(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2017 (05.10.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/168438 Al

(51) International Patent Classification:
C07D 205/08 (2006.01)

(21) International Application Number:
PCT/IN20 17/000065

(22) International Filing Date:
30 March 2017 (30.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2016 1101 1441 31 March 2016 (31.03.2016) IN

(71) Applicant: **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; S.C.O. No. 850, Shivalik Enclave, NAC Manimajra, Chandigarh - 160 101 (IN).

(72) Inventors: **ARUL RAMAKRISHNAN;** Ind-Swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali - 160 055, Punjab (IN). **SARIN GURDEEP SINGH;** Ind-Swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali - 160 055, Punjab (IN). **VYAS SANDEEP;** Ind-Swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali - 160 055, Punjab (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

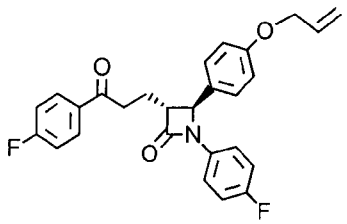
Declarations under Rule 4.17 :

— *of inventorship (Rule 4.17(iv))*

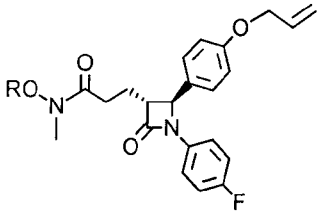
Published:

— *with international search report (Art. 21(3))*

(54) Title: PROCESS FOR PREPARING PURE ALLYL PROTECTED KETO DERIVATIVE



Formula-I



Formula-II

(57) Abstract: The present invention provides an industrially advantageous process for the preparation of pure allyl protected keto derivative of formula I, an intermediate of ezetimibe. by using a novel O-allyl amide derivative of formula II. *wherein R is methyl or ethyl*

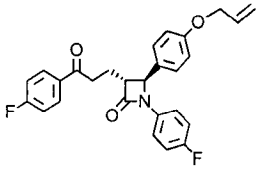
WO 2017/168438 A1

TITLE OF THE INVENTION

PROCESS FOR PREPARING PURE ALLYL PROTECTED KETO DERIVATIVE

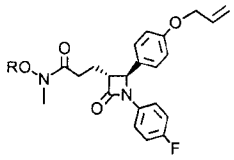
FIELD OF THE INVENTION

The present invention provides an industrially advantageous process for the preparation of pure allyl protected keto derivative of formula I,



Formula-I

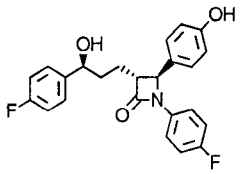
by using a novel O-allyl amide derivative of formula II.



Formula-II

wherein R is methyl or ethyl

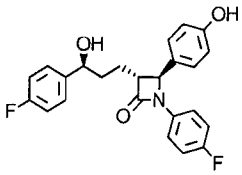
Allyl protected keto derivative of formula I is an important intermediate to obtain ezetimibe of formula III.



Formula-Ill

BACKGROUND OF THE INVENTION

Ezetimibe of formula-Ill is indicated as a monotherapy for the treatment of primary hypercholesterolemia and homozygous sitosterolemia and is chemically known as (3R,4S)-I-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone

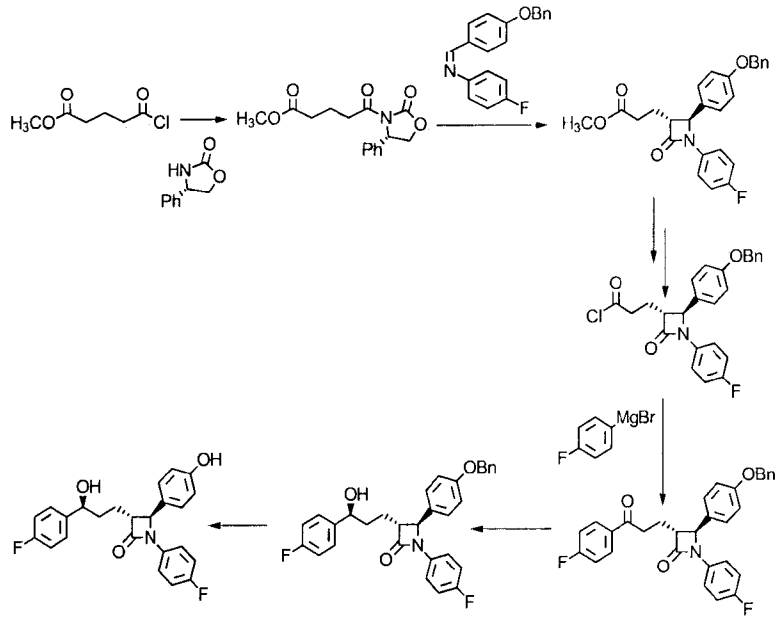


Formula-Ill

Ezetimibe was first disclosed in US Patent 5,767,115 (RE 37,721, herein US 721) as a useful hypocholesterolemic agent in the treatment and prevention of artherosclerosis. Several processes have been reported for the preparation of ezetimibe; most are total chemical synthesis and others involve application of few enzymatic steps. In general, the differences in the routes lay in introduction of different functionalities, such as 4-fluorophenyl group at the end of the aliphatic side-chain, formation of the azetidinone ring and stereospecific reduction of ketonic group. In one of the methodology, the azetidinone ring is generated

first via intramolecular cyclization, followed by introduction of the 4-fluorophenyl group and stereospecific reduction of ketonic group.

The process disclosed in product patent US 721 for preparing ezetimibe is depicted in below scheme 1

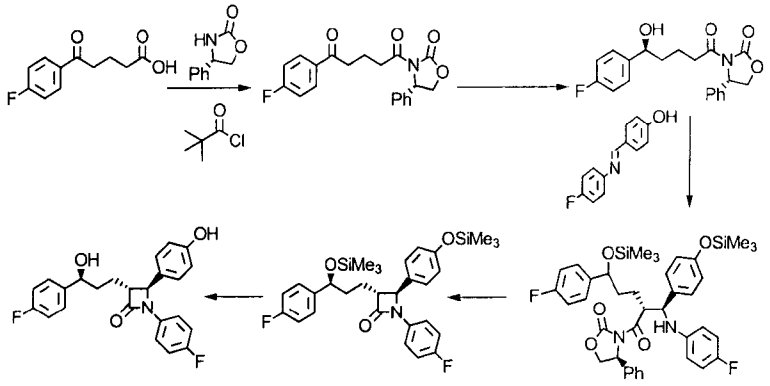


wherein, Bn is benzyl.

Scheme 1

The process involves reaction of (S)-4-phenyl-2-oxazolidinone with methyl-4-(chloroformyl)butyrate to obtain an ester, which is further condensed with 4-benzyloxybenzylidine-(4-fluoro)aniline followed by intramolecular cyclization to yield a protected lactam ester derivative. The protected lactam ester derivative so obtained is hydrolyzed to give the corresponding carboxylic acid, which is then successively reacted with oxalyl chloride to yield the corresponding acid chloride and with p-fluorophenyl magnesium bromide in the presence of zinc chloride and tetrakis(triphenyl phosphine) palladium to give benzylated keto derivative of ezetimibe. Stereospecific reduction of the resulting benzylated keto ezetimibe in presence of a chiral catalyst provides benzylated ezetimibe, which on debenzylation yields ezetimibe. The above patent fails to mention the yield and purity of ezetimibe so obtained.

In an another methodology to prepare ezetimibe, the 4-fluorophenyl group is introduced first at the end of the aliphatic side chain or alternatively , the whole side chain is attached onto this ring and the cyclization is carried out after the three substituted-phenyl groups have been incorporated into the molecule. This methodology was first disclosed in US Patent 6,207,822 and is depicted in below scheme 2:



wherein, Ph is phenyl and Me is methyl.

Scheme 2

The process involves reaction of p-fluorobenzoylbutyric acid with pivaloyl chloride followed by acylation of the obtained product with a chiral auxiliary to obtain a keto amide intermediate. The reduction of the keto amide intermediate in the presence of a chiral catalyst results in the formation of a corresponding chiral alcohol intermediate which is condensed with a suitable imine and silyl protecting agent to give β-(substituted-amino)amide compound. Intramolecular cyclization of β-(substituted-amino)amide compound followed by deprotcction gives ezetimibe.

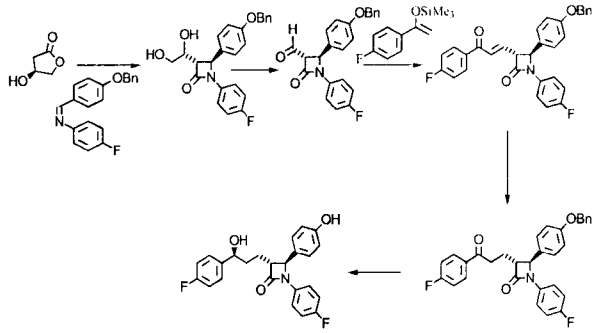
A number of publications US8,178,665, WO2007/1 20824, WO2007/1 19106, WO2008/1 06900, WO2009/106021 and WO2010/1 13182 have disclosed chemical synthesis using a similar strategy, wherein cyclization is carried out after the three substituted-phenyl groups have been incorporated into the molecule.

Of these above strategies, it has been observed that in the synthesis of this 1,4-diphenylazetidinone, the hydroxyl group is always introduced in the skeleton via the stereospecific reduction of the corresponding ketone functionality. In certain processes the reduction of the ketone to form the alcohol is performed in the first step itself, while in others the reduction of ketone to alcohol is carried out in the final stage. However, regardless of whether the reduction is carried out initially or later in the synthesis, the corresponding functional group has to be protected in order to avoid the formation of byproducts that lead to lowering in the yield of the desired product. When reduction is performed at the beginning of the process then the resulting alcohol group is protected by a suitable protecting group and if reduction is carried out later, then the ketone functionality is protected suitably.

A number of publications US5,739,321; US5,856,473; US5, 886,171 ; US2007/0049748; WO2007/108007A2 and WO2008/089984A2 and WO2009/157019A2 have disclosed chemical synthesis of ezetimibe by using the first strategy, wherein the intramolecular cyclization is carried out first and the keto derivative of ezetimibe is prepared by using

alternate intermediates and then stereospecifically reduced to prepare ezetimibe as is discussed one by one in the following paragraphs.

US Patents 5,739,321 and 5,886,171 disclose a process for preparing ezetimibe by reacting 4-(S)-hydroxy butyrolactone and a benzyl protected imine in the presence of a base to give a chiral diol, which is then oxidized to the corresponding aldehyde. The aldehyde so formed is condensed with an enolether to give 4-(4-benzyloxy-phenyl)-l-(4-fluoro-phenyl)-3-[3-(4-fluoro-phenyl)-3-oxo-propenyl]-azetidin-2-one, which is then successively subjected to reduction of double bond by hydrogenation followed by a chiral catalytic reduction and debenzylation to yield ezetimibe. The said process is depicted in below scheme 3

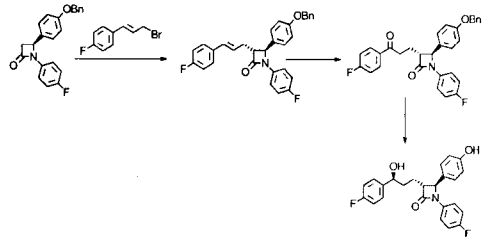


wherein, Bn is benzyl.

Scheme **3**

The above said patents are silent about the purity of ezetimibe, thus synthesized.

US Patent 5,856,473 discloses a process for preparing ezetimibe. The process involves alkylating l-(4-fluorophenyl)-4(S)-(4-benzyloxyphenyl)-2-azetidinone with 4-fluorocinnamyl bromide to give (3R,4S)-4-(4-benzyloxy-phenyl)-l-(4-fluorophenyl)-3-[(E)-3-(4-fluorophenyl)-allyl]-azetidin-2-one, which is then oxidized to give the corresponding benzylated ketone and then successively asymmetrically reduced and debenzylated to yield ezetimibe. The above patent is also silent about purity of ezetimibe so obtained. The process is as depicted in below scheme 4:

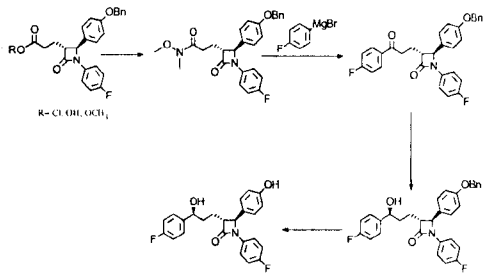


wherein, Bn is benzyl

Scheme **4**

US patent publication, US2007/049748 discloses a process, similar to that reported in US5,767,1 15 except that acid chloride intermediate is not generated. PCT publications, WO2007/108007A2 and WO2008/089984A2 disclose a process for preparing ezetimibe by

the reacting benzylated lactam acid derivative with *N*.O-dimcthoxylhydroxylamine salt to give the corresponding *N*-methyl, methoxy amide derivative, which is further reacted with p-fluorophenyl magnesium bromide to give benzylated keto derivative of ezetimibe. It is then successively stereospecifically reduced and debenzylated to afford ezetimibe and as shown below in scheme 5.

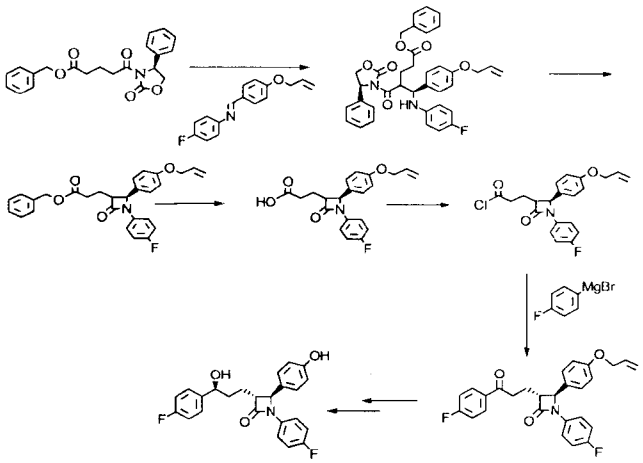


wherein, Bn is benzyl

Scheme 5

The above said patent applications are also silent about the purity of ezetimibe, thus obtained

In our effort to prepare an improved process for preparation of ezetimibe, a process is developed to prepare ezetimibe by involving use of corresponding allyl protected intermediates as given in PCT publication WO2009/157019A2 and further shown below in scheme 6



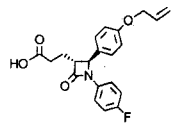
Scheme 6

Although this process is efficient on laboratory scale, but during scale up of the process, it has been found very difficult to achieve and maintain a temperature of -90°C to -80 °C while performing Grignard reaction, as the reaction is highly exothermic and becomes very difficult to control the temperature within the desired low temperature range. If temperature of the reaction is not controlled during the addition of the Grignard reagent it may lead to formation of impurities at industrial scale and require purification. Even few impurities are difficult to remove during workup and if remain in high amounts, may cause

problem in isolation and desired material may not get separated from the reaction mixture and could create reproducibly problems.

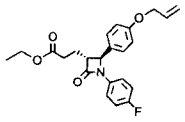
Moreover, it is also observed that purity of ezetimibe is dependent on the purity of allyl protected keto-ezetimibe derivative of formula I. It is therefore important to control impurities as this stage itself. The main impurities identified at this stage which create problems in next stages and in final ezetimibe compound are:

3-[2-(4-Allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid [the carboxylate impurity] of formula IV,



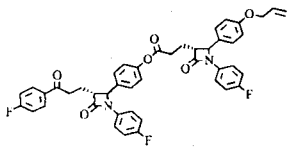
Formula-IV

Ethyl 3-[2-(4-allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid [the ethyl ester impurity] of formula **V,**



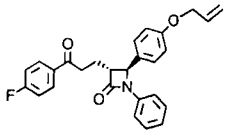
Formula-V

p-{(3*R*)-3-[2-(p-Fluorobenzoyl)ethyl]-l-(p-fluorophenyl)-4-oxo-2-azetidinyl} pheny!3-{(3i?)-4-[p-(allyloxy)phenyl]-l-(p-fluorophenyl)-2-oxo-3-azetidinyl} propionate [the dimer impurity] of formula VI,



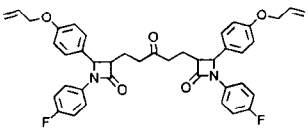
Formula-VI

3-{(3/?,45)-4-[p-(Allyloxy)phenyl]-2-oxo-l-phenyl-3-azctidinyl}-l-(p-fluorophcnyl)-l-propanone [the desflouro impurity] of formula VII,



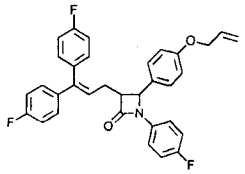
Formula-VII

4-[p-(Allyloxy**)phenyl**]-3-(5-{4-[p **-(allyloxy)phenyl**]-l **-(p-fluoiOphenyl**)-2-oxo-3-azctidinyl}-3-oxopentyl)-l-(p-fluorophenyl)-2-azetidinone [the bis-impurity] of formula VIII



Formula-VIII

4-[p-(Allyloxy)phenyl]-3-[3,3-bis (p-fluorophenyl)-2-propenyl]- 1-(*p*-fluoro phenyl)-2-azetidinone [the biphenyl impurity] of formula IX



Formula-IX

If these impurities remain in more than set limits, it is very difficult to control corresponding derivatized impurities in ezetimibe.

API manufacturers are required to maintain process impurities below set limits, at the intermediate stages, so that impurities are not carried forward to the final active pharmaceutical gradient (API) stages. This is done by specifying the quality of raw materials as well as by controlling process parameters, such as temperature, pressure, time and stoichiometric ratios of the chemical and reagents and by incorporating steps like purification via crystallization, distillation and liquid-liquid extraction. The analysis of the impurities present in an API is necessary and can be analyzed at certain stages during processing of an API, such as ezetimibe. The purity can be accessed by chromatographic techniques like high performance liquid chromatography (HPLC), thin layer chromatography (TLC) or gas chromatography (GC) to determine if intermediate is suitable for continued processing and ultimately, for use in a manufacture of pharmaceutical product. Generally, side products, by-products and adjunct reagents (collectively called as "impurities") are identified spectroscopically and/or with another physical method and are then associated with a peak position, such as that in a chromatogram, or a spot on a thin layer chromatography plate. Once a particular impurity has been correlated with a peak position, the impurity can be identified in a sample by its relative position in the chromatogram, where the position in the chromatogram is measured in time (minutes) between injection of the sample on the column and clution of the impurity through the detector. The position of the peak in the chromatogram with respect to time is known as the "retention time" (RT) and the position of the peak with respect to the largest or any specified peak is known as "relative retention time" (RRT). Impurities generated during commercial manufacturing processes must be limited to very small amounts and should be preferably absent or can be present in acceptable limits as per the regulatory requirements. Typically, these limits are less than about 0.15 % w/w of each identified impurity. Limits for unidentified and/or uncharacterized impurities arc lower, typically less than 0.1 % w/w.

Therefore, there is a need in the art to identify the impurities at intermediate stages itself, and methods should be developed to control the impurities there itself, so that the corresponding impurities are not carried forward so as to obtain pure ezetimibe. In view of the above requirements, the prior art approaches are not suitable from commercial point of

view since the desired ezetiinibe is not obtained in high purity and requires purification by tedious and cumbersome purification processes.

In order to achieve a high efficiency of the reaction for industrial synthesis of ezetiinibe, it is necessary to prepare pure intermediates or develop and alternate methods to minimize the formation of impurities. Thus, the present invention aims to provide an industrial process for the preparation of pure allyl intermediate of formula 1, to solve the problems pointed above wherein extreme conditions to have low temperature of -90°C to -80 °C can be avoided.

OBJECT OF THE INVENTION

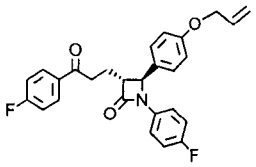
It is the prime object of the present invention, to provide an industrial process for the preparation of pure allyl protected keto-ezetimibe derivative of formula I,

Yet another object of the invention is to provide an industrial process for the preparation of pure allyl protected keto-ezetimibe derivative of formula I by using a novel intermediate.

Yet another object of the invention is to provide a process for the preparation of pure ezetimibe using pure allyl protected keto-ezetimibe derivative of formula I.

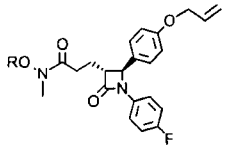
SUMMARY OF THE INVENTION

Accordingly, the present invention provides a novel industrially advantageous process for the preparation of pure allyl protected keto-ezetimibe derivative of formula I,



Formula-I

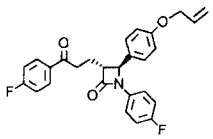
from novel *O*-allyl amide derivative of formula II



Formula-II

wherein R is methyl or ethyl

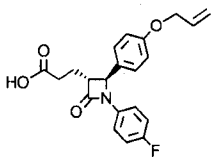
In one other aspect, the present invention provides an industrially advantageous process, for the preparation of pure allyl protected keto-ezetimibe derivative of formula I,



Formula-I

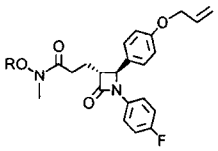
comprising the steps of:

a. reacting the compound of formula IV,



Formula-IV

or its salts thereof with an activating agent in a suitable solvent; subsequent reaction with salt of amine derivative, selected from *N*,<9-dialkylhydroxylamine optionally in the presence of suitable base to give O-allyl amide derivative of formula II,

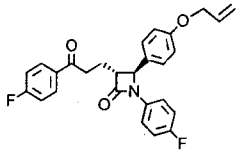


Formula-II

wherein R is methyl or ethyl

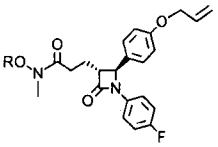
b. reacting O-allyl amide derivative of formula II with a suitable Grignard reagent or other organometallic reagent in the presence of a catalyst or ligand in a suitable solvent to obtain an pure allyl protected keto-ezetimibe derivative of formula I.

In one other aspect, the present invention provides an industrially advantageous process for the preparation of allyl protected keto- derivative of formula I,



Formula-!

by reacting *O*-allyl amide derivative of formula II,

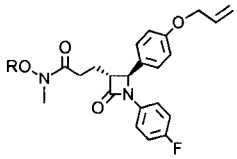


Formula-II

wherein R is methyl or ethyl

with a suitable Grignard reagent or other organometallic reagent in the presence of a catalyst or ligand in a suitable solvent to obtain allyl protected keto- derivative of formula I.

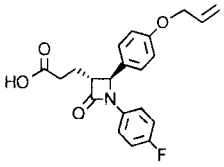
In one other aspect, the present invention provides a novel industrially advantageous process for the preparation of O-allyl amide derivative of fonnula II,



Formula-II

wherein R is methyl or ethyl

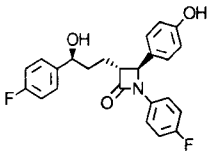
comprising the steps of reacting the compound of formula IV,



Formula-IV

or its salts thereof with an activating agent in a suitable solvent; subsequent reaction with salt of amine derivative, selected from *N*,0-dialkylhydroxylamine, optionally in the presence of suitable base to give O-allyl amide derivative of formula III.

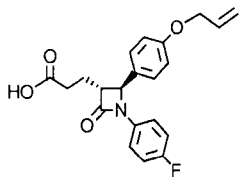
In one other aspect, the present invention provides an industrially advantageous process for the preparation of pure ezetimibe of formula 111,



Formula-Ill

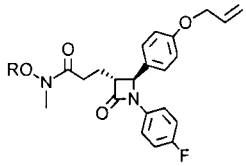
comprising the steps of:

a. reacting the compound of formula IV,



Formula-IV

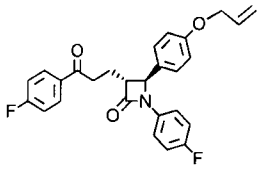
or its salts thereof with an activating agent in a suitable solvent; subsequent reaction with salt of amine derivative, selected from *N*.O-dialkylhydroxylamine, optionally in the presence of suitable base to give O-allyl amide derivative of formula II,



Formula-II

wherein R is methyl or ethyl

b. reacting O-allyl amide derivative of formula II with a suitable Grignard reagent or other organometallic reagent in the presence of a catalyst or ligand in a suitable solvent to obtain an pure allyl protected keto derivative of formula I;



Formula-I

c. converting the compound of formula I to pure ezetimibe of formula III.

DETAILED DESCRIPTION OF THE INVENTION

As described herein all the intermediates as well as the final product i.e. ezetimibe include solvates, isomers, hydrates and chiral isomers thereof.

The present invention provide a process for the preparation of pure allyl protected keto-derivative of formula I, prepared from novel O-allyl amide derivative of formula II, a novel and key intermediate and forms an inventive part of the invention.

Herein, pure allyl protected keto-ezetimibe derivative of formula I refers to allyl protected keto- derivative having purity more than 99.0% and and displays 0.02% or less than the carboxylate impurity of formula IV; 0.1% or less than the ethyl ester impurity of formula V; 0.1%) or less than the dimer impurity of formula VI; 0.06% or less than the des fluoro impurity of formula VII; 0.05%> or less than the bis impurity of formula VII I; 0.15% or less than the biphenyl impurity of formula IX and less than 0.05% of other unidentified impurities by HPLC or UPLC analyses . If these impurities are present in higher amounts than as specified above in allyl protected keto- derivative of formula I, they are further carried over to ezetimibe in unacceptable limits, and are difficult to remove, thereby making the process uneconomical and unviable.

According to one aspect of the present invention, process for the preparation of pure allyl protected keto- derivative of formula I is accomplished by starting from acid derivative of formula IV or salt thereof. The acid derivative of formula IV can be prepared by the processes known the art or as specified in PCT publication WO2009/1 570 19A2 or process as disclosed herein.

Generally, benzyl alcohol may be reacted with glutaric anhydride in the presence of a suitable solvent selected from hydrocarbon solvents such as toluene, hexane, heptane, 1,2-xylene, 1,4-xylene, alkylnitrile like acetonitrile , propionitrile and like or mixture thereof at reflux temperature. After completion of reaction, the resulting compound can be extracted in a suitable solvent and solvent is distilled out to give 4-(benzyloxycarbonyl)butyric acid. ´The resulting acid compound may then be reacted with (S)-phenyl-2-oxazolidinone to give 5-oxo-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-pentanoic acid benzyl ester. The resulting compound can be then condensed with (4-allyloxy-benzyl idene)-(4-fluoro-phenyl)-am ine to give 4-[(4-allyloxy-phenyl)-(4-fluoro-phenylamino)-methyl]-5-oxo-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-pentanoic acid benzyl ester, which may be then successively cyclized and hydrolyzed to give acid derivative of formula IV.

The acid derivative of formula IV can directly be converted to its reactive *O*-allyl amide derivative of formula II, which is a novel intermediate of present invention.

The acid derivative of formula IV can optionally be purified to remove identified and unidentified impurities by acid base treatment or by converting acid derivative of formula IV into its salt and again hydrolyzing to acid derivative of formula IV . ´The salt can be selected from organic amine salt such as methylamine, dimethylamine, diethylaminc, methylethylamine, n-propyl amine, di-n-propylamine, n-biitylamine, amylamine,

cyclopentylamine, cyclohexylamine, cycloheptyl- amine, dicyclohexylamine, /V-methylcyclo hexyl amine, *N,N*'-diisopropylethyIene diamine, *N,N*'-diethylene diamine, and the like.

Preferably, the dicyclohexylamine salt of the acid derivative of formula IV is prepared. The purification process can be repeated to enhance the purity of the compound and to remove the undesired impurities to acceptable limits.

The salt so formed, with or without purification, may be further converted into corresponding highly pure acid derivative of formula IV.

The salt of the acid derivative of formula IV so formed can optionally be converted into free acid by treating it with suitable acid such as hydrochloric acid.

The salt of acid derivative of formula IV can directly be converted to reactive *O*-allyl amide derivative of formula II.

Generally, the acid derivative of formula IV is reacted with acid activator in a suitable solvent at a suitable temperature and subsequent reaction with an amine derivative or salt thereof. The salt can be any suitable acid salt and preferably hydrochloride salt. The amine derivative can be selected from *N*,0-dialkyl hydroxylamine such as *N*,<3-dimethylhydroxylaminc. *O*-ethyl-N-methylhydroxyl amine, optionally in the presence of suitable base to give novel *O*-allyl amide derivative of formula II.

The reagent used to activate the acid of compound of formula IV can be selected from acetic anhydride, oxalyl chloride, ethyl chloroformate, methyl chloroformate, pivaloyl chloride; I-ethyl-3-(3-dimethylaminopropyl)carbodiimide. hydrochloride (EDC.HC1); n-hydroxy succinimide, hydroxybenzotriazole, *N,N*-carbonyl diimidazolc (CD1) and or combination thereof. These acid activators are usually used in moles ratio of 1 to 3 moles per mole of acid derivative of formula IV.

Suitable solvent used in the reaction can be selected from dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, tetrahydrofuran, 2-mcthyl tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, acetonitrile, propionitrile, dioxane. N.N-dimethylformamide, dimethylsulfoxide, tert-butyl methyl ether, diisopropyl ether.

The suitable base used for the reaction includes but are not limited to organic amines, selected from triethylamine, diethylpropylamine, diisopropylethylamine, tributylamine, N-methylpyrrolidine, N-methyl morpholine, pyridine and 4-N,N-dimethyaminopyridine.

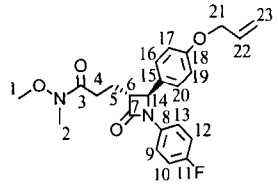
Particularly, the base and acid activator can be used in the ratio of 1.0 to 1.5 moles. Generally the reaction can be carried out at a temperature of -10 to 20°C for activating the acid compound of formula II. Preferably, reaction is carried out at a temperature of 0 to 15°C. The reaction between resulting activated acid and N,O-dialkyl hydroxylamine can be carried out at 0 to 45°C. The addition of N,O-dialkyl hydroxylamine can be done at 0 to 5°C and after

addition reaction mixture can be stirred at ambient temperature for few hours till completion of reaction.

The 0-allyl amide derivative of formula II can be isolated from the reaction mixture by the removal of the solvent or by extraction method.

Generally, after completion of reaction, the reaction mass can be diluted with water and the product can be extracted from the reaction by using suitable solvent. Solvent for extraction includes dichloromethane, chloroform, 1,2-dichloroethane, tert-butyl methyl ether, diisopropyl ether, diethyl ether, toluene, 1,2 xylene, 1,4 xylene and the like. The product can be isolated from the organic layer by distillation of the solvent.

O-Allyl amide derivative of formula II is a novel compound and it can be characterized by any characterization technique such as Proton Nuclear Magnetic Resonance (^{1}H NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C NMR), IR, Mass, UV and Liquid Chromatography-Mass Spectrometry (LCMS). In a specific embodiment, O-allyl amide derivative of formula II, wherein R is methyl is compound of formula IIa, as given below is characterized by ^{1}H NMR, ^{13}C NMR LCMS.



^{1}H NMR (400 MHz, CDC1$_3$) δ in ppm: 2.16-2.30 (m, 2H, C-5), 2.65-2.70 (m, 2H, C-4), 3.11-3.15 (m, 1H, C-6), 3.16 (s, 3H, C-2), 3.64 (s, 3H, C-l), 4.49-4.52 (m, 2H, C-21), 4.688-4.694 (d, 1H, J = 2.28 Hz, C-14), 5.25-5.28 (dd, 1H, **J** = 9.8 Hz, C-23), 5.36-5.41 (dd, 1H, J = 17.28 Hz, C-23), 5.97-6.07 (m, 1H, C-22), 6.88-6.93 (m, 4H, C-l 6, 17. 19, 20), 7.23-7.27 (m, 4H, C-9, 10, 12, 13).

^{13}C NMR (100.62 MHz, CDC1$_3$) δ in ppm: 23.58 (C-5), 29.10 (C-4), 32.07 (C-6), 59.37 (C-2), 60.93 (C-14), 61.17 (C-l), 68.73 (C-21), 115.26 (C-16, 17), 115.57 (C-19), 115.80 (C-20), 117.69 (C-23), 118.39 (C-22), 127.21 (C-9), 127.53 (C-10), 132.99 (C-12), 133.93 (C-13), 133.96 (C-15), 157.60 (C-8), 158.74 (C-18), 160.02 (C-l l), 167.24 (C-7), 173.13 (C-3)

LCMS: m/z 413.2792 ([M+H]$^+$).

Yet another aspect of the present invention provides a process for the conversion of O-allyl amide derivative of formula II into pure allyl protected keto-czetimibe derivative of formula I by condensing it [i.e. O-allyl amide derivative of formula II] with organometallic reagent derived from 4-fluorophenyl halide, preferably 4-fluorophenylmagncsium bromide.

Generally, organometallic reagent can be prepared by reacting with magnesium turnings in anhydrous tetrahydrofuran or aliphatic ether like diethyl ether, isopropyl ether or methyl terl-

butyl ether and iodine crystals are added as initiator. Initially small amount of 4-Bromofliioro benzene is added under nitrogen atmosphere to initiate the reaction. After initiating the reaction, the remaining solution of 4-bromofluoro benzene in a suitable solvent can be selected from tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethyl ether, 1,2-diethyl ether, diethyl ether, isopropyl ether, methyl tert-butyl ether, benzene, toluene, 1,2-xylene; 1,4-xylenc; 1,4-dioxane, 2,4-dioxane, preferably tetrahydrofuran can be slowly added to the reaction mixture at a temperature of 25-30°C. Temperature of reaction then may be raised up to 60-65°C and stirred for approximately 60 minutes. The reaction mixture can be cooled to a suitable temperature of 0 to -30°C, preferably cooled the reaction mixture to -10 to -15°C and reacted with N-methoxy-N-methyl3-[2-(4-allyloxy-phenyl)- 1-(4-lluoro-phenyl)-4-oxo-azetidin-3-yl]propanamide. The reaction can be carried out at -25°C to ambient temperature and preferably between -20°C to 10°C and most preferably between -15°C to 0°C.

After completion of the reaction, the mixture is acidified using a suitable acid compound like hydrochloric acid, acetic acid, a aqueous solution of ammonium chloride. Preferably aqueous ammonium chloride is used and pH of the reaction mass can be adjusted to 4.5 to 5 using an acid such as hydrochloric acid. Thereafter, the product can be extracted from the reaction mass using a suitable solvent. Solvent for extraction include halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane; alkyl ethers such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether; alkyl esters such as ethyl acetate, propyl acetate; aliphatic or aromatic hydrocarbon solvents such as toluene and the like or mixture thereof. The product is isolated as viscous oil from the organic layer by distillation of the solvent and crystallized by adding a suitable solvent like ethanol and isolated by Alteration.. The isolated product, if desired, can be purified using a suitable solvent that include alcoholic solvents such as methanol, ethanol, n-propanol, isopropanol, acetone, ethylmethylketone, acetonitrile, propionitrile and the like or mixture thereof with water. Specifically, the resulting product in a suitable solvent is stirred at a temperature of 0 to 50°C for 30 minutes to several hours. Thereafter, the solution was stirred and optionally, seeded with a pure compound followed by cooling of the solution. The product is isolated from the solution by suitable techniques like filtration or centrifugation.

The pure allyl protected keto- derivative of formula 1 prepared by present invention has a purity of greater than 99.0% and displays 0.02% or less than the carboxylate impurity of fonnula IV; 0.1% or less than the ethyl ester impurity of formula V; 0.1% or less than the dimer impurity of formula VI; 0.06% or less than the des fluoro impurity of formula VII; 0.05% or less than the bis impurity of formula VIII; 0.15% or less than the biphenyl impurity of formula IX and less than 0.05% of other unidentified impurities by HPLC or

UPLC analyses.

The reactants may be added to the reaction mixture as solids, or may be dissolved individually and combined as solutions. Further, any of the reactants may be dissolved together as sub-groups, and those solutions may be combined in any order. Wherever required, progress of the reaction is monitored by suitable chromatographic techniques such as High performance liquid chromatography (HPLC) or ultra performance liquid chromatography (UPLC) or thin layer chromatography (TLC). Isolation and purification of final compound and intermediates described here in the present invention can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, derivatisation, slurry wash, salt preparation or combination of these procedures. However, other equivalent procedures such as acid-base treatment could, also be used, to purify the intermediates. The solvents used for the purification of final compound and intermediates of the present invention can be selected from water, C_{1-6} alcohols, aliphatic C_{3-6} ketones, aliphatic or aromatic hydrocarbons, aliphatic esters, C_{3-6} ethers, C_{2-4} nitrile, halogenated solvents and the like or mixture thereof in suitable proportion.

Thereafter, pure allyl protected keto- derivative of formula I is converted to ezetimibe by using the method as disclosed in the PCT publication WO2009/1 57019A2 or by any known method reported in prior art.

Specifically, ezetimibe prepared by using the pure allyl protected keto- derivative of formula I, displays purity of more than 99.5%, preferably more than 99.8%, and impurities in the specified limits i.e. total impurities not more than 0.5%; known impurity not more than 0.15% and known impurity not more than 0.10% w/w

Although, the following examples illustrate the present invention in more detail, but the same should not be construed as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of 4-(4-aUyloxy-phenyl)-l-(4-lluoro-phcnyl)-3-[3-(4-lluoro-phenyl)-3-oxo-propyl]-azetidin-2-one

3-[2-(4-AUyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid (50g, 0.135 mol) was dissolved in dry dichloromethane (250ml). Triethylamine (27.4g) was added and the reaction mixture was cooled to 0-5°C. Hydroxybenzotriazole (16.4g, 0.121 mol), EDC.HC1 (28.2g, 0.147 mol) and *N*,0-dimethylhydroxylamine hydrochloride (14.Og, 0.144 mol) were then successively added to the reaction mixture at 0-5°C and the reaction mass was stirred overnight (~ 16 hours) at 25-30°C. After completion of the reaction, DM water (400ml) was added. The layers were separated and aqueous layer was washed with dichloromethane (200ml). The combined organic layers were washed with demincralizcd water (200ml) and solvent was distilled out completely to obtain *O*-allyl amide derivative.

In the mean time fresh Grignard reagent was separately prepared. 4-Bromoflourobenzcne (14g, 0.575mol) was added slowly to a mixture of magnesium turnings (11.6g) in anhydrous tetrahydrofuran (150ml) and iodine crystals, to initiate the reaction. Once reaction was initiated, all the remaining amount of 4-biOmoflourobenze (60. 18g, 0.343 mol) was added at temperature 25-30°C which was raised upto reflux. The reaction mixture was cooled at temperature -10 to -15 °C and O-allyl amide derivative diluted in tetrahydrofuran was added slowly to the Grignard reagent and after complete addition saturated solution of ammonium chloride (200ml) was added slowly. The pi! of the reaction mass was adjusted to 4.5-5 by using hydrochloric acid (2N) solution. The temperature of the reaction mass was raised to 25-30°C and reaction mixture was extracted with methyl tert-butyl ether (2 x 250ml). The organic layers were collected and washed with saturated sodium bicarbonate solution (250ml), brine solution (300ml). The solvent was distilled out completely under vacuum. Ethanol (75ml) was added and distilled out completely under vacuum to remove traces of tetrahydrofuran from the oily mass. Ethanol (150ml) was added at temperature 25-30°C and resulting mass was cooled to 10-15°C to start the crystallization of compound. Once product was crystallized, ethanol (225ml) was added again and the reaction mass was stirred for 2-3 hours. The resulting solid was filtered, washed with chilled ethanol (75ml), dried in oven at temperature 45-50 °C for 12-14 hours to obtain the title compound (23.2g). The resulting product was recrystallized in ethanol (450ml) to obtain pure product (24g) with HPLC purity 99.64% and the carboxylate impurity, the ethyl ester impurity, the dimcr impurity and bis-impurity are not detected; biphenyl impurity: 0.08% and des fiuoro impurity: 0.04% by HPLC.

Example 2: Preparation of 4-(4-allyloxy-phenyI)-l-(4-tluoro-phenyI)-3-[3-(4-tluoro-phenyl)-3-oxo-propyl]-azetidin-2-one

3-[2-(4-Allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid dicyclohexyl amine salt (lOg, 0.018 mol) was dissolved in dichloromethane (50ml) at 25-30 °C and pH was adjusted to 3-4 with hydrochloric acid (IN). The resulting solid was filtered and organic layer was separated and washed with demincralized water (2x25ml). Dichloromethane was distilled off completely at atmospheric pressure at 40-45°C and fresh dry dichloromethane (60ml) was added to dissolve the semisolid mass. Triethylamine (3.7g) was added and the reaction mixture was cooled to 0-5°C. Hydroxybenzotriazole (2.22g, 0.014mol), EDC.HC1 (3.81g, 0.019 mol) and N,O-dimethylhydroxylamine hydrochloride (1.94g, 0.019 mol) were then successively added to the reaction mixture at 0-5°C and the reaction mass was stirred for -16 hours at 25-30°C. After completion of the reaction demineralized water (40ml) was added, the layers were

separated and the aqueous layer was washed with dichloromethane (30ml). The combined organic layer was washed with demineralized water (40ml) and solvent was distilled out completely at atmospheric pressure at 40-45°C to obtain *O*-allyl amide derivative.

In the mean time fresh Grignard reagent was separately prepared. 4-Bromoflourobenzene (1.4g, 0.008mol) was added slowly to a mixture of magnesium turning (1.76g) in anhydrous tetrahydrofuran (20ml) and iodine crystals to initiate the reaction. Once reaction was initiated, all the remaining amount of 4-bromoflourobenze (10g, 0.057 mol) was slowly added at 25-30°C. During the addition, temperature rose upto 60-65 °C. The reaction mixture was cooled to 0 to 5°C and O-allyl amide derivative dissolved in tetrahydrofuran (20ml) was added slowly to the resulting Grignard reagent maintain the temperature at 0 to 5°C. After the reaction was completed, saturated solution of ammonium chloride (1.0L) was added slowly and the reaction mass pH was adjusted to 4.5-5 by using hydrochloric acid (2N, ~50ml) solution. The temperature of the reaction mass was raised to 25-30°C and reaction mixture was extracted with methyl tert-butyl ether (2 x 50ml). The combined organic layer was successively washed with saturated sodium bicarbonate solution (50ml) and brine solution (50ml). The separated organic layer was distilled off completely under vacuum and ethanol (10ml) was added and distilled off completely under vacuum to remove traces of tetrahydrofuran from the oily mass. Ethanol (20ml) was added to the residue at 25-30°C and resulting solution was cooled to 10-15°C to start the crystallization of compound. Once product was crystallized, ethanol (30ml) was added again and the reaction mass was stirred for 2-3 hours at 10-15°C. The resulting solid was fdtered, washed with chilled ethanol (10ml) and dried in oven under vacuum at 45-50 °C for 12-14 hours to obtain the title compound (3.0g). The resulting product was recrystallized from ethanol (60ml) to obtain pure product (2.3g)

Example 3: Preparation of 4-(4-allyloxy-phenyl)-l-(4-fluoro-phcnyl)-3-[3-(4-fluoro-phenyl)-3-oxo-propyl]-azetidin-2-one

3-[2-(4-Allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid dicyclohexyl amine salt (10g, 0.018 mol) was dissolved in dichloromethane (50ml) at 25-30 °C and pH was adjusted to 3-4 with hydrochloric acid (IN). The resulting solid was filtered and organic layer was separated and washed with demincralized water (2x25ml). Dichloromethane was distilled off completely at atmospheric pressure at 40-45°C and fresh dry dichloromethane (60ml) was added to dissolve the semisolid mass. Triethylamine (3.7g) was added and the reaction mixture was cooled to 0-5°C. Hydroxybenzotriazole (2.22g, 0.014mol), EDC.HC1 (3.8 Ig, 0.019 mol) and N,O-dimethylhydroxylamine hydrochloride (1.94g, 0.019 mol) were then successively added to the reaction mixture at 0-5°C and the reaction mass was stirred for ~16 hours at 25-30°C.

After completion of the reaction, demineralized water (40ml) was added, the layers were separated and the aqueous layer was washed with dichloromethane (30ml). The combined organic layer was washed with demineralized water (40ml) and solvent was distilled out completely at atmospheric pressure at 40-45°C to obtain O-allyl amide derivative.

In the mean time fresh Grignard reagent was separately prepared. 4-Bromoflourobenzcne (1.4g, 0.008mol) was added slowly to a mixture of magnesium turning (1.76g) in anhydrous tetrahydrofuran (20ml) and iodine crystals to initiate the reaction. Once reaction was initiated, all the remaining amount of 4-bromoflourobenze (lOg, 0.057 mol) was added at 25-30°C. During the addition, temperature rose upto 60-65 °C. The reaction mixture was cooled to 25 to 30°C and 0-allyl amide derivative dissolved in tetrahydrofuran (20ml) was added slowly to the resulting Grignard reagent maintaining the temperature at 25 to 30°C. After the reaction was completed, saturated solution of ammonium chloride (1.0L) was added slowly and the reaction mass pH was adjusted to 4.5-5 by using hydrochloric acid (2N, ~50ml) solution. The reaction mass temperature was raised to 25-30°C and reaction mixture was extracted with methyl tert-butyl ether **(2** x 50ml). The combined organic layer was successively washed with saturated sodium bicarbonate solution (50ml) and brine solution (50ml). The separated organic layer was distilled off completely under vacuum and ethanol (10ml) was added and distilled off completely under vacuum to remove traces of tetrahydrofuran from the oily mass. Ethanol (20ml) was added to the residue at 25-30°C and resulting solution was cooled to 10-15°C to start the crystallization of compound. Once product was crystallized, ethanol (30ml) was added again and the reaction mass was stirred for 2-3 hours at 10-15°C. The resulting solid was filtered, washed with chilled ethanol (10ml) and dried in oven under vacuum at 45-50 °C for 12-14 hours to obtain the title compound (4.7g). The resulting product was recrystallized from ethanol (60ml) to obtain pure product (1.2g)

Example 4: Preparation of 4-(4-allyloxy-phenyl)-l-(4-fluoro-phcnyl)-3-[3-(4-iluoro-phenyl)-3-oxo-propyl]-azetidin-2-one

3-[2-(4-Allyloxy-phenyl)-1-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-propionic acid dicyclohexyl amine salt (lOOg, 0.181 mol) was dissolved in dichloromethane (500ml) at 25-30 °C and pH was adjusted to 3-4 with hydrochloric acid (IN). The resulting solid was filtered and organic layer was separated and washed with demineralized water (2x250ml). Dichloromethane was distilled off completely at atmospheric pressure at 40-45°C and fresh dry dichloromethane (600ml) was added to dissolve the semisolid mass. Triethylamine (37g) was added and the reaction mixture was cooled to 0-5°C. Hydroxybenzotriazole (22.2g, 0.145mol), EDC.HC1 (38.lg, 0.199 mol) and *N,O*-dimethylhydroxylamine hydrochloride (19.4g, 0.199 mol) were then successively added to

the reaction mixture at 0-5°C and the reaction mass was stirred for ~16 hours at 25-30°C. After completion of the reaction demineralized water (400ml) was added, the layers were separated and the aqueous layer was washed with dichloromcthane (300ml). The combined organic layer was washed with demineralized water (400ml) and solvent was distilled out completely at atmospheric pressure at 40-45°C to obtain O-allyl amide derivative.

In the mean time fresh Grignard reagent was separately prepared. 4-Bromoflourobcnzene (14g, 0.08mol) was added slowly to a mixture of magnesium turning (17.6g) in anhydrous tetrahydrofuran (200ml) and iodine crystals to initiate the reaction. Once reaction was initiated, all the remaining amount of 4-bromoflourobenze (lOOg, 0.571 mol) was added at 25-30°C. During the addition, temperature raised upto 60-65 °C. The reaction mixture was cooled to -10 to -15°C and *O*-allyl amide derivative dissolved in tetrahydrofuran was added slowly to the resulting Grignard reagent. After the reaction was completed, saturated solution of ammonium chloride (1.0L) was added slowly and the reaction mass pH was adjusted to 4.5-5 by using hydrochloric acid (2N, ~500ml) solution. The temperature of the reaction mass was raised to 25-30°C and reaction mixture was extracted with methyl tert-butyl ether (2 x 500ml). The combined organic layer was successively washed with saturated sodium bicarbonate solution (500ml) and brine solution (500ml) and then separated organic layer was distilled off completely under vacuum. Ethanol (100ml) was added and distilled off completely under vacuum to remove traces of tetrahydrofuran from the oily mass. Ethanol (200ml) was added to the residue at 25-30°C and resulting solution was cooled to 10-15°C to start the crystallization of compound. Once product was crystallized, ethanol (300ml) was added again and the reaction mass was stirred for 2-3 hours at 10-15°C. The resulting solid was filtered, washed with chilled ethanol (100ml) and dried in oven under vacuum at 45-50 °C for 12-14 hours to obtain the title compound (47g). The resulting product was recrystallizcd from ethanol (600ml) to obtain pure product (40g) with HPLC purity 99.23% and carboxylate impurity, the ethyl ester impurity, the dimer impurity and bis-impurity were not detected; biphenyl impurity: 0.13% and des fluoro impurity: 0.06% by HPLC.

Example 5: Preparation of 4-(4-allyloxy-phenyl)-l-(4-fluoro-plienyI)-3-[3-(4-nuoi()-phenyl)-3-oxo-propyI]-azetidin-2-one

3-[2-(4-AUyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]-piOpionic acid dicyclohexyl amine salt (1.0 Kg, 1.81 mol) salt was dissolved in dichloromcthane (5.01.) at 25-30 °C and pH was adjusted to 3-4 with hydrochloric acid (IN). The resulting solid was filtered, the layers were separated and the organic layer was washed with demineralized water (2 x 2.5L). Dichloromethane was distilled off completely and dichloromcthane

(6.0L) was added to dissolve the semisolid mass. Triethylamine (0.37Kg) was added and the reaction mixture was cooled to 0-5 °C and then hydroxybenzotriazole (0.22Kg. 1.6 mol), EDC.HC1 (0.38 Kg, 1.98 mol) and *N* O-dimethylhydroxylamine hydrochloride (0. 19 Kg, 1.94 mol) were successively added to the reaction mixture at temperature 0-5°C. The reaction mass was stirred for ~ 16 hours at 25-30°C. After completion of the reaction, demineralized water (3.0L) was added and the layers were separated and aqueous layer was washed with dichloromethane (3.0L). The combined organic layer was washed with demineralized water (3.0 L) and solvent was distilled out completely to obtain O-allyl amide derivative (~0.7Kg).

In the mean time fresh Grignard reagent was separately prepared from magnesium turning (0.1 8Kg) in anhydrous tetrahydrofuran (2.0L) in the presence of odine crystals. Initially 4-bromoflourobenzene (0.1 IKg, 0.62 mol) in tetrahydrofuran was added to initiate the reaction and once reaction was initiated, all the remaining amount of 4-bromoflourobenze (1.3 Kg, 7.42 mol) were added at temperature 25-30 °C. During the addition, the reaction temperature raised up to 60-65 °C. The reaction mixture was cooled to -10°C to -15°C and O-allyl amide derivative diluted in tetrahydrofuran (2.0L) was added slowly to it. After completion of reaction, [monitored by TLC] saturated solution of ammonium chloride (4.0L) was added slowly followed by pH adjustment to 4.5-5 by using hydrochloric acid (2N, -1.5L) solution. The temperature of the reaction mass was raised to 25-30 °C and reaction mixture was extracted with methyl tert-butyl ether (3 x 2.0L). The combined organic layer was collected and successively washed with saturated sodium bicarbonate solution (4.0L) and brine solution (4.0L). The solvent of resulting organic layer was distilled off completely under vacuum. Ethanol (2.0L) was added and distilled out completely under vacuum to remove traces of tetrahydrofuran in the oily mass. Ethanol (2.0L) was added to the residue at 25-30°C and the resulting solution was cooled to 10-15°C to initiate the crystallization. Once the product was crystallized more quantity of ethanol (3.0L) was added and the reaction mass was stirred for further 2-3 hours. The resulting solid was filtered, washed with chilled ethanol (1.0L) and dried in oven at 45-50°C for 12-14 hours to obtain title compound (0.47 Kg), which was rccrystallized in ethanol (6.0L) and dried in oven at 45-50 °C for 12-14 hours. Pure product (0.4 Kg) thus obtained, displayed purity 99.78% by HPLC and carboxylate impurity: the ethyl ester impurity, the dimer impurity and bis-impurity: not detected; biphenyl impurity: 0.12% and des fluoro impurity: 0.065% by HPLC.

Example 6: Preparation of *N*-methoxy-*N*-methyl 3-[2-(4-allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]propanamide

To a solution of *N N*-dicyclohexylamine salt of 3-[2-(4-alIyloxy-phcnyl)-l-(4-fluoro-phcnyl)-4-oxo-azetidin-3-yl]-propionic acid (7.0 Kg, 12.72 mol) in dichloromethane (35.OL), hydrochloric acid (IN) was added to adjust the pH of the reaction mixture between 3 to 4 and stirred at a temperature of 25-30°C for 30 minutes. The layers were separated and the organic layer was washed with demineralized water (2 x 35.OL). The solvent was distilled off completely to give 3-[2-(4-allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl|-propionic acid as viscous oil.

To a solution of resulting compound in dichloromethane (28.OL), triethylamine (2.59Kg) was added at 20-30°C. The reaction mixture was cooled to 0-5 °C and hydroxybenzotriazolc (1.54Kg, 11.4mol), l-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (2.66Kg, 13.8 mol); *N*,0-dimethylhydroxyl amine hydrochloride (1.33 Kg, 13.6 mol) were successively added to the cooled reaction mixture and stirred for ~16 hours at 25-30°C. After completion of the reaction, demineralized water (21.0L) was added and reaction mixture was further stirred for 15 minutes. The layers (organic and aqueous) were separated and aqueous layer were washed with dichloromethane (21.0L). Combined organic layer was washed with demineralized water (21.0L) and solvent was distilled off completely to obtained 4.9Kg of *N*-methoxy-*N*-methyl **3**-[**2**-(**4**-**allyloxy**-**phenyl**)-**l**-(**4-fluoiO-**phenyl)-4-oxo-azetidin-3-yl]propanamide having purity 99.61% by I-1PLC. The product was also characterized by ^{1}H NMR, ^{13}C NMR and LCMS.

^{1}H NMR (400 MHz, CDC1$_3$) δ in ppm: 2.16-2.30 (m, 2H, C-5), 2.65-2.70 (m, 2H, C-4), 3.11-3.15 (m, 1H, C-6), 3.16 (s, 3H, C-2), 3.64 (s, 311, C-l), 4.49-4.52 (m, 2I-1, C-21), 4.688-4.694 (d, 1H, J = 2.28 Hz, C-14), 5.25-5.28 (dd, 1I-I, J = 9.8 Hz, C-23), 5.36-5.41 (dd, 1H, **J** = 17.28 Hz, C-23), 5.97-6.07 (m, 1H, C-22), 6.88-6.93 (m, 4H, C-l 6, I 7. 19, 20), 7.23-7.27 (m, 4H, C-9, 10, 12, 13).

^{13}C NMR (100.62 MHz, CDC1$_3$) δ in ppm: 23.58 (C-5), 29. 10 (C-4), 32.07 (C-6), 59.37 (C-2), 60.93 (C-14), 61.17 (C-l), 68.73 (C-21), I 15.26 (C-16, 17), I 15.57 (C-19), 115.80 (C-20), 117.69 (C-23), 118.39 (C-22), 127.21 (C-9), 127.53 (C-10), 132.99 (C-12), 133.93 (C-13), 133.96 (C-15), 157.60 (C-8), 158.74 (C-18), 160.02 (C-l 1), 167.24 (C-7), 173. 13 (C-3) ; **LCMS:** m/z 413.2792 ([M+H] $^{+}$).

Example 7: Preparation of 4-(4-allyloxy-phenyl)-l-(4-lluoro-phenyI)-3-[3-(4-fluoro-phenyl)-3-oxo-propyl]-azetidin-2-one

4-Bromofluoro benzene (0.84Kg, 4.8mol) was added to magnesium turnings (1.26Kg) in anhydrous tetrahydrofuran (14.0L) and iodine (7.0g) crystal under nitrogen atmosphere to initiate the reaction. Thereafter a solution of 4-bromofluoro benzene (7. 14Kg, 40.8 mol) in

tetrahydrofuran (14.0L) was slowly added to the reaction mixture at a temperature of 25-30"C. Thereafter during addition, the temperature of reaction mass was rose upto 60-65 °C and stirred for 60 minutes. The reaction mixture was cooled to -10 to -15°C and *N*-methoxy-*N*-methyl 3-[2-(4-allyloxy-phenyl)-l-(4-fluoro-phenyl)-4-oxo-azetidin-3-yl]propanamide (4.9Kg) dissolved in tetrahydrofuran (14.0L) was added slowly to it. After complete addition, the temperature of the reaction mass was maintained at -10 to -15°C for another one hour. After completion of reaction, saturated solution of ammonium chloride (25.0L) was added slowly and the pH of reaction was adjusted to 4.5-5 by using hydrochloric acid (~1 8.5L, 4N) solution. Thereafter the temperature was raised to 25-30 °C and the reaction mixture was extracted with methyl tert-butyl ether (2 x 28.0L). Methyl tert-biityl ether layers were combined and successively washed with saturated sodium bicarbonate solution (28.0L) and brine solution (2 x 35.0L). The organic layer was separated and solvent was distilled off completely under vacuum. Ethanol (2 x 3.5L) was added and distilled out completely under vacuum. Ethanol (14.0L) was added to the reaction mass at 25-30°C, and reaction mixture was cooled to 10-1 5°C to initiate crystallization. Ethanol (2 1.0L) was added and stirred for 2-3 hours and the resulting solid was filtered, washed with chilled ethanol (7.0L) and dried at temperature 45-50 °C for -14 hours to give 3.02Kg of title compound. The resulting compound was recrystallized from ethanol (42.0L) to obtain 2.7Kg of 4-(4-allyloxy-phenyl)-l-(4-fluoro-phenyl)-3-[3-(4-fluoro-phenyl)-3-oxo-propyl]-azetidin-2-one having purity 99.63% by HPLC and the carboxylate impurity: 0.01%; the ethyl ester impurity, the dimer impurity and bis-impurity: not detected; the biphenyl impurity: *0.06%* and des fluoro impurity: 0.03%.

Example 8: Preparation of ezetimibe

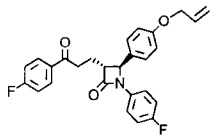
To a solution of (3R,4S)-l-(4-fluoro-phenyl)-3-[3-(4-fluorophenyl)-3-oxo-piOpyl]-4-(4-allyloxy-phenyl)-azetidin-2-one (10.0g,) in dichloromethane (25ml), morpholine (2.9 g, 33.2 mmol) and tetrakis(triphenyl phosphine)palladium (0.05g) were added. The reaction mass was refluxed at 40-45 °C for 30 minutes under nitrogen. After completion of reaction, the reaction mass was cooled to 20-30°C and dil. hydrochloric acid (50 ml, 10%) was added and stirred for further 15 minutes. The layers were separated and organic layer was successively washed with dil. hydrochloric acid (10%, 2 x50 ml), DM water (50 ml) and finally with brine solution (25%, 80 ml). The solvent was distill off at 50-55°C and under reduced pressure. To the resulting mass, dichloromethane (15 ml) was added at 20-30 °C and stirred to dissolve and dried over sodium sulphate (2.5g), filtered and washed with dichloro methane (15 ml). Filtrate was kept aside as SOLUTION A. In another reactor dichloromethane (20 ml) was charged and cooled to 0-5 °C. To the cooled solution borane dimethylsulfide complex (3.4 ml/2.7 g,) and (#)-2-mcthyl-CBS-oxaboiOlid inc

(2.23 ml/2.12 g,) were added. Reaction mass was stirred for 15 min at 0-5 °C and to this, SOLUTION A was added slowly and stirred for 2-4 hours at 0-5 °C. After completion of reaction, methanol (10 ml) was added slowly at 0-5 °C followed by addition of dilute hydrogen peroxide (5%, 50 ml,) slowly at 0-15 °C. Temperature was slowly raised to 25-30 °C and tetrahydrofuran (20 ml) was added and stirred the reaction mass for 15 min. The layers were separated and the organic layer was washed with dil. hydrochloric acid (50 ml, 10%) and with brine solution (25%, 80 ml,). The solvent was then distilled off at 50-55°C under reduced pressure. To the resulting residue isopropyl alcohol (10 ml) was added and distilled off under reduced pressure. Again isopropyl alcohol (15 ml) was added and heated to 65-70 °C till clear solution. Activated carbon (1.0 g) was added, stirred for 30 minutes and the solution was filtered through hyflo bed and the bed was washed with isopropyl alcohol (20 ml). To the filtrate, taken in reactor DM water (8.8 ml) was slowly added and stirred for 30 minutes, cooled to 20-25 °C slowly and stirred for 2 hours. The reaction mixture was further cooled to 0-5 °C and stirred for another 2 hours. The resulting solid was filtered, successively washed with isopropyl alcohol: DM water mixture (5 ml: 1 ml), DM water (20 ml) and dried for 12 hours to obtain 7.6 g of title compound having HPLC purity 99.83% w/w.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention and specific examples are provided herein without departing from the spirit and scope of the invention. Thus, it is intended that the present invention covers the modifications and variations of this invention that come within the scope of any claims and their equivalents.

WE CLAIM:

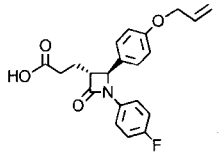
1. **A** process for the preparation of pure allyl protected keto-ezetimibe derivative of formula I,



Formula-I

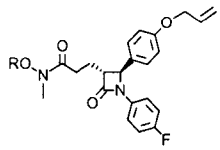
comprising the steps of:

i) reacting the compound of formula **IV,**



Formula-IV

or its salts thereof with an activating agent in a suitable solvent; subsequent reaction with salt of amine derivative, selected from *N,*(9-dialkylhydroxylamine optionally in the presence of suitable base to give O-allyl amide derivative of formula II,



Formula-II

wherein R is methyl or ethyl

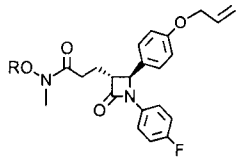
ii) reacting O-allyl amide derivative of formula II with a suitable Grignard reagent or other organometallic reagent in a suitable solvent to obtain an pure allyl protected keto-ezetimibe derivative of formula I.

2. The process as claimed in claim I, wherein in step i) the base is selected from triethylamine, diethylpropylamine, diisopropylethylamine, tributylaminc. N-methylpyrrolidine, N-methyl morpholine, pyridine and 4-N,N-dimethyaminopyridine.

3. The process as claimed in claim I, wherein in step ii) the suitable Grignard reagent or other organometallic reagent is 4-flourophenylmagnesium bromide.

4. The process as claimed in claim I, wherein in step ii) the suitable solvent is selected from tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethyl ether, 1,2-diethyl ether, diethyl ether, isopropyl ether, methyl tert-butyl ether, benzene, toluene, 1,2-xylene; 1.4-xylcnc; 1,4-dioxane, 2,4-dioxane.

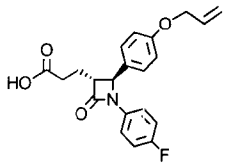
5. **A** process for the preparation of O-allyl amide derivative of formula II,



Formula-II

wherein R is methyl or ethyl

comprising the steps of reacting the compound of formula IV,

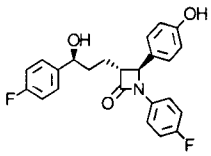


Formula-IV

or its salts thereof with an activating agent in a suatable solvent; subsequent reaction with salt of amine derivative, selected from *N*,<9-dialkylhydroxylamine, optionally in the presence of suitable base to give O-allyl amide derivative of formula III.

6. The process as claimed in claim 5, wherein the base is selected from triethylamine, diethylpropylamine, diisopropylethylamine, tributylamine, N-methylpyrrolidine, N-mcthyl morpholine, pyridine and 4-N,N-dimethyaminopyridine.

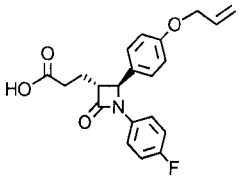
7. A process for the preparation of pure ezetimibe of formula III,



Formula-Ill

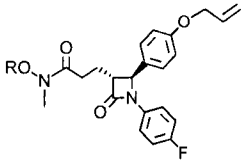
comprising the steps of:

i) reacting the compound of formula IV,



Formula-IV

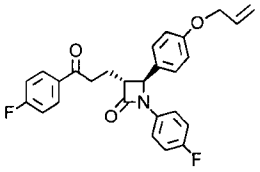
or its salts thereof with an activating agent in a suitable solvent; subsequent reaction with salt of amine derivative, selected from *N*,(2-dialkylhydroxylamine, optionally in the presence of suitable base to give O-allyl amide derivative of formula II,



Formula-II

wherein R is methyl or ethyl

ii) reacting O-allyl amide derivative of formula II with a suitable Grignard reagent or other organometallic reagent in the presence of a suitable solvent to obtain an pure allyl protected keto derivative of formula I;



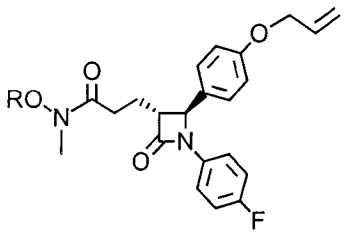
Forniula-I

iii) converting the compound of formula I to pure ezetimibe of formula III.

8. The process as claimed in claim 7, wherein in step i) the base is selected from triethylamine, diethylpropylamine, diisopropylethylamine, tributylamine, N-methylpyrrolidine, N-methyl morpholine, pyridine and 4-N,N-dimethyaminopyridine; wherein in step ii) the suitable Grignard reagent or other organometallic reagent is 4-flourophenylmagnesium bromide; wherein in step ii) the suitable solvent is selected from tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethyl ether, 1,2-diethyl ether, diethyl ether, isopropyl ether, methyl tert-butyl ether, benzene, toluene, 1,2-xylene; 1,4-xylcne; 1,4-dioxane, 2,4-dioxane.

9. The process as claimed in claim 7, wherein in step iiii) the conversion of the compound of formula I to pure ezetimibe of formula III is carried out by performing steps of deprotection of allyl group and chiral reduction of keto group using suitable reagents.

10. O-Allyl amide derivative of formula II



Formula-II

wherein R is methyl or ethyl

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000065

A. CLASSIFICATION OF SUBJECT MATTER
C07D205/08 Version=2017 .01

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007108007 A1 (UNICHEM LABORATORIES LIMITED) & 27-September-2007 Whole document	1-10
Y	WO 2009157019 A2 (IND-SWIFT LABORATORIES LIMITED) & 30-12-2009 Whole document	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13-07-2017	13-07-2017

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No. 32, Sector 14,Dwarka, New Delhi-110075 Facsimile No.	B. Ramamuni Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/000065

Citation	Pub.Date	Family	Pub.Date
WO 2007108007 A1	27-09-2007	IN MUM200600412 A	25-01-2008
WO 2009157019 A2	30-12-2009	WO 2009157019 A3	30-09-2010