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TOTAL SYNTHESIS OF EZETIMBIE AND THEIR KEY STERIOISOMERS

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Abstract
An efficient and scalable process for the synthesis ezetimibe using 4-(benzyloxy)benzaldehyde **(1)** with 2-fluorobenzenamine is described. The key steps in this process are the condensation of (*S*)-3-(5-(4-fluorophenyl)-5,5-dimethoxypentanoyl)-4-phenyloxazolidin-2-one and *N*-(4-((tert-butyldimethylsilyl)oxy)benzylidene)-4-fluoroaniline, and the stereoselective reduction of ezetimibe-ketone with $NaBH_4/I_2$, which is first applied in the synthesis of ezetimibe. The process is concise, mild, easy to operate, and highly stereoselective (99.6% of *de* value of ezetimibe). In addition, three diastereomers of ezetimibe are synthesized and served as the references in quality control of the product.

Introduction

There are two recognized sources of cholesterol in the serum: biosynthesis in the liver and absorption of dietary cholesterol in the small intestine[i,ii]. Statin inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the catalyst of the rate limiting step of cholesterol biosynthesis in the liver, and have been prescribed as the predominant class of cholesterol-lowering agents since 1980s[iii]. Ezetimibe, (3R, 4S)-1-(4-fluorophenyl)-3-((S)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one has become an important choice for reducing serum cholesterol level and it is the only marketed example of this new class of anticholesterolemia drugs[iv, v].

Ezetimibe is a potent, metabolically stable cholesterol absorption inhibitor[vi], which strongly blocks the absorption of biliary and dietary cholesterol from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides or bile acids[vii]. We achieved up to 99% yield by this method, where as Esen Bellur Atici et al[viii] obtained these compounds in 85%.

Ezetimibe, which selectively inhibits cholesterol absorption across the intestinal wall and is used as an antihyperlipidemic agent, because of this reason we synthesized Ezetimibe related isomers in highly pure form for commercial use.

Materials and methods

Analytical grade solvents and commercially available reagents were used without further purification. The column chromatography was carried out over silica gel (60-120 mesh), purchased from Sisco Research Laboratories Pvt Ltd. Melting points were determined in open capillaries in electrical melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 400-MHz Varian spectrometer in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants are given in Hz. Mass spectra were recorded using Agilent 1100 MSD spectrometer in electro spray mode.

Results & Discussion

Synthesis of 2-fluoro SRS-Ezetimibe

The condensation reaction of 4-(benzyloxy)benzaldehyde **(1)** with 2-fluorobenzenamine **(2)** in the presence of isopropyl alcohol, at 60 ^{0}C for 1 h without using any further catalyst gave a compound which has been identified as a Schiff's base i.e. (*Z*)-*N*-(4-(benzyloxy)benzylidene)-2-fluorobenzenamine **(3)** in 81.63% yield. The structure of this compound has been assigned based on its ^{1}H- NMR spectrum.

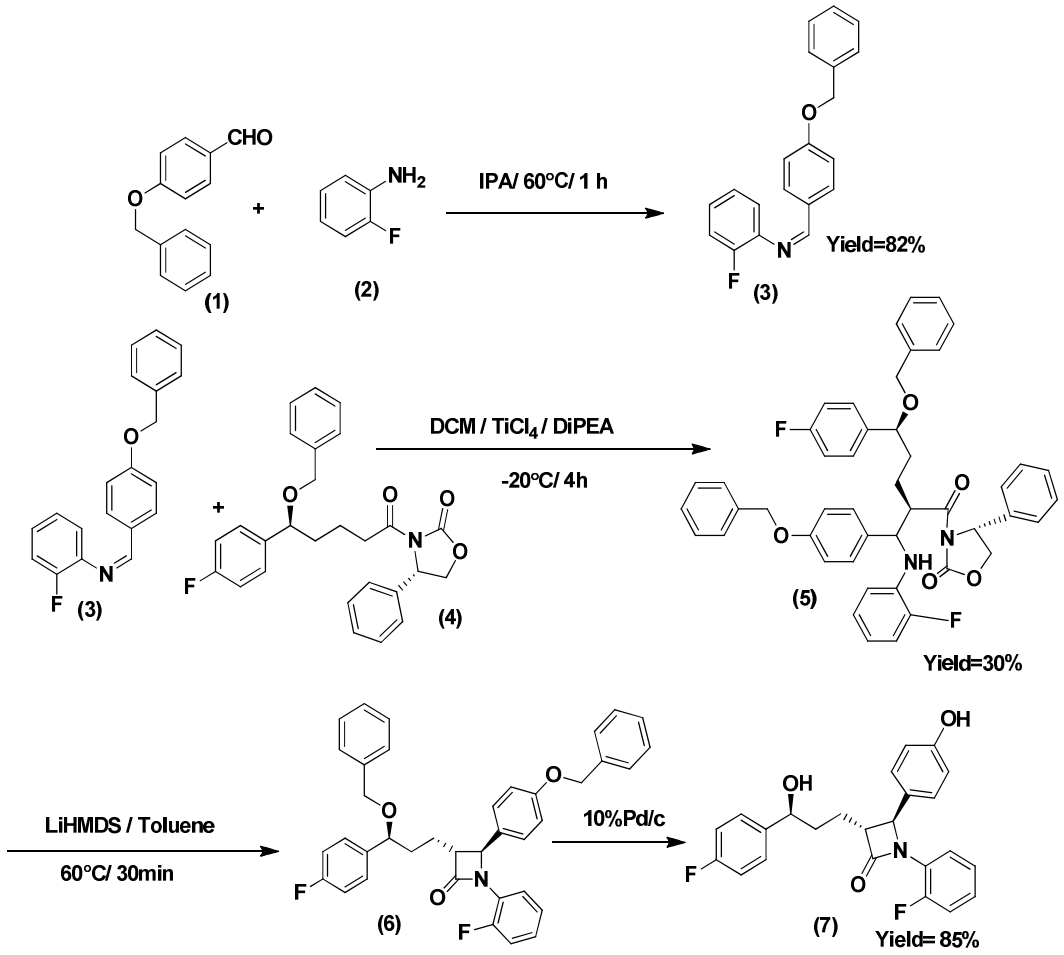
Treatment of the above Schiff's base **3** with (*S*)-3-((*S*)-5-(benzyloxy)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one **(4)** in the presence of strong base i.e *N*,*N*-Diisopropylethylamine (DIPA) and catalytic amount of $TiCl_4$ in DCM at -20°C for a period of 4h gave (different from the starting material)i.e. (*R*)-3-((2*R*,5*S*)-2-((2-fluorophenylamino)(4-(benzyloxy)phenyl)methyl)-5-(benzyloxy)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one **(5)** in 30% yield. The structure of this compound has been assigned based on its ^{1}H- NMR spectrum.

The above 2-fluoro compound **5** was treated with lithium bis(trimethylsilyl)amide (LiHMDS) and a catalytic amount of tetra butyl ammonium fluoride (TBAF) in the presence of toluene solvent. The reaction mixture was heating at 60°C for a period of 30 min to afford cyclized *β*-lactam product i.e. (3*R*,4*S*)-3-((*S*)-3-(benzyloxy)-3-(4-fluorophenyl)propyl)-4-(4-(benzyloxy)phenyl)-1-(2-fluorophenyl)azetidin-2-one **(6)** in 85% yield. Spectral data of compound indicated that the trans β-lactam coupling constant of C3 and C4 proton was 2.1 Hz, which showed significant difference compared to that of cis β-lactams (5–6 Hz) [11].

The structure of this compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.75 (2H, t, -C**H**$_2$ protons), δ 1.86 (2H, dd, -C**H**$_2$ protons), δ 3.13 (1H, m, -C**H** proton of the cyclic four member ring), δ 4.21-4.38 (2H, m, -C**H**$_2$ attached with –CH-O-CH$_2$), δ 5.00-5.05 (2H,s, -C**H**$_2$ attached with –OBn), δ 5.74 (1H, s, -C**H** proton in cyclic four member ring), δ 6.89-7.70 (22H, m, -Ph-).

Treatment of *β*-lactam compound **(6)** with 10%Pd/C in dioxane, stirring under hydrogen atmosphere for a period of 2h treated to the deprotection of benzyl groups resulting in the formation of pure compound of SRS-Ezetimibe **(7)** with retained stereochemistry in 57.63% yield. The HPLC purity of this isomer was 96.94% .The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.75 (4H, dd, 2xC**H**$_2$ protons), δ 3.14 (1H, t, -O**H** proton), δ 4.51 (1H, t, -CH proton attached to hydroxyl group), δ 4.93 (1H, s,-C**H** proton in four member cyclic ring), δ 5.28-5.29 (1H, d, -N-C**H** lactam proton), δ 6.70 (2**H**, d, benzene protons), δ 7.09-7.18 (7**H**, m, benzene protons), δ 7.65-7.70 (1**H**, m, benzene protons), δ 9.48 (1H,s,-PhO**H** proton). Its CI mass spectrum in M-OH mode showed a molecular ion peak at 392 (base peak) corresponding to a molecular mass of 409. The above total synthesis of SRS-Ezetimibe is shown in the below

Scheme-1



Synthesis of 3-fluoro SRS-Ezetimibe

The condensation reaction of 4-(benzyloxy)benzaldehyde **(1)** with 3-fluoroaniline **(8)** in the presence of isopropyl alcohol, at 60 ^{0}C for 1 h without using any further catalyst gave a compound which has been identified as a schiff's base i.e. (*Z*)-*N*-(4-(benzyloxy)benzylidene)-2-fluorobenzenamine **(9)** in 60% yield. The structure of this compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, DMSO-d_6/TMS): δ 5.13 (2H, s, -C**H**$_2$ benzyl protons), δ 6.87-6.97 (3H, m, benzene protons), δ 7.04-7.08 (2H, m, benzene protons), δ 7.28-7.46 (6H, m, phenyl protons), δ 7.82-7.85 (2H, m, fluorin attached benzene ring), δ 8.35 (1H,s, imine proton). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 305 (base peak) corresponding to a molecular mass of 304.

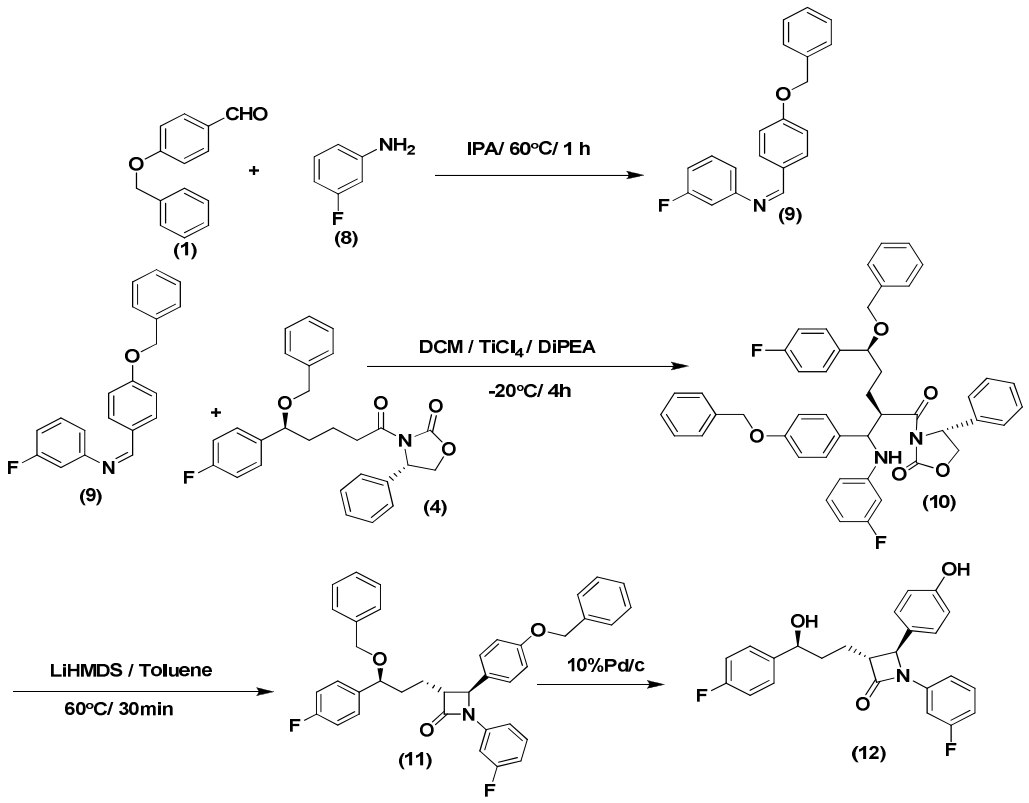
Treatment of the above Schiff's base **9** with (*S*)-3-((*S*)-5-(benzyloxy)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one **(4)** in the presence of *N*,*N*-Diisopropylethylamine (DIPE) and catalytic amount of $TiCl_4$ in DCM solvent under stirring at -20°C for a period of 4h gave different from the starting material i.e. (*R*)-3-((2*R*,5*S*)-2-((2-fluorophenylamino)(4-(benzyloxy)phenyl)methyl)-5-(benzyloxy)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one **(10)** in 30% yield. The structure of this

compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.56 (4H, dd, -2XC**H$_2$** proton), δ 4.02-4.07 (4H, m, –OCH_2 attached with benzene ring + second –CH_2 exist in five member ring), δ 4.29(1H, brs, D_2O-exchangble -N**H** proton + 1H, m, methine proton of the –C**H**-C=O), 4.72 (1H, t, -CH proton), δ 5.04 (2H, s, methylene proton of the –C**H$_2$**-Ph), δ 5.50 (1H, dd, -C**H** proton in five member ring), δ 6.17-6.49(4H, m, -C**H** proton is attached to –NH-Ph+ 3H, benzene ring proton) δ 6.90-6.98 (3H, m, benzene ring protons), δ 7.06-7.46 (22H, m, benzene protons). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 752 (base peak) corresponding to a molecular mass of 753.

The above 3-fluoro compound **10** was treated with Lithium bis(trimethylsilyl)amide (LiHMDS) and a catalytic amount of tetra butyl ammonium fluoride (TBAF) in the presence of toluene solvent. The reaction mixture was heated at 60°C for a period of 30 min to afford cyclized *β*-lactam product i.e. (3*R*,4*S*)-3-((*S*)-3-(benzyloxy)-3-(4-fluorophenyl)propyl)-4-(4-(benzyloxy)phenyl)-1-(2-fluorophenyl)azetidin-2-one **(11)** in 70% yield. The structure of this compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.72 (2H, t, -C**H$_2$** protons), δ 1.84 (2H, dd, -C**H$_2$** protons), δ 3.14 (1H, m, -C**H** proton of the cyclic four member ring), δ 4.20-4.36 (2H, m, -C**H$_2$** attached with –CH-O-CH_2 + 1H, -C**H** proton), δ 4.91-4.92 (1H, -CH proton) 5.08 (2H, s, -C**H$_2$** attached with –OBn), δ 6.83-7.44 (22H, m, -benzene ring protons) . Its CI mass spectrum in M+1 mode showed a molecular ion peak at 590 (base peak) corresponding to a molecular mass of 589.

Treatment of *β*-lactam compound **11** with 10%Pd/C in dioxane stirring under hydrogen atmosphere for a period of 2h, resulted in the deproduction of benzyl groups lead to forms the target pure compound of SRS-3-fluoro Ezetimibe **(12)** in 82% yield. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.74 (4H, dd, two –C**H$_2$** protons), δ 3.35 (1H, s, cis -CH proton in four member ring), δ 4.48 (1H, s, -C**H**-OH), δ 4.51 (1H, t, -CH proton attached to hydroxyl group), δ 4.93 (1H, s, trans -C**H** proton in four member cyclic ring), δ 5.29 (1H, broad, -OH proton), δ 6.60-7.34 (12**H**, m, benzene protons), δ 9.54 (1H, s, -PhO**H** proton). Its CI mass spectrum in M-OH mode showed a molecular ion peak at 393 (base peak) corresponding to a molecular mass of 409.

The above total synthesis of 3-fluoro SRS-Ezetimibe is shown in the below **Scheme-2.**



…Scheme-2.

Synthesis of 4-fluoro SRR-Ezetimibe

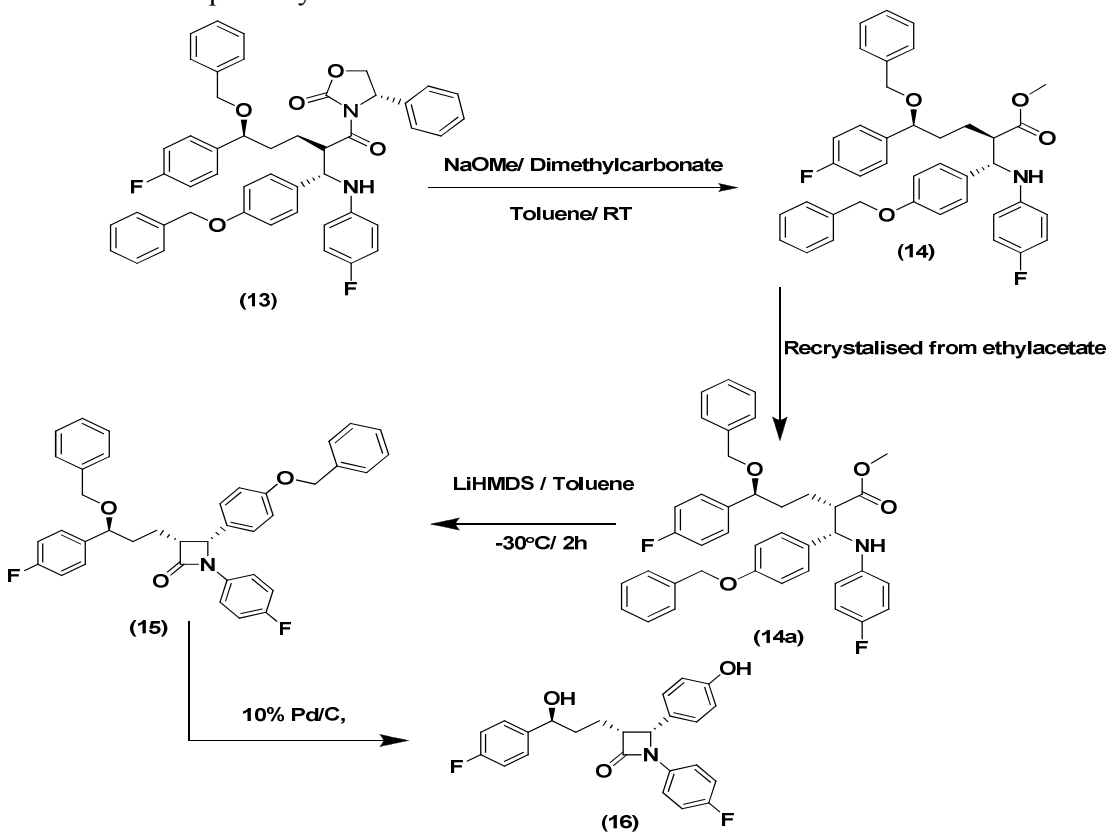
The commercial available furanone derivative **(13)** was treated with excess of sodium methoxide in the presence of toluene and followed by stirring at room temperature for a period of 90 min to obtained raw material **(14)**. The raw material was crystallized in ethylacetate solvent obtained amazingly the corresponding ester compound of SRR isomer in 60% yield **(14a)**. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.54-1.63 (2H, m, -C**H**$_2$ proton), δ 1.69-1.75 (2H, m, -C**H**$_2$ proton), δ 1.99 (1H, dd, -CH proton), δ 3.32 (3H, s, -OCH_3), δ 4.23 (2H, t, -OC**H**$_2$), δ 4.29-4.39 (2H, m, -C**H** proton +-NH proton), δ 5.01 (2H, s, -OCH_2), δ 6.05 (1H, d, -CH), δ 6.52-6.53 (2H, m, benzene protons), δ 6.85-6.88 (4H, m, benzene protons), δ 7.14-7.42 (17H, m, benzene ring protons).

Compound **14a** treated with Lithium bis(trimethylsilyl)amide (LiHMDS) and a catalytic amount of tetra butyl ammonium fluoride (TBAF) in the presence of toluene solvent. The reaction mixture was subject to stirred at -30°C for a period of 2h obtained cyclized *β*-lactam product i.e. (3R,4R)-3-((S)-3-(benzyloxy)-3-(4-fluorophenyl)propyl)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one **(15)** in 85% yield . The structure of this compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.50 (4H, dd, two –C**H**$_2$ protons), δ 3.58 (1H, dd, -CH cis proton in lactam ring), δ 4.17-4.20 (3H, m, -C**H**$_2$ attached with –CH-O-CH_2 + 1H, -C**H** proton), 5.06 (2H, s, -C**H**$_2$ attached with –OBn), 5.31 (1H, d, -CH proton), δ 6.90-7.46 (22H, m, -benzene ring protons).

Treatment of *β*-lactam compound **15** with 10%Pd/C in dioxane stirring under hydrogen atmosphere for a period of 6h, gave 98.81% (HPLC) of pure compound of SRR Ezetimibe

(16) in 98% yield. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.02-1.55 (4H, m, –2xC**H**$_2$ protons), δ 3.54 (1H, dd, cis -CH proton in four member ring), δ 4.35 (1H, d, -CH proton in four member ring), δ 4.48 (1H, s, -C**H**-OH), δ 5.11 (1H, d, -OH proton), δ 5.24 (1H, d, -CH proton), δ 6.72-7.23 (12**H**, m, benzene protons), δ 9.51 (1H, s, -PhO**H** proton).

The above all steps for synthesis of Ezetimibe SRR isomer are shown in the below



…Scheme-3

Synthesis of Ezetimibe SSS isomer

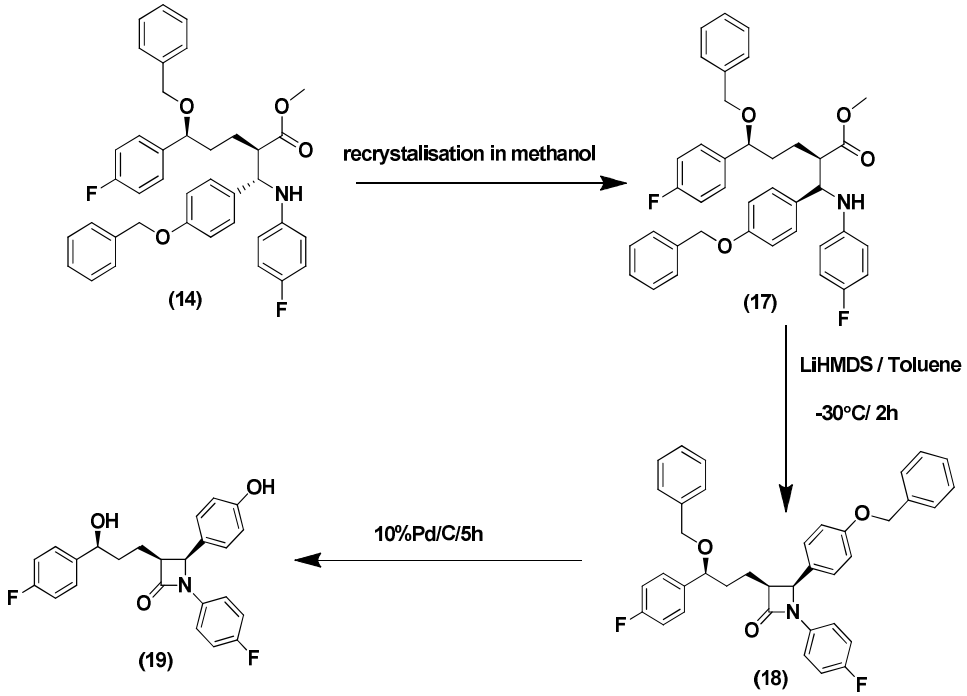
The above obtained SRR ester compound **14** recrystalized in methanol gave the corresponding isomer of SSS ester in 4.24% yield. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at δ 1.51-1.68 (2H, m, -C**H**$_2$ proton), δ 1.82(2H, t,-C**H**$_2$ proton), δ 2.69 (1H, dd, -CH proton), δ 3.32 (3H, s, -OCH_3), δ 4.24 (2H, t, -OC**H**$_2$), δ 4.34(1H, broad, -NH proton), δ 4.39 (1H, t, -C**H** proton), δ 4.99 (2H, s, -OCH_2), δ 6.01 (1H, d, -CH), δ 6.48-6.53 (2H, m, benzene protons), δ 6.80-6.87 (4H, m, benzene protons), δ 7.15-7.42 (16H, m, benzene ring protons). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 622 (base peak) corresponding to a molecular mass of 621.

The reaction of ester SSS isomer **17** treated with lithium bis(trimethylsilyl)amide (LiHMDS) and a catalytic amount of tetra butyl ammonium fluoride (TBAF) in the presence of toluene solvent. The reaction mixture was stirred at -30°C for a period of 1h, to obtain cyclized *β*-lactam product i.e. (3S,4S)-3-((S)-3-(benzyloxy)-3-(4-fluorophenyl)propyl)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one **(18)** in 93% yield. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d_6/TMS): showed signals at showed signals at δ 0.94 (1H, dd, one of the chiral proton in -

C**H**$_2$), δ 1.35-1.49 (2H, m, -C**H**$_2$), δ 1.70 (1H, d, one of the chiral proton in -C**H**$_2$), 3.56 (1H, dd, -CH proton in lactam ring), δ 4.05-4.21 (3H, m, -C**H**$_2$ attached with –CH-O-CH$_2$ + 1H, -C**H** proton), 5.07 (2H, t, -C**H**$_2$ attached with –OBn), 5.30 (1H, d, -CH proton), δ 6.98-7.47 (22H, m, -benzene ring protons).). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 590 (base peak) corresponding to a molecular mass of 589.

Treatment of *β*-lactam compound **18** with 10%Pd/C in dioxane and stirring under hydrogen atmosphere for a period of 6h, 99.24% (HPLC) of SSS Ezetimibe **(19)** in 79% yield. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d$_6$/TMS): showed signals at δ 1.02-1.59 (4H, m, –2xC**H**$_2$ protons), δ 3.55-3.64 (1H, m, -CH proton in four member ring), δ 3.99 (1H, dd, -CH proton in four member ring), δ 4.21 (1H, s, -C**H**-OH), δ 5.09(1H, d, -OH proton), δ 5.24 (1H, d, -CH proton), δ 6.72 (2H, d, benzene protons) δ 7.00-7.23 (10**H**, m, benzene protons), δ 9.51 (1H, S, -PhO**H** proton). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 410 (base peak) corresponding to a molecular mass of 409.

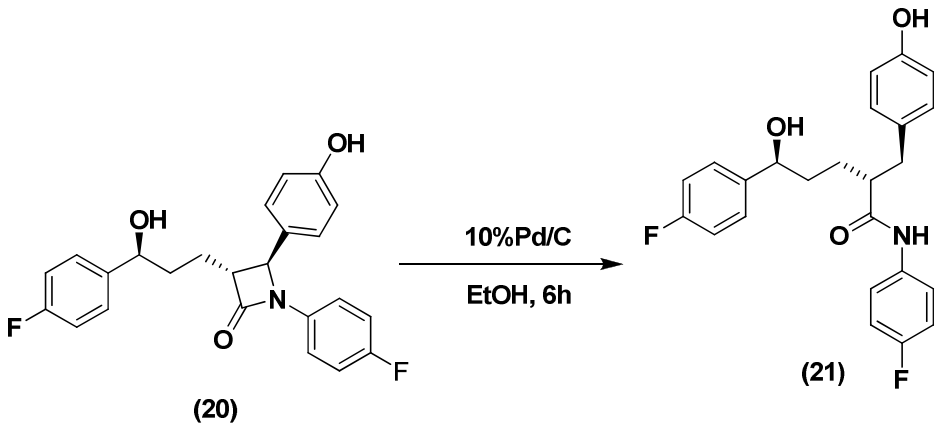
The above all steps for synthesis of 4-fluoro-Ezetimibe SSS isomer are shown given below.



…Scheme-4

Synthesis of 4-fluoro SRS-Ezetimibe amide isomer

The catalytic hydrogenation reaction on **20** with 10% Pd/C catalyst in the presence of ethanol under hydrogen pressure at room temperature for a period of 6h, afforded the corresponding amide isomer of 4-fluoro SRS Ezetimibe **(21)** in 90% yield with 99% purity without change in their stereochemistry. The structure of this compound has been assigned based on its ^{1}H-NMR spectrum (300 MHz, DMSO-d$_6$/TMS): showed signals at δ 1.48-1.61 (4H, m, –2C**H**$_2$), δ 2.50 (1H, t, one of the diasteromeric proton in –CH$_2$), δ 2.73 (1H, t, second diasteromeric proton in –CH$_2$), δ 4.45 (1H, d, -CH), δ 5.20 (1H, d, -OH proton), δ 6.62 (2H, d, benzene protons), δ 6.94 (2H, d, benzene protons), δ 7.06 (4H, t, benzene protons), δ 7.23 (2H, q, benzene protons), δ 7.50 (2H, t, benzene protons), δ 9.13 (1H, s, -NH proton), δ 9.79 (1H, phenol proton). Its CI mass spectrum in M+1 mode showed a molecular ion peak at 411 (base peak), 394 (M-OH) corresponding to a molecular mass of 412**.**



…Scheme-5

EXPERIMENTAL SECTION

Synthesis of 2-chloro-Ezedtimibe (SRS)

General Procedure for the synthesis of 3 from 1 and 2

4-(benzyloxy)benzaldehyde **(1)** (450mM, 9.54g, 1.0 eq.) was dissolved in isopropanol (50 mL) at 60 °C by stirring. 2-Fluoroaniline **(2)** (450 mM, 5g, 1.0 eq.) was added to the resulting solution and the mixture was stirred at 60 °C for 1 h. After completion of the reaction (TLC: 10% E.A/Hexane Rf value=0.6), the solution was allowed to cool to room temperature, during which the expected imine crystallized. The crystals were filtered out, washed with isopropanol and dried at room temperature to obtain (Z)-N-(4-(benzyloxy)benzylidene)-2-fluorobenzenamine**(3)** as off-white powder with 81% (11.2 g) yield.

It is to note that by using the same strategy prepared (*Z*)-*N*-(4-(benzyloxy)benzylidene)-3-fluorobenzenamine **(9)** in 60.66% yield**.**

General procedure for the preparation of 5 from 3 and 4

TO the mixture of DIPEA (73.79 mM, 9.52g, 3.3 equiv.),and (Z)-N-(4-(benzyloxy)benzylidene)-2-fluorobenzenamine **(3)** (44.74 mM, 2 eq. 13.64g) in DCM was added into a cooled suspension of (*S*)-3-((*S*)-5-(benzyloxy)-5-(4-fluorophenyl)pentanoyl)-4-phenyloxazolidin-2-one **(4)** (22.3mM, 10g, 1 eq.) in methylene chloride (100ML). In a separate reaction vessel, titanium complex was prepared by mixing titanium tetrachloride (22.3mM, 10g, 1eq.) in DCM (100ML) under cooling. Both of the above two solutions were added at very low temperature and it was followed by additional cooling to -20 °C. The titanium complex mixture was added slowly into this solution at -20 °C for 30 min. The reaction mixture was stirred for 4h at the same temperature (-20 °C). After completion of the reaction, (by TLC: 20% EA+Hexane; Rf value=0.4) the solution was quenched by addition of tartaric acid and extracted organic layer. The extracted organic layer was distilled out and purified with column chromatography eluted by Ethylacetate as solvent. Finally the compound was crystallized in the presence of Ethylacetate to obtained pure yellow solid **(5)** in 29% (5g).

It is to note that, By using the same strategy prepared (*Z*)-*N*-(4-(benzyloxy)benzylidene)-3-fluorobenzenamine **(10)** in 29% yield**.**

General procedure for the preparation 6 from 5.

Compound **5** (13.29 mM, 10g, 1eq.) was dissolved in toluene solvent (100 mL) and lithium bis(trimethylsilyl)amide (BSA) (39.8 mM, 8.13g, 3eq.) was added to the reaction mixture was heated at 60 °C until clear solution was obtained. Tetra butyl ammonium fluoride (TBAF) (2%w/w), (0.2g) was added to this clear solution and again maintained 60 °C for a

period of 30Min. After completion of the reaction (by TLC: 20% EA/Hexane; Rf value: 0.6) the solution was cooled to room temperature and washed with water (30ML). The toluene dried over sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was purified by column silicagel and eluted with 20%E.A/Hexane to obtain a pure yellow syrupy liquid **6** in 85% (10g).

By using the same strategy prepared (3R,4S)-3-((S)-3-(benzyloxy)-3-(4-fluorophenyl)propyl)-4-(4-(benzyloxy)phenyl)-1-(2-fluorophenyl)azetidin-2-one **(11)** in 70.51% (1.1g) yield.

General Procedure for the Synthesis of 2-fluoro-ezetimibe (SRS) isomer (7) from 6.

To the mixture of compound **6** (8.48 mM, 5g, 1eq.) in 1,4-Dioxane(133 ML) this solution of dioxane.HCl (1.65 mL) containing 10%Pd/C (1g) reagent. The reaction flask is placed in autoclave and stirring for a period of 2h, under hydrogen atmosphere (at 3kg pressure) at room temperature. If reaction is not completed added excess amount dioxane.HCl containing 10%Pd/C (20%w/w, 1g) reagent to reaction mixture. After completion of the reaction (by TLC: 50%EA+Hexane; Rf value: 0.1), the reaction mixture was filtered through celite bed. The celite bed was washed with little amount of water and the filtrate was extracted with ethyl acetate. The organic layer dried over sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was purified by column of silicagel and eluted with 50%EA+Hexane, obtained a solid of 2-chloro Ezetimibe (SRS) isomer **(7)** in 57.63% (2g) with 96.94% HPLC purity.

Note: By using the same strategy prepared 3-chloro-Ezedimbie (SRS) isomer **(12)** in 82% (0.8g) yield.

Synthesis of 4-fluoro-Ezedimbie (SRR) isomer

General Procedure for the preparation of 14 from 13.

The commercial available amide compound **13** (13.29 mM, 10g, 1eq.) and dimethyl carbonate (50 mL, 5eq.)were taken in a round bottomed flask containing 50 mL of toluene and methanol (0.8 mL) into round bottomed flask and stirred reaction mass for a period of 90 min at room temperature. After completion of the reaction (by TLC: 10%EA+Hexane) the reaction mixture was poured into aq HCl containing ice cubes and followed by stirred again for 20 min. The organic layer was washed with water, brine solution and dried over sodium sulphate. The solvent was distilled off under reduced pressure at 50 °C, to obtain raw compound. Finally the raw compound was purified by silica column chromatography eluting a mixture of 5%EA+Hexane. The purified compound crystallized in the presence of ethyl acetate gave a white powder of SRR isomer of ester **(14a)** in 60.6% yield (5g).

General procedure the preparation of 15 from 14a.

Compound **14a** (8.05 mM, 5g, 1eq.)dissolved in toluene solvent (100 mL) and added lithium bis(trimethylsilyl)amide (BSA) (15% in THF) (13.25 mM, 2.22g, 2eq.) at -30 °C to this reaction flask. The reaction mixture is stirred at -30 °C for a period of 2h. After completion of the reaction (by TLC: 10% EA/Hexane; Rf value: 0.3) the solution was quenched with 20% aq. HCl (30mL). The organic layer was washed with water, dried over with sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was purified by column of silicagel and eluted with 10%E.A/Hexane obtained a pure white solid **15** in 85.1% (4g).

General Procedure for the preparation of SRR-Ezetimibe (16) from 15.

Compound **15** (6.77 mM, 4g, 1eq.) was dissolved in 1,4-Dioxane(88.8 mL) and dioxane.HCl (2.2 mL) containing 10%Pd/C(1g) was added The reaction flask is placed in autoclave and stirring for a period of 2h, under hydrogen atmosphere (at 3kg pressure) at room temperature. If reaction is not completed added excess amount dioxane.HCl containing 10%Pd/C

(20%w/w, 1g) reagent to reaction mixture. After completion of the reaction (by TLC: 30%EA+Hexane; Rf value: 0.2), the reaction mixture was filtered through celite bed. The bed was washed with little amount of water and the filtrate was extracted with ethyl acetate. The organic layer dried over with sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was purified by column of silicagel and eluted with 30%EA+Hexane, obtained a white solid of 4-chloro Ezetimibe (SRR) isomer **(16)** in 99% (2.27g).

General Procedure for the preparation of SSS-Ezetimibe isomer

Preparation of 17 from 14

The above compound **14** recrystalised from methanol obtained SSS isomer of ester **17** in 4.24% yields (0.35g).

Preparation of SSS- Lactam 18 from 17.

Compound **17** (0.563 mM, 0.35g, 1eq.)was dissolved in toluene solvent (20 mL) and lithium bis(trimethylsilyl)amide (BSA) (15% in THF) (0.845 mM, 0.14g, 1.5eq.)was added at -30 °C to this reaction flask. The reaction mixture was stirred at -30 °C for a period of 1h. After completion of the reaction (by TLC: 10% EA/Hexane; Rf value: 0.2) the solution was quenched with 20% aq. HCl (30mL). The organic layer was washed with water and brine solution and dried over with sodium sulphate. Distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was crystalised with Di-iso propyl ether (15mL) obtained a pure off-white solid **18** in 93.75% (0.3g).

Preparation of SSS-Ezetimibe (19) from 18.

Taken **18** (0.254 mM, 0.15g, 1eq.) in 1,4-Dioxane(4 mL) and added to this solution of dioxane.0.5%H_2SO_4 (0.06 mL) containing 10%Pd/C(30mg) reagent. The reaction flask is placed in autoclave and stirring for a period of 5h, under hydrogen ballon pressure at room temperature. After completion of the reaction (by TLC: 30%EA+Hexane; Rf value: 0.2), the reaction mixture was filtered through celite bed. The bed was washed with little amount of water and the filtrate was extracted with ethyl acetate. The organic layer dried over with sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was purified by column of silicagel and eluted with 20%EA+Hexane, obtained a off-white solid of 4-chloro Ezetimibe (SSS) isomer **(19)** in 78.65% (70 mg).

General procedure for the Synthesis of 4-floro SRS-Ezetimibe amide isomer (21) from 20.

Taken **20** (19.54 mM, 8g, 1eq.) and triethyl amine (4.8mL) in ethyl acetate (80mL) containing round bottomed flask. Added 10%Pd/C(1.6g, 20%v/v) to this reaction flask obtain clear solution. The reaction mass was stirred under hydrogen balloon pressure for a period of 6h. After completion of the reaction (by TLC: 5%MeOH+$CHCl_3$; Rf value: 0.3), the reaction mixture was filtered through celite bed. The bed was washed with little amount of water and the filtrate was extracted. The organic layer dried over with sodium sulphate and distilled the solvent completely under reduced pressure from the reaction mixture. Finally the raw compound was with di-isopropyl ether (50mL) obtained a white solid of 4-floro Ezetimibe amide (RRS) isomer **(21)** in 90% (7.2 g).

Conclusions

We have synthesized 2-fluoro-Ezetimibe SRS isomer by using simple and feasible methodology towards industrial purpose. The title compound is obtained in three steps with good yields.

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