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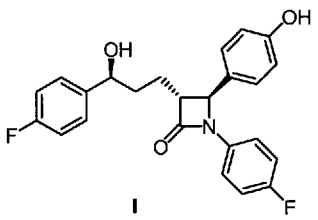
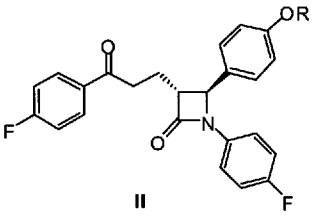
[Continued on next page]

(54) Title: A METHOD OF MANUFACTURING (3R,4S)-L-(4-FLUOROPHENYL)-3-[(3S)-3-(4-FLUOROPHENYL)-3- HYDROXYPROPYL)]-4-(4-HYDROXYPHENYL)-2-AZETIDINONE AND ITS INTERMEDIATES



I



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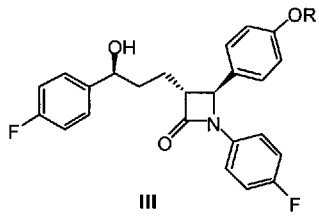

III

(57) Abstract: A method of manufacturing (3*R*,4*S*)-l-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3- hydroxypropyl)]-4-(4-hydroxyphenyl)-2-azetidinone (ezetimibe) of formula I, in which a protected ketone of general formula II, wherein R stands for a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl, is reduced with asymmetrical borane agents in an inert organic solvent in the temperature range of -30 to +40 °C, and finally the obtained protected alcohol of general formula III, wherein R has the same meaning as above, is deprotected by the action of hydro genolytic or acidic agents in an inert organic solvent.

WO 2009/067960 A2

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A method of manufacturing (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl)]-4-(4-hydroxyphenyl)-2-azetidinone and its intermediates

Technical Field

The invention deals with a new method of manufacturing (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl)]-4-(4-hydroxyphenyl)-2-azetidinone.

Background Art

(3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl)]-4-(4-hydroxyphenyl)-2-azetidinone of formula (I), known under the INN name ezetimibe, is described in US patent 5,631,365 as a hypo-lipidemic substance reducing intestinal absorption of cholesterol and other sterols.

In accordance with US patents 5,739,321 and 5,886,171 ezetimibe is produced in such a way that (*S*)-4-hydroxybutanolide is added onto *N*-(4-benzyloxybenzylidene)-4-fluoroaniline by means of LDA at -78 °C, the obtained diol is split with a periodate into an aldehyde, which reacts with 4-fluoroacetophenone *O*-trimethylsilylenol producing an aldol. The latter is dehydrated to produce an unsaturated ketone whose double bond or at the same time the protective benzyl group is hydrogenated on a palladium catalyst. Then, the ketone is asymmetrically reduced with a borane in the presence of a chiral ligand to produce ezetimibe or its *O*-benzyl derivative, which is hydrogenolyzed on a palladium catalyst. Disadvantages of this method consist in the necessity to work at very low temperatures and to repeatedly use expensive catalysts of the palladium type.

The production method of ezetimibe described in US patent 5,856,473 starts with 5-(4-fluorophenyl)-4-pentenoic acid, which is transformed to its chloride with oxalylchloride and further to the acyloxazolidide by reaction with (*S*)-4-phenyl-2-oxazolidinone. The latter is added onto *N*-(4-benzyloxybenzylidene)-4-fluoroaniline by means of titanium tetrachloride in the presence of diisopropylethylamine to obtain a product that is cyclized with the use of bistrimethylsilylacetamide and catalytic TBAF to olefine-azetidinone. This alkene is transformed to the ketone by the 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 ligand and finally the protective *O*-benzyl group is hydrogenolyzed. Again, repeated

using of expensive catalysts of the palladium type and using the toxic oxalylchloride in the procedure are considerable disadvantages.

In accordance with the above mentioned US patent 5,631,365 ezetimibe is produced in such a way that (*S*)-*N*-(4-methoxycarbonylbutanoyl)oxazolidide is synthesized from (*S*)-4-phenyl-2-oxazolidinone and glutaric acid esterchloride and then it is added onto the above-mentioned *N*-(4-benzyloxybenzylidene)-4-fluoroaniline in the presence of titanium tetrachloride, and the obtained product is cyclized by the action of bistrimethylsilylacetamide and catalytic TBAF to ester-azetidinone. Alkaline hydrolysis of the ester produces an acid, which is transformed to the acyl chloride whose reaction with a Grignard reagent in the presence of $ZnCl_2$ and $Pd(PPh_3)_4$ produces a ketone. The latter is asymmetrically reduced with a diborane in the presence of a chiral ligand and finally the protective *O*-benzyl group is hydrogenolyzed on a palladium catalyst. Again, repeated using of expensive catalysts of the palladium type as well as using the toxic oxalylchloride is a considerable disadvantage.

The production method of ezetimibe in accordance with WO 2006/137080 is similar to the above-mentioned one and it also has similar disadvantages. Glutaric acid methyl esterchloride is produced by the action of oxalylchloride on the corresponding acid and is reacted with (*S*)-4-phenyl-2-oxazolidinone to produce (*S*)-*N*-(4-methoxycarbonylbutanoyl)-oxazolidide. The latter is added onto the above-mentioned *N*-(4-benzyloxybenzylidene)-4-fluoroaniline in the presence of titanium tetrachloride, and the obtained product is cyclized by the action of bistrimethylsilylacetamide and catalytic TBAF to ester-azetidinone. With alkaline hydrolysis of the ester an acid is obtained that is transformed, with the use of oxalylchloride, to the acyl chloride whose reaction with a Grignard reagent in the presence of $ZnCl_2$ and an acetate of a transitional metal, such as e.g. palladium, produces a ketone. The latter is asymmetrically reduced with a diborane in the presence of a chiral ligand and finally the protective *O*-benzyl group is hydrogenolyzed on a palladium catalyst. Again, in this case a considerable disadvantage consists in the repeated use of expensive catalysts of the palladium type as well as the repeated use of the toxic oxalylchloride.

The production method of ezetimibe in accordance with WO 2007/072088 starts from 4-(4-fluorobenzoyl)butanoic acid, which is first converted into an ethyleneketal and then into (*S*)-3-[4-[2-(4-fluorophenyl)-[1,3]-dioxolan-2-yl]butanoyl]-4-phenyloxazolidin-2-one by reaction with (*S*)-4-phenyl-2-oxazolidinone. Its addition onto *O*-silylated *N*-(4-hydroxybenzylidene)-4-fluoroaniline by the effect of titanium trichlorodiisopropoxide provided a product that was cyclized with bistrimethylsilylacetamide and catalytic TBAF to

the ketal azetidinone and deprotected to the ketone azetidinone with the use of montmorillonite K10. The silylated ketone produced 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 sulfuric acid in isopropyl alcohol.

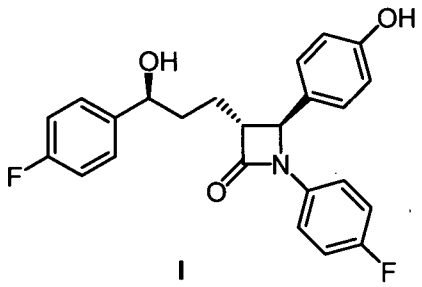
The production method in accordance with WO 2007/119106 includes not only the above mentioned ketal (*S*)-3-[4-[2-(4-fluorophenyl)-[1,3]-dioxolan-2-yl]butanoyl]-4-phenyloxazolidin-2-one, but also its analogue derived from 1,3-propanediol. Their addition onto *O*-benzylated or trimethylsilylated *N*-(4-hydroxybenzylidene)-4-fluoroaniline by the effect of titanium trichlorodiisopropoxide provided products that were cyclized to ketal azetidinones by means of bistrimethylsilylacetamide and catalytic TBAF, and then deprotected to ketone azetidinones with *p*-toluenesulfonic acid in acetone. The benzyloxy ketone produced this way was reduced with a borane in the presence of chiral (*R*)-2-methyl-CBS-oxazaborolidine and subsequently deprotected by hydrogenation on Pd/C. Alternatively, ezetimibe was also obtained through the same CBS reduction of a hydroxy-ketone.

A similar method of synthesizing ezetimibe from 5- and 6-membered ketals and protected imines is described in patent application WO 2007/120824.

Common problems of these three methods include diasteroselectivity of the CBS reduction of ketones with a diborane and subsequently the laborious final purification of the produced ezetimibe.

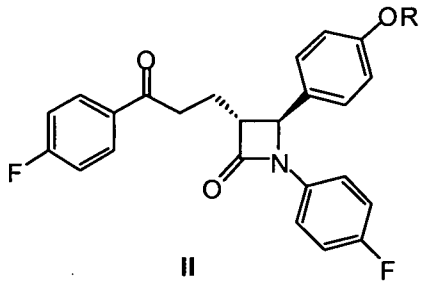
Disclosure of Invention

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



I

which comprises reduction of the protected ketone of general formula II

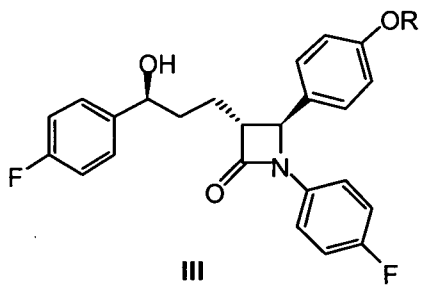


II

wherein R means a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl,

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

and deprotection of the obtained protected alcohol of general formula III



III

wherein R means the same as above

by the effect of hydrogenolytic or acidic agents in an inert organic solvent.

We have found out that ezetimibe can be produced by a method that uses highly diastereoselective CBS reduction of ketones having protected phenolic hydroxyl of general formula II by means of an asymmetrical borane agent consisting of a borane source and a chiral ligand. This way the final optical purification of the produced substance is simplified.

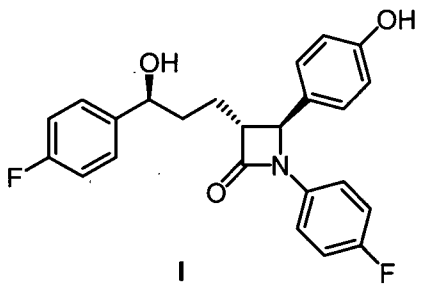
A borane complex, e.g. with dimethylsulfide, tetrahydrofuran, dimethylaniline or diethylaniline, can be used as the borane source and a 2-substituted (*R*)-CBS-oxazaborolidine, such as e.g. (*R*)-2-methyl-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-oxazaborolidine, can be used as the chiral ligand, in an amount of 1 to 100 mol%, preferably 5 to 25 mol%. The reduction is carried out in the presence of a catalytic amount of protic or Lewis acids, such as methanesulfonic acid, *p*-toluenesulfonic acid, trifluoroacetic acid or boron trifluoride etherate.

Suitable protective groups include the benzyloxycarbonyl, *tert*-butyloxycarbonyl, benzhydryl or trityl groups. Suitable inert organic solvents include e.g. tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene, or dichloromethane, or their mixtures.

The reduction is advantageously carried out at the temperatures from -25 to -15 °C, or at 20 to +30 °C.

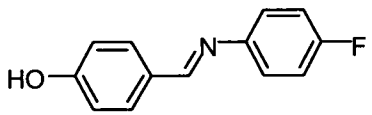
Deprotection of the protective group in the compound of general formula III is carried out with hydrogenolytic agents, such as e.g. hydrogen on a catalyst, e.g. on palladium or platinum. It can also be carried out with mineral or organic acids, such as e.g. hydrochloric, sulfuric, phosphoric, *p*-toluenesulfonic or trifluoroacetic acids. Methanol, ethanol, isopropyl alcohol, dioxan, ethyl acetate or toluene or their mixtures are used as the inert organic solvents in the process.

The present invention also includes a new method of manufacturing (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)]-4-(4-hydroxyphenyl)-2-azetidinone (ezetimibe) of formula I



I

starting from *N*-(4-hydroxybenzylidene)-4-fluoroaniline of formula IV



IV

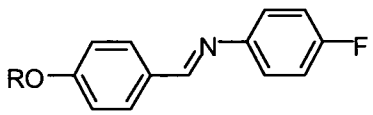
which is reacted with a protective agent of general formula V

R - X

V

wherein R means a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl, or trityl, and X is chlorine or bromine,
in an inert organic solvent in the presence of a base (step 1),

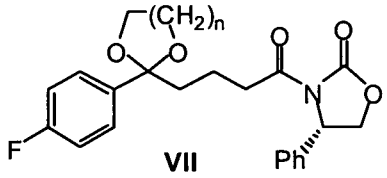
and the obtained protected imine of general formula VI



VI

wherein R means the same as above,

is subjected to reaction with an acetal-oxazolidide of general formula VII

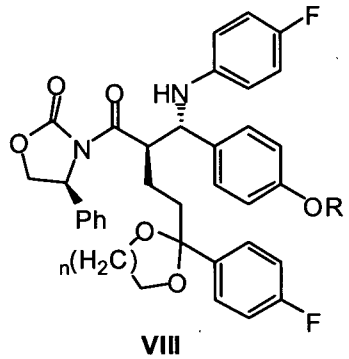


VII

wherein n = 1 or 2,

in the presence of a Lewis acid and a strong organic base in an inert organic solvent in the temperature range of -40 to 0 °C (step 2),

and the obtained amino-oxazolidide of general formula VIII

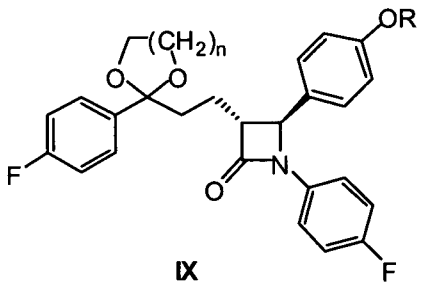


VIII

wherein both R and n have the above mentioned meanings,

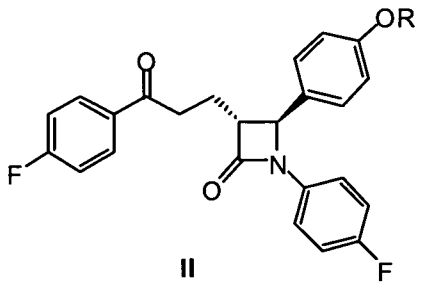
is cyclized by the effect of a silylation agent and a catalytic amount of a fluoride in the environment of an inert organic solvent in the temperature range of -20 to 50 °C (step 3),

and the obtained protected azetidinone of general formula IX



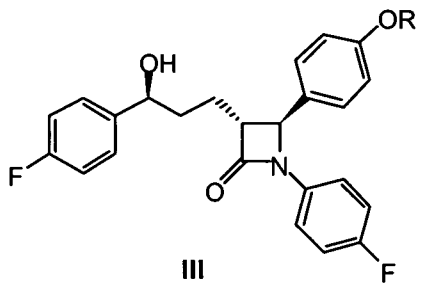
IX

wherein both R and n mean the same as above
is deketalized by the action of acidic agents in a mixture of water and a water-miscible solvent in the temperature range of 0 to 100 °C (step 4),
and the obtained protected ketone of general formula II



II

wherein R means the same as above,
is reduced with asymmetrical boron agents in an inert organic solvent in the temperature range of -30 to +40 °C (step 5),
and, finally, the obtained protected alcohol of general formula III



III

wherein R means the same as above,
is deprotected by the effect of hydrogenolytic or acidic agents in an inert organic solvent (step 6).

We have found out that ezetimibe can be produced by a method that makes use of the highly diastereoselective reduction of ketones having protected phenolic hydroxyl of general formula II by means of an asymmetrical borane agent consisting of a borane source and a chiral ligand. This way the final optical purification of the produced substance is simplified. The production procedure consists of six steps that are described in a detailed way below.

Step 1. The imine of formula IV is reacted with protective agents R - X of general formula V, wherein R stands for benzyloxycarbonyl (Cbz), diphenylmethyl (benzhydryl), or

triphenylmethyl/trityl (Tr) and X = Cl or Br, or R-X is the Boc anhydride $(Boc)_2O$. Suitable agents include e.g. benzyloxycarbonylchloride (Cbz-chloride), benzhydrylbromide or tritylchloride in the presence of a base such as e.g. triethylamine and DMAP, diisopropylethylamine, or an aqueous solution of potassium or sodium carbonates, in an inert solvent such as e.g. dichloromethane, chloroform or dimethylformamide.
The compound of general formula VI can also be prepared by first protecting 4-hydroxybenzaldehyde by reaction with agents R – X of general formula V and subsequently coupling the obtained protected 4-hydroxybenzaldehyde with 4-fluoroaniline in an inert organic solvent in the temperature range of from 20 °C to the boiling temperature of the mixture. Suitable solvents include aliphatic alcohols such as e.g. methanol, ethanol, or isopropyl alcohol, or dimethylformamide, preferably at the temperature of from 40 °C to the boiling temperature of the mixture.

Step 2. The protected imine of general formula VI, wherein R has the above mentioned meaning, is subjected to a reaction with (*S*)-*N*-acetal-oxazolidide of general formula VII, wherein n = 1 or 2, in the presence of a Lewis acid, e.g. titanium tetrachloride or titanium trichloride alkoxide, in the quantity of 1 to 2 equivalents, preferably 1.1 to 1.4 equivalents. The addition is carried out in the presence of a strong organic base, preferably diisopropylethylamine, in an amount of 2 to 5 equivalents, in a inert organic solvent such as dichloromethane, dichloroethane, toluene, *tert*-butylmethylether, tetrahydrofuran, in the temperature range of -40 to 0 °C, preferably at -35 to -20 °C.
The procedure can be advantageously executed using the one-pot method in such a way that first of all the protected imine of general formula VI is prepared in situ by reaction of the imine IV with protective agents R – X by the above-described procedure and then the acetal-oxazolidide of formula VII is added onto it by the above-mentioned method.

Step 3. The amino-oxazolidide of general formula of VIII, where both R and n have the above mentioned meanings, is cyclized by the effect of a silylation agent such as e.g. bis-(trimethylsilyl)acetamide and a catalytic amount of a fluoride, preferably tetrabutylammonium fluoride. The cyclization is carried out in an inert organic solvent, such as tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, in the temperature range of -20 to 50 °C, preferably at -5 to +10 °C.

Step 4. The ketal of general formula IX, wherein both R and n have the same meanings as above, is hydrolyzed by the action of acidic agents such as *p*-toluenesulfonic acid, methanesulfonic acid or acetic acid, in a mixture of water and a water-miscible solvent such as tetrahydrofuran, acetone, or isobutylmethylketone, in the temperature range of 0 to 80 °C, preferably at 50 to 70 °C.

Step 5. The protected ketone of general formula II, wherein both R and n have the above meanings, is reduced with asymmetrical borane agents consisting of a borane source and a chiral ligand, such as e.g. 2-substituted (*R*)-CBS-oxazaborolidine, in an inert organic solvent, e.g. in tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene, or dichloromethane, or their mixture, in the temperature range of -30 to +40 °C. A borane complex, e.g. with dimethylsulfide, tetrahydrofuran, dimethylaniline, or diethylaniline, can be used as the borane source and the chiral ligands can include e.g. (*R*)-2-methyl-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-oxazaborolidine in the quantity of 1 to 100 mol%, preferably 5 to 25 mol%. The reduction is advantageously carried out in the presence of catalytic amounts of protic or Lewis acids such as methanesulfonic, *p*-toluenesulfonic, trifluoroacetic acids or boron trifluoride etherate. The advantageous temperature range for the reduction is -25 to -15 °C, or 20 to +30 °C.

Step 6. The protected alcohol of general formula III is finally deprotected by the effect of hydrogenolytic agents, such as e.g. hydrogen on a catalyst, e.g. on palladium or platinum. It may also be carried out with mineral or organic acids, such as e.g. hydrochloric acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid or trifluoroacetic acid. Methanol, ethanol, isopropyl alcohol, dioxan, ethyl acetate, or toluene or their mixtures are used as inert organic solvents.

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

The following examples illustrate the general manufacturing process of the invention; however, they do not limit it in any way.

Example 1

Preparation of the compound of formula III (R = Cbz)

A solution of *R*-Me-CBS catalyst (831 µl, 0.83 mmol, 15 mol %) is added dropwise to a solution of the ketone of formula II (R = Cbz) (3.00 g, 5.54 mmol) in dry THF (25 ml) at -25 °C in an argon atmosphere. The reaction mixture is stirred for additional 15 minutes and then a 2 M solution of BH_3*Me_2S in THF (2.77 ml, 5.54 mmol, 1.0 equiv.) is added dropwise within 1 hour, the temperature of the reaction mixture being maintained in the range of -25 to -20 °C for the whole time. After another hour of stirring the reaction is terminated, after a TLC check, with slow addition of methanol (5 ml) and stirring is continued at -25 to -20 °C for 15 minutes. After the removal from the cooling bath 1 M HCl (10 ml) and water (10 ml) is added and after 15 min of stirring the mixture is washed with dichloromethane (4 x 20 ml). The combined organic fractions are washed with water (20 ml), saline (20 ml) and dried over sodium sulfate. Filtration and evaporation yields the crude product as a solid foam, 3.00 g, melting temp. 48-50 °C.

HRMS: $[M-H]^+$ $C_{32}H_{28}O_5N_1F_2$ theory: 544,1936, found: 544.1634.

^{1}H-NMR (250 MHz, $CDCl_3$): 7.46 – 7.10 (m, 13H), 7.10 – 6.46 (m, 4H), 5.27 (s, 2H), 4.73 (m, 1H), 4.63 (d, J = 2.5 Hz, 1H), 3.08 (m, 1H), 2.15 (d, J = 5 Hz, 1H), 2.04 – 1.66 (m, 4H).

Preparation of the compound of formula III (R = Tr)

2.60 g (4.0 mmol) of the compound of formula II (R = Tr) are dissolved in an inert atmosphere in 35 ml of THF. 1M solution of (*R*)-2-methyl-CBS-oxazaborolidine in toluene (0.6 ml) is added to this solution at the laboratory temperature and the mixture is stirred for 15 min. To the stirred mixture 1 M solution of BH_3.Me_2S in dichloromethane (2.4 ml) is added dropwise at the room temperature. After completion of the addition the reaction mixture is stirred for another 15 minutes (TLC) and then it is carefully decomposed with methanol (3.5 ml) and diluted with 1M solution of HCl (5.5 ml) and water (17 ml). The mixture is extracted with dichloromethane (50 ml and 35 ml). The combined organic fractions are washed with water (10 ml) and dried with anhydrous sodium sulfate. The organic solvents are evaporated in a rotatory vacuum evaporator and the crude product is chromatographed on silica gel; eluent: petroleum ether/ethyl acetate 7 : 3.

Yield: 1.63g (62.5 %) of an oily product of formula III (R = Tr).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.42 (m, 6H), 7.24 (m, 11H), 7.11 (dd, J = 9.1, 4.7 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 6.90 (m, 4H), 6.66 (d, J = 8.7 Hz, 2H), 4.66 (m, 1H), 4.40 (d, J = 2.3 Hz, 1H), 2.98 (m, 1H), 2.16 (d, J = 3.6 Hz, 1H), 1.88 (m, 4H).

Preparation of the compound of formula I (ezetimibe)

a) 10% of Pd/C (0.141 g, 3 mol %) are added to a solution of the crude compound of formula III (R = Cbz) (2.40 g, 4.42 mmol) in methanol (30 ml) and the mixture is reduced with hydrogen at the atmospheric pressure overnight (23 h). The catalyst is removed by filtration through a kieselguhr column, which is then washed with methanol (3 x 10 ml). The evaporation of the combined filtrates provides the product as brownish foam (1.8 g, ca. quant.). The crude product is dissolved in methanol (10 ml) and heated up to 60 °C in a water bath. While being stirred, the hot solution is slowly saturated with water until slight permanent turbidity (ca. 7 ml of water), which is removed by the addition of a few drops of methanol. The solution is removed from the bath and slowly cooled down while being stirred. The crystal suspension is then cooled in a refrigerator and the product is isolated by filtration. The quantity of 1.37 g (76%) of a white crystalline substance is obtained; further re-crystallization from $MeOH/H_2O$ provides 1.14 g (63%) of crystals. HPLC: 99.18%.

b) 1.63 g of the compound of formula III (R = Tr) (2.5 mmol) is dissolved in methanol (100 ml). A catalyst (3% of Pd/C; 150 mg) is added to the degasified solution and the mixture is hydrogenated at the laboratory pressure and room temperature for 18 hours. The catalyst is filtered through kieselguhr and the filtrate is evaporated in a rotatory vacuum evaporator until dry. The crude product is chromatographed on silica gel (eluent: petroleum ether/ethyl acetate 1 : 1). 1.03 g of a residue is obtained, which is crystallized from a methanol/water mixture. Yield: 0.75 g, i.e. 73.3% of the white crystalline substance of formula I (ezetimibe).

Example 2

Preparation of the compound of formula VI (R = Tr)

Diisopropylethylamine (8.58 ml, 49.25 mmol, 1.1 equiv.) is added to a suspension of the imine IV (9.82 g; 45.6 mmol) and tritylchloride (V; R = Tr, X = Cl) (13.73 g, 49.25 mmol; 1.08 equiv.) in dichloromethane (150 ml) under stirring and cooling to 10°C within 5 minutes. The obtained solution is heated up to the laboratory temperature while the course of the reaction is monitored with TLC. After 1 hour the reaction mixture is washed with water (80 and 50 ml)

and saline (50 ml), the organic phase is filtered off and evaporated in a rotatory vacuum evaporator. A glassy residue is obtained that is brought to boil with isopropylalcohol (55 ml), which causes the formation of crystals. The suspension is left to cool down to rt overnight. The crystals are sucked off, washed with isopropylalcohol (18 ml) and dried at 40°C. Melting temp. 138-140 °C.

Yield: 20.41 g, i.e. 97.8 % of the compound of formula VI (R = Tr).

Example 3

Preparation of the compound of formula VIII (n = 2, R = Cbz)

Diisopropylethylamine (8.0 ml, 46.7 mmol) is added to a stirred mixture of the imine of formula VI (R = Cbz) (8.73 g, 25.0 mmol, 1.25 equiv.) and the ketal of formula VII (n = 2) (8.20 g, 20.0 mmol) in CH_2Cl_2 (100ml) with cooling to 0°C within 5-10 minutes. The mixture is cooled to -33 °C, and stirred at this temperature for 40 minutes. In the course of 10 minutes at the temperature of -35 °C a previously prepared solution of the agent, made of 1 M solution of $TiCl_4$ (19 ml, 19.0 mmol) in CH_2Cl_2 (30 ml) and Ti(O*i*-Pr)$_4$ (1.95 ml, 6.55 mmol), stirred at 0°C for 1 hour, is added to the mixture. The reaction mixture is stirred at the temperature of -30°C for 3 hours and then acetic acid (6 ml) is added at the temperature of -30 °C under stirring during 5 - 10 minutes. 0.46 M solution of citrate buffer (50 ml) is added to the reaction mixture and the mixture is intensively stirred at 5°C for 1 hour. The organic layer is separated, the aqueous layer is extracted with CH_2Cl_2 (30 ml). The combined organic fractions are evaporated and the crystalline residue (30 g) is stirred in ethanol (125 ml) at 80 °C for 15 minutes and at the laboratory temperature for 2 hours. The obtained crystals (13.01 g) are stirred in ethyl acetate (50 ml) at the temperature of 76 °C for 15 min and then at the laboratory temperature for 2 hours. The crystals are filtered off, washed with ethyl acetate (10 ml) and dried; melting temp. 206.5-207.5 °C.

Yield: 9.93 g; 65.1 % of the compound of formula VIII (n = 2, R = Cbz).

Example 4

Preparation of the compound of formula IX (n = 2, R = Cbz)

BSA (1.44 ml, 5.76 mmol; 1.8 equiv.), and TBAF (0.07 g, 0.22 mmol; 0.067 equiv.) after 15 minutes of stirring, are added to the stirred amino-oxazolidide of formula VIII (n = 2, R = Cbz) (2.44 g, 3.20 mmol) in THF (25 ml). Being stirred the mixture is heated up from 0°C to the laboratory temperature during 1 hour while the course of the reaction is monitored with

TLC. After completion of the reaction acetic acid (1.0 ml, 17.5 mmol) is added and the mixture is stirred at the laboratory temperature for 15 minutes. The reaction mixture is diluted with ethyl acetate (25 ml), washed with an aqueous solution of $NaHCO_3$ (1x) and water (1x), and, after drying (Na_2SO_4), evaporated in a rotatory vacuum evaporator.

Yield: 1.71 g, i.e. 89 % of ketal IX (n = 2, R = Cbz).

Preparation of the compound of formula IX (n = 2, R = Tr)

BSA (1.22 ml, 5.0 mmol) is added to a suspension of the amino-oxazolidide of formula VIII (n = 2, R = Tr) (1.374 g, 5.0 mmol) in tetrahydrofuran (20 ml). The mixture is stirred at the laboratory temperature for 10 minutes, then it is cooled to 0 °C and 0.5 M solution of TBAF in THF (0.2 ml, 0.1 mmol; 0.05 equiv.) is added. The mixture is stirred at 0°C for 3 hours while a solution is formed (the course of the reaction is monitored with TLC). After completion of the reaction acetic acid (1.0 ml, 17.5 mmol) is added, the reaction mixture is stirred at the laboratory temperature for 15 minutes and then washed with a saturated solution of $NaHCO_3$ (1x) and water (2x). The organic phase is filtered and evaporated until dry in a rotatory vacuum evaporator.

Yield: 0.88 g.

Example 5

Preparation of the compound of formula II (R = Cbz)

a) A suspension of the ketal of formula IX (n = 2, R = Cbz) (3.36 g, 5.6 mmol) in a mixture of acetic acid (55 ml), THF (20 ml) and water (15 ml) is heated up to 60 °C under stirring and maintained at this temperature for 4-5 hours while a homogeneous solution is formed. After completion of the reaction the reaction mixture is concentrated in a rotatory vacuum evaporator and the residue is divided between toluene (120 ml) and a saturated aqueous solution of $NaHCO_3$ (40 ml). The separated organic layer is washed with the saturated solution of $NaHCO_3$ (1x) and water (1x), and after drying (Na_2SO_4) it is evaporated until dry in a rotatory vacuum evaporator. The obtained residue in the form of white foam is re-crystallized from isopropylalcohol. Melt. temp. 100.5-102 °C.

Yield: 2.55 g, 84.1 %.

HRMS: $[M-H]^+$ $C_{32}H_{26}O_5N_1F_2$ theory: 542.1779, found: 542.1776.

^{1}H-NMR (250 MHz, $CDCl_3$): 7.99 (m, 2H), 7.42 – 7.33 (m, 7H), 7.26 – 7.09 (m, 6H), 6.96 (m, 2H), 5.26 (s, 2H), 4.75 (d, J = 2.5 Hz, 1H), 3.36 – 3.08 (m, 3H), 2.49 – 2.21 (m, 2H).

b) A mixture of the ketal of formula IX (n = 2, R = Cbz) (3.30 g, 5.5 mmol) and p-toluenesulfonic acid in a mixture of acetone (50 ml) and water (5,5 ml) is heated up to 60°C while being stirred and maintained at this temperature for 2.5 h (TLC). The reaction mixture is concentrated in a rotatory vacuum evaporator and the residue is dissolved in dichloromethane (110 ml) and washed with a saturated aqueous solution of $NaHCO_3$ (40 ml). The separated organic layer is washed with saline (1x 25 ml) and evaporated until dry in a rotatory vacuum evaporator. The residue, white foam, is re-crystallized from isopropylalcohol. The product is sucked off and washed with cold isopropylalcohol and dried at 40 °C; melt. temp. 100-102 °C.

Yield: 2.69 g, i.e. 90.4 % of the ketone of formula II (R = Cbz).

Example 6

Preparation of the compound of formula III (R = Cbz)

2 M solution of $BH_3.Me_2S$ in THF (0.3 ml) is added dropwise to a solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.139 g, 0.5 mmol; 10 mol%) in CH_2Cl_2 (15 ml) and the resulting solution is stirred at 0 °C for 15 minutes. The solution is cooled down to -20 °C and then a solution of the compound of formula II (R = Cbz) (2.735 g, 5.05 mmol) in THF (15 ml) is added dropwise within 15 minutes, followed by 2 M solution of $BH_3.Me_2S$ in THF (2.5 ml, 5 mmol; 1.11 equiv. in total) at -20 to -25 °C in the course of 1 hour. The reaction mixture is stirred until the initial substance disappears according to TLC (1 h). The reaction is finished by the addition of MeOH (4 ml) and stirring at the same temperature for 15 min. Then, 0.5 M HCl (10 ml) and water (10 ml) is added and the mixture is still stirred at 0 °C for 10 min and at the laboratory temperature for 20 min. The organic phase is separated and the aqueous phase is extracted with dichloromethane (3x20 ml). The combined organic phases are washed with water (2x 15 ml), saline (20 ml), and after drying (Na_2SO_4) they are evaporated in a rotatory vacuum evaporator, white foam; melting temp. 48.5-51 °C.

Yield: 2.74 g of the compound of formula III (R = Cbz).

Example 7

Preparation of the compound of formula II (R = Cbz)

DMAP (0.369g, 3.02 mmol, 10 mol %) and triethylamine (8.4 ml, 60.36 mmol, 2.0 equiv.) are added to a solution of the compound of formula II (R = H) (12.29g, 30.18 mmol) in dry

dichloromethane (180 ml) in the argon atmosphere. The reaction mixture is cooled to 5°C in an ice bath and then a 50% solution of benzyl-chloroformate in toluene (11.6 ml, 34.71 mmol, 1.15 equiv.) is added dropwise during ca. 10 min. While being stirred the reaction mixture is heated up to 15 °C during 3 hours while the course of the reaction is monitored with TLC. Water (50 ml) is then added to the reaction mixture. The organic phase is separated and washed with 1 N HCl (2 x 50 ml), water (1 x 50 ml) and saline (1 x 50 ml) and is dried over sodium sulfate. The filtration and evaporation of the solvent provides a thick yellow oil that is dissolved in isopropanol (200 ml) during boiling. The solution is left to cool down to rt and then to 4°C; the white crystalline product is filtered off, washed with isopropylalcohol (50 ml) and dried in a vacuum drier at 45°C.

The amount of 13.50 g (83%) of a white crystalline substance is obtained; melting temp. 101.5-102.5 °C. HPLC: 99.25%.

Preparation of the compound of formula II (R = Tr)

Tritylbromide (5.03 g, 15.5 mmol) and diisopropylethylamine (2.1 g, 16.0 mmol) are gradually added to a solution of the hydroxyketone of formula II (R = H) (5.71 g; 14.14 mmol) in dichloromethane (100 ml) at the room temperature and the resulting solution is stirred at the room temperature for 2 h. The reaction mixture is then gradually extracted with 1N HCl (50 ml), water (20 ml), 9% solution of $NaHCO_3$ (50ml) and water (30 ml). After drying with anhydrous sodium sulfate the organic fraction is evaporated until dry in a rotatory vacuum evaporator. 10.09 g of the crude product is obtained, which is chromatographed on silica gel (eluent: 5% ethyl acetate in toluene).

Yield: 8.9 g (96.9 %) of the compound of formula II (R= Tr).

Example 8

Preparation of the compound of formula VI (R = Cbz)

a) DMAP (3.07 g, 25.1 mmol; 0.15 equiv.) is added to a suspension of *p*-hydroxybenzaldehyde (20.15 g, 165.1 mmol) in CH_2Cl_2 (80 ml) and then TEA (46 ml, 330 mmol; 2 equiv.) is added dropwise at the temperature of 0 °C. A 50% solution of benzyl-chloroformate in toluene (82.5 ml, 0,237 mmol, 1.4 equiv.) is added dropwise to the resulting solution at the temperature of 0°C during 40 minutes and the reaction mixture is stirred at the same temperature for 1.5 h. 1N HCl (80 ml) is added to the reaction mixture and it is stirred for 10 min. The organic layer is separated, washed with 1N HCl (1x 60 ml) and saline (1x 50

ml) and evaporated in a rotatory vacuum evaporator. A yellow oil (54 g) is obtained that crystallizes upon addition of methanol (20 ml). The crystals are sucked off, washed with methanol (10 ml) and dried.

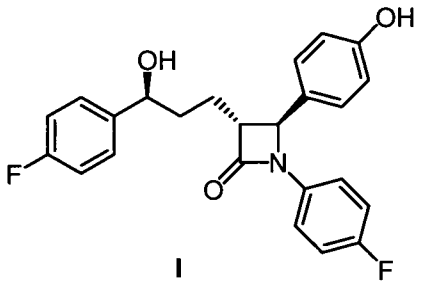
Yield: 33.0 g, 78.05 % of benzyl-(4-formylphenyl)-carbonate.

b) 2-Propanol (150 ml) is added to benzyl-(4-formylphenyl)-carbonate (32.93 g, 128.5 mmol) and the suspension is heated up to 55°C during 30 minutes. 4-Fluoroaniline (9.6 ml, 101 mmol) is added to the resulting solution and the mixture is stirred without heating on slowly cooling to the laboratory temperature for 3 hours altogether. The resulting crystals (34.05 g, 96.19% of the theoretical yield) are sucked off and washed with 2-propanol (20 ml). Melting temp. 88-90 °C.

Yield: 75.08 % of the compound of formula VI (R = Cbz).

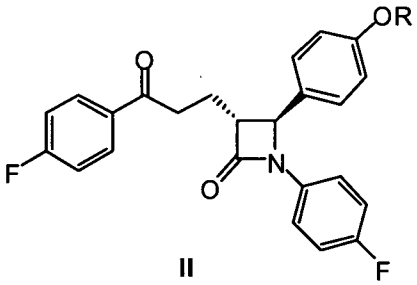
CLAIMS

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



I

characterized in that a protected ketone of general formula II

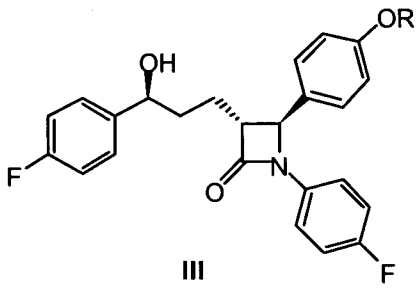


II

wherein R stands for a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl,

is reduced with at least one asymmetrical borane agent in an inert organic solvent in the range of temperatures of -30 to +40 °C,

and finally the obtained protected alcohol of general formula III



III

wherein R means the same as above,

is deprotected by the action of hydrogenolytic or acidic agents in an inert organic solvent.

2. The method according to claim 1, characterized in that a borane in the presence of a chiral ligand is used as the asymmetrical borane agent.

3. The method according to claims 1 or 2, characterized in that a borane complex, e.g. with dimethylsulfide, tetrahydrofuran, dimethylaniline or diethylaniline, is used as the borane source.

4. The method according to any of claims 1-3, characterized in that a 2-substituted (*R*)-CBS-oxazaborolidine, such as e.g. (*R*)-2-methyl-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-oxazaborolidine, in an amount of 1 to 100 mol%, preferably 5 to 25 mol%, is used as the chiral ligand.

5. The method according to any of claims 1-4, characterized in that the reduction is carried out in the presence of a catalytic amount of at least one protic or Lewis acid, such as methanesulfonic, *p*-toluenesulfonic or trifluoroacetic acids or boron trifluoride etherate.

6. The method according to any of claims 1-5, characterized in that tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane or their mixture are used as the inert organic solvents.

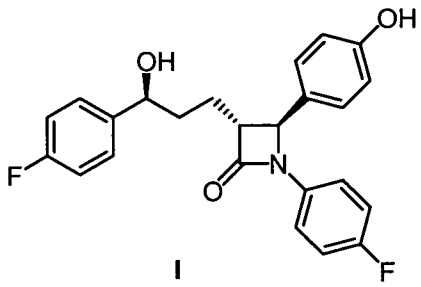
7. The method according to any of claims 1-6, characterized in that the reduction is carried out at -25 to -15 °C, or at 20 to +30 °C.

8. The method according to claim 1, characterized in that the deprotection is carried out with at least one hydrogenolytic agent, such as e.g. hydrogen or ammonium formate, on a catalyst, such as e.g. on palladium or platinum.

9. The method according to claims 1 or 8, characterized in that the deprotection is carried out with at least one mineral or organic acid, such as e.g. hydrochloric acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid or trifluoroacetic acid.

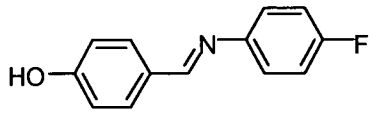
10. The method according to claims 1, 8 or 9, characterized in that methanol, ethanol, isopropylalcohol, dioxan, ethyl acetate or toluene or their mixtures are used as the inert organic solvents.

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



I

characterized in that *N*-(4-hydroxybenzylidene)-4-fluoraniline of formula IV



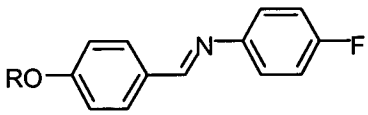
IV

is reacted with a protective agent of general formula V

R - X

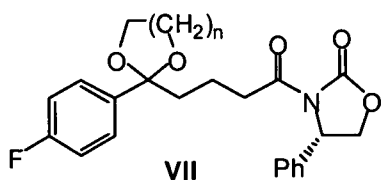
V

wherein R stands for a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl, and X is chlorine or bromine,
in an inert organic solvent in the presence of a base (step 1),
and the obtained protected imine of general formula VI



VI

wherein R means the same as above
is subjected to reaction with an acetal-oxazolidide of general formula VII

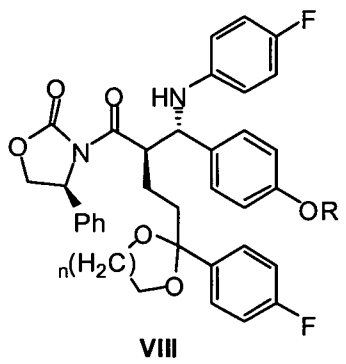


VII

wherein n = 1 or 2,

in the presence of a Lewis acid and a strong organic base in an inert organic solvent in the temperature range of -40 to 0 °C (step 2),

and the obtained amino-oxazolidide of general formula VIII

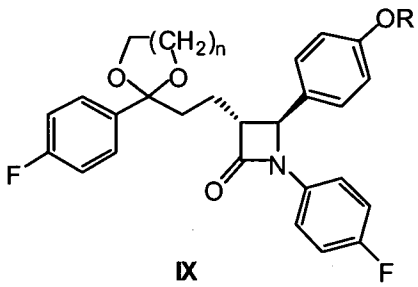


VIII

wherein both R and n have the above-mentioned meanings,

is cyclized by the action of a silylation agent and a catalytic amount of a fluoride in the environment of an inert organic solvent and the temperature range of -20 to 50 °C (step 3),

and the protected azetidinone of general formula IX

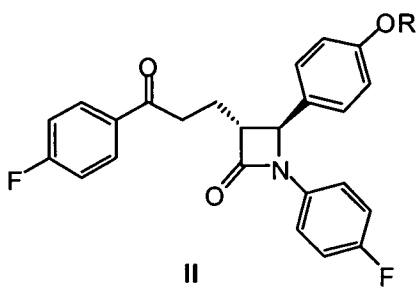


IX

wherein both R and n have the above-mentioned meanings,

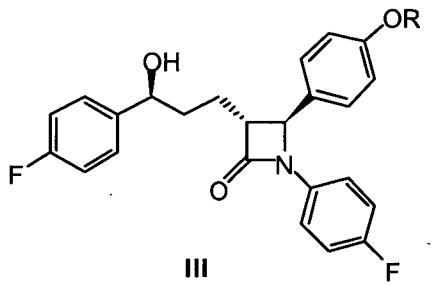
is deketalized by the action of at least one acidic agent in a mixture of water and a water-miscible solvent in the temperature range of 0 to 100 °C (step 4),

and the obtained protected ketone of general formula II



II

wherein R means the same as above,
is reduced with at least one asymmetrical borane agent in an inert organic solvent in the temperature range of -30 to +40 °C (step 5),
and finally the obtained protected alcohol of general formula III



III

wherein R means the same as above,
is deprotected by the effect of at least one hydrogenolytic or acidic agent in an inert organic solvent (step 6).

12. The method according to claim 11, characterized in that triethylamine and DMAP, diisopropylethylamine or an aqueous solution of potassium or sodium carbonates is used as the base in step 1.

13. The method according to claims 11 or 12, characterized in that methylenechloride, chloroform or dimethylformamide is used as the organic solvent in step 1.

14. The method according to claim 11, characterized in that, in step 2, titanium tetrachloride or a titanium trichloride alcoxide, such as titanium trichloride *i*-propoxide or titanium trichloride *n*-butoxide, in an amount of 1 to 2 equivalents is used as the Lewis acid and a strong organic base, such as diisopropylethylamine, in an amount of 2 to 5 equivalents is used.

15. The method according to claims 11 or 14, characterized in that titanium trichloride isopropoxide or titanium trichloride *n*-butoxide is used in an amount of 1.1 to 1.4 equivalents and diisopropylethylamine is used in an amount of 2.5 to 4 equivalents.

16. The method according to claims 11, 14 or 15, characterized in that dichloromethane, dichloroethane, toluene, or *tert*-butylmethylether, or their mixtures in the range of

temperatures of -40 to +0 °C, preferably at -35 to -15 °C, are used as the inert organic solvents in step 2.

17. The method according to any of claims 11, 14, 15 and 16, characterized in that in step 2 the imine of general formula VI is prepared in situ.

18. The method according to claim 11, characterized in that in step 3 the cyclization is carried out by the action of an silylation agent, such as bis-trimethylsilylacetamide, and a catalytic amount of a fluoride, preferably tetrabutylammonium fluoride, in an inert organic solvent such as tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane, or their mixture in the temperature range of -20 to 50 °C, preferably at -5 to +20 °C.

19. The method according to claim 11, characterized in that an acidic agent such as *p*-toluenesulfonic acid, methanesulfonic acid or acetic acid in a mixture of water and a water-miscible solvent such as tetrahydrofuran, 2-methyltetrahydrofuran, acetone or isobutymethylketone, or their mixtures, in the temperature range of 0 to 100 °C, preferably at 50 to 70 °C, are used for the deacetalization in step 4.

20. The method according to claims 11 or 19, characterized in that the deketalization is performed with the use of acetic acid in aqueous tetrahydrofuran or by means of catalytic *p*-toluenesulfonic acid in aqueous acetone.

21. The method according to claim 11, characterized in that borane in the presence of a chiral ligand is used as the asymmetrical borane agent in step 5.

22. The method according to claims 11 or 21, characterized in that a borane complex, e.g. with dimethylsulfide, tetrahydrofuran, dimethylaniline or diethylaniline, is used as the borane source.

23. The method according to claims 11, 21 or 22, characterized in that a 2-substituted (*R*)-CBS-oxazaborolidine, such as e.g. (*R*)-2-methyl-CBS-oxazaborolidine or (*R*)-2-(*o*-tolyl)-CBS-

oxazaborolidine, in an amount of 1 to 100 mol%, preferably 5 to 25 mol%, is used as the chiral ligand.

24. The method according to any of claims 11, 21, 22 and 23, characterized in that the reduction is carried out in the presence of a catalytic amount of at least one protic or Lewis acid such as methanesulfonic, *p*-toluenesulfonic, or trifluoroacetic acids, or boron trifluoride etherate.

25. The method according to any of claims 11, 21, 22, 23 and 24, characterized in that tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butylmethylether, toluene or dichloromethane or their mixture are used as the inert organic solvents.

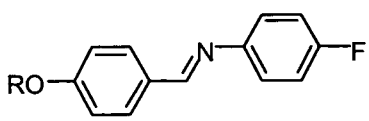
26. The method according to any of claims 11 and 21-25, characterized in that the reduction is carried out at -25 to -15 °C, or at 20 to +30 °C.

27. The method according to claim 11, characterized in that the deprotection in step 6 is carried out with at least one hydrogenolytic agent, such as e.g. hydrogen or ammonium formate, on a catalyst, such as e.g. on palladium or platinum.

28. The method according to claims 11 or 27, characterized in that the deprotection is carried out with at least one mineral or organic acid, such as e.g. hydrochloric acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid or trifluoroacetic acid.

29. The method according to any of claims 11, 27 and 28, characterized in that methanol, ethanol, isopropyl alcohol, dioxan, ethyl acetate or their mixture are used as the inert organic solvents.

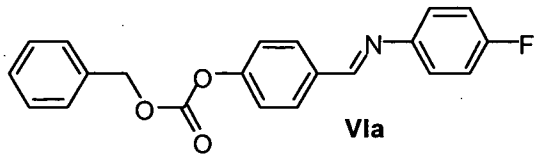
30. Protected imines of general formula VI



VI

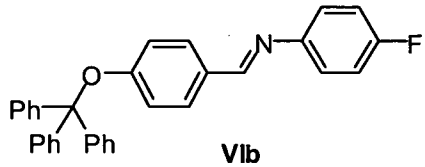
wherein R stands for a protective group such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl.

31. Benzyl-[4-(4-fluorophenyliminomethyl)phenyl]-carbonate of formula VIa



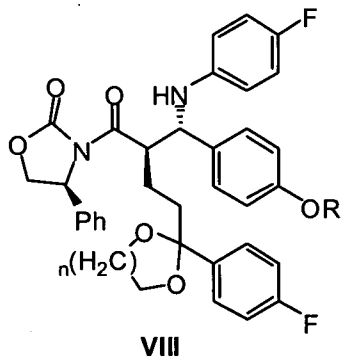
VIa

32. *N*-[4-Trityloxybenzylidene-4-fluoroaniline of formula VIb



VIb

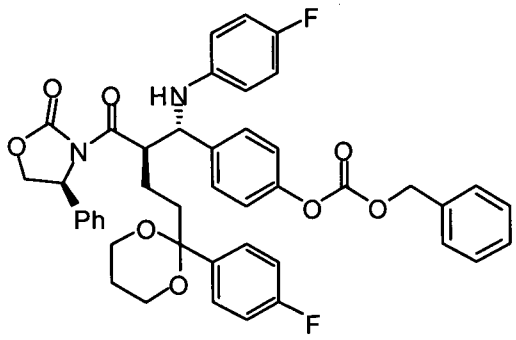
33. Amino-oxazolidides of general formula VIII



VIII

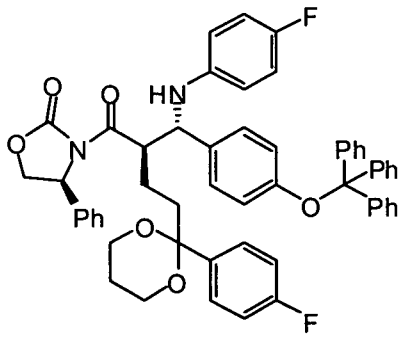
wherein R stands for a protective group such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl, and n = 1 or 2.

34. Amino-oxazolidide of formula VIIIa



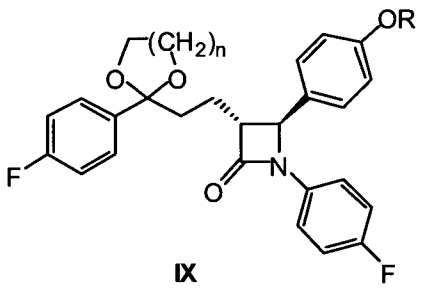
VIIIa

35. Amino-oxazolidide of formula VIIIb



VIIIb

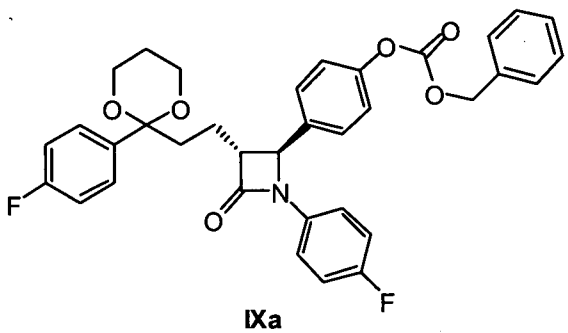
36. Protected azetidinones of general formula IX



IX

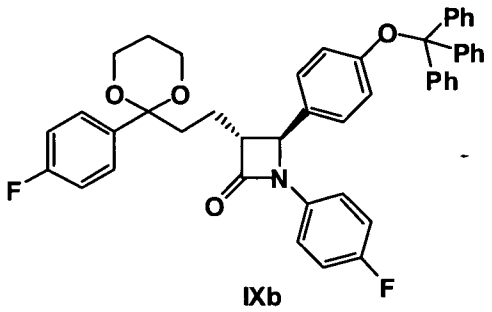
wherein R means a protective group such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl, and n = 1 or 2.

37. Protected azetidinone of formula IXa



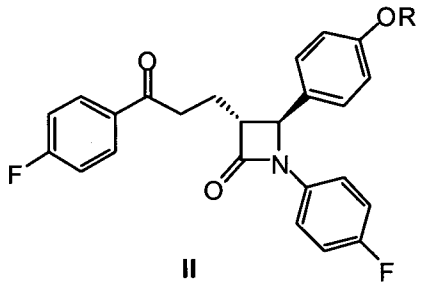
IXa

38. Protected azetidinone of formula IXb



IXb

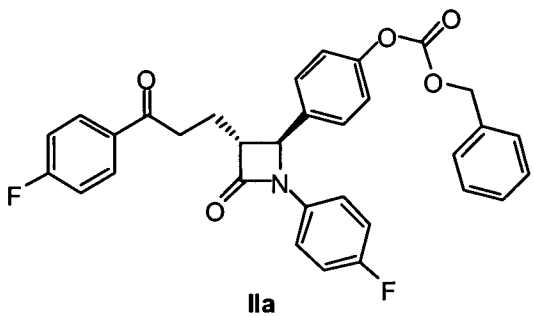
39. Protected ketones of general formula II



II

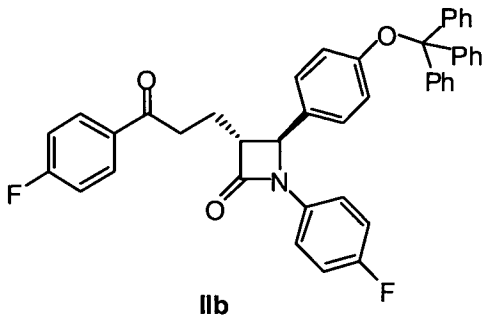
wherein R stands for a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl.

40. Protected ketone of formula IIa



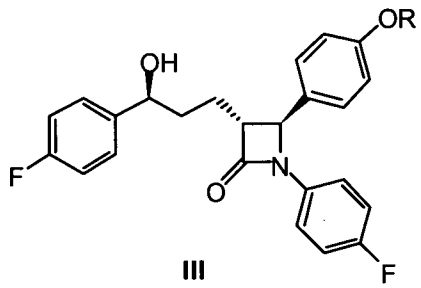
IIa

41. Protected ketone of formula IIb



IIb

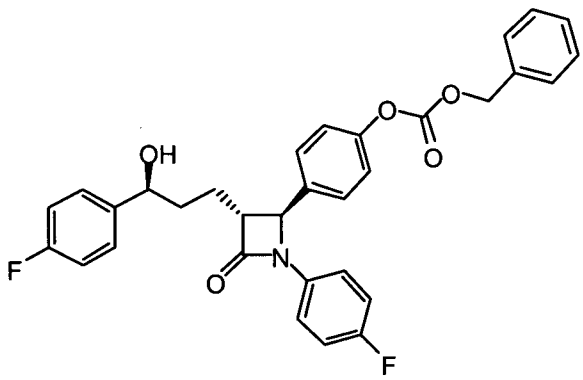
42. Protected alcohols of the general formula III



III

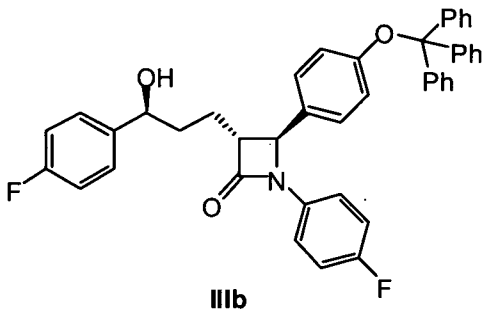
wherein R means a protective group, such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzhydryl or trityl.

43. Protected alcohol of formula IIIa



IIIa

44. Protected alcohol of formula IIIb



IIIb