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Synthesis of (3*S*,4*R*)-4-benzylamino-3-methoxypiperidine, an important intermediate for (3*S*,4*R*)-Cisapride

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ABSTRACT

An efficient synthesis of (3*S*,4*R*)-4-benzylamino-3-methoxypiperidine, an useful intermediate for the chiral synthesis of important drug molecule Cisapride and its analogs, from enantiopure 4-formylazetidin-2-one is described. Synthesis of trans as well as cis isomers of 4-amino-3-methoxypiperidine from 4-formylazetidin-2-one is also achieved in good yield.

1. Introduction

The strain energy associated with the four-membered azetidin-2-one ring makes it susceptible for nucleophilic ring cleavage. The selective bond cleavage of the strained ring coupled with further interesting transformations renders this fascinating molecule as a powerful building block.[1] One such synthon, 4-formylazetidin-2-one, has wide applications as a building block for the synthesis of monobactams, isocephams, carbapenems, and several other non-β-lactam compounds like α-hydroxyaspartate and hydroxybutanoic acids.[2,3] Enantiomerically pure 4-formylazetidin-2-one can be easily obtained from optically pure glyceraldehydes acetonide by employing Staudinger's ketene–imine *cyclo*-condensation reaction.[4–7] As a part of our research program on asymmetric synthesis of β-lactams and its applications for the preparation of various biologically important compounds[8,9] we have developed an efficient method for enantiopure 4-formylazetidin-2-one from easily accessible (−)-diethyl tartrate.

In continuation of our efforts toward the preparation of substituted β-lactams via the Staudinger reaction[10] and their utility as synthons[6,8,9] for synthesizing various biologically important compounds, we were interested in the chiral synthesis of an important drug molecule Cisapride (Fig. 1)[11] from 4-formyl-β-lactam. Cisapride and its analogs, such as ATI 7505 (I), are safe and effective for the treatment of various gastrointestinal disorders including, gastroparesis, gastroesophageal reflux, emesis, dyspepsia, constipation, intestinal pseudo-obstruction or postoperative ileus.[12–14]

Although a chiral version of Cisapride, which is obtained by resolution of the racemic mixture[12a–c] is well known for its improved activity. However, there are no reports on asymmetric synthesis of this molecule. There are few reports on the synthesis of racemic Cisapride and its analogs. Most of these syntheses are reported from piperidine-4-one in 9–13 steps,[15a–c] with very poor overall yields. A short synthesis by seven steps with an overall yield of 4.5% has been reported.[15d] The racemic *trans*- and *cis*-4-amino-3-methoxypiperidine is also used for the synthesis of Cisapride and its analogs using a multi-step reaction sequence in very poor overall yields.[11] To the best of our knowledge, there is no report on the synthesis of Cisapride or its analogs from azetidin-2-one. The biological activity associated with Cisapride and its analogs, the poor yield in the reported multi-step syntheses, and no reports on the chiral synthesis, inspired us to design and develop a chiral synthesis of this molecule from enantiopure azetidin-2-one. Based on our experience in the asymmetric synthesis and application of azetidin-2-ones in organic synthesis, we designed a retro-synthetic strategy for the synthesis of Cisapride (Scheme 1). The key intermediate, 3-methoxy-4-aminopiperidine can be obtained from corresponding 3-methoxypiperidine-2-one, which can be prepared from 4-formylazetidin-2-one in five steps by a well established reaction sequence. 3-Methoxy-4-aminopiperidine is also a core

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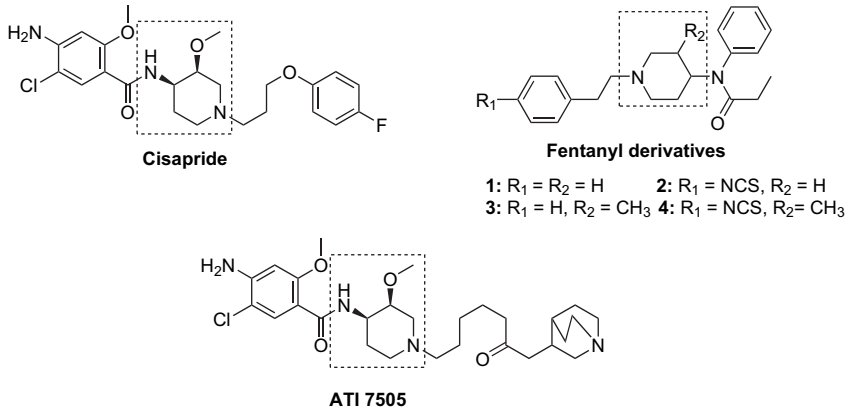
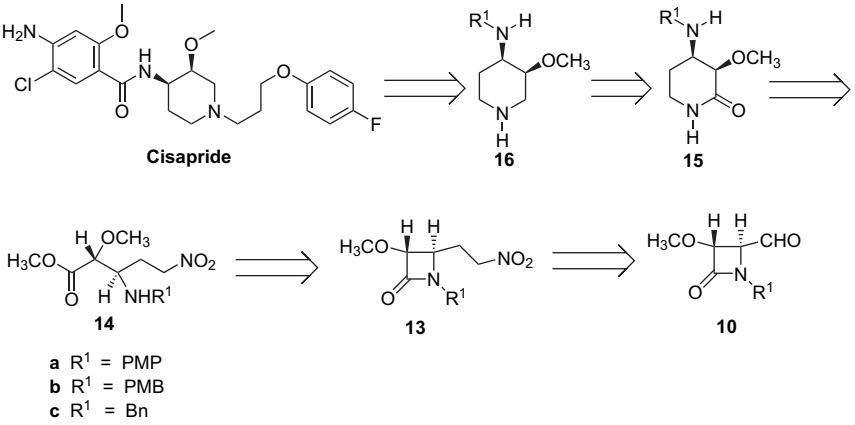


Figure 1. Cisapride, fentanyl derivatives, and analogs.



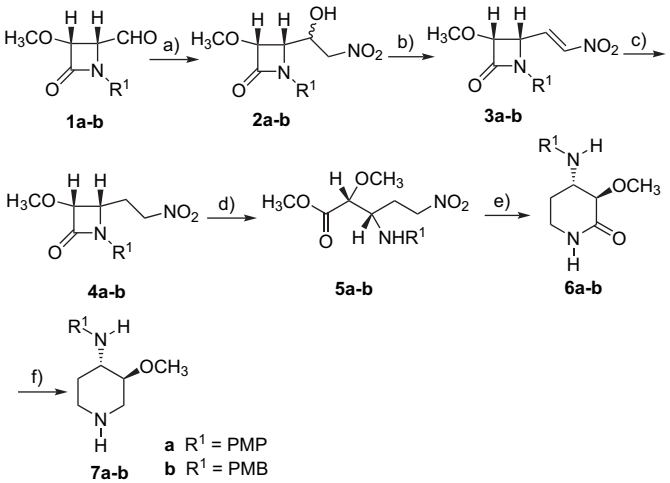
Scheme 1.

structure of fentanyl derivatives[16] and ATI 7505 (Fig. 1). The retrosynthesis is based on the well defined stereochemistry at both the stereocenters of *trans*-3-methoxy-4-formylazetidin-2-one ring, which is required for the synthesis of (3*S*,4*R*)-Cisapride and its analogs.

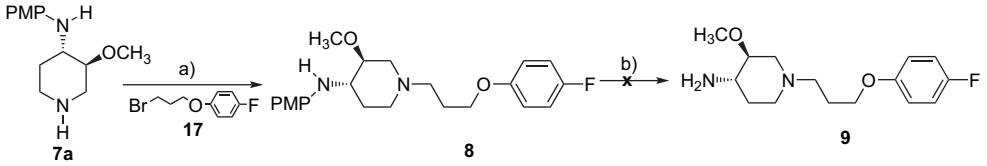
2. Results and discussion

Initially we planned the synthesis of (3*R*,4*R*)-Cisapride as it can be obtained from easily accessible (3*R*,4*R*)-*cis*-3-methoxy-4-formylazetidin-2-one. The enantiopure (3*R*,4*R*)-*cis*-4-formyl-β-lactams **1a**–**c** were either obtained from (−)-diethyl tartrate[6] or from D-glyceraldehyde acetonide using a reported procedure.[4–6] The reaction of *cis*-3-methoxy-4-formyl-β-lactams **1a**,**b** with nitromethane in the presence of a catalytic amount of triethylamine gave a 7:3 diastereomeric mixture of nitro-aldol products **2a**,**b** in quantitative yield. The hydroxy group of **2a**,**b** was acetylated using acetic anhydride[8] in the presence of catalytic amount of concentrated sulfuric acid at 0 °C to get a nitroacetate along with small amount of nitroalkenes **3a**,**b**. This crude mixture was refluxed in benzene in the presence of sodium bicarbonate to afford crude nitroalkenes, which were further purified by column chromatography to get pure nitroalkenes **3a**,**b** in 80–85% yield. The nitroalkenes **3a**,**b** were reduced to nitroalkanes **4a**,**b** with tributyltinhydride[17] in 60–70% yield. The β-lactam ring of the nitroalkanes **4a**,**b** was opened up by stirring with methanolic HCl (20%) at room temperature for 12 h to get the nitroesters **5a**,**b** in nearly quantitative yield. The reduction of nitro group by transfer hydrogenation[18] using ammonium formate and Pd/C (10%) in methanol at room temperature followed by in situ intramolecular cyclization gave 4-aminopiperidin-2-ones **6a**,**b** in 60–70% yield. The reduction of amide carbonyl of **6a**,**b** with BH_3/DMS afforded cleanly (3*S*,4*S*)-4-amino-3-methoxypiperidines **7a**,**b** in 50% yield (Scheme 2).

(3*S*,4*S*)-4-Amino-3-methoxypiperidine **7a** on alkylation with bromo compound **17** in anhydrous DMF using Et_3N gave *N*-alkylated aminopiperidine **8** in 35% yield (Scheme 3).[11] The deprotection of 4-methoxy-phenyl (PMP) group is normally achieved by



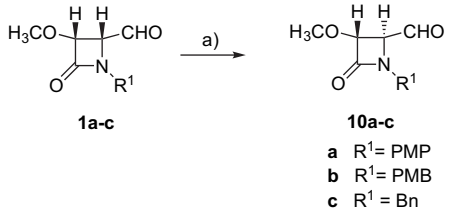
Scheme 2. Reagents and conditions: (a) CH_3NO_2, Et_3N, 5 h, 97–98%; (b) (i)Ac_2O, concd H_2SO_4, 0 °C, 1 h; (ii) $NaHCO_3$, benzene, reflux, 4 h, 80–85% (overall yield); (c) Bu_3SnH, CH_2Cl_2/MeOH (10:1), rt, 3 h, 60–70%; (d) Methanolic HCl (20%), rt, 12 h, 90–95%; (e) 10% Pd/C, $HCOONH_4$, MeOH, rt, 5 h, 60–70%; (f) BH_3/DMS, toluene, reflux, 4 h, 50–51%.



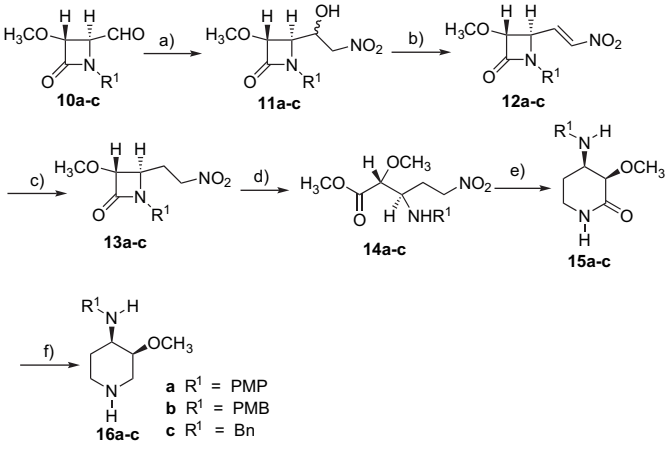
Scheme 3. Reagents and conditions: (a) DMF, Et_3N, **17**, rt, 18 h, 35%; (b) CAN, CH_3CN/H_2O, 30 min.

ceric ammonium nitrate (CAN). However, in case of **8** the cleavage of PMP group under various reaction conditions failed to give the desired product **9**.

Since the drug molecule Cisapride, fentanyl derivatives,[16] and its analogs with cis stereochemistry are more effective in potentiating the contractile response of the ileum to coaxial stimulation.[11] Therefore, we were also interested to get cis stereochemistry at C-3 and C-4 position of piperidine. To achieve cis stereochemistry at C-3 and C-4 position it is essential to start the synthesis from *trans*-4-formylazetidin-2-ones **10a**–**c**. This was achieved by epimerization of *cis*-4-formylazetidin-2-one **1a** by treatment with 40% dimethylamine to get *trans*-4-formylazetidin-2-one **10a** in 50% yield. The *cis*-4-formylazetidin-2-ones **1b**,**c** can also be converted to *trans*-4-formylazetidin-2-ones **10b**,**c** by treatment with sodium carbonate in acetonitrile/water (1:1) mixture in 65–70% yield (Scheme 4).[19]



Scheme 4. Reagents and conditions: (a) dimethylamine 40%, benzene, rt, 24 h, 50%, **1a**; Na_2CO_3, CH_3CN/H_2O, (1:1) rt, 48 h, 65–70%, **1b**,**c**.



Scheme 5. Reagents and conditions: (a) CH_3NO_2, Et_3N, 5 h, 75–85%; (b) (i) Ac_2O, concd H_2SO_4, 0 °C, 1 h; (ii) $NaHCO_3$, benzene, reflux, 4 h, 75–87% (overall yield); (c) Bu_3SnH, CH_2Cl_2/MeOH (10:1), rt, 3 h, 50–62%; (d) methanolic HCl (20%), rt, 12 h, 94–98%; (e) 10% Pd/C, $HCOONH_4$, MeOH, rt, 5 h, 55–67%; (f) BH_3/DMS, toluene, reflux 4 h, 49–52%.

The *trans*-4-formylazetidin-2-ones **10a**–**c** were further converted to (3*S*,4*R*)-*cis*-4-amino-3-methoxypiperidines **16a**–**c** by following a well established synthetic sequence (Scheme 5) similar to that shown in Scheme 2. The transformation of *N*-benzyl protected aminopiperidine **16c** into (3*S*,4*R*)-Cisapride can easily be achieved by using a known synthetic protocol[11] in just three steps (Scheme 6). Thus, the synthesis of (3*S*,4*R*)-4-benzylamino-3-methoxypiperidine, an important intermediate for (3*S*,4*R*)-Cisapride, was achieved in six steps from *trans*-4-formylazetidin-2-one **10c** with 12% overall yield.

3. Conclusion

In conclusion, we have accomplished the first chiral synthesis of an important intermediate **16c** of (3*S*,4*R*)-Cisapride. We have also synthesized various cis and trans aminopiperidines, which can be used for preparing analogs of Cisapride.

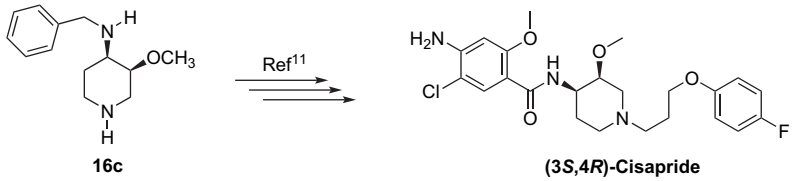
4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Brüker AV 200, AV 400 spectrometers, and chemical shifts are reported in parts per million downfield from tetramethylsilane for ^1H NMR. Infrared spectra were recorded on Perkin Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Buchi melting point apparatus and are uncorrected. The microanalyses were performed on a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Optical rotations were recorded on ADP 220 polarimeter Bellingham+ Stanley Ltd. under standard conditions. Mass spectra were recorded on API QSTAR PULSAR using electron spray ionization (ESI) method.

4.2. General procedure for the preparation of nitroalcohols (2a,b)

To a solution of 4-formylazetidin-2-ones **1a**,**b** (15 mmol) in nitromethane (30 mL) was added Et_3N (0.31 mL, 2.25 mmol) at room temperature and the reaction mixture was stirred for 6 h. The excess nitromethane was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (1×5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford a 7:3 diastereomeric mixture of nitroalcohols **2a**,**b**.



Scheme 6.

*4.2.1. (3R,4S)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-phenyl)-azetidin-2-one (**2a**)*

Yield 98%; pale yellow solid; mp 97–101 °C. [Found C, 52.93; H, 5.33; N, 9.43%. $C_{13}H_{16}N_2O_6$ requires C, 52.70; H, 5.44; N, 9.46%.] R_f (40% EtOAc/pet. ether) 0.20; $[\alpha]_D^{30}$ +77.8 (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.04 (br s, 1H, –O*H*), 3.71 (s, 3H, –OCH_3), 3.80 (s, 3H, Ar–OCH_3), 4.39–4.44 (m, 1H, *H*-4), 4.50–4.62 (m, 2H, *H*-5, *H*-3), 4.69–4.73 (m, 1H, H_a-6), 4.80–4.90 (m, 1H, H_b-6), 6.85–6.92 (m, 2H, Ar), 7.36–7.40 (m, 2H, Ar); δ_C (125.76 MHz) 55.4, 58.1, 58.7, 59.6, 59.7, 67.1, 68.6, 77.5, 77.7, 82.4, 82.8, 114.4, 114.6, 119.4, 119.9, 129.7, 129.9, 157.0, 164.0, 164.5; MS (*m*/*z*): 297 (M+1).

*4.2.2. (3R,4S)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (**2b**)*

Yield 97%; gummy compound. [Found C, 54.23; H, 5.77; N, 9.18%. $C_{14}H_{18}N_2O_6$ requires C, 54.18; H, 5.86; N, 9.03%.] R_f (50% EtOAc/pet. ether) 0.26; $[\alpha]_D^{30}$ +57.7 (*c* 0.52, $CHCl_3$); ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.55–3.75 (m, 4H, –OCH_3, *H*-4), 3.80 (s, 3H, Ar–OCH_3), 4.10–4.70 (m, 6H, *H*-3, *H*-5, *H*-6, –NCH_2), 6.80–6.95 (m, 2H, Ar), 7.15–7.25 (m, 2H, Ar); δ_C (125.76 MHz) 44.4, 44.9, 55.2, 57.4, 59.3, 59.6, 67.5, 68.9, 77.5, 77.9, 82.6, 83.7, 114.3, 126.6, 127.1, 129.7, 159.3, 159.4, 166.8, 167.2; MS (*m*/*z*): 311 (M+1).

4.3. General procedure for the preparation of nitroalkenes (3a,b)

Diastereomeric mixture of nitroalcohols **2a**,**b** (14 mmol) was dissolved in acetic anhydride (30 mL) and cooled to 0 °C. Three to four drops of concentrated H_2SO_4 were added to the reaction mixture and stirred for 1 h at 0 °C. After completion of the reaction (TLC), H_2O (2 mL) was added at 0 °C and the mixture was stirred for 10 min. It was extracted with EtOAc (2×40 mL) and the organic layer was washed with satd aq $NaHCO_3$ (3×15 mL), brine (15 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford nitroacetates **3a**,**b** along with small quantity of nitroalkene. This mixture was refluxed with benzene (50 mL) in the presence of $NaHCO_3$ (9.41 g, 112 mmol) for 6 h. After completion of reaction (TLC), solid was removed by filtration, and the solvent was removed under reduced pressure to afford the crude nitroalkenes **3a**,**b**, which was further purified by column chromatography on silica gel (EtOAc/pet. ether 3:7 as eluent) to get pure **3a**,**b**.

*4.3.1. (3R,4S)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-vinyl)-azetidine-2-one (**3a**)*

Yield 80%; yellow crystalline solid; mp 119 °C. [Found C, 56.43; H, 5.18; N, 10.33%. $C_{13}H_{14}N_2O_5$ requires C, 56.11; H, 5.07; N, 10.07%.] R_f (30% EtOAc/pet. ether) 0.25; $[\alpha]_D^{30}$ +177.4 (*c* 0.62, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.57 (s, 3H, –OCH_3), 3.80 (s, 3H, Ar–OCH_3), 4.83–4.92 (m, 2H, *H*-3, *H*-4), 6.88 (d, *J*=8.9 Hz, 2H, Ar), 7.12–7.32 (m, 4H, Ar, *H*-5, *H*-6); δ_C (100.61 MHz) 55.2, 59.1, 85.3, 114.5, 118.3, 129.7, 135.5, 142.6, 156.8, 162.4; MS (*m*/*z*): 279 (M+1).

*4.3.2. (3R,4S)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-vinyl)-azetidine-2-one (**3b**)*

Yield 76%; gummy compound. [Found C, 57.73; H, 5.43; N, 9.76%. $C_{14}H_{16}N_2O_5$ requires C, 57.52; H, 5.53; N, 9.58%.] R_f (50% EtOAc/pet. ether) 0.25; $[\alpha]_D^{30}$ +128.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 1763 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.47 (s, 3H, –OCH_3), 3.80 (s, 3H, Ar–OCH_3), 4.10–4.25 (m, 2H, –NC$H_a$$H_b$, *H*-4), 4.53 (d, *J*=14.7 Hz, 1H, –NC$H_a$$H_b$), 4.67 (d, *J*=4.5 Hz, 1H, *H*-3), 6.82–7.05 (m, 4H, Ar, *H*-5, *H*-6), 7.13 (d, *J*=8.7 Hz, 2H, Ar); δ_C (100.61 MHz) 44.5, 54.8, 55.3, 59.1, 85.9, 114.5, 126.1, 130.0, 135.6, 142.2, 159.7, 165.5; MS (*m*/*z*): 293 (M+1).

4.4. General procedure for the preparation of nitroalkanes (4a,b)

To a solution of nitroalkenes **3a**,**b** (10.26 mmol) in anhydrous CH_2Cl_2/MeOH (10:1, 30 mL), tributyltinhydride (3.30 mL, 11.29 mmol) was added at room temperature and the mixture was stirred for 2 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (EtOAc/pet. ether 2:8 as eluent) to give pure nitroalkanes **4a**,**b**.

*4.4.1. (3R,4S)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-ethyl)-azetidin-2-one (**4a**)*

Yield 70%; yellow solid; mp 140 °C. [Found C, 55.92; H, 5.85; N, 10.23%. $C_{14}H_{16}N_2O_5$ requires C, 55.71; H, 5.75; N, 9.99%.] R_f (30% EtOAc/pet. ether) 0.27; $[\alpha]_D^{30}$ +158.8 (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.35–2.49 (m, 1H, H_a-5), 2.66–2.79 (m, 1H, H_b-5), 3.68 (s, 3H, –OCH_3), 3.81 (s, 3H, Ar–OCH_3), 4.31–4.39 (m, 1H, *H*-4), 4.51–4.58 (m, 2H, *H*-6), 4.65 (d, *J*=5.1 Hz, 1H, H-3), 6.91 (d, *J*=8.8 Hz, 2H, Ar), 7.35 (d, *J*=8.8 Hz, 2H, Ar); δ_C (125.76 MHz) 25.0, 53.9, 55.4, 59.2, 71.6, 82.7, 114.7, 118.6, 129.9, 156.7, 163.9; MS (*m*/*z*): 281(M+1).

*4.4.2. (3R,4S)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-ethyl)-azetidin-2-one (**4b**)*

Yield 67%; gummy compound. [Found C, 57.47; H, 6.40; N, 9.57%. $C_{14}H_{18}N_2O_5$ requires C, 57.12; H, 6.18; N, 9.52%.] R_f (50% EtOAc/pet. ether) 0.31; $[\alpha]_D^{30}$ +81.2 (*c* 0.64, $CHCl_3$); ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.15–2.30 (m, 2H, *H*-5), 3.58 (s, 3H, –OCH_3), 3.62–3.73 (m, 1H, *H*-4), 3.80 (s, 3H, Ar–OCH_3), 4.18 (d, *J*=15.0 Hz, 1H, –NC$H_a$$H_b$), 4.28–4.37 (m, 2H, –NC$H_a$$H_b$, *H*-3), 4.38–4.50 (m, 2H, *H*-6), 6.87 (d, *J*=8.8 Hz, 2H, Ar), 7.17 (d, *J*=8.8 Hz, 2H, Ar); δ_C (125.76 MHz) 25.9, 44.0, 54.3, 55.2, 59.1, 71.7, 83.5, 114.3, 127.0, 129.5, 159.4, 167.0; MS (*m*/*z*): 295 (M+1).

4.5. General procedure for the preparation of nitroesters (5a,b)

A solution of nitroalkanes **4a**,**b** (10 mmol) in methanolic HCl (20%, 25 mL) was stirred at room temperature for 12 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL), neutralized with solid $NaHCO_3$, and filtered through Celite bed. Filtrate was concentrated in vacuo to give nitroesters **5a**,**b**.

*4.5.1. (2R,3S)-2-Methoxy-3-(4-methoxy-phenylamino)-5-nitro-pentanoic acid methyl ester (**5a**)*

Yield 92%; viscous liquid. [Found C, 53.81; H, 6.63; N, 8.90%. $C_{14}H_{20}N_2O_6$ requires C, 53.84; H, 6.45; N, 8.97%.] R_f (30% EtOAc/pet. ether) 0.32; $[\alpha]_D^{30}$ −27.7 (*c* 1.08, $CHCl_3$); ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.24–2.38 (m, 2H, *H*-4), 3.47 (s, 3H, –OCH_3), 3.51 (s, 3H, –COOCH_3), 3.73 (s, 3H, Ar–OCH_3), 3.78–4.02 (m, 3H, –N*H*, *H*-3, *H*-2), 4.51–4.61 (m, 2H, *H*-5), 6.60 (d, *J*=9.0 Hz, 2H, Ar), 6.75 (d, *J*=9.0 Hz, 2H, Ar); δ_C (75.48 MHz) 29.9, 51.7, 54.5, 55.5, 58.8, 72.4, 81.0, 114.7, 115.6, 140.5, 152.7, 170.6; MS (*m*/*z*): 313 (M+1).

*4.5.2. (2R,3S)-2-Methoxy-3-(4-methoxy-benzylamino)-5-nitro-pentanoic acid methyl ester (**5b**)*

Yield 95%; viscous liquid. [Found C, 55.44; H, 6.83; N, 8.76%. $C_{15}H_{22}N_2O_6$ requires C, 55.19; H, 6.81; N, 8.58%.] R_f (40% EtOAc/pet. ether) 0.32; $[\alpha]_D^{30}$ −2.8 (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.05–2.35 (m, 2H, *H*-4), 3.05–3.20 (m, 1H, *H*-3), 3.44 (s, 3H, –OCH_3), 3.60–3.73 (m, 2H), 3.79 (s, 3H, –COOCH_3), 3.80 (s, 3H, Ar–OCH_3), 3.85 (d, *J*=3.9 Hz, 1H, *H*-2), 4.51 (t, *J*=6.8 Hz, 2H, *H*-5), 6.86 (d, *J*=8.7 Hz, 2H, Ar), 7.22 (d, *J*=8.7 Hz, 2H, Ar); δ_C

(125.76 MHz) 29.2, 50.5, 52.1, 55.2, 55.9, 58.8, 72.6, 81.2, 113.8, 129.6, 158.9, 171.4; MS (*m*/*z*): 327 (M+1).

4.6. General procedure for the preparation of 4-amino-piperidin-2-ones (6a,b)

To a solution of nitroesters **5a**,**b** (10 mmol) in anhydrous MeOH (40 mL), 10% Pd/C (600 mg) was added, followed by ammonium formate (3.15 g, 50 mmol), and the reaction mixture was stirred at room temperature under argon for 5 h. After completion of reaction (TLC), the reaction mixture was filtered through a Celite bed and the bed was washed with MeOH. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (5 mL), brine (5 mL), and the organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crude product, which was purified by flash column chromatography (EtOAc/pet. ether 6:4 for **6a**; acetone/pet. ether 6:4 for **6b**) to get pure **6a**,**b**.

*4.6.1. (3R,4S)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine-2-one (**6a**)*

Yield 70%; white solid; mp 127–129 °C. [Found C, 62.32; H, 7.33; N, 11.47%. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19%.] R_f (60% EtOAc/pet. ether) 0.30; $[\alpha]_D^{30}$ +36.44 (*c* 1.18, $CHCl_3$); ν_{max} ($CHCl_3$) 1649 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.89–2.09 (m, 1H, H_a-5), 2.34–2.51 (m, 1H, H_b-5), 3.62 (s, 3H, –OCH_3), 3.64–3.74 (m, 3H, *H*-4, *H*-6), 3.76 (s, 3H, Ar–OCH_3), 3.87 (d, *J*=6.3 Hz, 1H, *H*-3), 6.76 (d, *J*=9.2 Hz, 2H, Ar), 6.82 (d, *J*=9.2 Hz, 2H, Ar); δ_C (125.76 MHz) 24.1, 46.1, 52.3, 55.6, 59.2, 79.8, 114.9, 116.1, 139.9, 153.2, 163; MS (*m*/*z*): 251 (M+1).

*4.6.2. (3R,4S)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine-2-one (**6b**)*

Yield 62%; gummy compound. [Found C, 63.83; H, 7.69; N, 10.74%. $C_{14}H_{20}N_2O_3$ requires C, 63.60; H, 7.64; N, 10.60%.] R_f (80% acetone/pet. ether) 0.32; $[\alpha]_D^{30}$ +70.0 (*c* 0.60, $CHCl_3$); ν_{max} ($CHCl_3$) 1651 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.75–1.95 (m, 1H, *H*-5), 2.20–2.40 (m, 1H, *H*-5), 3.00–3.10 (m, 1H, H-4), 3.47–3.71 (m, 5H, H-6, –OCH_3), 3.73–3.82 (m, 2H, –NCH_aH$_b$, H-3), 3.72–3.82 (m, 3H, –NCH$_a$$H_b$), 3.84 (s, 3H, Ar–OC$H_3$), 3.91 (d, *J*=12.9 Hz, 1H, –NCH$_a$$H_b$), 4.40 (br s, 2H, –N*H*), 6.91 (d, *J*=8.7 Hz, 2H, Ar), 7.28 (d, *J*=8.7 Hz, 2H, Ar); δ_C (125.76 MHz) 24.1, 46.2, 50.4, 55.0, 55.3, 59.9, 80.1, 114.0, 129.5, 130.7, 159.0, 164.0; MS (*m*/*z*): 265 (M+1).

4.7. General procedure for the preparation of 4-amino-piperidines (7a,b)

To a solution of 4-aminopiperidin-2-ones **6a**,**b** (10 mmol) in dry toluene (30 mL) BH_3/DMS (10.0 mM, 1.10 mL 10% excess) was added dropwise under nitrogen at 0 °C. The reaction mixture was stirred at this temperature for 15 min and then refluxed for 3 h. The reaction was quenched by adding 15 mL of 10% aq Na_2CO_3 at 20 °C, stirred for 3 h at 20 °C. The toluene layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed and the crude piperidine was purified by flash column chromatography (EtOAc/pet. ether 8:2 for **7a**; 9:1 for **7b**) to get pure 4-aminopiperidines **7a**,**b**.

*4.7.1. (3S,4S)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine (**7a**)*

Yield 50%; viscous liquid. [Found C, 66.24; H, 8.47; N, 12.03%. $C_{13}H_{20}N_2O_2$ requires C, 66.07; H, 8.53; N, 11.85%.] R_f (60% EtOAc/pet. ether) 0.27; $[\alpha]_D^{30}$ +12.9 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 3215, 3375 cm^{-1}; δ_H (400 MHz, $CDCl_3$, at room temperature) 1.35–1.44 (m, 0.6H, *H*-5), 1.68–1.85 (m, 0.4H, *H*-5), 2.17–2.20 (m, 1H, *H*-5), 2.45–2.60 (m, 1H, *H*-6) 2.86–3.37 (m, 4H, 1×*H*-6, *H*-2, *H*-4), 3.44 (s, 3H, –OCH_3), 3.46–3.73 (m, 1H, *H*-3), 3.75 (s, 3H, Ar–OCH_3), 6.67 (dd, *J*=7.8 Hz, 2H, Ar), 6.78 (m, 2H, Ar); δ_C (125.76 MHz) 25.8, 28.6, 50.4, 53.2, 55.4, 56.1, 56.8, 57.2, 60.4, 77.3, 79.6, 114.5, 114.7, 116.3, 140.5, 141.2, 152.1, 152.5; ^{1}H NMR at 55 °C δ_H (400 MHz, $CDCl_3$, at 55 °C) 1.41–1.75 (m, 1H, *H*-5), 2.13–2.20 (m, 1H, *H*-5), 2.30–2.90 (m, 2H, *H*-6), 2.95–3.35 (m, 3H, *H*-2, *H*-4), 3.44 (s, 3H, –OCH_3), 3.47–3.65 (m, 1H, *H*-3), 3.75 (s, 3H, Ar–OCH_3), 6.67 (d, *J*=7.8 Hz, 2H, Ar), 6.78 (d, *J*=7.8 Hz, 2H, Ar); MS (*m*/*z*): 237 (M+1).

*4.7.2. (3S,4S)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine (**7b**)*

Yield 51%; viscous liquid. [Found C, 67.34; H, 8.92; N, 11.27%. $C_{14}H_{22}N_2O_2$ requires C, 67.17; H, 8.86; N, 11.19%.] R_f (80% acetone/pet. ether) 0.30; $[\alpha]_D^{30}$ +33.3 (*c* 0.66, acetone); ν_{max} ($CHCl_3$) 3215, 3375 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.70–2.15 (m, 2H, *H*-5), 2.20–2.70 (m, 3H, *H*-6, –N*H*), 3.00–3.37 (m, 3H, *H*-2, *H*-4), 3.39 (s, 3H, –OCH_3), 3.50–3.95 (m, 7H, *H*-3, –NCH_2, Ar–OCH_3, –N*H*), 6.86 (d, *J*=8.5 Hz, 2H, Ar), 7.26 (d, *J*=8.5 Hz, 2H, Ar); δ_C (125.76 MHz) 27.0, 50.4, 55.2, 56.7, 57.2, 58.6, 59.9, 72.1, 113.9, 129.5, 131.0, 158.8; MS (*m*/*z*): 251 (M+1).

4.8. (3S,4S)-2-(3-(4-fluorophenoxy)propyl)-3-methoxy-*N*-(4-methoxy-phenyl)piperidin-4-amine (8)

To a solution of 4-aminopiperidine **7a** (0.236 mg, 1 mmol) in anhydrous DMF (5 mL), Et_3N (0.15 mL, 1.1 mmol) was added and the mixture was stirred for 10 min. To this solution, bromo compound (0.256 g, 1.1 mmol) in DMF (3 mL) was added dropwise and allowed to stir for 12 h at room temperature. DMF was removed in vacuo at 30 °C and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH 9:1 as eluent) to get pure **8** (0.155 g, 40%) as a faint brown liquid. [Found C, 68.23; H, 7.27; N, 7.33. $C_{22}H_{29}N_2O_3F$ requires C, 68.02; H, 7.52; N, 7.21%.] R_f (10% MeOH/CH_2Cl_2) 0.15; $[\alpha]_D^{30}$ +11.1 (*c* 0.36, $CHCl_3$); ν_{max} ($CHCl_3$) 3369 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.05–2.45 (m, 4H, *H*-5, *H*-8), 3.05–3.40 (m, 2H, *H*-6), 3.44 (s, 3H, –OCH_3), 3.46–3.70 (m, 3H, *H*-7, H_a-2), 3.71 (s, 3H, Ar–OCH_3), 3.72–3.92 (m, 3H, H_b-2, *H*-4, *H*-3), 4.02 (t, *J*=6.2 Hz, 2H, *H*-9), 6.73–7.00 (m, 8H, Ar); δ_C (100.61 MHz) 22.9, 24.8, 52.1, 55.7, 58.3, 62.2, 63.7, 65.6, 65.9, 76.9, 114.8, 115.4, 115.6, 115.9, 141.1, 152.5; MS (*m*/*z*): 389 (M+1).

4.9. (3R,4S)-3-Methoxy-1-(4-methoxy-phenyl)-4-oxo-azetidin-2-carbaldehyde (10a)

To a stirred solution of *cis*-4-formylazetidin-2-one **1a** (0.940 g, 4 mmol) in benzene (40 mL), dimethylamine (40% aq, 4.0 mL) was added and the reaction mixture was stirred at room temperature for 24 h. After completion of reaction (TLC), organic layer was separated, concentrated in vacuo, and further purified by flash column chromatography (EtOAc/pet. ether 25:75 as eluent) to get *trans*-4-formylazetidin-2-one **10a** as viscous liquid (0.470 g, 50%). [Found C, 61.34; H, 5.66; N, 5.87%. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95%.] R_f (25% EtOAc/pet. ether) 0.15; $[\alpha]_D^{30}$ −51.2 (*c* 0.82, $CHCl_3$); ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.56 (s, 3H, –OCH_3), 3.78 (s, 3H, Ar–OCH_3), 4.47 (dd, *J*=1.8, 3.2 Hz, 1H, *H*-4), 4.69 (d, *J*=1.8 Hz, 1H, *H*-3), 6.86 (d, *J*=9.0 Hz, 2H, Ar), 7.24 (d, *J*=9.0 Hz, 2H, Ar), 9.81 (d, *J*=3.2 Hz, 1H, –C*H*O); δ_C (50.32 MHz) 55.4, 58.1, 65.1, 85.0, 114.6, 118.3, 130.2, 156.9, 161.8, 197.1; MS (*m*/*z*): 236 (M+1).

4.10. (3R,4S)-3-Methoxy-1-(4-methoxy-benzyl)-4-oxo-azetidin-2-carbaldehyde (10b)

To a stirred solution of *cis*-4-formylazetidin-2-one **1b** (5 g, 17.79 mmol) in acetonitrile and water (1:1, 602 mL), Na_2CO_3 (3.77 g, 35.58 mmol) was added and stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure and the aqueous layer was extracted with EtOAc (5×75 mL). Organic layer was dried

over anhydrous Na_2SO_4, concentrated in vacuo to get crude **10b**, which was purified by flash column chromatography on silica gel (EtOAc/pet. ether 7:3 as eluent) to afford pure *trans*-4-formylazetidin-2-one **10b** as a gummy compound (3.5 g, 70%). [Found C, 59.44; H, 5.94; N, 10.68%. $C_{13}H_{15}NO_4$ requires C, 59.30; H, 5.75; N, 10.64%.] R_f (70% EtOAc/pet. ether) 0.20; $[\alpha]_D^{30}$ +42.8 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.48 (s, 3H, –OC*H*$_3$), 3.80 (s, 3H, Ar–OC*H*$_3$), 3.94 (t, 1H, *H*-4), 4.24 (d, *J*=14.6 Hz, 1H, –NC*H*$_a$H$_b$), 4.55 (d, *J*=1.5 Hz, 1H, *H*-3), 4.68 (d, *J*=14.6 Hz, 1H, –NCH$_a$*H*$_b$), 6.86 (d, *J*=8.7 Hz, 2H, Ar), 7.15 (d, *J*=8.7 Hz, 2H, Ar), 9.54 (d, *J*=3.2 Hz, 1H, –C*H*O); δ_C (125.76 MHz) 45.2, 55.2, 57.8, 64.5, 85.4, 114.4, 126.2, 130.0, 159.5, 164.9, 196.9; MS (*m*/*z*): 250 (M+1).

4.11. (3*R*,4*S*)-1-Benzyl-3-methoxy-4-oxo-azetidin-2-carbaldehyde (10c)

To a stirred solution of *cis*-4-formylazetidin-2-one **1c** (5 g, 22.83 mmol) in acetonitrile and water (1:1, 684 mL), Na_2CO_3 (4.84 g, 45.66 mmol) was added and stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure and the aqueous layer was extracted with EtOAc (5×80 mL). Organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo to give crude **10c**, which was purified by flash column chromatography on silica gel (EtOAc/pet. ether 8:2 as eluent) to get pure *trans*-4-formylazetidin-2-one **10c** as a viscous liquid (3.2 g, 64%). [Found C, 65.65; H, 6.14; N, 6.47%. $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39%.] R_f (80% EtOAc/pet. ether) 0.22; $[\alpha]_D^{30}$ +20.4 (*c* 0.44, $CHCl_3$); ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.50 (s, 3H, –OC*H*$_3$), 3.98–4.00 (m, 1H, *H*-4), 4.28 (d, *J*=14.8 Hz, 1H, –NC*H*$_a$H$_b$), 4.57 (d, *J*=1.9 Hz, 1H, *H*-3), 4.77 (d, *J*=14.8 Hz, 1H, –NCH$_a$*H*$_b$), 7.24–7.38 (m, 5H, Ar), 9.58 (d, *J*=1.9 Hz, 1H, –C*H*O); δ_C (125.76 MHz) 45.8, 57.8, 64.5, 85.5, 128.3, 128.6, 129.1, 134.2, 165.0, 196.7; MS (*m*/*z*): 220 (M+1).

*4.11.1. (3R,4R)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-phenyl)-azetidin-2-one (**11a**)*

Following the general procedure, as for **2a**,**b**, inseparable diastereomeric mixture of **11a** was obtained in 3:2 ratio as a viscous liquid in 77% yield. [Found C, 52.84; H, 5.57; N, 9.43%. $C_{13}H_{16}N_2O_6$ requires C, 52.70; H, 5.44; N, 9.46%.] R_f (40% EtOAc/pet. ether) 0.24; $[\alpha]_D^{30}$ −2.9 (*c* 0.70, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.57 (s, 3H, –OC*H*$_3$), 3.80 (s, 3H, Ar–OC*H*$_3$), 4.00–4.20 (m, 1H, H-4), 4.43–4.60 (m, 2H, *H*-3, *H*-5), 4.69–4.98 (m, 2H, *H*-6), 6.87–6.93 (m, 2H, Ar), 7.30–7.35 (m, 2H, Ar); δ_C (50.32 MHz) 55.5, 58.2, 60.6, 61.0, 63.0, 63.4, 64.3, 67.9, 77.2, 82.4, 83.9, 114.6, 114.8, 119.6, 120.6, 129.1, 157.1, 163.5; MS (*m*/*z*): 297 (M+1).

*4.11.2. (3R,4R)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (**11b**)*

Following the general procedure, as for **2a**,**b**, inseparable diastereomeric mixture of **11b** was obtained in 3:2 ratio as a viscous liquid in 82% yield. [Found C, 54.23; H, 5.77; N, 9.18%. $C_{14}H_{18}N_2O_6$ requires C, 54.18; H, 5.86; N, 9.03%.] R_f (60% EtOAc/pet. ether) 0.33; $[\alpha]_D^{30}$ +50.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.38–3.65 (m, 4H, –OC*H*$_3$, *H*-5), 3.79 (s, 3H, Ar–OC*H*$_3$), 4.08–4.72 (m, 6H, *H*-3, *H*-4, –NC*H*$_2$, *H*-6), 6.84–6.94 (m, 2H, Ar), 7.16–7.26 (m, 2H, Ar); δ_C (125.76 MHz) 44.0, 45.0, 55.2, 57.7, 57.9, 59.9, 60.2, 64.9, 69.1, 77.5, 77.7, 82.6, 84.3, 114.4, 114.5, 126.6, 126.9, 129.5, 129.6, 159.3, 166.7, 166.9; MS (*m*/*z*): 311 (M+1).

*4.11.3. (3R,4R)-4-(1-Hydroxy-2-nitro-ethyl)-3-methoxy-1-(4-methoxy-benzyl)-azetidin-2-one (**11c**)*

Following the general procedure, as for **2a**,**b**, inseparable diastereomeric mixture of **11c** was obtained in 3:2 ratio as a viscous liquid in 85% yield. [Found C, 55.56; H, 6.03; N, 10.11%. $C_{13}H_{16}N_2O_5$ requires C, 55.71; H, 5.75; N, 9.99%.] R_f (60% EtOAc/pet. ether) 0.32; $[\alpha]_D^{30}$ +51.4 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.42–3.64 (m, 4H, –OC*H*$_3$, *H*-5), 4.31–4.77 (m, 6H, –NC*H*$_2$, H-4, H-3, H-6), 7.25–7.46 (m, 5H, Ar); δ_C (125.76 MHz) 44.5, 45.6, 57.8, 57.9, 60.0, 60.2, 64.7, 69.1, 77.5, 77.7, 82.7, 84.3, 128.1, 128.2, 129.0, 129.2, 134.6, 135.0, 166.8, 167.0; MS (*m*/*z*): 281 (M+1).

*4.11.4. (3R,4R)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-vinyl)-azetidine-2-one (**12a**)*

Following the general procedure, as for **3a**,**b**, **12a** was obtained as a oil in 87% yield. [Found C, 56.27; H, 5.15; N, 10.22%. $C_{13}H_{14}N_2O_5$ requires C, 56.11; H, 5.07; N, 10.07%.] R_f (40% EtOAc/pet. ether) 0.34; $[\alpha]_D^{30}$ −162.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 1764 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.64 (s, 3H, –OC*H*$_3$), 3.84 (s, 3H, Ar–OC*H*$_3$), 4.60–4.70 (m, 2H, *H*-4, *H*-3), 6.94 (d, *J*=9.0 Hz, 2H, Ar), 7.17 (d, *J*=13.5 Hz, 1H, *H*-6), 7.30 (d, *J*=9.0 Hz, 2H, Ar), 7.44 (dd, *J*=6.7, 13.5 Hz, 1H, *H*-5); δ_C (50.32 MHz) 55.5, 56.6, 58.4, 89.0, 114.7, 118.6, 129.4, 136.6, 141.5, 157.0, 161.7; MS (*m*/*z*): 279 (M+1).

*4.11.5. (3R,4R)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-vinyl)-azetidine-2-one (**12b**)*

Following the general procedure, as for **3a**,**b**, **12b** was obtained as pale yellow oil in 81% yield. [Found C, 57.73; H, 5.43; N, 9.76%. $C_{14}H_{16}N_2O_5$ requires C, 57.52; H, 5.53; N, 9.58%.] R_f (35% EtOAc/pet. ether) 0.23; $[\alpha]_D^{30}$ −23.3 (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 1763 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.49 (s, 3H, –OC*H*$_3$), 3.80 (s, 3H, Ar–OC*H*$_3$), 3.98 (dd, *J*=1.5, 7.2 Hz, 1H, *H*-4), 4.08 (d, *J*=14.8 Hz, 1H, –NC*H*$_a$H$_b$), 4.43 (d, *J*=1.5 Hz, 1H, *H*-3), 4.63 (d, *J*=14.8 Hz, 1H, –NCH$_a$*H*$_b$), 6.85–7.20 (m, 6H, Ar, *H*-5, *H*-6); δ_C (100.61 MHz) 44.7, 55.3, 55.9, 58.2, 89.2, 114.5, 125.9, 129.9, 136.9, 141.1, 159.6, 165.2; MS (*m*/*z*): 293 (M+1).

*4.11.6. (3R,4R)-1-Benzyl-3-methoxy-4-(2-nitro-vinyl)-azetidine-2-one (**12c**)*

Following the general procedure, as for **3a**,**b**, **12c** was obtained as pale yellow viscous liquid in 75% yield. [Found C, 59.75; H, 5.41; N, 10.55%. $C_{13}H_{14}N_2O_4$ requires C, 59.54; H, 5.38; N, 10.68%.] R_f (40% EtOAc/pet. ether) 0.30; $[\alpha]_D^{30}$ −53.3 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 1767 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.50 (s, 3H, –OC*H*$_3$), 4.02 (dd, *J*=1.5, 7.2 Hz, 1H, *H*-4), 4.13 (d, *J*=14.8 Hz, 1H, –NC*H*$_a$H$_b$), 4.46 (d, *J*=1.5 Hz, 1H, *H*-3) 4.70 (d, *J*=14.8 Hz, 1H, –NCH$_a$*H*$_b$), 6.92–7.42 (m, 7H, Ar, *H*-5, *H*-6); δ_C (100.61 MHz) 45.2, 56.0, 58.2, 89.4, 128.4, 128.5, 129.1, 134.0, 136.8, 141.2, 165.2; MS (*m*/*z*): 263 (M+1).

*4.11.7. (3R,4R)-3-Methoxy-1-(4-methoxy-phenyl)-4-(2-nitro-ethyl)-azetidin-2-one (**13a**)*

Following the general procedure, as for **4a**,**b**, **13a** was prepared in 60% yield as gummy compound. [Found C, 55.92; H, 5.85; N, 10.23%. $C_{13}H_{16}N_2O_5$ requires C, 55.71; H, 5.75; N, 9.99%.] R_f (30% EtOAc/pet. ether) 0.23; $[\alpha]_D^{30}$ +14.9 (*c* 1.34, $CHCl_3$); ν_{max} ($CHCl_3$) 1754 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.09–2.32 (m, 1H, *H*$_a$-5), 2.74–2.90 (m, 1H, *H*$_b$-5), 3.57 (s, 3H, –OC*H*$_3$), 3.80 (s, 3H, Ar–OC*H*$_3$), 4.03–4.11 (m, 1H, *H*-4), 4.35 (d, *J*=1.6 Hz, 1H, *H*-3), 4.49–4.58 (m, 2H), 6.91 (d, *J*=9.0 Hz, 2H, Ar), 7.29 (d, *J*=9.0 Hz, 2H, Ar); δ_C (50.32 MHz) 27.3, 55.3, 56.7, 57.7, 71.2, 87.0, 114.5, 119.2, 129.0, 156.7, 162.6; MS (*m*/*z*): 281 (M+1).

*4.11.8. (3R,4R)-3-Methoxy-1-(4-methoxy-benzyl)-4-(2-nitro-ethyl)-azetidin-2-one (**13b**)*

Following the general procedure, as for **4a**,**b**, **13b** was prepared in 62% yield as gummy compound. [Found C, 57.47; H, 6.40; N, 9.57%. $C_{14}H_{18}N_2O_5$ requires C, 57.12; H, 6.18; N, 9.52%.] R_f (40% EtOAc/pet. ether) 0.18; $[\alpha]_D^{30}$ +63.3 (*c* 0.60, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.04–2.45 (m, 2H, *H*-5), 3.40–3.60 (m, 4H, H-4, –OC*H*$_3$), 3.81 (s, 3H, Ar–OC*H*$_3$), 4.15 (d, *J*=15.2 Hz, 1H, –NC*H*$_a$H$_b$), 4.20–4.36 (m, 3H, *H*-3, *H*-6), 4.55 (d, *J*=15.2 Hz, 1H, –NCH$_a$*H*$_b$), 6.89 (d, *J*=8.5 Hz, 2H), 7.19 (d, *J*=8.5 Hz, 2H); δ_C

(125.76 MHz) 28.5, 44.0, 55.3, 56.6, 57.9, 71.6, 87.5, 114.4, 126.8, 129.5, 159.4, 166.1; MS (*m*/*z*): 295 (M+1).

*4.11.9. (3R,4R)-1-benzyl-3-methoxy-4-(2-nitro-ethyl)-azetidin-2-one (**13c**)*

Following the general procedure, as for **4a**,**b**, **13c** was prepared in 50% yield as a pale yellow viscous liquid. [Found C, 58.87; H, 6.32; N, 10.42%. $C_{13}H_{16}N_2O_4$ requires C, 59.08; H, 6.10; N, 10.60%.] R_f (40% EtOAc/pet. ether) 0.18; $[\alpha]_D^{30}$ +70.0 (*c* 0.80, $CHCl_3$); ν_{max} ($CHCl_3$) 1759 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.07–2.39 (m, 2H, *H*-5), 3.45–3.51 (m, 4H, –OC*H*$_3$, *H*-4), 4.18–4.35 (m, 4H, *H*-3, *H*-6, –NC*H*$_a$H$_b$), 4.61 (d, *J*=15.1 Hz, 1H, –NCH$_a$*H*$_b$), 7.23–7.40 (m, 5H, Ar); δ_C (125.76 MHz) 28.4, 44.6, 56.8, 57.9, 71.5, 87.6, 128.1, 128.2, 129.1, 134.8, 166.1; MS (*m*/*z*): 265 (M+1).

*4.11.10. (2R,3R)-2-Methoxy-3-(4-methoxy-phenylamino)-5-nitro-pentanoic acid methyl ester (**14a**)*

Following the general procedure, as for **5a**,**b**, **14a** was obtained as a yellow viscous liquid in 95% yield. [Found C, 53.81; H, 6.63; N, 8.90%. $C_{14}H_{20}N_2O_6$ requires C, 53.84; H, 6.45; N, 8.97%.] R_f (30% EtOAc/pet. ether) 0.28; $[\alpha]_D^{30}$ +19.2 (*c* 0.52, $CHCl_3$); ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.10–2.23 (m, 2H, *H*-4), 3.40 (s, 3H, –OC*H*$_3$), 3.77 (s, 3H, –COOC*H*$_3$), 3.79 (s, 3H, Ar–OC*H*$_3$), 3.79–3.95 (m, 1H, *H*-3), 3.97 (d, *J*=3.1 Hz, 1H, *H*-2), 4.45–4.72 (m, 2H, *H*-5), 6.70 (d, *J*=9.0 Hz, 2H, Ar), 6.82 (d, *J*=9.0 Hz, 2H, Ar); δ_C (75.48 MHz) 27.6, 51.9, 54.7, 55.4, 59.0, 72.4, 79.9, 115.0, 116.6, 139.9, 153.3, 171.2; MS (*m*/*z*): 313 (M+1).

*4.11.11. (2R,3R)-2-Methoxy-3-(4-methoxy-benzylamino)-5-nitro-pentanoic acid methyl ester (**14b**)*

Following the general procedure, as for **5a**,**b**, **14b** was obtained as yellow viscous liquid in 94% yield. [Found C, 55.44; H, 6.83; N, 8.76%. $C_{15}H_{22}N_2O_6$ requires C, 55.19; H, 6.81; N, 8.58%.] R_f (30% EtOAc/pet. ether) 0.27; $[\alpha]_D^{30}$ +42.9 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.94–2.06 (m, 2H, *H*-4), 2.92–3.02 (m, 1H, *H*-3), 3.45 (s, 3H, –OC*H*$_3$), 3.63 (d, *J*=12.9 Hz, 1H, –NC*H*$_a$H$_b$), 3.75–3.87 (m, 7H, –NCH$_a$*H*$_b$, –COOC*H*$_3$, Ar–OC*H*$_3$), 4.06 (d, *J*=3.3 Hz, 1H, *H*-2), 4.40–4.62 (m, 2H, *H*-5), 6.87 (d, *J*=8.6 Hz, 2H, Ar), 7.24 (d, *J*=8.6 Hz, 2H, Ar); δ_C (125.76 MHz) 27.9, 50.5, 52.1, 55.3, 56.4, 59.1, 72.8, 79.4, 113.8, 129.2, 131.8, 158.8, 171.8; MS (*m*/*z*): 327 (M+1).

*4.11.12. (2R,3R)-3-Benzylamino-2-methoxy-5-nitro-pentanoic acid methyl ester (**14c**)*

Following the general procedure, as for **5a**,**b**, **14c** was obtained as yellow viscous liquid in 98% yield. [Found C, 56.83; H, 6.92; N, 9.63%. $C_{14}H_{20}N_2O_5$ requires C, 56.75; H, 6.80; N, 9.45%.] R_f (30% EtOAc/pet. ether) 0.26; $[\alpha]_D^{30}$ +42.5 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 1743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.98–2.08 (m, 2H, *H*-4), 2.31 (br s, 1H, –N*H*) 2.97–3.06 (m, 1H, *H*-3), 3.45 (s, 3H, –OC*H*$_3$), 3.69–3.79 (m, 4H, –NCH$_a$*H*$_b$Ph, –COOC*H*$_3$), 3.90 (d, *J*=13.1 Hz, –NC*H*$_a$H$_b$Ph), 4.08 (d, *J*=3.1 Hz, 1H, *H*-2), 4.44–4.61 (m, 2H, *H*-5), 7.26–7.37 (m, 5H, Ar); δ_C (50.32 MHz) 27.8, 51.1, 52.1, 56.5, 59.1, 72.7, 79.3, 127.4, 128.2, 128.5, 139.3, 171.6; MS (*m*/*z*): 297 (M+1).

*4.11.13. (3R,4R)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine-2-one (**15a**)*

Following the general procedure, as for **6a**,**b**, **15a** was prepared in 67% as a gummy compound. [Found C, 62.32; H, 7.33; N, 11.47%. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19%.] R_f (60% EtOAc/pet. ether) 0.33; $[\alpha]_D^{30}$ +38.2 (*c* 0.55, $CHCl_3$); ν_{max} ($CHCl_3$) 1651 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.00–2.28 (m, 2H, *H*-5), 3.56 (s, 3H, –OC*H*$_3$), 3.58–3.73 (m, 3H, *H*-4, *H*-6), 3.75 (s, 3H, Ar–OC*H*$_3$), 3.90 (d, *J*=3.5 Hz, 1H, *H*-3), 6.65 (d, *J*=9.0 Hz, 2H, Ar), 6.80 (d, *J*=9.0 Hz, 2H, Ar); δ_C (50.32 MHz) 23.3, 47.2, 51.7, 55.6, 59.3, 77.3, 114.9, 116.2, 139.5, 153.1, 162.9; MS (*m*/*z*): 251 (M+1).

*4.11.14. (3R,4R)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine-2-one (**15b**)*

Following the general procedure, as for **6a**,-**b**, **15b** was obtained in 61% yield as a gummy compound. [Found C, 63.85; H, 7.77; N, 10.55%. $C_{14}H_{20}N_2O_3$ requires C, 63.60; H, 7.64; N, 10.60%.] R_f (60% acetone/pet. ether) 0.16; $[\alpha]_D^{30}$ +48.0 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$) 1650 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.84–2.02 (m, 1H, *H*$_a$-5), 2.04–2.24 (m, 1H, *H*$_b$-5), 3.07–3.17 (m, 1H, *H*-4), 3.46–3.52 (m, 1H, *H*-6), 3.55 (s, 3H, –OC*H*$_3$), 3.67–3.79 (m, 3H, *H*-6, –NC*H*$_2$), 3.80 (s, 3H, Ar–OC*H*$_3$), 3.87 (d, *J*=3.5 Hz, 1H, *H*-3), 3.95–4.15 (br s, 2H, 2×N–*H*), 6.87 (d, *J*=8.6 Hz, 2H, Ar), 7.24 (d, *J*=8.6 Hz, 2H, Ar); δ_C (50.32 MHz) 23.3, 46.0, 49.9, 53.1, 55.3, 59.3, 77.3, 113.9, 129.3, 131.4, 158.8, 164.3; MS (*m*/*z*): 265 (M+1).

*4.11.15. (3R,4R)-4-Benzylamino-3-methoxypiperidine-2-one (**15c**)*

Following the general procedure, as for **6a**,**b**, **15c** was obtained in 55% yield as a gummy compound. [Found C, 66.53; H, 7.92; N, 11.67%. $C_{13}H_{18}N_2O_2$ requires C, 66.64; H, 7.74; N, 11.96%.] R_f (70% acetone/pet. ether) 0.32; $[\alpha]_D^{30}$ +36.8 (*c* 0.68, MeOH); ν_{max} ($CHCl_3$) 1655 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.02–2.33 (m, 2H, *H*-5), 3.22–3.30 (m, 1H, *H*-4), 3.53 (s, 3H, –OC*H*$_3$), 3.64–3.80 (m, 2H, *H*-6), 3.90–4.09 (m, 3H, *H*-3, –NC*H*$_2$), 7.28–7.40 (m, 5H, Ar), 7.50 (br s, 1H, –CON*H*); δ_C (50.32 MHz) 22.2, 47.0, 49.6, 52.7, 59.3, 76.3, 128.3, 128.8, 128.9, 135.3, 163.0; MS (*m*/*z*): 235 (M+1).

*4.11.16. (3S,4R)-3-Methoxy-4-(4-methoxy-phenylamino)-piperidine (**16a**)*

Following the general procedure, as for **7a**,**b**, **16a** was obtained in 52% yield as a viscous liquid. [Found C, 66.24; H, 8.47; N, 12.03%. $C_{13}H_{20}N_2O_2$ requires C, 66.07; H, 8.53; N, 11.85%.] R_f (60% EtOAc/pet. ether) 0.28; $[\alpha]_D^{30}$ +12.5 (*c* 0.72, $CHCl_3$); ν_{max} ($CHCl_3$) 3215, 3368 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.72–2.04 (m, 2H, *H*-5), 2.69–2.85 (m, 2H, *H*-6), 3.25–3.45 (m, 5H, *H*-2, –OC*H*$_3$), 3.57–3.70 (m, 2H, *H*-4, *H*-3), 3.74 (s, 3H, Ar–OC*H*$_3$), 6.62 (d, *J*=7.8 Hz, 2H, Ar), 6.78 (d, *J*=7.8 Hz, 2H, Ar), 7.63 (br s, 1H, Ar–N*H*); δ_C (125.76 MHz) 25.6, 52.9, 55.6, 55.9, 56.9, 57.0, 76.0, 114.9, 116.3, 140.2, 152.9; MS (*m*/*z*): 237 (M+1).

*4.11.17. (3S,4R)-3-Methoxy-4-(4-methoxy-benzylamino)-piperidine (**16b**)*

Following the general procedure, as for **7a**,**b**, **16b** was prepared in 50% yield as a viscous liquid. [Found C, 67.34; H, 8.92; N, 11.27%. $C_{14}H_{22}N_2O_2$ requires C, 67.17; H, 8.86; N, 11.19%.] R_f (70% acetone/pet. ether) 0.18; $[\alpha]_D^{30}$ +18.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3257, 3328 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.60–1.99 (m, 3H, *H*-5, *H*$_a$-2), 2.05 (br s, 1H, –N*H*), 2.40–2.78 (m, 3H, *H*-6, *H*-2), 3.18–3.26 (m, 1H, *H*-4), 3.36 (br s, 1H, –N*H*), 3.42 (s, 3H, –OC*H*$_3$), 3.47–3.58 (m, 1H, *H*-3), 3.73–3.87 (m, 5H, Ar–OC*H*$_3$, –NC*H*$_2$), 6.88 (d, *J*=8.7 Hz, 2H, Ar), 7.26 (d, *J*=8.7 Hz, 2H, Ar); δ_C (100.61 MHz) 26.5, 49.1, 52.1, 53.4, 54.3, 55.3, 57.5, 73.9, 114.0, 129.5, 130.5, 159.0; MS (*m*/*z*): 251 (M+1).

*4.11.18. (3S,4R)-4-Benzylamino-3-methoxypiperidine (**16c**)*

Following the general procedure, as for **7a**,**b**, **16c** was obtained in 49% yield as a gummy compound. [Found C, 71.12; H, 9.32; N, 12.95%. $C_{13}H_{20}N_2O$ requires C, 70.87; H, 9.15; N, 12.72%.] R_f (70% acetone/pet. ether) 0.25; $[\alpha]_D^{30}$ +11.2 (*c* 0.72, $CHCl_3$); ν_{max} ($CHCl_3$) 3211, 3319 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.65–1.95 (m, 2H, *H*-5), 2.35–2.70 (m, 2H, *H*-6), 2.80–3.45 (m, 6H, *H*-2, –N*H*, –OC*H*$_3$), 3.50–3.90 (m, 4H, *H*-4, *H*-3, –NC*H*$_2$), 4.34 (br s, 1H, –N*H*), 7.20–7.33 (m, 5H, Ar); δ_C (100.61 MHz) 26.6, 50.3, 55.0, 56.5, 56.9, 57.4, 75.9, 127.1, 128.1, 128.4, 139.6; MS (*m*/*z*): 221 (M+1).

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Supplementary data

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