Diastereoselective Synthesis of 4-Hydroxypiperidin-2-ones via Cu(I)-Catalyzed Reductive Aldol Cyclization

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General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 was distilled from CaH_2 . THF was distilled from sodium benzophenone ketyl. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH_2 . All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.¹ Melting points were recorded on a Gallenkamp melting point

1. W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl_3 . ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl_3 at 7.27 ppm, $\text{C}_2\text{D}_2\text{Cl}_4$ at 5.94 ppm, CD_3OD at 3.35 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl_3 at 77.0 ppm, $\text{C}_2\text{D}_2\text{Cl}_4$ at 74.2 ppm, CD_3OD at 49.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135° . High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

Preparation of the Cyclization Substrates

Preparation of β -Dimethylaminoketone Hydrochlorides: General Procedure A

A mixture of the appropriate methyl ketone (1.0 equiv), dimethylamine hydrochloride (1.1 equiv), paraformaldehyde (1.4 equiv), and conc. HCl (5 $\mu\text{L}/\text{mmol}$ of methyl ketone) in ethanol (2.0 M with respect to methyl ketone) was heated at reflux until TLC analysis showed the reaction to be complete. The reaction was cooled to room temperature and the ethanol was removed *in vacuo*. EtOAc was added, and the suspension was stirred for 15 min before the solid product was collected by filtration, washed with EtOAc (x 2) and dried under vacuum to leave the β -dimethylaminoketone hydrochloride.

1-Dimethylamino-5-methylhexan-3-one hydrochloride (9).² The title compound was prepared according to general procedure A from 4-methylpentan-2-one (1.25 mL, 10.0 mmol), dimethylamine hydrochloride (906 mg, 11.0 mmol), paraformaldehyde (443 mg, 14.0 mmol) and conc. HCl (50 μ L) for a reaction time of 20 h to give a white crystalline solid (700 mg, 36%) which displayed identical spectroscopic data to those previously reported.²

3-Dimethylamino-1-(4-methylphenyl)propan-1-one hydrochloride (10).

The title compound was prepared according to general procedure A from 4'-methylacetophenone (5.6 mL, 40 mmol), dimethylamine hydrochloride (3.62 g, 44.0 mmol), paraformaldehyde (1.77 g, 56.0 mmol) and conc. HCl (0.2 mL) for a reaction time of 36 h to give a white solid (8.03 g, 88%). m.p. 158-160 °C; ¹H NMR (360 MHz, CD₃OD) δ 7.99 (2H, d, J = 8.3 Hz, ArH), 7.37 (2H, d, J = 8.3 Hz, ArH), 3.69-3.59 (4H, m, CH₂CH₂N), 3.01 (6H, s, N(CH₃)₂), 2.45 (3H, s, CH₃C₆H₄); ¹³C NMR (62.9 MHz, CD₃OD) δ 197.8 (C), 146.1 (C), 134.7 (C), 130.5 (2 x CH), 129.4 (2 x CH), 54.3 (CH₂), 43.8 (2 x CH₃), 34.2 (CH₂), 21.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₂H₁₈NO [M-Cl]⁺: 192.1383, found: 192.1385.

3-Dimethylamino-1-(furan-2-yl)propan-1-one hydrochloride (11).

The title compound was prepared according to general procedure A from 2-furyl methyl ketone (2.22 g, 20.0 mmol), dimethylamine hydrochloride (1.81 g, 22.0 mmol), paraformaldehyde (885 mg, 28.0 mmol) and conc. HCl (0.1 mL) for a reaction time of 20 h to give an off-white crystalline solid (3.00 g, 74%). m.p. 180-182 °C; ¹H NMR (360 MHz, CD₃OD) δ 7.89 (1H, dd, J = 1.7, 0.7 Hz, CH), 7.52 (1H, dd, J = 3.7, 0.7 Hz, CH), 7.34 (1H, dd, J = 3.7, 1.7 Hz, CH), 3.61-3.57 (2H, m, CH₂N), 3.53-3.49 (2H, m, CH₂CH₂N); ¹³C NMR (62.9 MHz, CD₃OD) δ 186.6 (C), 153.0 (C), 149.2 (CH), 120.0 (CH), 113.8 (CH), 53.7 (CH₂), 43.9 (2 x CH₃), 33.8 (CH₂); HRMS (ES) Exact mass calcd for C₉H₁₄NO₂ [M-Cl]⁺: 168.1019, found: 168.1018.

Preparation of β -Arylamino ketones: General Procedure B

A solution of the appropriate alkyl vinyl ketone (1.2 equiv) and *p*-anisidine (1.0 equiv) in THF (1.0 M with respect to *p*-anisidine) was heated at reflux for 24 h. The mixture was cooled to room temperature

2. Spencer, T. A.; Watt, D. S.; Friary, R. J. *J. Org. Chem.* **1967**, 32, 1234–1236.

and washed with brine. The aqueous layer was extracted with EtOAc (x 2), and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the β -aminoketone.

4-(4-Methoxyphenylamino)butan-2-one (12). The title compound was prepared according to general procedure B from methyl vinyl ketone (7.0 mL, 85 mmol) and *p*-anisidine (8.86 g, 71.2 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give an orange/brown oil (13.6 g, 99%), which was judged to be *ca.* 90% pure by ^1H NMR spectroscopy. IR (film) 3379 (NH), 2935, 1711 (C=O), 1513, 1465, 1361, 1237, 1169, 1036, 822 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 6.78 (2H, d, J = 9.0 Hz, ArH), 6.58 (2H, d, J = 9.0 Hz, ArH), 3.74 (3H, s, OCH_3), 3.53 (1H, bs, NH), 3.34 (2H, t, J = 6.2 Hz, CH_2N), 2.71 (2H, t, J = 6.2 Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.15 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 208.2 (C), 152.1 (C), 141.7 (C), 114.7 (2 x CH), 114.4 (2 x CH), 55.6 (CH_3), 42.5 (CH_2), 39.3 (CH_2), 30.2 (CH_3); LRMS (ES) Mass calculated for $\text{C}_{11}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 194.1, found: 194.0;

4-(4-Methoxyphenylamino)pentan-3-one (13). The title compound was prepared according to general procedure B from ethyl vinyl ketone (1.47 mL, 14.3 mmol) and *p*-anisidine (1.48 g, 11.9 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a dark orange solid (1.84 g, 75%) that displayed identical spectroscopic data to those previously reported.³

Preparation of β -Arylamino ketones: General Procedure C

A solution of the appropriate β -dimethylaminoketone hydrochloride (1.0 equiv) and the appropriate aniline (1.0 equiv) in 1:1 EtOH/ H_2O (1.0 M) was heated at reflux for 24 h. After the mixture was cooled to room temperature, the precipitated solid was collected by filtration, washed with H_2O (x 2) and EtOH (x 2), and dried under vacuum to afford the β -aminoketone.

1-(4-Methoxyphenylamino)-5-methylhex-3-one (14). The title compound was prepared according to general procedure C from the dimethylamine hydrochloride **9**

3. G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, 125, 11253–11258.

(697 mg, 3.60 mmol) and *p*-anisidine (448 mg, 3.60 mmol) to give an orange solid (495 mg, 56%). m.p. 45-47 °C; IR (CHCl₃) 3385 (NH), 2956, 1707 (C=O), 1514, 1465, 1367, 1236, 1178, 1038, 820 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.78 (2H, d, *J* = 9.0 Hz, ArH), 6.59 (2H, d, *J* = 9.0 Hz, ArH), 3.75 (3H, s, OCH₃), 3.34 (2H, t, *J* = 6.1 Hz, CH₂N), 2.68 (2H, t, *J* = 6.1 Hz, CH₂CH₂N), 2.29 (2H, d, *J* = 6.9 Hz, CHCH₂), 2.19-2.08 (1H, m, CHCH₂), 0.91 (6H, d, *J* = 6.6 Hz, (CH₃)₂CH); ¹³C NMR (90.6 MHz, CDCl₃) δ 210.1 (C), 152.1 (C), 141.8 (C), 114.7 (2 x CH), 114.4 (2 x CH), 55.5 (CH₃), 51.9 (CH₂), 42.0 (CH₂), 39.4 (CH₂), 24.4 (CH), 22.4 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₄H₂₂NO₂ [M+H]⁺: 236.1645, found: 236.1644.

3-(4-Methoxyphenylamino)-1-phenylpropan-1-one (15). The title compound was prepared according to general procedure C from commercially available 3-(dimethylamino)propiophenone hydrochloride (4.32 g, 20.0 mmol) and *p*-anisidine (2.49 g, 20.0 mmol) to give a light yellow/green crystalline solid (4.80 g, 94%), which displayed identical spectroscopic data to those previously reported.⁴

3-(4-Methoxyphenylamino)-1-(4-methylphenyl)propan-1-one (16). The title compound was prepared according to general procedure C from the demethylamine hydrochloride **10** (4.55 g, 20.0 mmol) and *p*-anisidine (2.49 g, 20.0 mmol) to give a yellow/grey crystalline solid (4.13 g, 77%). m.p. 120-121 °C; IR (CHCl₃) 3377 (NH), 2856, 1672 (C=O), 1516, 1382, 1288, 1037, 908, 818, 732 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.86 (2H, d, *J* = 8.5 Hz, ArH), 7.26 (2H, d, *J* = 8.5 Hz, ArH), 6.81 (2H, d, *J* = 8.8 Hz, ArH), 6.64 (2H, d, *J* = 8.8 Hz, ArH), 3.75 (4H, br s, OCH₃ and NH), 3.55 (2H, t, *J* = 6.2 Hz, CH₂N), 3.23 (2H, t, *J* = 6.2 Hz, CH₂CH₂N), 2.42 (3H, s, CH₃C₆H₄); ¹³C NMR (62.9 MHz, CDCl₃) δ 198.9 (C), 152.1 (C), 144.0 (C), 141.9 (C), 134.1 (C), 129.1 (2 x CH), 128.0 (2 x CH), 114.8 (2 x CH), 114.4 (2 x CH), 55.6 (CH₃), 39.8 (CH₂), 37.4 (CH₂), 21.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₁₉NO₂ [M+H]⁺: 270.1489, found: 270.1487.

3-(4-Methoxyphenylamino)-1-furan-2-ylpropan-1-one (17). The title compound was prepared according to general procedure C from the dimethylamine hydrochloride **11** (2.44 g, 12.0 mmol) and *p*-anisidine (1.49 g, 12.0 mmol) to give a yellow/brown solid (1.10 g, 37%). m.p. 78-79 °C; IR (CHCl₃) 3380 (NH), 2832, 1670 (C=O), 1568,

4. T.-P. Loh, S. B. K. Y. Liung, K.-L. Tan, L.-L. Wei, *Tetrahedron* **2000**, *56*, 3227–3237.

1514, 1467, 1395, 1238, 1034, 822 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.58 (1H, dd, $J = 1.7, 0.6$ Hz, CH), 7.18 (1H, dd, $J = 3.6, 0.6$ Hz, CH), 6.79 (2H, d, $J = 8.9$ Hz, ArH), 6.62 (2H, d, $J = 8.9$ Hz, ArH), 6.53 (1H, dd, $J = 3.6, 1.7$ Hz, CH), 3.82 (1H, br s, NH), 3.75 (3H, s, OCH_3), 3.53 (2H, t, $J = 6.2$ Hz, CH_2N), 3.12 (2H, t, $J = 6.2$ Hz, $\text{CH}_2\text{CH}_2\text{N}$); ^{13}C NMR (90.6 MHz, CDCl_3) δ 188.3 (C), 152.6 (C), 152.3 (C), 146.5 (CH), 141.8 (C), 117.3 (CH), 114.9 (2 x CH), 114.5 (2 x CH), 112.3 (CH), 55.7 (CH_3), 39.8 (CH_2), 37.6 (CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 246.1125, found: 246.1126.

3-(2-Methoxyphenylamino)-1-phenylpropan-1-one (18). The title compound was prepared according to general procedure C from commercially available 3-(dimethylamino)propiofenone hydrochloride (6.48 g, 30.0 mmol) and *o*-anisidine (3.4 mL, 30 mmol) and purified by recrystallization from EtOH to give an off-white crystalline solid (5.80 g, 76%). m.p. 62–64 $^\circ\text{C}$; IR (CHCl_3) 3410 (NH), 2937, 1682 ($\text{C}=\text{O}$), 1601, 1514, 1457, 1251, 1223, 1028, 738 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.00–7.97 (2H, m, ArH), 7.61–7.57 (1H, m, ArH), 7.50–7.46 (2H, m, ArH), 6.94–6.89 (1H, m, ArH), 6.80–6.78 (1H, m, ArH), 6.73–6.69 (2H, m, ArH), 4.62 (1H, br s, NH), 3.84 (3H, s, OCH_3), 3.66 (2H, t, $J = 6.4$ Hz, CH_2N), 3.34 (2H, t, $J = 6.4$ Hz, $\text{CH}_2\text{CH}_2\text{N}$); ^{13}C NMR (90.6 MHz, CDCl_3) δ 198.9 (C), 147.0 (C), 137.6 (C), 136.6 (C), 133.1 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 121.1 (CH), 116.5 (CH), 109.6 (CH), 109.4 (CH), 55.2 (CH_3), 38.3 (CH_2), 37.8 (CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 256.1332, found: 256.1331.

4-(2-Methoxyphenylamino)butan-2-one (19)

A solution of methyl vinyl ketone (4.3 mL, 52 mmol), *o*-anisidine (5.6 mL, 50 mmol) and $\text{La}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ (1.47 g, 2.50 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 48 h. The mixture was washed with saturated aqueous NaHCO_3 solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol $\rightarrow$ 60% EtOAc/petrol) afforded the title compound as a pale pink crystalline solid (5.65 g, 57%). m.p. 40–42 $^\circ\text{C}$; IR (CHCl_3) 3408 (NH), 2939, 1713 ($\text{C}=\text{O}$), 1602, 1514, 1457, 1247, 1223, 1128, 1028 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 6.93 (1H, m, ArH), 6.81–6.76 (1H, m, ArH), 6.75–6.68 (1H, m, ArH), 6.66–6.63 (1H, m, ArH), 4.45 (1H, br s, NH), 3.84 (3H, s, OCH_3), 3.44 (2H, t, $J = 6.4$ Hz,

CH_2N), 2.76 (2H, t, $J = 6.4$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.16 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (90.6 MHz, CDCl_3) δ 207.5 (C), 146.8 (C), 137.4 (C), 121.0 (CH), 116.4 (CH), 109.5 (CH), 109.3 (CH), 55.1 (CH_3), 42.5 (CH_2), 37.8 (CH_2), 29.9 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 194.1176, found: 194.1177.

Acylation of β -Arylaminoketones: General Procedure D

The appropriate α,β -unsaturated acid chloride (1.5 equiv) was added dropwise to a vigorously stirred mixture of the appropriate β -arylaminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of β -arylaminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of β -arylaminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous NaHCO_3 solution and CH_2Cl_2 . The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclization substrate.

***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl) propenamide (1a).** The title compound

was prepared according to general procedure D from the amine **12** (1.46 g, 7.56 mmol) and acryloyl chloride (950 μL , 11.2 mmol) for a reaction time of 1.5 h and purified by column chromatography (50% EtOAc/petrol) to give a light brown oil (970 mg, 52%). IR (film) 2956, 1713 ($\text{C}=\text{O}$), 1656 ($\text{C}=\text{O}$), 1618, 1512, 1412, 1249, 1169, 1030, 838 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.02 (2H, d, $J = 8.9$ Hz, ArH), 6.87 (2H, d, $J = 8.9$ Hz, ArH), 6.27 (1H, dd, $J = 16.8, 2.0$ Hz, =CH), 5.94 (1H, dd, $J = 16.8, 10.3$ Hz, =CH), 5.44 (1H, dd, $J = 10.3, 2.0$ Hz, =CH), 3.94 (2H, t, $J = 7.4$ Hz, CH_2N), 3.78 (3H, s, OCH_3), 2.71 (3H, t, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.08 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (90.6 MHz, CDCl_3) δ 206.8 (C), 165.6 (C), 158.9 (C), 134.1 (C), 129.1 (2 x CH), 128.4 (CH), 127.3 (CH_2), 114.6 (2 x CH), 55.3 (CH_3), 44.9 (CH_2), 41.2 (CH_2), 29.8 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 248.1281, found: 248.1288.

***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl) propenamide (1b).** The title compound was prepared according to general procedure D from the amine **13** (500 mg, 2.41 mmol) and acryloyl chloride (305 μ L, 3.60 mmol) for a reaction time of 20 h and purified by column chromatography (EtOAc) to give an orange/brown solid (620 mg, 98%). m.p. 43-44 $^{\circ}$ C; IR (CHCl₃) 2938, 1712 (C=O), 1654 (C=O), 1615, 1510, 1412, 1249, 1182, 1031, 795 cm^{-1} ; ¹H NMR (360 MHz, CDCl₃) δ 7.06 (2H, d, J = 9.0 Hz, ArH), 6.91 (2H, d, J = 9.0 Hz, ArH), 6.33 (1H, dd, J = 16.8, 2.0 Hz, =CH), 5.99 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.50 (1H, dd, J = 10.3, 2.0 Hz, =CH), 4.00 (2H, t, J = 7.5 Hz, CH₂N), 3.83 (3H, s, OCH₃), 2.74 (2H, t, J = 7.5 Hz, CH₂CH₂N), 2.43 (2H, q, J = 7.3 Hz, CH₂CH₃), 1.02 (3H, t, J = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 209.7 (C), 165.8 (C), 159.0 (C), 134.3 (C), 129.2 (2 x CH), 128.5 (CH), 127.4 (CH₂), 114.7 (2 x CH), 55.5 (CH₃), 45.2 (CH₂), 40.1 (CH₂), 36.0 (CH₂), 7.6 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₀NO₃ [M+H]⁺: 262.1438, found: 262.1441.

***N*-(4-Methoxyphenyl)-*N*-(5-methyl-3-oxohexyl)propenamide (1c).** The title compound was prepared according to general procedure D from the amine **14** (500 mg, 2.12 mmol) and acryloyl chloride (260 μ L, 3.07 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give an orange oil (400 mg, 65%). IR (film) 2956, 1710 (C=O), 1657 (C=O), 1616, 1511, 1411, 1249, 1181, 1032, 839 cm^{-1} ; ¹H NMR (360 MHz, CDCl₃) δ 7.05 (2H, d, J = 8.9 Hz, ArH), 6.91 (2H, d, J = 8.9 Hz, ArH), 6.38 (1H, dd, J = 16.8, 2.0 Hz, =CH), 5.98 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.49 (1H, dd, J = 10.3, 2.0 Hz, =CH), 3.98 (2H, t, J = 7.5 Hz, CH₂N), 2.72 (2H, d, J = 6.9 Hz, (CH₃)₂CHCH₂), 2.15-2.03 (1H, m, (CH₃)₂CH), 0.88 (6H, d, J = 6.6 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 208.9 (C), 165.7 (C), 158.9 (C), 134.3 (C), 129.2 (2 x CH), 128.5 (CH), 127.3 (CH₂), 114.7 (2 x CH), 55.4 (CH₃), 51.8 (CH₂), 45.0 (CH₂), 40.8 (CH₂), 24.3 (CH), 22.5 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₄NO₃ [M+H]⁺: 290.1751, found: 290.1752.

***N*-(4-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)propenamide (1d).** The title compound was prepared according to general procedure D from the amine **15** (5.00 g, 19.6 mmol) and acryloyl chloride (2.60 mL, 30.7 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (5.76 g, 95%). m.p. 51-53 $^{\circ}$ C; IR (CHCl₃) 2933, 1681 (C=O), 1655 (C=O), 1614, 1510, 1446, 1411, 1249, 1210, 1180 cm^{-1} ; ¹H NMR (360 MHz, CDCl₃) δ 7.96-7.93 (2H, m, ArH), 7.57 (1H, m, ArH), 7.46-7.42

(2H, m, ArH), 7.11-7.06 (2H, m, ArH), 6.93-6.89 (2H, m, ArH), 6.36 (1H, dd, $J = 16.8, 2.0$ Hz, =CH), 6.03 (1H, dd, $J = 16.8, 10.3$ Hz, =CH), 5.52 (1H, dd, $J = 10.3, 2.0$ Hz, =CH), 4.14 (2H, t, $J = 7.5$ Hz, CH₂N), 3.81 (3H, s, OCH₃), 3.34 (2H, t, $J = 7.5$ Hz, CH₂CH₂N); ¹³C NMR (62.9 MHz, CDCl₃) δ 198.4 (C), 165.9 (C), 159.0 (C), 136.5 (C), 134.5 (C), 133.2 (CH), 129.1 (2 x CH), 128.5 (3 x CH), 128.0 (2 x CH), 127.4 (CH₂), 114.7 (2 x CH), 55.4 (CH₃), 46.1 (CH₂), 36.6 (CH₂); HRMS (FAB) Exact mass calcd for C₁₉H₂₀NO₃ [M+H]⁺: 310.1438, found: 310.1442.

***N*-(4-Methoxyphenyl)-*N*-[3-(4-methylphenyl)-3-oxopropyl]propenamide**

(1e). The title compound was prepared according to general procedure D

from the amine **16** (1.08 g, 4.01 mmol) and acryloyl chloride (509 μL, 6.02 mmol) for a reaction time of 20 h and purified by column chromatography (40% EtOAc/petrol) to give a pale yellow oil (1.26 g, 97%). IR (film) 2954, 1678 (C=O), 1656 (C=O), 1608, 1510, 1442, 1410, 1249, 1180, 1030 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.84 (2H, d, $J = 8.2$ Hz, ArH), 7.23 (2H, d, $J = 8.2$ Hz, ArH), 7.08 (2H, d, $J = 9.0$ Hz, ArH), 6.90 (2H, d, $J = 9.0$ Hz, ArH), 6.35 (1H, dd, $J = 16.8, 2.0$ Hz, =CH), 6.03 (1H, dd, $J = 16.8, 10.3$ Hz, =CH), 5.50 (1H, dd, $J = 10.3, 2.0$ Hz, =CH), 4.13 (2H, t, $J = 7.5$ Hz, CH₂N), 3.81 (3H, s, OCH₃), 3.30 (2H, t, $J = 7.5$ Hz, CH₂CH₂N), 2.38 (3H, s, CH₃C₆H₄); ¹³C NMR (62.9 MHz, CDCl₃) δ 198.0 (C), 165.9 (C), 158.9 (C), 143.9 (C), 134.5 (C), 134.1 (C), 129.2 (2 x CH), 129.1 (2 x CH), 128.6 (CH), 128.1 (2 x CH), 127.3 (CH₂), 114.7 (2 x CH), 55.4 (CH₃), 46.2 (CH₂), 36.4 (CH₂), 21.6 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₂NO₃ [M+H]⁺: 324.1594, found: 324.1594.

***N*-(4-Methoxyphenyl)-*N*-[3-(furan-2-yl)-3-oxopropyl]propenamide (1f).**

The title compound was prepared according to general procedure D from the amine

17 (1.00 g, 4.08 mmol) and acryloyl chloride (509 μL, 6.02 mmol) for a reaction

time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid. m.p. 93-94 °C; IR (CHCl₃) 2937, 1656 (C=O), 1614, 1569, 1510, 1469, 1411, 1249, 1182, 1029 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.57 (1H, dd, $J = 1.7, 0.7$ Hz, CH), 7.25 (1H, dd, $J = 3.6, 0.7$ Hz, CH), 7.07 (1H, d, $J = 9.0$ Hz, ArH), 6.90 (1H, d, $J = 9.0$ Hz, ArH), 6.52 (1H, dd, $J = 3.6, 1.7$ Hz, CH), 6.34 (1H, dd, $J = 16.8, 2.0$ Hz, =CH), 6.01 (1H, dd, $J = 16.8, 10.3$ Hz, =CH), 5.50 (1H, dd, $J = 10.3, 2.0$ Hz, =CH), 4.12 (2H, t, $J = 7.5$ Hz, CH₂N), 3.82 (3H, s, OCH₃), 3.18 (2H, t, $J = 7.5$ Hz, CH₂CH₂N); ¹³C NMR (62.9 MHz, CDCl₃) δ 187.1 (C), 165.9 (C), 159.0 (C), 152.3 (C), 146.5 (CH), 134.4 (C), 129.2 (2

x CH), 128.5 (CH), 127.5 (CH₂), 117.7 (CH), 114.7 (2 x CH), 112.2 (CH), 55.5 (CH₃), 45.9 (CH₂), 36.6 (CH₂); HRMS (ES) Exact mass calcd for C₁₇H₁₈NO₄ [M+H]⁺: 300.1230, found: 300.1229.

***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(E)-but-2-enamide (1g).** The title compound was prepared according to general procedure D from the amine **12** (970 mg, 5.02 mmol) and crotonoyl chloride (718 μ L, 7.50 mmol) for a reaction

time of 2 h and purified by column chromatography (50% EtOAc/petrol) to give a light brown oil (1.01 g, 77%). IR (film) 2936, 1713 (C=O), 1664 (C=O), 1627, 1511, 1444, 1292, 1249, 1168, 1031 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.06 (2H, d, J = 9.0 Hz, ArH), 6.94-6.84 (1H, m, =CH), 6.92 (2H, d, J = 9.0 Hz, ArH), 5.66 (1H, dq, J = 15.1, 1.7 Hz, =CH), 3.98 (2H, t, J = 7.4 Hz, CH₂N), 3.85 (3H, s, OCH₃), 2.14 (3H, s, CH₃C=O), 1.73 (3H, dd, J = 6.9, 1.7 Hz, CH₃CH=); ¹³C NMR (62.9 MHz, CDCl₃) δ 207.0 (C), 166.1 (C), 158.8 (C), 141.2 (CH), 134.5 (C), 129.2 (2 x CH), 122.6 (CH), 114.6 (2 x CH), 55.4 (CH₃), 44.9 (CH₂), 41.5 (CH₂), 29.9 (CH₃), 17.8 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₀NO₃ [M+H]⁺: 262.1438, found: 262.1437.

***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl)-(E)-but-2-enamide (1h).** The title compound was prepared according to general procedure D from the amine **13** (500 mg, 2.41 mmol) and crotonoyl chloride (345 μ L, 3.60 mmol) for a reaction

time of 20 h and purified by column chromatography (EtOAc) to give an orange oil (645 mg, 97%). IR (film) 2938, 1712 (C=O), 1665 (C=O), 1627, 1510, 1445, 1292, 1249, 1182, 1032 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.05 (2H, d, J = 9.0 Hz, ArH), 6.91 (2H, d, J = 9.0 Hz, ArH), 6.91-6.83 (1H, m, =CH), 5.65 (1H, dq, J = 15.1, 1.6 Hz, =CH), 3.96 (2H, t, J = 7.4 Hz, CH₂N), 3.83 (3H, s, OCH₃), 2.72 (2H, t, J = 7.5 Hz, CH₂CH₂N), 2.41 (2H, q, J = 7.3 Hz, CH₂CH₃), 1.71 (3H, dd, J = 6.9, 1.6 Hz, CH₃CH=), 1.01 (3H, t, J = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 209.8 (C), 166.2 (C), 158.8 (C), 141.3 (CH), 134.7 (C), 129.3 (2 x CH), 122.7 (CH), 114.6 (2 x CH), 55.5 (CH₃), 45.1 (CH₂), 40.2 (CH₂), 36.0 (CH₂), 17.9 (CH₃), 7.6 (CH₃); HRMS (ES) Exact mass calcd for C₁₆H₂₂NO₃ [M+H]⁺: 276.1594, found: 276.1594.

***N*-(2-Methoxyphenyl)-*N*-(3-oxobutyl)propenamide (1i).** The title compound was prepared according to general procedure D from the amine **19** (483 mg, 2.50 mmol) and acryloyl chloride (317 μ L, 3.75 mmol) for a reaction time of 20 h and purified

by column chromatography (50% EtOAc/petrol→EtOAc) to give a light orange oil (610 mg, 99%). IR

(film) 2944, 1713 (C=O), 1657 (C=O), 1618, 1595, 1500, 1415, 1267, 1024, 756 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.29-7.24 (1H, m, ArH), 7.02 (1H, dd, J = 8.0, 1.8 Hz, ArH), 6.92-6.88 (2H, m, ArH), 6.24 (1H, dd, J = 16.8, 2.1 Hz, =CH), 5.85 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.38 (1H, dd, J = 10.3, 2.1 Hz, =CH), 3.99-3.91 (1H, m, CH_2N), 3.82-3.74 (1H, m, CH_2N), 3.72 (3H, s, OCH_3), 2.71 (2H, t, J = 7.4 Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.04 (3H, s, $\text{CH}_3\text{C=O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 207.1 (C), 166.0 (C), 155.1 (C), 130.0 (C), 129.8 (CH), 129.5 (CH), 128.2 (CH), 127.0 (CH_2), 120.8 (CH), 111.7 (CH), 55.3 (CH_3), 43.9 (CH_2), 41.3 (CH_2), 29.8 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 248.1281, found: 248.1281.

***N*-(2-Methoxyphenyl)-*N*-(3-oxobutyl)-(E)-but-2-enamide (1j).** The title

compound was prepared according to general procedure D from the amine **19** (483 mg, 2.50 mmol) and crotonoyl chloride (360 μL , 3.76 mmol) for a reaction

time of 20 h and purified by column chromatography (50% EtOAc/petrol $\rightarrow$ EtOAc) to give a yellow oil (653 mg, >99%). IR (film) 2942, 1713 (C=O), 1666 (C=O), 1629, 1500, 1443, 1398, 1369, 1291, 1244 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.36-7.31 (1H, m, ArH), 7.08-7.05 (1H, m, ArH), 6.98-6.94 (2H, m, ArH), 6.90-6.82 (1H, m, =CH), 5.61-5.56 (1H, m, =CH), 4.07-3.99 (1H, m, CH_2N), 3.79 (3H, s, OCH_3), 2.84-2.69 (2H, m, $\text{CH}_2\text{CH}_2\text{N}$), 2.10 (3H, s, $\text{CH}_3\text{C=O}$), 1.68 (3H, app ddd, J = 6.9, 1.7, 0.9 Hz, $\text{CH}_3\text{CH=}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 207.3 (C), 166.3 (C), 155.2 (C), 140.8 (CH), 130.3 (C), 130.0 (CH), 129.3 (CH), 122.3 (CH), 120.7 (CH), 111.8 (CH), 55.3 (CH_3), 43.8 (CH_2), 41.5 (CH_2), 29.9 (CH_3), 17.7 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 262.1438, found: 262.1437.

***N*-(2-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)-(E)-but-2-enamide (1k).**

The title compound was prepared according to general procedure D from the amine **18** (1.03 g, 4.03 mmol) and crotonoyl chloride (575 μL , 6.00 mmol) for a

reaction time of 20 h and purified by column chromatography (50% EtOAc/petrol) to give an off-white solid (830 mg, 64%). m.p. 118-119 $^{\circ}\text{C}$; IR (CHCl_3) 2940, 1682 (C=O), 1666 (C=O), 1627, 1596, 1499, 1447, 1397, 1243, 1024 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.98-7.96 (2H, m, ArH), 7.56-7.52 (1H, m, ArH), 7.47-7.42 (2H, m, ArH), 7.36-7.31 (1H, m, ArH), 7.13-7.10 (1H, m, ArH), 7.00-6.88 (3H, m, ArH and =CH), 5.67-5.62 (1H, m, =CH), 4.18-4.10 (1H, m, CH_2N), 4.05-3.97 (1H, m, CH_2N), 3.75 (3H, s, OCH_3), 3.47-3.39 (1H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.36-3.27 (1H, m, $\text{CH}_2\text{CH}_2\text{N}$), 1.72 (3H, dd, J = 6.9, 1.7 Hz, $\text{CH}_3\text{CH=}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 198.8 (C), 166.6 (C), 155.3 (C), 141.0 (CH), 136.7 (C),

133.0 (CH), 130.8 (C), 130.0 (CH), 129.4 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 122.5 (CH), 120.8 (CH), 111.8 (CH), 55.4 (CH₃), 45.1 (CH₂), 37.0 (CH₂), 17.9 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₂NO₃ [M+H]⁺: 324.1594, found: 324.1594.

N-(4-Methoxyphenyl)-*N*-[2-methyl-3-oxo-3-phenylpropyl]propenamide (**3a**)

The title compound was prepared according to general procedure D from the amine **20**⁴ (808 mg, 3.00 mmol) for a reaction time of 16 h and purified by column chromatography (20 % EtOAc/petrol) to give a colorless oil (807 mg, 83 %). IR (film) 2934, 1681 (C=O), 1658 (C=O), 1617, 1510, 1446, 1409, 1248, 1031, 973 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.92-7.90 (2H, m, ArH), 7.56-7.52 (1H, m, ArH), 7.46-7.41 (2H, m, ArH), 6.93 (2H, d, *J* = 8.7 Hz, ArH), 6.82 (2H, d, *J* = 8.7 Hz, ArH), 6.34 (1H, dd, *J* = 16.8, 2.0 Hz, =CH), 5.98 (1H, dd, *J* = 16.8, 10.3 Hz, =CH), 5.48 (1H, dd, *J* = 10.3, 2.0 Hz, =CH), 4.17-3.95 (3H, m, CHCH₂N), 3.79 (3H, s, OCH₃), 1.22 (3H, d, *J* = 6.9 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 202.6 (C), 166.4 (C), 158.7 (C), 136.3 (C), 135.1 (C), 133.1 (CH), 129.0 (2 x CH), 128.7 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.4 (CH₂), 114.5 (2 x CH), 55.4 (CH₃), 53.4 (CH₂), 39.6 (CH), 16.0 (CH₃);

N-(4-Methoxyphenyl)-*N*-[*S*]-3-oxo-1-phenylbutyl]propenamide (**3b**)

The title compound was prepared according to general procedure D from the amine **21**⁵ (350 mg, 1.30 mmol, prepared in 85% ee according to a literature procedure⁵) and acryloyl chloride (165 μL, 1.95 mmol) for a reaction time of 5 h and purified by column chromatography (30% EtOAc/petrol) to give a colorless viscous oil (390 mg, 93%). [α]_D²² +20.9 (*c* 1.05, CHCl₃); IR (film) 2959, 1715 (C=O), 1653 (C=O), 1614, 1510, 1406, 1252, 1171, 1031, 834 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.26-7.24 (3H, m, ArH), 7.20-7.17 (2H, m, ArH), 6.77 (4H, br s, ArH), 6.50 (1H, dd, *J* = 9.1, 6.4 Hz, CHN), 6.35 (1H, dd, *J* = 16.8, 2.0 Hz, =CH), 5.81 (1H, dd, *J* = 16.8, 10.3 Hz, =CH), 5.46 (1H, dd, *J* = 10.3, 2.0 Hz,

5. W. Notz, S.-i. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, J. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131–1140.

=CH), 3.79 (3H, s, OCH₃), 3.16 (1H, dd, J = 15.7, 9.1 Hz, CH₂CHN), 2.96 (1H, dd, J = 15.7, 6.4 Hz, CH₂CHN), 2.24 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 205.8 (C), 165.6 (C), 159.0 (C), 138.8 (C), 131.1 (2 x CH), 130.5 (C), 128.8 (CH), 128.1 (2 x CH), 128.0 (2 x CH), 127.6 (CH), 127.4 (CH₂), 113.9 (2 x CH), 55.1 (CH), 54.5 (CH₃), 45.3 (CH₂), 29.7 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₂NO₃ [M+H]⁺: 324.1594, found: 324.1590.

Ethyl (2*S*)-2-*N*-(4-methoxyphenyl)acrylamido-4-oxopentanoate (**3c**)

The title compound was prepared according to general procedure D from the amine **22**⁵ (950 mg, 3.58 mmol, prepared in 96% ee according to a literature procedure⁵) and acryloyl chloride (457 μL, 5.40 mmol) for a reaction time of 1 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow solid (762 mg, 66%). m.p. 74-76 °C; [α]_D²² −41.9 (*c* 1.05, CHCl₃); IR (CHCl₃) 2981, 1739 (C=O), 1721 (C=O), 1659 (C=O), 1619, 1511, 1411, 1249, 1030, 841 cm^{−1}; ¹H NMR (360 MHz, CDCl₃) δ 7.19 (2H, d, J = 9.0 Hz, ArH), 6.90 (2H, d, J = 9.0 Hz, ArH), 6.33 (1H, dd, J = 16.8, 2.0 Hz, =CH), 5.96 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.51 (1H, dd, J = 10.3, 2.0 Hz, =CH), 4.96 (1H, app t, J = 6.5 Hz, CHCO₂Et), 4.26-4.16 (2H, m, CO₂CH₂CH₃), 3.83 (3H, s, OCH₃), 3.51 (1H, dd, J = 17.7, 6.9 Hz, CH₂CHCO₂Et), 2.87 (1H, dd, J = 17.7, 6.1 Hz, CH₂CHCO₂Et), 2.16 (3H, s, CH₃C=O), 1.27 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 205.3 (C), 170.1 (C), 165.9 (C), 159.2 (C), 134.0 (C), 129.6 (2 x CH), 128.1 (CH), 128.0 (CH₂), 114.5 (2 x CH), 61.5 (CH₂), 58.8 (CH), 55.4 (CH₃), 43.2 (CH₂), 30.1 (CH₃), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₁NO₅ [M+H]⁺: 320.1492, found: 320.1493.

Ethyl (2*S*,1'*S*)-2-*N*-(4-methoxyphenyl)acrylamido-2-(-2'-oxocyclohex-1'-yl)acetate (**3d**)

The title compound was prepared according to general procedure D from the amine **23**⁵ (1.07 g, 3.50 mmol, prepared in >99% ee according to a literature procedure⁵) and acryloyl chloride (444 μL, 5.25 mmol) for a reaction time of 2 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (1.21 g, 96%). m.p. 132-134 °C; [α]_D²² −187 (*c* 1.00, CHCl₃); IR (CHCl₃) 2939,

1741 (C=O), 1712 (C=O), 1659 (C=O), 1619, 1510, 1411, 1250, 1182, 1030 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.19 (2H, br s, ArH), 6.90 (2H, d, J = 9.1 Hz, ArH), 6.34 (1H, dd, J = 16.8, 2.0 Hz, =CH), 6.01 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.53 (1H, dd, J = 10.3, 2.0 Hz, =CH), 4.84 (1H, d, J = 6.9 Hz, CHCO_2Et), 4.18 (2H, q, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.83 (3H, s, OCH_3), 3.60 (1H, ddd, J = 14.0, 9.6, 5.4 Hz, CHCHCO_2Et), 2.57-2.37 (2H, m, $(\text{CH}_2)_4$), 2.24-2.11 (2H, m, $(\text{CH}_2)_4$), 1.95-1.92 (1H, m, $(\text{CH}_2)_4$), 1.84-1.57 (2H, m, $(\text{CH}_2)_4$), 1.49-1.39 (1H, m, $(\text{CH}_2)_4$), 1.25 (3H, t, J = 7.1 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 211.2 (C), 169.7 (C), 166.2 (C), 159.0 (C), 135.1 (C), 129.2 (2 x CH), 128.2 (CH_2), 127.9 (CH), 114.6 (2 x CH), 62.3 (CH), 61.2 (CH_2), 55.4 (CH_3), 49.9 (CH), 42.3 (CH_2), 31.7 (CH_2), 28.7 (CH_2), 25.3 (CH_2), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 360.1805, found: 360.1805.

Copper-Catalyzed Reductive Aldol Cyclizations

General Procedure E: (1 mmol Scale)

A solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10.0 mg, 0.05 mmol) and DPPF (28.6 mg, 0.05 mmol) in THF (2 mL) was stirred for 15 min before TMDS (182 μL , 1.00 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (1.00 mmol) in THF (2 mL + 1 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

General Procedure F: (0.2 mmol Scale)

A solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 mg, 0.01 mmol) and DPPF (5.7 mg, 0.01 mmol) in THF (1 mL) was stirred for 15 min before TMDS (36 μL , 0.20 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (0.20 mmol) in THF (0.5 mL + 0.5 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (0.5 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL)

and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

(±)-(3R,4R)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethylpiperidin-2-one (2a). The title compound was prepared according to general procedure E from **1a** (247 mg, 1.00 mmol) for a reaction time of 2.5 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (165 mg, 66%). Slow evaporation of a CDCl₃ solution of **2a** was found to give colorless crystals suitable for X-ray diffraction. m.p. 121-123 °C; IR (CHCl₃) 3410 (OH), 2942, 1631 (C=O), 1605, 1512, 1335, 1245, 1035, 830 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.15 (2H, d, *J* = 8.9 Hz, ArH), 6.90 (2H, d, *J* = 8.9 Hz, ArH), 3.90 (1H, ddd, *J* = 12.1, 8.8, 6.7 Hz, CH₂N), 3.81 (3H, s, OCH₃), 3.50-3.41 (1H, m, CH₂N), 2.49 (1H, q, *J* = 7.2 Hz, CH₃CH), 2.06-2.01 (2H, m, CH₂CH₂N), 1.77 (1H, br s, OH), 1.40 (3H, s, CH₃COH), 1.34 (3H, d, *J* = 7.2 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.9 (C), 158.0 (C), 136.3 (C), 127.4 (2 x CH), 114.3 (2 x CH), 70.2 (C), 55.4 (CH₃), 47.2 (CH₂), 47.0 (CH), 35.6 (CH₂), 28.4 (CH₃), 10.1 (CH₃); HRMS (FAB) Exact mass calcd for C₁₄H₂₀NO₃ [M+H]⁺: 250.1438, found: 250.1447.

(±)-(3R,4R)-4-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (2b). The title compound was prepared according to general procedure E from **1b** (261 mg, 1.00 mmol) for a reaction time of 5.5 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give a white solid (161 mg, 61%). m.p. 132-134 °C; IR (CHCl₃) 3410 (OH), 2962, 1631 (C=O), 1604, 1511, 1331, 1297, 1244, 1034, 830 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.15 (2H, d, *J* = 9.0 Hz, ArH), 6.90 (2H, d, *J* = 9.0 Hz, ArH), 3.86 (1H, ddd, *J* = 12.0, 8.3, 6.7 Hz, CH₂N), 3.80 (3H, s, OCH₃), 3.46 (1H, ddd, *J* = 12.0, 10.2, 5.2 Hz, CH₂N), 2.54 (1H, q, *J* = 7.2 Hz, CH₃CH), 2.00-1.96 (2H, m, CH₂CH₂N), 1.70-1.61 (3H, m, CH₃CH₂ and OH), 1.29 (3H, d, *J* = 7.2 Hz, CH₃CH), 0.97 (3H, t, *J* = 7.5 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.3 (C), 157.9 (C), 136.3 (C), 127.3 (2 x CH), 114.3 (2 x CH), 72.3 (C), 55.4 (CH₃), 47.1 (CH₂), 44.9 (CH), 33.1 (CH₂), 31.7 (CH₂), 9.8 (CH₃), 8.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₂NO₃ [M+H]⁺: 264.1594, found: 264.1591.

(±)-(3R,4R)-4-Hydroxy-4-iso-butyl-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (2c). The title compound was prepared according to general procedure E from **1c** (289 mg, 1.00 mmol) for a reaction time of 24 h and purified by column

chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a white solid (186 mg, 64%). m.p. 120-121 °C; IR (CHCl₃) 3417 (OH), 2952, 1632 (C=O), 1606, 1511, 1334, 1298, 1245, 1034, 829 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.15 (2H, d, *J* = 8.6 Hz, ArH), 6.90 (2H, d, *J* = 8.6 Hz, ArH), 3.87 (1H, ddd, *J* = 12.0, 9.9, 5.1 Hz, CH₂N), 3.80 (3H, s, OCH₃), 3.46 (1H, ddd, *J* = 12.0, 5.7, 4.4 Hz, CH₂N), 2.52 (1H, q, *J* = 7.2 Hz, CHC=O), 2.13-2.07 (1H, m, CH₂CH₂N), 2.04-1.96 (1H, m, CH₂CH₂N), 1.89-1.79 (1H, m, (CH₃)₂CH), 1.60-1.49 (2H, m, (CH₃)₂CHCH₂), 1.31 (3H, d, *J* = 7.2 Hz, CH₃CHC=O), 1.04 (3H, d, *J* = 6.6 Hz, (CH₃)₂CH), 1.00 (3H, d, *J* = 6.6 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.2 (C), 158.0 (C), 136.3 (C), 127.3 (2 x CH), 114.3 (2 x CH), 72.6 (C), 55.4 (CH₃), 49.3 (CH₂), 47.1 (CH₂), 46.5 (CH), 32.4 (CH₂), 25.0 (CH₃), 24.4 (CH₃), 24.0 (CH), 10.2 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₆NO₃ [M+H]⁺: 292.1907, found: 292.1910.

(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpiperidin-2-one (2d). The title compound was prepared according to general procedure F from **1d** (62 mg, 0.20 mmol) for a reaction time of 21 h and purified by column chromatography

(80% EtOAc/petrol) to give a white solid (43 mg, 69%). Slow evaporation of a CDCl₃ solution of **2d** was found to give colorless crystals suitable for X-ray diffraction. m.p. 159-161 °C; IR (CHCl₃) 3389 (OH), 2940, 1629 (C=O), 1605, 1511, 1444, 1335, 1299, 1245, 1034 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49-7.46 (2H, m, ArH), 7.43-7.39 (2H, m, ArH), 7.33-7.29 (1H, m, ArH), 7.19 (2H, d, *J* = 8.5 Hz, ArH), 6.91 (2H, d, *J* = 8.5 Hz, ArH), 4.06-3.98 (1H, m, CH₂N), 3.80 (3H, s, OCH₃), 3.48-3.44 (1H, m, CH₂N), 3.02 (1H, q, *J* = 7.1 Hz, CH₃CH), 2.48-2.39 (1H, m, CH₂CH₂N), 2.30 (1H, br s, OH), 2.12-2.08 (1H, m, CH₂CH₂N), 1.12 (3H, d, *J* = 7.1 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.0 (C), 158.0 (C), 145.8 (C), 136.2 (C), 128.5 (2 x CH), 127.4 (2 x CH), 127.2 (CH), 124.5 (2 x CH), 114.3 (2 x CH), 74.6 (C), 55.4 (CH₃), 47.6 (CH₂), 46.5 (CH), 36.7 (CH₂), 10.0 (CH₃); HRMS (FAB) Exact mass calcd for C₁₉H₂₂NO₃ [M+H]⁺: 312.1594, found: 312.1599.

(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-(4-methylphenyl)piperidin-2-one (2e). The title compound was prepared according to general procedure E from **1e** (323 mg, 1.00 mmol) for a reaction

time of 24 h and purified by column chromatography (30% EtOAc/CHCl₃) to give a white solid (207 mg, 64%). m.p. 173-174 °C; IR (CHCl₃) 3395 (OH), 2941, 1629 (C=O), 1605, 1510, 1335, 1299, 1244, 1034, 817 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.36 (2H, d, *J* = 8.1 Hz, ArH), 7.22 (2H, d, *J* = 8.1 Hz, ArH), 7.19 (2H, d, *J* = 8.9 Hz, ArH), 6.92 (2H, d, *J* = 8.9 Hz, ArH), 4.02 (1H, ddd, *J* = 11.7,

11.7, 4.6 Hz, CH_2N), 3.81 (3H, s, OCH_3), 3.47 (1H, ddd, $J = 11.7, 5.7, 2.8$ Hz, CH_2N), 3.02 (1H, q, $J = 7.2$ Hz, CH_3CH), 2.46-2.38 (1H, m, $\text{CH}_2\text{CH}_2\text{N}$), 2.38 (3H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.26 (1H, s, OH), 2.10 (1H, ddd, $J = 13.9, 4.6, 2.8$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 1.14 (3H, d, $J = 7.2$ Hz, CH_3CH); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.0 (C), 158.0 (C), 142.8 (C), 136.9 (C), 136.2 (C), 129.3 (2 x CH), 127.4 (2 x CH), 124.4 (2 x CH), 114.3 (2 x CH), 74.6 (C), 55.4 (CH_3), 47.6 (CH_2), 46.4 (CH), 36.8 (CH_2), 20.9 (CH_3), 10.1 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 326.1751, found: 326.1749.

(±)-(3R,4R)-4-Furan-2-yl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (2f).

The title compound was prepared according to general procedure E from **1f** (299 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (160 mg, 53%). m.p. 178-180 °C; IR (CHCl_3) 3375 (OH), 2938, 1631 ($\text{C}=\text{O}$), 1605, 1510, 1335, 1299, 1245, 1153, 1034 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.42-7.41 (1H, m, CH), 7.15 (2H, d, $J = 8.5$ Hz, ArH), 6.91 (2H, d, $J = 8.5$ Hz, ArH), 6.39-6.38 (1H, m, CH), 6.34-6.33 (1H, m, CH), 3.93 (1H, ddd, $J = 12.0, 9.8, 4.9$ Hz, CH_2N), 3.81 (3H, s, OCH_3), 3.43 (1H, app dt, $J = 12.0, 5.5$ Hz, CH_2N), 3.06 (1H, q, $J = 7.2$ Hz, CH_3CH), 2.47 (1H, ddd, $J = 13.8, 9.8, 5.5$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 2.36 (1H, br s, OH), 2.25 (1H, app dt, $J = 13.8, 4.9$ Hz, $\text{CH}_2\text{CH}_2\text{N}$), 1.28 (3H, d, $J = 7.2$ Hz, CH_3CH); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.5 (C), 158.0 (C), 157.5 (C), 142.0 (CH), 136.0 (C), 127.3 (2 x CH), 114.3 (2 x CH), 110.3 (CH), 105.4 (CH), 71.9 (C), 55.4 (CH_3), 47.0 (CH_2), 45.1 (CH), 33.8 (CH_2), 10.9 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 302.1387, found: 302.1391.

(±)-(3R,4R)-4-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (2g).

The title compound was prepared according to general procedure F from **1g** (52 mg, 0.20 mmol) for a reaction time of 22 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (29 mg, 55%). Slow diffusion of petrol into a dichloromethane solution of **2g** was found to give colorless crystals suitable for X-ray diffraction. m.p. 109-111 °C; IR (CHCl_3) 3412 (OH), 2963, 1633 ($\text{C}=\text{O}$), 1605, 1512, 1296, 1246, 1155, 1033, 832 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.14 (2H, d, $J = 8.9$ Hz, ArH), 6.90 (2H, d, $J = 8.9$ Hz, ArH), 3.82-3.75 (1H, m, CH_2N), 3.80 (3H, s, OCH_3), 3.47 (1H, ddd, $J = 12.2, 6.1, 6.1$ Hz, CH_2N), 2.25 (1H, dd, $J = 7.2, 4.1$ Hz, CH_2CH), 2.10-2.02 (1H, m, $\text{CH}_2\text{CH}_2\text{N}$), 1.97-1.76 (4H, m, CH_3CH_2 , $\text{CH}_2\text{CH}_2\text{N}$ and OH), 1.41 (3H, s, CH_3COH), 1.17 (3H, t, $J = 7.4$ Hz, CH_3CH_2); ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.1 (C), 158.0 (C), 136.1 (C), 127.4 (2 x CH), 114.4 (2 x CH), 70.9 (C), 55.4 (CH_3), 54.4 (CH), 47.4 (CH_2), 35.1 (CH_2),

28.5 (CH₃), 20.2 (CH₂), 14.6 (CH₃); HRMS (FAB) Exact mass calcd for C₁₅H₂₂NO₃ [M+H]⁺: 264.1594, found: 264.1597.

(±)-(3*R*,4*R*)-3,4-Diethyl-4-hydroxy-1-(4-methoxyphenyl)piperidin-2-one (2h). The title compound was prepared according to general procedure E from **1h** (275 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give a fluffy white solid (144 mg, 52%). m.p. 110-112 °C; IR (CHCl₃) 3419 (OH), 2963, 1634 (C=O), 1606, 1511, 1442, 1296, 1246, 1032, 832 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.14 (2H, d, *J* = 9.0 Hz, ArH), 6.90 (2H, d, *J* = 9.0 Hz, ArH), 3.80 (3H, s, OCH₃), 3.78-3.71 (1H, m, CH₂N), 3.50-3.44 (1H, m, CH₂N), 2.32 (1H, dd, *J* = 7.7, 3.5 Hz, CH₂CH), 2.05-1.64 (7H, CH₂CH₂N, 2 x CH₃CH₂ and OH), 1.17 (3H, t, *J* = 7.4 Hz, CH₃CH₂), 0.99 (3H, t, *J* = 7.5 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.4 (C), 157.9 (C), 136.0 (C), 127.3 (2 x CH), 114.3 (2 x CH), 73.0 (C), 55.4 (CH₃), 52.7 (CH), 47.3 (CH₂), 32.9 (CH₂), 31.4 (CH₂), 20.1 (CH₂), 14.4 (CH₃), 7.8 (CH₃); HRMS (ES) Exact mass calcd for C₁₆H₂₄NO₃ [M+H]⁺: 278.1751, found: 278.1748.

(±)-(3*R*,4*R*)-4-Hydroxy-1-(2-methoxyphenyl)-3,4-dimethylpiperidin-2-one (2i). The title compound was prepared according to general procedure E from **1i** (247 mg, 1.00 mmol) for a reaction time of 4 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give an off-white solid (175 mg, 70%). m.p. 139-140 °C; IR (CHCl₃) 3418 (OH), 2973, 1633 (C=O), 1595, 1503, 1462, 1437, 1334, 1265, 1025 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.26 (1H, m, ArH), 7.16 (1H, dd, *J* = 7.6, 1.7 Hz, ArH), 7.00-6.95 (2H, m, ArH), 3.82 (3H, s, OCH₃), 3.71-3.62 (1H, m, CH₂N), 3.52-3.43 (1H, m, CH₂N), 2.51 (1H, q, *J* = 7.2 Hz, CH₃CH), 2.12-2.05 (3H, m, CH₂CH₂N and OH), 1.38 (3H, s, CH₃COH), 1.33 (3H, d, *J* = 7.2 Hz, CH₃CH); ¹³C NMR (90.6 MHz, C₂D₂Cl₄, 353 K) δ 172.0 (C), 155.1 (C), 132.5 (C), 129.4 (CH), 128.8 (CH), 121.4 (CH), 112.9 (CH), 70.6 (C), 56.2 (CH₃), 47.6 (CH), 46.4 (CH₂), 35.8 (CH₂), 28.0 (CH₃), 10.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₄H₂₀NO₃ [M+H]⁺: 250.1438, found: 250.1440.

(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-1-(2-methoxyphenyl)-4-methylpiperidin-2-one (2j). The title compound was prepared according to general procedure E from **1j** (261 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (185 mg, 70%). m.p. 144-146 °C; IR (CHCl₃) 3408 (OH), 2964, 1636 (C=O), 1596, 1502, 1460, 1436, 1315, 1266, 1026 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.26

(1H, m, ArH), 7.15-7.13 (1H, m, ArH), 7.00-6.95 (2H, m, ArH), 3.82 (3H, s, OCH₃), 3.62-3.44 (2H, br m, CH₂N), 2.28 (1H, t, *J* = 5.8 Hz, CH₂CH), 2.20-2.06 (2H, m, CH₂CH₂N), 1.97-1.70 (3H, m, CH₃CH₂ and OH), 1.42 (3H, s, CH₃COH), 1.15 (3H, t, *J* = 7.4 Hz, CH₃CH₂); ¹³C NMR (90.6 MHz, C₂D₂Cl₄, 353 K) δ 171.8 (C), 155.2 (C), 132.4 (C), 129.4 (CH), 128.8 (CH), 121.4 (CH), 112.9 (CH), 71.4 (C), 56.2 (CH₃), 55.1 (CH), 46.5 (CH₂), 35.5 (CH₂), 28.3 (CH₃), 20.4 (CH₂), 14.4 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₂NO₃ [M+H]⁺: 264.1594, found: 264.1592.

(±)-(3R,4R)-3-Ethyl-4-hydroxy-1-(2-methoxyphenyl)-4-phenylpiperidin-2-one (2k).

The title compound was prepared according to general procedure E from **1k** (323 mg, 1.00 mmol) but using (EtO)₂MeSiH (330 μL, 2.00 mmol) in place of TMDS for a reaction time of 23 h and purified by column chromatography (30% EtOAc/CHCl₃) to give an off-white solid (212 mg, 65%). m.p. 180-182 °C; IR (CHCl₃) 3388 (OH), 2931, 1631 (C=O), 1595, 1502, 1436, 1332, 1266, 1027, 752 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.54 (2H, d, *J* = 7.5 Hz, ArH) 7.44-7.40 (2H, m, ArH), 7.34-7.30 (2H, m, ArH), 7.22 (1H, d, *J* = 7.1 Hz, ArH), 7.03-6.98 (2H, m, ArH), 3.87 (3H, s, OCH₃), 3.82-3.75 (1H, m, CH₂N), 3.53-3.50 (1H, m, CH₂N), 2.85-2.84 (1H, m, CH₂CH), 2.48-2.40 (2H, br m, CH₂CH₂N and OH), 2.18-2.12 (1H, m, CH₂CH₂N), 1.89-1.77 (1H, m, CH₃CH₂), 1.49-1.44 (1H, m, CH₃CH₂), 1.00 (3H, t, *J* = 7.3 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.1 (C), 154.4 (C), 145.8 (C), 131.6 (C), 128.9 (CH), 128.7 (CH), 128.3 (2 x CH), 126.9 (CH), 124.7 (2 x CH), 121.1 (CH), 112.0 (CH), 75.4 (C), 55.7 (CH₃), 53.2 (CH), 46.4 (CH₂), 37.1 (CH₂), 19.8 (CH₂), 14.5 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₄NO₃ [M+H]⁺: 326.1751, found: 326.1753.

(±)-(3R,4R,5R)-4-Hydroxy-1-(4-methoxyphenyl)-3,5-dimethyl-4-phenylpiperidin-2-one (4a). The title compound was prepared according to general procedure F from **3a** (65 mg, 0.20 mmol) for a reaction time of 16 h and purified by column chromatography

(50% EtOAc/petrol) to give a fluffy off-white solid (51 mg, 78%). Slow evaporation of a methanol/hexane solution of **4a** was found to give colorless crystals suitable for X-ray diffraction. m.p. 204-206 °C; IR (CHCl₃) 3452 (OH), 1626 (C=O), 1511, 1342, 1250, 1030, 980, 913, 839, 752 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.44-7.37 (4H, m, ArH), 7.32-7.27 (1H, m, ArH), 7.23 (2H, d, *J* = 8.8 Hz, ArH), 6.93 (2H, d, *J* = 8.8 Hz, ArH), 3.82 (3H, s, OCH₃), 3.78 (1H, t, *J* = 11.8 Hz, CH₂N), 3.48 (1H, dd, *J* = 11.8, 5.5 Hz, CH₂N), 3.00 (1H, q, *J* = 7.2 Hz, CHC=O), 2.65-2.55 (1H, m, CHCH₂N), 2.07 (1H, br s, OH), 1.04 (3H, d, *J* = 7.2 Hz, CH₃CHC=O), 0.66 (3H, d, *J* = 6.7 Hz, CH₃CHCH₂N); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.6 (C), 158.0 (C), 143.9 (C), 136.1 (C), 128.5 (2 x CH), 127.4 (2 x

CH), 126.9 (CH), 124.8 (2 x CH), 114.4 (2 x CH), 77.1 (C), 55.4 (CH₃), 54.6 (CH₂), 47.5 (CH), 38.4 (CH), 12.4 (CH₃), 9.8 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₄NO₃ [M+H]⁺: 326.1751, found: 326.1747.

(3R,4R,6S)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethyl-6-phenylpiperidin-2-one

(4b). The title compound was prepared according to general procedure F from **3b** (65 mg, 0.20 mmol) for a reaction time of 2 h and purified by column chromatography

(30% EtOAc/petrol→50% EtOAc/petrol) to give a fluffy off-white solid (38 mg, 58%). m.p. 84-86 °C; $[\alpha]_D^{22}$ -81.5 (*c* 1.01, CHCl₃); IR (CHCl₃) 3410 (OH), 2944, 1633 (C=O), 1606, 1510, 1331, 1295, 1248, 1041, 910 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.23-7.12 (5H, m, ArH), 6.92 (2H, d, *J* = 9.0 Hz, ArH), 6.68 (2H, d, *J* = 9.0 Hz, ArH), 5.08 (1H, dd, *J* = 11.3, 5.3 Hz, CHPh), 3.67 (3H, s, OCH₃), 2.68 (1H, q, *J* = 7.1 Hz, CH₃CH), 2.31 (1H, dd, *J* = 14.1, 11.3 Hz, CH₂CHPh), 1.79 (1H, br s, OH), 1.38 (3H, s, CH₃COH), 1.36 (3H, d, *J* = 7.1 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.0 (C), 157.5 (C), 141.5 (C), 134.6 (C), 128.9 (2 x CH), 128.4 (2 x CH), 127.4 (3 x CH), 113.8 (2 x CH), 70.3 (C), 61.5 (CH), 55.2 (CH₃), 46.6 (CH), 28.3 (CH₃), 9.2 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₄NO₃ [M+H]⁺: 326.1751, found: 326.1752.

Ethyl (2S,4R,5R)-4-hydroxy-1-(4-methoxyphenyl)-4,5-dimethyl-6-oxopiperidine-

2-carboxylate (4c). The title compound was prepared according to general procedure F from **3c** (64 mg, 0.20 mmol) for a reaction time of 24 h and purified by column

chromatography (30% EtOAc/petrol) to give a white solid (44 mg, 68%). Slow diffusion of pentane into a dichloromethane solution of **4c** was found to give colorless crystals suitable for X-ray diffraction. m.p. 170-172 °C; $[\alpha]_D^{22}$ -44.4 (*c* 0.90, CHCl₃); IR (CHCl₃) 3247 (OH), 2930, 1746 (C=O), 1640 (C=O), 1607, 1511, 1295, 1246, 1186, 1032 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.15 (2H, d, *J* = 9.0 Hz, ArH), 6.87 (2H, d, *J* = 9.0 Hz, ArH), 4.72 (1H, dd, *J* = 10.3, 5.9 Hz, CHCO₂Et), 4.05-3.99 (2H, m, CO₂CH₂CH₃), 3.79 (3H, s, OCH₃), 2.55 (1H, q, *J* = 7.1 Hz, CH₃CH), 2.33 (1H, dd, *J* = 13.7, 5.9 Hz, CH₂CHCO₂Et), 2.14 (1H, dd, *J* = 13.7, 10.3 Hz, CH₂CHCO₂Et), 1.79 (1H, br s, OH), 1.39 (3H, s, CH₃COH), 1.29 (3H, d, *J* = 7.1 Hz, CH₃CH), 1.10 (3H, t, *J* = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.9 (C), 171.6 (C), 158.3 (C), 134.3 (C), 128.6 (2 x CH), 114.1 (2 x CH), 70.4 (C), 61.3 (CH₂), 60.2 (CH), 55.4 (CH₃), 46.4 (CH), 39.8 (CH₂), 28.3 (CH₃), 13.9 (CH₃), 9.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₄NO₅ [M+H]⁺: 322.1649, found: 322.1652.

(1*S*,2*S*,5*R*,6*R*)-2-Carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-5-methyl-3-azabicyclo[4.4.0]decan-4-one (4d).

The title compound was prepared according to general procedure F from **3d** (72 mg, 0.20 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→40% EtOAc/petrol) to give an off-white solid (48 mg, 66%). Slow diffusion of petrol into a dichloromethane solution of **4d** was found to give colorless crystals suitable for X-ray diffraction. m.p. 141-143 °C; $[\alpha]_D^{22} +2.5$ (0.80, CH₂Cl₂); IR (CHCl₃) 3425 (OH), 2939, 1750 (C=O), 1642 (C=O), 1607, 1510, 1294, 1245, 1187, 1029 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.15 (2H, d, J = 8.9 Hz, ArH), 6.85 (2H, d, J = 8.9 Hz, ArH), 5.14 (1H, d, J = 5.7 Hz, CHCO₂Et), 4.03-3.94 (2H, m, CO₂CH₂CH₃), 3.77 (3H, s, OCH₃), 2.94 (1H, q, J = 7.1 Hz, CH₃CH), 2.24-2.17 (1H, m, CHCHCO₂Et), 2.05-1.99 (2H, m, (CH₂)₄ and OH), 1.86-1.84 (1H, m, (CH₂)₄), 1.73-1.61 (3H, m, (CH₂)₄), 1.55-1.51 (1H, m, (CH₂)₄), 1.41-1.29 (2H, m, (CH₂)₄), 1.22 (3H, d, J = 7.1 Hz, CH₃CH), 1.09 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.7 (C), 170.1 (C), 157.9 (C), 135.0 (C), 128.5 (2 x CH), 113.8 (2 x CH), 73.1 (C), 63.0 (CH), 60.8 (CH₂), 55.3 (CH₃), 44.0 (CH), 37.8 (CH), 37.5 (CH₂), 25.3 (CH₂), 25.0 (CH₂), 22.9 (CH₂), 14.0 (CH₃), 8.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₈NO₅ [M+H]⁺: 362.1962, found: 392.1966.

(±)-(3*S*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpiperidine (5)

BH₃·THF (1 M in THF, 1.6 mL, 1.6 mmol) was added to the piperidinone **1d** (125 mg, 0.4 mmol) and the resulting solution was heated at reflux for 4 h. The reaction was cooled to room temperature and quenched with H₂O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/petrol) gave the *piperidine* **5** (102 mg, 86%) as an off-white solid. m.p. 114-115 °C; IR (CHCl₃) 3501 (OH), 2959, 1511, 1464, 1388, 1284, 1245, 1200, 1036, 825 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.52-7.49 (2H, m, ArH), 7.41-7.36 (2H, m, ArH), 7.30-7.25 (1H, m, ArH), 7.01 (2H, d, J = 9.0 Hz, ArH), 6.88 (2H, d, J = 9.0 Hz, ArH), 3.80 (3H, s, OCH₃), 3.46-3.40 (1H, m, CH₂N), 3.35 (1H, ddd, J = 11.8, 4.2, 1.7 Hz, CH₂N), 2.85 (1H, app t, J = 11.6 Hz, CH₂N), 2.49-2.39 (1H, m, CH₃CH), 2.31 (1H, ddd, J = 13.4, 13.4, 4.7 Hz, CH₂CH₂N), 1.82 (1H, app dt, J = 14.0, 2.5 Hz, CH₂CH₂N), 1.70 (1H, br s, OH), 0.71 (3H, d, J = 6.9 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 154.7 (C), 147.0 (C), 145.9 (C), 128.2 (2 x CH), 126.6 (CH), 124.7 (2 x

CH), 118.7 (2 x CH), 114.4 (2 x CH), 73.8 (C), 55.5 (CH₃), 54.3 (CH₂), 47.2 (CH₂), 40.5 (CH₂), 39.1 (CH), 12.1 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₄NO₂ [M+H]⁺: 298.1802, found: 298.1806.

(±)-(3*S*,4*R*)-4-Hydroxy-1-(*tert*-butoxycarbonyl)-3-methyl-4-phenylpiperidine (6)

To a stirred solution of PhI(OAc)₂ (131 mg, 0.40 mmol) in MeOH (1.5 mL) was added a solution of the piperidine **5** (30 mg, 0.10 mmol) in MeOH (1.5 mL) dropwise over 2 min. The solution immediately became dark red. After 30 min, 1 M HCl (1 mL) was added and the mixture was stirred for 1.5 h. The mixture was washed with CH₂Cl₂ (3 x 1 mL) and the combined organic layers were back-extracted with 1 M HCl (1 mL). To the combined aqueous layers were added CH₂Cl₂ (3 mL) followed by Boc₂O (89 mg, 0.40 mmol). The aqueous layer was made basic (pH ~ 10) by the addition of saturated aqueous Na₂CO₃ and the mixture was left to stir for 16 h. The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 5 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *carbamate* **6** (14.4 mg, 49%) as a beige solid. m.p. 152-154 °C; IR (film) 3453 (OH), 2976, 1669 (C=O), 1429, 1366, 1251, 1168, 1004, 816, 701 cm⁻¹; ¹H NMR (360 MHz, C₂D₂Cl₄, 353K) δ 7.40-7.38 (2H, m, ArH), 7.35-7.30 (2H, m, ArH), 7.24-7.20 (1H, m, ArH), 4.01-3.96 (1H, m, CH₂N), 3.92 (1H, dd, *J* = 13.8, 3.8 Hz, CH₂N), 3.15 (1H, ddd, *J* = 13.0, 13.0, 2.9 Hz, CH₂N), 2.84 (1H, app t, *J* 12.4 Hz, CH₂N), 2.13-2.03 (1H, m, CH₃CH), 1.96 (1H, ddd, *J* = 13.5, 13.5, 5.0 Hz, CH₂CH₂N), 1.64 (1H, app dt, *J* = 14.0, 2.5 Hz, CH₂CH₂N), 1.60 (1H, br s, OH), 1.47 (9H, s, C(CH₃)₃), 0.62 (3H, d, *J* = 6.8 Hz, CH₃CH); ¹³C NMR (90.6 MHz, C₂D₂Cl₄, 353K) δ 155.0 (C), 147.1 (C), 128.5 (2 x CH), 127.0 (CH), 79.6 (C), 74.5 (C), 46.7 (CH₂), 40.6 (CH₂), 40.4 (CH₂), 39.3 (CH), 28.8 (3 x CH₃), 12.0 (CH₃); HRMS (FAB) Exact mass calcd for [M+H]⁺: 292.1908, found: 292.1907.

(2*S*,4*R*,5*S*)-4-Hydroxy-2-hydroxymethyl-1-(4-methoxyphenyl)-4,5-dimethylpiperidine (7)

BH₃·THF (1 M in THF, 1.84 mL, 1.84 mmol) was added to the piperidinone **4c** (74 mg, 0.23 mmol) and the resulting solution was heated at reflux for 48 h. The reaction was cooled to room temperature and quenched with H₂O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc

(3 x 5 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (80% EtOAc/petrol) gave the *piperidine* **7** (46 mg, 75%) as an off-white solid. m.p. 115-116 °C; $[\alpha]_D^{22} +11.4$ (*c* 0.70, CHCl₃); IR (CHCl₃) 3391 (OH), 2963, 2834, 1508, 1462, 1291, 1245, 1208, 1037, 835 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.18 (2H, d, *J* = 8.9 Hz, ArH), 6.86 (2H, d, *J* = 8.9 Hz, ArH), 3.79 (3H, s, OCH₃), 3.47 (1H, dd, *J* = 11.3, 3.8 Hz), 3.27-3.22 (2H, m), 2.80 (1H, app q, *J* = 11.5 Hz), 2.73 (1H, dd, *J* = 11.5, 4.4 Hz), 2.05 (1H, br s, OH), 1.96-1.89 (1H, m, CH₂CHN), 1.85-1.73 (2H, m, CH₂CHN and CH₃CH), 1.40 (1H, br s, OH), 1.28 (3H, s, CH₃COH), 0.86 (3H, d, *J* = 6.8 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 157.1 (C), 144.0 (C), 126.3 (2 x CH), 114.4 (2 x CH), 69.8 (C), 63.2 (CH₂), 59.8 (CH₂), 56.5 (CH), 55.4 (CH₃), 42.4 (CH₂), 39.6 (CH), 28.3 (CH₃), 11.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₄NO₃ [M+H]⁺: 266.1751, found: 266.1754.

(1*S*,2*S*,5*S*,6*S*)-2-Hydroxymethyl-3-(4-methoxyphenyl)-5-methyl-3-azabicyclo[4.4.0]decane (8**)**

BH₃·THF (1 M in THF, 1.84 mL, 1.84 mmol) was added to the piperidine **4d** (72 mg, 0.20 mmol) and the resulting solution was heated at reflux for 36 h. The reaction was cooled to room temperature and quenched with H₂O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (80% EtOAc/petrol) gave the *piperidine* **8** (39 mg, 64%) as an off white solid. m.p. 48-50 °C; $[\alpha]_D^{22} -84.8$ (*c* 0.83, CHCl₃); IR (CHCl₃) 3366 (OH), 2936, 1507, 1450, 1243, 1039, 836, 761 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.17 (2H, br d, ArH), 6.85 (2H, d, *J* = 9.0 Hz, ArH), 3.78 (3H, s, OCH₃), 3.49-3.73 (3H, m), 2.99 (1H, app t, *J* = 11.3 Hz), 2.68 (1H, br d), 2.38 (1H, br s, OH), 2.07 (2.04 (1H, m), 1.90-1.79 (2H, m), 1.69-1.61 (3H, m), 1.46-1.20 (5H, m); ¹³C NMR (62.9 MHz, CDCl₃) δ 157.2 (C), 144.6 (C), 126.9 (2 x CH), 114.4 (2 x CH), 71.9 (C), 63.8 (CH₂), 60.7 (CH), 59.3 (CH₂), 55.4 (CH₃), 47.6 (CH), 37.5 (CH₂), 30.9 (CH), 25.8 (CH₂), 22.9 (CH₂), 22.7 (CH₂), 10.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₈NO₃ [M+H]⁺: 306.2064, found: 306.2066.

Stereochemical Determinations

- The relative stereochemistries of the piperidinones **2a**, **2d**, **2g**, **4a**, **4c**, and **4d** were determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Numbers: CCDC 285175, CCDC 285176, CCDC 285177, CCDC 285178, CCDC 285179 and CCDC 285180 respectively. Data in CIF format also present as separate files in supporting information.

- For the piperidinone **4b**, the benzylic hydrogen atom indicated was assigned as residing in a pseudoaxial position on the basis of the large axial-axial coupling constant of 11.3 Hz. Therefore, the phenyl group lies in a pseudoequatorial position.

- The relative stereochemistries of the remaining piperidinones were assigned by analogy.

NMR Spectra