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(54) **Title**: PROCESS FOR THE PREPARATION OF INTERMEDIATE COMPOUNDS USEFUL IN THE PREPARATION OF EZETIMIBE

(57) **Abstract**: The present invention provides an improved process for preparing (3*R*, 4*S*)-4-(4- (benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one, which is a key intermediate for the preparation of Ezetimibe, and involves the use of new intermediate compounds.

PROCESS FOR THE PREPARATION OF INTERMEDIATE COMPOUNDS USEFUL IN THE PREPARATION OF EZETIMIBE

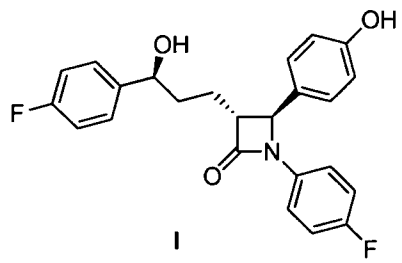
TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of (3*R*, 4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one, which is an intermediate compound useful in the process for the preparation of Ezetimibe, and novel intermediates obtained thereof.

BACKGROUND OF THE INVENTION

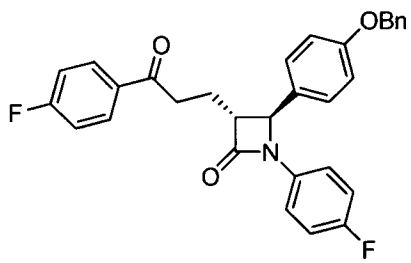
Hydroxy-alkyl substituted azetidinones are useful in the treatment of atherosclerosis. Ezetimibe is an agent used for reducing plasma cholesterol level. Ezetimibe is also used in combination with Simvastatin, when statins alone do not control cholesterol levels.

Ezetimibe is chemically designated as (3*R*, 4*S*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one and is presented by the chemical structure of Formula I.



I

Various methods for the preparation of Ezetimibe are already known. Compound of Formula VII is a common intermediate used in all the known processes. Ezetimibe can be further obtained by reducing the ketone functional group and removing the hydroxy-protecting group.



VII

Ezetimibe was first disclosed in EP-B-0720599, wherein a laborious process involving several steps and providing unsatisfactorily low yield of Ezetimibe is described. First an azetidinone ring is formed by cyclizing the coupling product of methyl 5-oxo-5[(*S*)-2-oxo-4-phenyl-oxazolidine-3-yl]pentanoate and [4-(benzyloxy)benzylidene]-(4-fluorophenyl)amine. Then the thus obtained methyl ester is activated into the carbonyl chloride form and subsequently reacted with 4-fluorophenylmagnesium chloride in the presence of a costly palladium catalyst in order to avoid secondary reactions and obtain intermediate compound of Formula VII. The use of the carbonyl

chloride intermediate is problematic and leads to low yield. Tedious purification steps are required in order to remove the process-related impurities.

WO-A-2007/072088 discloses a process for the preparation of Ezetimibe, wherein no carbonyl chloride intermediate is used. According to said process, the starting material 5-(4-fluorophenyl)-5-oxopentanoic acid is first converted into a ketal protecting form, which is then first reacted with a chiral oxazolidinone. The titanium enolate of said oxazolidinone is subsequently reacted with [4-(benzyloxy)benzylidene]-(4-fluorophenyl)amine, followed by transamidation to form the azetidinone ring. Then the ketal functional group is hydrolyzed to obtain intermediate compound of Formula VII. Although, acid chloride intermediate is not used in this process, still the yields of the key coupling reaction are moderate, due to ketal protecting group employed, which is labile when subjected to the described enolization conditions.

WO-A-2010/071358 discloses a process for the preparation of Ezetimibe, wherein (*S*)-1-(4-fluorophenyl)-5-(2-oxo-4-phenyloxazolidin-3-yl)pentane-1,5-dione is reacted with *O*-trimethylsilyl cyanohydrine to obtain a novel ketone-protected intermediate. Said intermediate is subsequently subjected to enolization followed by condensation with a trimethylacetyl protected imine and cyclization to obtain intermediate compound of Formula VII. During the enolization process, the amine base is added before the addition of the Lewis acid, so as to buffer the solution and avoid cleavage of the TMS-cyanohydrine. The change in the enolization sequence is known to compromise the yield of the transformation.

Although each of the above patents represents an attempt to overcome the disadvantages in the prior art processes, there still exists a need for a cost-effective and safer process which provides Ezetimibe in higher yield and higher purity.

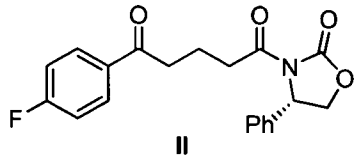
SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an improved process for the preparation of (3*R*, 4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one (compound of Formula VII) as a key intermediate for the synthesis of Ezetimibe, which overcomes the deficiencies of the prior art processes and results to a cost effective industrial production without sacrificing the yield and quality of the product.

Another object of the present invention is to provide novel intermediate compounds which are stable under standard enolization conditions, yet sufficiently reactive to provide the key products in high yield and purity, therefore efficient when used in the process for the preparation of Ezetimibe.

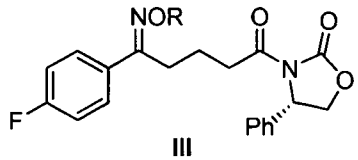
In accordance with the above objects of the present invention, a process for the preparation of (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one is provided, wherein (*S*)-*N*-acyl-oxazolidide of Formula II is converted to (3*R*, 4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one of Formula VII according to the following steps:

a) Reacting (*S*)-*N*-acyl oxazolidide of Formula II with a hydroxylamine compound and optionally a protecting agent in the presence of suitable solvents to obtain compound of Formula III,



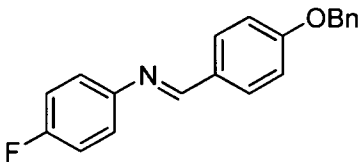
II

wherein R is selected from hydrogen and hydroxyl protecting groups;



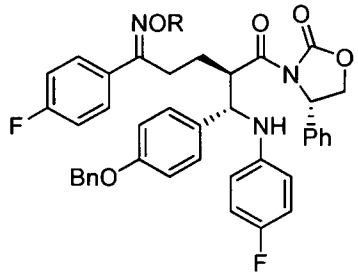
III

b) Reacting compound of Formula III with an imine of Formula IV, wherein Bn represents a benzyloxy group,



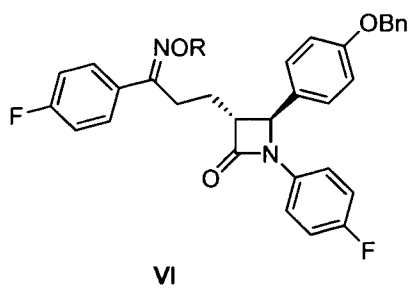
IV

in the presence of Lewis acid and base in a suitable solvent to obtain a compound of Formula V;



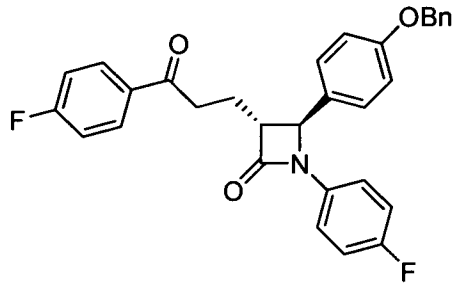
V

c) Treatment of compound of Formula V with a silylating agent and a fluoride anion source to obtain compound of Formula VI; and



VI

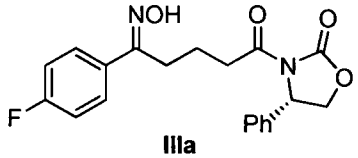
d) Hydrolysis of Compound of Formula VI to give azetidinone compound of Formula VII.



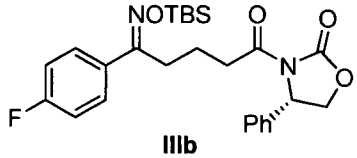
VII

Another object of the present invention is to provide compounds of Formula III, V, VI, and VII as defined in claims 13, 16, 19 and 22.

Another object of the present invention is to provide novel intermediate compounds of Formula IIIa, chemically designated as (*S*)-3-(5-(4-fluorophenyl)-5-(hydroxyimino)pentanoyl)-4-phenyloxazolidin-2-one and Formula IIIb, chemically designated as (*S*)-3-(5-(*tert*-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one.

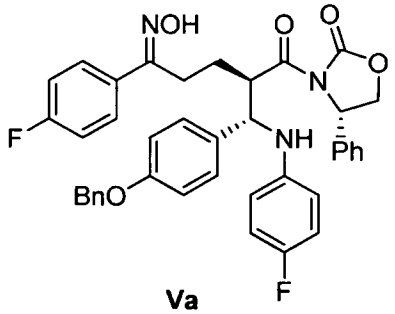


IIIa

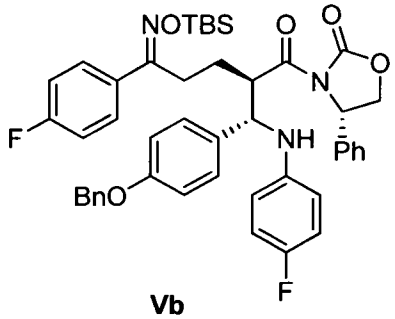


IIIb

A further object of the present invention is to provide novel intermediate compounds of Formula Va, chemically designated as (*S*)-3-((*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(4-fluorophenyl)-5-(hydroxyimino)pentanoyl)-4-phenyloxazolidin-2-one, and compound of Formula Vb, chemically designated as (*S*)-3-((*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one.

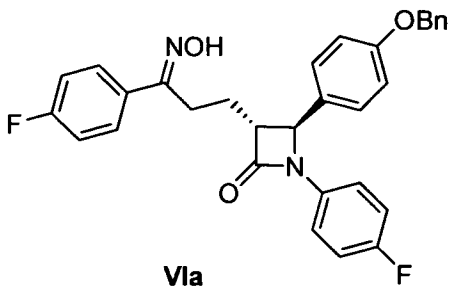


Va

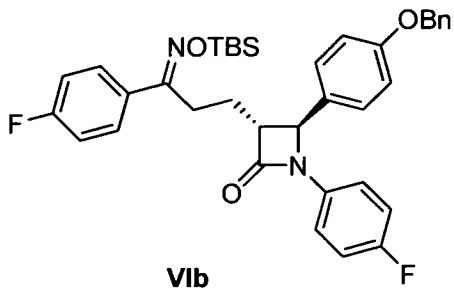


Vb

Another object of the present invention is to provide novel intermediate compounds of Formula VIa, chemically designated as (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-(hydroxyimino)propyl)azetidin-2-one, and compound of Formula VIb, chemically designated as (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-3-(3-(tert-butyldimethylsilyloxyimino)-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)azetidin-2-one.



VIa



VIb

Preferred embodiments of the present invention are set out in dependent claims 2 to 13.

Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel process for the preparation of Formula VII, which is an intermediate compound useful for the preparation of Ezetimibe.

According to the present invention, the process for the preparation of Formula VII comprises the following steps:

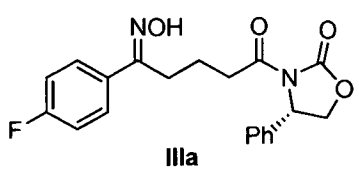
Step a): *Protection of compound of Formula II*

(*S*)-*N*-acyl-oxazolidide of Formula II is reacted with a hydroxylamine compound selected from hydroxylamine, hydroxylamine trimethylsilylether, hydroxylamine *tert*-butyldimethylsilyl ether, hydroxylamine *tert*-butyldiphenylsilyl ether, preferably hydroxylamine.

A protecting agent can be optionally added to the reaction of (*S*)-*N*-acyl-oxazolidide of Formula II with a hydroxylamine compound. Said protecting agent is selected from trialylsilylchloride of formula $R^1R^2R^3SiCl$, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups, preferably R^1 and R^2 represent a methyl group and R^3 represents a *tert*-butyl group.

The solvent used in the reaction of (*S*)-*N*-acyl-oxazolidide of Formula II with a hydroxylamine compound is selected from pyridine, ethanol, methanol or a mixture thereof. The preferred solvent is pyridine.

Free oxime of Formula IIIa is isolated as a white crystalline solid after aqueous workup. The preferred solvent for the crystallization is a 1:1 v/v mixture of ethyl acetate and cyclohexane.

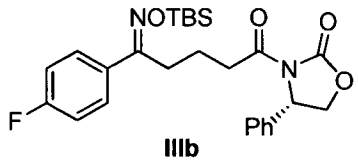


IIIa

Treatment of IIIa with an adequate trialkylsilylchloride in the presence of an organic base and solvent quantitatively provides the protected oxime of Formula III, wherein R represents $R^1R^2R^3Si$-, wherein R^1, R^2 and R^3 are independently C_{1-6} alkyl groups, most preferably R^1 and R^2 represent a methyl group and R^3 represents a *tert*-butyl group. The conditions employed for this protection may be selected from standard hydroxyl group silylation reagent combinations such as triethylamine/N,N'-dimethylaminopyridine/*tert*-butyldimethylsilylchloride and imidazole/N,N'-dimethylaminopyridine/*tert*-butyldimethylsilylchloride. The solvent is selected from methylene chloride or dimethylformamide, preferably methylene chloride.

Alternatively, compound of Formula II is consecutively reacted with hydroxylamine and an adequate trialkylsilylchloride in a basic solvent such as pyridine, providing the protected oxime of Formula III, wherein R is a hydroxyl protecting group, after slightly acidic aqueous workup. The preferred trialkylsilylchloride is *tert*-butyldimethylsilylchloride.

The TBS-protected oxime of Formula IIIb may be isolated in high yields through crystallization from ethanol.

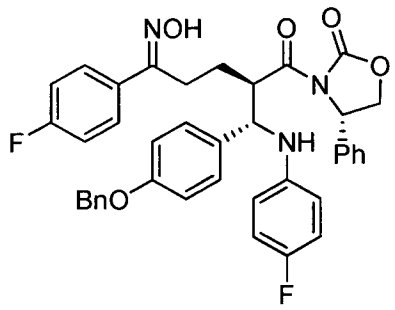


IIIb

Step b): *Titanium enolate coupling with imine of Formula IV*

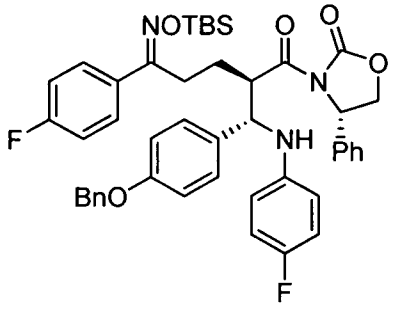
The obtained oximes of general formula III, are separately reacted with an imine of formula IV, in the presence of a Lewis acid selected from titanium tetrachloride, titanium tetraisopropoxide, or a mixture thereof and an organic base.
Base for this reaction is selected form substituted amines, such as triethylamine, diethylisopropylamine, sparteine, preferably diethylisopropylamine.
The reaction is carried out in chlorinated hydrocarbon solvents such as ethylene chloride and methylene chloride, preferably methylene chloride. A mildly acidic aqueous workup is followed by standard extraction procedure and the compounds of general formula V are isolated through precipitation from cold ethanol.

Using compound of Formula IIIa as starting material in this step, a compound of Formula Va is obtained. Purified compound of Formula Va is obtained through column chromatography eluted with 1% $MeOH/CH_2Cl_2$ or by crystallization from methanol.



Va

Using compound of Formula IIIb as starting material in this step, a compound of Formula Vb is obtained. Compound of Formula Vb is collected from ethanol as white flakes through filtration.



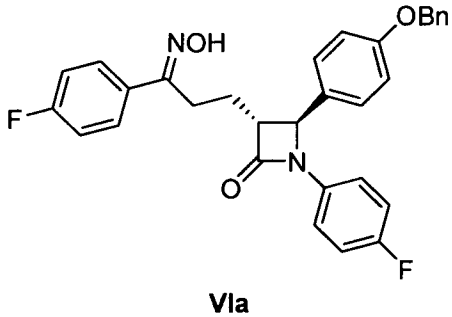
Vb

Step c): *Cyclization of compound of Formula V*

Compound of general formula V as obtained in step (a) is treated with a trimethylsilyl donor and converted to the N-TMS functionalized intermediate. Subsequent *in situ* treatment with a fluoride anion source triggers the nucleophilic attack on the *gamma*-positioned carbonyl which results in transamidation and formation of the *beta*-lactam, with concomitant regeneration of the chiral auxiliary which may be recycled. Further addition of fluoride anion source results in the deprotection of the oxime if needed.

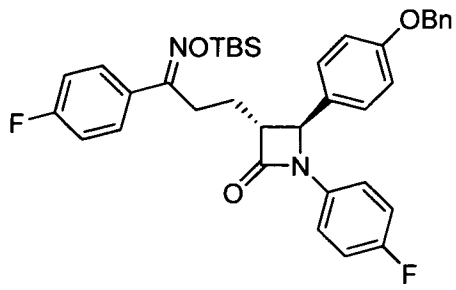
The trimethylsilyl donor may be selected from N,O-bis(trimethylsilyl)acetamide (BSA) and N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA), preferably BSA. The fluoride anion source is selected from tetra-*N*-butylammonium fluoride (TBAF), CsF, KF, preferably TBAF. The molar ratio of the fluoride anion source with respect to the starting compound of Formula V is between 0.1:1 and 2.5:1, preferably between 0.1:1 and 1.8:1. The reaction is carried out in an aprotic solvent selected from toluene and acetonitrile, preferably toluene. The reaction mixture temperature may be between 0 and 100°C, preferably between 10 and 80°C, more preferably between 25 and 60°C.

Purified compound of Formula VIa is obtained through column chromatography using 40% ethyl acetate:cyclohexane as eluent or by crystallization from methanol.



VIa

Purified compound of Formula VIb is obtained through column chromatography using 20-30% ethyl acetate:cyclohexane as eluent.



VIb

Step d): *Hydrolysis of compound of Formula VI*

The oxime *beta*-lactam compounds of general Formula VI are converted to the target ketone compound of Formula VII. Various methods for the regeneration of carbonyl compounds from their corresponding oximes may be selected from conventional deoximation conditions in aqueous and non-aqueous solution, heterogenous and solvent-free conditions and ultrasound, ultraviolet and microwave irradiation-assisted transformations. The preferred conditions comprise the use of an inorganic acid in aqueous formaldehyde in the presence of a polar aprotic solvent. The preferred inorganic acid is hydrochloric acid. The preferred solvent is tetrahydrofuran.

The parent ketone of Formula VII is obtained as a single compound, regardless of the E/Z isomeric ratio of the starting oximes. This is further confirmed by the examples provided below where the oxime intermediates are used without purification.

Compound of Formula VII can be reduced according to methods described in EP-B-0720599. Chiral catalysts used are methyl oxazaborolidine (Me-CBS), phenyl oxazaborolidine (Ph-CBS), etc, and BH_3 complexes are used as hydride donors, such as BH_3-DMS, BH_3-diethylaniline and BH_3-THF. The preferred solvent for this reaction is toluene.

Deprotection of the obtained reduced compound can also be carried out, if needed, according to methods described in EP-B-0720599, with hydrogen gas and a Pd catalyst such as Pd/C.

The process of the present invention will be demonstrated in more details with reference to the following examples, which are provided by way of illustration only and should not be construed as limit to the scope of the reaction in any manner.

EXAMPLES

Example 1: *Preparation of (S)-3-(5-(4-fluorophenyl)-5-(hydroxyimino)pentanoyl)-4-phenyloxazolidin-2-one*

30.0g of compound of formula II are dissolved in 100mL pyridine and 12.0g of hydroxylamine hydrochloride is added in two portions at temperature of about 0°C. The mixture is stirred at room temperature for 4 hours, and then the volatiles are evaporated under reduced pressure and the residue is taken up in 50mL ethyl acetate, 50mL HCl 1N are added and stirred vigorously for 1 hour. The layers are separated and the organic layer is further stirred with 50mL HCl 1N for 30min. The organic layer is washed twice with 20mL water and 20mL of brine then dried over sodium sulfate, filtered and evaporated under reduced pressure. Crystallization from 1:1 ethyl acetate:cyclohexane provided 30.6g of free oxime IIIa as a 10:1 mixture of diastereomers, separable through silica gel column chromatography eluting with 2% methanol:methylene chloride.

Analytical data for IIIa (major isomer):
mp: 119.6-124.1°C;
LC-MS (CI+) m/z: 485 (MH^+);
IR (KBr) cm^{-1}: 3473, 3290, 3248, 3065, 2924, 1784, 1708, 1598, 1510, 1458, 1376, 1327, 1208, 1160, 1082, 1068, 926, 912, 835, 772, 764, 727, 708, 589, 527, 511;
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (bs, 1H), 7.65 – 7.46 (m, 2H), 7.38 – 7.20 (m, 5H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.38 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.60 (t, *J* = 8.8 Hz, 1H), 4.20 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.11 – 2.91 (m, 2H), 2.89 – 2.70 (m, 2H),1.97 – 1.80 (m, 2H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.25, 165.08, 161.79, 158.00, 153.84, 139.19, 131.70, 131.66, 130.26, 129.19, 128.70, 128.30, 128.19, 125.94, 115.70, 115.42, 77.16, 70.09, 57.60, 35.15, 25.28, 20.80.

wherein:
^{1}H NMR: proton nuclear magnetic resonance spectroscopy
^{13}C NMR: carbon nuclear magnetic resonance spectroscopy
IR: infrared spectroscopy
δ: the chemical shift referenced against tetramethylsilane (TMS)
s, d, t and m are referred to singlet, doublet, triplet and multiplet peaks respectively
J: the spin-spin coupling coefficient observed in ^{1}H NMR measurement

Example 2: *Preparation of (S)-3-(5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one*

3.0g of free oxime IIIa are dissolved in 15mL methylene chloride. 1.1g imidazole and 90mg N,N'-dimethylaminopyridine are added at room temperature and the mixture is stirred for 10 minutes. 3.0g of TBSCl are added in two portions and stirring continues for 5 hours. 10mL of saturated ammonium chloride are added and the mixture is stirred vigorously for 10 minutes then 10mL water is added. The mixture is extracted three times with 20mL methylene chloride and the combined organic layer is washed with 10mL water and 10mL brine, dried over sodium sulfate, filtered and evaporated under reduced pressure to provide 3.8g of protected oxime IIIb as a white solid, which may be used without further purification. An analytical sample was purified by crystallization from ethanol as a 7:1 mixture of diastereomers, separable through silica gel column chromatography using 30% ethyl acetate:cyclohexane as eluent.

Analytical data for IIIb (major isomer):
mp: 81.2-82.4°C;
LC-MS (CI+) m/z: 485 (MH^+);
IR (KBr) cm^{-1}: 3478, 3069, 3035, 2955, 2931, 2858, 1790, 1769, 1703, 1603, 1512, 1457, 1391, 1325, 1243, 1234, 1207, 1197, 1160, 1067, 1037, 948, 836, 765, 698, 588, 525;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.45 – 7.29 (m, 6H), 7.16 – 6.95 (m, 8H), 6.89 – 6.79 (m, 2H), 6.78 – 6.66 (m, 2H), 6.41 – 6.32 (m, 2H), 5.36 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.99 (s, 2H), 4.66 – 4.43 (m, 2H), 4.32 (d, *J* = 8.9 Hz, 1H), 4.16 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.89 – 2.75 (m, 1H), 2.65 – 2.50 (m, 1H), 2.04 – 1.86 (m, 1H), 1.71 – 1.54 (m, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 172.23, 165.07, 161.78, 160.64, 157.81, 153.84, 153.74, 139.26, 132.08, 132.04, 129.23, 128.74, 128.32, 128.27, 128.21, 128.16, 125.95, 115.50, 115.22, 77.16, 70.08, 57.63, 35.36, 26.22, 25.78, 25.74, 25.35, 21.12, 20.83, 18.20, -2.87, -3.51, -5.08.

Example 3: *Preparation of (S)-3-(5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one*

3.0g of compound of formula II are dissolved in 50mL pyridine and 1.20g of hydroxylamine hydrochloride is added in one portion. The mixture is stirred at room temperature for 2 hours then 3.50g TBSCl are added in two portions and the resulting cloudy mixture is stirred at room temperature for 5 hours. The volatiles are evaporated under reduced pressure and the residue is taken up in 10mL of methylene chloride and 10mL HCl 1N and stirred vigorously for 30 minutes. It is then extracted with 3x30mL methylene chloride, the combined organic layers are washed with 2x10mL water and 10mL brine and the resulting solution is dried over sodium sulfate, filtered and evaporated under reduced pressure to provide 3.5g of protected oxime IIIb as a white solid, which may be used without further purification.

Example 4: *Preparation of (S)-3-((S)-2-((S)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(4-fluorophenyl)-5-(hydroxyimino)pentanoyl)-4-phenyloxazolidin-2-one*

In a heatgun-dried round bottom flask containing 6.0mL methylene chloride, 0.65mL $TiCl_4$ are added at 0°C, followed by 0.51mL $Ti(O^iPr)_4$ and the resulting creamy suspension is stirred at temperature of about 0°C for 30 minutes. 2.0g of free oxime IIIa are dissolved in 7.8mL methylene chloride and added dropwise at 0°C to the above mixture, stirring continues for 10 minutes then 2.35mL diisopropylethylamine are slowly added at 0°C and the resulting red enolate mixture is further stirred for 1 hour at this temperature then cooled to temperature about -15°C. A solution of 3.3g fluoroaniline IV in 22mL methylene chloride is added through an addition funnel at -15°C. Stirring continues at this temperature for 5 hours, then the mixture is quenched at this temperature using 5mL acetic acid, left to reach 0°C and 10mL HCl 1M and 30mL methylene chloride are added. After stirring at room temperature for 20 minutes, the organic layer is washed with 10mL HCl 1M, 10mL water and 10mL brine then dried over sodium sulfate and evaporated under reduced pressure to afford crude Va as a 16:1 mixture of diastereomers. The residue is purified through column chromatography eluting with 1% methanol:methylene chloride affording 512mg of pure Va.

Analytical data for Va (major isomer):
mp: 198.0-198.8°C;
LC-MS (CI+) m/z: 676 (M^+), 677 (MH^+), 678 ($M+2H^+$);
IR (KBr) cm^{-1}:3440, 3352, 3060, 3033, 2920 ,1759, 1688, 1609, 1509, 1456, 1390, 1323, 1271, 1241, 1223, 1115, 1107, 1043, 1021, 920, 836, 825, 759, 752, 719, 698, 586;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.29 (m, H), 7.21 – 6.94 (m, 1H), 6.85 – 6.64 (m, 1H), 6.44 (d, J = 5.0 Hz, 1H), 5.42 (d, J = 6.5 Hz, 1H), 4.96 (s, 1H), 4.61 (t, J = 8.5 Hz, 1H), 4.48 – 4.36 (m, 1H), 4.30 (d, J = 9.0 Hz, 1H), 4.17 (dd, J = 8.5, 2.3 Hz, 1H), 3.05 – 2.83 (m, 1H), 2.72 – 2.53 (m, 1H), 2.10 – 1.90 (m, 1H), 1.66 – 1.41 (m, 1H), 1.25 (s, 1H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 174.49, 165.31, 162.00, 158.58, 158.34, 154.64, 141.75, 138.49, 136.94, 130.66, 129.09, 128.76, 128.40, 128.20, 127.72, 125.44, 115.87, 115.84, 115.59, 115.54, 114.95, 77.16, 70.38, 70.07, 60.31, 58.21, 47.63, 29.86, 26.27.

Example 5: *Preparation of (S)-3-((S)-2-((S)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one*

In a heatgun-dried round bottom flask containing 21mL methylene chloride, 2.3mL $TiCl_4$ are added at 0°C, followed by 1.9mL $Ti(O^iPr)_4$ and the resulting creamy suspension is stirred at 0°C for 30 minutes. 10.0g of protected oxime IIIb are dissolved in 30mL methylene chloride and added dropwise at 0°C to the above mixture, stirring continues for 10 minutes then 8.0mL diisopropylethylamine are slowly added at 0°C and the resulting red enolate mixture is further stirred for 1 hour at this temperature. It is then cooled to -15°C (internal temperature) and a solution of 12.6g fluoroaniline IV in 100mL methylene chloride is added through an addition funnel during 1 hour at -15°C. Stirring continues at this temperature for 2 hours, then the mixture is quenched using 10mL acetic acid at this temperature and left to reach 0°C. 30mL HCl 1M are added and the mixture is stirred at this temperature for 10 mins, then left to reach 25°C. The layers are separated and the aqueous phase is washed with 30mL methylene chloride. The combined organic phases are washed with 20mL water and 20mL brine then dried over sodium sulfate and evaporated under reduced pressure. 120mL EtOH are added to the residue and the mixture is heated to 80°C for 1 hour then cooled to 0°C under stirring. 10.2g of pure compound Vb are collected as white flakes through filtration and a 10mL wash of cold EtOH.

Analytical data for Vb:
LC-MS (CI+) m/z: 789 (M^+);
IR (KBr) cm^{-1}: 3360, 3033, 2952, 2930, 2856, 1773, 1689, 1608, 1510, 1453, 1384, 1320, 1250, 1218, 1108, 950, 929, 840, 825, 801, 785, 700, 533, 528;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.45 – 7.29 (m, 6H), 7.16 – 6.95 (m, 8H), 6.89 – 6.79 (m, 2H), 6.78 – 6.66 (m, 2H), 6.41 – 6.32 (m, 2H), 5.36 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.99 (s, 2H), 4.66 – 4.43 (m, 2H), 4.32 (d, *J* = 8.9 Hz, 1H), 4.16 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.89 – 2.75 (m, 1H), 2.65 – 2.50 (m, 1H), 2.04 – 1.86 (m, 1H), 1.71 – 1.54 (m, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.26, 164.27, 161.01, 159.46, 159.44, 158.36, 157.68, 154.57, 143.05, 143.03, 138.60, 138.12, 138.08, 137.23, 133.28, 129.07, 128.74, 128.36, 128.24, 128.13, 127.66, 127.57, 125.49, 115.70, 115.40, 115.27, 115.18, 115.12, 114.91, 109.91, 77.16, 70.25, 64.78, 64.44, 64.37, 61.68, 58.26, 48.00, 37.60, 24.91, 18.58.

Example 6: *Preparation of (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-(hydroxyimino)propyl)azetidin-2-one*

177mg of compound of formula Va are dissolved in 3mL toluene and 0.15mL N,O-bis(trimethylsilyl)acetamide are added. The mixture is heated to 60°C for 30 minutes before 8mg of $TBAF.3H_2O$ are added in one portion. Stirring continues at 60°C for 8 hours and in-process TLC shows complete consumption of the starting material. The mixture is left to reach room temperature, 10mL ethyl acetate and 10mL HCl 1M are added and stirring continues for 20 minutes. 20mL ethyl acetate are added, the phases are separated and the organic layer is washed with 10mL water and 10mL brine, dried over sodium sulfate and evaporated under reduced pressure to afford crude VIa as a mixture of isomers. The residue is purified by silica gel column chromatography using 40% ethyl acetate:cyclohexane as eluent, affording 93mg of the oxime VIa as white crystals.

Analytical data for VIa (major isomer):
mp: 55.1-58.2°C;
LC-MS (CI+) m/z: 512(M), 513 (MH^+);
IR (KBr) cm^{-1}: 3377, 3064, 3034, 2926, 2852, 1745, 1610, 1510, 1454, 1386, 1354, 1305, 1228, 1175, 1158, 1140, 1105, 1024, 1013, 930, 834, 737, 697, 587, 515;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.36 (m, 5H), 7.23 (m, 4H), 7.06 – 6.85 (m, 6H), 5.04 (s, 2H), 4.63 (d, *J* = 2.1 Hz, 1H), 3.14 (td, *J* = 7.7, 2.1 Hz, 1H), 3.07 – 2.86 (m, 2H), 2.23 – 2.06 (m, 2H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.21, 165.36, 162.04, 160.82, 159.31, 157.82, 157.59, 136.87, 134.09, 131.36, 129.78, 128.78, 128.34, 128.23, 127.60, 127.45, 118.70, 118.60, 116.09, 115.96, 115.76, 115.67, 77.16, 70.35, 61.23, 60.45, 27.08, 25.64, 23.91.

Example 7: *Preparation of (3R,4S)-4-(4-(benzyloxy)phenyl)-3-(3-(tert-butyldimethylsilyloxyimino)-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)azetidin-2-one*

2.0g of compound of formula Vb are dissolved in 24mL toluene and 1.2mL N,O-bis(trimethylsilyl)acetamide is added. The mixture is heated to 60°C for 30 minutes before 100mg of TBAF.$3H_2O$ are added in one portion. Stirring continues at 60°C for 8 hours and in-process TLC shows complete consumption of the starting material. The mixture is left to reach room temperature, 20mL toluene are added. The organic layer is washed consecutively with 10mL saturated NH_4Cl, 10mL saturated $NaHCO_3$, 10mL water and 10mL brine, dried over sodium sulfate and evaporated under reduced pressure to afford crude VIb as a mixture of isomers. The residue is purified by silica gel column chromatography using 20-30% ethyl acetate:cyclohexane as eluent, affording 1.5g of the oxime VIb as colorless gum.

Analytical data for VIb (major isomer):
LC-MS (CI+) m/z: 626(M^+);
IR (KBr) cm^{-1}: 3484, 3065, 3035, 2953, 2930, 2895, 2857, 1749, 1675, 1610, 1510, 1454, 1385, 1355, 1229, 1175, 1158, 1138, 1104, 1013, 943, 835, 784, 737, 697, 550, 515;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.46 – 7.29 (m, 5H), 7.28 – 7.19 (m, 5H), 7.06 – 6.86 (m, 5H), 5.05 (s, 2H), 4.63 (d, *J* = 2.2 Hz, 1H), 3.17 – 3.09 (m, 1H), 3.00 (m, 1H), 2.89 (m, 1H), 2.11 (m, 1H), 0.97 (s, 9H), 0.22 (s, 6H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.10, 160.36, 159.34, 136.92, 134.18, 134.15, 131.88, 129.92, 128.81, 128.27, 128.19, 127.62, 127.38, 118.65, 116.11, 115.81, 115.49, 77.16, 70.39, 61.21, 60.69, 26.34, 25.88, 24.08, 18.35, -4.93.

Example 8: *Preparation of (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one*

500mg of oxime of formula VIa are dissolved in 10mL THF and 5mL 35% aqueous formaldehyde before the addition of 5mL of HCl 1N. The resulting colorless, biphasic mixture is stirred vigorously at room temperature during 6 hours until the organic layer becomes orange-yellow. It is then diluted with 10mL ethyl acetate and neutralized with saturated aqueous sodium bicarbonate. The aqueous layer is extracted with 2x10mL ethyl acetate and the combined organic layers are washed with 10mL water and 10mL brine, dried over sodium sulfate, filtered and evaporated. The residue is purified through silica gel column chromatography to provide 312mg of ketone VII as a yellow oil.

The **analytical data for VII**:
LC-MS (CI+) m/z: 498 (M^+);
IR (KBr) cm^{-1}: 3675, 3477, 3354, 3066, 3019, 2929, 2455, 1879, 1747, 1684, 1599, 1512, 1454, 1427, 1410, 1386, 1291, 1228, 1176, 1156, 1138, 1105, 1013, 991, 834, 755, 698, 667, 618, 596, 565, 515;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.43 – 7.29 (m, 5H), 7.24 (m, 4H), 7.10 (t, *J* = 8.6 Hz, 2H), 6.98 – 6.86 (m, 4H), 5.03 (s, 2H), 4.66 (d, *J* = 2.2 Hz, 2H), 3.27 (m, 1H), 3.13 (m, 2H), 2.48 – 2.16 (m, 2H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.42, 167.65, 167.31, 164.27, 160.76, 159.27, 157.54, 136.87, 134.09, 133.35, 133.32, 130.89, 130.76, 129.75, 128.74, 128.19, 127.55, 127.36, 118.64, 118.54, 116.07, 115.99, 115.75, 115.70, 77.16, 70.29, 61.32, 59.99, 35.67, 23.36.

Example 9: *Preparation of (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one*

415mg of compound of formula VIb are dissolved in 10mL THF and 5mL 35% aqueous formaldehyde before the dropwise addition of 5mL of HCl 1M. The resulting colorless, biphasic mixture is stirred vigorously at room temperature during 4 hours until the organic layer becomes orange-yellow. It is then diluted with 20mL ethyl acetate and neutralized with saturated aqueous sodium bicarbonate. The aqueous layer is extracted with 2x10mL ethyl acetate and the combined organic layers are washed with 10mL water and 10mL brine, dried over sodium sulfate, filtered and evaporated to provide 307mg of pure ketone VII as an oily solid.

Example 10: *Preparation of (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one*

2.0g of compound of formula Vb are dissolved in 20mL toluene and 1.2mL N,O-bis(trimethylsilyl)acetamide is added. The mixture is heated to 60°C for 30 minutes before 100mg of TBAF.$3H_2O$ are added in one portion. Stirring continues at 60°C for 2 hours and in-process TLC shows complete consumption of the starting material. The mixture is left to reach ambient temperature and 880mg TBAF.$3H_2O$ are added in two equal portions. Stirring continues for 2 hours then 30mL AcOEt are added and the organic layer is washed with 10mL HCl 1M, 10mL water and 10mL brine then dried over sodium sulfate and concentrated under vacuum. The residue is taken up in 50mL methanol, stirred for 10min at 50°C then allowed to gradually reach room temperature. The white precipitate is filtered off and washed with 5mL methanol to obtain pure oxime lactam VIa as a white crystalline solid.
The solid is then dissolved in 15mL THF and 10mL 35% aqueous formaldehyde before the addition of 0.8mL of concentrated HCl. The resulting colorless, biphasic mixture is stirred vigorously at room temperature during 3 hours until the organic layer becomes orange-yellow. It is then diluted with 30mL ethyl acetate and neutralized with saturated aqueous sodium bicarbonate. The aqueous layer is extracted with 2x10mL ethyl acetate and the combined organic layers are washed with 10mL water and 10mL brine, dried over sodium sulfate, filtered and evaporated to provide 1.1g of ketone VII.

It is apparent from the examples of the present invention that the use of oximes as carbonyl protecting group leads to a cost-effective, scalable and safe process for the preparation of Ezetimibe which makes it suitable for industrial application and at relative low production cost compared to the available processes for producing similar products.

The process of the present invention makes use of oximes as a carbonyl protecting group, previously undisclosed with respect to this type of substrates or these reaction conditions. The preparation of the oxime intermediates is quantitative, their isolation is paradigmatic as crystalline solids, their use as enolate precursors is advantageous over other carbonyl-masking

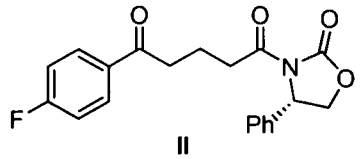
moieties in terms of stability and reactivity and their reversion to the parent carbonyl is uneventful under standard conditions. The reaction sequences, the reagents and the isolation procedures of the present process are cost-effective, scalable and of almost no safety concern, therefore suitable for industrial application.

While the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made in the invention without departing from the scope thereof, as defined in the appended claims

CLAIMS

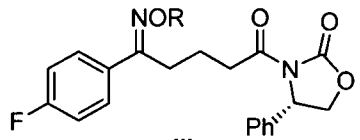
1. A process for the preparation of (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one of Formula VII, which comprises the following steps:

a) Reacting (*S*)-*N*-acyl oxazolidide of Formula II with a hydroxylamine compound and optionally a protecting agent in the presence of suitable solvents to obtain compound of Formula III,



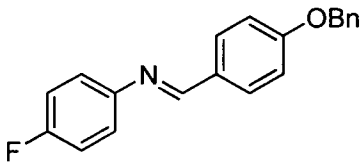
II

wherein R is selected from hydrogen and hydroxyl protecting groups;



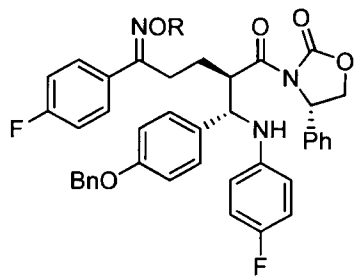
III

b) Reacting compound of Formula III with an imine of Formula IV, wherein Bn represents a benzyloxy group,



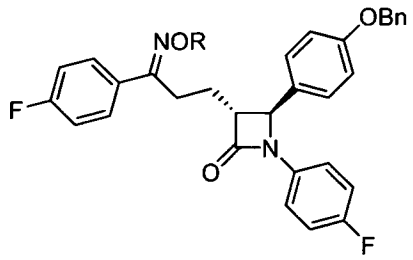
IV

in the presence of Lewis acid and base in a suitable solvent to obtain a compound of Formula V;



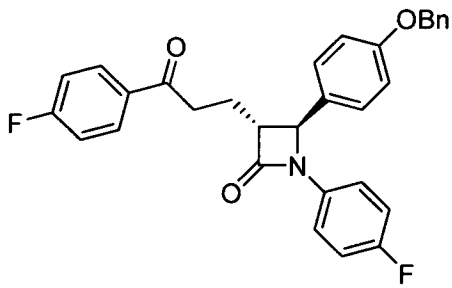
V

c) Treatment of compound of Formula V with a silylating agent and a fluoride anion source to obtain compound of Formula VI; and



VI

d) Hydrolysis of Compound of Formula VI to give azetidinone compound of Formula VII.



VII

2. The process according to claim 1, wherein the hydroxylamine compound of step (a) is selected from hydroxylamine, hydroxylamine trimethylsilylether, hydroxylamine *tert*-butyldimethylsilyl ether, hydroxylamine *tert*-butyldiphenylsilyl ether, preferably hydroxylamine.

3. The process according to claim 1, wherein (*S*)-*N*-acyl oxazolidide of Formula II is reacted with a hydroxylamine compound and a protecting agent, the protecting agent selected from trialkylsilylchloride of Formula $R^1R^2R^3SiCl$, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups, preferably R^1 and R^2 represent a methyl group and R^3 represents a *tert*-butyl group.

4. The process according to claim 1, wherein the solvent is selected from the group consisting of pyridine, methanol and ethanol or a mixture thereof, preferably pyridine.

5. The process according to claim 1, wherein R represents $R^1R^2R^3Si$- group, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups, preferably R^1 and R^2 represent a methyl group and R^3 represents a *tert*-butyl group.

6. The process according to claim 1, wherein the Lewis acid of step (b) is selected from titanium tetrachloride, titanium isopropoxide or a mixture thereof.

7. The process according to claim 1, wherein the base of step (b) is selected from substituted amines, such as triethylamine, diethylisopropylamine, sparteine, preferably diethylisopropylamine.

8. The process according to claim 1, wherein the solvent of step (b) is selected from chlorinated hydrocarbon solvents such as ethylene chloride and methylene chloride, preferably methylene chloride.

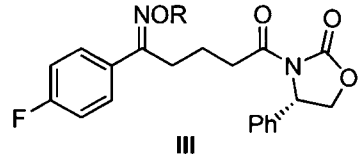
9. The process according to claim 1, wherein the silylating agent of step (c) is selected from BSA and BSTFA, preferably BSA.

10. The process according to claim 1, wherein the fluoride anion source of step (c) is selected form TBAF, CsF and KF, preferably TBAF.

11. The process according to claim 1, wherein compound of Formula VI is hydrolyzed in the presence of an inorganic acid in aqueous formaldehyde and THF.

12. The process according to claim 11, wherein the inorganic acid used is hydrochloric acid.

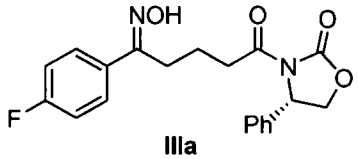
13. A compound of Formula III



III

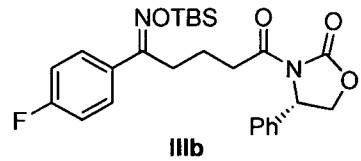
wherein R represents hydrogen or $R^1R^2R^3Si$, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups.

14. A compound of Formula IIIa, which is chemically designated as (*S*)-3-(5-(4-fluorophenyl)-5-(hydroxyimino)pentanoyl)-4-phenyloxazolidin-2-one



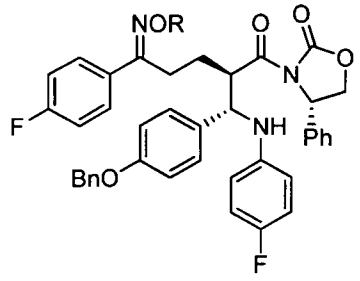
IIIa

15. A compound of Formula IIIb, which is chemically designated as (*S*)-3-(5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one.



IIIb

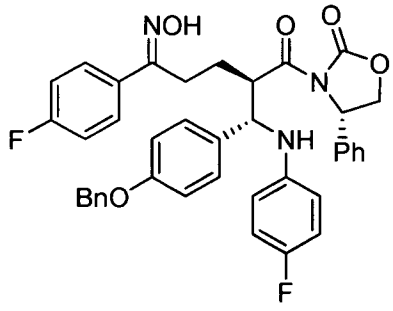
16. A compound of Formula V



V

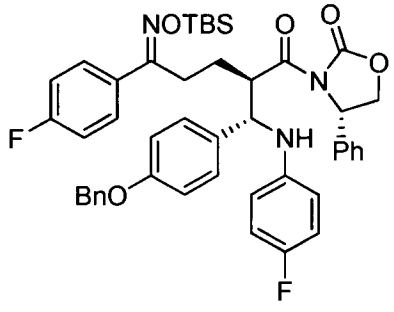
wherein R represents hydrogen or $R^1R^2R^3Si$, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups.

17. A compound of Formula Va, which is chemically designated as (*S*)-3-((*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(4-fluorophenyl)-5-(hydroxyimino)-pentanoyl)-4-phenyloxazolidin-2-one.



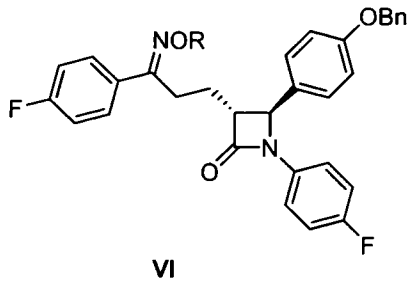
Va

18. A compound of Formula Vb, which is chemically designated as (*S*)-3-((*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(4-fluorophenylamino)methyl)-5-(tert-butyldimethylsilyloxyimino)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one



Vb

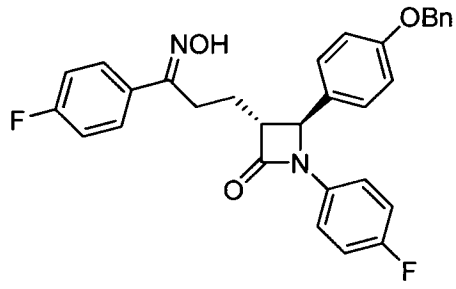
19. A compound of Formula VI



VI

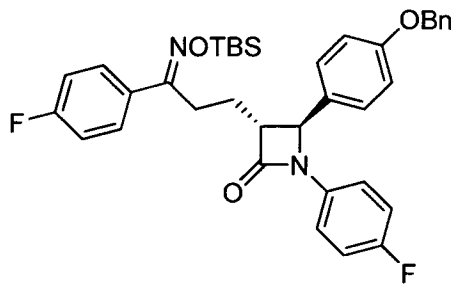
wherein R represents hydrogen or $R^1R^2R^3Si$, in which R^1, R^2 and R^3 represent independently C_{1-6} alkyl groups.

20. A compound of Formula VIa, which is chemically designated as (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-(hydroxyimino)propyl) azetidin-2-one



VIa

21. A compound of Formula VIb, which is chemically designated as (3*R*, 4*S*)-4-(4-(benzyloxy)phenyl)-3-(3-(tert-butyldimethylsilyloxyimino)-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)azetidin-2-one.



VIb

22. Use of compound of Formula VII obtained by the process of claim 1 for the preparation of Ezetimibe and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/007529

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D205/08 C07D263/20 C07D263/22
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 97/45406 A1 (SCHERING CORP [US]) 4 December 1997 (1997-12-04) claim 1	1-22
A	WO 00/34240 A1 (SCHERING CORP [US]) 15 June 2000 (2000-06-15) claim 1	1-22

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2011	06/05/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2008/106900 A1 (ZENTIVA AS [CZ]; SLAVIKOVA MARKETA [CZ]; VESILEK PETR [CZ]; OBADALOVA) 12 September 2008 (2008-09-12) claim 1	1-22
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A	WO 2008/151324 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; PERLMAN NURIT [IL]; FISHMAN AYELET) 11 December 2008 (2008-12-11) claim 1	22
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/007529

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