Supplementary Material

General

All reactions involving air- or water-sensitive reagents were carried out under an atmosphere of argon using flame- or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from Na-benzophenone ketyl immediately prior to use. Toluene, CH_2Cl_2, and Et_3N were distilled from calcium hydride. Anhydrous methanol, DMF, and acetonitrile were used as supplied by Acros. Unless otherwise indicated, organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel as the stationary phase. Chiral HPLC was performed using a Waters instrument equipped with a UV detector and a Chiracel OD-H column (internal diameter 4.6 mm, column length 250 mm). All solvents for use in HPLC analysis were vacuum filtered and degassed prior to use, and a standard flow rate of 0.5 cm^3min^{-1} was used. IR spectra were measured on a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 200, Bruker AC250, Bruker AM360 or Varian Inova 600 spectrometer; *J*-values are in Hz. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Optical rotations were measured on an AA-1000 polarimeter with a path length of 1.0 dm, at the sodium D-line at room temperature. Elemental analysis was carried out on a Perkin-Elmer 2400 CHN Elemental Analyser. Fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS50TC mass spectrometer at The University of Edinburgh.

(2'*R*,3'*S*,4*R*,4'*R*)-3-(2'-Benzyloxy-4'-*N*,*N*-dibenzylamino-3'-hydroxy-5'-(4''-methoxy-phenyl)-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one 7

To a solution of glycolate equivalent **3**[ref.12] (0.661 g, 2.00 mmol) in CH_2Cl_2 (5 cm^3) at -78 °C was added triethylamine (0.27 g, 0.37 cm^3, 2.7 mmol) followed by dropwise addition of dibutylboron triflate (2.50 cm^3, 1.0 M in CH_2Cl_2, 2.50 mmol). The solution was stirred at -78 °C for 45 min, then allowed to warm to 0 °C over 30 min and stirred at 0 °C for 1.25 h. The solution was then recooled to -78 °C and a -78 °C solution of aldehyde **2** (0.200 g, 0.554 mmol) in CH_2Cl_2 (3 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at -78 °C for 1 h, and allowed to warm to 0 °C over a period of 4 h. The reaction was quenched by the addition of methanol (8 cm^3) followed by pH 7 phosphate buffer (5 cm^3). Hydrogen peroxide (5 cm^3, 30% aq. solution) in methanol (5 cm^3) was added dropwise to the solution and the mixture was stirred and warmed to room temperature over *ca.* 1 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 cm^3); the combined organic phase was washed sequentially with saturated aq. sodium bicarbonate (25 cm^3) and brine (25 cm^3) then dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane-EtOAc (7 : 3)] to give **7** (0.286 g, 75%) as a foam. $[\alpha]_D$ -47.0 (*c* 2.8, $CHCl_3$); λ_{max} (neat)/cm^{-1} 3334, 1771, 1709, 1611, 1582, 1512 ; δ_H (200 MHz; $CDCl_3$) 7.38-7.09 (18H, m), 7.08 (2H, d, *J* 8.6), 6.90-6.88 (2H, m), 6.66 (2H, d, *J* 8.6), 4.89 (1H, d, *J* 1.6), 4.67 (1H, dddd, *J* 9.9, 6.8, 3.1, 2.2), 4.52 (1H, br s), 4.25 (1H, dd, *J* 8.9, 6.8), 4.24 (1H, d, *J* 11.4), 4.17 (1H, dd, *J* 8.9, 2.2), 4.06 (1H, dd, *J* 9.5, 1.6), 3.91 (2H, d, *J* 13.2), 3.69 (3H, s), 3.58 (1H, ddd, *J* 9.5, 7.7, 4.6), 3.46 (2H, d, *J* 13.2), 3.30 (1H, d, *J* 11.4), 3.31 (1H, dd, *J* 13.4, 3.1), 3.14 (1H, dd, *J* 14.6, 4.6), 2.74 (1H, dd, *J* 13.4, 9.9), 2.72 (1H, dd, *J* 14.6, 7.7); δ_C (62.9 MHz; $CDCl_3$) 170.0, 157.7, 153.4, 138.3, 137.5, 135.1, 131.7, 130.1, 129.2, 128.8, 128.7, 128.4, 127.7, 127.1, 126.7, 113.5, 76.9, 71.1, 70.9, 66.9, 59.9, 55.7, 55.0, 37.5, 30.1; *m/z* (FAB) 685 $([M + H])^+$, 5%), 307 (28), 289 (16), 154 (100); HRMS (FAB) (Found: $[M + H]^+$, 685.3260. $C_{43}H_{44}N_2O_6$ requires *m/z*, 685.3278).

(2*S*,3*S*,4*R*)-Benzyloxy-4-*N*,*N*,-dibenzylamino-3-hydroxy-5-(4'methoxy-phenyl)pentan-1-ol 8

To a solution of aldol adduct **7** (0.148 g, 0.216 mmol) in THF (10 cm^3) at 0 °C was added methanol (0.040 cm^3, 1.1 mmol) and $LiBH_4$ (0.024 g, 1.1 mmol). The solution was warmed to room temperature and stirred for 18 h then re-cooled to 0 °C and quenched by the addition of 1M sodium hydroxide (1 cm^3). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 cm^3); the combined organic phase was washed with brine (30 cm^3), dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane-EtOAc (7 : 3)] to give the diol **8** (0.0886 g, 80%) as a foam. $[\alpha]_D$ -29.6 (*c* 1.1, $CHCl_3$); λ_{max} (neat)/cm^{-1} 3402, 2927, 1609, 1510; δ_H (360 MHz; $CDCl_3$) 7.37-6.96 (15H, m), 7.04 (2H, d, *J* 8.7), 6.73 (2H, d, *J* 8.7), 4.46 (1H, d, *J* 11.8), 3.96 (2H, d, *J* 14.5), 3.90 (1H, d, *J* 11.8), 3.74 (3H, s), 3.72 (1H, dd, *J* 8.1, 3.5), 3.69 (1H, dd, *J* 11.7, 4.8), 3.52 (1H, dd, *J* 11.7, 3.8), 3.42 (2H, d, *J* 14.5), 3.40-3.31 (2H, m), 3.08 (1H, dd, *J* 14.1, 5.8), 2.70 (1H, dd, *J* 14.1, 7.2), 2.52 (1H, br s), 1.78 (1H, br s); δ_C (62.9 MHz; $CDCl_3$) 157.9, 138.7, 138.2, 131.6, 130.0, 129.0, 128.4, 128.1, 127.2, 127.1, 127.0, 113.8, 77.6, 72.1, 70.9, 61.6, 59.0, 55.1, 54.0, 31.0; *m/z* (FAB) 512 $([M + H]^+$, 25%), 330 (21), 154 (24), 91 (100); HRMS (FAB) (Found: $[M + H]^+$, 512.2801. $C_{33}H_{37}NO_4$ requires *m/z*, 512.2801).

(2*R*,3*S*,4*S*)- 4-(Benzyloxy)-1,1-dibenzyl-3-hydroxy-2-(4-methoxybenzyl)pyrrolidinium chloride 9

To a solution of alcohol **8** (0.110 g, 0.215 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C was added DMAP (0.118 g, 0.967 mmol) and toluene-4-sulphonyl-chloride (0.123 g, 0.646 mmol). The solution was stirred for 18 h then diluted with CH_2Cl_2 (20 cm^3) and water (25 cm^3). The organic phase was separated and washed with 1% HCl (2 × 25 cm^3) then dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [CH_2Cl_2-MeOH (19:1)] to give a white foam. The salt obtained was subjected to ion exchange chromatography [Dowex Cl^-; prepared by treatment of Dowex 1-X2 with 1% HCl, followed by flushing with methanol until the eluent returned to pH 7] eluting with methanol to give the chloride salt **9** (0.0963 g, 85%) as an amorphous solid. $[\alpha]_D$ +4.1 (*c* 0.8, $CHCl_3$); λ_{max} (neat)/cm^{-1} 3147, 1612, 1513, 1250; δ_H (360 MHz; $CDCl_3$) 7.73-6.71 (17H, m), 6.69 (2H, d, 8.7), 5.66 (1H, d, 13.5), 5.04 (2H, s), 4.71 (1H, br s), 4.42 (2H, s), 4.26 (1H, s), 4.26-4.18 (1H, m), 4.20 (1H, d, 13.5), 3.82 (1H, dt, 12.2, 2.9), 3.69 (3H, s), 3.66 (1H, br d, 13.3), 3.50 (1H, t, 12.2), 3.09 (1H, dd, 13.3, 3.1), 2.18 (1H, br s); δ_C (62.9 MHz; $CDCl_3$) 158.5, 137.1, 133.5, 133.0, 130.7, 130.5, 129.3, 128.1, 128.0, 127.5, 127.4, 126.9, 114.1, 80.2, 75.1, 72.3, 71.8, 63.8, 63.5, 62.2, 55.0, 27.7; *m/z* (FAB) 494 ($[M]^+$, 75%), 402 (6), 282 (11), 154 (43), 91 (100); HRMS (FAB) (Found: $[M]^+$, 494.2695. $[C_{33}H_{36}NO_3]^+Cl^-$ requires *m/z,* 494.2695).

(2*R*,3*S*,4*S*)-1-Benzyl-4-(benzyloxy)-3-hydroxy-2-(4-methoxybenzyl)pyrrolidine 10

To a solution of pyrrolidinium salt **9** (0.0493 g, 0.0931 mmol) in methanol (5 cm^3) was added 5% Pd/C (0.0057 g) and potassium carbonate (0.0446 g, 0.323 mmol). The mixture was exposed to an atmosphere of hydrogen (1 atm.) and stirred vigorously for 10 min. The suspension was filtered through a pad of Celite and concentrated under reduced pressure. To the residue was added CH_2Cl_2 (25 cm^3) and water (25 cm^3). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3); the combined organic extracts were washed with saturated aq. sodium bicarbonate (25 cm^3) then dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane-EtOAc (7 : 3)] to give pyrrolidine **10** (0.0353 g, 94%) as a solid; $[\alpha]_D$ -96.1 (*c* 0.4, $CHCl_3$); λ_{max} (neat)/cm^{-1} 3419, 2917, 1610, 1511; δ_H (250 MHz; $CDCl_3$) 7.33-7.19 (12H, m), 6.84 (2H, d, *J* 8.7), 4.46 (1H, d, *J* 11.9), 4.39 (1H, d, *J* 11.9), 4.14 (1H, d, *J* 12.9), 3.80 (2H, dd, *J* 6.5, 4.1), 3.79 (3H, s), 3.33 (1H, d, *J* 12.9), 3.32 (1H, dd, *J* 10.6, 6.7), 2.97-2.81 (3H, m), 2.20 (1H, dd, *J* 10.4, 4.4); δ_c (62.9 MHz; $CDCl_3$) 157.9, 138.4, 137.8, 130.8, 130.1, 128.7, 128.3, 128.2, 127.5, 127.0, 113.8, 82.6, 75.4, 71.2, 68.2, 58.4, 57.7, 55.1, 32.5; *m/z* (FAB) 404 ($[M + H])^+$, 16%), 307 (19), 154 (100) 136 (72), 91 (30); HRMS (FAB) (Found: $[M + H]^+$, 404.2226. $C_{26}H_{30}NO_3$ requires *m/z* 404.2226).

(2*R*,3*S*,4*S*)-3-Acetoxy-1-benzyl-4-(benzyloxy)-2-(4-methoxybenzyl)pyrrolidine 11

$[\alpha]_D$ -105.7 (*c* 1.1, $CHCl_3$); λ_{max} (neat)/cm^{-1} 2932, 1738, 1612, 1583, 1512, 1247; δ_H (250 MHz; $CDCl_3$) 7.33-7.20 (10H, m), 7.07 (2H, d, *J* 8.8), 6.81 (2H, d, *J* 8.8), 4.91 (1H, dd, *J* 4.9, 1.5), 4.62 (1H, d, *J* 12.1), 4.05 (1H, d, *J* 13.1), 3.82-3.71 (1H, m), 3.77 (3H, s), 3.38 (1H, d, *J* 13.1), 3.33 (1H, dd, *J* 10.7, 6.7), 3.10 (1H, dt, *J* 9.6, 5.0), 2.96 (1H, dd, *J* 13.6, 5.1), 2.76 (1H, dd, *J* 13.6, 9.6), 2.32 (1H, dd, *J* 10.7, 4.9), 2.11 (3H, s); δ_c (62.9 MHz; $CDCl_3$) 170.2, 157.9, 138.2, 137.9, 130.6, 129.6, 128.9, 128.2, 127.5, 127.4, 127.0, 113.8, 81.0, 77.8, 71.3, 66.5, 58.3, 55.1, 33.1, 21.1; *m/z* (FAB) 446 ($[M + H]^+$, 35%), 356 (10) 324 (10), 217 (19), 91 (100); HRMS (FAB) (Found: $[M + H]^+$, 446.2332. $C_{28}H_{32}NO_4$ requires *m/z* 446.2331).

(2*R*,3*S*,4*S*)-3-Acetoxy-4-(hydroxy)-2-(4-methoxybenzyl)pyrrolidine hydrochloride 1

mp 187-188 °C; $[\alpha]_D$ +4.0 (*c* 0.28, CH_3OH) {lit.,[ref.7w] $[\alpha]_D$ (*c* +4.2, CH_3OH)}; λ_{max} (KBr)/cm^{-1} 3395, 3291, 3252, 1749, 1612, 1514; δ_H (250 MHz; CD_3OD) 7.26 (2H, d, *J* 8.6), 6.95 (2H, d, *J* 8.6), 5.08 (1H, d, *J* 3.0), 4.38 (1H, d, *J* 4.2), 4.23-4.15 (1H, m), 3.81 (3H, s), 3.63 (1H, dd, *J* 12.8, 4.3), 3.22 (1H, d, *J* 12.8), 3.11 (1H, dd, *J* 14.3, 6.7), 2.99 (1H, dd, *J* 14.3, 8.8), 2.21 (3H, s); δ_c (62.9 MHz; CD_3OD) 169.8, 159.6, 130.0, 127.9, 114.5, 77.3, 72.4, 62.7, 54.7, 51.6, 31.2, 19.7.