ASIAN JOURNAL
OF ORGANIC CHEMISTRY

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Accepted Article

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To be cited as: Asian J. Org. Chem. 10.1002/ajoc.201600339

Link to VoR: http://dx.doi.org/10.1002/ajoc.201600339

A Journal of

ACES
Asian Chemical Editorial Society

A sister journal of **Chemistry – An Asian Journal** and **European Journal of Organic Chemistry**

WILEY-VCH

FULL PAPER WILEY-VCH

Stereoselective alkylation of imines and its application towards the synthesis of β-lactams

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Abstract: (*S*)-4-Isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one was evaluated as a chiral auxiliary for asymmetric acetate and propionate Mannich-type reactions, by generation of the titanium enolates, affording excellent yields and stereoselectivities. The application of the auxiliary was exemplified in the stereoselective synthesis of ezetimibe.

Introduction

β-Lactam (azetidin-2-one) constitutes the structure of numerous biologically important molecules[1] (**Fig. 1**). Beyond their potent antibacterial activity, they also possess diverse therapeutic activities, for instance as inhibitors of thrombin[2], prostate specific antigen[3], cysteine protease[4], human leukocyte elastase[5], human cytomegalovirus protein[6] and also as cholesterol absorption inhibitor[7]. Stereoselective construction of β-lactams generated considerable interests due to their use as versatile building blocks for the synthesis of numerous molecules which include peptides, amino acids, polyamines, polyamino alcohols and ethers[8]. The reported strategies[9] for the synthesis of β-lactams encompass Staudinger reaction[10], enolate-imine condensation[11], carbene insertion reaction[12], Kinugasa reaction[13] and asymmetric catalysis[9b]. However in most cases the yield, regioselectivity, and stereoselectivity were poor[14]. The synthesis of unsubstituted β-lactams employing an asymmetric variant of the Reformatsky reaction only afforded modest results[11d]. Synthesis of 3-(aryl)alkenyl β-lactams by olefin cross-metathesis involved multistep protocols giving low overall yields[15]. Rhodium[14a-g,16] and ruthenium[17] promoted carbene insertion reactions are not suitable for substrates bearing sensitive groups, and require lengthy procedures. All these drawbacks reiterated the need for the development of a new procedure for the stereoselective synthesis of β-lactams. We assumed that the cyclisation of enantiomerically pure β-amino carbonyl compounds resulting fom asymmetric Mannich-type reaction[18] would be one of the the easiest routes to access β-lactams stereoselectively. The chiral auxiliary (*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one was examined previously in our laboratory for aldol reactions and was found to afford excellent yields and selectivity.[19b]

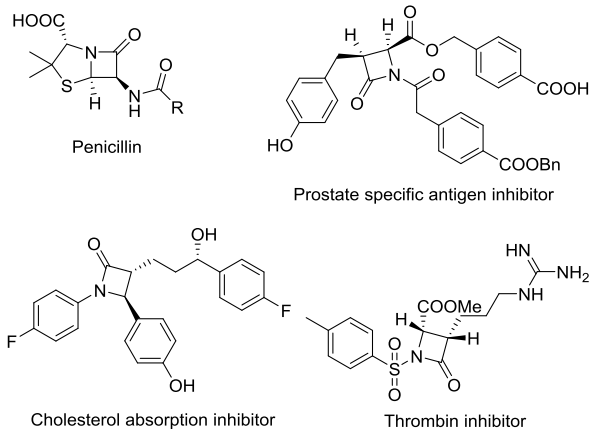
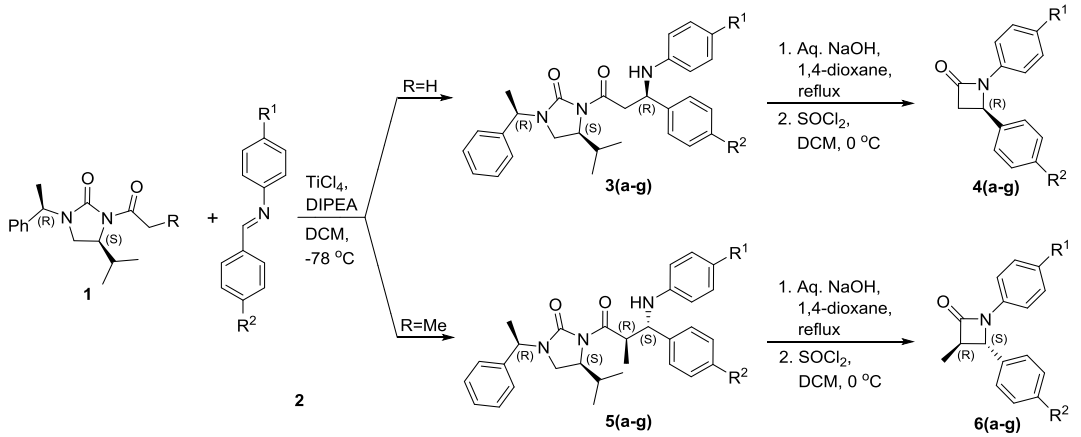


Figure 1. A few biologically active molecules with a β-lactam ring.

Results and Discussion

Based on this work[19] we decided to employ this methodology to imines as electrophiles to obtain enantiopure β-lactam derivatives. The acetylated chiral auxiliary **1** (1.0 equiv.) was treated with $TiCl_4$ (2.0 equiv.), and DIPEA (1.1 equiv.) in dichloromethane at -78 °C to generate the titanium enolate. Reaction of the enolate with an imine (1.1 equiv.), synthesized from benzaldehyde and aniline, afforded the Mannich adduct in good yield. ^{1}H NMR analysis of the crude product revealed a diastereoselectivity of 95:05. The major diastereomer **3a** was subjected to hydrolysis using aq. NaOH (4.0 equiv.) in dioxane-H_2O (1:1) medium to afford the corresponding β-amino acid with an 80% recovery of the chiral auxiliary. The β-amino acid underwent cyclisation with the $SOCl_2$ (1.1 equiv.) in DCM at 0 °C, to afford the β-lactam **4a**. The scope of the reaction was examined by employing various imines (**2a-g**) using the standardised condition (**Table 1, entries 1-7**). In all the cases the desired β-lactams (**4a-g**) were obtained with good yields and excellent selectivity. The optical rotation of the β-lactam **4e** was compared with the literature[11d] [observed $[\alpha]_D^{25}$ = -94.7 (c 0.11, $CHCl_3$), reported for the antipode $[\alpha]_D$ = +87.8 (c 0.115, $CHCl_3$) and a *syn* relation was concluded between the secondary amine at the newly generated stereocentre and the resident stereo directing isopropyl group of the auxiliary for the precursor **3e**.



Scheme 1. Synthesis of *β*-lactams.

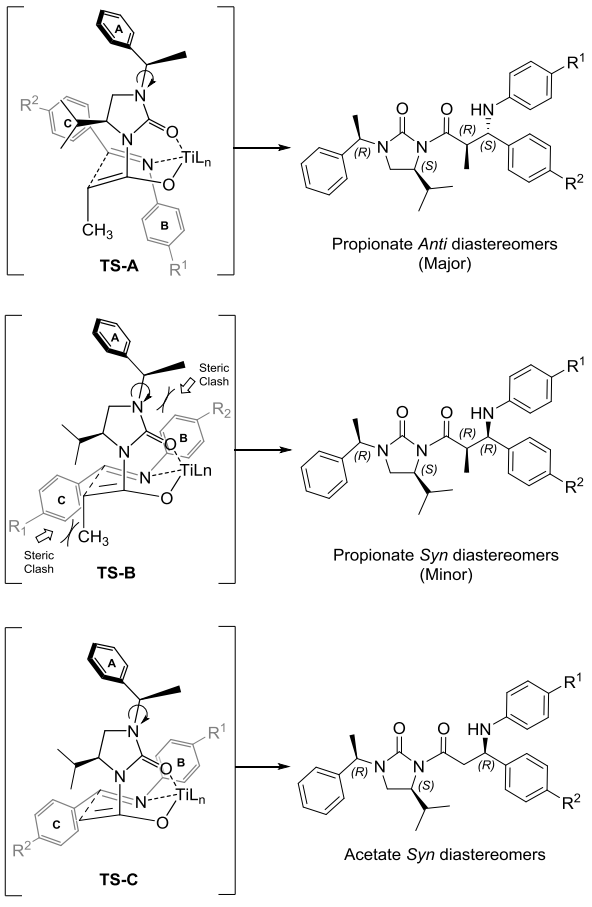
The conditions were then extrapolated to the propionyl variant of the chiral auxiliary **1** (**Scheme 1**) and the corresponding *β*-lactams (**6a**-**g**) were also obtained in good yields and excellent stereoselectivity (**Table 1, entries 8-14**).

Table 1. Evaluation of the chiral auxiliary in stereoselective Mannich-type reactions and synthesis of substituted *β*-lactams[a,b]

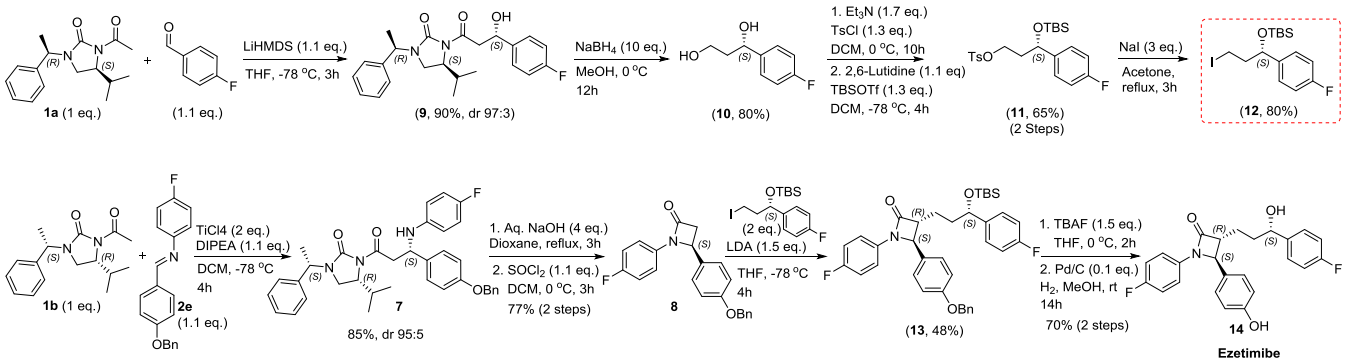
Entry	R	R^1	R^2	*syn:anti*[c]	Yield%[d]	Yield%[d]
1	H	H	H	92:08	**3a** (85)	**4a** (65)
2	H	H	OCH_3	90:10	**3b** (86)	**4b** (60)
3	H	H	F	93:07	**3c** (84)	**4c** (64)
4	H	F	H	94:06	**3d** (83)	**4d** (63)
5	H	F	OBn	95:05	**3e** (84)	**4e** (64)
6	H	CH_3	H	94:06	**3f** (82)	**4f** (62)
7	H	CH_3	CH_3	93:07	**3g** (83)	**4g** (63)
8	CH_3	H	H	09:91	**5a** (85)	**6a** (64)
9	CH_3	H	OCH_3	10:90	**5b** (80)	**6b** (60)
10	CH_3	H	F	08:92	**5c** (83)	**6c** (62)
11	CH_3	F	H	07:93	**5d** (84)	**6d** (63)
12	CH_3	F	OBn	06:94	**5e** (83)	**6e** (62)
13	CH_3	CH_3	H	05:95	**5f** (82)	**6f** (61)
14	CH_3	CH_3	CH_3	03:97	**5g (83)**	**6g (62)**

[a] 1 (1.0 equiv.), $TiCl_4$ (2.0 equiv.), DIPEA (1.1 equiv.), imine (1.1 equiv.). [b] 3(a-g) or 5(a-g) (1.0 equiv.), NaOH (4.0 equiv.), 1,4-dioxane-H_2O (1:1), $SOCl_2$ (1.1 equiv.). [c] *syn* and *anti* ratios are based on ^{1}H NMR analysis of the crude products. [d] Isolated yield.

An *anti* relation was concluded based upon coupling constant (J_{anti} = 2.4 Hz) between the two vicinal protons in the ^{1}H NMR spectra of the *β*-lactam **6a**[11f]. The optical rotation of the *β*-lactam **6a** was correlated with literature [observed $[\alpha]_D^{25}$ = −70.1 (c 1.0, $CHCl_3$), reported for the antipode $[\alpha]_D^{25}$ = +67.2 (c 1.0, $CHCl_3$)].[11e] Shinisha et al.,[20] had reported the transition state models for stereoinduction in Evans chiral auxiliary mediated asymmetric aldol reactions. Based on their study, the observed stereoselectivity in propionate and acetate alkylation reactions may be envisaged from the proposed transition state models (**TS-A**, **TS-B** and **TS-C**) depicted in Scheme 2. Soft enolisation of the *N*-acetyl/propionyl imidazolidinone based auxiliary at -78 °C using $TiCl_4$/DIPEA afforded the titanium enolate which upon reaction with the imine is expected to proceed through a six membered chelated transition state.



Scheme 2. Proposed transition state models for stereoselectivities in propionate/acetate alkylation reactions.



Scheme 3. Synthesis of Ezetimibe.

In the case of TS-A, the imine accommodates itself in such a way that it experiences least steric repulsion from CH_3 group of the *Z*-enolate and the (*R*)-α-methyl benzyl unit of the auxiliary which leads preferentially to the *anti* isomer as the major product. Contrary to this in TS-B, the steric repulsion experienced between the CH_3 group and the aromatic C ring which are oriented in a gauche conformation destabilises the transition state of the *syn* isomer. In TS-C, due to the absence of the CH_3 group, the electrophile flips its facial orientation to relieve the steric effects even further as compared to TS-A. The transition state is thus stabilized with the aryl group C poised in a pseudoequatorial position below the plane, and ultimately affords the *syn* isomer of the product (**Scheme 2**). The *anti* diastereoselectivity for the compounds **5a-g** has also been established by the NOE spectrum of the representative compound **5a** (Supporting information). The absolute stereochemistry of *β*-lactam in the case of propionate alkylation was finally concluded from a single crytal x-ray analysis of the compound **6e**.

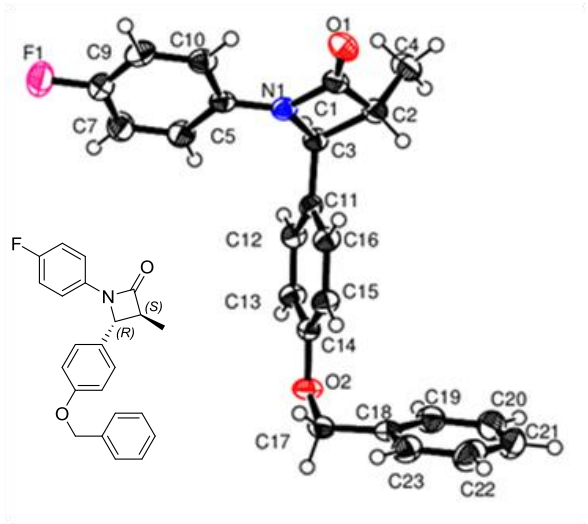


Figure 2. ORTEP diagram of compound **6e**.

The scope of this strategy was further demonstrated in the synthesis of ezetimibe (**Scheme 3**). Ezetimibe (Zetia or Ezetrol) an antihyperlipidemic drug lowers the plasma LDL level by decreasing the cholesterol absorption in the small intestine. It may be used alone or together with statins due to intolerance against other cholesterol lowering drugs. Owing to the therapeutic efficacy and safe pharmacological profile ezetimibe has attracted considerable attention over the past few years[21]. The synthesis of ezetimibe commenced with the formation of the *β*-lactam. To get the desired stereoisomer of the *β*-lactam, the chiral auxiliary was synthesized from D-valine. The acetylated chiral auxiliary **1b** was treated with $TiCl_4$ (2.0 equiv.) and DIPEA (1.1 equiv.) in DCM at -78 °C to generate the titanium enolate. Reaction of the enolate with the imine **2e** afforded the alkylated product **7** stereoselectively. The alkylated product was subjected to hydrolysis using aq. NaOH (4.0 equiv.) in 1,4-dioxane-water (1:1) medium. The reaction afforded the corresponding *β*-amino acid which was further cyclised using thionyl chloride (1.1 equiv.) in DCM at 0 °C to give the desired *β*-lactam **8**. Synthesis of the side chain was initiated by the aldol reaction of *N*-acetylated auxiliary **1a** obtained from L-valine. Reaction of **1a** with LiHMDS (1.1 equiv.) as base in THF at -78 °C followed by the addition of 4-fluorobenzaldehyde afforded the aldol product **9**. The reductive cleavage of the auxiliary was carried out in a subsequent step by using $NaBH_4$ (10.0 equiv.) in methanol at 0 °C temperature to give 1,3-diol **10**. The primary hydroxyl group of the diol was converted to tosylate by using Et_3N (1.5 equiv.) and *p*-toluenesulfonyl chloride (1.1 equiv.) in DCM at 0 °C to afford (*S*)-3-(4-fluorophenyl)-3-hydroxypropyl-4-methyl benzene sulfonate. Subsequently the TBS protection was incorporated on the secondary hydroxyl group by using 2,6-lutidine (1.1 equiv.) and TBSOTf (1.3 equiv.) in DCM at -78 °C to obtain the intermediate **11**. The *β*-lactam ring **8** was subjected to alkylation reaction with **11** under different conditions, but failed to give the desired product. Hence the leaving group was changed from tosyl to iodo using sodium iodide (3.0 equiv.) in acetone under reflux conditions to afford **12** which was subjected to alkylation reaction with the *β*-lactam **8** using LDA (1.5 equiv.) in THF at -78 °C to obtain the alkylated product **13**. The alkylated product was subjected to a selective deprotection of the *tert*-butyldimethylsilyl group using tetrabutylammonium fluoride in THF at 0 °C. A subsequent debenzylation by hydrogenation employing catalytic amount of Pd/C in methanol afforded ezetimibe **14** in good yields and high stereoselectivity. The optical rotation of the ezetimibe was found to be in good agreement with the literature reported value [observed $[\alpha]_D^{25}$ = -27.7 (c 0.15, MeOH), reported $[\alpha]_D^{25}$ = -28.1 (c 0.15, MeOH)[20e]].

Conclusions

In conclusion, a convenient synthetic strategy to obtain substituted *β*-lactams stereoselectively was explored by

employing an imidazolidinone based chiral auxiliary mediated alkylation reactions of imines. The strategy was further extended to the synthesis of the antihyperlipidemic drug ezetimibe.

Experimental Section

Representative procedure for the synthesis of *β*-amino carbonyl compound:

To a solution of (*S*)-3-acetyl-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one (0.50 g, 1.8 mmol, 1.0 equiv.) / (*S*)-4-isopropyl-1-((*R*)-1-phenylethyl)-3-propionylimidazolidin-2-one (0.50 g, 1.7 mmol, 1.0 equiv.) in anhydrous DCM (10 mL) under N_2 atmosphere, was added anhydrous $TiCl_4$ (2.0 equiv.) at –78 °C. The reaction mixture was warmed to 0°C, and again cooled to –78 °C. To this reaction mixture, DIPEA (1.1 equiv.) was added and stirred for 1 h. Further *N*-benzylideneaniline (1.1 equiv. in 5mL DCM) under N_2 atmosphere was introduced into it and stirred for another 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl solution, extracted with DCM and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.

Representative procedure for the synthesis of *β*-lactam:

To a solution of (*S*)-4-isopropyl-3-((*R*)-3-phenyl-3-(phenylamino)propanoyl)-1-((*R*)-1-phenylethyl) imidazolidin-2-one (0.50 g, 1.1 mmol, 1.0 equiv.) / (*S*)-4-isopropyl-3-((2*R*,3*S*)-2-methyl-3-phenyl-3-(phenylamino) propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one (0.50 g, 1.0 mmol, 1.0 equiv.) in dioxane-water (1:1, 10 mL) sodium hydroxide (4.0 equiv.) was added. The reaction mixture was refluxed for 3 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated to dryness, after which it was extracted with DCM. To the aqueous layer conc. HCl was added till the pH became acidic (1-2) and then further extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was dissolved in anhydrous DCM (5 mL). To this solution, thionyl chloride (1.1 equiv.) was added at 0 °C and was allowed to stir further for 3 h. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with saturated aq. $NaHCO_3$, extracted with DCM and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.Experimental Details.

(*S*)-4-isopropyl-3-((*R*)-3-phenyl-3-(phenylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (3a):

Light yellowish solid; m.p. = 82-84 °C; $[\alpha]^{25}_D$ = +89.1 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.45 (d, *J* = 7.3 Hz, 2H), 7.26-7.36 (m, 7H), 7.17-7.21 (m, 1H), 7.01-7.05 (m, 2H), 6.58 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 2H), 5.38 (q, *J* = 7.1 Hz, 1H), 5.23 (brs, 1H), 4.90 (dd, *J* = 4.2 Hz, 9.8 Hz, 1H), 4.11-4.15 (m, 1H), 3.69 (dd, *J* = 9.9 Hz, 13.6 Hz, 1H), 3.27 (dd, *J* = 4.3 Hz, 13.6 Hz, 1H), 3.02 (dd, *J* = 2.3 Hz, 9.6 Hz, 1H), 2.86 (t, *J* = 9.5 Hz, 1H), 2.30-2.34 (m, 1H), 1.59 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.17, 154.79, 147.10, 143.02, 138.87, 129.05, 128.84, 128.63, 128.06, 127.21, 127.10, 126.43, 117.07, 113.47, 55.66, 55.60, 50.60, 43.37, 37.19, 28.75, 18.02, 16.17, 14.33; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{29}H_{34}N_3O_2$, 456.2651, found 456.2651.

(*R*)-1,4-diphenylazetidin-2-one, (4a):

Light yellowish solid; m.p. = 110-112 °C; $[\alpha]^{25}_D$ = -44.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.21-7.38 (m, 9H), 7.01-7.04 (m, 1H), 5.00 (dd, *J* = 2.6 Hz, 5.7 Hz, 1H), 3.55 (dd, *J* = 5.7 Hz, 15.1 Hz, 1H), 2.94 (dd, *J* = 2.6 Hz, 15.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.64, 138.25, 137.80, 129.19, 129.07, 128.54, 125.91, 123.86, 116.82, 54.03, 47.04; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{15}H_{13}NNaO$, 246.0895, found 246.0895.

(*S*)-4-isopropyl-3-((*R*)-3-(4-methoxyphenyl)-3-(phenylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (3b):

White solid; m.p. = 84-86 °C; $[\alpha]^{25}_D$ = +118.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30-7.40 (m, 7H), 7.03-7.07 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 2H), 5.39 (q, *J* = 7.1 Hz, 1H), 5.19 (brs, 1H), 4.85 (dd, *J* = 4.4 Hz, 9.7 Hz, 1H), 4.12-4.16 (m, 1H), 3.76 (s, 3H), 3.67 (dd, *J* = 9.8 Hz, 13.6 Hz, 1H), 3.27 (dd, *J* = 4.3 Hz, 13.6 Hz, 1H), 3.04 (dd, *J* = 2.4 Hz, 9.6 Hz, 1H), 2.87 (t, *J* = 9.5 Hz, 1H), 2.31-2.35 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.21, 158.63, 154.76, 147.08, 138.84, 135.00, 128.99, 128.79, 128.00, 127.47, 127.16, 116.98, 113.98, 113.46, 55.51, 55.23, 55.05, 50.52, 43.40, 37.11, 28.69, 17.98, 16.10, 14.26; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{30}H_{36}N_3O_3$, 486.2757, found 486.2757.

(*R*)-4-(4-methoxyphenyl)-1-phenylazetidin-2-one, (4b):

Light yellowish solid; m.p. = 92-95 °C; $[\alpha]^{25}_D$ = -128.0 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.24-7.34 (m, 6H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.99 (dd, *J* = 2.5 Hz, 5.6 Hz, 1H), 3.83 (s, 3H), 3.56 (dd, *J* = 5.6 Hz, 15.1 Hz, 1H), 2.95 (dd, *J* = 2.5 Hz, 15.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.82, 159.74, 137.84, 130.08, 129.02, 127.21, 123.78, 116.84, 114.55, 55.32, 53.70, 47.12; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{16}H_{15}NNaO_2$, 276.1000, found 276.1001.

(*S*)-3-((*R*)-3-(4-fluorophenyl)-3-(phenylamino)propanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (3c):

White solid; m.p. = 90-92 °C; $[\alpha]^{25}_D$ = +158.0 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.29-7.45 (m, 7H), 6.96-7.08 (m, 4H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 2H), 5.38 (q, *J* = 7.2 Hz, 1H), 5.21 (brs, 1H), 4.86 (dd, *J* = 4.3 Hz, 9.6 Hz, 1H), 4.12-4.16 (m, 1H), 3.65 (dd, *J* = 9.6 Hz, 13.6 Hz, 1H), 3.27 (dd, *J* = 4.4 Hz, 13.6 Hz, 1H), 3.04 (dd, *J* = 2.5 Hz, 9.7 Hz, 1H), 2.89 (t, *J* = 9.4 Hz, 1H), 2.28-2.34 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.95, 163.12, 160.69, 154.70, 146.82, 138.75, 138.61, 129.06, 128.82, 128.06, 127.93, 127.16, 117.22, 115.52, 115.31, 113.42, 55.52, 54.98, 50.57, 43.32, 37.11, 28.67, 17.98, 16.13, 14.23; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{29}H_{33}FN_3O_2$, 474.2557, found 474.2557.

(*R*)-4-(4-fluorophenyl)-1-phenylazetidin-2-one, (4c):

Light yellowish solid; m.p. = 97-100 °C; $[\alpha]^{25}_D$ = -126.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32-7.37 (m, 2H), 7.22-7.28 (m, 4H), 7.01-7.09 (m, 3H), 4.99 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.55 (dd, *J* = 5.7 Hz, 15.2 Hz, 1H), 2.91 (dd, *J* = 2.6 Hz, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.40, 163.94, 161.48, 137.64, 134.03, 129.11, 127.61, 123.98, 116.78, 116.32, 116.10, 53.40, 47.13; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{15}H_{12}FNNaO$, 264.0801, found 264.0802.

(*S*)-3-((*R*)-3-((4-fluorophenyl)amino)-3-phenylpropanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (3d):

Light yellowish solid; m.p. = 121-123 °C; $[\alpha]^{25}_D$ = +117.3 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.43-7.46 (m, 2H), 7.19-7.38 (m, 8H), 6.73-6.77 (m, 2H), 6.40-6.44 (m, 2H), 5.38 (q, *J* = 7.1 Hz, 1H), 5.12 (brs, 1H),

4.82 (dd, *J* = 4.3 Hz, 9.8 Hz, 1H), 4.13-4.17 (m, 1H), 3.71 (dd, *J* = 9.8 Hz, 13.7 Hz, 1H), 3.23 (dd, *J* = 4.3 Hz, 13.7 Hz, 1H), 3.05 (dd, *J* = 2.5 Hz, 9.6 Hz, 1H), 2.89 (t, *J* = 9.4 Hz, 1H), 2.29-2.36 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.14, 154.76, 154.40, 143.40, 142.75, 138.81, 128.80, 128.63, 128.04, 127.16, 126.38, 115.52, 115.30, 114.21, 114.14, 56.26, 55.56, 50.56, 43.27, 37.16, 28.73, 17.97, 16.12, 14.28; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{29}H_{33}FN_3O_2$, 474.2557, found 474.2558.

(*R*)-1-(4-fluorophenyl)-4-phenylazetidin-2-one, (4d):

Light yellowish solid; m.p. = 94-97 °C; $[\alpha]^{25}_D$ = -84.1 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.24-7.39 (m, 7H), 6.91-6.96 (m, 2H), 4.99 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.57 (dd, *J* = 5.7 Hz, 15.2 Hz, 1H), 2.96 (dd, *J* = 2.6 Hz, 15.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.31, 160.20, 157.78, 137.94, 134.04, 129.25, 128.69, 125.90, 118.26, 118.18, 115.95, 115.73, 54.28, 47.20; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{15}H_{13}FNO$, 242.0981, found 242.0981.

(*S*)-3-((*R*)-3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl)amino)propanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (3e):

Light yellowish solid; m.p. = 119-124 °C; $[\alpha]^{25}_D$ = +102.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30-7.42 (m, 12H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.75 (t, *J* = 8.7 Hz, 2H), 6.42 (q, *J* = 4.3 Hz, 2H), 5.38 (q, *J* = 7.0 Hz, 1H), 5.10 (brs, 1H), 5.02 (s, 2H), 4.78 (dd, *J* = 4.2 Hz, 9.6 Hz, 1H), 4.15 (d, *J* = 9.4 Hz, 1H), 3.68 (dd, *J* = 9.8 Hz, 13.6 Hz, 1H), 3.21 (dd, *J* = 4.2 Hz, 13.6 Hz, 1H), 3.04 (dd, *J* = 1.8 Hz, 9.5 Hz, 1H), 2.89 (t, *J* = 9.4 Hz, 1H), 2.30-2.35 (m, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.24, 158.01, 156.74, 154.81, 154.41, 143.51, 138.88, 137.13, 135.11, 128.86, 128.61, 128.09, 127.98, 127.56, 127.21, 115.57, 115.35, 114.98, 114.29, 114.22, 70.05, 55.74, 55.58, 50.60, 43.39, 37.19, 28.79, 18.02, 16.17, 14.34; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{36}H_{39}FN_3O_3$, 580.2975, found 580.2975.

(*R*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one, (4e):

White solid; m.p. = 112-116 °C; $[\alpha]^{25}_D$ = -94.7 (c 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.25-7.44 (m, 9H), 6.91-6.99 (m, 4H), 5.06 (s, 2H), 4.94 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.54 (dd, *J* = 5.6 Hz, 15.2 Hz, 1H), 2.94 (dd, *J* = 2.6 Hz, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.49, 160.16, 159.06, 157.75, 136.65, 134.09, 134.07, 130.01, 128.66, 128.13, 127.51, 127.25, 118.29, 118.21, 115.93, 115.70, 115.51, 70.11, 53.93, 47.26; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{22}H_{19}FNO_2$, 348.1400, found 348.1397.

(*S*)-4-isopropyl-3-((*R*)-3-phenyl-3-(p-tolylamino)propanoyl)-1-((*R*)-1-phenylethyl) imidazolidin-2-one, (3f):

White solid; m.p. = 138-142 °C; $[\alpha]^{25}_D$ = +122.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.49 (d, *J* = 7.7 Hz, 2H), 7.31-7.41 (m, 7H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 8.2 Hz, 2H), 5.42 (q, *J* = 7.2 Hz, 1H), 5.10 (brs, 1H), 4.89 (dd, *J* = 4.2 Hz, 9.7 Hz, 1H), 4.15-4.19 (m, 1H), 3.70 (dd, *J* = 10.0 Hz, 13.6 Hz, 1H), 3.31 (dd, *J* = 4.3 Hz, 13.6 Hz, 1H), 3.07 (dd, *J* = 2.4 Hz, 9.7 Hz, 1H), 2.90 (t, *J* = 9.4 Hz, 1H), 2.33-2.41 (m, 1H), 2.19 (s, 3H), 1.63 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.21, 154.73, 144.73, 143.12, 138.82, 129.51, 128.80, 128.57, 128.01, 127.19, 127.01, 126.41, 126.12, 113.55, 55.82, 55.52, 50.50, 43.32, 37.07, 28.66, 20.36, 18.00, 16.12, 14.27; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{30}H_{35}N_3NaO_2$, 492.2627, found 492.2627.

(*R*)-4-phenyl-1-(p-tolyl)azetidin-2-one, (4f):

White solid; m.p. = 112-116 °C; $[\alpha]^{25}_D$ = -102.9 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32-7.42 (m, 5H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 5.01 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.57 (dd, *J* = 5.6 Hz, 15.1 Hz, 1H), 2.95 (dd, *J* = 2.6 Hz, 15.0 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.36, 138.36, 135.39, 133.44, 129.54, 129.15, 128.47, 125.91, 116.77, 53.97, 46.98, 20.90; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{16}H_{15}NNaO$, 260.1051, found 260.1051.

(*S*)-4-isopropyl-1-((*R*)-1-phenylethyl)-3-((*R*)-3-(p-tolyl)-3-(p-tolylamino)propanoyl) imidazolidin-2-one, (3g):

Sticky solid; $[\alpha]^{25}_D$ = +90.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.33-7.38 (m, 7H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 8.4 Hz, 2H), 5.42 (q, *J* = 7.1 Hz, 1H), 5.04 (brs, 1H), 4.86 (dd, *J* = 4.4 Hz, 9.7 Hz, 1H), 4.14-4.19 (m, 1H), 3.68 (dd, *J* = 9.8 Hz, 13.6 Hz, 1H), 3.28 (dd, *J* = 4.4 Hz, 13.6 Hz, 1H), 3.07 (dd, *J* = 2.5 Hz, 9.6 Hz, 1H), 2.89 (t, *J* = 9.4 Hz, 1H), 2.34-2.41 (m, 1H), 2.32 (s, 3H), 2.19 (s, 3H), 1.63 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.27, 154.76, 144.81, 140.12, 138.85, 136.50, 129.49, 129.25, 128.78, 128.00, 127.18, 126.31, 126.02, 113.55, 55.54, 55.51, 50.49, 43.38, 37.07, 28.67, 21.09, 20.36, 18.00, 16.11, 14.26; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{31}H_{37}N_3NaO_2$, 506.2783, found 506.2771.

(*R*)-1,4-di-p-tolylazetidin-2-one, (4g):

White solid; m.p. = 107-110 °C; $[\alpha]^{25}_D$ = -43.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.27-7.29 (m, 2H), 7.18-7.22 (m, 4H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.97 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.54 (dd, *J* = 5.6 Hz, 15.0 Hz, 1H), 2.93 (dd, *J* = 2.6 Hz, 15.1 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.48, 138.30, 135.43, 135.30, 133.35, 129.80, 129.51, 125.85, 116.78, 53.83, 47.00, 21.17, 20.88; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{17}H_{17}NNaO$, 274.1208, found 274.1209.

(*S*)-4-isopropyl-3-((2*R*,3*S*)-2-methyl-3-phenyl-3-(phenylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, 5(a):

White solid; m.p. = 140-142 °C; $[\alpha]^{25}_D$ = +74.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.17-7.43 (m, 10H), 7.02-7.06 (m, 2H), 6.51-6.58 (m, 3H), 5.68 (brs, 1H), 5.42 (q, *J* = 7.1 Hz, 1H), 4.50-4.64 (m, 2H), 4.16-4.20 (m, 1H), 3.05 (dd, *J* = 2.4 Hz, 9.7 Hz, 1H), 2.92 (t, *J* = 9.4 Hz, 1H), 2.22-2.28 (m, 1H), 1.62 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.08, 154.97, 147.07, 141.82, 138.88, 128.88, 128.76, 128.35, 127.99, 127.31, 127.18, 127.09, 116.70, 113.38, 61.68, 55.80, 50.52, 42.74, 36.96, 28.70, 17.93, 16.11, 15.68, 14.06; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{30}H_{36}N_3O_2$, 470.2808, found 470.2809.

(3*R*,4*S*)-3-methyl-1,4-diphenylazetidin-2-one, (6a):

White solid; m.p. = 134-137 °C; $[\alpha]^{25}_D$ = -70.1 (c 1, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 13.45 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.22-7.39 (m, 9H), 7.01-7.05 (m, 1H), 4.58 (d, *J* = 2.4 Hz, 1H), 3.10-3.15 (m, 1H), 1.48 (d, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.38, 137.97, 137.85, 129.14, 129.04, 128.45, 125.83, 123.75, 116.97, 62.73, 55.34, 13.11; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{16}H_{15}NNaO$, 260.1051, found 260.1051.

(*S*)-4-isopropyl-3-((2*R*,3*S*)-3-(4-methoxyphenyl)-2-methyl-3-(phenylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5b):

Yellow solid; m.p. = 102-107 °C; $[\alpha]^{25}_D$ = +94.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34-7.43(m, 7H), 7.05-7.08 (m, 2H), 6.84-6.87 (m, 2H), 6.53-6.61 (m, 3H), 5.63 (brs, 1H), 5.45 (q, *J* = 7.1 Hz, 1H), 4.55-4.62 (m, 1H), 4.49 (d, *J* = 8.8 Hz, 1H), 4.19-4.23 (m, 1H), 3.78 (s, 3H), 3.08 (dd, *J* = 2.3 Hz, 9.6 Hz, 1H), 2.95 (t, *J* = 9.4 Hz, 1H), 2.26-2.32 (m, 1H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.21, 158. 67, 155.06, 147.14, 138.93, 133.92, 128.90, 128.81, 128.37, 128.03, 127.23,

116.68, 113.81, 113.47, 61.18, 55.84, 55.21, 50.56, 42.91, 37.01, 28.75, 17.98, 16.16, 15.68, 14.12; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{31}H_{38}N_3O_3$, 500.2913, found 500.2913.

(3*R*,4*S*)-4-(4-methoxyphenyl)-3-methyl-1-phenylazetidin-2-one, (6b):

White solid; m.p. = 106-108 ^oC; $[\alpha]^{25}_D$ = -43.3 (c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 20.78 min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.29 (m, 6H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.53 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 3.07-3.14 (m, 1H), 1.46 (d, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.60, 159.71, 137.86, 129.81, 129.02, 127.16, 123.70, 116.99, 114.52, 62.39, 55.33, 13.06; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{17}H_{17}NNaO_2$, 290.1157, found 290.1159.

(*S*)-3-((2*R*,3*S*)-3-(4-fluorophenyl)-2-methyl-3-(phenylamino)propanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5c):

White solid; m.p. = 104-107 ^oC; $[\alpha]^{25}_D$ = +64.5 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.39 (m, 7H), 6.94-7.06 (m, 4H), 6.57 (t, *J* = 7.3 Hz, 1H), 6.48-6.50 (m, 2H), 5.69 (brs, 1H), 5.39 (q, *J* = 7.1 Hz, 1H), 4.54-4.61 (m, 1H), 4.49 (d, *J* = 8.5 Hz, 1H), 4.14-4.18 (m, 1H), 3.04 (dd, *J* = 2.3 Hz, 9.7 Hz, 1H), 2.91 (t, *J* = 9.4 Hz, 1H), 2.19-2.26 (m, 1H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.57 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.93, 163.18, 160.75, 154.95, 146.90, 138.86, 137.63, 128.98, 128.88, 128.82, 128.06, 127.22, 116.93, 115.35, 115.14, 113.38, 61.01, 55.83, 50.62, 42.75, 37.02, 28.77, 17.96, 16.16, 15.72, 14.06; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{30}H_{34}FN_3NaO_2$, 510.2533, found 510.2534.

(3*R*,4*S*)-4-(4-fluorophenyl)-3-methyl-1-phenylazetidin-2-one, (6c):

White solid; m.p. = 130-132 ^oC; $[\alpha]^{25}_D$ = -43.9 (c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 18.33 min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.37 (m, 6H), 7.04-7.11 (m, 3H), 4.59 (d, *J* = 2.4 Hz, 1H), 3.10-3.14 (m, 1H), 1.51 (d, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.17, 163.92, 161.47, 137.67, 133.73, 129.09, 127.58, 123.88, 116.93, 116.27, 116.06, 62.05, 55.45, 13.06; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{16}H_{14}FNNaO$, 278.0957, found 278.0957.

(*S*)-3-((2*R*,3*S*)-3-((4-fluorophenyl)amino)-2-methyl-3-phenylpropanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5d):

White solid; m.p. = 102-105 ^oC; $[\alpha]^{25}_D$ = +76.5 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m, 9H), 7.18-7.21 (m, 1H), 6.71-6.76 (m, 2H), 6.41-6.44 (m, 2H), 5.52 (brs, 1H), 5.41 (q, *J* = 7.0 Hz, 1H), 4.53-4.60 (m, 1H), 4.41 (d, *J* = 8.8 Hz, 1H), 4.16-4.20 (m, 1H), 3.05 (dd, *J* = 2.3 Hz, 9.7 Hz, 1H), 2.92 (t, *J* = 9.4 Hz, 1H), 2.23-2.31 (m, 1H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.10, 156.59, 155.04, 143.37, 141.61, 138.86, 128.81, 128.44, 128.04, 127.34, 127.26, 127.22, 115.44, 115.22, 114.24, 114.17, 62.57, 55.88, 50.56, 42.80, 37.02, 28.74, 17.96, 16.15, 15.63, 14.12; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{30}H_{35}FN_3O_2$, 488.2713, found 488.2713.

(3*R*,4*S*)-1-(4-fluorophenyl)-3-methyl-4-phenylazetidin-2-one, (6d):

Light yellow solid; m.p. = 94-98 ^oC; $[\alpha]^{25}_D$ = -18.1(c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 12.92 min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.29 (m, 7H), 6.82-6.86 (m, 2H), 4.47 (d, *J* = 2.4 Hz, 1H), 3.03-3.09 (m, 1H), 1.40 (d, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.09, 160.17, 157.75, 137.63, 134.09, 134.07, 129.22, 128.60, 125.84, 118.40, 118.32, 115.92, 115.70, 62.94, 55.54, 13.06; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{16}H_{15}FNO$, 256.1138, found 256.1139.

(*S*)-3-((2*R*,3*S*)-3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl)amino)-2-methylpropanoyl)-4-isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5e):

White solid; m.p. = 164-167 ^oC; $[\alpha]^{25}_D$ = +63.7 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.45 (m, 12H), 6.92-6.94 (m, 2H), 6.74-6.78 (m, 2H), 6.43-6.46 (m, 2H), 5.48 (brs, 1H), 5.43 (q, *J* = 7.2 Hz, 1H), 5.03 (s, 2H), 4.51-4.58 (m, 1H), 4.39 (d, *J* = 8.9 Hz, 1H), 4.18-4.22 (m, 1H), 3.08 (dd, *J* = 2.4 Hz, 9.7 Hz, 1H), 2.95 (t, *J* = 9.4 Hz, 1H), 2.26-2.34 (m, 1H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.19, 158.02, 156.57, 155.08, 154.25, 143.43, 138.88, 137.07, 133.96, 128.81, 128.56, 128.37, 128.04, 127.95, 127.54, 127.21, 115.42, 115.20, 114.74, 114.20, 70.02, 62.02, 55.88, 50.56, 42.93, 37.04, 28.75, 17.95, 16.15, 15.60, 14.14 ; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{37}H_{41}FN_3O_3$, 594.3132, found 594.3133.

(3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-methylazetidin-2-one, (6e):

White solid; m.p. = 127-130 ^oC; $[\alpha]^{25}_D$ = -34.7 (c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 7.32 min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.46 (m, 9H), 6.93-7.02 (m, 4H), 5.08 (s, 2H), 4.53 (d, *J* = 2.2 Hz, 1H), 3.11-3.17 (m, 1H), 1.49 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.24, 160.14, 159.05, 157.72, 136.68, 134.10, 129.76, 128.65, 128.11, 127.49, 127.20, 118.34, 115.90, 115.67, 115.49, 70.12, 62.61, 55.53, 13.02; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{23}H_{21}FNO_2$, 362.1556, found 362.1556.

(*S*)-4-isopropyl-3-((2*R*,3*S*)-2-methyl-3-phenyl-3-(p-tolylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5f):

Sticky solid; $[\alpha]^{25}_D$ = +67.8 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.43 (m, 9H), 7.18-7.22 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.46 (d, *J* = 8.4 Hz, 2H), 5.50 (brs, 1H), 5.44 (q, *J* = 7.2 Hz, 1H), 4.57-4.64 (m, 1H), 4.49 (d, *J* = 8.6 Hz, 1H), 4.18-4.22 (m, 1H), 3.07 (dd, *J* = 2.3 Hz, 9.6 Hz, 1H), 2.94 (t, *J* = 9.4 Hz, 1H), 2.25-2.33 (m, 1H), 2.17 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.16, 155.03, 144.79, 141.99, 138.92, 129.43, 128.79, 128.36, 128.01, 127.36, 127.22, 127.07, 125.78, 113.57, 62.02, 55.82, 50.52, 42.81, 36.96, 28.70, 20.34, 17.98, 16.14, 15.67, 14.12; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{31}H_{37}N_3NaO_2$, 506.2783, found 506.2769.

(3*R*,4*S*)-3-methyl-4-phenyl-1-(p-tolyl)azetidin-2-one, (6f):

White solid; m.p. = 102-106 ^oC; $[\alpha]^{25}_D$ = -72.1 (c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 12.14 min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.41 (m, 5H), 7.19-7.22 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.58 (d, *J* = 2.3 Hz, 1H), 3.11-3.17 (m, 1H), 2.28 (s, 3H), 1.50 (d, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.11, 138.07, 135.41, 133.34, 129.53, 129.11, 128.39, 125.83, 116.91, 62.67, 55.28, 20.88, 13.13; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{17}H_{17}NNaO$, 274.1208, found 274.1209.

(*S*)-4-isopropyl-3-((2*R*,3*S*)-2-methyl-3-(p-tolyl)-3-(p-tolylamino)propanoyl)-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (5g):

Sticky solid; $[\alpha]^{25}_D$ = +47.3 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m, 7H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.43 (d, *J* = 8.4 Hz, 2H), 5.42 (q, *J* = 7.1 Hz, 1H), 5.42 (brs, 1H), 4.51-4.58 (m, 1H), 4.43 (d, *J* = 8.9 Hz, 1H), 4.16-4.20 (m, 1H), 3.05 (dd, *J* = 2.3 Hz, 9.6

Hz, 1H), 2.91 (t, *J* = 9.4 Hz, 1H), 2.23-2.30 (m, 1H), 2.27 (s, 3H), 2.14 (s, 3H), 1.62 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 176.25, 155.07, 144.84, 138.94, 138.90, 136.52, 129.40, 129.05, 128.79, 128.00, 127.25, 127.23, 125.70, 113.61, 61.79, 55.81, 50.50, 42.85, 36.95, 28.70, 21.08, 20.35, 17.99, 16.15, 15.62, 14.08; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{32}H_{39}N_3NaO_2$, 520.2940, found 520.2934.

(3*R*,4*S*)-3-methyl-1,4-di-p-tolylazetidin-2-one, (6g):

Sticky solid; $[\alpha]^{25}_D$ = -63.7 (c 0.5, $CHCl_3$); 100% *ee* [determined by HPLC analysis using a Chiralcel OD-H column; n-Hex / i-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R (major) = 11.89 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.18-7.27 (m, 6H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.55 (d, *J* = 2.3 Hz, 1H), 3.08-3.14(m, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.49 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.23, 138.23, 135.47, 135.03, 133.25, 129.77, 129.50, 125.81, 116.92, 62.55, 55.28, 21.18, 20.88, 13.09; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{18}H_{19}NNaO$, 288.1364, found 288.1369.

Synthesis of Ezetimibe

Synthesis of (*R*)-3-((*S*)-3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl) amino)propanoyl)-4-isopropyl-1-((*S*)-1-phenylethyl)imidazolidin-2 one, (7):

To a solution of (*R*)-3-acetyl-4-isopropyl-1-((*S*)-1-phenylethyl)imidazoli din-2-one (4.0 g, 14.6 mmol, 1.0 equiv.) in anhydrous DCM (30 mL) under N_2 atmosphere, was added anhydrous $TiCl_4$ (3.2 mL, 29.1 mmol, 2.0 equiv.) at –78 °C. The reaction mixture was warmed to 0 °C and again cooled to –78 °C. To this reaction mixture, DIPEA (2.7 mL, 16.0 mmol, 1.1 equiv.) was added and stirred for 1 h. Thereafter (*E*)-1-(4-(benzyloxy)phenyl)-*N*-(4-fluorophenyl)methanimine (4.9 g, 16.0 mmol, 1.1 equiv.) was introduced into it and stirred for another 4h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl solution, and the DCM layer was washed with brine, dried over anhydrous sodium sulphate and concentrated to afford crude product which was purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.

White solid; Yield = 85%; m.p. = 155-158 ^{o}C; $[\alpha]^{25}_D$ = -104.3 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.28-7.46 (m, 12H), 6.94-6.97 (m, 2H), 6.76-6.81 (m, 2H), 6.44-6.47 (m, 2H), 5.41 (q, *J* = 7.1 Hz, 1H), 5.11 (brs, 1H), 5.05 (s, 2H), 4.81 (dd, *J* = 4.4 Hz, 9.7 Hz, 1H), 4.16-4.20 (m, 1H), 3.71 (dd, *J* = 9.7 Hz, 13.6 Hz, 1H), 3.24 (dd, *J* = 4.4 Hz, 13.7 Hz, 1H), 3.08 (dd, *J* = 2.5 Hz, 9.6 Hz, 1H), 2.92 (t, *J* = 9.4 Hz, 1H), 2.33-2.38 (m, 1H), 1.63 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.21, 157.96, 156.71, 154.76, 154.38, 143.41, 138.81, 137.07, 135.05, 128.81, 128.58, 128.04, 127.95, 127.52, 127.50, 127.17, 115.53, 115.30, 114.92, 114.24, 114.16, 70.02, 55.69, 55.53, 50.53, 43.35, 37.13, 28.71, 17.99, 16.12, 14.27; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{36}H_{38}FN_3NaO_3$, 602.2795, found 602.2799.

Synthesis of (*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one, (8):

To a solution of (*R*)-3-acetyl-4-isopropyl-1-((*S*)-1-phenylethyl)imidazoli din-2-one (6.0 g, 10.3 mmol, 1.0 equiv.) in 1,4-dioxane-water (1:1, 30 mL) sodium hydroxide (1.6 g, 41.4mmol, 4.0 equiv.) was added. The reaction mixture was refluxed for 3h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated to dryness, after which it was extracted with DCM. To the aqueous layer, conc. HCl was added till the pH became 1-2 and then further extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was dissolved in anhydrous DCM (20 mL). To this solution, thionyl chloride (1.1 equiv.) was added at 0 ^{o}C and was allowed to stir further for 3h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. $NaHCO_3$ solution, extracted with DCM and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.

White solid; Yield = 77% (2 Steps); m.p. = 128-130 ^{o}C; $[\alpha]^{25}_D$ = +90.1 (c 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.24-7.42 (m, 9H), 6.89-6.98 (m, 4H), 5.04 (s, 2H), 4.92 (q, *J* = 2.5 Hz, 1H), 3.51 (dd, *J* = 5.6 Hz, 15.2 Hz, 1H), 2.91 (dd, *J* = 2.6 Hz, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.49, 160.16, 159.08, 157.75, 136.68, 134.13, 134.11, 130.04, 128.67, 128.13, 127.52, 127.27, 118.30, 118.22, 115.93, 115.70, 115.53, 70.12, 53.93, 47.26; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{22}H_{18}FNNaO_2$, 370.1219, found 370.1215.

Synthesis of (*S*)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropanoyl)-4-iso propyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one, (9):

To a solution of *N*-acetylated auxiliary **1a** (10.0 g, 36.4 mmol, 1.0 equiv.) in THF (50 mL) under N_2 atmosphere was added LiHMDS (40.1 mL, 40.1 mmol, 1.1 equiv., 1M solution in THF) gradually at -78 ºC. After 1h, 4-fluorobenzaldehyde (4.1 mL, 38.2 mmol, 1.05 equiv.) was added to it and the reaction mixture was further allowed to stir at the same temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, saturated aq. NH_4Cl solution was added to the reaction mixture at the same temperature to quench the reaction. The reaction mixture was extracted with ethyl acetate and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.3:0.7) as the eluent to afford the desired product.

White solid; Yield = 90%; m.p. = 104-107 ^{o}C; $[\alpha]^{25}_D$ = +156.7 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.28-7.41 (m, 7H), 7.00-7.05 (m, 2H), 5.32 (q, *J* = 7.1 Hz, 1H), 5.10-5.17 (m, 1H), 4.20-4.24 (m, 1H), 4.14 (d, *J* = 4.7 Hz, 1H), 3.48-3.55 (m, 1H), 3.29 (dd, *J* = 3.0 Hz, 16.5 Hz, 1H), 3.09 (dd, *J* = 2.7 Hz, 9.7 Hz, 1H), 2.95 (t, *J* = 9.5 Hz, 1H), 2.34-2.42 (m, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.40, 163.36, 160.93, 154.53, 138.97, 138.79, 128.79, 128.05, 127.52, 127.44, 127.15, 115.27, 115.06, 70.20, 55.35, 50.55, 44.35, 37.33, 28.74, 18.03, 16.09, 14.44; ESI-HRMS (m/z): $[M+H]^+$ calculated for $C_{23}H_{28}FN_2O_3$, 399.2084, found 399.2081.

Synthesis of (*S*)-1-(4-fluorophenyl)propane-1, 3-diol, (10):

To a solution of compound **9** (12.0 g, 30.1 mmol, 1.0 equiv.) in methanol (70 mL) at 0 ºC, was gradually added $NaBH_4$ (11.4 g, 301 mmol, 10.0 equiv.). Progress of reaction was checked with TLC. After completion of the reaction, the reaction mixture was evaporated to dryness under reduced pressure. The solid compound left behind was washed with water to remove the excess $NaBH_4$ under ice cold condition and then the reaction mixture was extracted with ethyl acetate and again washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (8.0:2.0) as the eluent to afford the desired product.

Colourless liquid; Yield = 80%; $[\alpha]^{25}_D$ = -7.9 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30-7.33 (m, 2H), 7.00-7.05 (m, 2H), 4.91 (dd, *J* = 3.8 Hz, 8.8 Hz, 1H), 3.76-3.84 (m, 2H), 3.17 (brs, 2H), 1.85-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.35, 160.91, 139.99, 127.33, 127.25,

115.38, 115.17, 73.39, 61.12, 40.42; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_9H_{11}FN_aO_2$, 193.0641, found 193.0615.

Synthesis of (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-3-(4-fluorophenyl) propyl-4-methyl benzenesulfonate, (11):

To a solution of diol **10** (3.5 g, 20.5 mmol, 1.0 equiv.) in DCM (30 mL) at 0 ºC, triethylamine (4.9 mL, 35.0 mmol, 1.7 equiv.) was gradually added. After 1 h, tosyl chloride (5.1 g, 26.7 mmol, 1.3 equiv.) was slowly added. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. $NaHCO_3$ solution. The reaction mixture was extracted into DCM and washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was dissolved in DCM (30 mL), 2,6-lutidine (1.1 equiv.) and TBSOTf (1.3 equiv.) was added sequentially at -78 ºC under anhydrous condition. Progress of the reaction was monitored by TLC. After completion of the reaction, DCM was evaporated to dryness. The crude residue was diluted with aq. NH_4Cl and extraced with DCM and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.

Colourless liquid; Yield = 65% (2 steps); $[\alpha]^{25}_D$ = -17.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19-7.22 (m, 2H), 6.96-7.00 (m, 2H), 4.76 (dd, *J* = 4.8 Hz, 7.9 Hz, 1H), 4.17-4.23 (m, 1H), 3.99-4.04 (m, 1H), 2.48 (s, 3H), 1.921-2.01 (m, 2H), 0.84 (s, 9H), -0.01 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.26, 160.82, 144.76, 139.98, 133.14, 129.83, 127.94, 127.35, 127.27, 115.22, 115.00, 70.37, 67.33, 39.94, 25.70, 21.60, 18.01, -4.70, -5.24; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{22}H_{31}FNaO_4SSi$, 461.1594, found 461.1591.

Synthesis of (*S*)-*tert*-butyl(1-(4-fluorophenyl)-3-iodopropoxy)dimeth ylsilane, (12):

To a solution of compound **11** (4.0 g, 10.1 mmol, 1.0 equiv.) in acetone (20 mL), NaI (4.56 g, 30.4 mmol, 3.0 equiv.) was added. The reaction mixture was refluxed for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated to dryness. The residue was diluted with water, extracted with EtOAc and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.9:0.1) as the eluent to afford the desired product.

Colourless liquid; 80% ; $[\alpha]^{25}_D$ = -10.1 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.31 (m, 2H), 7.00-7.05 (m, 2H), 4.74 (dd, *J* = 4.2 Hz, 7.9 Hz, 1H), 3.23-3.29 (m, 1H), 3.13-3.18 (m, 1H), 2.16-2.25 (m, 1H), 2.03-2.11 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.29, 160.85, 140.04, 127.52, 127.44, 115.22, 115.01, 74.09, 44.52, 25.80, 18.11, 2.85, -4.55, -4.81.

Synthesis of (3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-3-((*S*)-3-((*tert*-butyldi methylsilyl)oxy)-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)azetidin -2-one, (13):

To a solution of (*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one (0.7 g, 2.0 mmol, 1.0 equiv.) in dry THF (10 mL) under N_2 atmosphere, was added LDA (1.7 mL, 1.8M in THF/Heptane/ Ethylbenzene, 1.5 equiv.) at -78 ^{o}C and stirred for 1h. To this solution, (*S*)-*tert*-butyl(1-(4-fluorophenyl)-3-iodopropoxy)dimethylsilane (1.6 g, 4.0 mmol, 2.0 equiv.) was added and stirred for another 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH_4Cl. The reaction mixture was extracted with ethyl acetate and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (9.7:0.3) as the eluent to afford the desired product.

Colourless liquid; Yield 48% ; $[\alpha]^{25}_D$ = -10.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.43 (m, 5H), 7.20-7.26 (m, 6H), 6.88-7.00 (m, 6H), 5.04 (s, 2H), 4.64-4.70 (m, 1H), 4.50 (d, *J* = 2.3 Hz, 1H), 3.03-3.07 (m, 1H), 1.75-2.05 (m, 4H), 0.86 (s, 9H), -0.00 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.42, 163.13, 160.70, 160.12, 159.01, 157.71, 140.59, 140.56, 136.69, 133.99, 133.96, 129.82, 128.65, 128.11, 127.48, 127.40, 127.32, 127.17, 118.38, 118.31, 115.87, 115.65, 115.53, 115.10, 114.89, 73.82, 70.12, 60.92, 60.48, 37.80, 25.84, 24.40, 18.18, -4.66, -4.95; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{37}H_{41}F_2NNaO_3Si$, 636.2721, found 636.2719.

Synthesis of (3*R*,4*S*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one, (Ezetimibe, 14):

To a solution of (3*R*,4*S*)-4-(4-(benzyloxy) phenyl)-3-((*S*)-3-(*tert*-butyl dimethylsilyloxy)-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl) azetidin-2-one (0.3 g, 0.5 mmol, 1.0 equiv.) in THF (10 mL) was added TBAF (0.7 mL, 1.0 M solution in THF) and stirred for 2h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated aq. $NaHCO_3$. The reaction mixture was extracted with ethyl acetate and further washed with brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude product which was dissolved in MeOH (10 mL). To this solution Pd/C (0.1 equiv. 10 wt. % loading) was added and hydrogen gas was purged under a pressure of 5 atm in a Parr hydrogenator. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered using celite pad, concentrated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel (60-120 mesh) using a mixture of Hexane/EtOAc (8.0:2.0) as the eluent to afford the desired product.

White Solid; Yield 70%; (2 steps); m.p. = 160-162 ^{o}C; $[\alpha]^{25}_D$ = -27.7 (c 0.15, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.28-7.32 (m, 2H), 7.19-7.23 (m, 4H), 7.09-7.15 (m, 4H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.28 (d, *J* = 4.5 Hz, 1H), 4.80 (d, *J* = 2.3 Hz, 1H), 4.47-4.51 (m, 1H), 3.06-3.08 (m, 1H), 1.67-1.86 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.82, 162.71, 160.31, 159.69, 157.89, 157.30, 142.63, 142.60, 134.48, 134.46, 128.37, 128.01, 127.95, 118.75, 118.68, 116.39, 116.19, 115.23, 115.02, 71.53, 60.07, 59.88, 36.84, 24.99; ESI-HRMS (m/z): $[M+Na]^+$ calculated for $C_{24}H_{21}F_2NNaO_3$, 432.1387, found 432.1384.

Acknowledgements

Research funding from the Department of Science and Technology, Government of India, and a research fellowship to S.G. from the University Grants Commission (UGC-RGNF), are gratefully acknowledged.

Keywords: *β*-lactam • chiral auxiliary • asymmetric synthesis • ezetimibe • $TiCl_4$

Supporting Information

Crystallographic data for the compound **6e** has been deposited with the Cambridge Crystallographic Data Centre, CCDC No.

1495549. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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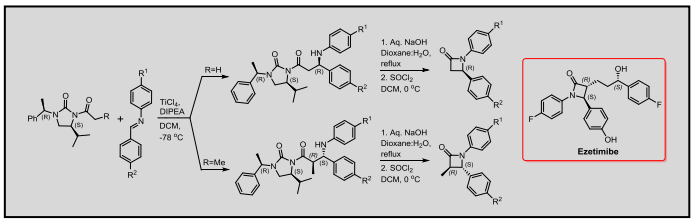

(*S*)-4-Isopropyl-1-((*R*)-1-phenylethyl)imidazolidin-2-one mediated asymmetric Mannich-type reactions are described. The adducts were conveniently transformed to β-lactams.