Diastereoselective Cobalt-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant

Hon Wai Lam,^{*,†} Pekka M. Joensuu,[†] Gordon J. Murray,[†] Euan A. F. Fordyce,[†] Oscar Prieto[†] and Thomas Luebbbers[‡]

[†]*School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, United Kingdom*

[‡]*F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4070 Basel, Switzerland*

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General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH₂Cl₂ and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH₂. Commercially available CoCl₂ was dried by heating under vacuum until it turned from purple to blue. 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 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 CHCl₃. 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 (CDCl₃ at 7.27 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 ¹³C 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 (CDCl₃ at 77.0 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. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

Preparation of Aminoketones

4-(4-Methoxyphenylamino)butan-2-one (16).² Prepared according to a previously reported procedure.²

5-(4-Methoxyphenylamino)pentan-3-one (17).^{2,3} Prepared according to a previously reported procedure.^{2,3}

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1-[(4-Methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (18)

A solution of *p*-anisidine (4.73 g, 38.4 mmol) and aqueous formaldehyde solution (37% wt in H₂O, 2.88 mL, 38.4 mmol) in EtOH (200 mL) was stirred at room temperature for 10 min. Ethyl 2-oxocyclopentanecarboxylate (4.00 g, 25.6 mmol) was added in one portion, the resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$, and KOH (4.31 g, 76.8 mmol) was then added portionwise over 5 min. The reaction mixture was stirred at $-20\text{ }^{\circ}\text{C}$ for 30 min and then poured into saturated aqueous NH₄Cl solution (200 mL). The mixture was extracted with CH₂Cl₂ (3 x 150 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 *aminoketone* **18** (7.01 g, 94%) as a pale brown oil. IR (film) 3388 (NH), 2959, 1747 (C=O), 1719 (C=O), 1514, 1465, 1234, 1176, 1036, 822 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 6.76 (2H, dm, J = 9.0 Hz, ArH), 6.60 (2H, d, J = 9.0 Hz, ArH), 4.16 (2H, qd, J = 7.1, 1.2 Hz, OCH₂CH₃), 3.73 (3H, s, OCH₃), 3.48 (1H, d, J = 13.1 Hz, CH₂N), 3.42 (1H, d, J = 13.1 Hz, CH₂N), 2.56-2.41 (2H, m, CH₂CH₂CH₂), 2.34-1.93 (5H, m, CH₂CH₂CH₂ and NH), 1.23 (3H, t, J = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 214.7 (C), 170.9 (C), 152.3 (C), 142.2 (C), 114.7 (2 x CH), 114.5 (2 x CH), 61.5 (CH₂), 61.0 (C), 55.6 (CH₃), 47.7 (CH₂), 38.1 (CH₂), 32.0 (CH₂), 19.6 (CH₂), 13.9 (CH₃).

1-(4-Methoxyphenyl)aminopropanone (19)

A solution of *p*-anisidine (5.00 g, 40.6 mmol), chloroacetone (3.56 mL, 44.7 mmol) and Et₃N (11.3 mL, 81.2 mmol) in THF (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature before the addition of brine (25 mL) and water (25 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) gave the *aminoketone* **19** as a yellow/orange crystalline solid (4.60 g, 68%). m.p. 70-71 $^{\circ}\text{C}$; IR (CHCl₃) 3397 (NH), 2961, 2839, 1715 (C=O), 1511, 1436, 1345, 1254, 1036, 821 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.79 (2H, dm, J = 9.0 Hz, ArH), 6.56 (2H, dm, J = 9.0 Hz, ArH), 4.31 (1H, bs, NH), 3.95 (2H, s, CH₂N), 3.74 (3H, s, OCH₃), 2.23 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 204.5 (C), 152.2 (C), 141.2 (C), 114.9 (2 x CH), 113.9 (2 x CH), 55.7

(CH₃), 55.1 (CH₂), 27.3 (CH₃); HRMS (FAB) Exact mass calcd for C₂₁H₂₄NO₃ [M+H]⁺: 180.1020, found: 180.1032.

2-(4-Methoxyphenyl)aminoacetophenone (**20**)⁴

A solution of 2-bromoacetophenone (3.98 g, 20.0 mmol), *p*-anisidine (2.23 g, 18.1 mmol) and Et₃N (5.05 mL, 36.2 mmol) in THF (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and washed with brine (100 mL). The aqueous layer was separated and extracted with EtOAc (2 x 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by recrystallization (EtOAc/petrol) to give the aminoketone **23** as a dark orange solid (1.80 g, 40%) that displayed identical spectroscopic data to those reported previously.⁴

2-(4-Methoxybenzyl)aminoacetophenone hydrochloride (**21**)⁵

To a solution of *p*-methoxybenzylamine (5.20 mL, 40.0 mmol) in Et₂O (20 mL) at 0 °C was added a solution of 2-bromoacetophenone (3.90 g, 20.0 mmol) in Et₂O (20 mL) over 5 min. The mixture was stirred at 0 °C for 12 h, and the resulting white precipitate was removed by filtration. The precipitate was washed with Et₂O (2 x 20 mL), and the combined filtrate and washings were cooled to 0 °C. 38% Aqueous HCl solution (2.5 mL) was added dropwise over 1 min to give a brown precipitate, which was filtered, washed with acetone (2 x 5 mL) and recrystallized from EtOH/Et₂O to give the aminoketone hydrochloride **21** as a white solid (1.40 g, 24%) that displayed identical spectroscopic data to those reported previously.⁵

Preparation of α,β-Unsaturated Acid Chlorides: General Procedure A

Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in CH₂Cl₂ (0.55 M with respect to

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carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β -unsaturated acid chloride which was used directly in the next step.

Preparation of Cyclization Precursors: General Procedure B

The appropriate α,β -unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate aminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of aminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of aminoketone). 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 afforded the cyclization substrate.

Preparation of Cyclization Precursors: General Procedure C

A solution of benzylamine (1.0 equiv) and methyl vinyl ketone (1.1 equiv) in CH_2Cl_2 (2.5 mL/mmol of benzylamine) was stirred at 0 °C for 18 h. Saturated aqueous Na_2CO_3 solution (2.5 mL/mmol of benzylamine) followed by the appropriate acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.21 equiv) were then added dropwise or portionwise and 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 washed with 10% HCl solution (x 1), dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.

Preparation of Cyclization Precursors: General Procedure D

Benzylamine (1.0 equiv) was added over 1 min to a solution of 3-chloropropiophenone (1.1 equiv) and Et₃N (3.3 equiv) in THF (2.5 mL/mmol of benzylamine) at room temperature and the mixture was stirred for 18 h. The reaction was partitioned between saturated aqueous NaHCO₃ solution and EtOAc. The aqueous layer was separated and extracted with EtOAc (x 2), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The resulting amine **22** was used directly in the next step without further purification.

The appropriate α,β -unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH₂Cl₂ prepared according to General Procedure A, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the unpurified amine **22** (1.0 equiv) in CH₂Cl₂ (1 mL/mmol of **22**) and saturated aqueous Na₂CO₃ solution (1 mL/mmol of **22**). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous NaHCO₃ solution and CH₂Cl₂. The aqueous layer was separated and extracted with CH₂Cl₂ (x 3), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.

***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenoate (1a).** The title compound was prepared according to General Procedure B from the amine **16**

(2.00 g, 10.3 mmol) and cinnamoyl chloride (2.10 g, 12.4 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→40% EtOAc/petrol) followed by recrystallization from EtOAc/petrol to give a colorless crystalline solid (1.84 g, 55%). m.p. 85-86 °C; IR (CHCl₃) 2955, 1713 (C=O), 1654 (C=O), 1615, 1510, 1394, 1249, 1183, 1030, 765 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.63 (1H, d, J = 15.6 Hz, PhCH=), 7.29-7.26 (5H, m, ArH), 7.11 (2H, dm, J = 8.9 Hz, ArH), 6.93 (2H, dm, J = 8.9 Hz, ArH), 6.26 (1H, d, J = 15.6 Hz, PhCH=CH), 4.03 (2H, t, J = 7.4 Hz, CH₂N), 3.84 (3H, s, OCH₃), 2.78 (2H, t, J = 7.4 Hz, CH₂CH₂N), 2.14 (3H, s, CH₃C=O); ¹³C NMR (69.2 MHz, CDCl₃) δ 207.0 (C), 166.2 (C), 158.9 (C), 141.8 (CH), 135.1 (C), 134.5 (C), 129.5 (CH), 129.3 (2 x CH), 128.6 (2 x CH), 127.8 (2 x CH), 118.7 (CH), 114.8 (2 x CH), 55.5 (CH₃), 45.2 (CH₂), 41.5 (CH₂), 30.0 (CH₃); HRMS (FAB) Exact mass calcd for C₂₀H₂₂NO₃ [M+H]⁺: 324.1595, found: 324.1599.

***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl)-(*E*)-3-phenylpropenoate (1b).** The title compound was prepared according to General Procedure B from the amine **17** (415 mg, 2.00 mmol) and cinnamoyl chloride (500 mg, 3.00 mmol) for a

reaction time of 18 h and purified by column chromatography (15% EtOAc/CHCl₃) to give a light beige solid (656 mg, 97%). m.p. 105-107 °C; IR (CHCl₃) 2936, 1710 (C=O), 1660 (C=C), 1509, 1395, 1247, 1180, 836, 765, 684 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.66 (1H, d, *J* = 15.6 Hz, PhCH=), 7.31-7.29 (5H, m, ArH), 7.14 (2H, d, *J* = 8.7 Hz, ArH), 6.96 (2H, d, *J* = 8.7 Hz, ArH), 6.30 (1H, d, *J* = 15.6 Hz, PhCH=CH), 4.07 (2H, d, *J* = 7.3 Hz, CH₂N), 3.86 (3H, s, OCH₃), 2.79 (2H, t, *J* = 7.3 Hz, CH₂CH₂N), 2.45 (2H, q, *J* = 7.3 Hz, CH₃CH₂), 1.04 (3H, t, *J* = 7.3 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 209.5 (C), 166.1 (C), 158.9 (C), 141.7 (CH), 135.0 (C), 134.4 (C), 129.4 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 127.7 (2 x CH), 118.6 (CH), 114.7 (2 x CH), 55.4 (CH₃), 45.3 (CH₂), 40.1 (CH₂), 35.9 (CH₂), 7.5 (CH₃); HRMS (ES) Exact mass calcd for C₂₁H₂₄NO₃ [M+H]⁺: 338.1751, found: 338.1752.

***N*-Benzyl-*N*-(3-oxobutyl)propenamide (1c).** The title compound was prepared according to General Procedure C from methyl vinyl ketone (0.94 mL, 11.0 mmol),

benzylamine (2.18 mL, 20.0 mmol) and acryloyl chloride (1.02 mL, 12.1 mmol) for a reaction time of 3 h. The product was purified by column chromatography (50% EtOAc/petrol) to give a colorless oil (1.08 g, 47%) as a 2:1 mixture of rotamers. IR (film) 3063, 1714 (C=O), 1648 (C=C), 1613, 1471, 1447, 1371, 978, 732, 699 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.39-7.28 (4H, m, ArH), 7.20-7.18 (1H, m, ArH), 6.56 (1H, dd, *J* = 16.7, 10.2 Hz, CH₂=CH), 6.41 (1H, dd, *J* = 16.7, 2.1 Hz, CH₂=CH), 5.70 (1H, dd, *J* = 10.2, 2.1 Hz, CH₂=CH), 4.70 (2H, s, CH₂Ph), 3.65 (2H, t, *J* = 6.7 Hz, CH₂CH₂N), 2.85 (2H, t, *J* = 6.7 Hz, CH₂CH₂N), 2.14 (3H, s, CH₃C=O); (Minor rotamer) δ 7.39-7.28 (4H, m, ArH), 7.20-7.18 (1H, m, ArH), 6.68 (1H, dd, *J* = 16.7, 10.3 Hz, CH₂=CH), 6.48 (1H, dd, *J* = 16.7, 1.9 Hz, CH₂=CH), 5.79 (1H, dd, *J* = 10.3, 1.9 Hz, CH₂=CH), 4.68 (2H, s, CH₂Ph), 3.63 (2H, t, *J* = 7.0 Hz, CH₂CH₂N), 2.66 (2H, t, *J* = 7.0 Hz, CH₂CH₂N), 2.09 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 206.9 (C), 205.6 (C), 166.5 (C), 165.9 (C), 137.2 (C), 136.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH₂), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.0 (CH), 51.8 (CH₂), 48.9 (CH₂), 42.3 (CH₂), 42.0 (CH₂), 41.5 (CH₂), 41.4 (CH₂), 29.8 (CH₃), 29.6 (CH₃); HRMS (ES) Exact mass calcd for C₁₄H₁₈NO₂ [M+H]⁺: 232.1332, found: 232.1332.

***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (1d).** The title

compound was prepared according to General Procedure C from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from 4-methyl-2-pentenoic acid (2.76 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a white solid (2.36 g, 43%) as a 2:1 mixture of rotamers. m.p. 59-61 °C; IR (CHCl₃) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.35-7.23 (4H, m, ArH), 7.17-7.15 (1H, m, ArH), 6.90 (1H, dd, *J* = 15.1, 7.0 Hz, CHCH=), 6.12 (1H, dd, *J* = 15.1, 1.0 Hz, CHCH=CH), 4.64 (2H, s, CH₂Ph), 3.59 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 2.80 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 2.43-2.34 (1H, m, (CH₃)₂CH), 2.10 (3H, s, CH₃C=O), 0.99 (6H, *J* = 6.8 Hz, (CH₃)₂CH); (Minor rotamer) δ 7.35-7.23 (4H, m, ArH), 7.17-7.15 (1H, m, ArH), 6.97 (1H, dd, *J* = 15.1, 7.0 Hz, CHCH=), 6.21 (1H, d, *J* = 15.1 Hz, CHCH=CH), 4.64 (2H, s, CH₂Ar), 3.59 (2H, t, *J* = 7.1 Hz, CH₂CH₂N), 2.62 (2H, t, *J* = 7.1 Hz, CH₂CH₂N), 2.51-2.43 (1H, m, (CH₃)₂CH), 2.06 (3H, s, CH₃C=O), 1.07 (6H, d, *J* = 6.7 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 167.4 (C), 166.8 (C), 153.9 (CH), 153.4 (CH), 137.7 (C), 137.2 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 117.3 (CH), 116.9 (CH), 52.2 (CH₂), 49.3 (CH₂), 42.8 (CH₂), 42.3 (CH₂), 41.9 (CH₂), 41.7 (CH₂), 31.1 (CH), 30.2 (CH₃), 30.0 (CH₃), 21.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₄NO₂ [M+H]⁺: 274.1802, found: 274.1803.

***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenamide (1e).** The title compound

was prepared according to General Procedure C from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and cinnamoyl chloride (4.03 g, 24.2 mmol) for a reaction time of 3 h. The product was purified by column chromatography (30% EtOAc/petrol) to give a yellow solid (2.10 g, 34%) as a 2:1 mixture of rotamers. m.p. 71-73 °C; IR (CHCl₃) 3027, 1713 (C=O), 1648 (C=C), 1426, 1203, 1161, 1028, 978, 764, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.79 (1H, d, *J* = 15.4 Hz, PhCH=), 7.61-7.26 (10H, m, ArH), 6.86 (1H, d, *J* = 15.4 Hz, PhCH=CH), 4.80 (2H, s, CH₂Ph), 3.73 (2H, t, *J* = 6.7 Hz, CH₂CH₂N), 2.90 (2H, t, *J* = 6.7 Hz, CH₂CH₂N), 2.17 (3H, s, CH₃C=O); (Minor rotamer) δ 7.85 (1H, d, *J* = 15.3 Hz, PhCH=), 7.61-7.26 (10H, m, ArH), 7.01 (1H, d, *J* = 15.3 Hz, PhCH=CH), 4.76 (2H, s, CH₂Ph), 3.76 (2H, t, *J* = 7.1 Hz, CH₂CH₂N), 2.74 (2H, t, *J* = 7.1 Hz, CH₂CH₂N), 2.13 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.0 (C), 167.0 (C), 166.4 (C), 143.5 (CH),

143.1 (CH), 137.5 (C), 137.0 (C), 135.0 (C), 129.6 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.4 (CH), 117.1 (CH), 116.9 (CH), 52.3 (CH₂), 49.5 (CH₂), 42.9 (CH₂), 42.6 (CH₂), 41.8 (2 x CH₂), 30.2 (CH₃), 30.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₁NO₂ [M+Na]⁺: 330.1465, found: 330.1465.

N-benzyl-N-(3-oxobutyl)-(E)-3-furan-2-ylpropenamide (1f). The title compound was prepared according to General Procedure C from methyl vinyl

ketone (0.94 mL, 11.0 mmol), benzylamine (1.09 mL, 10.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (2-furyl)acrylic acid (1.67 g, 12.1 mmol) for a reaction time of 14 h. The product was purified by column chromatography (40% EtOAc/petrol) to give an orange/red oil (1.56 g, 53%) as a 2:1 mixture of rotamers. IR (film) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.55 (1H, d, *J* = 15.1 Hz, CH=CHC=O), 7.50-7.24 (6H, m, ArH and CH), 6.78 (1H, d, *J* = 15.1 Hz, CH=CHC=O), 6.58 (1H, bs, CH), 6.46-6.45 (1H, m, CH), 4.77 (2H, s, CH₂Ph), 3.69 (2H, t, *J* = 6.4 Hz, CH₂CH₂N), 2.87 (2H, t, *J* = 6.4 Hz, CH₂CH₂N), 2.15 (3H, s, CH₃C=O); (Minor rotamer) δ 7.61 (1H, d, *J* = 15.2 Hz, CH=CHC=O), 7.50-7.24 (6H, m, ArH and CH), 6.84 (1H, d, *J* = 15.2 Hz, CH=CHC=O), 6.62-6.58 (1H, m, CH), 6.50-6.49 (1H, m, CH), 4.74 (2H, s, CH₂Ar), 3.71 (2H, t, *J* = 6.9 Hz, CH₂CH₂N), 2.74 (2H, t, *J* = 6.9 Hz, CH₂CH₂N), 2.13 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 166.9 (C), 166.3 (C), 151.5 (C), 143.9 (CH), 137.6 (C), 137.1 (C), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 114.6 (CH), 114.3 (CH), 114.2 (CH), 114.0 (CH), 112.1 (CH) 52.2 (CH₂), 49.6 (CH₂), 43.1 (CH₂), 42.5 (CH₂), 41.9 (CH₂), 30.2 (CH₃), 30.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₀NO₃ [M+H]⁺: 298.1438, found: 298.1441.

N-Benzyl-N-(3-oxo-3-phenylpropyl)-(E)-but-2-enamide (1g). The title

compound was prepared according to General Procedure D from 3-chloropropiophenone (927 mg, 5.50 mmol), benzylamine (0.55 mL, 5.0 mmol) and crotonoyl chloride (0.72 mL, 7.5 mmol) for a reaction time of 5 h. The product was purified by column chromatography (20% EtOAc/CHCl₃) to give a colorless gum (1.27 g, 86%) as a 2:1 mixture of rotamers. IR (CHCl₃) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.96 (2H, d, *J* = 6.7 Hz, ArH), 7.60-7.53 (1H, m, ArH), 7.47-7.43 (2H, m, ArH), 7.38-7.20 (5H, m, ArH), 7.11-6.95 (1H, m, CH₃CH=), 6.24 (1H, dd, *J* = 14.9,

1.4 Hz, CH₃CH=CH), 4.72 (2H, s, CH₂Ph), 3.79 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 3.37 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 1.82 (3H, dd, *J* = 6.8, 1.4 Hz, CH₃CH=); (Minor rotamer) δ 7.85 (2H, d, *J* = 6.7 Hz, ArH), 7.60-7.53 (1H, m, ArH), 7.47-7.43 (2H, m, ArH), 7.38-7.20 (5H, m, ArH), 7.11-6.95 (1H, m, CH₃CH=), 6.36 (1H, d, *J* = 14.6 Hz, CH₃CH=CH), 4.71 (2H, s, CH₂Ph), 3.79 (2H, t, *J* = 7.4 Hz, CH₂CH₂N), 3.17 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 1.91 (3H, d, *J* = 6.5, 1.4 Hz, CH₃CH=); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.7 (C), 167.3 (C), 166.5 (C), 143.0 (CH), 142.4 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.5 (CH), 133.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 121.6 (CH), 121.2 (CH), 52.3 (CH₂), 49.3 (CH₂), 43.2 (CH₂), 42.5 (CH₂), 38.0 (CH₂), 37.2 (CH₃), 18.1 (CH₃); IR (CHCl₃) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm⁻¹; HRMS (ES) Exact mass calcd for C₂₀H₂₂NO₂ [M+H]⁺: 308.1645, found: 308.1643.

***N*-benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-5-methylhex-2-enamide (1h).**

The title compound was prepared according to General Procedure D from 3-chloropropiophenone (1.85 mg, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-methylhex-2-enoic acid (1.92 g, 15.0 mmol) for a reaction time of 15 h. The product was purified by column chromatography (15% EtOAc/CHCl₃) to give a yellow oil (1.62 g, 46%) as a 2:1 mixture of rotamers. IR (CHCl₃) 2955, 1680 (C=O), 1656 (C=C), 1447, 1368, 1211, 1028, 980, 844, 742 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 8.02-8.00 (2H, m, ArH), 7.62-7.58 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 7.41-7.24 (5H, m, ArH), 7.01 (1H, dt, *J* = 15.0, 7.5 Hz, CH₂CH=), 6.24 (1H, d, *J* = 15.0 Hz, CH₂CH=CH), 4.76 (2H, s, CH₂Ph), 3.83 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 3.41 (2H, t, *J* = 6.8 Hz, CH₂CH₂N), 2.10-2.06 (2H, m, CH₂CH=), 1.86-1.68 (1H, m, (CH₃)₂CH), 0.92 (6H, d, *J* = 6.8 Hz, (CH₃)₂CH); (Minor rotamer) δ 7.88 (2H, d, *J* = 15.0 Hz, ArH), 7.64-7.58 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 7.41-7.24 (5H, m, ArH), 7.08 (1H, dt, *J* = 14.9, 7.4 Hz, CH₂CH=), 6.35 (1H, d, *J* = 14.9 Hz, CH₂CH=CH), 4.75 (2H, s, CH₂Ph), 3.83 (2H, t, *J* = 7.4 Hz, CH₂CH₂N), 3.21 (2H, t, *J* = 7.4 Hz, CH₂CH₂N), 2.18-2.14 (2H, m, CH₂CH=), 1.86-1.68 (1H, m, (CH₃)₂CH), 0.97 (6H, d, *J* = 6.6 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.6 (C), 167.3 (C), 166.5 (C), 146.8 (CH), 146.1 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.4 (CH), 133.1 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 126.4 (CH), 121.1 (CH), 120.7 (CH), 52.3 (CH₂), 49.3 (CH₂), 43.3 (CH₂), 42.5 (CH₂), 41.7 (CH₂), 41.6

(CH₂), 38.0 (CH₂), 37.2 (CH₂), 27.8 (CH), 22.2 (CH₃); HRMS (ES) Exact mass calcd for C₂₃H₂₈NO₂ [M+H]⁺: 350.2115, found: 350.2114.

1-[N-Acryloyl-N-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (1i). The title compound was prepared by General Procedure B from the amine **18** (2.33 g, 8.00 mmol) and acryloyl chloride (1.02 mL, 12.0 mmol) for a

reaction time of 65 h and purified by column chromatography (40% EtOAc/petrol) to give a pale brown oil (1.78 g, 64%). IR (film) 2977, 1751 (C=O), 1721 (C=O), 1659 (C=O), 1618, 1511, 1408, 1249, 1173, 1030 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.10 (2H, d, *J* = 8.5 Hz, ArH), 6.88-6.87 (2H, m, ArH), 6.30 (1H, dd, *J* = 16.8, 2.0 Hz, CH₂=), 5.97 (1H, dd, *J* = 16.8, 10.3 Hz, CH₂=CH), 5.50 (1H, dd, *J* = 10.3, 2.0 Hz, CH₂=), 4.30 (2H, d, *J* = 5.2 Hz, CH₂N), 3.86-3.78 (1H, m, OCH₂CH₃), 3.81 (3H, s, OCH₃), 3.72-3.63 (1H, m, OCH₂CH₃), 2.54-2.27 (3H, m, CH₂CH₂CH₂), 2.19-1.97 (3H, m, CH₂CH₂CH₂), 1.01 (3H t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 212.3 (C), 169.6 (C), 166.7 (C), 159.0 (C), 134.0 (C), 129.5 (2 x CH), 128.0 (CH and CH₂), 114.4 (2 x CH), 61.5 (CH₂), 60.7 (C), 55.4 (CH₃), 50.9 (CH₂), 38.1 (CH₂), 31.6 (CH₂), 19.5 (CH₂), 13.7 (CH₃); HRMS (FAB) Exact mass calcd for C₁₉H₂₄NO₅ [M+H]⁺: 346.1650, found: 346.1644.

1-[N-(E)-But-2-enoyl-N-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (1j). The title compound was prepared by General Procedure B from the amine **18** (295 mg, 1.00 mmol) and

crotonoyl chloride (143 μL, 1.50 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a pale brown oil (307 mg, 84%). IR (film) 2965, 1750 (C=O), 1719 (C=O), 1666 (C=O), 1629, 1510, 1445, 1289, 1249, 1029 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.09 (2H, d, *J* = 8.4 Hz, ArH), 6.92-6.82 (3H, m, ArH and CH₃CH=), 5.65 (1H, dd, *J* = 15.1, 1.7 Hz, CH₃CH=CH), 4.33 (1H, d, *J* = 13.9 Hz, CH₂N), 4.25 (1H, d, *J* = 13.9 Hz, CH₂N), 3.87-3.78 (1H, m, OCH₂CH₃), 3.83 (3H, s, OCH₃), 3.72-3.63 (1H, m, OCH₂CH₃), 2.55-1.97 (6H, m, CH₂CH₂CH₂), 1.71 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃CH=), 1.01 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 212.4 (C), 169.6 (C), 167.0 (C), 158.9 (C), 142.0 (CH), 134.3 (C), 129.5 (2 x CH), 122.2 (CH), 114.3 (2 x CH), 61.4 (CH₂), 60.8 (C), 55.4 (CH₃), 50.8 (CH₂), 38.1 (CH₂), 31.5 (CH₂), 19.5 (CH₂), 18.0 (CH₃), 13.7 (CH₃); HRMS (FAB) Exact mass calcd for C₂₀H₂₆NO₅ [M+H]⁺: 360.1806, found: 360.1809.

1-[N-(4-Methoxyphenyl)-N-((E)-3-phenylacryloyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (1k). The title compound was prepared by General Procedure B from the amine **18** (2.33 g, 8.00 mmol) and

cinnamoyl chloride (2.04 g, 12.0 mmol) for a reaction time of 65 h and purified by column chromatography (10% EtOAc/petrol→30% EtOAc/petrol) to give a pale brown gum (2.19 g, 65%). IR (film) 2961, 1750 (C=O), 1720 (C=O), 1655 (C=O), 1616, 1510, 1249, 1029, 839, 806 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.62 (1H, d, $J = 15.6$ Hz, PhCH=), 7.29 (5H, br s, ArH), 7.16 (2H, app d, $J = 7.8$ Hz, ArH), 6.92 (2H, d, $J = 9.1$ Hz, ArH), 6.27 (1H, d, $J = 15.6$ Hz, PhCH=CH), 4.40 (1H, d, $J = 13.9$ Hz, CH_2N), 4.34 (1H, d, $J = 13.9$ Hz, CH_2N), 3.90-3.81 (1H, m, OCH_2CH_3), 3.85 (3H, s, OCH_3), 3.77-3.67 (1H, m, OCH_2CH_3), 2.58-2.30 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.24-2.13 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.09-1.98 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.04 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (90.6 MHz, CDCl_3) δ 212.5 (C), 169.6 (C), 167.1 (C), 159.0 (C), 142.5 (CH), 135.0 (C), 134.1 (C), 129.6 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 118.1 (CH), 114.4 (2 x CH), 61.5 (CH_2), 60.9 (C), 55.5 (CH_3), 51.0 (CH_2), 38.2 (CH_2), 31.6 (CH_2), 19.6 (CH_2), 13.7 (CH_3); LRMS (ES) Mass calcd for $\text{C}_{25}\text{H}_{28}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 422.2, found: 422.0.

N-(4-Methoxyphenyl)-N-(2-oxopropyl)propenamide (1l). The title compound was prepared according to general procedure B from the amine **19** (1.07 g, 6.00 mmol) and acryloyl chloride (762 μL , 9.00 mmol) for a reaction time of 2.5 h and purified by

column chromatography (30% EtOAc/petrol→60% EtOAc/petrol) to give a beige solid (1.21 g, 87%). m.p. 48-51 $^\circ\text{C}$; IR (CHCl_3) 2960, 1732 (C=O), 1652 (C=O), 1618, 1512, 1427, 1250, 1172, 1030, 843 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.21 (2H, dm, $J = 8.9$ Hz, ArH), 6.88 (2H, dm, $J = 8.9$ Hz, ArH), 6.35 (1H, dd, $J = 16.8, 2.0$ Hz, $\text{CH}_2=$), 6.10 (1H, dd, $J = 16.8, 10.3$ Hz, $\text{CH}_2=\text{CH}$), 5.54 (1H, dd, $J = 10.3, 2.0$ Hz, $\text{CH}_2=$), 4.47 (2H, s, CH_2N), 3.81 (3H, s, OCH_3), 2.18 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 202.3 (C), 165.9 (C), 159.1 (C), 135.0 (C), 129.2 (2 x CH), 128.1 (CH_2), 127.7 (CH), 114.6 (2 x CH), 59.7 (CH_2), 55.4 (CH_3), 27.2 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 234.1125, found: 234.1125.

N-(4-Methoxyphenyl)-N-(2-oxopropyl)-(E)-3-phenylpropenamide (1m). The title compound was prepared according to General Procedure B from the amine **19**

(1.07 g, 6.00 mmol) and cinnamoyl chloride (1.50 g, 9.00 mmol) for a reaction time of 2.5 h and purified by column chromatography (30% EtOAc/petrol→60% EtOAc/petrol) followed by

recrystallization (EtOAc/petrol) to give a beige solid (590 mg, 32%). m.p. 115-117 °C; IR (CHCl₃) 2918, 1731 (C=O), 1654 (C=O), 1616, 1511, 1378, 1250, 1214, 1171, 1030 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.67 (1H, d, *J* = 15.6 Hz, PhCH=), 7.67-7.29 (7H, m, ArH), 6.92 (2H, dm, *J* = 8.8 Hz, ArH), 6.39 (1H, d, *J* = 15.6 Hz, PhCH=CH), 4.52 (2H, s, CH₂N), 3.34 (3H, s, OCH₃), 2.20 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 202.5 (C), 159.0 (C), 142.4 (CH), 135.1 (C), 135.0 (C), 129.5 (CH), 129.2 (2 x CH), 128.6 (2 x CH), 127.8 (2 x CH), 117.8 (CH), 114.6 (2 x CH), 59.8 (CH₂), 55.4 (CH₃), 27.2 (CH₃); HRMS (FAB) Exact mass calcd for C₁₉H₂₀NO₃ [M+H]⁺: 310.1438, found: 310.1437.

***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(E)-3-(2-methoxyphenyl)propenamide (1n).** The title compound was prepared according to General Procedure B from the amine **19** (537 mg, 3.00 mmol) and

the acid chloride (prepared according to General Procedure A) derived from 2-methoxycinnamic acid (801 mg, 4.30 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a beige solid (617 mg, 61%). m.p. 111-112 °C; IR (CHCl₃) 2935, 1733 (C=O), 1652 (C=O), 1613, 1510, 1376, 1248, 1070, 1028, 755 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.97 (1H, d, *J* = 15.7 Hz, ArCH=), 7.30-7.24 (4H, m, ArH), 6.93 (2H, dd, *J* = 8.9 Hz, ArH), 6.88-6.83 (2H, m, ArH), 6.52 (1H, d, *J* = 15.7 Hz, ArCH=CH), 4.53 (2H, s, CH₂N), 3.85 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 2.22 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 202.7 (C), 166.8 (C), 158.9 (C), 158.1 (C), 137.8 (CH), 135.9 (C), 130.7 (CH), 129.2 (2 x CH), 128.7 (CH), 124.0 (C), 120.4 (CH), 118.5 (CH), 114.5 (2 x CH), 110.9 (CH), 59.7 (CH₂), 55.4 (CH₃), 55.2 (CH₃), 27.2 (CH₃); HRMS (FAB) Exact mass calcd for C₂₀H₂₂NO₄ [M+H]⁺: 340.1544, found: 340.1549.

***N*-(4-Methoxyphenyl)-*N*-(2-oxo-2-phenylethyl)propenamide (4a).** The title compound was prepared according to general procedure B from the amine **20** (1.00 g,

4.12 mmol) and acryloyl chloride (500 μL, 6.10 mmol) for a reaction time of 20 h and purified by column chromatography (40% EtOAc/petrol) to give a yellow solid (790 mg, 65%). m.p. 78-80 °C; IR (CHCl₃) 2925, 1699 (C=O), 1655 (C=C), 1509, 1421, 1248, 1221, 979, 754 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.00-7.97 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.50-7.45 (2H, m, ArH), 7.33 (2H, dm, *J* = 8.9 Hz, ArH), 6.93 (2H, dm, *J* = 9.0 Hz, ArH), 6.42 (1H, dd, *J* = 16.8, 2.1 Hz, CH₂=), 6.21 (1H, dd, *J* = 16.8, 10.3 Hz, CH₂=CH), 5.60 (1H, dd, *J* = 10.3, 2.1 Hz, CH₂=), 5.18 (2H, s, CH₂N), 3.83 (3H, s, OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 193.4 (C), 166.0 (C), 159.0 (C), 135.1 (C), 135.0 (C), 133.4 (2 x CH), 129.4 (2 x CH), 128.6 (2 x CH₂), 128.0 (CH), 127.9 (2 x CH), 127.8 (CH), 114.5 (2 x CH), 56.4

(CH₂), 55.4 (CH₃); HRMS (FAB) Exact mass calcd for C₁₈H₁₈NO₃ [M+H]⁺: 296.1282, found: 296.1286.

***N*-(4-Methoxybenzyl)-*N*-(2-oxo-2-phenylethyl)propenamide (4b).** The title compound was prepared according to general procedure B from the amine hydrochloride **21** (870 mg, 3.00 mmol) and acryloyl chloride (360 μ L, 4.48 mmol) for

a reaction time of 20 h and purified by column chromatography (40% EtOAc/petrol) to give a pale yellow solid (650 mg, 46%) as a 3:1 mixture of rotamers. m.p. 78-80 °C; IR (CHCl₃) 2930, 1698 (C=O), 1650 (C=C), 1512, 1448, 1247, 1031, 754 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) (Major rotamer) δ 7.95-7.93 (2H, m, ArH), 7.62-7.56 (1H, m, ArH), 7.50-7.43 (2H, m, ArH), 7.16-7.14 (2H, m, ArH), 6.90-6.88 (2H m, ArH), 6.72 (1H, dd, J = 16.7, 10.4 Hz, CH₂=CH), 6.45 (1H, dd, J = 16.7, 1.9 Hz, CH₂=), 5.77 (1H, dd, J = 10.4, 1.9 Hz, CH₂=), 4.81 (2H, s, NCH₂C=O), 4.68 (2H, s, CH₂Ar), 3.80 (3H, s, OCH₃); (Minor rotamer) δ 7.89-7.86 (2H, m, ArH), 7.62-7.60 (1H, m, ArH), 7.50-7.43 (2H, m, ArH), 7.21-7.13 (2H, m, ArH), 6.86-6.83 (2H, m, ArH), 6.40 (1H, dd, J = 16.7, 2.2 Hz, CH₂=), 6.29 (1H, dd, J = 16.7, 10.1 Hz, CH₂=CH), 5.66 (1H, dd, J = 10.1, 2.2 Hz, CH₂=), 4.81 (2H, s, NCH₂C=O), 4.69 (2H, s, CH₂Ar), 3.78 (3H, s, OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) (Mixture of rotamers – not fully assigned) δ 194.1 (C), 193.5 (C), 167.4 (C), 167.2 (C), 159.3 (C), 159.1 (C), 135.2 (C), 134.6 (C), 134.0 (C), 133.5 (CH), 129.9 (CH), 129.2 (CH₂), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH₂), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 114.3 (CH), 114.3 (CH), 55.3 (CH₃), 52.5 (CH₃), 51.5 (CH₂), 49.4 (CH₂); HRMS (ES) Exact mass calcd for C₁₉H₂₀NO₃ [M+H]⁺: 310.1438, found: 310.1438.

Cobalt-Catalyzed Reductive Aldol Cyclizations

Using Co(acac)₃/Et₂Zn: General Procedure E

A solution of the substrate (0.20 mmol) and Co(acac)₃·2H₂O (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Using CoCl₂/Cy₂PPh/Et₂Zn: General Procedure F

A solution of the substrate (0.20 mmol), CoCl₂ (1.3 mg, 0.01 mmol) and Cy₂PPh (3.0 mg, 0.011 mmol) in THF (1.5 mL) was stirred at room temperature for 30 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Using Co(acac)₂/Et₃Al: General Procedure G

A solution of the substrate (0.20 mmol) and Co(acac)₂·2H₂O (2.6 mg, 0.01 mmol) in THF (3 mL) was stirred at room temperature for 15 min. The mixture was cooled 0 °C and Et₃Al (1 M solution in hexane, 0.40 mL, 0.40 mmol) was added dropwise over 5 min. The reaction was stirred at 0° C for 1 h and then at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched carefully by the addition of 1 M HCl (5 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup A

The reaction mixture was filtered through a short plug of SiO₂ (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup B

The reaction was quenched carefully with saturated aqueous NH₄Cl solution (10 mL) and the mixture was then extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (2a). On a 0.20 mmol scale: The title compound was prepared according to General Procedure E from **1a** (65 mg, 0.20 mmol) for a reaction time of 4 h followed by

Workup A and purification by column chromatography (30% EtOAc/CHCl₃) to give a white solid (58 mg, 89%).

On a 5.00 mmol scale: A solution of **1a** (1.62 g, 5.00 mmol) and Co(acac)₂·2H₂O (6.4 mg, 0.025 mmol) in THF (10 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 10.0 mL, 10.0 mmol) was then added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2.5 h. The reaction was filtered through a short pad of SiO₂ (ca. 5 cm high x 3 cm diameter) using EtOAc (200 mL) as eluent and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/CHCl₃) gave the *lactam* **2a** (1.28 g, 79%) as a white solid.

m.p. 156-157 °C; IR (CHCl₃) 3409, 2935, 1630 (C=O), 1605, 1511, 1442, 1334, 1245, 1141, 1033 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.38 (2H, d, *J* = 7.3 Hz, ArH), 7.27 (2H, t, *J* = 7.5 Hz, ArH), 7.18 (1H, d, *J* = 7.3 Hz, ArH), 7.15 (2H, d, *J* = 9.0 Hz, ArH), 6.90 (2H, dm, *J* = 9.0 Hz, ArH), 3.82 (1H, ddd, *J* = 12.1, 7.4, 7.4 Hz, CH₂CH₂N), 3.84 (3H, s, OCH₃), 3.41 (1H, ddd, *J* = 10.5, 5.3, 5.3 Hz, CH₂CH₂N), 3.34 (1H, dd, *J* = 14.5, 5.3 Hz, CH₂CH), 3.14 (1H, dd, *J* = 14.5, 5.3 Hz, CH₂CH), 2.72 (1H, t, *J* = 5.3 Hz, CH₂CH), 1.95 (2H, app dd, *J* = 7.4, 5.3 Hz, CH₂CH₂N), 1.79 (1H, s, OH), 1.34 (3H, s, CH₃COH); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.4 (C), 158.0 (C), 142.1 (C), 136.2 (C), 129.2 (2 x CH), 128.4 (2 x CH), 127.4 (2 x CH), 125.9 (CH), 114.4 (2 x CH), 71.1 (C), 55.4 (CH₃), 54.6 (CH), 47.3 (CH₂), 36.1 (CH₂), 32.3 (CH₂), 29.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₃NO₃Na [M+Na]⁺: 348.1570, found: 348.1571.

(±)-(3*R*,4*R*)-3-Benzyl-4-ethyl-4-hydroxy-1-(4-methoxyphenyl)piperidin-2-one

(2b). The title compound was prepared according to General Procedure E from **1b** (67 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by

column chromatography (50% EtOAc/hexane) to give a white solid (60 mg, 88%). m.p. 131-132 °C; IR (CHCl₃) 3419 (OH), 2963, 1633 (C=O), 1510, 1442, 1296, 1244, 829, 732, 701 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.42 (2H, dm, *J* = 7.1 Hz, ArH), 7.34-7.30 (2H, m, ArH), 7.24-7.18 (3H, m, ArH), 6.96 (2H, dm, *J* = 9.0 Hz, ArH), 3.87-3.80 (1H, m, CH₂N), 3.84 (3H, s, OCH₃), 3.52-3.46 (1H, m, CH₂N), 3.35 (1H, dd, *J* = 14.3, 5.6 Hz, CH₂CH), 3.19 (1H, dd, *J* = 14.3, 4.8 Hz, CH₂CH), 2.84 (1H, app t, *J* = 5.2 Hz, CH₂CH), 2.05-1.93 (2H, m, CH₂CH₂N), 1.79-1.71 (2H, m, CH₃CH₂), 1.66 (1H, br s, OH), 0.95 (3H, t, *J* = 7.5 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.7 (C), 158.0 (C), 141.8 (C), 136.2 (C), 129.4 (2 x CH), 128.4 (2 x CH), 127.3 (2 x CH), 126.0 (CH), 114.4 (2 x CH), 73.5 (C),

55.4 (CH), 52.8 (CH₃), 47.2 (CH₂), 33.4 (CH₂), 32.2 (CH₂), 32.0 (CH₂), 7.8 (CH₃); HRMS (FAB) Exact mass calcd for C₂₁H₂₆NO₃ [M+H]⁺: 340.1908, found: 340.1913.

(±)-(3R,4R)-1-Benzyl-4-hydroxy-3,4-dimethylpiperidin-2-one (2c). The title compound was prepared according to General Procedure E from **1c** (46 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (80% EtOAc/petrol) to give a white solid (41 mg, 88%). m.p. 155-157 °C; IR (CHCl₃) 3335 (OH), 2980, 1605 (C=O), 1496, 1509, 1360, 1236, 1196, 927, 735 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.33-7.22 (5H, m, ArH), 4.76 (1H, d, *J* = 14.8 Hz, CH₂Ph), 4.40 (1H, d, *J* = 14.8 Hz, CH₂Ph), 3.44 (1H, ddd, *J* = 12.1, 10.2, 5.3 Hz, CH₂CH₂N), 3.09 (1H, ddd, *J* = 12.1, 6.1, 3.9 Hz, CH₂CH₂N), 2.38 (1H, q, *J* = 7.3 Hz, CH₃CH), 1.99 (1H, br s, OH), 1.90 (1H, ddd, *J* = 13.6, 5.3, 3.9 Hz, CH₂CH₂N), 1.79 (1H, ddd, *J* = 13.6, 10.2, 6.1 Hz, CH₂CH₂N), 1.33 (3H, d, *J* = 7.3 Hz, CH₃CH), 1.31 (3H, s, CH₃COH); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.7 (C), 137.2 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 69.9 (C), 50.2 (CH₂), 46.7 (CH), 42.9 (CH₂), 34.8 (CH₂), 28.3 (CH₃), 10.4 (CH₃); HRMS (ES) Exact mass calcd for C₁₄H₁₉NO₂ [M+H]⁺: 234.1489, found: 234.1491.

(±)-(3R,4R)-1-Benzyl-3-iso-butyl-4-hydroxy-4-methylpiperidin-2-one (2d). The title compound was prepared according to General Procedure E from **1d** (55 mg, 0.20 mmol) for a reaction time of 8 h using Workup A and purified by column chromatography (50% EtOAc/petrol) to give a white solid (55 mg, >99%). m.p. 113-115 °C; IR (CHCl₃) 3407 (OH), 2954, 1620 (C=O), 1495, 1452, 1267, 1150, 1116, 732, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.27 (5H, m, ArH), 4.72 (1H, d, *J* = 14.7 Hz, CH₂Ph), 4.49 (1H, d, *J* = 14.8 Hz, CH₂Ph), 3.41 (1H, ddd, *J* = 12.3, 7.9, 5.8 Hz, CH₂CH₂N), 3.15-3.08 (1H, m, CH₂CH₂N), 2.32 (1H, dd, *J* = 8.2, 2.8 Hz, CH₂CH), 2.11-1.93 (2H, m), 1.84-1.71 (3H, m) and 1.46 (1H, ddd, *J* = 13.6, 9.2, 3.0 Hz, CH₂CH₂N, (CH₃)₂CHCH₂ and OH), 1.32 (3H, s, CH₃COH), 1.03 (3H, d, *J* = 6.7 Hz, (CH₃)₂CH), 0.99 (3H, d, *J* = 6.7 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.3 (C), 137.3 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 127.9 (2 x CH), 127.2 (CH), 70.6 (C), 50.2 (CH), 50.0 (CH₂), 43.0 (CH₂), 36.4 (CH₂), 34.2 (CH₂), 28.2 (CH₃), 27.7 (CH), 23.5 (CH₃), 21.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₆NO₂ [M+H]⁺: 276.1958, found: 276.1960.

(±)-(3R,4R)-1,3-Dibenzyl-4-hydroxy-4-methylpiperidin-2-one (2e). The title compound was prepared according to General Procedure E from **1e** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (60% EtOAc/petrol) to give a white solid (60 mg, 97%). m.p. 137-139 °C; IR (CHCl₃) 3399 (OH), 2928, 1617 (C=O), 1495, 1452, 1353, 1267, 1030, 740, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.44-7.41 (2H, m, ArH), 7.39-7.28 (7H, m, ArH), 7.26-7.21 (1H, m, ArH), 4.76 (1H, d, *J* = 14.7 Hz, NCH₂Ph), 4.58 (1H, d, *J* = 14.7 Hz, NCH₂Ph), 3.47 (1H, ddd, *J* = 12.2, 9.1, 5.6 Hz, CH₂CH₂N), 3.37 (1H, dd, *J* = 14.4, 5.4 Hz, CH₂CH), 3.23 (1H, dd, *J* = 14.4, 5.4 Hz, CH₂CH), 3.16-3.09 (1H, m, CH₂CH₂N), 2.73 (1H, t, *J* = 5.4 Hz, CH₂CH), 1.92-1.78 (3H, m, CH₂CH₂N and OH), 1.31 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.1 (C), 141.9 (C), 137.1 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (C), 126.0 (C), 71.0 (C), 54.2 (CH), 50.4 (CH₂), 43.0 (CH₂), 35.2 (CH₂), 32.8 (CH₂), 28.9 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₄NO₂ [M+H]⁺: 310.1802, found: 310.1802.

(±)-(3R,4R)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-methylpiperidin-2-one (2f). The title compound was prepared according to General Procedure E from **1f** (59 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and

purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, >99%). Slow diffusion of petrol into a CH₂Cl₂ solution of **2f** was found to give colorless crystals suitable for X-ray diffraction. m.p. 120-122 °C; IR (CHCl₃) 3409 (OH), 2925, 1620 (C=O), 1496, 1452, 1270, 1146, 1008, 731, 705 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.26 (6H, m, ArH and CH), 6.36-6.34 (1H, m, CH), 6.20-6.19 (1H, m, CH), 4.72 (1H, d, *J* = 14.7 Hz, NCH₂Ar), 4.57 (1H, d, *J* = 14.7 Hz, NCH₂Ar), 3.46 (1H, ddd, *J* = 12.1, 9.1, 5.9 Hz, CH₂CH₂N), 3.40 (1H, dd, *J* = 15.5, 4.9 Hz, CH₂CH), 3.32 (1H, dd, *J* = 15.5, 6.2 Hz, CH₂CH), 3.14-3.08 (1H, m, CH₂CH₂N), 2.76 (1H, app t, *J* = 5.6 Hz, CH₂CH), 2.11 (1H, br s, OH), 1.87-1.76 (2H, m, CH₂CH₂N), 1.29 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.1 (C), 154.5 (C), 140.7 (CH), 137.1 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 110.8 (CH), 106.9 (CH), 70.2 (C), 51.5 (CH), 50.4 (CH₂), 42.9 (CH₂), 35.5 (CH₂), 28.4 (CH₂), 25.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₂NO₃ [M+H]⁺: 300.1594, found: 300.1593.

(±)-(3R,4R)-1-Benzyl-3-ethyl-4-hydroxy-4-phenylpiperidin-2-one (2g). The title compound was prepared according to General Procedure E from **1g** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column

chromatography (50% EtOAc/petrol) to give a white solid (58 mg, 94%). m.p. 199-201 °C; IR (CHCl₃) 3384 (OH), 2948, 1604 (C=O), 1491, 1445, 1238, 1146, 755, 705, 682 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.50-7.28 (10H, m, ArH), 4.77 (1H, d, *J* = 14.7 Hz, CH₂Ph), 4.61 (1H, d, *J* = 14.7 Hz, CH₂Ph), 3.57 (1H, ddd, *J* = 12.1, 10.5, 5.2 Hz, CH₂CH₂N), 3.16 (1H, ddd, *J* = 12.1, 6.2, 3.5 Hz, CH₂CH₂N), 2.74 (1H, dd, *J* = 7.3, 3.4 Hz, CH₂CH), 2.26 (1H, ddd, *J* = 14.0, 10.5, 6.2 Hz, CH₂CH₂N), 2.01 (1H, ddd, *J* = 14.0, 5.2, 3.5 Hz, CH₂CH₂N), 1.98 (1H, br s, OH), 1.92-1.80 (1H, m, CH₃CH₂), 1.59-1.48 (1H, m, CH₃CH₂), 1.07 (3H, t, *J* = 7.4 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.8 (C), 145.9 (C), 137.3 (C), 128.6 (4 x CH), 127.9 (2 x CH), 127.3 (2 x CH), 124.5 (2 x CH), 75.6 (C), 52.7 (CH), 50.2 (CH₂), 43.3 (CH₂), 36.6 (CH₂), 20.2 (CH₂), 14.9 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₄NO₂ [M+H]⁺: 310.1802, found: 310.1803.

(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(3-methylbutyl)-4-phenylpiperidin-2-one

(2h). The title compound was prepared according to General Procedure E from **1h** (70 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and

purification by column chromatography (50% EtOAc/petrol) to give a white solid (66 mg, 94%). m.p. 134-136 °C; IR (CHCl₃) 3399 (OH), 2952, 1617 (C=O), 1494, 1451, 1353, 1242, 758, 733, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49-7.28 (10H, m, ArH), 4.80 (1H, d, *J* = 14.7 Hz, CH₂Ph), 4.56 (1H, d, *J* = 14.7 Hz, CH₂Ph), 3.57 (1H, ddd, *J* = 12.1, 10.6, 5.2 Hz, CH₂CH₂N), 3.16 (1H, ddd, *J* = 12.1, 6.2, 3.5 Hz, CH₂CH₂N), 2.78 (1H, dd, *J* = 7.4, 3.1 Hz, CHC=O), 2.27 (1H, ddd, *J* = 14.0, 10.6, 6.2 Hz, CH₂CH₂N), 2.10 (1H, br s, OH), 2.02 (1H, ddd, *J* = 14.0, 5.2, 3.5 Hz, CH₂CH₂N), 1.87-1.77 (1H, m), 1.68-1.58 (1H, m), 1.48-1.38 (2H, m) and 1.15-1.05 (1H, m, (CH₃)₂CHCH₂CH₂), 0.78 (3H, d, *J* = 6.0 Hz, (CH₃)₂CH), 0.76 (3H, d, *J* = 6.0 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.9 (C), 145.8 (C), 137.2 (C), 128.5 (4 x CH), 127.9 (2 x CH), 127.2 (2 x CH), 124.6 (2 x CH), 75.4 (C), 51.5 (CH), 50.2 (CH₂), 43.3 (CH₂), 39.4 (CH₂), 36.3 (CH₂), 28.1 (CH), 24.6 (CH₂), 22.4 (CH₃), 22.2 (CH₃); HRMS (FAB) Exact mass calcd for C₂₃H₃₀NO₂ [M+H]⁺: 352.2272, found: 352.2272.

(±)-(1*R*,5*R*,6*S*)-1-Carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-5-methyl-3-

azabicyclo[4.3.0]nonan-4-one (2i). The title compound was prepared according to

General Procedure F from **1i** (69 mg, 0.20 mmol) for a reaction time of 3 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol→60% EtOAc/petrol) to give a white solid (39 mg, 56%). Slow evaporation of an Et₂O solution of **1i** was found to give colorless crystals suitable for X-ray diffraction. m.p. 111-112 °C; IR (CHCl₃) 3434 (OH), 2941, 1724

(C=O), 1666 (C=O), 1512, 1465, 1443, 1246, 1033, 832 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.20 (2H, dm, $J = 9.0$ Hz, ArH), 6.87 (2H, dm, $J = 9.0$ Hz, ArH), 4.14 (1H, d, $J = 13.5$ Hz, CH_2N), 4.15-4.09 (2H, m, OCH_2CH_3), 3.79 (3H, s, OCH_3), 3.6 (1H, d, $J = 13.5$ Hz, CH_2N), 3.21 (1H, s, OH), 2.68 (1H, q, $J = 6.9$ Hz, CH_3CH), 2.43-2.33 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.16-2.09 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.00-1.89 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.74-1.62 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.33 (3H, d, $J = 6.9$ Hz, CH_3CH), 1.11 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.8 (C), 171.6 (C), 157.4 (C), 135.7 (C), 126.4 (2 x CH), 113.8 (2 x CH), 85.5 (C), 61.5 (CH_2), 57.4 (C), 55.4 (CH_3), 54.6 (CH_2), 44.7 (CH), 40.8 (CH_2), 36.3 (CH_2), 23.1 (CH_2), 13.9 (CH_3), 9.4 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 348.1806, found: 348.1805.

(±)-(1R,5R,6S)-1-Carbethoxy-5-ethyl-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (2j). The title compound was prepared according to

General Procedure F from **1j** (72 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) to give a colorless oil (58 mg, 80%). IR (film) 3431 (OH), 2965, 1725 (C=O), 1666 (C=O), 1512, 1288, 1247, 1101, 1033, 836 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.20 (2H, dm, $J = 9.1$ Hz, ArH), 6.87 (2H, dm, $J = 9.1$ Hz, ArH), 4.16 (1H, d, $J = 13.6$ Hz, CH_2N), 4.10 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 3.61 (1H, d, $J = 13.6$ Hz, CH_2N), 3.27 (1H, br s, OH), 2.42-2.34 (2H, m), 2.17-2.03 (2H, m), 2.00-1.91 (2H, m) and 1.78-1.62 (3H, m, $\text{CH}_3\text{CH}_2\text{CH}$ and $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.10 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.08 (3H, t, $J = 7.4$ Hz, $\text{CH}_3\text{CH}_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.6 (C), 170.9 (C), 157.4 (C), 135.7 (C), 126.3 (2 x CH), 113.8 (2 x CH), 85.8 (C), 61.4 (CH_2), 57.8 (C), 55.4 (CH_3), 54.6 (CH_2), 53.2 (CH), 41.8 (CH_2), 36.6 (CH_2), 23.5 (CH_2), 18.3 (CH_2), 14.1 (CH_3), 13.9 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 362.1963, found: 348.1962.

(±)-(1R,5R,6S)-5-Benzyl-1-carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (2k). The title compound was prepared by General

Procedure F from **1k** (84 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol) to give a colorless oil (75 mg, 88%). IR (film) 3438 (OH), 2962, 1724 (C=O), 1671 (C=O), 1512, 1465, 1287, 1247, 1115, 832 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.39-7.36 (2H, m, ArH), 7.29-7.24 (2H, m, ArH), 7.21-7.15 (1H, m, ArH), 7.18 (2H, dm, $J = 9.1$ Hz, ArH), 6.86 (2H, dm, $J = 9.1$ Hz, ArH), 4.11 (2H, q, $J =$

7.1 Hz, OCH₂CH₃), 4.11 (1H, d, J = 13.7 Hz, CH₂N), 3.79 (3H, s, OCH₃), 3.63 (1H, d, J = 13.7 Hz, CH₂N), 3.59 (1H, dd, J = 14.4, 8.1 Hz, CH₂CH), 3.51 (1H, s, OH), 2.96 (1H, dd, J = 14.4, 2.8 Hz, CH₂CH), 2.78 (1H, dd, J = 8.1, 2.8 Hz, CH₂CH), 2.40-2.23 (2H, m, CH₂CH₂CH), 2.05-1.91 (2H, m, CH₂CH₂CH₂), 1.73-1.62 (2H, m, CH₂CH₂CH₂), 1.08 (3H, t, J = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.7 (C), 170.3 (C), 157.3 (C), 142.1 (C), 135.6 (C), 129.3 (2 x CH), 128.2 (2 x CH), 126.2 (2 x CH), 125.8 (CH), 113.8 (2 x CH), 86.4 (C), 61.5 (CH₂), 58.0 (C), 55.4 (CH₃), 54.4 (CH₂), 53.6 (CH), 41.8 (CH₂), 36.4 (CH₂), 31.0 (CH₂), 23.4 (CH₂), 13.8 (CH₃); HRMS (FAB) Exact mass calcd for C₂₅H₃₀NO₅ [M+H]⁺: 424.2119. found: 424.2129.

(±)-(3R,4S)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethylpyrrolidin-2-one (2l).

The title compound was prepared according to General Procedure E from **1l** (47 mg, 0.20 mmol) for a reaction time of 2 h followed by Workup B and purification by column chromatography (30% EtOAc/CHCl₃) to give a white solid (22 gm, 47%). m.p. 155-156 °C; IR (CHCl₃) 3410, 2934, 1675 (C=O), 1614, 1513, 1468, 1401, 1248, 1181, 1033 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49 (2H, dm, J = 9.0 Hz, ArH), 6.88 (2H, dm, J = 9.0 Hz, ArH), 3.80 (3H, s, OCH₃), 3.78 (1H, d, J = 10.4 Hz, CH₂N), 3.69 (1H, d, J = 10.4 Hz, CH₂N), 2.51 (1H, q, J = 7.3 Hz, CH₃CH), 1.98 (1H, bs, OH), 1.47 (3H, s, CH₃COH), 1.24 (3H, d, J = 7.3 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.2 (C), 156.4 (C), 132.6 (C), 121.4 (2 x CH), 114.0 (2 x CH), 73.0 (C), 60.7 (CH₂), 55.4 (CH₃), 48.6 (CH), 24.7 (CH₃), 7.5 (CH₃); HRMS (FAB) Exact mass calcd for C₁₃H₁₈NO₃ [M+H]⁺: 236.1282, found: 236.1293.

(±)-(3R,4S)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (2m).

The title compound was prepared according to General Procedure E from **1m** (62 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and purification by column chromatography (30% EtOAc/CHCl₃) to give a white solid (35 mg, 56%). Slow evaporation of a CDCl₃ solution of **2m** was found to give colorless crystals suitable for X-ray diffraction. m.p. 158-160 °C; IR (CHCl₃) 3346, 2928, 1661 (C=O), 1514, 1439, 1391, 1250, 1216, 1173, 1028 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.50 (2H, dm, J = 9.2 Hz, ArH), 7.37-7.20 (5H, m, ArH), 6.90 (2H, dm, J = 9.2 Hz, ArH), 3.81 (3H, s, OCH₃), 3.70 (1H, d, J = 10.4 Hz, CH₂N), 3.60 (2H, d, J = 10.4 Hz, CH₂N), 3.37 (1H, dd, J = 14.3, 4.5 Hz, CH₂CH), 2.97 (1H, dd, J = 14.3, 9.7 Hz, CH₂CH), 2.81 (1H, dd, J = 9.7, 4.5 Hz, CH₂CH), 1.94 (1H, br s, OH), 1.14 (3H, s, CH₃COH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2 (C), 156.5 (C), 140.1 (C), 132.4 (C), 129.1 (2 x CH), 128.5 (2 x CH), 126.3 (CH),

121.5 (2 x CH), 114.0 (2 x CH), 73.3 (C), 61.1 (CH₂), 55.4 (CH₃), 55.1 (CH), 30.8 (CH₂), 25.8 (CH₃); HRMS (FAB) Exact mass calcd for C₂₀H₂₂NO₄ [M+H]⁺: 312.1594, found: 312.1594.

(±)-(3*R*,4*S*)-4-Hydroxy-3-(2-methoxybenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (2n). The title compound was prepared according to General Procedure F from **1n** (68 mg, 0.20 mmol) for a reaction time of 24 h

followed by Workup B and purification by column chromatography (30% EtOAc/CHCl₃) to give a white solid (50 mg, 74%). m.p. 136-137 °C; IR (film) 3451, 2935, 1687 (C=O), 1587, 1495, 1466, 1246, 1031, 829, 755, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.51 (2H, dm, *J* = 9.2 Hz, ArH), 7.28-7.24 (1H, m, ArH), 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, ArH), 6.99 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 6.94-6.91 (1H, m, ArH), 6.90 (2H, dm, *J* = 9.2 Hz, ArH), 3.92 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.65 (1H, br s, OH), 3.62 (2H, s, CH₂N), 3.24 (1H, dd, *J* = 14.3, 4.2 Hz, CH₂CH), 3.12 (1H, dd, *J* = 14.3, 11.2 Hz, CH₂CH), 2.75 (1H, dd, *J* = 11.2, 4.2 Hz, CH₂CH), 1.01 (3H, s, CH₃COH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.0 (C), 156.4 (2 x C), 132.5 (C), 131.0 (CH), 128.0 (C), 127.9 (CH), 121.9 (CH), 121.6 (2 x CH), 114.0 (2 x CH), 110.9 (CH), 72.6 (C), 60.4 (CH₂), 55.7 (CH₃), 55.4 (CH₃), 55.3 (CH), 26.0 (CH₃), 24.6 (CH₂); HRMS (FAB) Exact mass calcd for C₂₀H₂₄NO₄ [M+H]⁺: 342.1700, found: 342.1700.

(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpyrrolidin-2-one (5a). The title compound was prepared according to General Procedure G from **4a** (60 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography

(50% EtOAc/petrol) to give a white solid (34 mg, 57%). m.p. 123-125 °C; IR (CHCl₃) 3403 (OH), 2936, 1677 (C=O), 1511 (C=C), 1461, 1400, 1247, 1032, 829 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.57-7.55 (2H, m, ArH), 7.51 (2H, dm, *J* = 9.2 Hz, ArH), 7.46-7.41 (2H, m, ArH), 7.38-7.33 (1H, m, ArH), 6.89 (2H, dm, *J* = 9.2 Hz, ArH), 4.06 (1H, d, *J* = 10.6 Hz, CH₂N), 3.87 (1H, d, *J* = 10.6 Hz, CH₂N), 3.79 (3H, s, OCH₃), 3.11 (1H, q, *J* = 7.2 Hz, CH₃CH), 2.50 (1H, s, OH), 1.22 (3H, d, *J* = 7.2 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2 (C), 156.5 (C), 141.5 (C), 132.5 (C), 128.8 (2 x CH), 128.1 (CH), 125.2 (2 x CH), 121.4 (2 x CH), 114.1 (2 x CH), 77.2 (C), 61.6 (CH₂), 55.5 (CH₃), 48.5 (CH₂), 7.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₀NO₃ [M+H]⁺: 298.1438, found: 298.1439.

(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxybenzyl)-3-methyl-4-phenylpyrrolidin-2-one

(5b). The title compound was prepared according to General Procedure G from **4b** (62 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (50% EtOAc/petrol) to give a white solid (33 mg, 53%). m.p. 133-135 °C; IR (CHCl₃) 3385 (OH), 2932,

1671 (C=O), 1512 (C=C), 1445, 1245, 1032, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.46-7.28 (5H, m, ArH), 7.20 (2H, dm, *J* = 8.7 Hz, ArH), 6.85 (2H, dm, *J* = 8.7 Hz, ArH), 4.50 (2H, s, CH₂Ar), 3.76 (3H, s, OCH₃), 3.51 (1H, d, *J* = 10.8 Hz, HOCCH₂N), 3.35 (1H, d, *J* = 10.8 Hz, HOCCH₂N), 2.97 (1H, q, *J* = 7.2 Hz, CH₃CH), 2.10 (1H, br s, OH), 1.20 (3H, d, *J* = 7.2 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.1 (C), 159.1 (C), 141.9 (C), 129.4 (2 x CH), 128.6 (2 x CH), 128.2 (C), 127.9 (CH), 125.1 (2 x CH), 114.1 (2 x CH), 75.5 (C), 59.6 (CH₂), 55.2 (CH₃), 47.7 (CH), 45.9 (CH₂), 7.3 (CH₃); HRMS (FAB) Exact mass calcd for C₁₉H₂₂NO₃ [M+H]⁺: 312.1595, found: 312.1600.

Conjugate Reduction of α,β-Unsaturated Amide **14⁶**

A solution of the known cinnamic amide **14**⁷ (66 mg, 0.20 mmol) and Co(acac)₂·2H₂O (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et₂Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature for 2h. The reaction mixture was filtered through a short plug of SiO₂ (ca. 4 cm high x 2 cm diameter) using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) afforded the amide **15** (48 mg, 73%) that displayed identical spectroscopic data to those reported previously.⁶

6. Aoyagi, Y.; Asakura, R.; Kondoh, N.; Yamamoto, R.; Kuromatsu, T.; Shimura, A.; Ohta, A. *Synthesis* **1996**, 970–974.
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Stereochemical Determinations

- The relative stereochemistries of **2f**, **2i** and **2m** were determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Numbers: CCDC 607850–607852 respectively.

- The relative stereochemistry of **5b** was assigned by a NOESY experiment, which displayed the following enhancement:

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

NMR Spectra of New Compounds