Supplementary Information

Catalytic and stoichiometric approaches to the desymmetrisation of centrosymmetric piperazines by enantioselective acylation: A total synthesis of Dragmacidin A

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General experimental

Tetrahydrofuran and diethyl ether were freshly distilled from sodium, with benzophenone as indicator. Dichloromethane, xylene, toluene, methanol, ethanol and dimethylsuphoxide were distilled from calcium hydride. Acetone and trifluoroacetic acid were freshly distilled before use. Acetic acid was treated with potassium permanganate and 1 mol% acetic anhydride, and then distilled onto magnesium sulfate. Dimethylformamide was used, as supplied by Aldrich, from sure/seal™ bottles. Organolithium reagents were titrated against diphenylacetic acid before use. Triethylamine was dried and stored over potassium hydroxide pellets. *N*-bromosuccinimide was recrystallised from boiling water. All other solvents and reagents were of analytical grade and used as supplied. All non-aqueous reactions were carried out under nitrogen or argon in oven- or flame-dried glassware.

Flash chromatography[1] was carried out using silica gel 60 (35-70 μm particles). Thin layer chromatography was carried out using commercially available precoated glass plates (Merck silica gel 60 F_{254}). Ether refers to diethylether, petrol refers to petroleum spirit (bp 40-60 °C) and MeOH/NH_3 refers to 7 N ammonia solution in methanol. Analytical HPLC was performed on a Dionex system using either Daicel, 250 × 4.6 mm 10 μm Chiralpak® AD, 250 × 4.6 mm 10 μm Chiralcel® OD, or 150 × 4.6 mm 5 μm Chiralcel® OD-RH columns.

Melting points were obtained on a Reichert hotstage microscope or with a Griffin melting point apparatus and are uncorrected. Micro analyses were carried by staff in the School of Chemistry using a Carlo Erba 1108 automatic analyser. Optical rotations were recorded on an Optical Activity AA-1000 polarimeter at room temperature and $[\alpha]_D$ are given

in units of 10^{-1} deg cm^2 g^{-1}. Infra-Red spectra were recorded on a Perkin Elmer spectrum one FT-IR spectrometer. Proton and Carbon NMR spectra were recorded on Brucker DPX 300, or Avance 500, Fourier transform spectrometers at room temperature unless otherwise stated. Chemical shifts are quoted in ppm and coupling constants are quoted in Hz. Carbon NMR spectra were recorded with broad band proton decoupling.

Nominal mass spectrometry was routinely performed on a Waters/Micromass ZMD spectrometer (ES). Nominal and accurate mass spectrometry was carried out by the EPSRC National Mass Spectrometry Service (ES, EI, CI, FAB) and by staff at the School of Chemistry using either a Micromass Autospec magnetic sector spectrometer (EI, FAB), a Micromass LCT-KA11 (TOF) spectrometer (ES), or a Brucker Daltonics micrOTOF spectrometer (ES). Spectra were obtained in positive ionisation mode unless otherwise stated. X-ray crytal structures were recorded and solved by staff at the School of Chemistry using a Nonius KappaCCD diffractometer.

(2*R,5*S**)-1,4-Bis(methoxycarbonyl)-2,5-dimethylpiperazine 9, (2*R**,5*S**)-1-methoxycarbonyl-4-(2'-napthoyl)-2,5-dimethylpiperazine 10a and (2*R**,5*S**)-1,4-bis(2'-napthoyl)-2,5-dimethylpiperazine 11**

Methyl chloroformate (170 μL, 2.19 mmol) was added to a stirred solution of *trans*-2,5-dimethylpiperazine (250 mg, 2.19 mmol) and triethylamine (767 μL, 5.50 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 2 hours at room temperature, cooled to 0 °C and a solution of 2-naphthoyl chloride (438 mg, 2.30 mmol) in dichloromethane (5 mL) added. The reaction mixture was stirred for 30 min at room temperature, 1 M aqueous hydrochloric acid (20 mL) was added and the mixture extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of crude products which were separated by flash chromatography (gradient elution: 4:1→1:1 petrol–EtOAc) to give the disubstituted *piperazine* **9** (159 mg, 32%) as colourless needles, mp 139-141 °C (from CH_2Cl_2); R_f 0.39 (1:1 petrol–EtOAc); (Found: C, 52.4; H, 7.65; N, 11.9; $C_{10}H_{18}N_2O_4$ requires C, 52.2; H, 7.65; N, 12.2%); ν_{max}/cm^{-1} (film) 2956, 1698, 1438 and 1183; δ_H (500 MHz;

DMSO–d_6; 120 °C) 4.19 (2H, m, 2-H), 3.65 (6H, s, OMe), 3.60 (2H, dd, *J* 13.7 and 1.8 3-H_AH_B), 3.25 (2H, dd, *J* 13.7 and 4.2, 3-H_AH_B) and 1.10 (6H, d, *J* 6.7, 2-Me); δ_C (125 MHz; DMSO–d_6; 120 °C) 155.0, 51.3, 45.8, 41.9, and 14.3; *m/z* (ES) 231 (100%, MH^+).

Also obtained was the disubstituted *piperazine* **10a** (223 mg, 31%) as an oil which crystallised as colourless plates on standing, mp 117-119 °C; R_f 0.24 (1:1 petrol–EtOAc); (Found: C, 69.7; H, 7.05; N, 8.4; $C_{19}H_{22}N_2O_3$ requires C, 69.9; H, 6.79; N, 8.6%); ν_{max}/cm^{-1} (film) 3055, 2975, 2873, 1699 and 1635; δ_H (500 MHz; DMSO–d_6; 120 °C); 7.97 (3H, m, Nap), 7.92 (1H, s, Nap), 7.58 (2H, m, Nap), 7.49 (1H, d, *J* 8.4, Nap), 4.41 (1H, br s, 5-H), 4.28 (1H, m, 2-H), 3.76 (1H, br d, *J* 13.9, 3-H_AH_B), 3.69 (1 H, dd, *J* 13.7 and 1.9 6-H_AH_B), 3.68 (3H, s, OMe), 3.42 (1H, dd, *J* 13.9 and 4.1, 3-H_AH_B), 3.35 (1H, dd, *J* 13.7 and 4.1, 6-H_AH_B), 1.24 (3H, d, *J* 6.7, Me) and 1.17 (3H, d, *J* 6.7, Me); δ_C (125 MHz; DMSO–d_6; 120 °C) 169.6, 155, 133.2, 132.6, 131.9, 127.5, 127.4, 126.9, 126.2, 125.9, 125.2, 123.4, 51.5, 46.1, 42.1, 14.6 and 14.3 (2 peaks missing); *m/z* (ES) 372 (100%, MH^+).

Also obtained was the disubstituted *piperazine* **11** (263 mg, 26%) as colourless needles, mp 264-265 °C (from CH_2Cl_2); R_f 0.15 (1:1 petrol–EtOAc); (Found: C, 79.7; H, 6.20; N, 6.3; $C_{28}H_{26}N_2O_2$ requires C, 79.6; H, 6.20; N, 6.6%); ν_{max}/cm^{-1} (film) 1617, 1470 and 1422; δ_H (500 MHz; DMSO–d_6; 120 °C) 7.79 (8H, m, Nap), 7.58 (4H, m, Nap), 7.51 (2H, m, Nap), 4.45 (2H, br s, 2-H), 3.81 (2H, br d, *J* 13.8, 3-H_AH_B), 3.51 (2H, dd, *J* 13.8 and 3.8, 3-H_AH_B) and 1.30 (6H, d, *J* 6.7 2-Me); δ_C (125 MHz; DMSO–d_6; 120 °C) 169.5, 133.1, 132.5, 131.8, 127.5, 127.3, 126.8, 126.1, 125.8, 125.2, 123.3, 46.5, 42.8 and 14.6; *m/z* (ES) 423 (100%, MH^+).

(2*R,5*S**)-1-Benzyloxycarbonyl-2,5-dimethylpiperazine[2] 12**

Benzyl chloroformate, 95% (330 μL, 2.19 mmol) was added to a stirred solution of *trans*-2,5-dimethylpiperazine (250 mg, 2.19 mmol) and triethylamine (420 μL, 3.0 mmol) in dichloromethane (10 ml) at 0 °C. The reaction mixture was stirred for 3.5 hours at room temperature, water (30 mL) was added and the mixture extracted with dichloromethane (3 × 15 ml). The aqueous layer was cooled to 0 °C, freebased by adding sodium hydroxide (7.50 g) and extracted with dichloromethane (3 x 15mL). These extracts were dried ($MgSO_4$) and

concentrated under reduced pressure to give *trans*-2,5-dimethylpiperazine (62 mg, 25%). The organic extractions from the crude reaction mixture were washed with 1 M aqueous hydrochloric acid (3 × 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give (2*R**,5*S**)-1,4-dibenzyloxycarbonyl-2,5-dimethylpiperazine (299 mg, 36%) as a colourless waxy solid, R_f 0.62 (1:1 petrol–EtOAc); (Found: C, 68.9; H, 6.65; N, 7.5; $C_{22}H_{26}N_2O_6$ requires C, 69.1; H, 6.85; N, 7.3%); ν_{max}/cm^{-1} (film) 3033, 2972, 2875, 1698, 1424 and 1105; δ_H (500 MHz; DMSO–d_6; 120 °C) 7.37-7.28 (10H, m, Ph), 5.14 (2H, d, *J* 12.6, PhCH_AH$_B$), 5.09 (2H, d, *J* 12.6, PhCH$_A$$H_B$), 4.27 (2H, m, 2-H), 3.67 (2H, d, *J* 13.5, 3-H_AH$_B$), 3.24 (2H, d, *J* 13.5, 3-H$_A$$H_B$) and 1.09 (6H, d, *J* 6.4, 2-Me); δ_C (12 5 MHz; DMSO–d_6; 120 °C) 168.5, 136.5, 127.7, 127.1, 126.8, 66.0, 46.2, 42.3, and 14.3; *m/z* (ES) 383 (100%, MH^+).

The combined acid washings were baseified by adding 2 M aqueous sodium hydroxide (200 mL) and extracted with dichloromethane (3 × 15 mL). These extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the monosubstituted piperazine[2] **12** (121 mg, 22%) as a colourless oil, ν_{max}/cm^{-1} (film) 3329, 3032, 2968, 2872, 1694, 1424 and 1100; δ_H (500 MHz; $CDCl_3$) 7.34 (5H, m, Ph), 5.17 (1H, d, *J* 12.5, PhCH_AH$_B$), 5.12 (1H, d, *J* 12.5, PhCH$_A$$H_B$), 4.19 (1H, m, 2-H), 3.62 (1H, dd, *J* 13.3 and 1.2, 6-H_AH$_B$), 3.29 (1H, dd, *J* 13.3 and 4.0, 6-H$_A$$H_B$), 3.22 (1H, dd, *J* 13.0 and 4.6, 3-H_AH$_B$), 3.14 (1H, m, 5-H), 2.50 (1H, dd, *J* 13.0 and 2.7, 3-H$_A$$H_B$), 1.24 (3H, d, *J* 6.8, 2-Me) and 1.17 (3H, d, *J* 6.7, 5-Me); *m/z* (ES) 249 (100%, MH^+).

(2*R,5*S**)-1-Acetyl-4-benzyloxycarbonyl-2,5-dimethylpiperazine 13**

Acetyl chloride (142 μL, 2.00 mmol) was added dropwise to a stirred solution of triethylamine (350 μL, 2.50 mmol) and the piperazine **12** (408 mg, 1.64 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 90 min at room temperature, water (20 mL) was added and the mixture extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 1:1 petrol–EtOAc to give the *acetamide* **13** (452 mg, 95%) as a colourless oil, R_f 0.41

(EtOAc); (Found: C, 65.9; H, 7.70; N, 9.4; $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.64; N, 9.7%); ν_{max}/cm^{-1} (film) 2973, 2935, 2875, 1699, 1645 and 1425; δ_H (500 MHz; $CDCl_3$) 7.38-7.33 (5H, m, Ph), 5.20-5.10 (2H, m, C*H*$_2$Ph), 4.88-2.96 (6H, m, 2-H, 3-H, 5-H and 6-H), 2.15-2.04 (3H, m, OMe) and 1.27-1.12 (6H, m, 2-Me and 5-Me); δ_C (125 MHz; DMSO–d_6; 110 °C) 167.6, 153.9, 135.9, 127.1, 126.5, 126.1, 65.3, 45.5, 41.7, 19.6, 13.9 and 13.7 (2 peaks missing); *m/z* (ES) 291 (100%, MH^+).

(2*R,5*S**)-1-Acetyl-4-(2'-napthoyl)-2,5-dimethylpiperazine 10b**

10% Palladium on charcoal (40 mg) was added to a solution of the piperazine **13** (422 mg, 1.45 mmol) in ethanol (5 mL), the mixture was stirred under hydrogen (~ 1 atm) for 3 days, filtered through celite and concentrated under reduced pressure to give the acetylated piperazine (126 mg) as a yellow oil which was dissolved in dichloromethane (10 ml). Triethylamine (209 μL, 1.50 mmol) and a solution of β-napthoyl chloride (190 mg, 1.00 mmol) in dichloromethane (1 mL) was added. The reaction mixture was stirred for 16 hours at room temperature, water (20 mL) was added and the mixture extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with ethyl acetate, to give the *napthamide* **10b** (235 mg, 93%) as pale brown needles, mp 120-123 °C (from EtOAc); R_f 0.12 (EtOAc); (Found: C, 73.3; H, 7.15; N, 8.8; $C_{19}H_{22}N_2O_2$ requires C, 73.5; H, 7.14; N, 9.0%); ν_{max}/cm^{-1} (film) 2974, 2933, 2873, 1635 and 1423; δ_H (500 MHz; $CDCl_3$); 7.90-7.85 (4H, m, Nap), 7.56-7.44 (3H, m, Nap), 5.06-2.97 (6H, m, 2-H, 3-H, 5-H and 6-H), 2.19-2.03 (3H, m, COMe) and 1.37-1.12 (6H, m, 2-Me and 5-Me) δ_C (125 MHz; DMSO–d_6; 110 °C) 169.5, 168.1, 133.2, 132.6, 131.9, 127.5, 127.4, 126.9, 126.2, 125.9, 125.2, 123.4, 65.4, 46.3, 46.1, 43.2, 43.0, 20.1, and 14.4; *m/z* (ES) 310 (100%, MH^+).

(2*R,5*S**)-1,4-Diacetyl-2,5-dimethylpiperazine[3] 23b**

Acetyl chloride (156 μL, 2.19 mmol) was added to a solution of triethylamine (420 μL, 3.00 mmol) and *trans*-2,5-dimethylpiperazine (250 mg, 2.19 mmol) in dichloromethane (10 mL) at

0 °C. The reaction mixture was stirred for 90 min at room temperature, water (20 mL) was added and the mixture extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give bisacetylated piperazine[3] **23b** (190 mg, 87%) as colourless needles, mp 176-177 °C (from CH_2Cl_2); ν_{max}/cm^{-1} (film) 2969 and 1629; δ_H (500 MHz; $CDCl_3$) conformer 1: 4.89 (2H, m, 2-H), 3.47 (2H, dd, *J* 13.7 and 3.8, 3-H_AH_B), 3.37 (2H, d, *J* 13.7, 3-H_AH_B), 2.08 (6H, s, COMe) and 1.18 (6H, d, *J* 6.9, 2-Me); conformer 2: 4.35 (2H, d, *J* 13.8, 3-H_AH_B), 4.04 (2H, m, 2-H), 3.01 (2H, dd, *J* 13.8 and 4.3, 3-H_AH_B), 2.17 (6H, s, COMe) and 1.22 (6H, d, *J* 6.8, 2-Me); conformer 3: 4.89 (1H, m, 2-H), 4.27 (1H, d, *J* 13.7, 3-H_AH_B), 4.04 (1H, m, 5-H), 3.56 (1H, dd, *J* 13.7 and 3.9, 6-H_AH_B), 3.41 (1H, d, *J* 13.7, 6-H_AH_B), 2.95 (1H, dd, *J* 13.7 and 4.3, 3-H_AH_B), 2.16 (3H, s, COMe) 2.08 (3H, s, COMe), 1.28 (3H, d, *J* 6.8, 5-Me) and 1.12 (3H, d, *J* 6.9, 2-Me); *m/z* (EI) 198 (42%, M^+), 155 (18), 113 (48) and 43 (100).

(2*R,5*S**)-1-(2'-Napthoyl)-2,5-dimethylpiperazine 15**

n-Butyllithium (3.10 mL 1.55 M solution in hexanes, 4.82 mmol) was added to a stirred solution of *trans*-2,5-dimethylpiperazine (250 mg, 2.19 mmol) in tetrahydrofuran (10 mL) and the mixture stirred for 1 hour at room temperature. A solution of 2-naphthoyl chloride (396 mg, 2.08 mmol) in tetrahydrofuran (5 mL) was added dropwise. After 5 min the reaction mixture was quenched with methanol (10 mL) and concentrated under reduced pressure. The residue was partitioned between saturated aqueous sodium hyrogencarbonate (25 mL) and ethyl acetate (25ml). The aqueous layer was separated and extracted with ethyl acetate (2 × 25 mL), the combined organic extracts were concentrated under reduced pressure, the residue dissolved in dichloromethane and extracted with 1 M aqueous hydrochloric acid (3 × 20 mL). The combined acidic extracts were basified with sodium hydroxide (3.50 g) and extracted with dichloromethane (3 × 20 mL). These extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the *napthamide* **15** (240 mg, 42%) as a yellow oil, R_f 0.38 (7:3:1 EtOAc–MeOH–Et_3N); ν_{max}/cm^{-1} (film) 3314, 3055, 2968, 2932, and 1619; δ_H (300 MHz; $CDCl_3$) 7.87, (4H, m, Nap), 7.60-7.43 (3H, m Nap), 4.44 (1H, m, 2-H), 3.76 (1H, br d, *J* 13.7, 6-H_AH_B), 3.45 (1 H, dd, *J* 13.7 and 4.2, 6-H_AH_B), 3.33 (1H, dd, *J* 13.0 and 4.5, 3-

H_AH_B), 3.22 (1H, m, 5-H), 2.59 (1H, dd, *J* 13.0 and 1.9, 3-H_AH_B), 1.39 (3H, d, *J* 6.9, 2-CH*Me*) and 1.24 (3H, d, *J* 6.8, 5-CH*Me*); δ_C (75 MHz; $CDCl_3$) 171.8, 134.7, 133.9, 133.2, 128.9, 128.7, 128.3, 127.4, 127.1, 126.6, 124.4, 47.8, 43.9, 16.9 and 16.8 (2 peaks missing); *m/z* (ES) 269 (100%, MH^+); *m/z* (ES) (Found: MH^+, 269.1659; $C_{17}H_{21}N_2O$ requires *MH*, 269.1654).

(2*R,5*S**)-1-Formyl-4-(2'-napthoyl)-2,5-dimethylpiperazine 10c**

Formic acid (250 μL, 6.62 mmol), was added to acetic anhydride (500 μL, 5.30 mmol), heated at 60 ºC for 2 hours, cooled and diluted with tetrahydrofuran (5 mL). A solution of the napthamide **15** (185 mg, 0.745 mmol) in tetrahydrofuran (10 mL) was added, the reaction mixture stirred for 3 hours at room temperature and concentrated under reduced pressure. The residue was suspended in toluene (10 mL) and concentrated under reduced pressure; this was repeated twice more to give a crude product which was purified by flash chromatography, eluting with ethyl acetate to give the *formamide* **10c** (195 mg, 77%) as colourless needles, mp 138-142 °C (from CH_2Cl_2); R_f 0.20 (EtOAc); (Found: C, 72.7; H, 6.85; N, 9.5; $C_{19}H_{22}N_2O_2$ requires C, 73.0; H, 6.80; N, 9.5%); ν_{max}/cm^{-1} (film) 3057, 2976, 2936, 2873, 2242, 1672, 1634 and 1429; 8.25 and 8.01 (1H, 2 × s, CHO), 7.97-7.86 (4H, m, Nap), 7.57-7.44 (3H, m, Nap), 5.13-2.98 (6H, m, 2-H, 3-H, 5-H and 6-H) and 1.36-1.17 (6H, m, 2-Me and 5-Me); δ_C (125 MHz; DMSO–d_6; 120 °C) 169.6, 160.8, 133.1, 132.6, 131.9, 127.5, 127.4, 126.9, 126.1, 125.9, 125.1,123.3, 47.8, 46.0, 44.0, 42.2, 15.8 and 14.0; *m/z* (ES) 297 (100%, MH^+).

(2*R,5*S**)-1,4-Diformyl-2,5-dimethylpiperazine 23c**

Formic acid (509 μL, 13.5 mmol) was added to acetic anhydride (1.04 mL, 11.0 mmol), heated at 60 ºC for 2 hours, cooled to room temperature and a solution of *trans*-2,5-dimethylpiperazine (250 mg, 2.19 mmol) in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred for 16 hours at room temperature and concentrated under reduced pressure. The crude product was suspended in toluene (10 mL) and concentrated under reduced pressure, this was repeated twice more to give the formylated *piperazine* **268** (366

mg, 98%) as colourless needles, mp 161-162 °C (from CH_2Cl_2); (Found: C, 56.7; H, 8.40; N, 16.2; $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.29; N, 16.4%); ν_{max}/cm^{-1} (film) 2976, 2940, 2879 and 1651; δ_H (500 MHz; $CDCl_3$) conformer 1: 8.00 (2H, s, CHO), 4.73 (2H, m, 2-H), 3.52 (2H, dd, *J* 13.7 and 4.3, 3-H_AH_B), 3.13 (2H, d, *J* 13.7, 3-H_AH_B) and 1.21 (6H, d, *J* 6.8, 2-Me); conformer 2: 8.26 (2H, s, CHO), 4.11 (2H, d, *J* 13.7, 3-H_AH_B), 3.89 (2H, m, 2-H), 3.22 (2H, dd, *J* 13.7 and 4.3, 3-H_AH_B) and 1.27 (6H, d, *J* 6.8, 2-Me); conformer 3: 8.26 (1H, s, CHO), 8.00 (1H, s, CHO), 4.73 (1H, m, 2-H), 4.07 (1H, d, *J* 13.7, 3-H_AH_B), 3.89 (1H, m, 5-H), 3.60 (1H, dd, *J* 13.7 and 3.9, 6-H_AH_B), 3.21 (1H, d, *J* 13.7, 6-H_AH_B), 3.02 (1H, dd, *J* 13.7 and 4.3, 3-H_AH_B), 1.30 (3H, d, *J* 6.8, 5-Me) and 1.18 (3H, d, *J* 6.8, 2-Me); δ_C (75 MHz; $CDCl_3$) 162.0, 161.9, 161.8, 161.8, 49.5, 49.5, 46.5, 45.2, 43.0, 43.0, 40.6, 39.2, 17.0, 16.7, 15.2 and 14.8; *m/z* (EI) 171 (100%, MH^+).

(1*R*,2*R*)-*N*-Formyl-1,2-bis(pentafluorobenzenesulfonamido)cyclohexane 22

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (1.17 g, 6.09 mmol) was added to a stirred solution of (1*R*,2*R*)-1,2-bis(pentafluorobenzenesulfonamido)cyclohexane[4] (1.00 g, 1.74 mmol) and formic acid (197 μL, 5.22 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 90 min at room temperature and concentrated under reduced pressure. The mixture was subjected to flash chromatography, (gradient elution: 37:3→17:3 petrol–EtOAc) to give the formylated *sulfonamide* **22** (283 mg, 27%) as colourless plates, mp 142-143 °C (from CH_2Cl_2); R_f 0.33 (4:1 petrol–EtOAc); $[\alpha]_D$ –27.2 (*c* 1.0 in $CHCl_3$); (Found: C, 38.1; H, 2.00; F, 31.7; N, 4.6; S, 10.8; $C_{19}H_{12}F_{10}N_2O_5S_2$ requires C, 37.9; H, 2.01; F, 31.5, N, 4.7, S, 10.7%); ν_{max}/cm^{-1} (film) 3295, 2945, 2868, 1716, 1645, 1523 and 1500; δ_H (300 MHz; $CDCl_3$) 9.00 (1H, s, CHO), 5.19 (1H, br s, NH), 4.19 (1H, br s, 1-H), 3.77 (1H, br s, 2-H), 2.27 (1H, br s), 1.85 (1H, br s), 1.80-1.60 (3H, m) and 1.45-1.12 (3H, m).

Also obtained was the starting material (632 mg, 63%).

6-Bromo-3-(*N*-*tert*-butoxycarbonylaminoacetyl)indole 25

2,3-Dichloro-5,6-dicyanobenzoquinone (9.57 g, 62.42 mmol) was added to a stirred solution of the tryptamine[5] **24** (7.15 g, 21.08 mmol) in tetrahydrofuran (250 mL) and water (25 mL) at

0 ºC. The reaction mixture was stirred for 6 hours at 0 ºC, diluted with ethyl acetate (1 L), washed with saturated aqueous sodium hydrogencarbonate (8 × 250 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Ethyl acetate (25 mL) was added to the crude product, which was collected by filtration and washed with ethyl acetate to give the aminoketone **25** (~5 g). The filtrate was concentrated, subjected to flash chromatography, (gradient elution with 1:3→2:3 petrol–EtOAc) to give a crude product which was washed with ethyl acetate and combined with that already obtained to provide the *aminoketone* **25** (6.02 g, 81%) as tiny pale brown plates, mp 216-218 °C; R_f 0.25 (1:1 petrol–EtOAc); (Found: C, 51.0; H, 4.95; N, 7.9; Br, 22.8; $C_{15}H_{17}N_2O_3Br$ requires C, 51.0; H, 4.85; N, 7.9; Br, 22.6%); ν_{max}/cm^{-1} (film) 3398, 1683 and 1649; δ_H (300 MHz; DMSO–d_6); 12.00 (1H, br s, 1-NH), 8.43 (1H, s, 2-H), 8.09 (1H, d, *J* 8.5, 4-4), 7.67 (1H, s, 7-H), 7.34 (1H, d, *J* 8.5, 5-H), 7.04 (1H, t, *J* 5.7, NH), 4.29 (2H, d, *J* 5.7, 3-$COCH_2$) and 1.40 (9H, s, ^{t}Bu); δ_C (75 MHz; DMSO–d_6) 191.3, 156.3, 137.6, 134.5, 125.0, 124.8, 123.2, 115.8, 115.2, 114.2, 78.2, 47.2 and 28.6; *m/z* (ES) 355 (63%, MH^+), 353 (61), 299 (100) and 297 (98).

2,5-Bis(6'-bromoindol-3'-yl)pyrazine[6] 26

The protected aminoketone **25** (5.01 g, 14.19 mmol) was dissolved in cold trifluoroacetic acid and after 45 min the solution was concentrated under reduced pressure. The residue was dissolved in ethanol (30 mL), toluene (30 mL) was added and concentrated under reduced pressure; this was repeated twice more to give a trifluoroacetate salt which was dissolved in degassed xylene–ethanol (4:1, 175 mL). The solution was heated in a sealed tube at 130 ºC under argon for 72 hours, cooled and the crude product collected by filtration and washed with methanol to give the pyrazine[6] **26** (1.56 g, 47%) as a yellow powder, mp 338-340 °C; R_f 0.63 (EtOAc); ν_{max}/cm^{-1} (film) 3402, 1545, 1436 and 1418; δ_H (300 MHz; DMSO–d_6); 11.80 (2H, s, NH), 9.14 (2H, s, 3-H), 8.40 (2H, d, *J* 8.6, 4'-H), 8.29 (2H, s, 2'-H), 7.67 (2H, s, 7'-H) and 7.29 (2H, d, *J* 8.6, 5'-H); *m/z* (ES) 469 40%, MH^+), 467 (100) and 465 (38).

2,5-Bis[6-bromo-1'-(2''-trimethylsilanylethoxymethyl)indol-3'-yl]pyrazine 27

Sodium hydride (60% dispersion in mineral oil, 360 mg, 9.03 mmol) was added to a stirred solution of the pyrazine **26** (1.69 g, 3.61 mmol) in tetrahydrofuran (75 mL). The mixture was stirred for 45 min at room temperature, cooled to 0 ºC and 2-trimethylsilylethoxymethyl chloride (1.92 mL, 10.83 mmol) added dropwise. After stirring for 90 min at room temperature, water (10 mL) was added and the mixture concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient elution: 9:1→4:1 petrol–EtOAc) to give the protected *pyrazine* **27** (1.94 g, 75%) as pale yellow plates, mp 186-188 °C (from CH_2Cl_2); R_f 0.37 (7:3 petrol–EtOAc); (Found: C, 52.6; H, 5.45; N, 7.5; Br 21.9; $C_{32}H_4N_4O_2BrSi_2$ requires C, 52.7; H, 5.53; N, 7.7; Br; 21.9%); ν_{max}/cm^{-1} (film) 3119, 2953, 2922, 2895, 1569 and 1556; δ_H (300 MHz; $CDCl_3$) 8.97 (2H, s, 3-H), 8.29 (2H, d, *J* 8.6, 4'-H), 7.78 (2H, s, 2'-H), 7.73 (2H, d, *J* 1.7, 7'-H), 7.41 (2H, dd, *J* 8.6 and 1.7 5'-H), 5.52 (4H, s, 1'-NCH_2), 3.54 (4H, t, *J* 8.1, 1''-H), 0.94 (4H, t, *J* 8.1, 2''-H), and –0.03 (18H, s, $SiMe_3$); δ_C (75 MHz; $CDCl_3$) 146.4, 140.8, 138.0, 127.8, 125.4, 124.9, 123.0, 116.9, 114.4, 113.7, 76.2, 66.4, 17.7 and –1.41; *m/z* (ES) 731 (70%, MH^+), 729 (100) and 727 (49).

(2*R,5*S**)-2,5-Bis[6-bromo-1'-(2''-trimethylsilanylethoxymethyl)indol-3'-yl]piperazine 29**

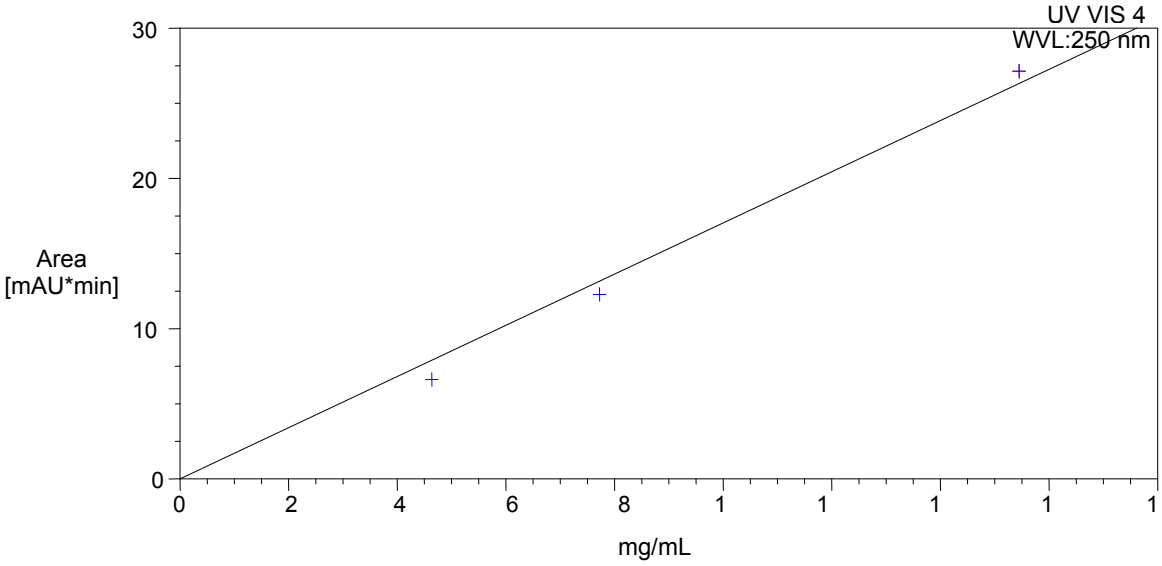
Sodium cynanoborohydride (166 mg, 2.65 mmol) was added to a stirred suspension of the pyrazine **27** (76 mg, 0.106 mmol) in dry acetic acid (15 mL). The reaction mixture was stirred for 3 hours at room temperature and concentrated under reduced pressure. The residue was partitioned between dichloromethane (25 mL) and saturated aqueous sodium hydrogencarbonate (50 mL). The aqueous layer was separated and extracted with dichloromethane (25 mL), the combined organic extracts were washed with water (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product which was purified by flash chromatography eluting with 99:1 CH_2Cl_2–MeOH/NH_3) to give the *piperazine* **29** (55 mg, 71%) as a pale yellow powder, mp 180-183 °C; R_f 0.36 (97:3 CH_2Cl_2–MeOH/NH_3); (Found: C, 52.6; H, 6.20; N, 7.6; Br, 21.9; $C_{32}H_{46}N_4O_2BrSi_2$ requires

C, 52.3; H, 6.31; N, 7.6; Br 21.8%); ν_{max}/cm^{-1} (film) 2952, 2894, 2814, 1664, 1607 and 1466; δ_H (300 MHz; $CDCl_3$) 7.65 (2H, d, *J* 8.4, 4'-H), 7.64 (2H, d, *J* 1.8, 7'-H), 7.27 (2H, dd, *J* 8.4 and 1.8, 5'-H), 7.20 (2H, s, 2'-H), 5.40 (4H, s, 1'-NCH_2), 4.27 (2H, dd, *J* 10.4 and 2.8, 2-H), 3.47 (4H, t, *J* 8.1, 1''-H), 3.39 (2H, dd, *J* 11.3 and 2.8, 3-H_AH_B), 3.05 (2H, dd, *J* 11.3 and 10.4, 3-H_AH_B), 0.90 (4H, t, *J* 8.1, 2''-H), and –0.04 (18H, s, $SiMe_3$); δ_C (75 MHz; $CDCl_3$) 137.4, 126.2, 125.3, 123.3, 120.7, 117.4, 116.1, 113.4, 75.8, 66.1, 54.1, 53.3, 17.7 and –1.42; *m/z* (ES) 737 (12%, MH^+), 735 (24), 733 (11), 619 (64), 617 (100), 615 (52), 501 (18), 499 (33) and 497 (15).

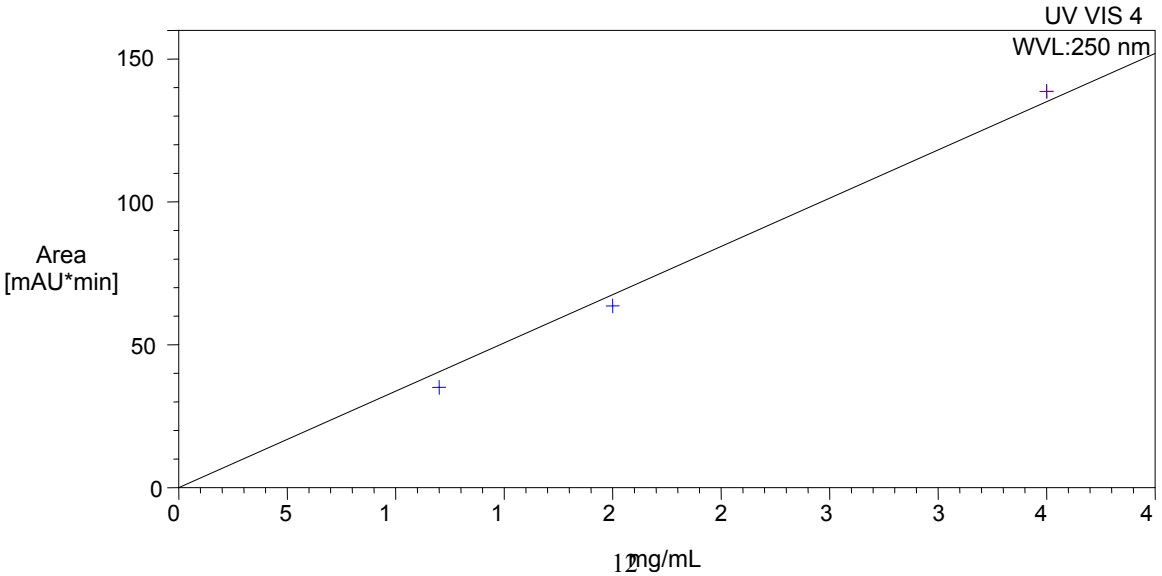
Determination of the yields of the piperazines 10a and 11 and the enantiomeric excess of the piperazine 10a by chiral analytical HPLC

Yields of the substituted piperazines **10a** and **11** were determined by analytical HPLC using a standard solution of the piperazine **10a** (30.9 mg, 0.0946 mmol) and the piperazine **11** (40.0 mg, 0.0946 mmol) chloroform (15.0 mL); the components were separated on a Chiralcel® OD column, monitoring at λ = 250 nm, eluting with 9:1 hexane–IPA, 1 mL min^{-1} over 60 min, then 3:2 hexane–IPA, 1 mL min^{-1} over 30 min; retention times: **10a**, 24.1 min and 32.5 min; **11**, 68.4 min

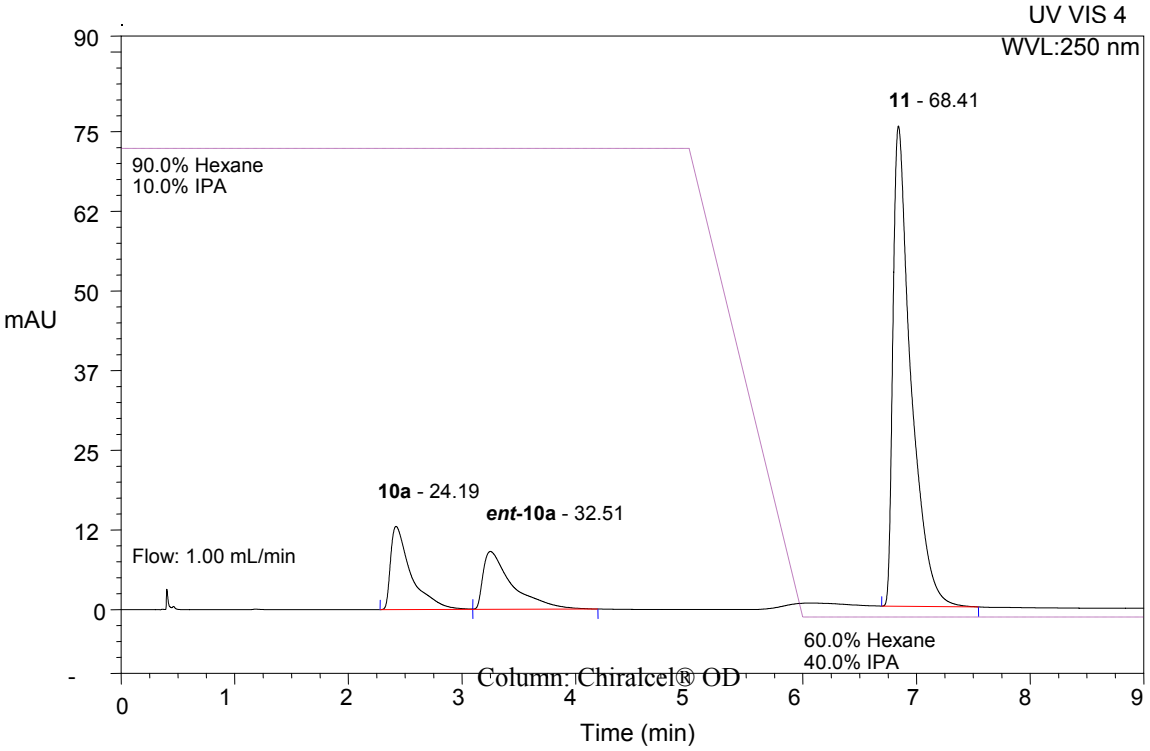
Calibration Plot for **10a**



Calibration Plot for **11**



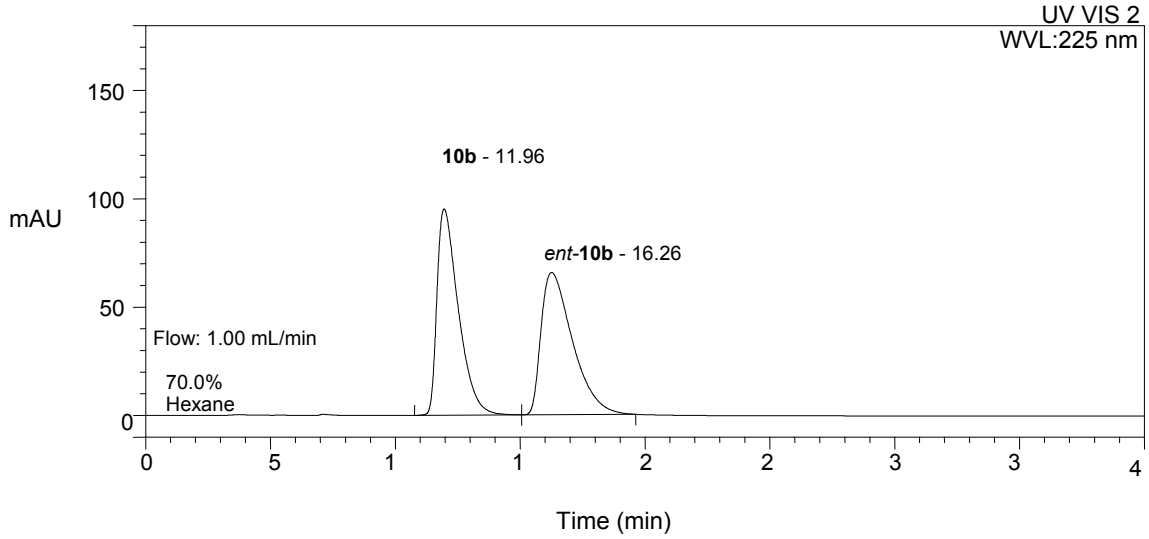
Chiral analytical HPLC trace of the standard solution



Peak	Retention Time (min)	Height (mAU)	Area (mAU*min)	Relative area (%)	Amount (mg/mL)
10a	24.19	130.562	271.42	50.29	15.93
***ent*-10a**	32.51	90.81	268.25	49.71	16.02
11	68.41	753.73	1386.70	-	41.07

Chiral analytical HPLC trace of a racemic sample of the piperazine 10b

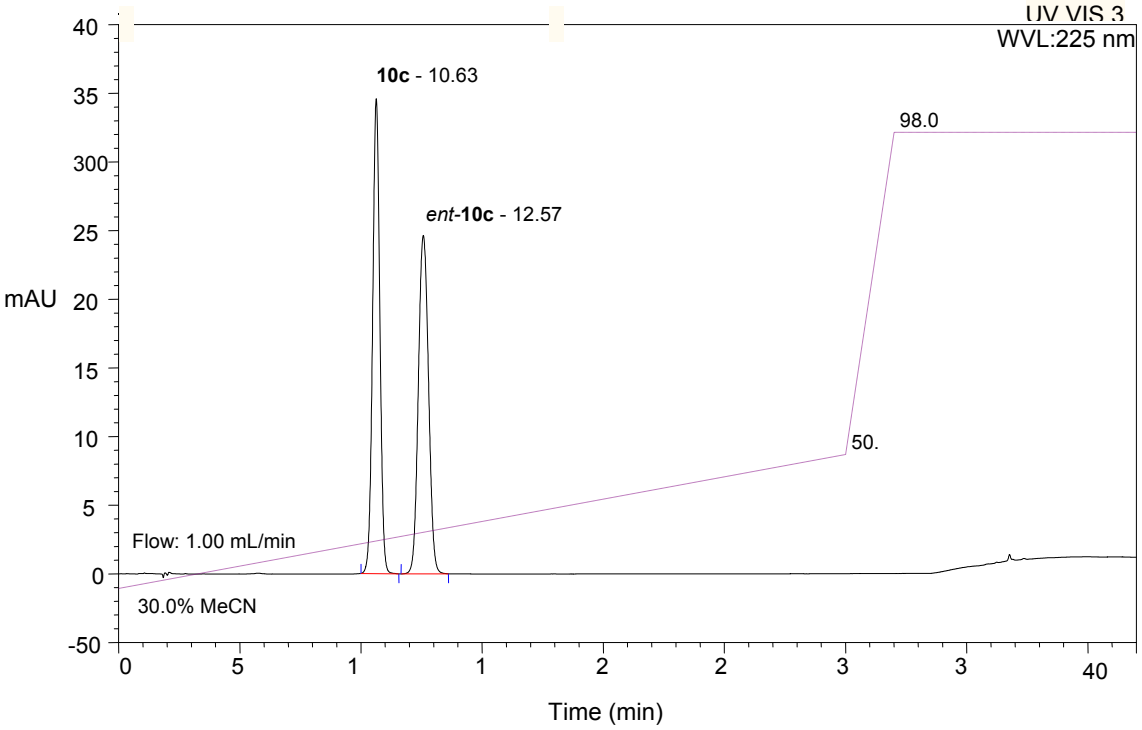
The enantiomeric excess of **10b** was determined using a Chiralcel® OD column, monitoring at λ = 225 nm, eluting with 7:3 hexane–IPA, 1 mL min^{-1} over 40 min; retention times: 12.0 min and 16.3 min).



Peak	Retention Time (min)	Height (mAU)	Area (mAU*min)	Relative area (%)
10b	11.96	953.52	945.61	49.66
ent-**10b**	16.26	657.17	958.61	50.34

Chiral analytical HPLC trace of a racemic sample of the piperazine 10c

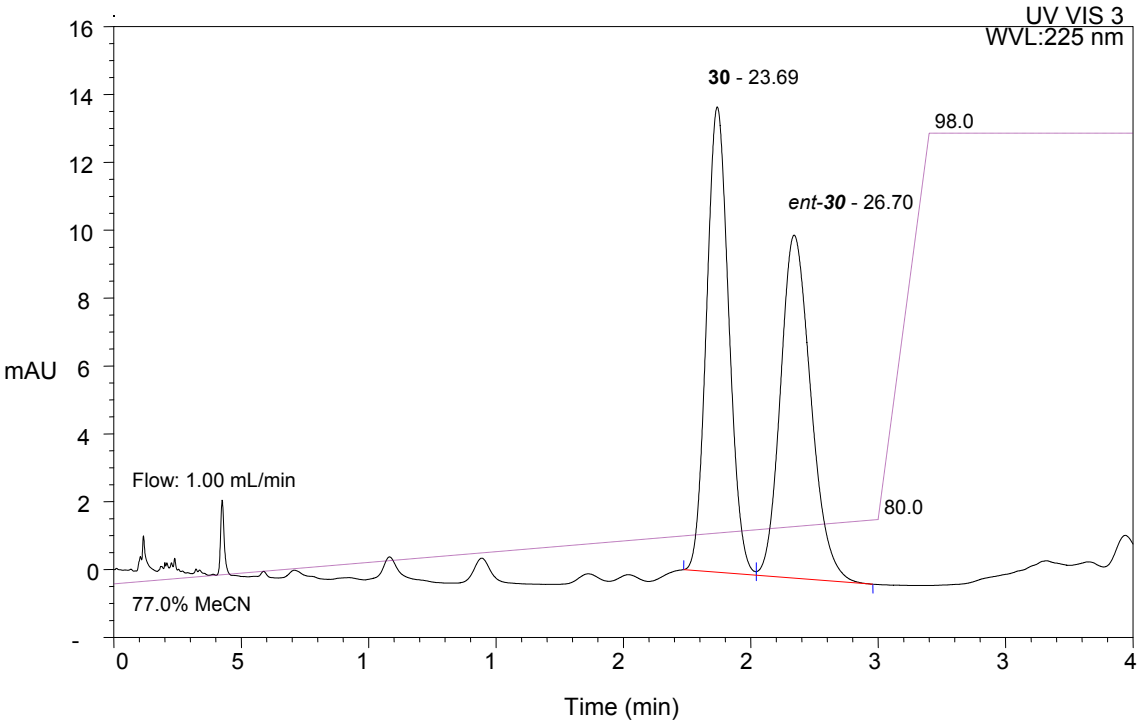
The enantiomeric excess of **10c** was determined using a Chiralcel® OD-RH column, monitoring at λ = 225 nm (gradient elution: 7:3→1:1 water–MeCN), 1 mL min^{-1} over 40 min; retention times: 10.6 min and 12.6 min.



Peak	Retention Time (min)	Height (mAU)	Area (mAU*min)	Relative area (%)
10c	10.63	345.85	119.40	49.88
ent-**10c**	12.57	246.40	119.99	50.12

Chiral analytical HPLC trace of a racemic sample of the piperazine 30

The enantiomeric excess of **30** was determined using a Chiralcel® OD-RH column, monitoring at λ = 225 nm, (gradient elution: 23:77→1:4 water–MeCN), 1 mL min^{-1} over 30 min; retention times: 23.7 min and 26.7 min.



Peak	Retention Time (min)	Height (mAU)	Area (mAU*min)	Relative area (%)
30	23.69	99.92	101.18	49.88
ent-30	26.70	73.59	101.67	50.12

References

1. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* 1978, **43**, 2923.
2. J. W. Janetka, M. S. Furness, X. Zhang, A. Coop, J. E. Folk, M. V. Mattson, A. E. Jacobson and K. C. Rice, *J. Org. Chem.* 2003, **68**, 3976.
3. T. Fujita, D. Makishima, K. Akiyama and H. Hayashi, *Biosci. Biotechnol. Biochem.* 2002, **66**, 1697.

4. H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka and S. Kobayashi, *Tetrahedron* 1992, **48**, 5691.
5. B. E. A. Burm, M. M. Meijler, J. Korver, M. J. Wanner and G. -J. Koomen, *Tetrahedron* 1998, **54**, 6135.
6. (a) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.* 2000, **2**, 3185; (b) F. Tonsiengsom, F. Y. Miyake, K. Yakushijin and D. A. Horne, *Synthesis* 2006, 49.