Abstract: The present invention provides an improved process for the preparation of compound of Formula II, which is a key intermediate for the preparation of Ezetimibe, through stereoselective addition of an organometallic reagent to novel aldehyde intermediates under chiral catalysis.
IMPROVED PROCESS FOR THE PREPARATION OF EZETIMIBE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of (3R, 4S)-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 (3R, 4S)-1-(4-fluorophenyl)-3-(5)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one and is presented by the chemical structure of Formula I.

Ezetimibe was first disclosed in EP-B-0720599, wherein a laborious process for the preparation thereof comprising three focal points of the synthesis using well-established and name-accredited procedures (Scheme 1) is described. The configuration of the beta-lactam ring is ensured by Evans oxazolidinone enolate chemistry (step a), the 4-fluorobenzyl group of the side chain is introduced through Negishi coupling (step d) and the alcohol moiety is stereoselectively constructed under influence of the Corey-Bakshi-Shibata chiral oxazaborolidine complex (step e). The overall process employs expensive reagents but affords low yields, while extensive purification steps are needed in order to remove the process-related impurities.

Various methods for the preparation of Ezetimibe are already known, said methods attempting to improve the pivotal synthetic checkpoints.

With respect to the beta-lactam ring construction, pathways employing the Evans chemistry, along with the manageable cost of the relevant chiral reagents, enjoy a clear advantage in terms of yield and diastereoselectivity and lead to the most cost-efficient processes.
The Negishi coupling, used for the introduction of the 4-fluorobenzyl group (step d), requires initial transmetalation from the low-cost aryl-MgX to the aryl-ZnCl species. The actual coupling employs the acid chloride and a transition metal complex, most commonly an expensive Pd-based catalyst such as Pd(PPh₃)₄ see e.g. in EP-B-0720599 and Pd(OAc)₂ as disclosed in WO-A-2006/137080, rendering the respective processes lacking in cost-efficiency. Improved synthetic approaches regarding the 4-fluorobenzyl group introduction include alternative carbonyl activation, in order to avoid the need of a catalyst as in WO-A-2007/108007 or moderation of the Grignard reactivity, to suppress double addition as disclosed in WO-A-2008/089984. Apart from the additional derivatization steps required in each of these processes, their common resulting ketone intermediate still needs to be stereoselectively reduced (step e).

The Corey-Bakshi-Shibata technology is mentioned to be more efficient at this transformation see e.g. in EP-B-0906278 than alternative methodologies. Similar conditions have also been described for the early installation of the desired chiral alcohol moiety with comparable results in EP-B-1373230. The cost of the CBS complex variants, however, is significant, compromising the efficiency of the respective processes.

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 process which provides Ezetimibe in higher yield and higher purity. In particular, a process that could avoid the use of expensive Pd-based catalysts and CBS reagents would hold a substantial relative advantage with respect to existing ones in terms of cost and industrial applicability.
SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an improved process for the preparation of compounds of general Formula II such as (3R, 45)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-[(35)-(4-fluorophenyl)-3-hydroxypropyl] azetidin-2-one, depicted below as Formula IIa to be used 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 compromising the yield and quality of the product.

In particular, the process according to the present invention features a novel synthetic pathway to enantiomerically pure alcohols of Formula II through stereoselective addition of an organometallic reagent to novel aldehyde intermediates under chiral catalysis.

Another object of the present invention is to provide novel intermediate compounds adequately functionalized in order to afford the products of key reactions 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 compound of Formula II is provided, wherein the aldehyde of Formula IV is converted to the alcohol of Formula II which comprises reacting compound of Formula IV, wherein R1 is selected from hydrogen and hydroxyl protecting groups

with an organometallic reagent of Formula V,
wherein \( k \) is an integer selected from 1 and 2;
\( m \) is an integer selected from 1, 2 and 3;
\( n \) is an integer selected from 0, 1, 2, 3 and 4;
\( M \) is independently selected from \( \text{Mg}, \text{Zn}, \text{Li}, \text{Cu}, \text{B}, \text{Zr} \) and \( \text{Ce} \); and
\( X \) is independently selected from halogen, cyano, hydroxy, alkyl, alkoxy, acetyloxy, aryloxy, aryl, substituted aryl and heteroaryl groups,
which is optionally pre-treated with an additive, in the presence of a metal complex containing
one or more chiral ligands, optionally prepared in situ, to provide compound of Formula II,
wherein \( R^1 \) is as defined above.

Another object of the present invention is a process to provide the aldehyde of Formula IV,
comprising reacting compound of Formula III, wherein \( R^1 \) is as defined above and \( R^2 \) is selected
from alkyl, alkylaryl, aryl

with a reducing reagent, and optionally with an oxidizing reagent to provide compound of
Formula IV;

A further object of the invention is to provide a process for the preparation of aldehyde of
Formula IV, comprising reaction of compound of Formula III in the presence of an adequate
reducing agent and a solvent in order to obtain and isolate an alcohol compound of Formula VI
wherein $R^1$ is defined as above.

A further object of the present invention is to provide enantiomerically pure compounds of Formula IV and VI as defined in claims 17 and 19.

Another object of the present invention is to provide novel intermediate compound of Formula IVa, chemically designated as enantiomerically pure $3\{-[(2S,3R)-2-[4-(benzyloxy)phenyl]-1-(4-fluorophenyl)-4-oxoazetidin-3-yl]propanol.

Another object of the present invention is to provide novel intermediate compound of Formula VJa, chemically designated as enantiomerically pure $3\{-[(2S,3S)-2-[4-(benzyloxy)phenyl]-1-(4-fluorophenyl)-4-oxoazetidin-3-yl]propanal.

Preferred embodiments of the present invention are set out in dependent claims 2-16, 18 and 20.

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 II, which is an intermediate compound useful for the preparation of Ezetimibe.

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

**Step a): Preparation of aldehyde compound of Formula IV**

Ester of Formula III is reacted with a reducing agent, for example borane complexes, such as BH$_3$.DMS, BH$_3$.THF, lithium aminoborohydrides (LAB), such as LiH$_3$BNMe$_2$, metal hydrides, such as NaBH$_4$, LiBH$_4$, LiAIH$_4$, Na(CN)BH$_3$, or more selective metal hydrides, such as diisobutylaluminum hydride (DIBALH), sodium bis(2-methoxyethoxy)aluminum hydride and modified DIBALH reagents, such as sodium, lithium or potassium diisobutyl-t-butoxyaluminum hydride, preferably LiBH$_4$.

The solvent used in the reaction is selected from ethers such as THF, diethylether, methyl(tert-butyl)ether, glymes, such as monoglyme and diglyme, lower weight alcohols, such as methanol and ethanol, haloalkanes such as dichloromethane and dichloroethane, hexanes such as hexane and cyclohexane, water, toluene and mixtures thereof. Optionally, water, methanol or ethanol may be added portion wise during the course of the reaction.

The reaction temperature may be from about -90 to about 50°C, preferably between about -30 and about 30°C, more preferably between about -10 and about 25°C.

The reaction is quenched with excess water or aqueous acid when TLC analysis shows complete consumption of the starting ester. Standard workup procedure provides the crude product which may be used without further purification. Optionally, an analytical sample may be obtained through chromatography or crystallization.
In one aspect of the invention, the preferred reducing agent is L1BH₄, the preferred solvent is a THF/water mixture and the preferred temperature is about -15 to about 0 °C. Standard aqueous workup affords the alcohol of Formula VI as a white solid, which may be further purified through crystallization or column chromatography.

Said alcohol is then subjected to alcohol oxidation conditions known in the art, such as the Swern, Dess-Martin, TEMPO/NaOCl, PCC, PDC and MnO₂ conditions.

The preferred oxidation process involves the addition of a sodium hypochlorite solution to an ice-cold mixture of the starting alcohol, a catalytic amount of 2,2,6,6-Tetramethylpiperidine 1-oxyl free radical (TEMPO), potassium bromide and sodium bicarbonate in dichloromethane. Filtration from celite and aqueous workup affords pure aldehyde of Formula IV, which may be directly used in the next step.

**Step b): Stereoselective addition of a reagent of Formula V to an aldehyde of Formula IV**

The catalytic asymmetric addition of organometallic reagents to carbonyl compounds is a reaction of fundamental importance in modern synthetic organic chemistry. Less reactive reagents, such as diarylzinc derivatives, may be used to achieve this transformation in the presence of a chiral additive, such as naturally-occurring or modified aminoalcohols. Further, more reactive organometallics, such as lithiates, cuprates, zirconates and, most importantly, the easily accessible Grignard reagents, are known to proceed through a competing, direct, non-catalyzed reaction that compromises the stereoselectivity of the transformation. The known asymmetric alkylation reactions with Grignard reagents require more than a stoichiometric amount of a chiral modifier in order to obtain high stereoselectivities, rendering them unsuitable for industrial application.

All known methodology studies have reported high yields and stereoselectivities through initial transmetallation of the Grignard to the respective organotitanate species and subsequent addition to simple aldehydes, previously activated by a chiral Lewis acid. However, the known processes are either reported to be efficient only with non-aryl Grignard reagents (*J. Org. Chem. 2010*, 75, 6869), or suffer scale-up limitations, such as the tedious removal of residual Mg salts and the use of expensive chiral ligands under cryogenic conditions.

The process according to the present invention, the stereoselective addition step (b) is carried out by reacting an organometallic compound of Formula V, optionally pre-treated with an appropriate additive, with a metal complex containing one or more chiral ligands. Subsequent addition of an aldehyde of Formula IV provides a reaction mixture which is stirred at a suitable temperature until TLC analysis shows complete consumption of the starting aldehyde. Standard aqueous quench and workup procedures afford the enantiomerically pure compound of Formula II, after optional purification through crystallization or column chromatography.
The organometallic compound of Formula V is prepared in situ and consists of the 4-fluorophenyl group (Ar) linked to a metal center, which is optionally substituted by one or more X groups, such as halogen, cyano, hydroxy, alkyl, alkoxy, acetoxy, aryloxyl, aryl, substituted aryl and heteroaryl groups.

Examples of organometallic compounds include Grignard reagents, such as ArMgX, aryl-zinc species, such as Ar₂Zn and ArZnX, organolithium compounds, such as ArLi, high and low-order organocuprates, such as Ar₂CuLi, Ar₂Cu(X)₂Li₂ and Ar(X)Cu(X)?Li₂, boronic acids and boronates, such as ArB(OH)₂, ArB(OX)₃, and ArBX₂, organozirconium and aryl-zirconocene species, such as ArZrX₂, ArZrX₂, and organocerium compounds, such as ArCeX₂, ArMgX-CeX₃ and ArLi-CeX₃. The preferred organometallic reagents are the Grignard and the organozinc reagents. More preferred are the Grignard reagents.

The molar ratio of the organometallic compound with respect to the aldehyde of Formula IV may be between about 1:1 and 4:1, preferably between about 1.5:1 and 2.5:1.

The solvent used for this transformation may be selected from ethers, such as diethyl ether, tetrahydrofuran (THF), 2-methylytetrahydrofuran, t-butylmethyl ether (TBME), disopropylether, cyclopentymethyl ether, glymes, such as monoglyme and diglyme, dioxane, toluene or mixtures thereof. The preferred solvent is a mixture of THF and diethyl ether.

Additives suitable for pre-treatment of the organometallic reagent may be selected from diamines such as N-methylmorpholine (NMM), N,N-dimethylaminopyridine (DMAP), N,N,N′N′'-tetramethylethylenediamine (TMEDA), N,N,N′N′'-tetraethylthlenediamine (TEEDA), N,N,N′N′'-pentamethyldiethylenediamine, hexamethylenetetramine (urotropine) and bis[2-(NN'-dimethylamino)ethyl]ether (BDMAEE). The preferred additive is BDMAEE.

The molar ratio of the additive with respect to the aldehyde of Formula IV may be between about 1:1 and 4:1, preferably between about 1.5:1 and 2.5:1.

The metal complex containing one or more chiral ligands may be prepared previously or may be generated in situ. Preferably, the metal complex containing one or more chiral ligands is generated in situ.

The metal center of the metal complex employed may be Ti, from reagents such as Ti(0Pr)₄, TiCl₄ and mixtures thereof, Si from SiCl₄, Fe from common reagents, such as FeCl₃, Fe(CO)₅, and ferrocenes, such as 1,1'-bis(chlorocarbonyl)ferrocene, Ru from common reagents, such as RuCl₃, [Ru₃(CO)i₂], and ruthenocenes, such as 1,1'-ruthenocene dicarboxylic acid and 1,1'-bis(chlorocarbonyl) ruthenocene, and Re from rhenium oxides, halides and sulfides, common starting complexes, such as ReCl(CO)₅ and [Re₂(CO)i₀], cyrhetrenes and η⁵-cyclopentadienylrhenium(I)tricarbonyl complexes, such as cyrhetrenyl carboxylic acid and derivatives thereof.

The preferred metal center is Ti and the preferred reagent used is Ti(0Pr)₄.

The molar ratio of this reagent with respect to the aldehyde of Formula IV may be between about 0.1:1 and 5:1, preferably between about 0.5:1 and 3:1, more preferably between about 0.8:1 and 1.2:1.

Chiral ligands of the metal complex may be selected from chiral diols, such as 1,1'-bi-2-naphthol (BINOL), (4i?,5i?)-2,2-dimethyl-a, a'-tetraphenylidioxolane-4,5-dimethanol (TADDOL) and derivatives thereof, such as 2-dialkylaminomethyl-2'-hydroxy-1,1'-binaphthyls, chiral beta- and
gamma-dialkylaminoalcohols and derivatives thereof, such as 3-exo-(dimethylamino)isoborneol (DAIB), chiral piperidinyl-alcohols such as 3-ethyl-6-methyl-4-(piperidin-1-yl)heptan-3-ol, 2-piperidino-1,1,2-triphenylethanol and deriving ligands, chiral sulfoxides, chiral mono- and bis-phosphoramides and chiral N-oxides.

The preferred chiral ligand is (/?)-BINOL.

The molar ratio of the chiral ligand with respect to the aldehyde of Formula IV may be between about 0.01:1 and 1:1, preferably between about 0.05:1 and 0.7:1, more preferably between about 0.1:1 and 0.4:1.

The aldehyde of Formula IV may be prepared according to the process of the present invention described above, or by any other means.

The reaction may be carried out at a temperature between about -80°C and the boiling point of the solvent, preferably between about -60 °C and about 40 °C, more preferably between about -30°C and about 25 °C.

The reaction progress is monitored by TLC analysis and aqueous acid is added to the cooled mixture when no more starting aldehyde is detected. Layer separation and evaporation is followed by precipitation of the desired compound of Formula II from lower alcohols, such as methanol, ethanol or isopropanol, preferably methanol. An analytical sample may be obtained by recrystallization from methanol or through column chromatography.

As an additional feature of the present invention, when the chiral ligand used in the process described above is (S)-BINOL, (3i?,45)-4-(4-(benzyloxy)phenyl)-l-(4-fluorophenyl)-3-[t/H]-3-(4-fluorophenyl)-3-hydroxy propyl]azetidin-2-one is selectively obtained.

Compounds of Formula II may be deprotected, if needed, according to known methods described in EP-B-0720599, with hydrogen gas and a Pd catalyst such as Pd/C, to obtain ezetimibe.

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 compound of Formula Ilia from compound of formula Via

2g of ester Ilia are dissolved in 25mL THF and cooled to about -10°C. 0.5g L1BH4 is added in two portions at this temperature, followed by sequential addition of 1mL water over about 2 hours.

When TLC showed complete consumption of the starting material, the reaction is quenched carefully with HC1 1N and the layers are separated. The organic layer is washed with water and brine, dried over sodium sulfate, evaporated to dryness and then treated with 20mL cyclohexane and 5mL ethyl acetate for 1 hour at about 0°C. Filtration afforded 1.6g of the desired alcohol Via. An analytical sample may be obtained by recrystallization from hexane or by silica gel column chromatography, eluting with 35% ethylacetate : cyclohexane.
Analytical data for (3R,4S)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-hydroxy propyl)azetidin-2-one:

mp: 94.9 - 95.5 °C; LC-MS (APCI+) m/z: 406 (M+H)+, 388, 306; IR (KBr) cm⁻¹: 3584, 3447, 3064, 3034, 2933, 2883, 2856, 1732, 1611, 1513, 1453, 1427, 1388, 1251, 1229, 1170, 1157, 1106, 1041, 839, 834, 732, 695, 517; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.22 (m, 9H), 6.96-6.85 (m, 4H), 5.01 (s, 2H), 4.58 (d, J = 2.1, 1H), 3.64 (t, J = 6.1, 2H), 3.08 (dt, J = 7.5, 2.1, 1H), 2.59 (bs, 1H), 1.95 (m, 2H), 1.73 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 167.94, 160.64, 159.14, 157.41, 153.79, 134.04, 134.01, 129.83, 128.63, 128.08, 127.47, 127.27, 118.56, 118.46, 115.95, 115.66, 77.16, 70.20, 61.97, 61.28, 60.48, 30.30, 26.95, 25.26.

wherein
mp: melting point, uncorrected

Example 2: Preparation of compound of Formula IVa from compound of Formula Via

Method A: Swern oxidation
A solution of 1.05mL oxalyl chloride in 50mL dichloromethane is cooled to -78°C. 1.75mL DMSO are added dropwise and the mixture is stirred for 5mins. 2.0g of alcohol Via are dissolved in 50mL dichloromethane, added to the above mixture and stirring continued for about 30mins. 4.12mL triethylamine are added slowly and the mixture is left to reach about 25°C under stirring. When TLC analysis showed complete consumption of the starting material, 20mL HCl 1N are added and the mixture is stirred for 10mins. The layers are separated and the aqueous layer is washed with 30mL dichloromethane. The combined organic layers are washed with 30mL water and 30mL brine, then dried over sodium sulfate, filtered and evaporated to dryness to afford 1.99g of aldehyde IVa, which may be used in the next step without further purification. An analytical sample may be obtained through silica gel column chromatography eluting with 30% ethylacetate : cyclohexane.

Method B: TEMPO/NaOCl oxidation
To an ice-cold mixture containing 1mg TEMPO, 2mg KBr and 125mg NaHCO₃ in 3mL dichloromethane are added 430mg of alcohol Via dissolved in 2mL dichloromethane. 1.5mL of a NaOCl solution (available chlorine 10-15%) are then added at this temperature and the mixture is left to reach about 25°C under stirring. When TLC analysis showed complete consumption of the starting alcohol, the mixture is filtered through celite with a 10mL dichloromethane wash and the organic phase is washed consecutively with 3mL saturated aqueous thiosulfate solution, 5mL water and 5mL brine, then dried over sodium sulfate, filtered and evaporated to dryness to afford 400mg of aldehyde IVa.
Analytical data for 3-[(2S,3S)-2-(4-(benzyloxy)phenyl)-l-(4-fluorophenyl)-4-oxoazetidin-3-ylpropanal:

LC-MS (APCI+) m/z: 404 (M+H)^+, 386, 237, 192; IR (KBr) cm^-1: 2930, 2737, 2677, 1746, 1610, 1509, 1386, 1226, 1175, 1144, 1012, 834, 739, 698, 515; \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.79 (s, 1H), 7.37 (m, 5H), 7.23 (m, 4H), 6.98-6.88 (m, 4H), 5.04 (s, 2H), 4.62 (d, \(J = 2.4 \text{ Hz}\), 1H), 3.08 (td, \(J = 7.6, 2.4 \text{ Hz}\), 4H), 2.72 (m, 2H), 2.19 (ddd, \(J = 14.5, 7.6, 3.1 \text{ Hz}\), 2H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 200.65, 166.91, 160.74, 159.29, 157.52, 136.82, 133.98, 129.56, 128.70, 128.15, 127.52, 127.31, 118.62, 118.51, 116.03, 115.75, 70.28, 61.22, 59.73, 46.00, 41.24, 21.17, 8.71.

Example 3: Preparation of compound of Formula IIa from compound of Formula IVa

In flask A 20mL diethylether and 10mL of a 1M THF solution of 4-fluorophenylmagnesium bromide are added, previously prepared from 4-fluorophenylbromide and magnesium turnings. 1.9mL of BDMAEE is added dropwise at about 0°C and the resulting mixture is stirred at about 0°C for 30 mins.

In flask B, 1.6mL Ti(0’Pr) \(_4\) are added to a solution of 283mg of (7’)-BINOL in 27mL diethylether at about 25°C. After stirring for 30 mins at this temperature, the contents of flask B are transferred into flask A and stirring continued for another hour at 0°C, then the mixture is cooled to about -20°C. 2g of aldehyde IVa is dissolved in 15mL diethylether and added dropwise to the above mixture over 15 minutes. The resulting orange-yellow suspension is stirred at this temperature for about 10 more minutes, then left to reach about 25°C. When TLC analysis showed complete consumption of the starting aldehyde, the reaction is cooled to about 0°C and aqueous HC1 IN is slowly added under stirring until the aqueous phase became transparent. The layers are separated and the aqueous layer is washed with ethyl acetate until it was rendered colorless. The combined organic layers are washed with water and brine, then dried over sodium sulfate, filtered and evaporated to dryness. Treatment with MeOH at about 0°C for 1 hour and subsequent filtration afforded 2g of alcohol IIa as a white solid (80% yield, 91% HPLC chiral purity, 99% after recrystallization). The analytical data are acquired from a purified sample by recrystallization from MeOH or by silica gel column chromatography, eluting with 30% ethylacetate : cyclohexane) and are in complete accordance with previously reported values.

Analytical data for (3R,4S)-4-(4-(benzyloxy)phenyl)-l-(4-fluorophenyl)-3-[l-(5)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one:

\(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.28 (m, 5H), 7.26-7.18 (m, 6H), 6.98-6.84 (m, 6H), 5.01 (s, 2H), 4.65 (t, \(J = 5.5 \text{ Hz}\), 1H), 4.53 (d, \(J = 2.2 \text{ Hz}\), 1H), 3.02 (td, \(J = 7.3, 2.2 \text{ Hz}\), 1H), 2.85 (bs, 1H), 1.89 (m, 4H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 167.78, 163.84, 160.69, 160.59, 159.18, 157.46, 140.35, 140.31, 136.81, 134.03, 134.00, 129.80, 128.68, 128.13, 127.50, 127.42, 127.26, 118.58, 118.48, 115.99, 115.71, 115.45, 115.17, 73.00, 70.23, 61.21, 60.38, 36.67, 26.99, 25.04.

From the examples stated above, it is apparent that the objects described in the present invention lead to a novel, cost-effective, scalable and safe process for the preparation of Ezetimibe, which is industrially applicable at a relatively low production cost, compared to the available processes for producing similar products.
The process of the present invention makes use of a previously undisclosed stereoselective addition of an aryl-organometallic reagent to a conveniently prepared aliphatic aldehyde intermediate, under the influence of an inexpensive and readily accessible chiral metal complex.

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.
1. A process for the preparation of compound of Formula II, wherein $R^1$ is selected from hydrogen and hydroxyl protecting groups,

which comprises reacting compound of Formula IV, wherein $R^1$ is as defined above,

with an organometallic reagent of Formula V,

wherein

- $k$ is an integer selected from 1 and 2;
- $m$ is an integer selected from 1, 2 and 3;
- $n$ is an integer selected from 0, 1, 2, 3 and 4;
- $M$ is independently selected from Mg, Zn, Li, Cu, B, Zr and Ce; and
- $X$ is independently selected from halogen, hydroxy, cyano, alkyl, alkoxy, acetyloxy, aryl, aryloxy, aryl and substituted aryl and heteroaryl groups,

which is optionally pre-treated with an additive, in the presence of a metal complex containing one or more chiral ligands, optionally prepared in situ, to provide compound of Formula II.

2. The process according to claim 1, wherein the organometallic reagent is 4-fluorophenylmagnesium bromide, bis(4-fluorophenyl)zinc, 4-fluorophenylzinc chloride, ethyl(4-fluorophenyl)zinc, preferably 4-fluorophenylmagnesium bromide.
3. The process according to claim 1, wherein the organometallic reagent of Formula V is pre-treated with an additive selected from N-methylmorpholine (NMM), N,N-dimethylaminopyridine (DMAP), NNN'/N'-tetramethylethlenediamine (TMEDA), N,N,N,N'-tetraethylethlenediamine (TEEDA), N,NN',N'-pentamethyldiethylenediamine, hexamethylenetetramine (urotropine) and bis[2-α,N,N-dimethylamino]ethyl]ether (BDMAEE), preferably BDMAEE.

4. The process according to claim 1, wherein the metal center of the metal complex is titanium (Ti), iron (Fe), ruthenium (Ru) or rhenium (Re), preferably Ti.

5. The process according to claim 1, wherein the chiral ligand of the metal complex is selected from chiral diols, such as 1,1'-bi-2-naphthol (BINOL) and derivatives thereof, such as 3-(3,5-diphenylphenyl)-2,2'-dihydroxy-1,1'-binaphthyls, (4i?,5?)-2,2-Dimethyl-α, α',α'-tetraphenyldioxolane-4,5-dimethanol (TADDOL), chiral beta- and gamma-dialkylaminooalcohols and derivatives thereof, such as 3-exo-(dimethylamino)isobomeol (DAIB), chiral piperidinyl-alcohols such as 3-ethyl-6-methyl-4-(piperidin-1-yl)heptan-3-ol, 2-piperidino-1,1,2-triphenylethanol, chiral substituted η⁵-cyclopentadienes such as t-butyloxazolidinylcyclopentadiene, chiral sulfoxides, chiral mono- and bis-phosphoramides and chiral N-oxides.

6. The process according to claim 1, wherein the metal complex containing one or more chiral ligands is prepared in situ from a metal-containing reagent and a chiral ligand.

7. The process according to claim 6, wherein the metal-containing reagent is Ti(OPr)₄, TiCl₄ and mixtures thereof, preferably Ti(OPr)₄.

8. The process according to claim 6, wherein the chiral ligand is (i?)-BINOL, (5)-BINOL, BINOL derivatives such as DPP-BINOL, and TADDOL, preferably (i?)-BINOL.

9. The process according to claim 1, wherein the reaction with the organometallic compound of Formula V is carried out in an organic solvent selected from ethers, such as diethylether, THF, 2-methyltetrahydrofuran, TBME, diisopropylether, cyclopentylmethylether, glymes, such as monoglyme and diglyme, dioxane, toluene or mixtures thereof.

10. The process according to claim 1, wherein the reaction with the organometallic compound of Formula V is carried out in a mixture of THF and diethylether.

11. The process according to claim 1 for the preparation of compound of Formula II, wherein compound of Formula IV is prepared by reacting compound of Formula III, wherein R¹ is as defined in claim 1 and R² is selected from alkyl, alkylaryl, aryl.
with a reducing reagent, and optionally with an oxidizing reagent to obtain a compound of Formula IV;

12. The process according to claim 11, wherein the reducing reagent is selected from borane complexes, such as BH$_3$-DMS and BH$_3$-THF, lithium aminoborohydrides (LAB), such as LiH$_2$BNMe$_2$ and metal hydrides, such as NaBH$_4$, LiBH$_4$, LiAlH$_4$, Na(CN)BH$_3$, diisobutylaluminum hydride (DIBALH), sodium diisobutyl/-butoxyaluminum hydride (SDBBA), lithium diisobutyl -t-butoxyaluminum hydride (LDBBA), potassium diisobutyl-t-butoxyaluminum hydride (PDBBA), sodium bis(2-methoxyethoxy)aluminum hydride.

13. The process according to claim 11, wherein it further comprises an oxidizing reagent, said oxidizing agent is selected from a dimethylsulfoxide / oxalyl chloride combination [DMSO/(COCl)$_2$], a 2,2,6,6-Tetramethylpiperidine-1-oxyl free radical / sodium hypochlorite combination (TEMPO/NaOCl), pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), manganese oxide (MnO$_2$).

14. The process according to claim 11 which it further comprises:
   i. reacting compound of Formula III, wherein R$_1$ and R$_2$ are as defined above,

   with a reducing agent to obtain a compound of formula VI; and
ii. reacting compound of formula VI with an oxidizing agent to obtain compound of Formula IV.

15. The process according to claim 14, wherein said reducing agent is LiBFL–.

16. The process according to claim 14, wherein said oxidizing agent is TEMPO/NaOCl.

17. A compound represented by Formula IV, wherein R¹ is hydrogen or a hydroxy protecting group.

18. The compound according to claim 17 of Formula IVa, which is chemically designated as enantiomerically pure 3-{(2S,3R)-2-[4-(benzyloxy)phenyl]-4-fluorophenyl)-4-oxoazetidin-3-yl}propanal.

19. A compound represented by Formula VI, wherein R¹ is hydrogen or a hydroxy protecting group.
20. The compound according to claim 19 of Formula Vla, which is chemically designated as enantiomerically pure 3-\{(2S,3R)-2-[4-(benzyloxy)phenyl]-l-(4-fluorophenyl)-4-oxoazetidin-3-yl\}propanol

21. Use of compound of Formula II obtainable according to the process claims 1 and 11 for the preparation of Ezetimibe and pharmaceutically acceptable salts thereof.
A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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