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A concise enantioselective synthesis of L-(−)-733,061 and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate using catalytic enantioselective aza-Henry reaction as key step

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ABSTRACT

An efficient enantioselective synthesis of L-(−)-733,061 and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate is accomplished by means of catalytic enantioselective aza-Henry reaction. A key feature of this protocol is organocatalysis as genesis of chirality to ensure high degree of distereo- and enantiocontrol.

1. Introduction

Piperidine motif containing alkaloids are medicinally significant owing to their anaesthetic, analgesic and antibiotic activity.[1] In general, substituted piperidines are becoming progressively more important because of their distinctive biological activities, such as neurokinin-1 (NK-1) receptor antagonist and as a glycosidase inhibitors.[2] Recently, potential therapeutic value was recognized for substituted piperidines, for instance, in (2*R*,3*R*)-3-hydroxypipecolic acid, febrifugine, (+)-*epi*-deoxoprosopinine and (−)-cassine molecules[3] (Fig. 1).

The successful methods that provide enantioselective routes to chiral substituted piperidine derivatives are based on the chiral pool, especially aminoacids; the use of the reagent that utilize chiral catalyst and chiral auxiliaries.[4] It was pragmatic that chiral functional group variation on piperidine ring is expected to generate distinctive properties, that enhance the therapeutic potential of the compounds for the treatment of diseases.

With this initiative, and our continued interest in developing catalytic routes to bioactive small molecules,[5] we have embarked on a program to synthesize L-(−)-733061 **1**, synthetic variants of chiral piperidine derivatives, such as (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2**, and their C3 epimers, **1a** and **2a**. Further, we are interested to evaluate their biological activities based on functional modifications (Fig. 2).

2. Results and discussion

Herein, we report a highly practical and organocatalyzed enantioselective synthetic route to L-(−)-733060 **1**, (2*S*,3*S*)-methyl

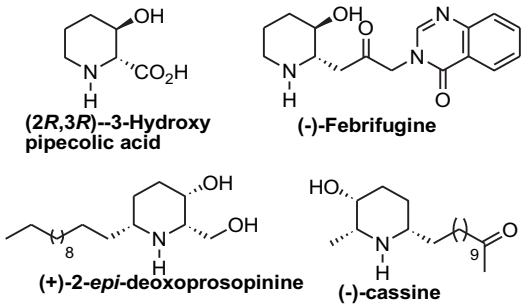

Fig. 1. Substituted piperidine motif molecules.

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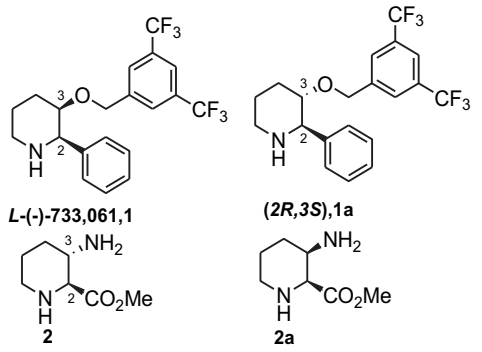
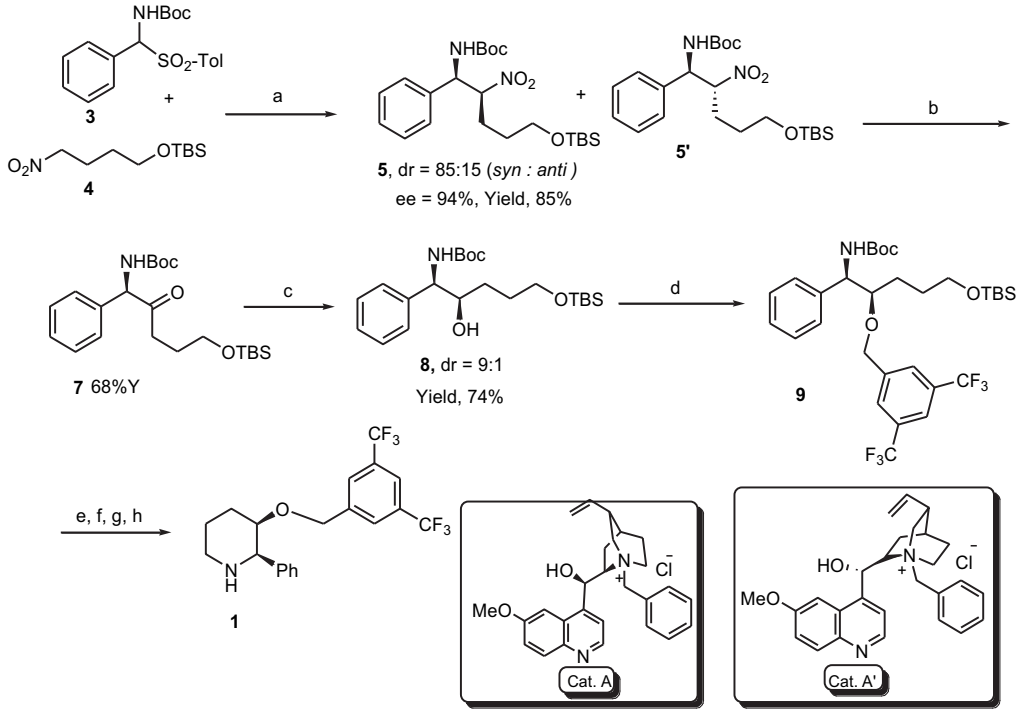


Fig. 2. Synthetic variants of chiral substituted piperidine derivatives.

the presence of 15 mol % of **Cat A′** under identical conditions led to the complete racemic mixture of the expected product.

Thus, oxidation of nitro functionality **5** by Gissot's protocol ($NaNO_2$ (6 equiv),[7] DMF/H_2O (7:1; 0.4 M), 45 °C, 12 h)[7] led to keto compound **7** in 68% yield. Then, the amino ketone **7** was reduced with $NaBH_4$ under Luche's conditions ($CeCl_3 \cdot 7H_2O$, CH_2Cl_2/EtOH [1:1]) furnished a *syn*-selective (dr=9:1) secondary alcohol **8** (74%). The secondary alcohol **8** was protected with 3,5-bistriflouromethyl benzyl bromide under basic conditions resulted in a separable pure *syn*-isomer **9** (74% yield) and then following deprotection of TBS (TBAF, THF, 0 °C, 3 h) led to a primary alcohol in 80% yield. Mesylation of primary alcohol followed removal of *N*-Boc group with TFA results TFA salt. Then, cyclization under basic condition (Et_3N, MeOH, 2 h, 60 °C) resulted in the desired compound **1** in 65% isolated yield (over three steps).[10] The spectral and analytical data of **1**[4j], **1a**[4f,g] were in full agreement with that reported data, **1** $[\alpha]_D^{25}$ −32.56 (*c* 0.60, $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ +34.29 (*c* 0.99, $CHCl_3$)} (Scheme 1).

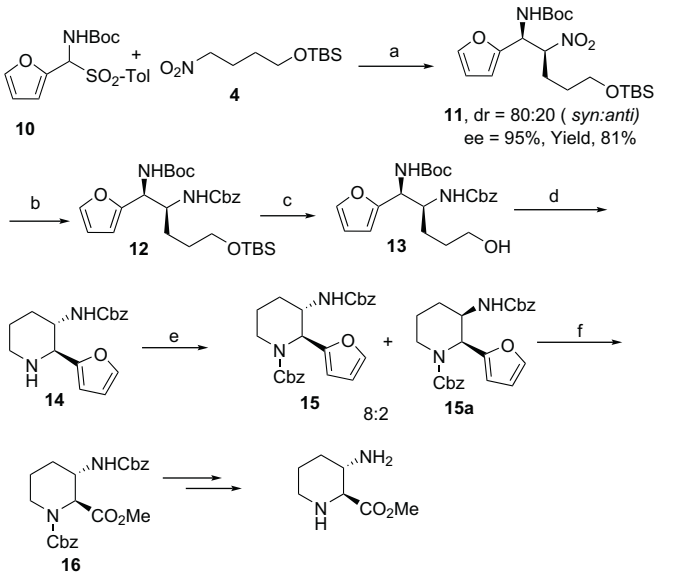


Scheme 1. (a) **Cat A** (15 mol %), CsOH H_2O (1.3 equiv), toluene (0.8 M), −55 °C, 44 h; (b) $NaNO_2$ (6 equiv), DMF/H_2O (7:1), 45 °C, 12 h; (c) $NaBH_4$, $CeCl_3$ $7H_2O$, −78 °C to −40 °C; (d) (i) NaH, TBAI, THF, (ii) 3,5-bis trifluromethyl benzyl bromide, 12 h, rt; (e) TBAF, 0 °C, THF; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (g) TFA, CH_2Cl_2; (h) Et_3N, MeOH, 2 h, 60 °C.

3-aminopiperidine-2-carboxylate **2** and stereoisomer **2a**. In principle, the stereogenic centers at C2 and C3 in L-(−)-733061 **1**, and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2** could be accessed through a catalytic *syn*-selective aza-Henry reaction with high degrees of diastereo- and enantioselectivity using *N*-Boc-sulfone **3**, **10** and nitro compound **4**. To this end, we have appraised the recently reported Palomo-reaction[6] conditions for this transformation. Accordingly, the reaction of *N*-Boc-sulfone **3** with nitro compound **4** employing phase transfer catalyst 15 mol % of **Cat A** in toluene at −55 °C for 44 h resulted in the anticipated product **5** in 85% yield with 85:15 diastereomeric ratio in favour of *syn* isomer. The ee of major *syn* isomer **5** estimated by chiral HPLC analysis in comparison with a racemic mixture and was found to be 94% [corresponding TBS deprotected alcohol **6**, Chiralpak AD-H, 210 nm, flow rate=1 mL/min, *n*-hexane/EtOH (85:15)[6c]]. The absolute stereochemistry of major diastereomer **5** was assigned by analogy.[6] It was anticipated that the use of complementary sense **Cat A′**, i.e., quinidine salt would generate the *anti*-selective diastereomer **5′**. Nevertheless, subjecting *N*-Boc-sulfone **3** and nitro compound **4** in

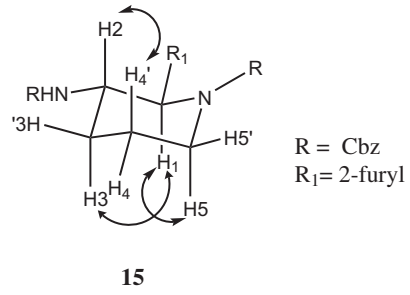
En route to the synthesis of L-(−)-733,061, we have also considered the synthesis of chiral substituted piperidine derivatives, (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2**, and stereoisomer **2a** (Scheme 2). Consequently, the reaction of *N*-Boc-sulfone **10** with nitro compound **4** in the presence of **Cat A** (15 mol %) in toluene at −50 °C for 44 h resulted in the desired product **11** in 81% yield with 80:20 diastereomeric ratio in favour of *syn* isomer with 92% ee. The ee was assessed by chiral HPLC analysis using corresponding racemic mixture [Chiralpak AD-H, 220 nm, flow rate=0.5 mL/min, *n*-hexane/2-propanol (95:5)]. The absolute stereochemistry of major diastereomer **11** was assigned by analogy.[6]

Reduction of **11** with sodium borohydride in the presence of $NiCl_2 \cdot 6H_2O$ (−5 °C, MeOH, 15 min) led to amine, which on protection with CbzCl under basic conditions afforded **12** in 78% yield. Exposure of **12** to TBAF in THF at ambient temperature led to desilylation, and resulting primary alcohol was then converted to mesylate **13** under basic conditions. Deprotection of *N*-Boc under acidic conditions (TFA in CH_2Cl_2) followed by cyclization using Et_3N/MeOH at ambient temperature led to **14** (65%). Subsequent



Scheme 2. (a) **Cat A** (15 mol %), CsOH H_2O (1.3 equiv), toluene (0.8 M), −55 °C, 44 h; (b) (i) $NiCl_2$ $6H_2O$, $NaBH_4$, MeOH, (ii) CbzCl, $NaHCO_3$, MeOH; (c) (i) TBAF, THF, rt, (ii) $MeSO_2Cl$, Et_3N, 30 min, (iii) TFA, 0 °C, 2 h CH_2Cl_2; (d) Et_3N, MeOH, 3 h, 90 °C; (e) CbzCl, $NaHCO_3$, MeOH; (f) (i) $RuCl_3 \times H_2O$ (2 mol %), $NaIO_4$, EtOAc/CH_3CN/H_2O, (ii) CH_2N_2, Et_2O.

secondary amine protection with CbzCl furnished **15** and **15a** as separable diastereomeric mixture. The major diastereomer **15** was separated by column chromatography (silica gel) and the relative stereochemistry was determined by 2DNMR experiment by using NOESY and DQFCOSY.



15

Fig. 3. *Noe* correlation of **15**.

The significant NOE correlations are shown in Fig. 3. In the major diastereomer **15**, observation of strong NOE between H1−H3, H1−H5 and H2−H4′ confirms that they are spatially closer and hence considered to be the H1−H2 are in a *trans*-relationship (J_{H1-H2}=8.7 Hz).

The oxidative cleavage of furyl moiety of **15** ($RuCl_3$, $NaIO_4$),[9] followed by esterification of resulting acid (CH_2N_2, Et_2O) provided **16** (62%), which on then hydrogenation under balloon pressure (10% Pd−C/H_2) resulted in the desired diamino compound **2** in 85% yield. The analytical data is in agreement with proposed structure. The minor diastereomer **15a** was also subjected to oxidation/esterification and hydrogenation (vide infra) led to **2a** in 83% yield (Scheme 2). As logical extension, further, in an effort to synthesize (2*S*,3*S*)-3-hydroxy pipecolicacid using similar strategy was failed.[8]

3. Conclusions

A highly practical, organocatalyzed enantioselective synthesis of L-(−)-733061 **1** and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2** has been accomplished. The salient feature of this protocol is that two stereo centers are delivered with high degree of diastereo- and enantioselectivity in single operation by means of a catalytic enantioselective aza-Henry reaction. Further work is under progress for the synthesis of chiral hetero-analogues of piperidine moiety.

4. Experimental

4.1. General information

Starting materials: DCM was distilled from P_2O_5, THF from sodium benzophenone ketyl. All other chemicals used were commercially available. All reactions were conducted under an atmosphere of nitrogen (IOLAR Grade I). Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F-254 precoated. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. Column chromatography was carried out with silica gel grade 60−120 and 100−200 mesh. ^1H NMR spectra were recorded at 300, 400 and 500 MHz and ^{13}C NMR 75 and 125 MHz in $CDCl_3$. *J* values were recorded in hertz and abbreviations used were s-singlet, d-doublet, m-multiplet, br-broad. Chemical shifts (δ) are reported relative to TMS (δ=0.0) as an internal standard. IR spectra were recorded on Thermo Nicolet FT/IR-5700. Mass spectral data were compiled using MS (ESI), HRMS data obtained using quadrupole time-of-flight (QTOF) mass spectrometer (QSTAR XL, Applied Biosystems MDS Sciex, Foster City, USA). Optical rotations were recorded on HORIBA high sensitive polarimeter with 10 mm cell. Concentration of the samples was expressed as g/mL×100. HPLC was carried on a Shimadzu LC-10ATvp dual pump system.

*4.1.1. tert-Butyl (1R,2S)-5-(tert-butyldimethylsilyloxy)-2-nitro-1-phenylpentylcarbamate (**5**).* To a mixture of *N*-Boc sulfone **3** (1.81 g, 5 mmol), and **Cat A** (0.342 g, 0.75 mmol) in anhydrous toluene (0.8 M) at −55 °C were added **4** (5.13 g, 25 mmol) and CsOH.H_2O (1.09 g, 6.5 mmol) successively under inert atmosphere. The resulting reaction mixture was stirred vigorously for 40 h at −55 °C. Then, it was quenched with 0.1 N HCl (20 mL), and the reaction mixture was slowly allowed to warm to ambient temperature. The aqueous layer was extracted with $CHCl_3$ (3×20 mL), washed with brine (2×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and contents were evaporated under reduced pressure. The crude residue was purified over silica gel column chromatography with hexane/EtOAc (9:1) as eluent to afford **5** as semi solid (1.86 g, 85%). The dr and ee were determined by HPLC using chiral AD-H of corresponding primary alcohol (220 nm, 95:5 hexane/IPA, 0.5 mL/min). The dr of *syn*/*anti* was found to be 85:15 and the major *syn* isomer ee was 95%. $[\alpha]_D^{25}$ −16.8 (*c* 1.5, $CHCl_3$); R_f (20% EtOAc/Hex) 0.60; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28−7.12 (m, 5H, ArH), 5.61 (d, *J*=9.8 MHz, 1H, NHCO), 5.08−4.97 (dd, *J*=6.8, 9.8 MHz, 1H, CHNH), 4.83−4.70 (m, 1H, CHNO), 3.61−3.44 (m, 2H, CHOSi), 1.91−1.73 (m, 2H, CHNO), 1.56−1.42 (m, 2H, $CHCH_2$), 1.35 (s, 9H, *t*-Bu), 0.76 (s, 9H, *t*-Bu), −0.54 (d, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1, 137.6, 128.9, 128.3, 126.2, 92.0, 61.6, 56.0, 28.5 and −5.4; IR (neat): 2923, 2854, 2362, 1695, 1518, 1460, 1263 cm^{-1}; ESIMS: 461 $(M+Na)^+$; HRMS calcd for $C_{22}H_{38}N_2O_5NaSi$ 461.2447 and found 461.2428.

*4.1.2. tert-Butyl(1R,2S)-5-hydroxy-2-nitro-1-phenylpentylcarbamate (**6**).* To the solution of **5** (1.38 g, 3.1 mmol) in THF (10 mL) was added TBAF (6.0 mL, 6 mmol, 1 M in THF) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Then, it was quenched with an aqueous solution of NH_4Cl (5 mL) and aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified with silica gel column chromatography with hexane/EtOAc (6:4) as eluent to

afford **6** as white solid (0.85 g, 83%). Mp 152–153. The dr and ee were determined by HPLC analysis (Chiralpak AD-H, 85/15 hexane/EtOH, 1.0 mL/min, 210 nm). The dr of *syn*/*anti* was found to be 85:15. The major diastereomer was determined to have 94% ee by chiral HPLC analysis t_R (major)=5.92 min, t_R (minor)=7.92 min; and the minor diastereomer was determined to have 86% ee under the same HPLC analysis conditions: t_R (major)=16.1 min, t_R (minor)=17.5 min; $[\alpha]_D^{25}$ −3.95 (*c* 2.10, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +3.72 (*c* 1.50, $CHCl_3$)); R_f (60% EtOAc/hexane) 0.45; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ 7.36–7.20 (m, 5H, ArH), 5.78 (d, *J*=6.8 Hz, 1H, NHCO), 5.22–4.88 (m, 2H, NHCH, NOCH), 3.70–3.58 (m, 2H, CHOSi), 2.05–1.88 (m, 2H, CHNO), 1.69–1.53 (m, 2H, $CHCH_2$), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.1, 137.6, 128.9, 128.3, 126.2, 92.0, 82.2, 61.6, 56.0, 28.5, 28.1, 26.4; IR (neat): 2975, 1690, 1549, 1499, 1365, 1250, 1164 cm^{-1}; ESIMS: 347 $(M+Na)^+$; HRMS calcd for $C_{16}H_{24}N_2O_5Na$ 347.1582, found 347.1593.

*4.1.3. (R)-tert-Butyl 5-(tert-butyldimethylsilyloxy)-2-oxo-1-phenylpentylcarbamate (**7**).* To the stirred solution of **5** (1.8 g, 4.1 mmol) in DMF/H_2O (7:1, 0.4 M) was added solid $NaNO_2$ (1.70 g, 24.6 mmol) at room temperature. The resulting reaction mixture was heated to 45 °C for 12 h. Then, it was quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic extracts were washed water (2×10 mL) and brine (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography with hexane/EtOAc (9:1) as eluent to afford **7** (1.14 g, 68%) as semi yellow solid $[\alpha]_D^{25}$ −9.65 (*c* 1.2, $CHCl_3$); R_f (20% EtOAc/Hex) 0.70; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.25 (m, 5H, ArH), 5.83 (d, *J*=3.9 Hz, 1H, NHCO), 5.22 (d, *J*=5.6 Hz, 1H, NHCH), 3.53–3.44 (m, 2H, CHOSi), 2.49–2.33 (m, 2H, COCH), 1.77–1.60 (m, 2H, $CHCH_2$), 1.39 (s, 9H, *t*-Bu), 0.82 (s, 9H, *t*-Bu), −0.04 (s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.3, 154.9, 137.6, 129.0, 128.3, 126.3, 61.8, 56.3, 29.3, 28.6, 28.2, 25.8, 18.2, −5.0; IR (neat): 2928, 2857, 1710, 1695, 1551, 1495, 1363, 1250, 1165, 1097 cm^{-1}; ESIMS: 430 $(M+Na)^+$; HRMS calcd for $C_{22}H_{37}NO_4SiNa$ 430.2389, found 430.2385.

*4.1.4. tert-Butyl (1R,2R)-5-(tert-butyldimethylsilyloxy)-2-hydroxy-1-phenylpentylcarbamate (**8**).* To the stirred solution of keto compound **6** (1.1 g, 2.70 mmol) in EtOH/CH_2Cl_2 (1:1, 10 mL) was added $CeCl_3\cdot 6H_2O$ (1.0 g, 2.7 mmol) at room temperature. Then, the resulting suspension was cooled to −78 °C followed by addition of $NaBH_4$ (0.12, 3.24 mmol) under nitrogen atmosphere. Stirring was continued for 5 h at −78 °C and for 2 h at −40 °C. The reaction mixture was quenched with saturated NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL), and the combined organic extracts were washed with brine (2×10 mL). The organic contents were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with hexane/EtOAc (7:3), furnished alcohol **8** (0.82 g, 74%) as a dense liquid $[\alpha]_D^{25}$ −28.65 (*c* 1.5, $CHCl_3$); R_f (30% EtOAc/Hex) 0.40; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.18 (m, 5H, ArH), 5.47 (d, *J*=8.3 Hz, 1H, NHCO), 4.54 (br s, 1H, CHNH), 3.89–3.82 (m, 1H, CHOH), 3.66–3.49 (m, 2H, CHOSi), 2.89 (br s, 1H, OHCH), 1.66–1.58 (m, 4H, $CHCH_2$, CHOH), 1.39 (s, 9H, *t*-Bu), 0.82 (s, 9H, *t*-Bu), 0.01(s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.4, 144.5, 128.2, 127.9, 127.4, 73.8, 63.2, 31.5, 29.7, 29.2, 28.3, 18.2, −5.5; IR (neat): 3438, 2925, 2855, 2362, 1693, 1497, 1463, 1366, 1251, 1169, 1095 cm^{-1}; ESIMS: 410 $(M+1)^+$; HRMS calcd for $C_{22}H_{39}NO_4Si$ 410.2726, found 410.2741.

*4.1.5. tert-Butyl (1R,2R)-2-(3,5-bis(trifluoromethyl)benzyloxy)-5-(tert-butyldimethylsilyloxy)-1-phenylpentylcarbamate (**9**).* To a DMF solution containing **8** (0.63 g, 1.54 mmol), 3,5-$(CF_3)_2C_6H_3CH_2Br$ (0.945 g, 3.08 mmol) and TBAI (0.56 g, 1.54 mmol) was cooled to 0 °C under nitrogen atmosphere. To this, NaH (70 mg, 60% dispersion in mineral oil, 1.54 mmol) was added in two portions over 5 min, and stirring was continued for 30 min. Then, the reaction mixture was quenched with aqueous NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with water (2×10 mL) followed by brine solution (1×15 mL) and dried over anhydrous Na_2SO_4. Filtered the solids and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (9:1) to afford **9** (0.61 g, 70%) as a semi solid (*syn*/*anti*, **9**:**9a**, 9:1); **9**; $[\alpha]_D^{25}$ −16.62 (*c* 0.8, $CHCl_3$); R_f (20% EtOAc/Hex) 0.65; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.81 (s, 1H, ArH), 7.53 (br d, 2H, ArH), 7.24–7.19 (m, 5H, ArH), 5.17 (d, *J*=8.4 Hz, 1H, NHCO), 4.73 (s, 2H, CHAr), 4.61 (t, *J*=5.4 Hz, 1H, CHNH), 4.33 (d, *J*=12.2 Hz, 1H, CHOAr), 3.65–3.53 (m, 2H, CHOSi), 1.79–1.69 (m, 2H, CHCH), 1.63–1.52 (m, 2H, $CHCH_2$), 1.38 (s, 9H, *t*-Bu), 0.83 (s, 9H, *t*-Bu), 0.02(s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.3, 141.1, 138.9, 131.7, 131.5, 128.4, 127.5, 127.4, 121.4 (q), 82.5, 70.5, 62.7, 56.2, 29.7, 28.9, 28.2, 26.6, 25.9, −5.4; IR (neat): 2956, 2862, 1703, 1498, 1364, 1279, 1133 cm^{-1}; ESIMS: 658 $(M+Na)^+$; HRMS calcd for $C_{31}H_{43}F_6NO_4NaSi$ 658.2658, found 658.2662; **9a** (0.068 g); $[\alpha]_D^{25}$ +18.50 (*c* 0.8, $CHCl_3$); R_f (20% EtOAc/Hex) 0.60; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (s, 1H, ArH), 7.70 (br s, 2H, ArH), 7.35–7.22 (m, 5H, ArH), 5.15 (d, *J*=8.6 Hz, 1H, NHCO), 4.92 (br s, 1H, CHNH), 4.65 (q, *J*=8.8 Hz, 2H, CHOAr), 3.70 (br d, *J*=3.3 Hz, 1H, CHNH), 3.58–3.48 (m, 2H, CHOSi), 1.78–1.43 (m, 4H, $CHCH_2$, CHOH), 1.39 (s, 9H, *t*-Bu), 0.83 (s, 9H, *t*-Bu), −0.03 (s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.5, 135.5, 128.4, 127.8, 127.5, 127.4, 127.1, 126.2, 122.4 (q), 83.8, 71.1, 62.8, 56.3, 29.6, 28.9, 28.3, 25.9, 22.6, −5.3; IR (neat): 2953, 2860, 1702, 1496, 1368, 1276, 1132 cm^{-1}; ESIMS: 658 $(M+Na)^+$; HRMS calcd for $C_{31}H_{43}F_6NO_4NaSi$ 658.2763, found 658.2738.

*4.1.6. (2R,3R)-3-(3,5-Bis(trifluoromethyl)benzyloxy)-2-phenylpiperidine (**1**).* To a solution of **8** (0.31 g, 0.5 mmol) in THF was added TBAF (2.0 mL, 2.0 mmol 1 M in THF) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was quenched with aqueous NH_4Cl (10 mL), aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To a cooled (0 °C) solution of the above crude alcohol (0.20 g, 0.4 mmol) and Et_3N (0.4 g, 0.4 mmol) in CH_2Cl_2 (10 mL) was added drop wise MsCl (0.50 g, 0.4 mmol), and the mixture was stirred at 0 °C for 30 min, diluted with Et_2O (30 mL) and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over (Na_2SO_4), filtered and concentrated under reduced pressure. The resultant crude product dissolved in CH_2Cl_2, and to this added TFA (0.58 g, 2.6 mmol) via syringe. The resulting reaction mixture was stirred for 3 h. Then, the reaction mixture was concentrated under reduced pressure led to the crude TFA salt, which was again dissolved in dry MeOH (10 mL). To this stirred solution, Et_3N (0.21 g, 2.0 mmol) was added slowly and refluxed for 2 h at 60 °C. The solvent was removed under reduced pressure; the crude residue was purified by silica gel column chromatography using $CHCl_3$/MeOH (85:15) as eluent gave to **1** (0.11 g, 65%) as light brown liquid; $[\alpha]_D^{26}$ −32.56 (*c* 0.60, $CHCl_3$); R_f (10% EtOAc/MeOH) 0.50; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (br s, 1H, ArH), 7.42 (br d, *J*=5.8 Hz, 2H, ArH), 7.41–7.28 (m, 5H, ArH), 4.52(d, *J*=12.8 Hz, 1H, OCH_AH_B), 4.11(d, *J*=12.8 Hz, 1H, CH_ACH), 3.83 (br s, 1H, H-2), 3.68 (s, 1H, H-2), 3.26 (m, 1H, H-6), 2.85 (td, *J*=3.2, 12.8 Hz, 1H, H-6), 2.22 (br d, *J*=13.2 Hz, 1H, H-4), 1.95 (br s, 1H, CH), 1.88–1.75 (qt, *J*=4.3, 13.2 Hz, 1H, H-5), 1.64–1.48 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz): 141.4, 141.2, 131.3 (q, *J*=33.3 Hz), 128.1, 127.4, 127.1, 126.7, 123.2 (q, *J*=272.6 Hz), 121.3 (quint), 77.4, 70.0, 64.6, 46.8, 28.2, 20.2: IR ($CHCl_3$) 2924, 2855, 1734, 1694, 1461, 1278, 1175, 1138 cm^{-1}; ESIMS *m*/*z* 404.1 $(M+H)^+$; HR-ESI-MS *m*/*z* calcd for $C_{20}H_{20}F_6NO$ $(M+H)^+$ 404.1449, found 404.1429; **1a**; $[\alpha]_D^{26}$ +38.45 (*c* 0.40, $CHCl_3$); a light yellow liquid (0.012 g); R_f (10% EtOAc/MeOH)

0.45; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H, ArH), 7.45–7.29 (m, 7H, ArH), 4.45 (d, J=12.1 Hz, 1H, $OCHCH_B$), 4.07 (d, J=12.1 Hz, 1H, OCH_ACH), 3.52 (d, J=9.1 Hz, 1H, H-2), 3.43–3.35 (dt, J=4.5, 10.6 Hz, 1H, H-2), 3.13–3.01 (m, 1H, H-6), 2.77–2.66 (td, J=1.8, 11.3 Hz, 1H, H-6), 2.36–2.26 (dd, J=3.0, 12.1 Hz, 1H, H-4), 1.98 (br s, 1H, CH), 1.88–1.79 (m, 1H, H-5), 1.77–1.66 (m, 1H, H-5), 1.54–1.41 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.2, 141.8141.1, 128.3127.9, 127.5, 127.3 (q), 121.2 (quint), 81.4, 70.0, 67.7, 46.7, 31.9, 31.4, 29.7, 25.0; IR (neat): 2918, 2852, 1732, 1689, 1466, 1274, 1172, 1135 cm^{-1}; ESIMS m/z 404.1 $(M+H)^+$; HR-ESI-MS m/z calcd for $C_{20}H_{20}F_6NO$, 404.1327 and found 404.1338.

*4.1.7. tert-Butyl (1S,2S)-5-(tert-butyldimethylsilyloxy)-1-(furan-2-yl)-2-nitropentylcarbamate(**11**).* To the stirred solution of *N*-Boc-sulfone **10** (1.75 g, 5 mmol), **Cat A** (0.342 g, 0.75 mmol) in dry toluene (0.8 M) was added nitro compound **3** (5.13 g, 25 mmol) and CsOH H_2O (1.09 g, 6.5 mmol) sequentially under inert atmosphere at −55 °C. The reaction mixture was stirred vigorously for 40 h and thereafter, quenched with 0.1 N HCl (20 mL). The resulting reaction mixture was slowly warmed to ambient temperature. The aqueous layer was extracted with $CHCl_3$ (3×20 mL), washed with brine (2×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography with hexanes/EtOAc (9:1) as eluent afforded **11** (1.72 g, 81%) as an oily liquid. The dr and er were determined by HPLC using chiral AD-H (220 nm, hexane/IPA (95:5), 0.5 mL/min). The dr is 80:20 (*syn*/*anti*) and the major diastereomer was determined to have 92% ee by chiral HPLC analysis t_R (major)=11.32 min, t_R (minor)=12.27 min; and the minor diastereomer was determined to have 99% ee under the same HPLC analysis conditions: t_R (minor)=13.79 min, t_R (major)=16.25 min; $[\alpha]_D^{25}$ −13.6 (*c* 1.6, $CHCl_3$); R_f (10% EtOAc/hexane) 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (s, 1H, ArH), 6.28–6.27 (dd, J=1.8, 3.0 Hz, 1H, ArH), 6.24–6.21 (m, 1H, ArH), 5.43 (d, 1H, NHCO), 5.24–5.16 (d, J=7.8 Hz, 1H, CHNH), 4.81–4.76 (m, 1H, CHNO), 3.66–3.54 (m, 2H, CHOSi), 2.10–2.00 (m, 1H, CHCHN), 1.99–1.89 (m, 1H, CHCH), 1.58–1.48 (m, 2H, CHCH), 1.42 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*-Bu), 0.01 (s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.4, 111.5, 108.4, 107.8, 90.0, 62.6, 52.0, 28.8, 28.4, 27.3, 26.7, 26.2, 18.9 and −05.4; IR (neat): 3417, 2925, 2855, 1695, 1456, 1371, 1277, 1172, 1129 cm^{-1}; ESIMS: 451 (M+Na); HRMS calcd for $C_{20}H_{36}N_2O_6Si$ 451.1449, found 451.1429.

*4.1.8. tert-Butyl(1S,2S)-5-(tert-butyldimethylsilyloxy)-1-(furan-2′-yl)-2-Cbz-aminopentylcarbamate (**12**).* The nitro compound **11** (1.50 g, 3.5 mmol) and $NiCl_2\cdot 6H_2O$ (0.83 g, 3.5 mmol) were dissolved in dry MeOH (15 mL) and cooled to −5 °C. To this, $NaBH_4$ (0.65 g, 17.5 mmol) was added portion wise over a period of 10 min. The resulting reaction mixture was stirred for 15 min at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (10 mL). To this biphasic reaction mixture CbzCl (1.53 mL, 4.5 mmol 50% w/v in toluene) was added, and stirred for 3 h at room temperature. The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layer washed with brine and dried over anhydrous $NaSO_4$. The organic layers were filtered and evaporated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography with hexane/acetone (7:3) to afford **12** (1.45 g, 78%) as semi solid; $[\alpha]_D^{25}$ −36.00 (*c* 1.5, $CHCl_3$); R_f (30% acetone/hexane) 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54–7.43 (m, 6H, ArH), 6.50–6.45 (d, J=5.5 Hz, 1H, ArH), 6.43–6.37 (d, J=7.7 Hz, 1H, ArH), 5.56 (d, J=8.8 Hz, 1H, NHCO), 5.27 (d, J=7.7 Hz, 1H, CHNH), 4.89–4.83 (d, J=8.8 Hz, 2H, CHOCN), 4.27–4.15 (m, 1H, CHNH), 3.79–3.67 (m, 2H, CHOSi), 1.80–1.66 (m, 2H, CHCH), 1.63–1.58 (m, 2H, $CHCH_2$), 1.55 (s, 9H, *t*-Bu), 1.02 (s, 9H, *t*-Bu), 0.16 (s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.2, 155.8, 152.2, 142.1, 136.5, 128.4, 128.1, 128.0, 110.2, 107.3, 79.8, 66.9, 66.7, 62.4, 55.4, 52.7, 29.1, 28.7, 28.3, 25.9 and −05.4; IR (neat): 2931, 2362, 1693, 1518, 1247, 1166, 1096 cm^{-1}; ESIMS: 555 $(M+Na)^+$; HRMS calcd for $C_{28}H_{44}N_2O_6NaSi$ 555.2866, found 555.2859.

*4.1.9. tert-Butyl(1S,2S)-5-1-(furan-2′-yl)-2-Cbz-aminopentylcarbamate (**13**).* To the stirred solution of TBS ether **12** (1.33 g, 2.5 mmol) was added TBAF solution (4 mL, 4 mmol, 1 M in THF) via syringe in dry THF at 0 °C. The resulting reaction mixture was stirred at room temperature. After 2 h, the reaction was quenched with saturated ammonium chloride (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using acetone/hexane (6:4) as eluent to give deprotected alcohol as a white solid (0.84 g, 80%); $[\alpha]_D^{25}$ −20.50 (*c* 1.0, $CHCl_3$); R_f (60% acetone/hexane) 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.25 (m, 6H, ArH), 6.28 (d, J=1.7 Hz, 1H, ArH), 6.21 (d, J=2.8 Hz, 1H, ArH), 5.38 (d, J=9.6 Hz, 1H, NHCO), 5.32 (d, J=8.5 Hz, 1H, NHCO), 5.20 (d, J=7.7 Hz, 1H, CHNH), 4.86–4.79 (d, J=8.4 Hz, 2H, CHOCN), 4.16–4.03 (m, 1H, CHNH), 3.67–3.52 (m, 2H, CHOSi), 2.07–1.66 (m, 2H, CHCH), 1.65–1.48 (m, 2H, $CHCH_2$), 1.42 (s, 1H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.6, 155.0, 142.1, 128.4, 128.3, 128.0, 127.9, 110.3, 107.9, 96.1, 66.8, 61.9, 62.1, 54.1, 51.9, 28.7, 28.5, 26.6; IR (neat): 2932, 2362, 1690, 1518, 1241, 1163 cm^{-1}; ESIMS: 441 $(M+Na)^+$; HRMS calcd for $C_{22}H_{30}N_2O_6Na$ 441.2001, found 441.2013.

*4.1.10. Benzyl (2S,3S)-2-(furan-2′-yl)piperidin-3-ylcarbamate (**14**).* To the stirred solution of above deprotected alcohol (0.80 g, 1.92 mmol) in CH_2Cl_2 was added Et_3N (0.192 g, 1.93 mmol) followed by $MeSO_2Cl$ (0.22 g, 1.93 mmol) at 0 °C. The reaction mixture was stirred for 15 min and then quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant crude product dissolved in CH_2Cl_2, and was added TFA (0.58 g, 5.1 mmol) via syringe. The resulting reaction mixture was stirred for 3 h. Then, the reaction mixture was concentrated under reduced pressure led to the crude TFA salt, which was again dissolved in dry MeOH (10 mL). To this stirred solution, Et_3N (0.34 g, 3.4 mmol) was added slowly and refluxed for 3 h at 90 °C. The solvent were removed under reduced pressure; the crude residue was purified by silica gel column chromatography using $CHCl_3$/MeOH (85:15) as eluent gave a yellow liquid (0.36 g, 65%) (over three steps); $[\alpha]_D^{25}$ −62.4 (*c* 1.2, MeOH); R_f (10% EtOAc/MeOH) 0.60; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 7.35–7.20 (m, 5H, ArH), 6.23 (dd, J=1.8, 3.0 Hz, 1H, ArH), 6.12(d, J=3.0 Hz, ArH), 5.65 (d, J=8.8 Hz, 1H, NHCO), 5.01(d, J=6.8 Hz, 2H), 4.96 (d, J=9.8 Hz, 1H, CH_ACH_B), 4.11 (d, J=6.0 Hz, 1H, CH_BNH), 3.13 (m, 1H, H-1), 2.92–2.73 (m, H-2), 2.57 (br s, 1H, NH), 1.82–1.48 (m, 4H, H-3, H-4, H-5, H-6); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz): δ 160.6, 142.6, 128.4, 127.9, 127.7, 119.1, 110.6, 66.1, 49.3, 47.6, 30.6, 29.5, 21.3; IR (neat): 2924, 2856, 2362, 1694, 1249, 1153 cm^{-1}; ESIMS: 301 $(M+1)^+$; HRMS calcd for $C_{17}H_{21}N_2O_3$ 301.1522 and found 301.1566.

*4.1.11. (2S,3S)Benzyl 3-(benzyloxycarbonylamino)-2-(furan-2′-yl)piperidine-1-carbamate (**15**).* To a stirred methanol solution (5 mL, 0 °C) of secondary amine **14** (0.35 g, 1.2 mmol) were added $NaHCO_3$ (0.26 g, 3 mmol) and benzyl chloroformate (0.64 mL, 1.2 mmol, 50% w/v in toluene) successively. The reaction mixture was allowed to stir for 1 h at same temperature followed by evaporation under reduced pressure resulted in aqueous layer, which was extracted with EtOAc (2×10 mL) and washed with brine (10 mL). The organic extracts were dried over anhydrous $NaSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel (100–200 mesh) column chromatography using acetone/hexane (1:9) as eluent furnished **15** (0.34 g) and **15a** (0.09 g) as

clear liquid; (2*S*,3*S*)-major diastereomer **15**; $[\alpha]_D^{25}$ −29.5 (*c* 1.8, $CHCl_3$); R_f (20% EtOAc/hexane) 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.27 (m, 11H, ArH), 6.30 (s, 1H, ArH), 6.17 (br s, 1H, ARH), 5.59 (d, *J*=5.1 Hz, 1H, NHCO), 5.29–5.02 (m, 3H, NHCO, CHOCNH), 4.76 (d, *J*=9.6 Hz, 1H, CH_ACH_BN), 4.12–3.95 (m, 2H, CH_ACH_BN), 3.09–2.97 (t, *J*=11.8 Hz, 1H, CHCHN), 1.96–1.55 (m, 5H, CHCH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.4, 155.2, 142.4, 128.5, 128.4, 128.2, 127.9, 110.3, 67.4, 66.8, 51.6, 49.8, 39.9, 31.9, 27.2 and 24.2; IR ($CHCl_3$) 2927, 2842, 2349, 1668, 1543, 1456, 1235 cm^{-1}; ESIMS: 457 $(M+Na)^+$; HRMS calcd for $C_{25}H_{26}N_2O_5Na$ 457.1736 and found 457.1732; (2*S*,3*R*)-minor diastereomer **15a** (0.09 g); $[\alpha]_D^{25}$ +18.5 (*c* 1.0, $CHCl_3$); R_f (20% EtOAc/hexane) 0.55; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.28 (m, 13H, ArH), 6.34–6.33 (dd, *J*=1.8, 31 Hz, 1H, ArH), 6.16 (br s, 1H, NHCO), 5.27 (d, *J*=7.73 Hz, 1H, NHCO), 5.16–5.09 (m, 4H, CHOCNH), 4.39 (d, *J*=6.18 Hz, 1H, CH_ACH_BN), 4.08 (dd, *J*=6.1, 11.0 Hz, 1H, CH_ACH_BN), 2.97–2.86 (t, *J*=11.0 Hz, 1H, CHCHN), 1.84–1.55 (m, 5H, CHCH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.5, 151.0, 142.9, 136.3, 128.5, 128.4, 128.2, 128.0, 110.3, 107.5, 67.5, 66.9, 54.4, 46.8, 40.0, 31.9, 29.6, 24.5 and 19.5; IR ($CHCl_3$) 2923, 2854, 2362, 1695, 1518, 1460, 1263 cm^{-1}; ESIMS: 457 $(M+Na)^+$; HRMS calcd for $C_{25}H_{26}N_2O_5Na$ 457.1739 and found 457.1735.

*4.1.12. (2S,3S)-1-Benzyl-2-methoxycarbonyl-3-(benzyloxycarbonyl-amino) piperidinecarbamate (**16**).* To an ice-cold solution of $NaIO_4$ (0.52 g, 2.41 mmol) in EtOAc (2.5 mL), CH_3CN (4.5 mL) and H_2O (2 mL) was added $RuCl_3xH_2O$ (2 mg, 0.007 mol) and stirring continued for 15min at 0 °C. Thereafter, compound **15** (0.15 g, 0.35 mmol) in EtOAc (2 mL) was added and continued stirring for additional 10 min at 0 °C. The resultant reaction mixture was quenched with 10 mL of water and aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (1×10 mL), dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in dry CH_2Cl_2 (15 mL) and benzene (5 mL) solvent mixture at 0 °C. To this, CH_2N_2 in Et_2O (10 mmol) was added. After 3 h of stirring at ambient temperature, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using acetone/hexane (2:8) as eluent gave **16** (0.093 g, 62%) as a colourless syrup. The ^{1}H NMR spectra of **16** indicated 1:1 rotamers as a result of *N*-Cbz and ester functionality; **16**; $[\alpha]_D^{25}$ −7.36 (*c* 1.2, $CHCl_3$); R_f (20% EtOAc/hexane) 0.60; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.27 (m, 10H, ArH), 6.00–5.79 (dd, *J*=8.8 Hz, 1H, NHCO), 5.32–4.97 (m, 4H, CHOCNH), 4.16–3.87 (m, 2H, CH_A,CH_B), 3.69 (s, 3H, −OMe), 2.89–2.60 (m, 1H, CH_BCH), 1.98–1.43 (m, 5H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.4, 155.3, 151.4, 136.1, 128.6, 128.5, 128.3, 127.6, 66.9, 58.9, 52.5, 46.1, 41.4, 41.0, 37.1, 31.9, 29.3 22.7; IR (neat): 2964, 2854, 2362, 1696, 1519, 1423, 1246, 1212 cm^{-1}; ESIMS: 444 $(M+NH_4)^+$; HRMS calcd for $C_{23}H_{26}N_2O_6NH_4$ 444.1739 and found 444.1743; (0.052 g) **16a**; $[\alpha]_D^{25}$ +3.75 (*c* 0.45, $CHCl_3$); R_f (20% EtOAc/hexane) 0.65; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.27 (m, 10H, ArH), 5.23–5.03 (m, 4H, CHOCNH), 4.97 (br s, 1H, NHCO), 4.56–4.43 (d, *J*=6.6 Hz, 1H, NHCO), 4.19–4.00 (m, 1H, CH_ACH_B), 3.75 (s, 3H, OMe), 3.12–2.86 (m, 1H, CH_BCH), 1.94–1.48 (m, 5H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.2, 157.7, 136.6, 128.8, 128.4, 128.2, 89.5, 67.8, 67.0, 57.0, 52.6, 49.4, 34.0, 32.2, 29.9, 24.2, 22.9; IR (neat): 2960, 2764, 2652, 1695, 1543, 1246, 1234 cm^{-1}; ESIMS: 444 $(M+NH_4)^+$; HRMS calcd for $C_{23}H_{26}N_2O_6NH_4$ 444.1736, found 444.1742.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.031.

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10. Cyclization under reported condition (NaH, ^{t}BuOK) generates only 10–15% of **1**, stirring at rt for 44 h. But, deprotection of Boc, followed by cyclization with Et_3N yields **1**, with 65%.