Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supplementary Information

Asymmetric synthesis of 3,4-*anti*- and 3,4-*syn*-substituted aminopyrrolidines via lithium amide conjugate addition

Stephen G. Davies,* A. Christopher Garner, Euan C. Goddard, Dennis Kruchinin, Paul M. Roberts, Andrew D. Smith, Humberto Rodriguez-Solla, James E. Thomson and Steven M. Toms

Department of Organic Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK

e-mail: steve.davies@chem.ox.ac.uk

Experimental

General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[351] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the

---

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 1518.

relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure 1 for pyrrolidinone alkylation

BuLi was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine in THF at −78°C. After 1 h a solution of the requisite pyrrolidinone in THF was added dropwise *via* cannula, and the reaction mixture stirred at −78°C for 2 h, after which a solution of the requisite electrophile in THF was added *via* cannula. The reaction mixture was allowed to warm slowly to rt over 16 h before being quenched with sat aq NH_4Cl. The mixture was then partitioned between DCM and brine, dried and concentrated *in vacuo*.

General procedure 2 for tandem lithium amide conjugate addition and enolate alkylation

BuLi (2.5 M in hexanes, 1.55 eq) was added dropwise *via* syringe to a stirred solution of the requisite amine (1.6 eq) in THF at −78°C. After stirring for 30 min a solution of α,-β-unsaturated ester **4** (1.0 eq) in THF at −78°C was added dropwise *via* cannula. After stirring for a further 2 h at −78°C the reaction mixture was quenched with the requisite alkyl halide and allowed to warm to rt over 12 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between DCM and 10% aq citric acid. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed sequentially with sat aq $NaHCO_3$ and brine, dried and concentrated *in vacuo*.

General procedure 3 for *N*-deallylation and concomitant cyclisation

$Pd(PPh_3)_4$ (10 mol %) was added to a stirred solution of the requisite substrate (1 eq) and 1,3-DMBA (3 eq) in DCM at rt. After stirring for 12 h, SiO_2 was added to the reaction mixture and stirring continued for a further 6 h before the reaction mixture was concentrated in *vacuo*.

General procedure 4 for $LiAlH_4$ reduction of pyrrolidinones

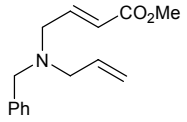
$LiAlH_4$ (1.0 M in hexanes) was added to a solution of the requisite substrate in THF at 0°C, and then heated under reflux. After 16 h, the reaction was cooled to rt and quenched with 'wet' Et_2O. Sat aq sodium

potassium tartrate solution and DCM were added, the organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were dried and concentrated in *vacuo*.

General procedure 5 for hydrogenolysis

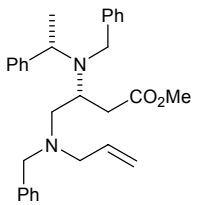
$Pd(OH)_2/C$ (50% w/w) was added to a stirred solution of the requisite substrate in degassed MeOH, and placed under a hydrogen atmosphere. After 16 h the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*.

Methyl (*E*)-(*N*-allyl-*N*-benzylamino)but-2-enoate 4



N-Allyl-*N*-benzylamine (3.0 g, 20.4 mmol) and $^{i}Pr_2NEt$ (4.6 mL, 27.8 mmol) were added sequentially to a stirred solution of methyl 4-bromocrotonate (2.6 mL, 18.6 mmol) in DCM (20 mL) at 0°C. After 16 h the reaction was quenched with sat aq K_2CO_3 (20 mL), the organic layer separated and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried and concentrated in *vacuo*. Chromatography (silica, eluent 30-40° petrol:EtOAc 5:2) gave **4** as a yellow oil (4.54 g, quant); ν_{max} (film) 1436, 1495, 1659, 1725, 2360, 2801, 2949; δ_H (400 MHz, $CDCl_3$) 3.08 (2H, d, *J* 6.3, $NCH_2CH{=}CH_2$), 3.21 (2H, d, *J* 5.9 C(4)H_2), 3.59 (2H, s, CH_2Ph), 3.77 (3H, s, O*Me*), 5.12-5.20 (2H, m, $CH{=}CH_2$), 5.81-5.92 (1H, m, $CH{=}CH_2$), 6.03 (1H, d, *J* 15.6, C(2)*H*), 6.99 (1H, dt, *J* 15.6, 5.9, C(3)*H*), 7.22-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 51.5, 54.1, 56.8, 58.0, 95.7, 117.8, 122.3, 127.0, 128.3, 128.7, 135.4, 138.2, 146.7; *m/z* (CI^+) 246 ($[M+H]^+$, 42%), 204 (100); HRMS (CI^+) $C_{15}H_{20}NO_2^+$ ($[M+H]^+$) requires 246.1494; found 246.1493.

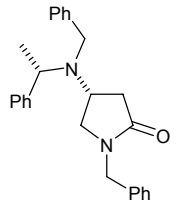
Methyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino)butanoate 5



BuLi (2.5 M in hexanes, 25.3 mL, 63.3 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (13.6 mL, 65.3 mmol) in THF (100 mL) at −78°C. After stirring for 30 min a solution of **4** (10.0 g, 40.8 mmol) in THF (60 mL) at −78°C was added dropwise via cannula. After stirring

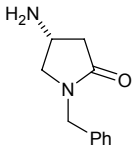
for a further 2 h at −78°C the reaction mixture was quenched with sat aq NH_4Cl (5 mL) and allowed to warm to rt over 5 min before being concentrated *in vacuo*. The residue was partitioned between DCM (50 mL) and 10% aq citric acid (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (50 mL) and brine (50 mL), dried and concentrated *in vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 5:1) gave **5** as a colourless oil (15.0 g, 81%, >98% de); $[\alpha]_D^{24}$ +28.0 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3062, 3027, 2948, 2805, 1951, 1735, 1643, 1602, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, J 6.9, C(α)*Me*), 2.15 (1H, dd, *J* 14.6, 6.1, C(2)H_A), 2.38 (1H, dd, *J* 14.6, 6.6 C(2)H_B), 2.45 (1H, dd, *J* 12.8, 4.6, C(4)H_A), 2.59 (1H, dd, *J* 12.8, 4.4, C(4)H_B), 2.84 (1H, dd, *J* 13.9, 7.6, C(6)H_A), 3.11 (1H, dd, *J* 8.7, 5.3, C(6)H_B), 3.32 (1H, d, *J* 16.5, NCH_A), 3.53 (3H, s, O*Me*), 3.59-3.66 (1H, m, C(3)*H*), 3.64 (2H, app d, *J* 3.2, NCH_2), 3.71 (1H, d, *J* 16.5, NCH_B), 3.89 (1H, q, *J* 6.9, C(α)H), 5.08-5.12 (2H, m, CH=CH_2), 5.79 (1H, m, C*H*=CH_2), 7.18-7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0, 36.2, 50.1, 51.3, 52.7, 56.9, 57.1, 58.0, 58.8, 117.6, 126.6, 126.7, 126.8, 128.0, 128.1, 128.3, 129.1, 135.7, 139.2, 141.6, 143.8, 173.4; *m/z* (CI^+) 457 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{30}H_{26}N_2O_2^+$ ($[M+H]^+$) requires 457.2855; found 457.2857.

(4*R*,α*S*)-*N*(1)-Benzyl-4-[*N′*-benzyl-*N′*-(α-methylbenzyl)amino]pyrrolid-2-one 6



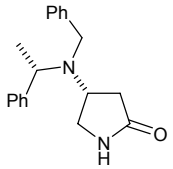
$Pd(PPh_3)_4$ (5.1 g, 4.39 mmol) was added to a stirred solution of **5** (20.0 g, 43.9 mmol) and 1,3-DMBA (20.6 g, 132 mmol) in DCM (200 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated in *vacuo*. Chromatography (silica, eluent DCM) gave **6** as a brown viscous oil (15.8 g, 94%); $[\alpha]_D^{24}$ −30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3045, 1687, 1453; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.0, C(α)*Me*), 2.33 (2H, app d, *J* 15.0, C(3)H_2), 3.24 (1H, dd, *J* 11.5, 6.0, C(5)H_A), 3.36 (1H, dd, *J* 11.5, 6.0, C(5)H_B), 3.68 (2H, d, *J* 9.5, NCH_2Ph), 3.69-3.78 (1H, m, C(4)*H*), 3.88 (1H, q, *J* 7.0, C(α)*H*), 4.36 (1H, d, *J* 14.6, NCH_A), 4.52 (1H, d, *J* 14.6, NCH_B), 7.21-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 34.9, 46.3, 50.3, 50.9, 51.1, 57.8, 125.5, 125.6, 125.7, 126.1, 127.0, 127.2, 128.7, 136.3, 140.6, 142.8, 173.3; *m/z* (CI^+) 385 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{26}H_{29}N_2O^+$ ($[M+H]^+$) requires 385.2280; found 385.2282.

(*R*)-*N*(1)-Benzyl-4-aminopyrrolid-2-one 7



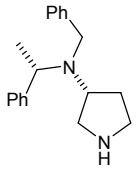
$Pd(OH)_2/C$ (100 mg, 50% w/w), **6** (200 mg, 0.54 mmol) in MeOH (5 mL), and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent DCM:MeOH 100:1) gave **7** as a colourless oil (87 mg, 89%); $[\alpha]_D^{24}$ +21.1 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3341, 3001, 1642; δ_H (400 MHz, $CDCl_3$) 1.50 (2H, br s, NH_2), 2.22 (1H, dd, *J* 8.9, 5.1, C(3)H_A), 2.63 (1H, dd, *J* 8.9, 5.1, C(3)H_B), 2.91 (1H, dd, *J* 10.5, 6.0, C(5)H_A), 3.44 (1H, dd, *J* 10.5, 6.0, C(5)H_B), 3.69-3.78 (1H, m, C(4)*H*), 4.48 (2H, s, NCH_2Ph), 7.21-7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 36.2, 50.8, 51.6, 57.1, 125.5, 127.0, 127.4, 128.7, 142.1, 178.3; *m/z* (CI^+) 191 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{11}H_{15}N_2O^+$ ($[M+H]^+$) requires 191.2497; found 191.2492.

(4*S*,α*S*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]pyrrolidin-2-one 8



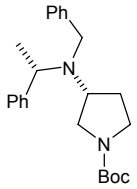
Ammonia gas (100 mL) was condensed into a flask containing sodium chips (507 mg, 22.0 mmol) at −78ºC. After stirring for 10 min at −78°C, **6** (1.60 g, 5.44 mmol) in THF (10 mL) was added dropwise *via* syringe and the resulting solution was left to stir at −78°C for 30 min. The reaction was quenched at −78°C with sat aq NH_4Cl and allowed to warm slowly to rt, after which it was partitioned between Et_2O (10 mL) and water (10 mL), dried and concentrated *in vacuo*. Purification *via* recrystallisation from Et_2O/pentane (1:1) gave **8** as a white solid (902 mg, 74%); $[\alpha]_D^{22}$ −74.9 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3226, 1695; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.13 (2H, dd, *J* 8.0, 4.8, C(3)H_2), 3.30 (1H, dd, *J* 9.6, 6.8, C(5)H_A), 3.45 (1H, app t, *J* 9.6, C(5)H_B), 3.71 (1H, d, *J* 15.6, C$H_A$$H_B$Ph), 3.78 (1H, d, *J* 15.6, C$H_A$$H_B$Ph), 3.85-3.91 (2H, m, C(4)*H*, C(α)*H*), 5.53 (1H, br s, N*H*), 7.25-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9, 33.5, 46.6, 50.4, 54.2, 57.9, 126.9, 127.2, 127.5, 128.4, 140.7, 142.1, 176.1; *m/z* (ESI^+) 295 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{23}N_2O^+$ ($[M+H]^+$) requires 295.1810; found 295.1805.

(3*S*,α*S*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]pyrrolidine 9



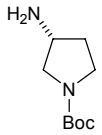
$LiAlH_4$ (1.0 M in THF, 7.7 mL, 7.73 mmol) and **8** (568 mg, 1.93 mmol) in THF (10 mL) were reacted according to *general procedure 4* to give **9** as a yellow oil that was used without further purification (471 mg, 87%); $[\alpha]_D^{22}$ −24.9 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3423; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.56 (1H, dd, *J* 13.0, 8.2, C(4)H_A), 1.68 (1H, dd, *J* 13.0, 7.5, C(4)H_B), 2.76-2.85 (2H, m, C(2)H_A, C(5)H_A), 2.89-2.95 (1H, m, C(5)H_B), 3.00 (1H, dd, *J* 10.9, 7.9, C(2)H_B), 3.43-3.50 (1H, m, C(3)*H*), 3.74 (2H, app s, CH_2Ph), 3.89 (1H, q, *J* 6.8, C(α)*H*), 7.20-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.0, 29.5, 45.8, 49.5, 50.7, 57.9, 59.4, 126.6, 126.7, 127.7, 128.0, 128.2, 128.4, 128.5, 141.8, 143.8; *m/z* (ESI^+) 281 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{26}N_2^+$ ($[M+H]^+$) requires 281.2018, found 281.2020.

(3*S*,α*S*)-*N*(1)-*tert*-Butyloxycarbonyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolidine 10



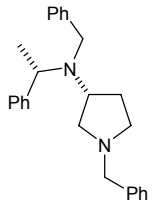
A solution of **9** (407 mg, 1.45 mmol), Boc_2O (349 mg, 1.60 mmol) and $NaHCO_3$ (244 mg, 2.91 mmol) in MeOH (10 mL) was sonicated for 24 h after which the reaction mixture was concentrated *in vacuo*, partitioned between sat aq NH_4Cl (30 mL) and Et_2O (2 × 30 mL) and the combined organic extracts dried and concentrated *in vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 1:1) gave **10** as a clear oil (526 mg, 95%); $[\alpha]_D^{24}$ −0.3 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1696; δ_H (250 MHz, DMSO-d_6, 363K) 1.39 (3H,d *J* 6.8, C(α)*Me*), 1.44 (9H, s, CMe_3), 1.62-1.73 (2H, m, C(4)H_2), 2.95-3.13 (2H, m, C(2)H_A, C(5)H_A), 3.23-3.49 (3H, m, C(2)H_B, C(5)H_B, C(3)*H*), 3.69 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.77 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.95 (1H, q, 6.8, C(α)*H*), 7.19-7.42 (10H, m, *Ph*); δ_C (62.5 MHz, DMSO-d_6) 16.7, 29.1, 29.5, 44.8, 49.3, 51.2, 58.6, 59.1, 79.0, 127.2, 127.4, 128.3, 128.5, 128.8, 142.7, 144.5, 154.5; *m/z* (ESI^+) 381 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}N_2O_2^+$ ($[M+H]^+$) requires 381.2542, found 381.2530.

(*S*)-*N*(1)-*tert*-Butoxycarbonyl-3-aminopyrrolidine 11



$Pd(OH)_2/C$ (100 mg, 50% w/w), **10** (200 mg, 0.53 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (silica, eluent DCM:MeOH:Et_3N 100:1:1) gave **11** as a yellow oil (60 mg, 61%);[2,3] $[\alpha]_D^{22}$ −3.3 (*c* 0.2 in $CHCl_3$); {lit.[3] $[\alpha]_D^{20}$ −2.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.64-1.79 (1H, s, C(4)H_A), 1.99 (2H, br s, NH_2), 2.00-2.13 (1H, m, C(4)H_B), 3.02-3.18 (1H, m, C(2)H_A), 3.32-3.65 (4H, m, C(2)H_B, C(3)*H*, C(5)H_2).

(3*R*,α*S*)-*N*(1)-Benzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolidine 12



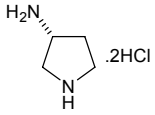
$LiAlH_4$ (1.0 M in THF, 2.34 mL, 2.34 mmol) and **6** (300 mg, 0.78 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent DCM) gave **12** as a colorless, viscous oil (258 mg, 89%); $[\alpha]_D^{25}$ −17.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3027, 2967, 2799, 1968, 1601, 1493; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.4, C(α)*Me*), 1.64-1.71 (1H, m, C(4)H_A), 1.75-1.84 (1H, m, C(4)H_B), 2.34 (1H, app q, *J* 8.8, C(5)H_A), 2.51-2.64 (3H, m, C(2)H_2, C(5)H_B), 3.54 (2H, ABq, J_{AB} 7.1, NCH_2), 3.62 (1H, m, C(3)*H*), 3.80 (1H, q, *J* 6.4, C(α)*H*), 3.88 (2H, app d, *J* 4.7, NCH_2), 7.20-7.51 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8, 28.7, 50.5, 53.6, 57.0, 57.5, 57.9, 60.7, 126.5, 126.6, 126.7, 127.7, 127.8, 127.9, 128.6, 139.3, 142.2, 144.3; *m/z* (ESI^+) 371 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{31}N_2^+$ ($[M+H]^+$) requires 371.2487; found 371.2510.

---

[2] A. E. Shchekotikhin, V. A. Glazunova, Y. N. Luzikov, V. N. Buyanov, O. Y. Susova, A. A. Shtil and M. N. Preobrazhenskaya, *Bioorg. Med. Chem.*, **2006**, *14*, 5241.

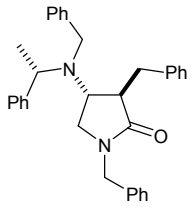
[3] (*S*)-*N*(1)-*tert*-Butoxycarbonyl-3-aminopyrrolidine **11** is commercially available from the Aldrich Chemical Company.

(*R*)-3-Ammoniopyrrolidinium dichloride 13



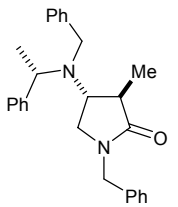
$Pd(OH)_2/C$ (125 mg, 50% w/w), **12** (250 mg, 0.68 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Hydrogen chloride (2.0 M in Et_2O, 0.2 mL) was added to the reaction mixture prior to filtration and gave **13** as a white solid (48 mg, 45%); mp 121-122°C (MeOH); $[\alpha]_D^{24}$ −4.7 (*c* 0.9 in H_2O); ν_{max} (KBr) 3414, 3339, 1412; δ_H (400 MHz, D_2O) 2.01-2.14 (1H, m, C(4)H_A), 2.40-2.52 (1H, m, C(4)H_B), 3.32-3.41 (2H, m, C(2)H_A, C(5)H_A), 3.44-3.54 (1H, m, C(5)H_B), 3.71 (1H, dd, *J* 11.0, 4.6, C(2)H_B), 4.04-4.12 (1H, m, C(3)*H*), 4.61-4.73 (3H, br s, NH_3); δ_C (100 MHz, D_2O) 28.9, 45.0, 48.0, 49.1; *m/z* (ESI^+) 144 ($[M-HCl+Na]^+$, 76%), 122 (100); HRMS (ESI^+) $C_4H_{11}N_2^+$ ($[M-Cl]^+$) requires 122.0611; found 122.0610.

(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-benzyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 14



BuLi (1.6 M in hexanes, 0.60 mL, 0.94 mmol), 2,2,6,6-tetramethylpiperidine (0.17 mL, 0.96 mmol) in THF (5 mL), **6** (300 mg, 0.78 mmol) in THF (5 mL), and benzyl bromide (0.18 mL, 1.56 mmol) in THF (5 mL) were reacted according to *general procedure 1* to give **14** in >98% de. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:2) gave **14** as a white crystalline solid (348 mg, 94%, >98% de); $C_{12}H_{20}O_4$ requires C, 83.5; H, 7.2; N, 5.9%; found C, 83.3; H, 7.1; N, 5.9%; mp 164-165°C (DCM); $[\alpha]_D^{25}$ +61.1 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3085, 3061, 3029, 2921, 2851, 1952, 1811, 1683, 1603, 1584, 1494, 1452, 1373; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, C(α)*Me*), 2.60 (1H, dd, *J* 11.0, 5.0 C(3)CH_A), 2.69 (1H, app t, *J* 8.9, C(5)H_A), 2.86 (1H, q, *J* 5.2, C(3)*H*), 3.05 (1H, dd, *J* 11.0, 5.2 C(3)CH_B), 3.14 (1H, dd, *J* 8.9, 4.7, C(5)H_B), 3.29-3.32 (1H, m, C(4)*H*), 3.63 (1H, d, *J* 8.3, NCH_A), 3.75 (1H, d, *J* 8.3, NCH_B), 3.81 (1H, q, *J* 6.5, C(α)*H*), 4.19 (1H, d, *J* 9.9 NCH_A), 4.51 (1H, d, *J* 9.9 NCH_B), 6.60-7.40 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6, 34.5, 46.4, 47.5, 48.1, 50.0, 52.9, 56.9, 126.2, 126.7, 127.1, 127.4, 128.0. 128.2, 128.3, 128.6, 128.9, 129.6, 129.9, 136.0, 138.0, 140.3, 143.9, 174.6; *m/z* (CI^+) 475 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{33}H_{35}N_2O^+$ ($[M+H]^+$) requires 475.2745; found 475.2749.

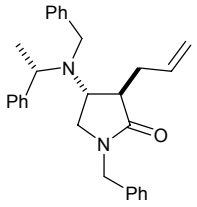
(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-methyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 15



BuLi (1.6 M in hexanes, 0.60 mL, 0.94 mmol), 2,2,6,6-tetramethylpiperidine (0.17 mL, 0.96 mmol) in THF (5 mL), **6** (300 mg, 0.78 mmol) in THF (5 mL), and methyl iodide (0.10 mL, 1.56 mmol) in THF (5 mL) were reacted according to *general procedure 1* to give **15** in >98% de. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:2) gave **15** as a colourless oil (295 mg, 95%, >98% de); $[\alpha]_D^{25}$ +24.0 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3029, 2968, 2929, 1951, 1689, 1603, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 7.2, C(3)*Me*), 1.24 (3H, d, *J* 7.0, C(α)*Me*), 2.52 (1H, app quin, *J* 7.0, C(3)*H*), 3.12-3.18 (2H, m, C(4)*H*, C(5)H_A), 3.26-3.29 (1H, m, C(5)H_B), 3.65 (1H, d, *J* 14.0, NCH_A), 3.83 (1H, d, *J* 14.0, NCH_B), 3.92 (1H, q, *J* 7.0, C(α)*H*), 4.43 (2H, ABq, *J* 14.6, NCH_2); 6.93-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4, 15.6, 40.9, 47.0, 47.9, 50.5,

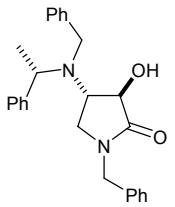
57.4, 58.8, 127.4, 127.5, 127.6, 128.0, 128.1, 128.5, 128.7, 128.8, 129.1, 136.7, 140.9, 144.0, 176.1; *m/z* (CI^+) 399 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{27}H_{31}N_2O^+$ ($[M+H]^+$) requires 399.2436; found 399.2423.

(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-allyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 16



BuLi (1.6 M in hexanes, 0.91 mL, 1.45 mmol), 2,2,6,6-tetramethylpiperidine (0.26 mL, 1.51 mmol) in THF (5 mL), **6** (465 mg, 1.21 mmol) in THF (5 mL), and allyl bromide (0.21 mL, 2.42 mmol) in THF (5 mL) were reacted according to *general procedure 1* to give **16** in >98% de. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:2) gave **16** as a yellow oil (412 mg, 80%, >98% de); $[\alpha]_D^{27}$ +54.5 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1680, 1631; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.8, C(α)*Me*), 2.13-2.19 (1H, m, C(3)CH_A), 2.40-2.47 (1H, m, C(3)CH_B), 2.66 (1H, app q, *J* 5.8, C(3)*H*), 3.16 (1H, dd, *J* 10.1, *J* 8.7, C(5)H_A), 3.29-3.38 (2H, m, C(4)*H*, C(5)H_B), 3.65 (1H, d, *J* 14.3, NCH_A), 3.81 (1H, d, *J* 14.3, NCH_B), 3.89 (1H, q, *J* 6.8, C(α)*H*), 4.42 (1H, d, *J* 14.6, NCH_A), 4.50-4.58 (2H, m, CH=CH_AH$_B$, NCH_B), 4.81 (1H, app d, *J* 10.0, CH=CH$_A$$H_B$), 5.41-5.51 (1H, m, C*H*=CH_2), 7.24-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.4, 33.3, 46.1, 46.5, 50.0, 53.5, 56.7, 117.8, 127.0, 127.1, 127.6, 127.9, 128.1, 128.4, 128.5, 128.7, 134.2, 136.4, 140.3, 143.7, 174.5; *m/z* (CI^+) 425 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{29}H_{33}N_2O^+$ ($[M+H]^+$) requires 425.2593; found 425.2607.

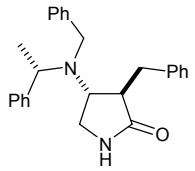
(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-hydroxy-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 17



BuLi (1.6 M in hexanes, 0.60 mL, 0.94 mmol), 2,2,6,6-tetramethylpiperidine (0.17 mL, 0.96 mmol) in THF (5 mL), **6** (300 mg, 0.78 mmol) in THF (5 mL), and (+)-CSO (358 mg, 1.56 mmol) were reacted according to *general procedure 1* to give a 98:2 mixture of *anti*-**17**:*syn*-**18**. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:2) gave *anti*-**17** as a yellow oil (342 mg, 97%, >98% de); $[\alpha]_D^{24}$ +2.3 (*c* 0.3 in $CHCl_3$); ν_{max} (film) 3534, 3029, 2967, 2926, 1682, 1603, 1494; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 3.09 (1H, app t, *J* 8.4, C(5)H_A), 3.13 (1H, app t, *J* 8.4, C(5)H_B), 3.52 (1H, q, *J* 8.2, C(4)*H*), 3.70 (1H, d, *J* 15.3, NCH_A), 3.79 (1H, d, *J* 15.3, NCH_B), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.24 (1H, d, *J* 8.5, C(3)*H*); 4.37 (1H, d, *J*

14.7, NCH_A), 4.42 (1H, d, *J* 14.7, NCH_B), 7.12-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1, 46.8, 47.2, 50.6, 58.6, 62.3, 72.1, 126.8, 127.1, 127.7, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.8, 141.2, 143.1, 143.4, 172.8; *m/z* (CI^+) 401 ($[M+H]^+$, 52%), 268 (100); HRMS (CI^+) $C_{26}H_{28}N_2O_2^+$ ($[M+H]^+$) requires 401.2229; found 401.2220.

(3*S*,4*R*,α*S*)-3-Benzyl-4-[*N*-methyl-*N*-(α-methylbenzyl)amino]pyrrolidin-2-one 19



Ammonia gas (20 mL) was condensed into a flask containing sodium chips (82 mg, 3.56 mmol) at −78ºC. After stirring for 10 min at −78°C, **14** (420 mg, 0.89 mmol) in THF (10 mL) was added dropwise *via* syringe and the resulting solution was left to stir at −78°C for 30 min. The reaction was quenched at −78°C with sat aq NH_4Cl and allowed to warm slowly to rt, after which it was partitioned between Et_2O (10 mL) and water (10 mL), dried and concentrated *in vacuo* to give a 90:10 mixture of *anti*-**19**:*syn*-**20**. Chromatography (silica, eluent 30-40° petrol:Et_2O 1:5) gave *anti*-**19** as a white crystalline solid (300 mg, 88%, >98% de); mp 49-51ºC; $[\alpha]_D^{24}$ +54.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3215, 1695, 1495; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.64 (1H, dd, *J* 11.4, 5.0, CH_AH$_B$Ph), 2.74 (1H, m, C(3)*H*), 2.91 (1H, d, *J* 10.0, C(5)H_A), 2.95 (1H, dd, *J* 11.4, 5.0, CH$_A$$H_B$Ph), 3.31 (1H, dd, *J* 10.0, 5.0, C(5)H_B), 3.48 (1H, m, C(4)*H*), 3.78 (1H, d, *J* 14.4, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 3.90 (1H, q, *J* 6.8, C(α)*H*), 6.51 (1H, br s, N*H*), 6.70 (2H, d, *J* 6.1, *Ph*), 7.10–7.14 (3H, m, *Ph*), 7.26–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9, 34.1, 43.0, 46.7, 50.1, 56.5, 57.1, 126.1, 127,1, 127.1, 128.1, 128.1, 128.3, 128.4, 129.7, 138.3, 140.4, 143.9, 178.3; *m/z* (ESI^+) 385 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{29}N_2O^+$ ($[M+H]^+$) requires 385.2274; found 385.2274.

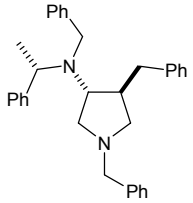
X-ray crystal structure determination for 19

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-*Kα* radiation using standard procedures at 190K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

[4] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

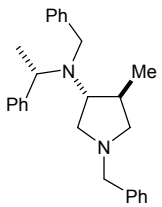
X-ray crystal structure data for **19** [$C_{26}H_{28}N_2O$]: M = 769.04, monoclinic, space group P 1 21 1, a = 9.5595(2) Å, b = 17.1047(5) Å, c = 13.6097(3) Å, β = 98.2945(16)º, V = 2202.08(9) Å^3, Z = 4, μ = 0.071 mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm^3. A total of 5060 unique reflections were measured for $5 < \theta < 27$ and 4299 reflections were used in the refinement. The final parameters were wR_2 = 0.058 and R_1 = 0.047 [$I>1.5\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 629877. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]-4-benzylpyrrolidine 21



$LiAlH_4$ (1.0 M in THF, 1.3 mL, 1.3 mmol) and **14** (200 mg, 0.42 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **21** as a yellow, viscous oil (183 mg, 94%); $[\alpha]_D^{25}$ +11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061, 3027, 2930, 1602, 1494, 1452; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.88-1.92 (1H, m, C(5)H_A), 2.09 (1H, dd, *J* 13.6, 10.7, C(4)CH_A), 2.33 (1H, app t, *J* 4.5, C(2)H_A), 2.39-2.45 (1H, m, C(4)*H*), 2.77 (1H, app t, *J* 9.1, C(5)H_B), 2.74 (1H, dd, *J* 13.6, 10.1, C(4)CH_B), 2.93 (1H, dd, *J* 9.8, 4.3, C(2)H_B), 2.96-3.02 (1H, m, C(3)*H*), 3.43 (1H, d, *J* 13.3, NCH_A), 3.64 (1H, d, *J* 14.8, NCH_B), 3.80 (1H, d, *J* 14.8, NCH_A), 3.93 (1H, q, *J* 6.7, C(α)*H*), 4.19 (1H, d, *J* 14.7, NCH_B), 7.20-7.51 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.3, 38.6, 46.0, 50.4, 55.8, 56.6, 58.4, 60.6, 61.8, 126.7, 126.8, 128.6, 128.8, 127.8, 128.1, 128.3, 128.4, 128.7, 139.3, 141.6, 141.9, 144.7; *m/z* (CI^+) 461 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{33}H_{37}N_2^+$ ($[M+H]^+$) requires 461.2957; found 461.2965.

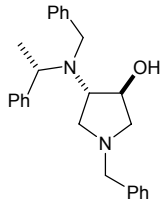
(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]-4-methylpyrrolidine 22



$LiAlH_4$ (1.0 M in THF, 3.0 mL, 2.96 mmol) and **15** (468 mg, 0.99 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **22** as a colourless, viscous oil

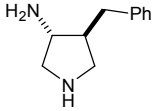
(408 mg, 90%); $[\alpha]_D^{22}$ +90.1 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 3061, 3027, 2962, 2868, 2788; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.7, C(4)*Me*), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 1.76 (1H, t, *J* 8.9, C(5)H_A), 2.12-2.19 (1H, m, C(4)*H*), 2.30 (1H, app t, *J* 9.2, C(2)H_A), 2.77-2.84 (2H, m, C(3)*H*, C(5)H_B), 2.89-2.91 (1H, m, C(2)H_B), 3.49 (1H, d, *J* 12.9, NCH_A), 3.60 (1H, d, *J* 12.9, NCH_B), 3.77 (1H, d, *J* 14.6, NCH_A), 3.86 (1H, q, *J* 6.7, C(α)*H*), 4.09 (1H, d, *J* 14.6, NCH_B), 7.17-7.48 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5, 17.1, 38.3, 50.3, 56.1, 56.5, 60.7, 63.6, 126.4, 126.6, 126.7, 127.6, 128.0, 128.1, 128.5, 139.3, 142.0, 144.5; *m/z* (ESI^+) 385 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{33}N_2^+$ ($[M+H]^+$) requires 385.2644; found 385.2659.

(3*S*,4*S*,α*S*)-*N*(1)-Benzyl-3-hydroxy-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolidine 23



$LiAlH_4$ (1.0 M in THF, 2.0 mL, 2.0 mmol) and **17** (200 mg, 0.5 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **23** as a yellow oil (149 mg, 82%); $[\alpha]_D^{25}$ +5.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3411, 2968, 2799, 1602, 1494; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.9, C(α)*Me*), 2.41 (1H, dd, *J* 7.2, 4.6, C(2)H_A), 2.61 (1H, dd, *J* 8.2, 6.6, C(5)H_A), 2.60-2.81 (2H, m, C(2)H_B, C(5)H_B), 3.41-3.52 (1H, m, C(4)*H*), 3.51 (1H, d, *J* 15.3, NCH_A), 3.69 (1H, d, *J* 15.3, NCH_B), 3.81 (1H, d, *J* 14.6, NCH_A), 3.92 (1H, d, *J* 14.6, NCH_B), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.16 (1H, m, C(3)*H*), 7.22-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.0, 51.2, 56.1, 57.1, 57.9, 60.4, 60.5, 75.1, 125.5, 126.8, 126.9, 127.8, 128.2, 128.6, 128.8, 138.5, 143.1, 144.4; *m/z* (ESI^+) 387 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{31}N_2O^+$ ($[M+H]^+$) requires 387.2436; found 387.2455.

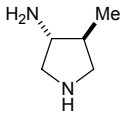
(3*R*,4*S*)-3-Amino-4-benzylpyrrolidine 24



$Pd(OH)_2/C$ (50 mg, 25% w/w), **21** (200 mg, 0.43 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **24** as a colourless crystalline solid (70 mg, 60%); mp 65-67°C; $[\alpha]_D^{24}$ +35.0 (*c* 1.6 in MeOH); ν_{max} (film) 3406, 1604, 1495; δ_H (400 MHz, $CDCl_3$) 2.23-2.33 (1H, m, C(4)*H*), 2.60 (1H, dd, *J* 11.4, 6.1, C(5)H_A), 2.83-2.93 (2H, m, C(2)H_A, C(4)CH_A), 3.01 (1H, dd, *J* 11.1, 5.4, C(5)H_B), 3.20-3.32 (2H, m, C(3)*H*, C(4)CH_B), 3.39 (1H, dd, *J* 10.4, 5.7,

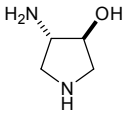
C(2)H_B), 7.11-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 37.3, 48.7, 50.3, 55.5, 56.1, 126.5, 128.6, 128.7, 128.9, 140.4; *m/z* (ESI^+) 177 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{17}N_2^+$ ($[M+H]^+$) requires 177.1392; found 177.1395.

(3*R*,4*S*)-3-Amino-4-methylpyrrolidine 25



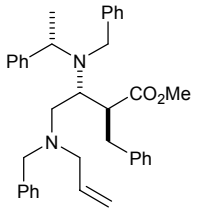
$Pd(OH)_2/C$ (68 mg, 25% w/w), **22** (272 mg, 0.71 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **25** as a colourless crystalline solid (109 mg, 81%); mp 43-44°C; $[\alpha]_D^{24}$ −4.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3412, 3402, 1611; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8, C(4)*Me*), 1.93-2.07 (1H, m, C(4)*H*), 2.81 (1H, dd, *J* 11.3, 8.3, C(5)H_A), 2.99 (1H, dd, *J* 11.5, 6.2, C(2)H_A), 3.15 (1H, app q, *J* 6.4, C(3)*H*), 3.46 (1H, dd, *J* 11.5, 6.5, C(2)H_B), 3.54 (1H, dd, *J* 11.3, 7.5, C(5)H_B), 4.56-4.82 (3H, br s, N*H*, NH_2); δ_C (100 MHz, $CDCl_3$) 15.8, 41.5, 50.8, 51.7, 57.9; *m/z* (ESI^+) 101 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_5H_{13}N_2^+$ ($[M+H]^+$) requires 101.1079; found 101.1078.

(3*S*,4*S*)-3-Hydroxy-4-aminopyrrolidine 26



$Pd(OH)_2/C$ (50 mg, 25% w/w), **22** (192 mg, 0.5 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **26** as a colourless, viscous oil (63 mg, 66%); $[\alpha]_D^{22}$ +6.5 (*c* 0.6 in MeOH); ν_{max} (film) 3405, 1563, 1417; δ_H (400 MHz, MeOH-d_4) 1.99 (3H, br s, O*H*, NH_2), 3.18 (1H, dd, *J* 10.0, 5.0, C(5)H_A), 3.22 (1H, dd, *J* 7.4, 5.5, C(2)H_A), 3.54-3.59 (2H, m, C(2)H_B, C(5)H_B), 3.60 (1H, app s, C(4)*H*), 4.24 (1H, br d, *J* 1.3, C(3)*H*); δ_C (100 MHz, MeOH-d_4) 49.9, 51.3, 57.4, 74.9; *m/z* (CI^+) 222 ($[2M+NH_4]^+$, 100%); HRMS (CI^+) $C_8H_{24}N_5O_2^+$ ($[2M+NH_4]^+$) requires 222.1930; found 222.1928.

Methyl (2*S*,3*R*,α*S*)-2-benzyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino) butanoate *anti*-27



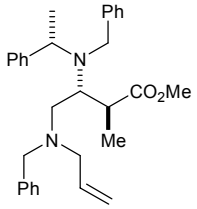
Tandem procedure: BuLi (2.5 M in hexanes, 0.63 mL, 1.58 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.34 mL, 1.63 mmol) in THF (5 mL), **4** (0.25 g, 1.02 mmol) in THF (5 mL), and BnBr (0.6 mL, 5.10 mmol)

were reacted according to *general procedure 2* and gave a 97:3 mixture of *anti*-**27**:*syn*-**28**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave *anti*-**27** as a yellow oil (522 mg, 94%, 90% de); $[\alpha]_D^{22}$ −4.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1644, 1733, 2834, 3441; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8, C(α)*Me*), 2.37 (1H, dd, *J* 17.0, 2.9 C(4)H_A), 2.72 (1H, dd, *J* 10.8, 3.2 C(2)CH_A), 2.78 (1H, dd, *J* 17.0, 2.4, C(4)H_B), 2.91-3.01 (2H, m, C(2)CH_B, C$H_A$$H_B$CH=$CH_2$), 3.03-3.12 (1H, m, C(2)*H*), 3.17 (1H, dd, *J* 14.2, 5.8 $CH_A$$H_B$CH=$CH_2$), 3.21-3.26 (1H, m, C(3)*H*), 3.32 (3H, s, O*Me*), 3.48 (1H, d, *J* 12.8, NCH_A), 3.73 (1H, d, *J* 12.8, NCH_B), 3.77 (2H, s, NCH_2), 3.98 (1H, q, *J* 6.8, C(α)*H*), 5.10-5.19 (2H, m, CH=CH_2), 5.71-5.92 (1H, m, C*H*=CH_2), 6.85-7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8, 35.6, 50.3, 50.8, 50.9, 55.4, 56.7, 57.0, 57.2, 58.9, 117.7, 125.7, 126.7, 126.9, 127.8, 128.0, 128.1, 128.2, 128.4, 128.7, 128.9, 129.1, 135.5, 138.8, 140.7, 141.0, 144.1, 173.3; *m/z* (CI^+) 547 ($[M+H]^+$, 100); HRMS (EI^+) $C_{37}H_{43}N_2O_2^+$ ($[M+H]^+$) requires 547.3325; found 547.3328.

Data for *syn*-**28**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.42 (3H, d, *J* 6.7, C(α)*Me*), 2.30 (1H, d, *J* 14.0, C(4)H_A), 2.55-2.62 (2H, m, C(2)CH_A, C(4)H_B), 2.82-3.01 (3H, m, C(2)*H*, C(2)CH_B, C$H_A$$H_B$CH=$CH_2$), 3.25 (3H, s, O*Me*), 3.36-3.52 (3H, m, C(3)*H*, $CH_A$$H_B$CH=$CH_2$, NC$H_A$), 3.68 (1H, d, *J* 12.6, NCH_B), 3.80 (1H, d, *J* 12.7, NCH_A), 3.91 (1H, d, *J* 12.7, NCH_B), 4.07 (1H, q, *J* 6.7, C(α)*H*).

Stepwise Procedure: BuLi (2.5 M in hexanes, 1.72 mL, 4.30 mmol) was added dropwise to a solution of di-*iso*-propylamine (0.62 mL, 4.40 mmol) in THF (5 mL) at 0°C. After 1 h the LDA solution was added to a solution of **5** (1.00 g, 2.20 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 2 h before being quenched with BnBr (1.60 mL, 13.2 mmol), and allowed to warm slowly to rt overnight. Sat aq NH_4Cl (25 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (25 mL) and brine (25 mL), dried and concentrated *in vacuo* to give a 92:8 mixture of *anti*-**27**:*syn*-**28**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave a mixture of *anti*-**27** and *syn*-**28** as a yellow oil (1.07 g, 89%, 84% de).

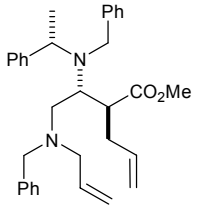
Methyl (2*S*,3*R*,α*S*)-2-methyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino) butanoate *anti*-29



Tandem procedure: BuLi (2.5 M in hexanes, 0.62 mL, 1.55 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.33 mL, 1.6 mmol) in THF (5 mL), **4** (245 mg, 1.00 mmol) in THF (5 mL), and MeI (0.3 mL, 2.50 mmol) were reacted according to *general procedure 2* and gave a 96:4 mixture of *anti*-**29**:*syn*-**30**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave *anti*-**29** as a yellow oil (390 mg, 83%, >98% de); $[\alpha]_D^{22}$ +43.3 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3444, 3062, 3028, 2973, 2834, 1733, 1494; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7.1, C(2)*Me*), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.70 (1H, dd, *J* 13.2, 2.1, C(4)H_A), 2.71-2.75 (1H, m, C(2)*H*), 2.80 (1H, dd, *J* 13.2, 9.2, C(4)H_B), 2.96 (1H, dd, *J* 14.2, 7.1, CH_AH$_B$CH=CH_2), 3.09 (1H, dd, *J* 14.2, 6.1, $CH_AH_BCH=CH_2$), 3.28-3.35 (1H, m, C(4)*H*), 3.47 (3H, s, O*Me*), 3.52 (1H, d, *J* 15.8, NCH_A), 3.66 (1H, d, *J* 15.8, NCH_B), 3.74 (2H, s, NCH_2), 3.94 (1H, q, *J* 6.8, C(α)*H*), 5.11-5.19 (2H, m, CH=CH_2), 5.80-5.93 (1H, m, C*H*=CH_2), 7.11-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8, 15.7, 41.7, 51.1, 51.2, 54.6, 56.6, 56.8, 57.4, 58.7, 117.7, 126.6, 126.9, 127.8, 128.1, 128.3, 128.6, 129.2, 135.4, 139.3, 141.6, 144.2, 175.9; *m/z* (CI^+) 471 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{31}H_{38}N_2O_2^+$ ($[M+H]^+$) requires 471.3012; found 471.3005.

Stepwise procedure: BuLi (2.5 M in hexanes, 6.92 mL, 17.3 mmol) was added dropwise to a solution of di-*iso*-propylamine (2.45 mL, 17.4 mmol) in THF (5 mL) at 0°C. After 1 h the LDA solution was added to a solution of **5** (4.0 g, 8.7 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 2 h before being quenched with MeI (6.6 mL, 43.7 mmol), and allowed to warm slowly to rt overnight. Sat aq NH_4Cl (25 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (25 mL) and brine (25 mL), dried and concentrated *in vacuo* to give a 95:5 mixture of *anti*-**29**:*syn*-**30**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave a mixture of *anti*-**29** and *syn*-**30** as a yellow oil (3.72 g, 90%, 90% de).

Methyl (2*S*,3*R*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-allyl-*N′*-benzylamino) butanoate *anti*-31



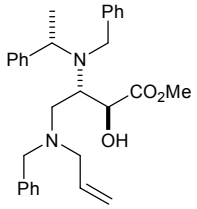
Tandem procedure: BuLi (2.5 M in hexanes, 0.63 mL, 1.58 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.34 mL, 1.63 mmol) in THF (5 mL), **4** (0.25 g, 1.02 mmol) in THF (5 mL), and allyl bromide (0.21 mL, 2.5 mmol) were reacted according to *general procedure 2* and gave a 90.5:9.5 mixture of *anti*-**31**:*syn*-**32**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave a *anti*-**31** as a yellow oil (414 mg, 82%, 81%

de); $[\alpha]_D^{21}$ −5.5 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3444, 3028, 1733, 1641, 1494; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.74-1.86 (1H, m, C(2)CH_A), 2.15-2.27 (1H, m, C(2)CH_B), 2.75 (1H, dd, *J* 12.9, 4.0 C(4)H_A), 2.81 (1H, app quintet, *J* 4.9, C(2)*H*), 2.89 (1H, dd, *J* 12.9, 10.5, C(4)H_B), 2.99 (1H, dd, *J* 9.7, 7.1 NCH_AH$_B$CH=CH$_2$), 3.14 (1H, dd, *J* 9.7, 4.1 NCH$_A$$H_B$CH=CH$_2$), 3.18-3.25 (1H, m, C(3)*H*), 3.46 (3H, s, O*Me*), 3.48 (1H, d, *J* 12.5, NCH_A), 3.70 (1H, d, *J* 12.5, NCH_B), 3.73 (2H, s, NCH_2), 3.94 (1H, q, C(α)*H*), 4.73-4.84 (2H, m, CH=CH_2), 5.11-5.20 (2H, m, CH=CH_2), 5.39-5.50 (1H, m, C*H*=CH$_2$), 5.80-5.97 (1H, m, C*H*=CH$_2$), 7.13-7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9, 33.6, 48.1, 50.9, 51.0, 55.2, 56.4, 56.8, 57.0, 58.8, 115.6, 117.7, 126.6, 126.7, 126.9, 127.8, 127.9, 128.1, 128.2, 128.4, 128.7, 128.8, 129.1, 129.7, 135.4, 136.8, 139.4, 141.1, 144.1, 174.6; *m/z* (CI^+) 497 ($[M+H]^+$, 100%; HRMS (CI^+) $C_{33}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 497.3168; found 497.3157.

Data for *syn*-**32**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.74-1.94 (1H, m, C(2)CH_A), 2.34 (1H, br t, *J* 8.8, C(2)CH_B), 2.43-2.52 (1H, m, C(2)*H*), 2.62-2.70 (1H, m, C(4)H_A), 2.72-2.80 (1H, m, NCH_AH$_B$CH=CH$_2$), 3.00 (1H, dd, *J* 10.4, 2.1 C(4)H_B), 3.11-3.18 (1H, m, NCH$_A$$H_B$CH=CH$_2$), 3.38 (1H, d, *J* 12.3, NCH_A), 3.49 (3H, s, O*Me*), 3.61 (1H, d, *J* 12.3, NCH_B), 3.67 (1H, d, *J* 12.6, NCH_A), 3.80 (1H, d, *J* 12.6, NCH_B), 4.00 (1H, q, *J* 6.9, C(α)*H*).

Stepwise procedure: BuLi (2.5 M in hexanes, 0.88 mL, 2.20 mmol) was added dropwise to a solution of di-*iso*-propylamine (0.31 mL, 2.20 mmol) in THF (5 mL) at 0°C. After 1 h the LDA solution was added to a solution of **5** (0.5 g, 1.1 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 2 h before being quenched with allyl bromide (0.45 mL, 5.5 mmol), and allowed to warm slowly to rt overnight. Sat aq NH_4Cl (25 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (25 mL) and brine (25 mL), dried and concentrated *in vacuo* to give a 81.5:18.5 mixture of *anti*-**31**:*syn*-**32**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave a mixture of *anti*-**31** and *syn*-**32** as a yellow oil (450 mg, 83 %, 63% de).

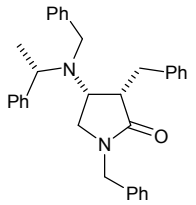
Methyl (2*R*,3*R*,α*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-allyl-*N′*-benzylamino) butanoate *anti*-33



Tandem procedure: BuLi (2.5 M in hexanes, 2.53 mL, 6.33 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.36 mL, 6.53 mmol) in THF (15 mL), **4** (1.00 g, 4.1 mmol) in THF (10 mL), and (+)-CSO (2.34 g, 10.2 mmol) were reacted according to *general procedure 2* and gave a >99:<1 mixture of *anti*-**33**:*syn*-**34**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave *anti*-**33** as a yellow oil (1.66 g, 86%, >98% de); $[\alpha]_D^{21}$ +54.0 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1453, 1494, 1602, 1643, 1732, 1951, 2248, 2971, 3517; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.7, C(α)*Me*), 2.58 (1H, dd, *J* 12.6, 3.4 C(4)H_A), 2.75 (1H, dd, *J* 15.0, 7.9 NCH_AH$_B$CH=CH_2), 3.05 (1H, app t, *J* 12.4, C(4)H_B), 3.13 (1H, dd, *J* 15.0, 2.3 NCH$_A$$H_B$CH=$CH_2$), 3.21 (1H, d, *J* 12.6, NCH_A), 3.48-3.53 (1H, m, C(3)*H*), 3.53 (3H, s, O*Me*), 3.71 (1H, d, *J* 12.6, NCH_B), 3.77 (1H, d, *J* 12.3, NCH_A), 3.91 (1H, d, *J* 12.3, NCH_B), 3.93 (1H, q, *J* 6.7, C(α)*H*), 5.07-5.21 (2H, m, CH=CH_2), 5.20-5.84 (1H, m, C*H*=CH_2), 7.15-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.6, 50.8, 52.0, 53.9, 55.7, 56.3, 58.4, 58.5, 73.8, 118.6, 126.7, 126.9, 127.8, 128.1, 128.2, 128.3, 128.4, 129.4, 140.2, 141.5, 144.7, 174.6; *m/z* (EI^+) 473 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{30}H_{37}N_2O_3^+$ ($[M+H]^+$) requires 473.2804; found 473.2811.

Stepwise procedure: BuLi (2.5 M in hexanes, 0.72 mL, 1.80 mmol) was added dropwise to a solution of di-*iso*-propylamine (0.26 mL, 1.84 mmol) in THF (5 mL) at 0°C. After 1 h the LDA solution was added to a solution of **5** (0.42 g, 0.92 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 2 h before being quenched with (+)-CSO (0.84 g, 3.7 mmol), and allowed to warm slowly to rt overnight. Sat aq NH_4Cl (25 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (25 mL) and brine (25 mL), dried and concentrated *in vacuo* to give a >99:<1 mixture of *anti*-**33**:*syn*-**34**. Chromatography (silica, eluent 30-40° petrol:Et_2O 20:1) gave *anti*-**33** as a yellow oil (400 mg, 92%, >98% de).

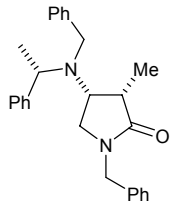
(3*S*,4*R*,α*S*)-*N*(1),3-Dibenzyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 35



$Pd(PPh_3)_4$ (451 mg, 0.39 mmol) was added to a rapidly stirred solution of *anti*-**27** (2.0 g, 3.7 mmol, 94% de) and 1,3-DMBA (2.01 g, 13.0 mmol) were reacted according to *general procedure 3*. Chromatography (silica, eluent 30-40° petrol:Et_2O 30:1) gave **35** as a colourless oil (1.60 g, 92%, 96% de); $[\alpha]_D^{21}$ +5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2968, 1733, 1687, 1603, 1494; δ_H (400 MHz, *d*$_4$-MeOH) 1.22 (3H, d, *J* 7.0, C(α)*Me*), 2.66-2.74 (1H, m, C(4)*H*), 2.95 (1H, dd, *J* 14.7, 5.3 C(5)H_A), 3.11 (1H, dd, *J* 14.7, 7.4

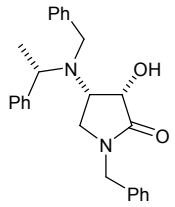
C(5)H_B), 3.29 (2H, s, NCH_2Ph), 3.32-3.41 (2H, m, C(3)CH_2), 3.60-3.67 (1H, m, C(3)*H*), 3.80 (1H, q, *J* 7.0, C(α)*H*), 4.24 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 4.59 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 6.90-7.41 (15H, m, *Ph*); δ_C (100 MHz, d_4-MeOH) 12.8, 29.4, 46.4, 47.6, 48.0, 50.3, 53.5, 56.1, 125.7, 127.0, 127.3, 128.1, 128.2, 128.3, 128.5, 128.8, 136.6, 139.7, 141.4, 142.7, 176.8; *m/z* (CI^+) 475 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{33}H_{35}N_2O^+$ ($[M+H]^+$) requires 475.2749; found 475.2757.

(3*S*,4*R*,α*S*)-*N*(1)-Benzyl-3-methyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 36



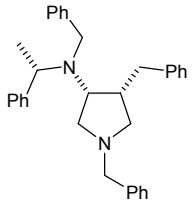
$Pd(PPh_3)_4$ (0.83 g, 0.72 mmol), and *anti*-**29** (3.33 g, 7.09 mmol) and 1,3-DMBA (3.40 g, 21.7 mmol) in DCM (20 mL) were reacted according to *general procedure 3*. Chromatography (silica, eluent 30-40° petrol:Et_2O 30:1) gave **36** as a brown oil (2.65 g, 94%); $[\alpha]_D^{21}$ −23.7 (*c* 1.8 in $CHCl_3$); ν_{max} (film) 3028, 2972, 1687, 1493, 1454; δ_H (400 MHz, $CDCl_3$) 1.23-1.32 (6H, m, C(3)*Me*, C(α)*Me*), 2.54 (1H, quintet, *J* 7.5, C(3)*H*), 3.12 (1H, dd, *J* 10.5, 10.1 C(5)H_A), 3.20 (1H, dd, *J* 10.5, 3.9 C(5)H_B), 3.36-3.41 (2H, m, C(4)*H*, C$H_A$$H_B$Ph), 3.50 (1H, d, *J* 12.3, CH_AH_BPh), 3.88 (1H, q, *J* 6.9, C(α)*H*), 4.34 (1H, d, *J* 13.5, C$H_A$$H_B$Ph), 4.48 (1H, d, *J* 13.5, CH_AH_BPh), 7.14-7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.1, 13.9, 40.7, 46.4, 48.0, 50.2, 54.0, 55.7, 126.9, 127.0, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 136.4, 140.0, 142.4, 176.7; *m/z* (CI^+) 399 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{27}H_{31}N_2O^+$ ($[M+H]^+$) requires 399.2436; found 399.2426.

(3*S*,4*R*,α*S*)-*N*(1)-Benzyl-3-hydroxy-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 37



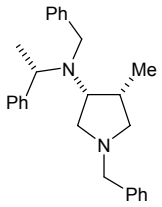
$Pd(PPh_3)_4$ (243 mg, 0.21 mmol), and *anti*-**33** (1.00 g, 2.12 mmol) and 1,3-DMBA (0.99 g, 6.36 mmol) in DCM (25 mL) were reacted according to *general procedure 3*. Chromatography (silica, eluent 30-40° petrol:Et_2O 5:2) gave **37** as a colourless oil (797 mg, 94%); $[\alpha]_D^{24}$ −28.5 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3336, 3028, 2967, 1681, 1494, 1453; δ_H (400 MHz, C_6D_6) 1.02 (3H, d, *J* 6.8, C(α)*Me*), 2.61 (1H, dd, *J* 10.5, 7.2, C(5)H_A), 3.03 (1H, dd, *J* 10.5, 4.1, C(5)H_B), 3.26-3.32 (1H, m, C(4)*H*), 3.48 (1H, d, *J* 14.6, C$H_A$$H_B$Ph), 3.87 (1H, d, *J* 14.6, CH_AH_BPh), 4.04-4.09 (1H, m, C(3)*H*), 4.10-4.14 (2H, m, C(α)*H*, C$H_A$$H_B$Ph), 4.25 (1H, d, *J* 13.6, CH_AH_BPh), 4.51 (1H, d, *J* 2.7, O*H*), 7.01-7.42 (15H, m, *Ph*); δ_C (100 MHz, C_6D_6) 15.8, 46.7, 47.3, 51.2, 54.4, 57.7, 70.2, 127.4, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.9, 136.8, 141.4, 144.2, 176.0; *m/z* (CI^+) 401 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{26}H_{29}N_2O_2^+$ ($[M+H]^+$) requires 401.2229; found 401.2223.

(3*R*,4*R*,α*S*)-*N*(1),4-Dibenzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolidine 38



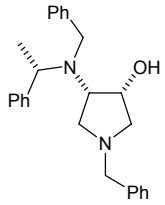
$LiAlH_4$ (1.0 M in THF, 3.16 mL, 3.16 mmol) and **35** (500 mg, 1.05 mmol, 96% de) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **38** as a colourless oil (418 mg, 86%, >98% de); $[\alpha]_D^{22}$ −53.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3084, 3061, 3026, 2965, 2795; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.8, C(α)*Me*), 2.32-2.43 (2H, m, C(4)*H*, C(5)H_A), 2.54-2.62 (1H, m, C(4)CH_A), 2.66 (1H, dd, *J* 9.1, 7.2, C(5)H_B), 2.74 (1H, dd, *J* 9.4, 7.6, C(2)H_A), 2.83 (1H, dd, *J* 9.4, 7.3, C(2)H_B), 3.32 (1H, dd, *J* 11.8, 1.7, C(4)CH_B), 3.54 (1H, q, *J* 7.5, C(3)*H*), 3.61 (2H, s, NCH_2Ph), 3.99 (2H, s, NCH_2Ph), 4.08 (1H, q, *J* 6.8, C(α)*H*), 7.10-7.62 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6, 36.2, 44.4, 53.1, 56.0, 56.6, 58.7, 59.3, 60.8, 125.7, 126.7, 126.9, 128.0, 128.1, 128.3, 128.4, 128.6, 128.9, 139.4, 141.3, 142.5, 143.8; *m/z* (CI^+) 461 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{33}H_{37}N_2^+$ ($[M+H]^+$) requires 461.2957; found 461.2957.

(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]-4-methylpyrrolidine 39



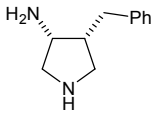
$LiAlH_4$ (1.0 M in THF, 7.25 mL, 7.25 mmol) and **36** (1.00 g, 2.41 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **39** as a colourless oil (862 mg, 89%); $[\alpha]_D^{21}$ −20.4 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3424, 3061, 3027, 2966, 2795, 1602; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 7.2, C(4)*Me*), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 2.13 (1H, dd, *J* 8.6, 6.3, C(5)H_A), 2.22-2.31 (1H, m, C(4)*H*), 2.57 (1H, dd, *J* 8.9, 8.2, C(2)H_A), 2.64 (1H, dd, *J* 8.9, 7.5, C(2)H_B), 2.83 (1H, dd, *J* 8.6, 7.8, C(5)H_B), 3.34 (1H, app q, *J* 7.7, C(3)*H*), 3.59 (2H, ABq, J_{AB} 14.5, NCH_2Ph), 3.74 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.91 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.94 (1H, q, *J* 6.9, C(α)*H*), 7.17-7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.5, 15.6, 36.1, 52.8, 56.0, 56.7, 59.3, 61.0, 61.5, 126.5, 126.6, 126.7, 126.8, 126.9, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 139.4, 141.8, 143.5; *m/z* (CI^+) 385 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{27}H_{33}N_2^+$ ($[M+H]^+$) requires 385.2644; found 385.2649.

(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-hydroxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]pyrrolidine 40



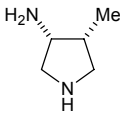
$LiAlH_4$ (1.0 M in THF, 2.25 mL, 2.25 mmol) and **37** (300 mg, 0.75 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **40** as a colourless oil (272 mg, 94%); $[\alpha]_D^{21}$ −12.7 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3418, 3061, 3028, 2967; δ_H (400 MHz, $CDCl_3$) 1.21-1.34 (1H, br s, O*H*), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 2.53-2.61 (2H, m, C(2)H_A, C(5)H_A), 2.69 (1H, dd, *J* 9.1, 7.2, C(5)H_B), 2.80 (1H, dd, *J* 10.7, 5.6, C(2)H_B), 3.29 (1H, app q, *J* 6.8, C(4)*H*), 3.54 (1H, d, *J* 12.9, NCH_AH$_B$Ph), 3.62-3.70 (3H, m, C(3)*H*, NCH$_A$$H_BPh, NCH_AH_B$Ph), 3.94 (1H, d, *J* 12.6, NCH$_A$$H_B$Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 7.20-7.38 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9, 52.4, 54.7, 56.5, 60.6, 61.3, 61.4, 69.4, 127.0, 127.1, 127.2, 127.9, 128.3, 128.5, 128.6, 128.7, 140.2, 142.3; *m/z* (CI^+) 387 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{26}H_{32}N_2O^+$ ($[M+H]^+$) requires 387.2436; found 387.2440.

(3*R*,4*R*)-3-Amino-4-benzylpyrrolidine 41



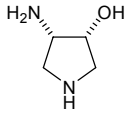
$Pd(OH)_2$/C (140 mg, 50% w/w), **38** (280 mg, 0.61 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **41** as a colourless oil (103 mg, 64%); $[\alpha]_D^{22}$ −39.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3358, 2928, 1495; δ_H (400 MHz, MeOH-d_4) 2.53-2.66 (1H, m, C(4)*H*), 2.69 (1H, dd, *J* 11.5, 3.8, C(4)CH_A), 2.93 (1H, dd, *J* 11.5, 7.6, C(4)CH_B), 3.16-3.23 (3H, m, C(2)H_A, C(5)H_2), 3.40 (1H, dd, *J* 12.1, 6.8, C(2)H_B), 3.62-3.65 (1H, m, C(3)*H*), 4.89 (1H, br s, NH_2), 7.16-7.34 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 33.6, 44.9, 48.9, 52.3, 52.7, 126.6, 128.7, 128.8, 139.8; *m/z* (CI^+) 177 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{11}H_{17}N_2^+$ ($[M+H]^+$) requires 177.1392; found 177.1393.

(3*R*,4*R*)-3-Amino-4-methylpyrrolidine 42



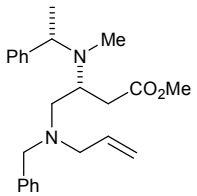
$Pd(OH)_2/C$ (53 mg, 25% w/w), **39** (212 mg, 0.53 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **42** as a colourless oil (50 mg, 48%); $[\alpha]_D^{21}$ −4.9 (*c* 1.0 in MeOH); ν_{max} (film) 3363, 2936; δ_H (400 MHz, MeOH-d_4) 1.00 (3H, d, *J* 7.0, C(4)*Me*), 2.19-2.28 (1H, m, C(4)*H*), 2.51-2.70 (2H, m, C(2)H_A, C(5)H_A), 3.02 (1H, app quintet, *J* 7.4, C(2)H_B), 3.08-3.15 (1H, m, C(5)H_B), 3.22-3.36 (1H, m, C(3)*H*), 4.09 (1H, s, N*H*), 4.88-4.92 (2H, br s, NH_2); δ_C (100 MHz, MeOH-d_4) 11.7, 37.5, 53.9, 55.0, 57.5; *m/z* (CI^+) 101 ($[M+H]^+$, 100%); HRMS (CI^+) $C_5H_{13}N_2^+$ ($[M+H]^+$) requires 101.1079; found 101.1081.

(3*R*,4*S*)-3-Hydroxy-4-aminopyrrolidine 43



$Pd(OH)_2/C$ (38 mg, 25% w/w), **40** (150 mg, 0.39 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **43** as a colourless oil (32 mg, 43%); $[\alpha]_D^{20}$ −16.9 (*c* 1.6 in MeOH); ν_{max} (film) 3363, 1564; δ_H (400 MHz, MeOH-d_4) 1.90 (1H, s, N*H*), 2.51 (1H, s, O*H*), 2.93-3.02 (1H, m, C(5)H_A), 3.20 (1H, br d, *J* 11.0, C(2)H_A), 3.26-3.41 (2H, m, C(2)H_B, C(5)H_B), 3.54 (1H, br s, C(4)*H*), 4.21 (1H, br s, C(3)*H*), 4.90 (2H, s, NH_2); δ_C (100 MHz, MeOH-d_4) 48.6, 52.3, 53.6, 69.8; *m/z* (CI^+) 103 ($[M+H]^+$, 100%); HRMS (CI^+) $C_4H_{11}N_2O^+$ ($[M+H]^+$) requires 103.0871; found 103.0873.

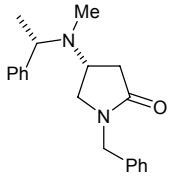
Methyl (3*R*,α*S*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino)butanoate 48



BuLi (1.6 M in hexanes, 2.33 mL, 3.73 mmol) was added dropwise to a stirred solution of (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amine (0.81 mL, 3.85 mmol) in THF (10 mL) at −78°C. After stirring for 30 min a solution of **4** (590 mg, 2.41 mmol) in THF (10 mL) at −78°C was added dropwise via cannula. After stirring for a further 2 h at −78°C the reaction mixture was quenched with sat aq NH_4Cl (20 mL) and allowed to warm to rt over 5 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed brine (50 mL), dried and concentrated *in vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 10:1) gave **48** as a colourless oil (832 mg, 91%, >98%

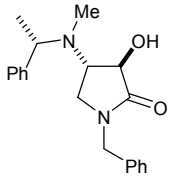
de); $[\alpha]_D^{22}$ +45.6 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 1734; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.7, C(α)*Me*), 2.06 (3H, s, N*Me*), 2.36 (1H, dd, *J* 14.5, 7.6, C(2)H_A), 2.37-2.47 (2H, m, C(4)H_2), 2.53 (1H, dd, *J* 14.5, 6.2, C(2)H_B), 2.86 (1H, dd, *J* 14.1, 7.4, NCH_AH$_B$CH=CH$_2$), 3.09 (1H, dd, *J* 14.1, 5.5, NCH$_A$$H_B$CH=CH$_2$), 3.32 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.57-3.60 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 3.67 (3H, s, O*Me*), 3.68 (1H, q, *J* 6.7, C(α)*H*), 5.10-5.13 (2H, m, CH=CH_2), 5.76-5.86 (1H, m, C*H*=CH$_2$), 7.21-7.32 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9, 32.6, 35.3, 51.3, 54.0, 54.2, 57.1, 58.8, 62.2, 117.5, 126.7, 126.8, 127.2, 128.1, 128.2, 129.0, 135.8, 139.4, 146.1, 173.7; *m/z* (ESI^+) 381 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{33}N_2O_2^+$ ($[M+H]^+$) requires 381.2542; found 381.2543.

(4*R*,α*S*)-*N*(1)-Benzyl-4-[*N*′-methyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 49



$Pd(PPh_3)_4$ (96 mg, 0.083 mmol) was added to a stirred solution of **48** (630 mg, 1.66 mmol) and 1,3-DMBA (776 mg, 4.97 mmol) in DCM (100 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated in *vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 10:1) gave **49** as a yellow oil (455 mg, 89%); $[\alpha]_D^{22}$ +9.4 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 2974, 1686; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.03 (3H, s, N*Me*), 2.49 (2H, d, *J* 8.1, C(3)H_2), 3.11 (1H, dd, *J* 10.1, 6.3, C(5)H_A), 3.21 (1H, dd, *J* 10.1, 7.8, C(5)H_B), 3.34-3.41 (1H, m, C(4)*H*), 3.66 (1H, q, *J* 6.8, C(α)*H*), 7.20-7.69 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8, 32.3, 34.4, 46.4, 50.7, 53.3, 60.6, 127.2, 127.5, 128.0, 128.2, 128.5, 128.6, 136.2, 142.5, 173.1; *m/z* (CI^+) 309 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{20}H_{25}N_2O^+$ ($[M+H]^+$) requires 309.1967; found 309.1969.

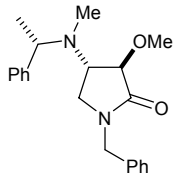
(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-hydroxy-4-[*N*′-methyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 50



BuLi (1.6 M in hexanes, 0.92 mL, 1.48 mmol), 2,2,6,6-tetramethylpiperidine (0.26 mL, 1.54 mmol) in THF (2 mL), **49** (380 mg, 1.23 mmol) in THF (5 mL), and (+)-CSO (565 mg, 2.46 mmol) were reacted according to *general procedure 1* to give **50** in >98% de. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:1) gave **50** as a colourless oil (343 mg, 86%, >98% de); $[\alpha]_D^{23}$ +4.7 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1686; δ_H (400 MHz,

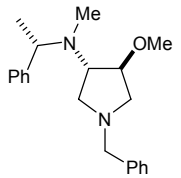
$CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 2.14 (3H, s, N*Me*), 3.09 (1H, app t, *J* 9.0, C(5)H_A), 3.16 (1H, app t, *J* 9.0, C(5)H_B), 3.32 (1H, q, *J* 5.2, C(4)*H*), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.42 (1H, d, *J* 14.8, NCH_A), 4.44-4.48 (1H, m, C(3)*H*), 4.50 (1H, d, *J* 14.8, NCH_B), 7.20-7.41 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8, 32.9, 46.9, 47.4, 59.2, 63.2, 73.2, 126.9, 127.9, 128.1, 128.3, 128.5, 128.8, 129.3, 135.4, 142.0, 173.6; *m/z* (CI^+) 325 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{20}H_{25}N_2O_2^+$ ($[M+H]^+$) requires 325.1916; found 325.1913.

(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-methoxy-4-[*N′*-benzyl-*N′*-(α-methylbenzyl)amino]pyrrolidin-2-one 51



50 (60 mg, 0.19 mmol) in THF (5 mL) was added a suspension of NaH (6.7 mg, 0.28 mmol) in THF (5 mL) at 0°C and allowed to warm to rt over 2 h. MeI (0.04 mL, 0.23 mmol) was added and the solution was stirred overnight, after which time sat. aq. NH_4Cl (5 mL) and brine (5 mL) were added sequentially. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 10:1) gave **51** as a colourless oil (60 mg, 95%); $[\alpha]_D^{22}$ +19.6 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1684; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 2.15 (3H, s, N*Me*), 3.09 (1H, dd, *J* 9.7, 7.4, C(5)H_A), 3.19 (1H, dd, *J* 9.7, 8.1, C(5)H_B), 3.42-3.46 (1H, m, C(4)*H*), 3.75 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, d, *J* 7.2, C(3)*H*), 4.45 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 4.50 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 7.26-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6, 32.8, 46.5, 58.3, 60.0, 60.4, 80.6, 127.0, 127.6, 127.7, 128.2, 128.8, 135.7, 142.8, 172.0; *m/z* (ESI^+) 339 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) requires 339.2073; found 339.2074.

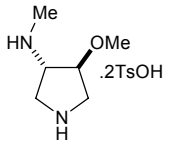
(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-methoxy-4-[*N′*-benzyl-*N′*-(α-methylbenzyl)amino]pyrrolidine 52



$LiAlH_4$ (1.0 M in THF, 0.33 mL, 0.33 mmol) and **51** (37 mg, 0.11 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **52** as a colourless oil (34 mg, 94%); $[\alpha]_D^{22}$ +10.0 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1667; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.8, C(α)*Me*),

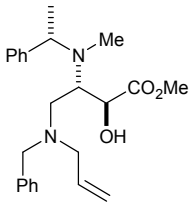
2.18 (3H, s, N*Me*), 2.40 (1H, app t, *J* 8.1, C(5)H_A), 2.66 (1H, dd, *J* 10.0, 6.3, C(2)H_A), 2.81 (1H, dd, *J* 10.0, 2.8, C(2)H_B), 2.86 (1H, app t, *J* 8.1, C(5)H_B), 3.33-3.36 (1H, m, C(4)*H*), 3.37 (3H, s, O*Me*), 3.58 (1H, d, *J* 13.0, NC$H_A$$H_B$Ph), 3.68 (1H, d, *J* 13.0, NCH$_A$$H_B$Ph), 3.87-3.93 (2H, m, C(3)*H*, C(α)*H*), 7.27-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 33.5, 55.3, 57.0, 58.4, 60.4, 60.5, 67.2, 83.7, 126.8, 127.0, 127.1, 128.1, 128.2, 128.8, 138.5, 143.0; *m/z* (ESI^+) 325 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}N_2O^+$ ($[M+H]^+$) requires 325.2280; found 325.2274.

(3*S*,4*S*)-3-Methoxy-4-(*N*-methylammonio)pyrrolidinium di-*p*-toluenesulphonate 53



$Pd(OH)_2$/C (10 mg, 25% w/w), **52** (41 mg, 0.13 mmol) in MeOH (3 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. *p*-Toluenesulphonic acid monohydrate (49 mg, 0.26 mmol) was added to the reaction mixture prior to filtration and gave **53** as a white solid (45 mg, 73%); mp 162-164°C; $[\alpha]_D^{24}$ +10.1 (*c* 1.1 in MeOH); {lit.[5] $[\alpha]_D^{29}$ +10.3 (*c* 1.0 in MeOH)}; δ_H (400 MHz, DMSO-d_6) 2.32 (6H, s, 2 × Ar*Me*), 2.73 (3H, s, N*Me*), 3.28-3.51 (3H, m, C(2)H_2, C(5)H_A) 3.36 (3H, s, O*Me*), 3.67-3.72 (1H, m, C(5)H_B), 3.80-3.89 (1H, m, C(4)*H*), 4.19-4.25 (1H, m, C(3)*H*), 7.17 (4H, d, *J* 7.6, *Ar*), 7.49 (4H, d, *J* 7.6, *Ar*).

Methyl (2*S*,3*S*,α*S*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino)butanoate 54

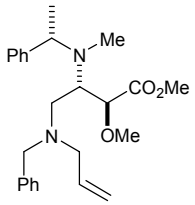


BuLi (2.5 M in hexanes, 2.12 mL, 5.30 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.15 mL, 5.48 mmol) in THF (5 mL), **4** (0.84 g, 3.42 mmol) in THF (5 mL), and (+)-CSO (2.75 g, 12.0 mmol) were reacted according to *general procedure 2* and gave **54** in >98% de. Chromatography (silica, eluent 30-40° petrol:Et_2O 4:1) gave **54** as a colourless oil (1.25 g, 92%, >98% de); $[\alpha]_D^{24}$ +69.1 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3063, 2964, 1740, 1646; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.1, C(α)*Me*), 2.12 (3H, s, N*Me*), 2.41

[5] Y. Tsuzuki, K. Chiba, K. Mizuno, K. Tomita and K. Suzuki, *Tetrahedron: Asymmetry*, **2001**, *12*, 2989.

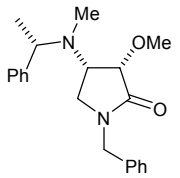
(1H, br d, *J* 8.1, C(4)H_A), 2.70-2.75 (1H, m, NC$H_A$$H_B$CH=$CH_2$), 2.92 (1H, t, *J* 6.7, C(4)H_B), 3.12-3.24 (2H, m, NC$H_A$$H_BPh, NCH_A$$H_B$CH=$CH_2$), 3.41-3.52 (1H, m, C(3)*H*), 3.62 (3H, s, O*Me*), 3.83 (1H, d, *J* 12.2, NC$H_A$$H_B$Ph), 4.32 (1H, d, *J* 4.2, C(2)*H*), 5.12-5.24 (2H, m, CH=CH_2), 5.71-5.90 (1H, m, C*H*=CH_2), 7.14-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 34.8, 49.7, 52.1, 55.2, 56.5, 59.0, 59.8, 83.1, 118.7, 126.7, 127.1, 127.8, 128.3, 128.4, 128.6, 128.8, 129.2, 141.5, 144.7, 174.8; *m/z* (CI^+) 397 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{24}H_{33}N_2O_3^+$ ($[M+H]^+$) requires 397.2491; found 397.2491.

Methyl (2*S*,3*S*,α*S*)-2-methoxy-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-4-(*N′*-benzyl-*N′*-allylamino)butanoate 55



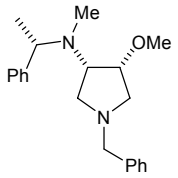
54 (225 mg, 0.57 mmol) in THF (10 mL) was added a suspension of NaH (30 mg, 1.25 mmol) in THF (10 mL) at 0°C and allowed to warm to rt over 2 h. MeI (0.05 mL, 0.72 mmol) was added and the solution was stirred overnight, after which time sat. aq. NH_4Cl (10 mL) and brine (10 mL) were added sequentially. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Chromatography (silica, eluent 30-40° petrol:Et_2O 10:1) gave **55** as a colourless oil (144 mg, 62%); $[\alpha]_D^{24}$ +27.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3028, 2974, 1810, 1755, 1493; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.2, C(α)*Me*), 2.12 (3H, s, N*Me*), 2.41 (1H, dd, *J* 11.2, 2.2, C(4)H_A), 2.87-3.00 (2H, m, C(4)H_B, NC$H_A$$H_B$CH=$CH_2$), 3.12 (1H, dd, *J* 11.1, 3.2, NC$H_A$$H_B$CH=$CH_2$), 3.30 (3H, s, O*Me*), 3.42 (1H, d, *J* 12.4, NC$H_A$$H_B$Ph), 3.52-3.58 (1H, m, C(3)*H*), 3.63 (1H, q, *J* 6.2, C(α)*H*), 3.70 (1H, d, *J* 12.4, NC$H_A$$H_B$Ph), 3.78 (3H, s, CO_2*Me*), 4.29 (1H, d, *J* 1.2, C(2)*H*), 5.12 (2H, br d, *J* 14.1, CH=CH_2), 5.76-5.92 (1H, m, C*H*=CH_2), 7.02-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 35.3, 48.9, 51.9, 57.2, 58.5, 58.9, 59.3, 63.2, 83.5, 117.5, 126.6, 126.9, 127.11, 128.2, 128.9, 129.9, 135.6, 136.0, 169.2; *m/z* (CI^+) 411 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{25}H_{34}N_2O_3^+$ ($[M+H]^+$) requires 411.2648; found 411.2638.

(3*S*,4*S*,α*S*)-*N*(1)-Benzyl-3-methoxy-4-(*N′*-methyl-*N′*-α-methylbenzylamino)pyrrolidin-2-one 56



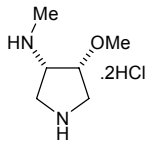
$Pd(PPh_3)_4$ (81 mg, 0.07 mmol), and **55** (1.49 g, 3.65 mmol) and 1,3-DMBA (1.77 g, 11.3 mmol) in DCM (100 mL) were reacted according to *general procedure 3*. Chromatography (silica, eluent 30-40° petrol:Et_2O 3:1) gave **56** as a white solid (0.81 g, 66%); mp 71-72°C; $[\alpha]_D^{23}$ −77.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970, 1690, 1495; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.0, C(α)*Me*), 2.08 (3H, s, N*Me*), 3.05 (1H, dd, *J* 9.3, *J* 6.3, C(5)H_A), 3.16 (1H, q, *J* 6.3, C(4)*H*), 3.24 (1H, dd, *J* 9.3, *J* 6.3, C(5)H_B), 3.68 (3H, s, O*Me*), 3.88 (1H, q, *J* 7.0, C(α)*H*), 3.93 (1H, d, *J* 6.3, C(3)*H*), 4.34 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 4.51 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 7.19–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2, 33.1, 46.3, 48.2, 57.2, 58.7, 59.9, 78.5, 127.2, 127.9, 128.2, 128.7, 135.8, 141.1, 171.2; *m/z* (ESI^+) 339 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) requires 339.2067, found 339.2065.

(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-methoxy-4-(*N*'-methyl-*N*'-α-methylbenzylamino)pyrrolidine 57



$LiAlH_4$ (1.0 M in THF, 4.4 mL, 4.35 mmol) and **56** (490 mg, 1.45 mmol) in THF (15 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **57** as a yellow oil (470 mg, quant); $[\alpha]_D^{23}$ −67.4 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 2795, 1450, 1110; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.0, C(α)*Me*), 2.22 (3H, s, N*Me*), 2.58 (1H, dd, *J* 10.8, *J* 2.7, C(2)H_A), 2.65 (1H, dd, *J* 10.0, *J* 8.5, C(5)H_A), 2.83 (1H, dd, *J* 8.5, *J* 6.7, C(5)H_B), 2.96 (1H, m, C(4)*H*), 3.18 (1H, dd, *J* 10.8, *J* 5.3, C(2)H_B), 3.39 (3H, s, O*Me*), 3.65 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 3.72 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 3.89 (1H, m, C(3)*H*), 3.98 (1H, q, *J* 7.0, C(α)*H*), 7.35–7.24 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0, 34.7, 55.6, 57.1, 58.7, 59.7, 61.2, 63.2, 80.0, 126.9, 127.0, 127.9, 128.3, 128.7, 138.9, 141.3; *m/z* (ESI^+) 325 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}N_2O^+$ ($[M+H]^+$) requires 325.2272, found 325.2274.

(3*R*,4*S*)-3-Methoxy-4-(*N*-methylammonio)pyrrolidinium dichloride 58



$Pd(OH)_2$/C (15 mg, 50% w/w), **57** (30 mg, 0.10 mmol) in MeOH (3 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Hydrogen chloride (2.0 M in Et_2O, 0.2 mL) was added to the reaction mixture prior to filtration and gave **58** as a white crystalline solid (17 mg, 84%); mp 178-179°C; $[\alpha]_D^{24}$ –52.4

(*c* 1.0 in MeOH); {lit.[6] $[\alpha]_D^{25}$ –52.0 (*c* 0.75 in MeOH)}; δ_H (400 MHz, MeOH-d_4) 2.82 (3H, s, N*Me*), 3.37-3.54 (2H, m, C(2)H_A, C(5)H_A), 3.54 (3H, s, O*Me*), 3.80-3.92 (2H, m, C(2)H_B, C(5)H_B), 4.15 (1H, m, C(3)*H*), 4.44 (1H, m, C(4)*H*).

[6] A. Madhan and B. V. Rao, *Tetrahedron: Lett*, **2005**, *46*, 323.