formula I, in which alcohol-oxazolidide of general formula II, wherein PG is a phenol pro-
tecting group, such as a carbonate group, for instance benzyloxycarbonyl or *tert*-butyloxycarbonyl, or an arylmethyl group, for in-
stance benzyl, benzhydryl or trityl, or a silyl group, for instance *tert*- butyldimethylsilyl or hexyldimethylsilyl, is silylated by sily-
lation agents in an inert organic solvent in the temperature range of -10 °C to the boiling temperature of the mixture; the obtained
silylether-oxazolidide of general formula III, wherein PG is as defined above and X is a silyl group of general formula SiR¹R²R³,
wherein R¹ to R³ are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, is cyclized by action of
bis(trimethylsilyl)acetamide and a base in an inert organic solvent in the temperature range of -20 to 40 °C; and, finally, the ob-
tained protected azetidinone of general formula IV, wherein PG is as defined above and Y is hydrogen or the group X as defined
above, is deprotected by action of deprotecting hydrogenolytic agents and/or acidic agents in an inert organic solvent.



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Method of producing (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

Technical Field

5 The invention relates to a new method of producing (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone.

State of the Art

10 (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone of formula (I), known under the INN name ezetimibe, is disclosed in US Pat. 5,631,365 as a hypolipidemic reducing intestinal absorption of cholesterol and other sterols.

15 According to US patents 5,739,321 and 5,886,171, ezetimibe is produced by addition of (*S*)-4-hydroxybutanolide onto *N*-(4-benzyloxybenzylidene)-4-fluoroaniline by means of LDA at -78 °C; the obtained diol is split by a periodate to the aldehyde, which reacts with 4-fluoroacetophenone *O*-trimethylsilylenol to form the aldol. The latter is dehydrated to form the unsaturated ketone the double bond of which, or also the benzyl protecting group, is hydrogenated on a palladium catalyst. Then, the ketone is asymmetrically reduced with a borane in the presence of a chiral ligand to form ezetimibe, or its *O*-benzyl derivative, which is
20 hydrogenolyzed on a palladium catalyst. Disadvantage of the process lies in necessity to work at very low temperatures and in repeated using of expensive catalysts of the palladium type.

25 The process of producing ezetimibe disclosed in US patent 5,856,473 starts from 5-(4-fluorophenyl)-4-pentenoic acid, which is converted by means of oxalylchloride to its chloride and then to the acyloxazolidide by reacting with (*S*)-4-phenyl-2-oxazolidinone. The latter is added onto *N*-(4-benzyloxybenzylidene)-4-fluoroaniline by means of titanium(IV) chloride in the presence of diisopropylethylamine to form a product, which is cyclized by means of bistrimethylsilylacetamide and catalytic TBAF to an olefine-azetidinone. This alkene is converted to the ketone by action of Pd(OAc)₂ and benzoquinone in the presence of perchloric acid. The ketone is again asymmetrically reduced with a borane in the presence of a chiral
30 ligand; finally, the *O*-benzyl protecting group is hydrogenolyzed. Considerable disadvantage

again consists in repeated using of expensive catalysts of the palladium type and using of toxic oxalylchloride in this process.

According to said US patent 5,631,365, ezetimibe is produced by synthesizing (*S*)-*N*-(4-methoxycarbonylbutanoyl)oxazolidide from (*S*)-4-phenyl-2-oxazolidinone and glutaric acid esterchloride, followed by adding it onto said *N*-(4-benzyloxybenzylidene)-4-fluoroaniline in the presence of titanium(IV) chloride; the obtained product is cyclized by action of bistrimethylsilylacetamide and catalytic TBAF to an ester-azetidinone. The acid obtained by alkaline hydrolysis of the ester is converted to the acid chloride, which is reacted with a Grignard reagent in the presence of ZnCl_2 and $\text{Pd(PPh}_3)_4$ to produce the ketone. The latter is asymmetrically reduced with a diborane in the presence of a chiral ligand; finally, the *O*-benzyl protecting group is hydrogenolyzed on a palladium catalyst. Considerable disadvantage again consists in repeated using of expensive catalysts of the palladium type as well as using of toxic oxalylchloride.

The process of producing ezetimibe according to WO 2006/137080 is similar to that described above and has similar disadvantages. Glutaric acid methylesterchloride is produced by action of oxalylchloride on the respective acid and is reacted with (*S*)-4-phenyl-2-oxazolidinone to form (*S*)-*N*-(4-methoxycarbonylbutanoyl)oxazolidide. The latter is added to said *N*-(4-benzyloxybenzylidene)-4-fluoroaniline in the presence of titanium(IV) chloride; the obtained product is cyclized by action of bistrimethylsilylacetamide and catalytic TBAF to the ester-azetidinone. The acid obtained by alkaline hydrolysis of the ester is converted by means of oxalylchloride to the acid chloride, which reacts with a Grignard reagent in the presence of ZnCl_2 and an acetate of a transition metal, e.g. palladium, to produce a ketone. The latter is asymmetrically reduced with a diborane in the presence of a chiral ligand; finally, the *O*-benzyl protecting group is hydrogenolyzed on a palladium catalyst. In this case, as well, considerable disadvantage of the process lies in repeated using of expensive catalysts of the palladium type and repeated using of toxic oxalylchloride.

The process of producing ezetimibe according to WO 2007/072088 starts from 4-(4-fluorobenzoyl)butanoic acid, which is first converted into the ethyleneketal and then reacted with (*S*)-4-phenyl-2-oxazolidinone to form (*S*)-3-[4-[2-(4-fluorophenyl)-[1,3]-dioxolane-2-yl]butanoyl]-4-phenyloxazolidine-2-one. Its addition onto *O*-silylated *N*-(4-hydroxybenzylidene)-4-fluoroaniline by action of titanium(IV) trichlorideisopropoxide provided a product, which was cyclized by means of bis-trimethylsilylacetamide and catalytic TBAF to the ketal azetidinone and deprotected to the ketone azetidinone by means of

montmorillonite K10. The silylated ketone produced in this way was reduced with a diborane in the presence of chiral (*R*)-*o*-tolyl-CBS-oxazaborolidine. The obtained *O*-silylated ezetimibe with de > 98 % was finally deprotected with sulphuric acid in isopropanol.

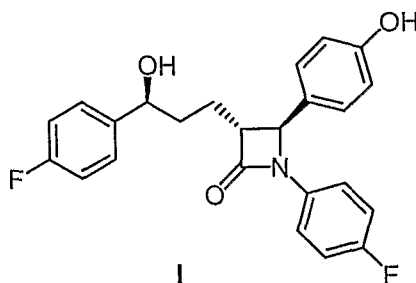
The process of production according to WO 2007/119106 comprises not only the above-mentioned ketal (*S*)-3-[4-[2-(4-fluorophenyl)-[1,3]-dioxolane-2-yl]butanoyl]-4-phenyloxazolidine-2-one but also its analogue derived from 1,3-propanediol. Their addition onto *O*-benzylated or trimethylsilylated *N*-(4-hydroxybenzylidene)-4-fluoroaniline by action of titanium(IV) isopropoxide trichloride provided products, which were cyclized to ketal azetidinones by means of bis-trimethylsilylacetamide and catalytic TBAF, and then deprotected to ketone azetidinones by means of *p*-toluenesulphonic acid in acetone. The produced benzyloxy ketone was reduced with a borane in the presence of chiral (*R*)-2-methyl-CBS-oxazaborolidine and then deprotected by hydrogenation on Pd/C. Alternatively, ezetimibe was also obtained by CBS reduction of the hydroxy ketone.

A similar process of ezetimibe synthesis from 5- and 6-membered ketals and protected imines is disclosed in patent application WO 2007/120824.

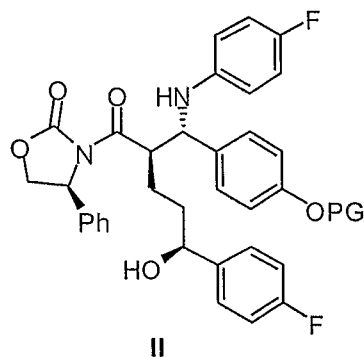
Common problem of these three processes involves chemoselectivity and diastereoselectivity of CBS reduction of ketones with the borane and laborious final purification of the produced ezetimibe.

Disclosure of Invention

The invention provides a method of producing (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone (ezetimibe) of formula I



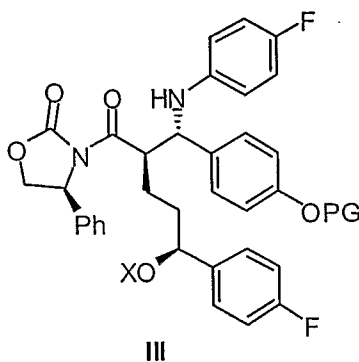
which comprises silylating an alcohol-oxazolidide of general formula II



wherein PG represents a phenol protecting group such as a carbonate group, for example
 5 benzyloxycarbonyl or *tert*-butoxycarbonyl groups, or an arylmethyl group, such as for instance benzyl, benzhydryl or trityl groups, or a silyl group, such as for instance *tert*-butyldimethylsilyl or hexyldimethylsilyl groups,

with silylation agents in an inert organic solvent in the temperature range of -10 °C to the boiling temperature of the mixture (step A);

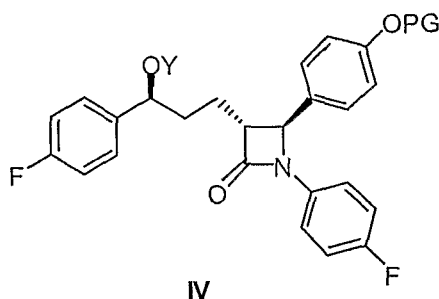
10 cyclizing the obtained silylether-oxazolidide of general formula III



wherein PG is as defined above and X represents a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$,
 wherein R^1 to R^3 represent identical or different alkyl groups with 1 to 5 carbon atoms or the
 15 phenyl group,

by action of *bis*(trimethylsilyl)acetamide and a base in an inert organic solvent in the temperature range of -20 to 40 °C (step B);

followed by deprotection of the obtained protected azetidinone of general formula IV



5

wherein PG is as defined above and Y is hydrogen or the above defined group X,

by action of deprotecting hydrogenolytic agents and/or acidic agents in an inert organic solvent (step C).

It has been found that ezetimibe can be produced by a process starting from alcohol-oxazolidides of general formula II, which are well accessible by highly chemoselective and diastereoselective CBS reduction of the respective ketones with protected phenolic hydroxyl by means of asymmetric agents. Easily attainable high quality of these alcohols makes final chemical and optical purification of the produced substance simpler. The process of producing ezetimibe of formula I from alcohol-oxazolidides of formula II consists of three steps.

Step A. An alcohol-oxazolidide of general formula II, wherein PG represents a phenol protecting group, such as a carbonate group, for instance benzyloxycarbonyl (Cbz) or *tert*-butyloxycarbonyl, or an arylmethyl group, for instance benzyl, benzhydryl or trityl, or a silyl group, for instance *tert*-butyldimethylsilyl or hexyldimethylsilyl, is silylated with silylation agents in an inert organic solvent in the temperature range of from -10 °C to the boiling temperature of the mixture. The silylation agents used herein include a trialkylsilylchloride of general formula $\text{ClSiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, in the amount of 1 to 2 equivalents, in the presence of a base, or hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate, preferably in the temperature range of -5 to 35 °C. The trialkylsilylchloride in the presence of base is preferably trimethylsilylchloride, *tert*-butyldimethylsilylchloride or

thexyldimethylsilylchloride in the amount 1 to 1.6 equivalents in the presence of triethylamine or ethyldiisopropylamine, more preferably trimethylsilylchloride in the amount 1.05 to 1.4 equivalents and triethylamine in the temperature range of -5 to 25 °C. In using hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate, the reaction is preferably carried out at a temperature of 10 to 30 °C. The reaction is carried out in an inert organic solvent, such as, for instance, tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene, dichloroethane or dichloromethane, or their mixtures.

Step B. Cyclization of silylethers of general formula III, wherein PG is as defined above and X is a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 represent identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, is carried out by action of *bis*(trimethylsilyl)acetamide (BSA) and a base in the amount of 0.5 to 30 %, in an inert organic solvent in the temperature range of -20 to 40 °C. The bases used include, for instance, a quaternary tetraalkylammonium compound such as tetrabutylammonium fluoride or tetrabutylammonium hydroxide in the amount of 0.5 - 20 molar %. Cyclization is carried out in an inert organic solvent, such as tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, preferably in the temperature range of -15 to +35 °C.

Preferably, cyclization is carried out by means of BSA and tetrabutylammonium hydroxide in the amount 1 to 10 %, at -15 to +5 °C. According to another preferred method, cyclization is carried out by means of BSA and tetrabutylammonium fluoride in the amount of 1 to 10 %, at 15 to +25 °C.

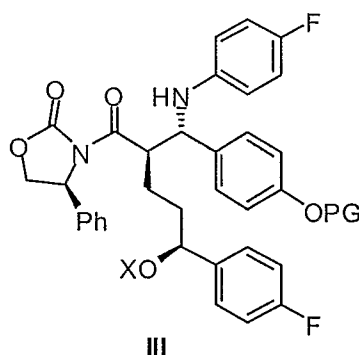
Step C. Deprotection of protecting groups in the compound of general formula IV, wherein PG, X and Y are as defined above, is carried out by means of deprotecting agents, such as hydrogenolytic agents, for instance, hydrogen on a catalyst, such as for instance on palladium or platinum, or acidic agents, such as mineral or organic acids, for instance hydrochloric acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid or trifluoroacetic acid. Herewith, methanol, ethanol, isopropyl alcohol, 1,4-dioxane, ethyl acetate or toluene, or their mixtures are used as inert organic solvents.

According to a preferred form of embodiment, for instance, hydrogen on Pd/C is used in an alcohol, such as methanol, ethanol or isopropyl alcohol, or in ethyl acetate or toluene, or their mixtures. According to another preferred form of embodiment, deprotection is carried out with an acid in alcohols, such as for instance with sulphuric acid, phosphoric acid,

methanesulphonic acid or trifluoroacetic acid in methanol, ethanol or isopropyl alcohol, or 1,4-dioxane.

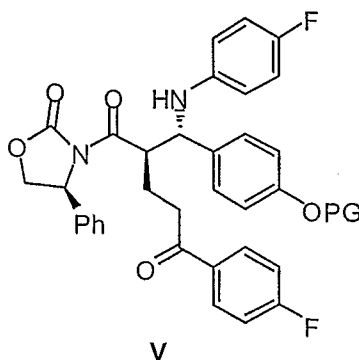
The obtained compound of formula I (ezetimibe) is finally purified by crystallization from a mixture of water and an alcohol, for instance 2-propanol or methanol.

- 5 This invention also provides a new method of producing *O,O*-protected (4*S*)-3-{{(2*R*,5*S*)-5-(4-fluorophenyl)-2-[(*S*)-[(4-fluorophenyl)amino](4-hydroxyphenyl)methyl]-5-hydroxypentanoyl}-4-phenyl-1,3-oxazolidine-2-ones (hereinafter "silylether-oxazolidides") of general formula III



- 10 wherein PG represents a phenol protecting group, such as a carbonate group, for instance benzyloxycarbonyl or *tert*-butyloxycarbonyl, or an arylmethyl group, for instance benzyl, benzhydryl or trityl, or a silyl group, for instance *tert*-butyldimethylsilyl or hexyldimethylsilyl, and X is a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, which comprises

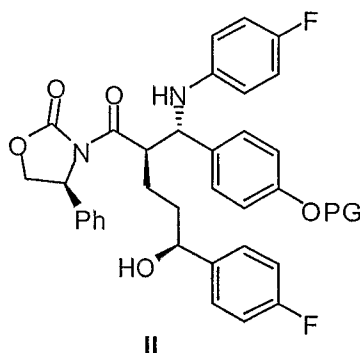
- 15 reducing a ketone-oxazolidide of general formula V



wherein PG is defined as above,

with asymmetrical borane agents in an inert organic solvent in the temperature range of -30 to +40 °C

5 and silylating the obtained alcohol-oxazolidide of general formula II



wherein PG is defined as above,

10 by means of a silylation agent in an inert organic solvent in the temperature range of -10 °C to the boiling temperature of the mixture (step 2).

It has been found that the compounds of general formulas II and III are useful intermediates in the synthesis of ezetimibe of formula I. These compounds can be produced by a process, which is based on highly chemoselective and diastereoselective reduction of ketones with protected phenolic hydroxyl of general formula V by means of an asymmetrical borane agent consisting of a source of borane and a chiral ligand. Final optical purification of the produced substance is thus simplified.

20 Step 1. Reduction of ketones of general formula V with protected phenolic hydroxyl is carried out using an asymmetrical borane agent consisting of a source of borane and a chiral ligand. The sources of borane that can be used include a complex of borane, for instance with dimethylsulphide, tetrahydrofuran, dimethylaniline or diethylaniline, and the chiral ligands that can be used include a 2-substituted (*R*)-CBS-oxazaborolidine, such as for example (*R*)-2-methyl-CBS-oxazaborolidine, (*R*)-2-methoxy-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-oxazaborolidine in the amount of 1 to 100 mol %, preferably 1 to 25 mol %; more preferred is

using of 4 to 10 % of the chiral ligand. Reduction can be preferably carried out in the presence of a catalytic amount of protic or Lewis acids, such as methanesulphonic, *p*-toluenesulphonic, trifluoroacetic acids or borotrifluoride etherate.

Suitable protecting groups PG include a carbonate group, such as for instance benzyloxycarbonyl or *tert*-butoxycarbonyl, or an arylmethyl group, such as for instance benzyl, benzhydryl or trityl, or a silyl group, such as for instance *tert*-butyldimethylsilyl or hexyldimethylsilyl. Suitable inert organic solvents are, for instance, tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, or their mixtures. Herewith, reduction is preferably carried out at -25 to -15 °C, or at 20 to +30 °C.

Step 2. An alcohol-oxazolidide of general formula II, wherein PG is a phenol protecting group, such as a carbonate group, such as for instance benzyloxycarbonyl or *tert*-butoxycarbonyl, or an arylmethyl group, such as for instance benzyl, benzhydryl or trityl, or a silyl group, such as for instance *tert*-butyldimethylsilyl or hexyldimethylsilyl, is silylated with silylation agents in an inert organic solvent in the temperature range of -10 °C to the boiling temperature of the mixture. Herewith, silylation agents that can be used include trialkylsilylchloride of general formula $\text{ClSiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, in the presence of a base, such as for instance trimethylsilylchloride, *tert*-butyldimethylsilylchloride or hexyldimethylsilylchloride in the presence of triethylamine or ethyldiisopropylamine, or hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate, preferably in the temperature range of -5 to 35 °C. The trialkylsilylchlorides in the presence of bases that can be used preferably include trimethylsilylchloride, *tert*-butyldimethylsilylchloride or hexyldimethylsilylchloride in the amount of 1 to 1.6 equivalents in the presence of triethylamine or ethyldiisopropylamine, more preferably trimethylsilylchloride in the amount of 1.05 to 1.4 equivalents and triethylamine in the temperature range of -5 to 25 °C. In using hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate, the reaction is preferably carried out at temperature of 10 to 30 °C. The reaction is carried out in an inert organic solvent, such as, for instance, tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, or their mixtures.

Examples

The following working examples illustrate, however without any limitation, general character of the method of production according to this invention.

5 Example 1

a) Preparation of a silylether-oxazolidide of general formula III (PG = Cbz, X = SiMe₃)

Lithium perchlorate (100 mg) is added to a solution of 5.0 g (6.42 mmol) of an alcohol-oxazolidide of general formula II (PG = Cbz) in 50 ml dichloromethane and then, during ca. 5 minutes, hexamethyldisilazane (1.04 g, 6.42 mmol) is added dropwise at a temperature of 20 -
10 23 °C. The reaction mixture is stirred at this temperature for 2 h. During the reaction, small amount of ammonia is released. Progress of the reaction is monitored by TLC (silica gel; eluent PE : ethyl acetate 1 : 1). After the starting substance has disappeared, the reaction is terminated by addition of 10 ml of water at room temperature. The water layer is separated, the organic phase is dried with anhydrous sodium sulphate and evaporated in a rotary vacuum
15 evaporator to dryness. The crystalline evaporation residue (5.91 g) is dissolved under reflux in 40 ml of ethyl acetate and 40 ml of petroleum ether is added to the solution when hot. The solution is seeded and left to cool down to room temperature. It is stirred at temperature 22 °C for 18 h. The eliminated product is separated on sintered glass and dried in the air at room temperature. Melting temperature 184 - 186 °C.

20 Yield 6.56 g (88.52 %) of crystalline substance; HPLC 99.4 %.

HRMS: [M-H]⁺ theory C₄₄H₄₅O₇N₂F₂²⁸Si₁: 779.295, found: 779.295.

¹H-NMR (250 MHz, CDCl₃): δ 7.54 - 7.45 (m, 5H), 7.34 - 7.14 (m, 11H), 7.04 (t, J = 8.7 Hz, 2H), 6.82 (t, J = 8.7 Hz, 2H), 6.44 (m, 2H), 5.46 (dd, J = 8.5 Hz, J = 3.1 Hz, 1H), 5.35 (s, 2H), 5.02 (d, J = 9.9 Hz, 1H), 4.72 (t, J = 8.6 Hz, 1H), 4.56 - 4.43 (m, 3H), 4.26 (dd, J = 8.8
25 Hz, J = 3.1 Hz, 1H), 1.68-1.42 (m, 4H), 0.00 (s, 9H).

b) Preparation of the compound of formula I (ezetimibe)

1) Crude ezetimibe

A solution of 6.49 g (8.33 mmol) of a silylether-oxazolidide of general formula III (PG = Cbz, X = SiMe₃) in 100 ml of dry THF is cooled to a temperature of -5 to -10 °C, and then
30

N,O-bis-(trimethylsilyl)-acetamide (BSA; 4.15 ml, 16.97 mmol, 2.03 eq.) and a 40 % solution of tetrabutylammonium hydroxide (TBAH) in methanol (0.25 g, 0.38 mmol) is gradually added. The reaction mixture is stirred at a temperature of -5 to -10 °C for 2 h, progress of the reaction being monitored by TLC (silica gel; eluent PE : ethyl acetate 7 : 3). After complete
5 conversion of the starting substance, the reaction is terminated by addition of 4.2 ml of acetic acid. The solution is taken out from the cooling bath, left to temper at about 0 °C, and diluted with 120 ml of dichloromethane and 45 ml of water. The organic portion is separated and evaporated in a rotary vacuum evaporator to dryness (temperature of the bath up to 45 °C). Before deprotection, the evaporation residue is poured over with 50 ml of methanol and
10 evaporated once again in order to remove residues of dichloromethane. An oily evaporation residue is obtained, which is used for deprotection without purification.

The obtained oil is dissolved in 150 ml of methanol, 3 % Pd/C (0.66 g, 50 % of water) is added, and the mixture is hydrogenated at atmospheric pressure for 18 h. Then, completeness of hydrogenation is checked by means of TLC (silica gel; eluent PE : ethyl
15 acetate 1 : 1). The catalyst is filtered and washed with methanol (Seitz filter). The filtrate is concentrated in a rotary vacuum evaporator to the volume of 70 ml (or is diluted to this volume); bath temperature up to 45 °C. The concentrated filtrate is mixed with 35 ml of water under stirring at room temperature and the turbid solution is seeded with ezetimibe. The formed ezetimibe starts crystallizing and the mixture is stirred at room temperature for 1 h.
20 The eliminated product is sucked off on sintered glass and washed with 12 ml of a mixture methanol : water (2:1). The obtained product is dried in the air at room temperature.

2.40 g of crude ezetimibe of formula I (70.4 %) is obtained. The crude product is further crystallized from a mixture of isopropyl alcohol and water.

25 2) Crystallization:

2.40 g of crude ezetimibe is dissolved in 18 ml of isopropyl alcohol at 50 °C; at the same temperature, 9 ml of water is added dropwise to the solution and the solution is seeded. Then, heating is switched off and ezetimibe is left to crystallize under stirring at laboratory temperature for 2 h. The eliminated product is sucked off and washed with 12 ml of a mixture
30 *i*-PrOH : water (2:1). The product is dried in the air.

1.96 g (57.5 %) of ezetimibe is obtained. HPLC: 99.8 %; HPLC on chiral column 99.90 %.

1.86 g of ezetimibe is dissolved in 12.4 ml of isopropyl alcohol at 50 °C; at the same temperature, 5.25 ml of water is added dropwise to the solution and the solution is seeded. Then, heating is switched off and the suspension is left to crystallize under stirring at laboratory temperature for 2 h. The eliminated product is sucked off and washed with 5 ml of
5 a mixture *i*-PrOH : water (2:1). The product is dried at 60 °C in a vacuum drying oven to constant weight (3 to 6 h). Melting temperature 163 - 164 °C.

1.49 g (46.06 %) of ezetimibe is obtained in the form of polymorph A. HPLC 99.88 %; HPLC on chiral column 99.94 %.

10 Example 2

Preparation of protected azetidinone of general formula IV (PG = Cbz, X = SiMe₃)

A solution of 2.46 g (3.15 mmol) of a silylether-oxazolidide of general formula III (PG = Cbz, X = SiMe₃) in 100 ml of dry THF (35 ml) is cooled down to the temperature 0 °C; BSA (1.44 ml, 5.76 mmol; 1.8 eq.), and, after 15 min of stirring, tetrabutylammonium fluoride
15 (TBAF) (0.07 g, 0.22 mmol; 0.07 eq.) are added. The mixture is left to heat under stirring from 0 °C to the laboratory temperature during 1 h, progress of the reaction being monitored by TLC (silica gel; eluent hexane : ethyl acetate 8 : 3). After complete conversion of the starting substance, the reaction mixture is diluted with ethyl acetate (25 ml), washed with an aqueous solution of NaHCO₃ (1x) and with water (1x); and after drying (Na₂SO₄), it is
20 evaporated in a rotary vacuum evaporator. The oily evaporation residue is purified by chromatography on silica gel (eluent hexane : ethyl acetate 7 : 3).

Oily protected azetidinone of general formula IV (PG = Cbz, X = SiMe₃) is obtained.

HRMS: [M-H]⁺ theory C₃₅H₃₆O₅N₁F₂ : 616.2331, found: 616.2321.

¹H-NMR (250 MHz, CDCl₃): 7.48-7.15 (m, 13H), 7.63 – 6.88 (m, 4H), 6.26 (s, 2H),
25 4.63 (t, 6.0 Hz, 1H), 4.56 (d, 2.2 Hz, 1H), 3.03 (ddd, 2.1 Hz, 7.0 Hz, 7.1 Hz, 1H), 2.04 – 1.81 (m, 4H), 0.02 (s, 9H).

Example 3

Preparation of a silylether-oxazolidide of general formula III (PG = Cbz, X = SiMe₃)

Trimethylsilylchloride (1.32 ml, 9.87 mmol; 1.2 eq.) is added dropwise to a stirred mixture of the alcohol-oxazolidide of general formula II (PG = Cbz) (5.81 g, 8.22 mmol) and triethylamine (1.49 ml, 10.7 mmol; 1.75 eq.) in dry dichloromethane (50 ml) under cooling at 0 °C during about 5 min. The reaction mixture is stirred at a temperature of 0 - 10 °C for 2.5 h, the reaction process being monitored by means of TLC (silica gel; eluent petrol ether : ethyl acetate 1 : 1). After the reaction is completed, water (20 ml) is added at laboratory temperature, the reaction vessel is rinsed with dichloromethane (20 ml). The separated organic phase and the rinsed portion are combined, washed with brine (20 ml), and dried with sodium sulphate. A crystalline residue (6.44 g) is obtained by concentrating the organic phase in a vacuum evaporator, which is dissolved in boiling ethyl acetate (35 ml). Hot hexane (80 ml) is added to the obtained solution under stirring. The product starts crystallizing quickly during cooling to laboratory temperature. Crystallization is completed during 2 hours of cooling to 4 °C. The crystalline product is filtered and dried at laboratory temperature. Melting temperature 183 - 187 °C.

90.7 % (5.81 g) of trimethylsilylether-oxazolidide of general formula III (PG = Cbz, X = SiMe₃) is obtained. HPLC purity 99.20 %; content of diastereoisomer according to HPLC 0.18 %.

Example 4

Preparation of an alcohol-oxazolidide of general formula II (PG = Cbz)

a) 4.5 mol % of R-Me-CBS catalyst

10 ml of dried THF, 0.193 ml (0.19 mmol, 4.5 mol %) of a 1 M toluene solution of (*R*)-2-Me-CBS-oxazaborolidine, and 4.24 ml (4.24 mmol, 0.975 eq.) of a 1 M solution of BH₃.Me₂S in dichloromethane are charged into a three-neck 100 ml flask fitted with a magnetic stirrer, a thermometer and an inert gas inlet. The obtained solution is stirred for 15 min and then a solution of a ketone-oxazolidide of general formula V (PG = Cbz) (3.06 g, 4.35 mmol) in dry dichloromethane (20 ml) is slowly added dropwise using a dosing pump at a temperature of 20 - 23 °C during 4 h. After completed adding, the reaction mixture is stirred for additional 45 min, progress of the reaction being monitored by means of TLC (silica gel; eluent hexane : ethyl acetate 70 : 30). After complete conversion of the starting substance, the reaction is terminated by careful dropwise adding of 3 ml of methanol. During decomposition, the reaction mixture foams and releases hydrogen and dimethylsulphide. After adding

methanol, the reaction mixture is stirred at room temperature for additional 15 min; then, it is diluted with 10 ml of 1 N HCl and stirred for additional 15 min; foam is again formed and gases released.

After shaking, the phases are separated and the aqueous phase is shaken with dichloromethane (2 x 15 ml). The combined organic layers are washed with water (10 ml) and brine (10 ml), and dried with anhydrous sodium sulphate. The extract is concentrated in a rotary vacuum evaporator to dryness (temperature of bath 40 - 45 °C). The obtained crystalline evaporation residue (3.16 g) is crystallized from a mixture of ethyl acetate and methanol: the evaporation residue is mixed in 4 ml of ethyl acetate and heated under reflux. Methanol is slowly added to the boiling solution until turbidity develops (about 12 ml). Then, the heating is switched off and, after cooling down to room temperature, the mixture is kept overnight at the temperature +5 °C. The formed crystalline portion is sucked off on sintered glass, washed with minimum amount of methanol, and dried at laboratory temperature.

2.54 g, i.e. 82.7 % of an alcohol-oxazolidide of general formula II (PG = Cbz) is obtained; HPLC purity 97.5 %, content of diastereoisomer 1.6 %.

¹H-NMR (250 MHz, CDCl₃): δ 7.47-7.35 (m, 5H), 7.27 - 7.03 (m, 11H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.73 (t, *J* = 8.7 Hz, 2H), 6.34 (m, 2H), 5.39 (dd, *J* = 8.5 Hz, *J* = 3.3 Hz, 1H), 5.26 (s, 2H), 4.97 (d, *J* = 10.1 Hz, 1H), 4.65 (t, *J* = 8.7 Hz, 1H), 4.60 - 4.49 (m, 2H), 4.37 (dd, *J* = 10.1 Hz, *J* = 8.4 Hz, 1H), 4.18 (dd, *J* = 8.8 Hz, *J* = 3.4 Hz, 1H), 1.86 (d, *J* = 3.4 Hz, 1H), 1.85 - 1.41 (m, 4H).

b) 10 mol % of R-MeO-CBS catalyst

40.6 ml (2.03 mmol; 10 mol %) of a 0.05 M tetrahydrofuran solution of (*R*)-2-MeO-CBS-oxazaborolidine is added to a solution of a ketone-oxazolidide of general formula V (PG = Cbz) (14.32 g, 20.32 mmol) in dry THF (550 ml) at the temperature 23 °C. The obtained solution is stirred for 10 to 15 min and, then, 14.22 ml (28.44 mmol) of a 2 M solution of BH₃.Me₂S in THF is slowly added dropwise using a dosing pump at a temperature of 20 - 23°C during 3.5 h. After completed addition, the reaction mixture is stirred for additional 45 min, progress of reduction being monitored by means of TLC (silica gel; eluent petrol ether : ethyl acetate 1 : 1). After the starting substance has disappeared, the reaction is terminated by careful dropwise addition of 50 ml of methanol. During decomposition, the reaction mixture foams and releases hydrogen and dimethylsulphide. After adding methanol, the reaction

mixture is stirred at room temperature for additional 0.5 h and then it is diluted with 120 ml of 1 N HCl; the mixture again foams and releases gases.

The reaction mixture is diluted with 250 ml of dichloromethane, the organic portion is separated and dried with anhydrous sodium sulphate. The extract is concentrated in a rotary vacuum evaporator to dryness (temperature of bath 40 - 45 °C). The crystalline evaporation residue (18.82 g) is crystallized from the mixture of ethyl acetate and methanol: the evaporation residue is mixed in 250 ml of methanol and the obtained suspension is heated under reflux. Ethyl acetate is slowly added to the boiling suspension until a solution is formed (about 100 ml). Heating is switched off and, after cooling down to room temperature, the mixture is stored at +5 °C overnight. The eliminated crystalline substance is sucked off on sintered glass and washed with minimum amount of methanol. The obtained product is dried in a vacuum drying oven at 50 °C.

12.28 g of the alcohol-oxazolidide of general formula II (PG = Cbz) (85.5 %) is obtained; HPLC purity 97.3 %; content of diastereoisomer 1.7 %.

Example 5

Preparation of a ketone-oxazolidide of general formula V (PG = Cbz)

a) Preparation of (*S*)-3-[5,5-dimethoxy-5-(4-fluorophenyl)-1-oxopentyl]-4-phenyloxazolidin-2-one

Methanol (750 ml) and trimethyl orthoformate (43.5 ml, 397.6 mmol; 2.82 eq.) are added to a mixture of (*S*)-3-[4-(4-fluorobenzoyl)-1-oxobutyl]-4-phenyloxazolidin-2-one (50.1 g, 141.1 mmol) and *p*-toluenesulphonic acid monohydrate (0.83 g, 4.36 mmol; 3 mol %); the mixture is heated to boiling, wherein the suspension gradually changes to a clear solution. Progress of the reaction can be monitored by TLC in the system hexane : ethyl acetate (7 : 3). After heating to boiling under reflux for 5 h, the reaction mixture is cooled to about 30 °C, and poured into a mixture of 1000 ml of toluene and 54 g of sodium hydrogen-carbonate dissolved in 800 ml of water. The mixture is stirred for 10 min; then, the phases are separated and the organic layer is shaken with 1x 250 ml of water. The combined aqueous layers are shaken with 1x 300 ml of toluene; the combined organic layers are washed with 1x 250 ml of water and evaporated in a rotary vacuum evaporator at the temperature of bath 50 °C. The evaporation residue is a yellow oil; after perfect evaporation, it is solid, almost white.

56.08 g, i.e. 99.02 % of the product is obtained; HPLC purity 96.1 %.

¹H-NMR (250 MHz, CDCl₃): δ 7.44-7.19 (m, 7H), 6.99 (t, *J* = 8.8 Hz, 2H), 5.33 (dd, *J* = 8.7 Hz, *J* = 3.6 Hz, 1H), 4.59 (t, *J* = 8.8 Hz, 1H), 4.19 (dd, *J* = 8.9 Hz, *J* = 3.6 Hz, 1H), 3.10 (s, 3H), 3.08 (s, 3H), 2.79 (t, *J* = 7.4 Hz, 2H), 1.93-1.82 (m, 2H), 1.36-1.20 (m, 2H).

5

b) Preparation of the titanium agent TiCl₃(*Oi*-Pr)

A 1 M solution of titanium(IV) chloride in CH₂Cl₂ (29.5 ml, 29.5 mmol; 0.94 eq.) and titanium(IV) isopropoxide (2.95 ml, 9.9 mmol; 0.32 eq.) is gradually added to 50 ml of dry CH₂Cl₂ under stirring at temperature 0 - 5 °C. The solution is stirred under cooling for 1 h.

10

c) Preparation of a ketone-oxazolidide of general formula V (PG = Cbz)

A suspension of *N*-(4-hydroxybenzylidene)-4-fluoroaniline (8.44 g; 39.2mmol; 1.25 eq.) in dichloromethane (70 ml) is cooled under stirring to 0 °C and a 50 % toluene solution of benzyl chloroformate (13.8 ml, 41.4 mmol; 1.3 eq.) is added. Then diisopropylethylamine (21.5 ml, 125.6 mmol, 4.02 eq.) is added at temperature 0 to 5 °C (slightly exothermic) within 10 min, wherein the suspension changes to a solution. The reaction mixture is left to warm up spontaneously to laboratory temperature (about 1.5 h), and then cooling is started again. At a temperature of about -5 °C, a solution of (*S*)-3-[5,5-dimethoxy-5-(4-fluorophenyl)-1-oxopentyl]-4-phenyloxazolidin-2-one (12.55 g, 31.26 mmol) in 50 ml of CH₂Cl₂ is added and the mixture is cooled down to the temperature -35 °C under stirring (about 20 min). At this temperature, a solution of the titanium agent (corresponding to 1.26 eq. TiCl₃(*Oi*-Pr)) is added dropwise in such a way that the temperature does not exceed -30 °C (about 20 min). The reaction mixture is getting dark, stirred at the temperature -35 °C for 3 h and then terminated by addition of acetic acid (8.4 ml, 147 mmol), which is added dropwise under cooling during 5 - 10 min. After additional 10 min, cooling of the reaction mixture is stopped, 0.46 M citrate buffer (180 ml) is added and the two-phase mixture is stirred for at least 3 h (possibly also overnight), wherein it is left to warm up slowly to laboratory temperature.

The water phase is separated and shaken with 100 ml of CH₂Cl₂. The combined organic portions are washed with 100 ml of water and evaporated in a rotary vacuum evaporator at the bath temperature 40 °C. 75 ml of ethyl acetate and 75 ml of methanol are added to the evaporation residue and the thick suspension is boiled under reflux for 1 h and

30

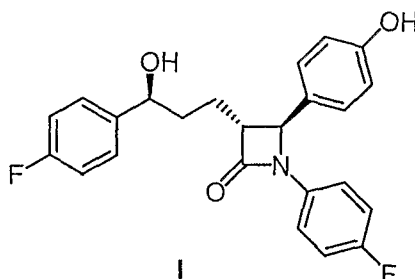
then stirred at laboratory temperature for 2 h. The eliminated crystals are sucked off and washed with 30 ml of a mixture methanol ethyl acetate (1 : 1). Melting temperature 178 – 179.5 °C.

11.4 g, i.e. 51.76 % of the ketone-oxazolidide of general formula V is obtained; HPLC
5 98.5 %.

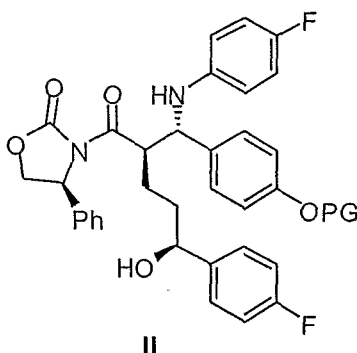
¹H-NMR (250 MHz, CDCl₃): δ 7.87 (m, 2H), 7.50-7.34 (m, 6H), 7.27-6.99 (m, 10H),
6.74 (t, *J* = 8.7 Hz, 2H), 6.37 dd, *J* = 9.0 Hz, *J* = 4.4 Hz, 2H), 5.42 (dd, *J* = 8.5 Hz, *J* = 3.5 Hz,
1H), 5.26 (s, 2H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.65 (t, *J* = 8.6 Hz, 1H), 4.59 (dt, *J* = 8.5 Hz, *J* =
4.6 Hz, 1H), 4.47 (m, 1H), 4.18 (dd, *J* = 8.8 Hz, *J* = 3.5 Hz, 1H), 2.88 (dt, *J* = 7.3 Hz, *J* = 1.4
10 Hz, 2H), 2.21 (m, 1H), 1.85 (m, 1H).

CLAIMS

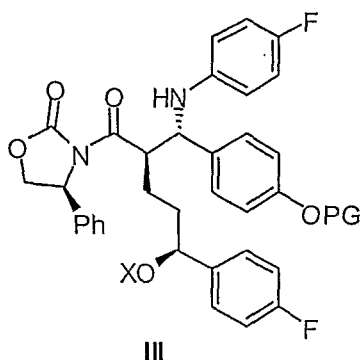
1. A method of producing (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone (ezetimibe) of formula I



characterized in that an alcohol-oxazolidide of general formula II



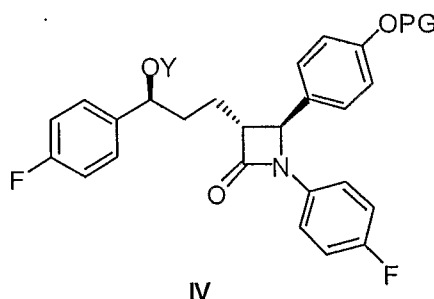
- 5 wherein PG represents a phenol protecting group, such as a carbonate group, preferably benzyloxycarbonyl or *tert*-butyloxycarbonyl, or an arylmethyl group, such as benzyl, benzhydryl or trityl, or a silyl group, such as *tert*-butyldimethylsilyl or hexyldimethylsilyl, is silylated with a silylation agent in an inert organic solvent in the temperature range of from -10 °C to the boiling temperature of the mixture (step A);
- 10 the obtained silylether-oxazolidide of general formula III



wherein PG is as defined above and X represents a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 represent identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group,

is cyclized by action of *bis*(trimethylsilyl)acetamide and a base in an inert organic solvent in the temperature range of -20 to 40 °C (step B);

and, finally, the obtained protected azetidinone of general formula IV



wherein PG is as defined above and Y is hydrogen or the group X as defined above,

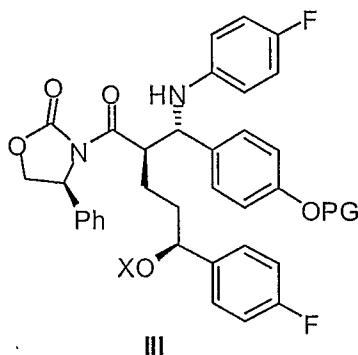
is deprotected by action of a deprotecting hydrogenolytic agent and/or acidic agent in an inert organic solvent (step C).

2. The method according to Claim 1, characterized in that the silylation agent in step A is a trialkylsilylchloride of general formula $\text{ClSiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, in the amount of 1 to 2 equivalents in presence of a base in the temperature range -5 to 35 °C.

3. The method according to Claims 1 or 2, characterized in that the trialkylsilylchloride in the presence of a base in step A is trimethylsilylchloride, *tert*-butyldimethylsilylchloride or hexyldimethylsilyl chloride in the amount of 1 to 1.6 equivalents in the presence of triethylamine or ethyldiisopropylamine.

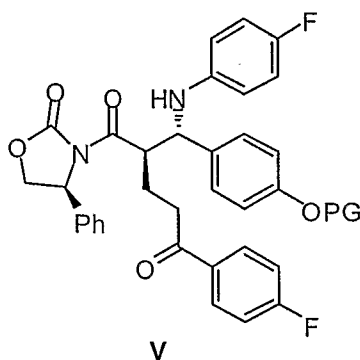
4. The method according to Claim 1, characterized in that silylation in step A is carried out by means of hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate in the temperature range of 10 to 30 °C.
- 5 5. The method according to any of Claims 1 to 4, characterized in that the inert organic solvent in step A is tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene, dichloroethane or dichloromethane, or a mixture thereof.
- 10 6. The method according to any of Claims 1, 2, 3 and 5, characterized in that silylation in step A is carried out by means of trimethylsilylchloride in the amount of 1.05 to 1.4 equivalent and triethylamine in the temperature range of -5 to 25 °C.
- 15 7. The method according to Claim 1, characterized in that the base for cyclization in step B is a tetraalkylammonium compound in an amount of 0.5 to 30 %.
8. The method according to Claims 1 or 7, characterized in that the tetraalkylammonium compound for cyclization in step B is tetrabutylammonium fluoride or tetrabutylammonium hydroxide, preferably in an amount of 0.5 to 20 %.
- 20 9. The method according to any of Claims 1, 7 and 8, characterized in that cyclization in step B is carried out in an inert organic solvent, such as tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, preferably in a temperature range of -15 to 35 °C.
- 25 10. The method according to any of Claims 1, 7, 8 and 9, characterized in that cyclization is carried out by means of *bis*-(trimethylsilyl)acetamide and tetrabutylammonium hydroxide in an amount of 1 to 10 % at -15 to +5 °C.

11. The method according to any of Claims 1, 7, 8 and 9, characterized in that cyclization is carried out by means of *bis*-(trimethylsilyl)acetamide and tetrabutylammonium fluoride in an amount of 1 to 10 % at 15 to +25 °C.
- 5 12. The method according to Claim 1, characterized in that the deprotecting agent in step C is a hydrogenolytic agent, such as hydrogen on a catalyst, preferably on palladium or platinum.
13. The method according to Claim 1, characterized in that the deprotecting agent in step C is a strong acidic agent, such as a mineral or organic acid, preferably hydrochloric acid, sulphuric
10 acid, phosphoric acid, methanesulphonic acid or trifluoroacetic acid.
14. The method according to any of Claims 1, 12 and 13, characterized in that the inert organic solvent is methanol, ethanol, isopropyl alcohol, tetrahydrofuran, 1,4-dioxane, ethyl acetate or toluene, or a mixture thereof.
- 15 15. The method according to any of Claims 1, 12 and 14, characterized in that hydrogen on Pd/C in an alcohol, such as methanol, ethanol or isopropyl alcohol, or in ethyl acetate or toluene, or a mixture thereof, is used for deprotection.
- 20 16. The method according to any of Claims 1, 13 and 14, characterized in that deprotection is carried out with a strong acid in an alcohol, such as sulphuric acid, phosphoric acid, methanesulphonic acid or trifluoroacetic acid in methanol, ethanol or isopropyl alcohol, or in dioxane.
- 25 17. A method of producing *O,O*-protected (4*S*)-3-[(2*R*,5*S*)-5-(4-fluorophenyl)-2-[(*S*)-[(4-fluorophenyl)amine](4-hydroxyphenyl)methyl]-5-hydroxypentanoyl]-4-phenyl-1,3-oxazolidin-2-ones (silylether-oxazolidides) of general formula III



wherein PG represents a phenol protecting group, such as a carbonate group, preferably benzyloxycarbonyl or *tert*-butyloxycarbonyl, or an arylmethyl group, preferably benzyl, benzhydryl or trityl, or a silyl group, preferably *tert*-butyldimethylsilyl or hexyldimethylsilyl, and X is a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group,

5 characterized in that a ketone oxazolidide of general formula V

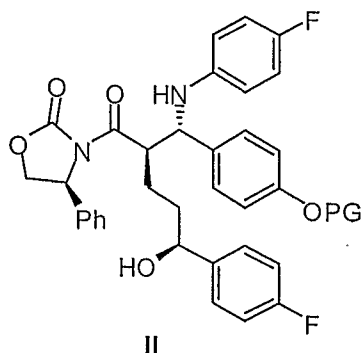


wherein PG is as defined above,

is reduced by asymmetrical borane agents in an inert organic solvent in the temperature range

10 of -30 to +40 °C,

and the obtained alcohol-oxazolidide of general formula II



wherein PG is as defined above,

is silylated by means of a silylation agent in an inert organic solvent in the temperature range
 5 of from -10 °C to the boiling temperature of the mixture (step 2).

18. The method according to Claim 17, characterized in that the asymmetrical borane agent in
 step 1 is a borane in the presence of a chiral ligand.

10 19. The method according to Claims 17 or 18, characterized in that the source of a borane in
 step 1 is a borane complex, preferably with dimethylsulphide, tetrahydrofuran, dimethylaniline
 or diethylaniline.

20. The method according to any of Claims 17, 18 and 19, characterized in that the chiral
 15 ligand in step 1 is 2-substituted (*R*)-CBS-oxazaborolidine, such as (*R*)-2-methyl-CBS-
 oxazaborolidine, (*R*)-2-methoxy-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-
 oxazaborolidine, in an amount of 1 to 100 mol %, preferably 1 to 25 mol %, more preferably 4
 to 10 mol %.

20 21. The method according to any of Claims 17, 18, 19 and 20, characterized in that reduction
 in step 1 is carried out in the presence of a catalytic amount of protic or Lewis acids, such as
 methanesulphonic, *p*-toluenesulphonic, trifluoroacetic acids or borotrifluoride etherate.

22. The method according to any of Claims 17 to 21, characterized in that the inert organic solvent in step 1 is tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, or a mixture thereof.

5

23. The method according to any of Claims 17 to 22, characterized in that reduction in step 1 is carried out at -25 to -15 °C, or at 15 to +30 °C.

24. The method according to Claim 17, characterized in that the silylating agent in step 2 is a trialkylsilylchloride of general formula $\text{ClSiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group, in an amount of 1 to 2 equivalents in the presence of a base in the temperature range of -5 to 35 °C.

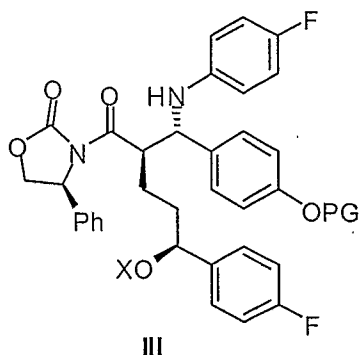
25. The method according to any of Claims 17 and 24, characterized in that the trialkylsilylchloride in the presence of a base in step 2 is trimethylsilylchloride, *tert*-butyldimethylsilylchloride or hexyldimethylsilylchloride in an amount of 1 to 1.6 equivalents in the presence of triethylamine or ethyldiisopropylamine.

26. The method according to Claim 17, characterized in that silylation in step 2 is carried out by means of hexamethyldisilazane in the presence of a catalytic amount of lithium perchlorate in the temperature range of 10 to 30 °C.

27. The method according to any of Claims 17, 24, 25 and 26, characterized in that the inert organic solvent in step 2 is tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene, dichloroethane or dichloromethane, or a mixture thereof.

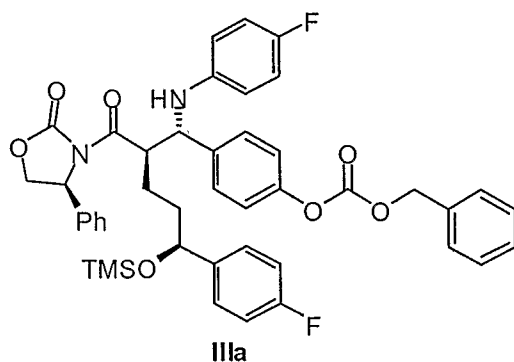
28. The method according to any of Claims 17, 24, 25 and 27, characterized in that silylation in step 2 is carried out using trimethylsilylchloride in an amount of 1.05 to 1.4 equivalents and triethylamine in the temperature range -5 to 25 °C.

29. Silylether-oxazolidides of general formula III

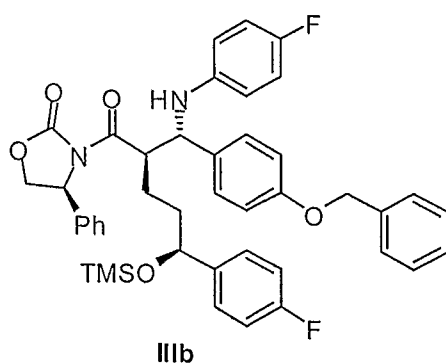


wherein PG represents a phenol protecting group, such as a carbonate group, preferably benzyloxycarbonyl or *tert*-butyloxycarbonyl, or an arylmethyl group, preferably benzyl, benzhydryl or trityl, or a silyl group, preferably *tert*-butyldimethylsilyl or hexyldimethylsilyl, and X is a silyl group of general formula $\text{SiR}^1\text{R}^2\text{R}^3$, wherein R^1 to R^3 are identical or different alkyl groups with 1 to 5 carbon atoms or the phenyl group.

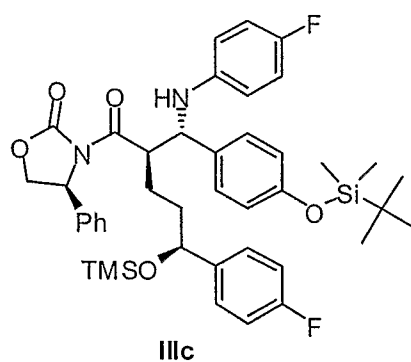
10 30. The silylether-oxazolidide of formula IIIa



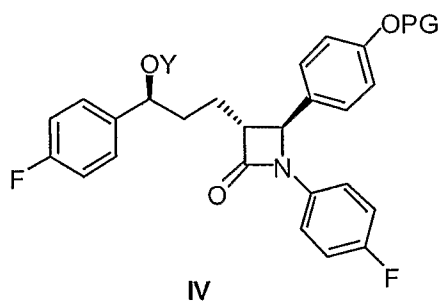
31. The silylether-oxazolidide of formula IIIb



32. The silylether-oxazolidide of formula IIIc



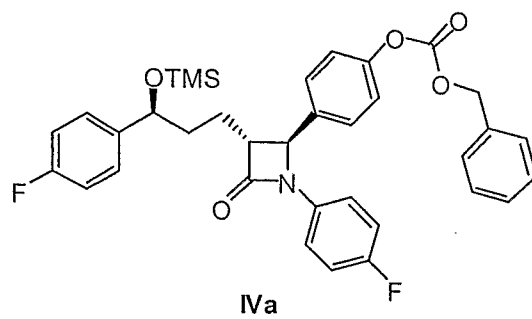
33. A protected azetidinone of general formula IV



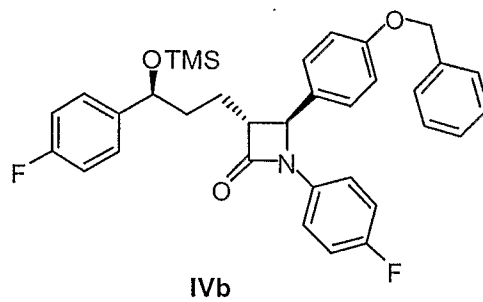
5

wherein PG is as defined above and Y is hydrogen or group X as defined above.

34. The protected azetidinone of formula IVa



35. The protected azetidinone of formula IVb



5

36. The protected azetidinone of formula IVc

