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Synthesis of fluorinated Ezetimibe analogue using radical alkylation of α-bromo-α-fluoro-β-lactam

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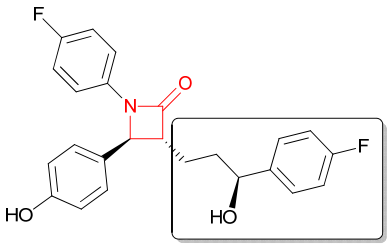
The synthesis of α-fluoro-β-lactam-containing Ezetimibe analogue was accomplished starting from α-bromo-α-fluoro-β-lactam readily prepared from ethyl dibromofluoroacetate. A facile and efficient method for the introduction of C3 alkyl side chain was realized by a radical alkylation. The diastereoselective alkylation of α-bromo-α-fluoro-β-lactam was successfully applied to construct relative conformation of β-lactam nucleus between C3 and C4. Further modification of alkyl side chain gave 3'-(4-fluorophenyl)-3'-hydroxypropyl group through Wacker oxidation and nucleophilic arylation.

Introduction



Ezetimibe : β-lactam core
C3-alkyl side chain

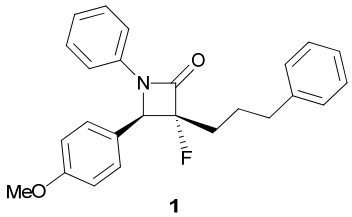


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Fig. 1. Ezetimibe, antihyperlipidemic agent, and reported 3-fluoroazetidinone **1**.

Ezetimibe has been attracted as a novel type of antihyperlipidemic agent on a modern adult disease. This type of drug inhibits a transporter for intestinal cholesterol absorption, Niemann-Pick C1 like 1 (NPC1L1).[1] NPC1L1 is known as a main route of cholesterol absorption, thereby Ezetimibe has provided a newly course of medication different from a HMG-CoA reductase inhibitor such as statins. The backbone structure of Ezetimibe has a β-lactam core and an alkyl side chain at C3 position of the β-lactam ring (Figure 1). Many structure-activity relationship (SAR) studies of several azetidinone compounds have been reported as a candidate compound of cholesterol absorption inhibitor during past two decate.[2-7] Among the candidate compounds, Clader and co-workers have reported that a 3-fluoroazetidinone compound (**1**) worked well as a cholesterol absorption inhibitor (Figure 1).[4] However, the synthetic method of the 3-fluoroazetinone core was not described clearly, and then there are no reports on the bioactivity of 3-fluoroazetidinone analogues. Nowadays, organofluorine compounds are important in medicinal chemistry, therefore this class of structure modification is accepted as a standard target modification in modern SAR study.[8] In this paper, we describe effective and short synthetic route of fluorine-containing ezetimibe analogue on the β-lactam core using α-bromo-α-fluoro-β-lactam as a key intermediate.

Recently, total synthesis of Ezetimibe has been reported from many research groups.[9-12] Most of the known methods for the synthesis of Ezetimibe have been achieved by cyclocondensation between diaryl imine and an ester or amide enolate (Scheme 1). Very recently, the research group of Chmielewski has reported a total synthesis of Ezetimibe via the rearrangement of isoxazolidine (Scheme 2).[13] This method has provided the powerful strategy for the formation of the consecutive chiral centers on Ezetimibe, however it is difficult to construct the fluoro-β-lactam analogue using this manner. To achieve the construction of fluorinated Ezetimibe with fluoro-β-lactam core, we planned an original synthetic strategy via the direct introduction of C3-side chain into fluoro-β-lactam.

Results and discussion

A model substrate, 3-bromo-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (**2**), was synthesized from the Reformatsky-type reaction of ethyl dibromofluoroacetate with the corresponding imine using our reported method.[14] To construct the side chain, the direct allylation of **2** was carried

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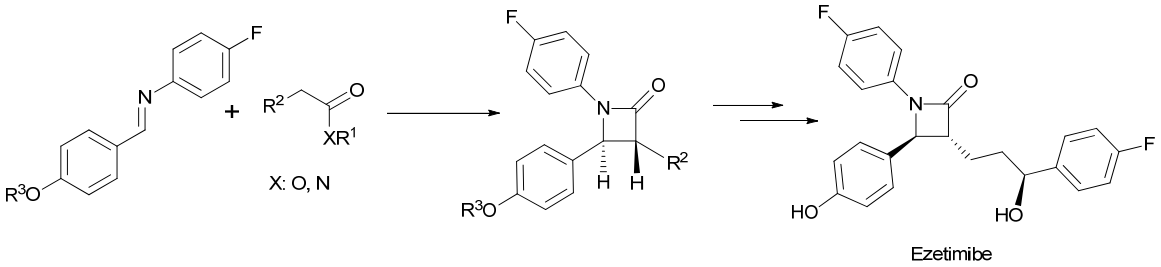
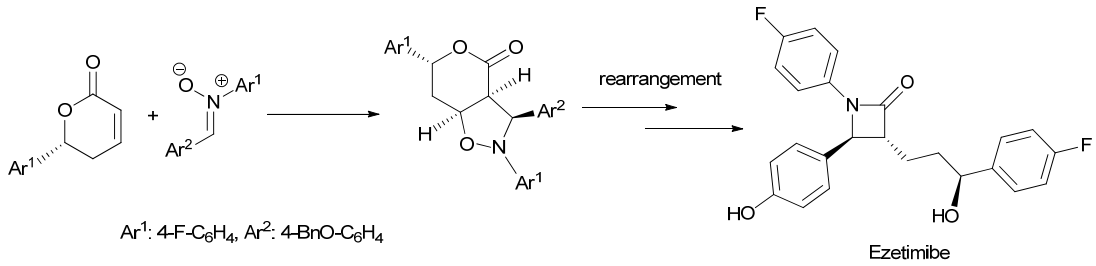
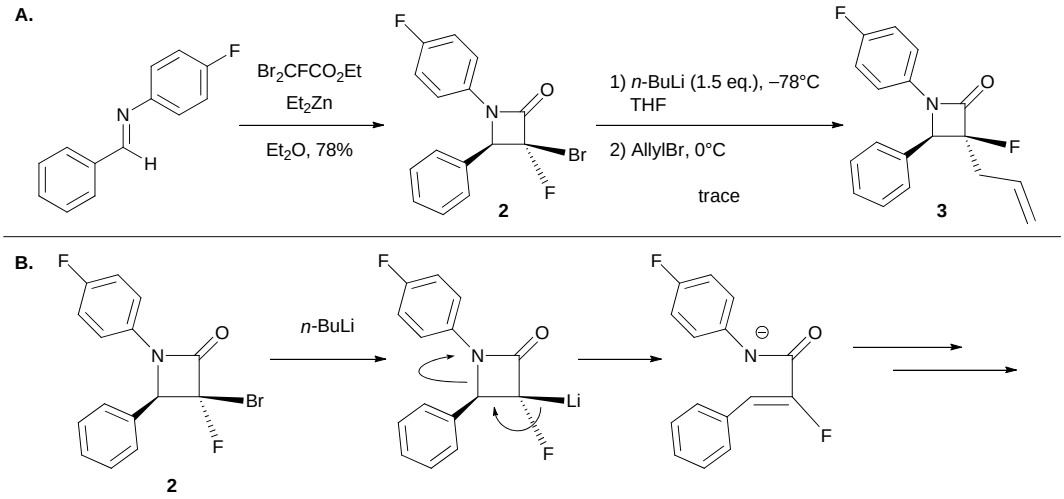
Electronic Supplementary Information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x



Scheme 1 Known strategy for synthesis of Ezetimibe.



Scheme 2 Synthesis of Ezetimibe through rearrangement of isoxazolidine.



Scheme 3 (A) Further alkylation of the key intermediate **2**. (B) Proposal decomposition process of lithiated **2**.

out using a halogen-lithium exchange reaction on the basis of corresponding previous reports.[15-16] However, the allylation of **2** did not progress in this reaction and the starting material **2** was not recovered from the reaction mixture. It suggested that the lithiated **2** with an *N*-arylamide structure was decomposed via the ring opening process (Scheme 3).

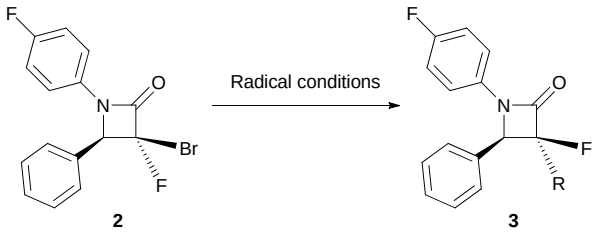
Next, we tried radical alkylation of **2** using the combination of allyltributyltin, Et_3B and oxygen condition (Table 1).[17-18] As shown in entry 1, the addition of **2** to double bond such as methyl acrylate did not afford the corresponding alkylated product. When tributyltin hydride was used as a radical promotor, the hydrogenated product (**3b**) was obtained in good yield (entry 2). The radical allylation worked well with allyltributyltin used as an alkyl source to provide the corresponding product (**3c**) in excellent yield with high diastereoselectivity (entries 3 and 4). In both the cases (3*S*,4*R*/3*R*,4*S*)-isomer was obtained as a single diastereomer.

On the other hand, the allylation promoted by AIBN provided the diastereomixtures of **3** with the ratio of *SR*/*RS* : *RR*/*SS* = 95:5. Finally, we found the optimal radical alkylation condition using 3 equivalent of allyltributyltin, Et_3B and oxygen bubbling (entry 3).

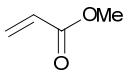
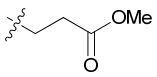
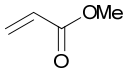
Further structure modification was conducted by Pd catalyzed terminal Wacker oxidation of the allyl group to give the corresponding aldehyde (**4**) regioselectively. Then, the nucleophilic arylation of **4** using Grignard reagent provided the final product (**5**) with the C3 alkyl side chain of fluorinated Ezetimibe analogue as a diastereomixtures. Consequently, we achieved the synthesis of fluorinated Ezetimibe analogue on the β-lactam ring via 3 steps in 51 % total yield (Scheme 4).

Conclusion

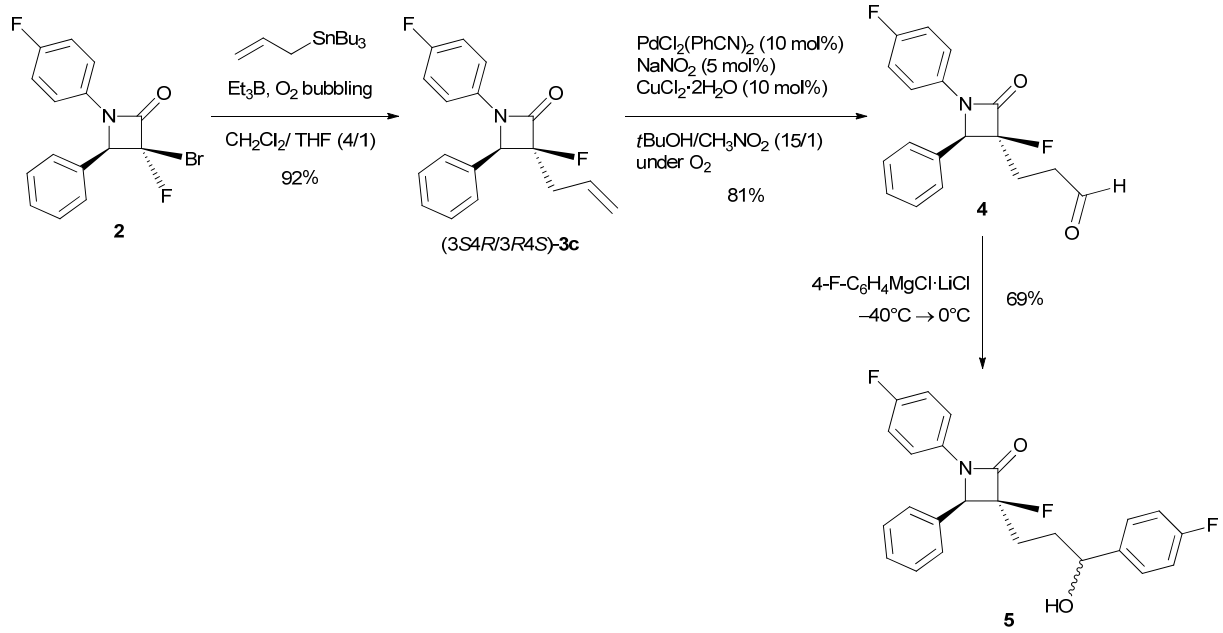
Table 1 Screening radical alkylation of **2**.



2 **3**

Entry	Condition[a]	Reactant	Tributyltin reagent	Time (h)	Yield of **3** (%)	R	
1	A		–	16	NR		**3a**
2	A		Bu_3Sn-H (3 equiv)	1	86[b]	H	**3b**
3	A[c]	–	Bu_3Sn-allyl (3 equiv)	21	92		**3c**
4	A	–	Bu_3Sn-allyl (1 equiv)	19	78		**3c**
5	B	–	Bu_3Sn-allyl (3 equiv)	20	89[d]		**3c**

[a]Condition A: Et_3B and O_2 bubbling in CH_2Cl_2/THF (4/1) at −78°C. Condition B: 5 mol% AIBN in benzene at reflux. [b]Diastereomixture was obtained (*SR*/*RS*:*RR*/*SS* = 85:15). [c]The reaction was carried out at −78°C to −40°C. [d]Diastereomixture was obtained (*SR*/*RS*:*RR*/*SS* = 95:5).



2 (3*S*4*R*/3*R*4*S*)-**3c** **4** **5**

Scheme 4 Synthesis of fluorinated Ezetimibe analogue **5**.

A fluorinated ezetimibe analogue was synthesized diastereoselectively in 3 steps from an easy available intermediate **2** that was prepared from commercial available ethyl dibromofluoroacetate. The successful introduction of the C3-side chain into fluoro-β-lactam was achieved by a diastereoselective radical allylation and following modifications. Efforts toward the asymmetric synthesis of fluorinated Ezetimibe are in progress in our laboratory.

Experimental

NMR spectra were obtained from a solution in $CDCl_3$ or DMSO-d_6 using 600 and 400 MHz for ^1H, 150 and 100 MHz for ^{13}C, and 84 MHz for ^{19}F. Chemical shifts of ^1H NMR and ^{13}C NMR are reported in ppm from TMS as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from benzotrifluoride as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, br = broad, brs = broad-singlet, m = multiplet), coupling constants (Hz). HRMS experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI. IR spectra were recorded in KBr tablets. Melting points were measured uncorrected.

All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted. Anhydrous THF and diethyl ether (Et_2O) were distilled over benzophenone ketyl sodium just before use. Anhydrous CH_2Cl_2 was distilled over P_2O_5 just before use. Anhydrous *tert*-BuOH was distilled over CaH_2 just before use. All commercially available materials were used as received without further purification. Diethyl zinc 1.0 M in hexane and isopropylmagnesium chloride lithium chloride complex 1.3 M in THF were purchased from Aldrich. Triethylboran 1.0 M in hexane was purchased from Kanto chemical Co.. Imine was synthesized from amine and aldehyde using $MgSO_4$ as a desiccant.

Synthesis of α-bromo-α-fluoro-β-lactam

(3*S*,4*R*/3*R*,4*S*)-3-Bromo-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (2) Ethyl dibromofluoroacetate (2 mmol) was added to a solution of *N*-benzylidene-4-fluoroaniline (1 mmol) in Et_2O (8 mL) at ambient temperature. Then the mixture was cooled to 0 °C, and 1.0 M Et_2Zn in hexane (3 mL, 3 mmol) was slowly added to the mixture at same temperature. The whole mixture was stirred at same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and was filtered through Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:9) to give the corresponding product (**2**).

Yield: 262 mg (78%); colorless solid; mp 133-134 °C; IR (KBr) cm^{-1} 1772 (C=O); δ_H ($CDCl_3$, 400 MHz), 5.41 (1H, d, *J* 10.6 Hz), 6.99-7.03 (2H, m), 7.25-7.32 (4H, m), 7.42-7.45 (3H, m); δ_C ($CDCl_3$, 100 MHz), 70.5 (d, *J* 26 Hz), 105.6 (d, *J* 296 Hz), 116.2 (d, *J* 23 Hz), 119.5 (d, *J* 8 Hz), 127.3, 128.8, 129.7, 131.7 (m), 131.8 (d, *J* 1 Hz), 157.4 (d, *J* 27 Hz), 159.7 (d, *J* 246 Hz); δ_F ($CDCl_3$, 84 MHz), −54.0 (1F, d, *J* 10.6 Hz), −52.8-−52.5 (1F, m); *m/z* (EI) 336.9918 (M^+. 100%. $C_{15}H_{10}BrF_2NO$ requires 336.9914), 338.9894 (99.8).

Radical allylation of α-bromo-α-fluoro-β-lactam

(3*S*,4*R*/3*R*,4*S*)-3-allyl-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (3c) To a solution of (3*S*,4*R*/3*R*,4*S*)-3-bromo-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (**2**, 1 mmol) in CH_2Cl_2/THF (10 mL, 4/1) at −78 °C was added allyltributyltin (3 mmol), a 1.0 M solution of Et_3B in C6 (1.5 mL, 1.5 mmol), and an oxygen gas (8 mL) was bubbled to the mixture via gastight syringe over 15 min at same temperature. The whole mixture was stirred at −40 °C for overnight. The reaction was quenched with aqueous 10% HCl, and was filtered through Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography on 10% w/w K_2CO_3-silica gel (AcOEt/hexane = 1:9) and recrystallization in Et_2O to give the allylated product (**3c**). A single diastereomer was obtained.

Yield: 276 mg (92%); colorless solid; mp 154-155 °C; IR (KBr) cm^{-1} 1752 (C=O); δ_H ($CDCl_3$, 600 MHz), 2.76-2.84 (1H, m), 2.92-2.98 (1H, m), 5.09 (1H, d, *J* 3.7 Hz), 5.32 (1H, d, *J* 10.3 Hz), 5.37 (1H, d, *J* 17.1 Hz), 5.86-5.93 (1H, m), 6.95-6.98 (2H, m), 7.29-7.32 (4H, m), 7.37-7.39 (3H, m); δ_C ($CDCl_3$, 150 MHz), 36.9 (d, *J* 37 Hz), 65.7 (d, *J* 24 Hz), 100.8 (d, *J* 227 Hz), 116.1 (d, *J* 23 Hz), 119.2 (d, *J* 8 Hz), 120.9, 127.6, 128.9, 129.1, 129.5 (d, *J* 6 Hz), 131.9, 132.8 (m), 159.6 (d, *J* 244 Hz), 162.5 (d, *J* 25 Hz); δ_F ($CDCl_3$, 84 MHz), −105.1 (1F, ddd, *J* 25.2, 16.5, 3.7 Hz), −54.0-−53.7 (1F, m); *m/z* (EI) 299.1118 (M^+. $C_{18}H_{15}F_2NO$ requires 299.1122).

Diastereomixture of 3-allyl-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (3c) (3*S*,4*R*/3*R*,4*S*)-3-Bromo-3-fluoro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (**2**, 1 mmol) and AIBN (0.05 mmol) were dissolved in benzene (10 mL). Allyltributyltin (3 mmol) was added to the mixture. The whole mixture was stirred under reflux for overnight. The reaction was quenched with water, and was filtered through Celite pad. The filtrate was extracted with AcOEt and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography on 10% w/w K_2CO_3-silica gel (AcOEt/hexane = 1:9) to give the allylated product (**3c**). Two diastereomer were obtained (*SR*/*RS* : *RR*/*SS* = 95:5), which could be separated by column chromatography.

Yield: 267 mg (89%, *SR*/*RS* : *RR*/*SS* = 95:5); major isomer data consisted with the above *SR*/*RS* isomer. *Minor isomer*; colorless liquid; δ_H ($CDCl_3$, 600 MHz), 2.26-2.34 (1H, m), 2.45-2.53 (1H, m), 4.85-4.88 (1H, m), 5.01-5.03 (1H, m),5.21 (1H, d, *J* 12.7 Hz), 5.61-5.68 (1H, m), 6.96-6.99 (2H, m), 7.25-7.30 (4H, m), 7.39-7.41 (3H, m); δ_C ($CDCl_3$, 150 MHz), 34.2 (d, *J* 24 Hz), 67.5 (d, *J* 27 Hz), 103.8 (d, *J* 219 Hz), 116.1 (d, *J* 23 Hz), 119.4 (d, *J* 8 Hz), 119.9, 127.1, 128.6 (d, *J* 4 Hz), 129.1, 129.2, 132.4 (d, *J* 2 Hz), 132.8 (m), 159.5 (d, *J* 245 Hz), 162.5 (d, *J* 25 Hz); δ_F ($CDCl_3$, 84 MHz), −96.9 (1F, ddd, *J* 26.6, 25.9, 12.7 Hz), −54.1-−53.9 (1F, m); *m/z* (EI) 299.1123 (M^+. $C_{18}H_{15}F_2NO$ requires 299.1122).

Terminal Wacker oxidation of allyl group

3-((3*S*,4*R*/3*R*,4*S*)-3-fluoro-1-(4-fluorophenyl)-2-oxo-4-phenylazetidin-3-yl)propanal (4) The titled product was synthesized according to the corresponding literature.[19-20] This reaction was conducted in 0.2 mmol scale based on **3**.

Yield: 51 mg (81%); colorless solid; mp 106-107 °C; IR (KBr) cm^{-1} 1752 (C=O), 1725 (C=O); δ_H ($CDCl_3$, 600 MHz), 2.45-2.52 (2H, m),

2.84 (1H, dt, *J* 19.1, 7.5 Hz), 2.96 (1H, dt, *J* 19.1, 7.1 Hz), 5.11 (1H, d, *J* 3.6 Hz), 6.96-6.99 (2H, m), 7.28-7.33 (4H, m), 7.39-7.41 (3H, m), 9.85 (1H, s); δ_C ($CDCl_3$, 150 MHz), 25.2 (d, *J* 24 Hz), 37.4 (d, *J* 2 Hz), 67.1 (d, *J* 24 Hz), 100.6 (d, *J* 226 Hz), 116.1 (d, *J* 24 Hz), 119.3 (d, *J* 8 Hz), 127.5, 128.9, 129.3, 131.8, 132.7, 159.6 (d, *J* 246 Hz), 162.4 (d, *J* 25 Hz), 199.9; δ_F ($CDCl_3$, 84 MHz), −107.8 (1F, td, *J* 23.6, 3.6 Hz), −54.0-−53.5 (1F, m); *m/z* (EI) 315.1072 (M^+. $C_{18}H_{15}F_2NO_2$ requires 315.1071).

Nucleophilic arylation

(3*S*,4*R*,3'*S*/3*R*,4*S*,3'*R*)-3-fluoro-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-hydroxypropyl)-4-phenylazetidin-2-one and (3*S*,4*R*,3'*R*/3*R*,4*S*,3'*S*)-isomer (5) A 1.3M solution of *i*PrMgCl-LiCl complex in THF (0.8 mL, 1.05 mmol) was placed in a reaction vessel under Ar. 4-Bromofluorobenzene (1 mmol) was added to the above solution, and the reaction mixture was stirred for 3 h at ambient temperature. The reaction mixture was cooled to −40 °C, and then a solution of 3-((3*S*,4*R*/3*R*,4*S*)-3-fluoro-1-(4-fluorophenyl)-2-oxo-4-phenylazetidin-3-yl)propanal (**4**, 0.5 mmol) in THF was added slowly to the cooled reaction mixture. The whole mixture was stirred at 0 °C for overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. Then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluted with AcOEt/hexane = 3:7 → 4:6) to give the product (**5**). Two diastereomer (*SRS*/*RSR* and *SRR*/*RSS*) were obtained. These diastereomer could not be separated by column chromatography, so all spectrum data were obtained from the diastereomixtures of **5** on the hydroxyl group carbon.

Yield: 141 mg (69%); colorless solid; δ_H (DMSO-d_6, 600 MHz), 1.80-1.91 (2H, m), 2.02-2.12 (1H, m), 2.15-2.27 (1H, m), 5.33 (1H, dd, *J* 4.6, 1.2 Hz), 5.52 (1H, d, *J* 4.0 Hz), 7.12-7.15 (2H, m), 7.17-7.20 (2H, m), 7.28-7.31 (2H, m), 7.33-7.34 (2H, m), 7.36-7.41 (5H, m); δ_C (DMSO-d_6, 150 MHz), 28.2 (d, *J* 23 Hz), 28.4 (d, *J* 24 Hz), 32.2 (d, *J* 3 Hz), 32.3 (d, *J* 3 Hz), 65.0 (d, *J* 24 Hz), 65.0 (d, *J* 24 Hz), 70.8, 70.9, 101.8 (d, *J* 222 Hz), 101.9 (d, *J* 222 Hz), 114.6 (d, *J* 21 Hz), 116.0 (d, *J* 23 Hz), 119.2 (d, *J* 8 Hz), 119.2 (d, *J* 8 Hz), 127.4, 127.5, 127.6, 128.6, 132.5, 132.6 (m), 141.6 (d, *J* 6 Hz), 141.6 (d, *J* 6 Hz), 158.6 (d, *J* 242 Hz), 161.1 (d, *J* 242 Hz), 162.4 (d, *J* 25 Hz), 162.5 (d, *J* 25 Hz); δ_F (DMSO-d_6, 84 MHz), −108.0-−107.2 (1F, m), −56.1-−55.8 (1F, m), −55.5-−55.1 (1F, m); m/z (EI) 411.1447 (M^+. $C_{24}H_{20}F_3NO_2$ requires 411.1446).

All aromatic carbon peaks could not be observed due to overlapping some both diastereomer peaks.

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A facile and efficient synthesis of fluorinated Ezetimibe analogue was achieved by radical alkylation, Wacker oxidation, and nucleophilic arylation of α-bromo-α-fluoro-β-lactam.