

Stereospecific Construction of Substituted Piperidines. Synthesis of (-)-Paroxetine and (+)-Laccarin.

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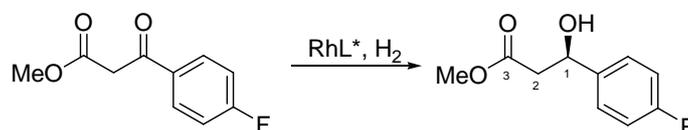
Electronic Supporting Information – 26 pages

(A) General experimental details

Starting materials sourced from commercial suppliers were used as received. Dry solvents, where necessary, were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering based on the Grubbs' design. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 °C. The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen; glassware, syringes and needles were either flame dried immediately prior to use or placed in an oven (150 °C) for at least 2 h and allowed to cool either in a desiccator or under an atmosphere of dry nitrogen; liquid reagents, solutions or solvents were added *via* syringe through rubber septa; solid reagents were added *via* Schlenk type adapters. Commercially available Merck Kieselgel 60F₂₅₄ aluminium backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence, acidic KMnO₄ solution and heat, ninhydrin stain and heat, ammonium molybdate solution and heat or iodine vapour. Flash column chromatography (FCC) was performed using Fluorochem 60 silica: 230-400 mesh (40-63 µm). The crude material was applied to the column as a solution in CH₂Cl₂ or by pre-adsorption onto silica, as appropriate. Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analysis was performed by the University of Bristol microanalytical

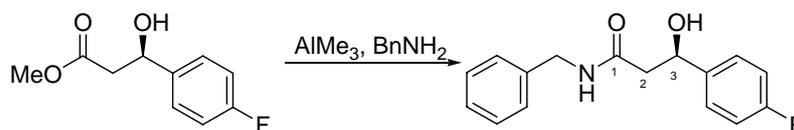
service. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad). NMR spectra were recorded on a JEOL GX270, JEOL GX400, JEOL Lambda 300, JEOL Eclipse 400, JEOL Eclipse 300 or JEOL Alpha 500 spectrometer. Chemical shifts are quoted in parts per million (ppm); ^1H NMR spectra are referenced to TMS or residual protium of the deuterated solvent; ^{13}C NMR are referenced to TMS or the deuterated solvent. Coupling constants (J) are quoted to the nearest 0.5 Hz. Other abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Assignments of ^1H NMR and ^{13}C NMR signals were made where possible, using COSY, DEPT, HMQC and HMBC experiments. Where mixtures of isomers (*e.g.* diastereomers) have been characterised together, they are referred to as *A* and *B*. Mass spectra were determined by the University of Bristol mass spectrometry service by either electron impact (EI) or chemical ionisation (CI) using a Fisons VG Analytical Autospec spectrometer, or by electrospray ionisation (ESI) using a Brüker Daltonics Apex IV spectrometer. Chiral HPLC was performed using either the racemate or the antipode as a standard on an Agilent 1100 LC system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified in each case. Chiral GC was performed using the racemate as a standard on a Hewlett-Packard 5890 Series II GC system equipped with a flame ionisation detector (FID) under the conditions noted. *N.B.* Compound numbers used in the Supplementary Information correspond to those used in the main paper.

(B) Experimental Procedures for the Synthesis of (-)-Paroxetine



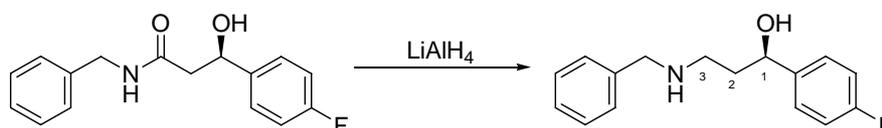
(*R*)-3-(4-Fluorophenyl)-3-hydroxypropionic acid methyl ester (6): In an Aldrich Atmosbag[®] (N_2 atmosphere), MeOH (20 mL, deoxygenated by passage of N_2 for 2 h) was added to a 50 mL r.b. flask containing β -keto ester **5** (4.00 g, 20.4 mmol) and [((*S*)-Cl-MeO-BIPHEP)Ru(*p*-cymene)Cl]Cl- CH_2Cl_2 (98 mg, 0.5 mol %) and the reaction vessel was sealed inside a hydrogenation bomb. The system was then purged

with H₂ (6 purge cycles at a pressure of 8 bar) and stirred vigorously at 60 °C for 37 h. The mixture was then cooled, depressurised, and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (50 mL), DMSO (200 μL) was added and the mixture was stirred at r.t. for 12 h. Concentration onto SiO₂ (60) and purification by FCC (EtOAc-hexanes 1:1) afforded alcohol **6** (3.84 g, 95 %, 97 % e.e.) as a pale yellow oil which darkened on standing due to traces of ruthenium derived impurities; $[\alpha]_D^{20} +32.7$ (c = 1.0, CHCl₃); ν_{\max} /cm⁻¹ (film) 3455 (br s), 2956 (m), 1724 (s), 1605 (m), 1509 (s), 1217 (s), 1156 (s), 1032 (m), 835 (s); δ_H (400 MHz, CDCl₃) 2.69-2.81 (2H, m, C2-H), 3.29 (1H, br s, C3-OH), 3.75 (3H, s, CO₂CH₃), 5.11-5.18 (1H, m, C3-H), 6.97-7.10 (2H, m, ArCH), 7.38 (2H, dd, *J* = 8.5 and 5.5, ArCH); δ_C (100 MHz, CDCl₃) 43.2 (C-2), 52.1 (CO₂CH₃), 69.8 (C-3), 115.5 (d, ²*J*_{FC} = 21.5) and 127.5 (d, ³*J*_{FC} = 7.5) (ArCH × 4), 138.3 (d, ⁴*J*_{FC} = 3.0) and 162.4 (d, ¹*J*_{FC} = 244.5) (ArC × 2), 172.8 (C-1); HRMS: (ESI⁺) Found: [M+Na]⁺ 221.0593, C₁₀H₁₁O₃FNa requires 221.0584. The enantiomeric purity of this compound was determined by chiral GC (J & W Scientific, HP-Chiral, 30 m × 0.25 mm × 0.25 μm, isothermal, 150 °C) prepared by NaBH₄ reduction of β-keto ester **5**; *t*_R (minor) = 29.2 min and *t*_R (major) = 29.9 min.



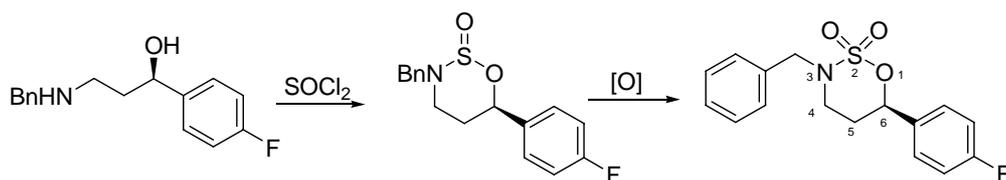
(R)-N-Benzyl-3-(4-fluorophenyl)-3-hydroxypropionamide: To an ice/salt cooled (-5 °C) solution of AlMe₃ in toluene (2.0 M, 5.05 mL) was added a solution of benzylamine (1.10 mL, 10.1 mmol) in anhydrous toluene (1 mL) dropwise, *via* syringe, over 8 minutes. During this addition the internal temperature was maintained below 10 °C. The mixture was then stirred at 10 °C for 1 h and subsequently at r.t. for a further 50 minutes before being re-cooled to -5 °C. A solution of alcohol **6** (1.00 g, 5.05 mmol) in anhydrous toluene (1 mL) was then added dropwise, *via* syringe, over 5 minutes. The mixture was stirred at -5 °C for 0.5 h and subsequently at r.t. for 14 h and then cooled to 0 °C. Water (7 mL) was added dropwise (**caution:** exotherm and vigorous gas evolution) to form a thick, colourless suspension which was adjusted to pH 5 by addition of aq. 5 M HCl. The mixture was then diluted with water (20 mL) and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed

with aq. 1 M HCl (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford the amide (1.38 g, 100 %) as a colourless solid; m.p. 104.5-106 °C (CHCl₃); [α]_D²⁰ +14.5 (c = 1.1, CHCl₃); ν_{max} /cm⁻¹ (solid) 3300 (br s), 2926 (m), 1638 (s), 1562 (m), 1510 (s), 1222 (s), 1061 (s), 1029 (s), 836 (s), 731 (s); δ_H (400 MHz, CDCl₃) 2.52-2.64 (2H, m, C2-H), 4.29 (1H, br s, C3-OH), 4.42-4.48 (2H, m, NCH₂Ph), 5.11 (1H, dd, *J* = 7.5 and 4.5, C3-H), 6.17 (1H, br s, CONHCH₂Ph), 6.95-7.09 (2H, m, ArCH), 7.17-7.38 (7H, m, ArCH); δ_C (100 MHz, CDCl₃) 43.6 (NCH₂Ph), 44.7 (C-2), 70.4 (C-3), 115.5 (d, ²J_{FC} = 20.5), 127.4 (d, ³J_{FC} = 8.5), 127.8 (2 signals) and 128.9 (ArCH × 9), 137.8, 138.8 (d, ⁴J_{FC} = 3.0) and 162.4 (d, ¹J_{FC} = 244.0) (ArC × 3), 171.6 (C-1); δ_F (283 MHz, CDCl₃) 114.9 (tt, *J* = 8.0 and 4.5); HRMS: (ESI⁺) Found: [M+Na]⁺ 296.1068, C₁₆H₁₆NO₂FNa requires 296.1057.



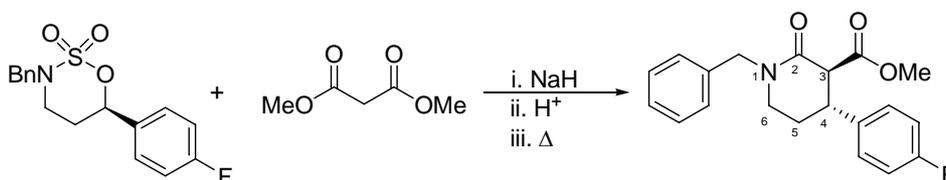
(R)-3-Benzylamino-1-(4-fluorophenyl)propan-1-ol (7): To a solution of amide (3.00 g, 11.0 mmol) in anhydrous THF (18 mL) was added dropwise, *via* syringe, over 10 minutes a solution of LiAlH₄ in THF (1.0 M, 22.0 mmol) (**caution:** exotherm). The resulting mixture was heated at reflux for 15 h and then cooled to 0 °C. Water (0.83 mL), aq. 4 M NaOH (0.83 mL) and water (2.50 mL) were then sequentially added dropwise (**caution:** exotherm and vigorous gas evolution). The resulting colourless suspension was filtered through Celite®, washing copiously with CH₂Cl₂ (*ca.* 100 mL), and then concentrated *in vacuo* to afford amino alcohol **7** (2.93 g, 100 %) as a colourless oil; [α]_D²⁰ +47.6 (c = 1.3, CHCl₃); ν_{max} /cm⁻¹ (film) 3290 (br s), 2918 (m), 2842 (m), 1603 (m), 1508 (s), 1453 (m), 1218 (s), 1075 (s), 1014 (m), 834 (s), 735 (s); δ_H (400 MHz, CDCl₃) 1.67-1.93 (2H, m, C2-H), 2.82-3.02 (2H, m, C3-H), 3.71-3.87 (2H, m, NCH₂Ph), 4.91 (1H, dd, *J* = 8.5 and 2.0, C1-H), 6.94-7.03 (2H, m, ArCH), 7.23-7.38 (7H, m, ArCH), signals attributable to C1-OH and NHCH₂Ph were not observed; δ_C (100 MHz, CDCl₃) 37.5 (C-2), 47.9 (C-3), 54.0 (NCH₂Ph), 75.3 (C-1), 115.0 (d, ²J_{FC} = 21.5), 127.2 (d, ³J_{FC} = 8.5), 127.5, 128.4 and 128.7 (ArCH × 9), 139.3, 140.0 (d, ⁴J_{FC} = 3.5) and 162.0 (d, ¹J_{FC} = 243.0) (ArC × 3);

δ_F (283 MHz, $CDCl_3$) 116.2 (tt, $J = 9.0$ and 5.5); HRMS: (ESI⁺) Found: $[M+H]^+$ 260.1453, $C_{16}H_{19}NOF$ requires 260.1445.



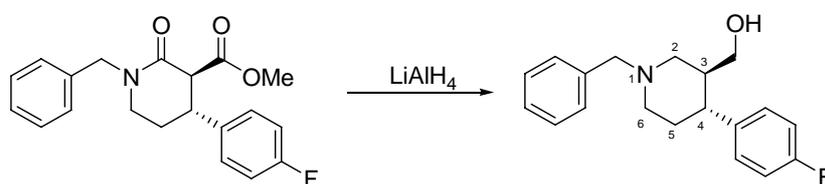
(R)-3-Benzyl-6-(4-fluorophenyl)[1,2,3]oxathiazinane-2,2-dioxide (1): To a solution of Et_3N (2.16 mL, 15.5 mmol), imidazole (1.98 g, 28.9 mmol), and amino alcohol **7** (2.00 g, 7.72 mmol) in anhydrous CH_2Cl_2 (80 mL) at -20 °C was added, *via* syringe pump, a solution of $SOCl_2$ (600 μ L, 8.15 mmol) in anhydrous CH_2Cl_2 (12.5 mL) dropwise over 30 minutes. The mixture was stirred at -20 °C for a further 30 minutes and subsequently at 0 °C for 5 h. Water (100 mL) was added and the organic portion was isolated, washed with aq. 1 M HCl (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. The residue was filtered through a pad of SiO_2 (60, eluting with EtOAc) and the eluent was concentrated *in vacuo* to afford intermediate sulfamidite (2.12 g, 96 %, 3:2 d.r.) as a pale yellow oil which solidified on standing; δ_H (400 MHz, $CDCl_3$) 1.53-1.62 (1H, m), 1.72-1.80 (1H, m), 2.11-2.35 (2H, m), 2.81 (1H, ddd, $J = 12.5, 4.5$ and 3.5), 3.35 (1H, ddd, $J = 12.5, 4.0$ and 2.0), 3.53 (1H, ddd, $J = 13.0, 12.5$ and 3.5), 3.76 (1H, d, $J = 14.0$), 3.84 (1H, ddd, $J = 13.0, 13.0$ and 3.0), 3.93 (1H, d, $J = 14.0$), 4.19 (1H, d, $J = 14.0$), 4.77 (1H, d, $J = 14.0$), 5.31 (1H, dd, $J = 11.5$ and 2.0), 5.82 (1H, d, $J = 12.0$ and 2.0), 7.01-7.11 (4H, m), 7.24-7.42 (14H, m). To an ice cooled (0 °C) solution of sulfamidite (76 mg, 0.25 mmol) in MeCN (4.5 mL) was added sequentially ($NaIO_4$ (84 mg, 0.40 mmol), $RuCl_3$ (0.2 mg, 0.25 mol %) and water (6 mL). The resulting mixture was vigorously stirred at 0 °C for 1 h after which time, careful TLC analysis showed full consumption of starting material to a slightly more polar species. The mixture was extracted with Et_2O (2×20 mL) and the combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale brown oil. This residue was filtered through a pad of SiO_2 (60, eluting with EtOAc) and the eluent was concentrated *in vacuo* to afford sulfamidate **1** (70 mg, 87 %, 97 % e.e.) as a pale yellow, crystalline solid; m.p. 118 - 119 °C (Et_2O -hexanes); $[\alpha]_D^{20}$ -16.5 ($c = 1.2, CHCl_3$); ν_{max} / cm^{-1} (solid) 2951 (w), 1607 (m), 1516 (s), 1372 (s), 1230 (m), 1174 (s), 1003 (m), 864 (s), 823 (s), 781 (m);

δ_{H} (400 MHz, CDCl_3) 1.72-1.81 (1H, m, C5-H), 2.09-2.22 (1H, m, C5-H), 3.27 (1H, ddd, $J = 14.0, 4.5$ and 2.0 , C4-H), 3.78 (1H, ddd, $J = 14.0, 13.5$ and 2.5 , C4-H), 4.40 (1H, d, $J = 14.0$, NCH_2Ph), 4.48 (1H, d, $J = 14.0$, NCH_2Ph), 5.79 (1H, dd, $J = 12.0$ and 2.0 , C6-H), 7.07-7.16 (2H, m, ArCH), 7.32-7.46 (7H, m, ArCH); δ_{C} (100 MHz, CDCl_3) 28.1 (C-5), 46.6 (C-4), 52.6 (NCH_2Ph), 85.5 (C-6), 115.9 (d, $^2J_{\text{FC}} = 21.5$), 128.3 (d, $^3J_{\text{FC}} = 8.5$), 128.5, 128.9 and 129.0 (ArCH \times 9), 133.3 (d, $^4J_{\text{FC}} = 4.0$), 135.0 and 163.2 (d, $^1J_{\text{FC}} = 247.0$) (ArC \times 3); δ_{F} (283 MHz, CDCl_3) 116.0 (tt, $J = 9.0$ and 5.5); m/z (CI^+) 322 ($[\text{M}+\text{H}]^+$, 10 %), 91 (100); HRMS: (CI^+) Found: $[\text{M}+\text{H}]^+$ 322.0907, $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{FS}$ requires 322.0913. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralpak AD-H, isocratic hexane - *i*-PrOH 85:15, 0.5 mL/min, 35 °C); t_{R} (major) = 21.4 min and t_{R} (minor) = 22.3 min.



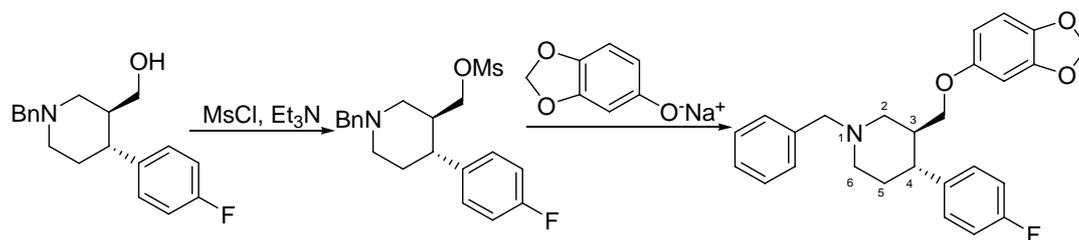
(3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid methyl ester (8): To a solution of dimethyl malonate (242 μL , 2.12 mmol) in anhydrous DMF (12 mL) was added NaH (60 % dispersion in mineral oil, 85 mg, 2.12 mmol) and the resulting mixture was stirred at r.t. for 25 minutes. Sulfamidate **1** (340 mg, 1.06 mmol) was added and the mixture was heated at 60 °C for 64 h. After cooling to r.t., aq. 5 M HCl (1.06 mL) was added and the mixture was stirred at r.t. for 2.5 h. The mixture was then neutralised with saturated aq. NaHCO_3 and extracted with CH_2Cl_2 (3 \times 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown residue which was dissolved in toluene (10 mL) and heated at reflux for 16.5 h. The mixture was then cooled to r.t. and concentrated *in vacuo* to leave a brown residue which was purified by FCC (hexanes-EtOAc 3:2) to afford lactam **8** (250 mg, 70 %, 97 % e.e.) as a colourless, crystalline solid; m.p. 97-99 °C (Et_2O -hexanes); $[\alpha]_{\text{D}}^{20}$ -8.8 ($c = 0.9$, CHCl_3); ν_{max} / cm^{-1} (film) 2952 (m), 1740 (s), 1642 (s), 1511 (s), 1494 (m), 1435 (m), 1225 (s), 1161 (s), 837 (m), 736 (m); δ_{H} (400 MHz, CDCl_3) 1.94-2.12 (2H, m, C5-H), 3.28-3.35 (1H, m, C6-H), 3.38-3.51 (2H, m, C4-H and C6-H), 3.62 (1H, d, $J = 11.0$, C3-H), 3.67 (3H, s, CO_2CH_3), 4.50 (1H, d, J

= 14.5, NCH₂Ph), 4.83 (1H, d, $J = 14.5$, NCH₂Ph), 6.98-7.06 (2H, m, ArCH), 7.13-7.21 (2H, m, ArCH), 7.26-7.42 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 29.5 (C-5), 41.9 (C-4), 46.3 (C-6), 50.6 (NCH₂Ph), 52.5 (CO₂CH₃), 115.9 (d, $^2J_{FC} = 21.5$), 127.8, 128.3, 128.4 (d, $^3J_{FC} = 9.0$), and 128.9 (ArCH $\times 9$), 136.7, 137.2 (d, $^4J_{FC} = 4.0$) and 162.1 (d, $^1J_{FC} = 244.0$) (ArC $\times 3$), 165.8 and 170.6 (C-2 and CO₂CH₃); δ_F (283 MHz, CDCl₃) 115.1 (tt, $J = 8.0$ and 5.5); HRMS: (ESI⁺) Found: [M+Na]⁺ 364.1328, C₂₀H₂₀NO₃FNa requires 364.1319. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralpak AD-H, isocratic hexane - *i*-PrOH 80:20, 1.0 mL/min, 20 °C); t_R (major) = 12.7 min and t_R (minor) = 17.0 min.



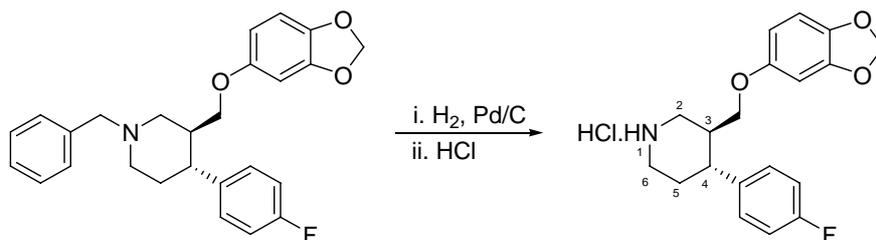
(3S,4R)-[1-Benzyl-4-(4-fluorophenyl)piperidin-3-yl]-methanol: To a solution of lactam **8** (210 mg, 0.62 mmol) in anhydrous THF (4 mL) was added dropwise, *via* syringe, over 5 minutes a solution of LiAlH₄ in THF (1.0 M, 2 mmol) (**caution:** exotherm) and the resulting mixture was heated at reflux for 20 h. The mixture was cooled to 0 °C and water (80 μ L), aq. 4 M NaOH (80 μ L) and water (240 μ L) were added sequentially (**caution:** exotherm and vigorous gas evolution). The resulting colourless suspension was filtered through Celite ®, washing with CH₂Cl₂ (40 mL), and concentrated *in vacuo* to afford the alcohol (186 mg, 100 %) as a colourless oil. *This material was used in the next stage without further purification.* An analytical sample was purified by FCC (CH₂Cl₂-MeOH-Et₃N 97:3:2): $[\alpha]_D^{20}$ -16.0 (c = 0.8, CHCl₃), $[\text{lit.}^1]$ -15.8 (c = 1.1, CHCl₃); δ_H (300 MHz, CDCl₃) 1.45-1.91 (3H, m, C5-H and C3-CH₂OH), 1.92-2.10 (3H, m, C2-H, C3-H and C6-H), 2.26-2.39 (1H, m, C4-H), 2.92-3.01 (1H, m, C6-H), 3.15-3.26 (2H, m, C2-H and C3-CH₂OH), 3.38 (1H, dd, $J = 11.0$ and 2.5, C3-CH₂OH), 3.54 (1H, d, $J = 13.0$, NCH₂Ph), 3.63 (1H, d, $J = 13.0$, NCH₂Ph), 6.94-7.02 (2H, m, ArCH), 7.12-7.39 (7H, m, ArCH); δ_C (75 MHz, CDCl₃) 29.7 (C-5), 44.2 (C-3), 44.3 (C-4), 53.9 (C-6), 57.3 (C-2), 63.5 (NCH₂Ph), 64.3 (C3-CH₂OH), 115.3 (d, $^2J_{FC} = 21.0$), 127.1, 128.2, 128.8 (d, $^3J_{FC} = 8.0$), and 129.3 (ArCH $\times 9$), 138.1, 140.1 (d, $^4J_{FC} = 3.0$) and 162.4 (d, $^1J_{FC} = 242.0$) (ArC $\times 3$); δ_F (283 MHz,

CDCl₃) 116.7 (tt, $J = 9.5$ and 5.5). The spectroscopic properties of this compound were consistent with the data available in the literature.¹



(-)-N-Benzyl paroxetine (9): To an ice-cooled (0 °C) solution of crude alcohol (161 mg, 0.54 mmol) in anhydrous CH₂Cl₂ (0.80 mL) was added sequentially, *via* syringe, Et₃N (109 μL, 0.78 mmol) and MsCl (60 μL, 0.78 mmol) resulting in the immediate formation of a colourless precipitate. The mixture was stirred at r.t. for 20 minutes, diluted with water (20 mL) and saturated aq. NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (2 × 20 mL). The combined organic portions were dried (Na₂SO₄) and concentrated *in vacuo* to afford intermediate mesylate (210 mg, *ca.* 100 %) as a yellow solid; δ_H (270 MHz, CDCl₃) 1.67-1.78 (1H, m), 1.90-2.04 (1H, m), 2.07-2.23 (1H, m), 2.24-2.37 (1H, m), 2.74 (3H, s), 2.85-2.97 (3H, m), 3.02-3.12 (1H, m), 3.76 (1H, d, $J = 13.0$), 3.55 (1H, d, $J = 13.0$), 3.71 (1H, dd, $J = 10.0$ and 6.5), 3.83 (1H, dd, $J = 10.0$ and 3.0), 6.87-6.98 (2H, m), 7.03-7.33 (7H, m). To a solution of sesamol (429 mg, 3.11 mmol) in anhydrous DMF (13 mL) was added NaH (60 % dispersion in mineral oil, 124 mg, 3.11 mmol) and the resulting mixture was stirred at r.t. for 20 minutes. Mesylate (587 mg, 1.55 mmol) was then added and the mixture was heated at 90 °C for 14 h. The mixture was then cooled to r.t., diluted with EtOAc (50 mL) and washed sequentially with water (25 mL), aq. 1 M NaOH (2 × 25 mL) and brine (25 mL). The organic portion was dried (Na₂SO₄) and concentrated *in vacuo* to afford a residue which was purified by FCC (hexanes-EtOAc 3:1-0:1) to yield *N*-benzyl paroxetine **9** (338 mg, 52 %) as a pale yellow oil; [α]_D²⁰ -49.1 (c = 0.6, CHCl₃); δ_H (400 MHz, CDCl₃) 1.73-1.91 (2H, m, C5-H), 2.04-2.14 (2H, m, C2-H and C6-H), 2.15-2.26 (1H, m, C3-H), 2.47 (1H, ddd, $J = 11.0$, 11.0 and 4.5 , C4-H), 2.95-3.03 (1H, m, C6-H), 3.21-3.28 (1H, ddd, $J = 11.0$, 3.5 and 2.0 , C2-H), 3.43 (1H, dd, $J = 9.5$ and 7.0 , C3-CH₂OAr), 3.51-3.57 (2H, m, C3-CH₂OAr and NCH₂Ph), 3.64 (1H, d, $J = 13.0$, NCH₂Ph), 5.87 (2H, s, OCH₂O), 6.10 (1H, dd, $J = 8.5$ and 2.5 , ArCH), 6.31 (1H, d, $J = 2.5$, ArCH), 6.61 (1H, d, $J = 8.5$, ArCH), 6.92-6.99 (2H, m, ArCH), 7.11-

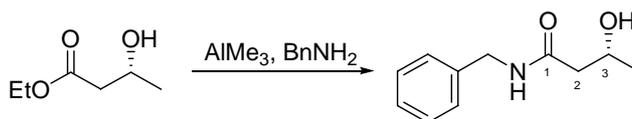
7.19 (2H, m, ArCH), 7.24-7.38 (5H, m, ArCH); δ_C (100 MHz, $CDCl_3$) 34.4 (C-5), 42.3 (C-4), 44.2 (C-3), 53.9 (C-6), 57.7 (C-2), 63.5 (NCH₂Ph), 69.7 (C3-CH₂OAr), 98.1 (ArCH \times 1), 101.2 (OCH₂O), 105.7, 107.9, 115.4 (d, $^2J_{FC} = 20.5$), 127.2, 128.4, 129.0 (d, $^3J_{FC} = 8.0$), and 129.4 (ArCH \times 11), 138.2, 139.9 (d, $^4J_{FC} = 4.0$), 141.6, 148.2, 154.5 and 161.6 (d, $^1J_{FC} = 243.0$) (ArC \times 6). *The spectroscopic properties of this compound were consistent with the data available in the literature.*²



(-)-Paroxetine (2): A suspension of 10 % Pd/C (100 mg) and *N*-benzyl paroxetine **9** (290 mg, 0.69 mmol) in AcOH (2 mL) and *i*-PrOH (5 mL) was sealed inside a hydrogenation bomb. The vessel was purged with hydrogen (6 purge cycles at 6 bar) and heated at 50 °C for 15 h. The mixture was cooled to r.t. and then depressurised, filtered through Celite ®, washing with AcOH (20 mL), MeOH (20 mL) and CH₂Cl₂ (20 mL), and concentrated *in vacuo* to afford a colourless oil. This was dissolved in saturated aq. Na₂CO₃ solution (20 mL) and extracted with CH₂Cl₂ (5 \times 25 mL). The organic extracts were dried (Na₂SO₄), concentrated *in vacuo* to afford free amine (219 mg, 96 %) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.65-1.76 (2H, m), 1.81 (1H, ddd, $J = 13.0, 4.0, 2.5$ and 2.5), 2.01-2.11 (1H, m), 2.58 (1H, ddd, $J = 11.5, 11.5$ and 4.0), 2.67 (1H, dd, $J = 12.0$ and 11.0), 2.74 (1H, ddd, $J = 12.0, 12.0$ and 3.0), 3.15-3.21 (1H, m), 3.39-3.46 (2H, m), 3.57 (1H, dd, $J = 9.5$ and 3.0), 5.87 (2H, s), 6.11 (1H, dd, $J = 8.5$ and 2.5), 6.34 (1H, d, $J = 2.5$), 6.62 (1H, d, $J = 8.5$), 6.94-7.00 (2H, m), 7.13-7.19 (2H, m). This oil was dissolved in *i*-PrOH (10 mL), treated with aq. 5 M HCl (0.20 mL) and concentrated *in vacuo* (azeotroping with EtOH (2 \times 25 mL)) to afford the title compound **2** (242 mg, 96 %) as a colourless foam. This material was crystallised from *i*-PrOH and then dried (60 °C, 15 mmHg, 12 h) to afford (-)-paroxetine **2** (207 mg, 82 %) as colourless needles; m.p. 121-123 °C (*i*-PrOH), [lit.³ 128-132 °C (*i*-PrOH)]; $[\alpha]_D^{20} -78.1$ (c = 1.0, MeOH), [lit.⁴ $[\alpha]_D^{20} -86.5$ (c = 1.0, MeOH); lit.⁵ $[\alpha]_D^{22} -80.8$ (c = 1.3, MeOH)]; δ_H (400 MHz, $CDCl_3$) 2.04 (1H, m, C5-H), 2.39 (1H, ddd, $J = 13.0, 13.0$ and 13.0, C5-H), 2.59-2.70 (1H, m, C3-H), 2.92

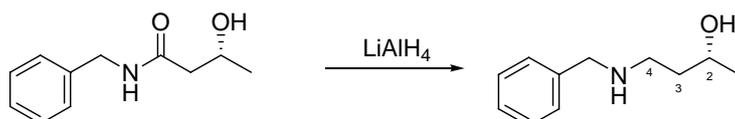
(1H, ddd, $J = 13.0, 11.5$ and 3.0 , C4-H), 2.96-3.09 (1H, m, C6-H), 3.09-3.23 (1H, m, C2-H), 3.49 (1H, dd, $J = 10.0$ and 4.5 , C3-OCH₂Ar), 3.60 (1H, dd, $J = 10.0$ and 2.5 , C3-OCH₂Ar), 3.63-3.77 (2H, m, C2-H and C6-H), 5.89 (2H, s, OCH₂O), 6.12 (1H, dd, $J = 8.5$ and 2.5 , ArCH), 6.34 (1H, d, $J = 2.5$, ArCH), 6.62 (1H, d, $J = 8.5$, ArCH), 7.00 (2H, dd, $J = 8.5$ and 8.5 , ArCH), 7.21 (2H, dd, $J = 8.5$ and 5.5 , ArCH), 9.23 (2H, br s, NH₂) δ_C (100 MHz, CDCl₃) 30.0 (C-5), 39.4 (C-4), 41.7 (C-3), 44.5 (C-6), 46.8 (C-2), 67.5 (C3-CH₂OAr), 97.9 (ArCH \times 1), 101.2 (OCH₂O), 105.6, 107.9, 115.8 (d, $^2J_{FC} = 21.0$), 128.9 (d, $^3J_{FC} = 8.0$) (ArCH \times 6), 137.0 (d, $^4J_{FC} = 4.0$), 142.1, 148.2, 153.7 and 162.0 (d, $^1J_{FC} = 245.0$) (ArC \times 5). *The spectroscopic properties of this compound were consistent with the data available in the literature.*⁴

(C) Experimental Procedures for the Synthesis of (+)-Laccarin

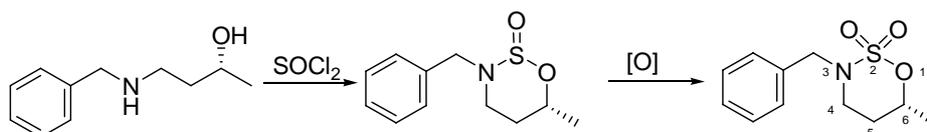


(R)-N-Benzyl-3-hydroxybutanamide (11): To an ice/salt cooled (-5 °C) solution of AlMe₃ in toluene (2.0 M, 34.1 mL) was added a solution of benzylamine (7.45 mL, 68.2 mmol) in anhydrous toluene (7 mL) dropwise, *via* syringe, over 10 minutes. During this addition the internal temperature was maintained below 10 °C. The mixture was then stirred at 10 °C for 1 h and subsequently at r.t. for a further 50 minutes before being re-cooled to -5 °C. A solution of alcohol **10** (4.50 g, 34.1 mmol) $\{[\alpha]_D^{20} -42.0$ ($c = 1.0$, CHCl₃); lit.⁶ $[\alpha]_D^{20} -44.4$ ($c = 1.4$, CHCl₃) $\}$ in anhydrous toluene (7 mL) was then added dropwise, *via* syringe, over 10 minutes. The mixture was stirred at -5 °C for 0.5 h and subsequently at r.t. for 15 h and then cooled to 0 °C. Water (40 mL) was added dropwise (**caution:** exotherm and vigorous gas evolution) to form a thick, colourless suspension which was adjusted to pH 5 by addition of aq. 5 M HCl. The mixture was then diluted with water (40 mL) and extracted with EtOAc (4 \times 200 mL). The combined organic extracts were washed with aq. 1 M HCl (100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford amide **11** (5.81 g, 88 %) as a colourless, crystalline solid; m.p. 83-83 °C (CHCl₃); $[\alpha]_D^{20} -10.1$ ($c = 0.8$, CHCl₃); ν_{max} /cm⁻¹ (film) 3296 (br s), 2972 (m), 1634 (s), 1552 (s),

1426 (m), 1132 (m), 1082 (m), 947 (m), 847 (m); δ_{H} (400 MHz, CDCl_3) 1.20 (3H, d, $J = 6.5$, C4-H), 2.24-2.39 (2H, m, C2-H), 3.90 (1H, br s, C3-OH), 4.13-4.23 (1H, m, C3-H), 4.42 (2H, *app.* d, $J = 5.5$, NCH_2Ph), 6.35 (1H, br s, CONHCH_2Ph), 7.21-7.37 (5H, m, ArCH); δ_{C} (100 MHz, CDCl_3) 22.8 (C-4), 43.4 (NCH_2Ph), 43.9 (C-2), 64.8 (C-3), 127.5, 127.7 and 128.7 (ArCH \times 5), 137.9 (ArC), 172.2 (C-1); HRMS: (ESI^+) Found: $[\text{M}+\text{H}]^+$ 194.1179, $\text{C}_{11}\text{H}_{16}\text{NO}_2$ requires 194.1176.

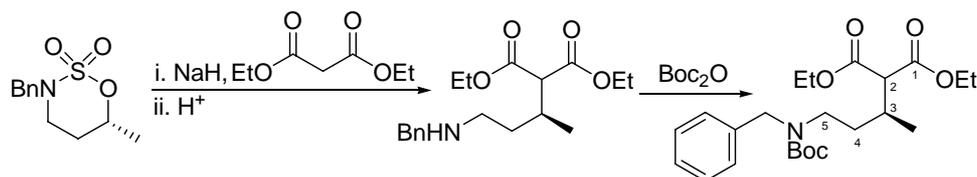


(R)-4-Benzylaminobutan-2-ol; To a solution of amide **11** (5.70 g, 29.5 mmol) in anhydrous THF (57 mL) was added dropwise, *via* syringe, over 10 minutes a solution of LiAlH_4 in THF (1.0 M, 50.0 mmol) (**caution:** exotherm). The resulting mixture was heated at reflux for 15.5 h and then cooled to 0 °C. Water (1.90 mL), aq. 4 M NaOH (1.90 mL) and water (5.70 mL) were then sequentially added dropwise (**caution:** exotherm and vigorous gas evolution). The resulting colourless suspension was filtered through Celite®, washing copiously with CH_2Cl_2 (*ca.* 100 mL), and then concentrated *in vacuo* to afford the amino alcohol (5.35 g, 98 %) as a colourless oil; $[\alpha]_{\text{D}}^{20} +21.1$ ($c = 0.6$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3295 (br s), 2843 (m), 1739 (m), 1453 (s), 1371 (s), 1103 (s); δ_{H} (400 MHz, CDCl_3) 1.13 (3H, d, $J = 6.0$, C1-H), 1.41-1.66 (2H, m, C3-H), 2.74 (1H, ddd, $J = 12.0, 10.5$ and 3.5 , C4-H), 2.96 (1H, ddd, $J = 12.0, 4.0$ and 3.5 , C4-H), 3.55 (2H, br s, NHCH_2Ph and C2-OH), 3.70 (1H, d, $J = 13.0$, NCH_2Ph), 3.78 (1H, d, $J = 13.0$, NCH_2Ph), 3.90-3.99 (1H, m, C2-H), 7.18-7.33 (5H, m, ArCH); δ_{C} (100 MHz, CDCl_3) 23.4 (C-1), 36.6 (C-3), 48.1 (C-4), 53.6 (NCH_2Ph), 69.4 (C-2), 127.1, 128.1 and 128.4 (ArCH \times 5), 139.1 (ArC); m/z (CI^+) 180 ($[\text{M}+\text{H}]^+$, 73 %), 91 (100); HRMS: (CI^+) Found: $[\text{M}+\text{H}]^+$ 180.1381, $\text{C}_{11}\text{H}_{18}\text{NO}$ requires 180.1388.



(R)-3-Benzyl-6-methyl-[1,2,3]-oxathiazinane-2,2-dioxide (3); To a solution of Et₃N (7.72 mL, 55.4 mmol), imidazole (7.07 g, 103.9 mmol), and amino alcohol (4.97 g, 27.8 mmol) in anhydrous CH₂Cl₂ (280 mL) at -20 °C was added, *via* syringe pump, a solution of SOCl₂ (2.13 mL, 29.2 mmol) in anhydrous CH₂Cl₂ (40 mL) dropwise over 1 h. The mixture was stirred at -20 °C for a further 1 h and subsequently at 0 °C for 12 h. Water (200 mL) was added and the organic portion was isolated, washed with aq. 1 M HCl (200 mL), brine (200 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford a yellow oil. This residue was filtered through a pad of SiO₂ (60, eluting with EtOAc) and the eluent was concentrated *in vacuo* to afford intermediate sulfamidite (5.22 g, 84 %) as a pale yellow oil; δ_H (400 MHz, CDCl₃) 1.21 (3H, d, *J* = 6.5), 1.28-1.37 (4H, m), 1.46-1.54 (1H, m), 1.71 (1H, ddd, *J* = 14.0, 11.5 and 5.0), 1.86 (1H, ddd, *J* = 13.5, 12.5 and 4.5), 2.60 (1H, ddd, *J* = 12.5, 4.5 and 3.5), 3.17-3.31 (2H, m), 3.52-3.63 (2H, m), 3.73 (1H, d, *J* = 14.0), 4.06 (1H, d, *J* = 14.0), 4.39 (1H, dqd, *J* = 10.0, 6.5 and 3.0), 4.59 (1H, d, *J* = 14.0), 4.90 (1H, dqd, *J* = 11.5, 6.5 and 4.5), 7.16-7.32 (10H, m). To an ice cooled (0 °C) solution of sulfamidite (6.80 g, 30.2 mmol) in MeCN (545 mL) was added sequentially NaIO₄ (10.3 g, 48.3 mmol), RuCl₃ (30 mg, 0.25 mol %) and water (740 mL). The resulting mixture was vigorously stirred at 0 °C for 40 minutes after which time, careful TLC analysis showed full consumption of starting material to a slightly more polar species. The mixture was extracted with Et₂O (3 × 500 mL) and the combined organic portions were washed with water (400 mL), brine (400 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford a pale brown oil. This residue was dissolved in CH₂Cl₂ (100 mL) and DMSO (300 μL) was added. After stirring at r.t. for 2 h the mixture was pre-adsorbed onto SiO₂ (60) and purified by short FCC (EtOAc-hexanes 1:1) to afford sulfamidate **3** (6.17 g, 85 %, > 98 % e.e.) as a pale yellow, crystalline solid; 96-97.5 °C (EtOAc-hexanes); [α]_D²⁰ +16.8 (c = 1.0, CHCl₃); ν_{max} /cm⁻¹ (film) 2971 (m), 1739 (s), 1455 (m), 1377 (s), 1183 (s), 1094 (m), 873 (s); δ_H (400 MHz, CDCl₃) 1.45 (3H, d, *J* = 6.0, C6-CH₃), 1.54-1.63 (1H, m, C5-H), 1.79-1.93 (1H, m, C5-H), 3.15 (1H, ddd, *J* = 14.0, 4.5 and 2.0, C4-H), 3.60 (1H, ddd, *J* = 14.0, 14.0 and 3.0, C4-H), 4.29 (1H, d, *J* = 14.0, NCH₂Ph), 4.35 (1H, d, *J* = 14.0, NCH₂Ph), 4.98 (1H, dqd, *J* = 12.5, 6.0 and 2.0, C6-H), 7.31-7.44 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 21.2 (C6-CH₃), 27.7 (C-5), 46.4 (C-4), 52.2 (NCH₂Ph), 82.1 (C-6), 128.2, 128.6 and 128.7 (ArCH × 5), 135.1 (ArC); HRMS: (ESI⁺) Found: [M+H]⁺ 242.0851, C₁₁H₁₆NO₃S requires 242.0845. The enantiomeric purity of this

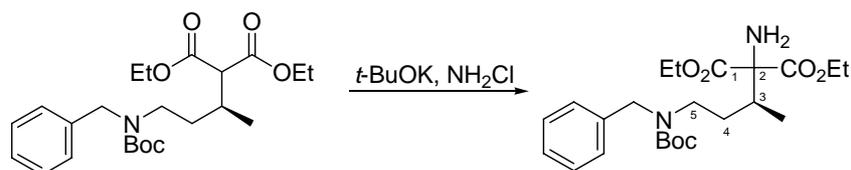
compound was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexane - *i*-PrOH 97:3, 1.0 mL/min, 20 °C); t_R (major) = 63.1 min and t_R (minor) = 49.4 min.



(*S*)-2-[3-(Benzyl-*tert*-butoxycarbonylamino)-1-methylpropyl]-malonic acid diethyl ester (13**);** To a solution of diethyl malonate (7.61 mL, 50.1 mmol) in anhydrous DMF (290 mL) was added in one portion NaH (60 % dispersion in mineral oil, 1.96 g, 48.9 mmol) and the mixture was stirred at r.t. for 30 minutes to form a clear solution. Sulfamidate **3** (6.04 g, 25.1 mmol) was then added and the mixture was heated at 110 °C for 30 h. The mixture was then cooled to r.t. and aq. 5 M HCl (25 mL) was added. After stirring at r.t. for 2 h the mixture was concentrated *in vacuo* to afford a brown oil. This residue was dissolved in aq. 0.1 M HCl (200 mL), washed with Et₂O (2 × 200 mL) and then neutralised by addition of saturated aq. NaHCO₃. The mixture was then extracted with CH₂Cl₂ (3 × 200 mL) and the combined organic extracts were washed with brine (200 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford crude amine **12** (6.90 g, 21.5 mmol) as an orange oil; δ_H (400 MHz, CDCl₃) 0.97 (3H, t, $J = 7.0$), 1.24 (6H, t, $J = 7.0$), 1.35-1.47 (1H, m), 1.58-1.69 (1H, m), 2.27-2.39 (1H, m), 2.58-2.73 (2H, m), 3.25 (1H, d, $J = 8.0$), 3.76 (2H, AB q, $J = 13.0$), 4.16 (4H, q, $J = 7.0$), 7.18-7.35 (5H, m), a signal attributable to NH was not observed. This material was then immediately dissolved in MeCN (100 mL) and NaHCO₃ (3.65 g, 43.5 mmol) and Boc₂O (4.50 g, 21.5 mmol) were sequentially added. After stirring at r.t. for 3 h the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with water (100 mL) and then brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford an orange oil. Purification by short FCC (EtOAc-hexanes 1:1) afforded protected amine **13** (8.58 g, 81 %) as a colourless oil; $[\alpha]_D^{20}$ -4.3 ($c = 0.9$, CHCl₃); ν_{\max} /cm⁻¹ (film) 2979 (m), 1750 (m), 1730 (s), 1689 (s), 1367 (s), 1239 (s), 1162 (s), 1119 (s), 1029 (s); δ_H (400 MHz, CDCl₃) 0.92-1.03 (3H, m, C3-CH₃), 1.24 (6H, *app.* t, $J = 7.0$, CO₂CH₂CH₃), 1.36-1.55 (10H, m, NCO₂C(CH₃)₃ and C4-H), 1.59-1.73 (1H, m, C4-H), 2.11-2.27 (1H, m, C3-H), 3.05-3.39 (3H, m, C2-H and C5-H), 4.11-4.20 (4H, m, CO₂CH₂CH₃), 4.32-4.49 (2H, m,

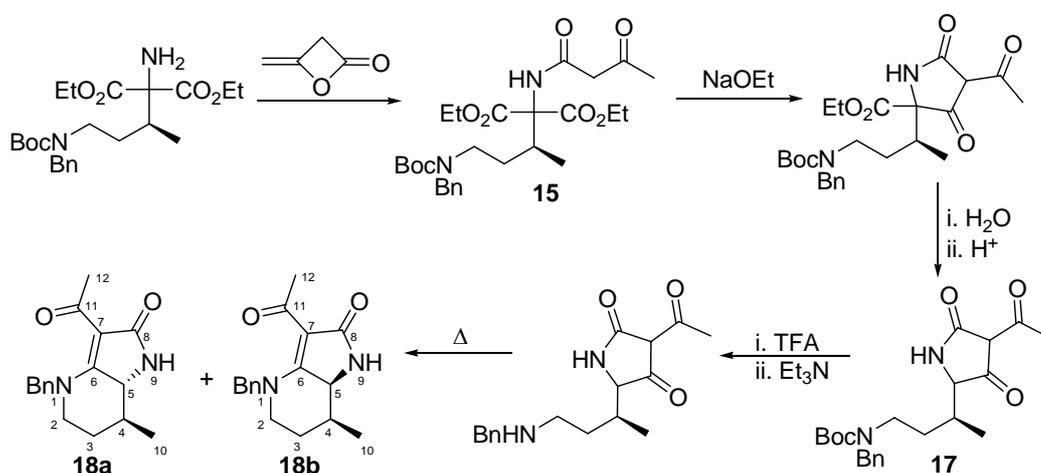
NCH₂Ph), 7.15-7.34 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 14.1 (2 × CO₂CH₂CH₃), 17.0 (C3-CH₃), 28.5 (NCO₂C(CH₃)₃), 31.1 (C-3), *ca.* 32.3 (br, C-4), 44.2 (C-5), *ca.* 50.0 (br, NCH₂Ph), 57.5 (C-2), 61.1 and 61.2 (CO₂CH₂CH₃), 79.7 (NCO₂C(CH₃)₃), 127.2, *ca.* 127.5 (br) and 128.5 (ArCH × 5), 138.6 (ArC), *ca.* 155.8 (br, NCO₂C(CH₃)₃), 168.6 and 168.7 (CO₂CH₂CH₃); HRMS: (ESI⁺) Found: 444.2366 [M+Na]⁺, C₂₃H₃₅NO₆Na requires 444.2357. NMR analysis of this compound was complicated due to N-Boc resonance.

Preparation of anhydrous, ethereal monochloramine solution (*ca.* 0.15 M);⁷ To a cooled (-5 °C) suspension of NH₄Cl (3.00 g) in Et₂O (100 mL) was added, in one portion, concentrated aq. ammonia solution (4.70 mL). Sodium hypochlorite solution (72 mL) was then added dropwise over 15 minutes, whilst maintaining an internal temperature of less than 5 °C, and the mixture was stirred at -5 °C for a further 15 minutes. The organic portion was then isolated, washed with brine (50 mL) and then dried in a freezer over CaCl₂ for 2 h prior to use.



(S)-2-Amino-2-[3-(benzyl-*tert*-butoxycarbonylamino)-1-methylpropyl]-malonic acid diethyl ester (14); To a solution of protected amine **13** (282 mg, 0.67 mmol) in anhydrous THF (5 mL) was added *t*-BuOK (77 mg, 0.96 mmol) and the resulting suspension was stirred at r.t. for 10 minutes to form a colourless solution. The mixture was then cooled to 0 °C and NH₂Cl in Et₂O (*ca.* 0.15 M, 1.05 mmol) was added rapidly *via* syringe. The reaction mixture was stirred at 0 °C for 2 h and subsequently at r.t. for 30 minutes prior to the addition of saturated aq. NaHCO₃ (25 mL). The mixture was extracted with CH₂Cl₂ (2 × 25 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford a colourless oil. Purification by FCC (EtOAc-hexanes 8:3 – 1:0) afforded recovered starting material **13** (64 mg, 23 %) as a colourless oil and subsequently aminated adduct **14** (219 mg, 75 %) as a colourless oil; [α]_D²⁰ +10.8 (c = 0.7, CHCl₃); ν_{max} /cm⁻¹ (film) 3398 (w), 2977 (s), 1737 (s), 1691 (s), 1416 (m), 1366 (m), 1240 (s), 1169 (s); δ_H (400 MHz, CDCl₃)

0.83-0.94 (3H, m, C3-CH₃), 1.20-1.28 (6H, m, CO₂CH₂CH₃), 1.36-1.66 (11H, m, NCO₂C(CH₃)₃ and C4-H), 1.87 (2H, s, NH₂), 2.27-2.39 (1H, m, C3-H), 3.05-3.36 (2H, m, C5-H), 4.13-4.24 (4H, m, CO₂CH₂CH₃), 4.29-4.58 (2H, m, NCH₂Ph), 7.14-7.34 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 14.1 (2 signals) (C3-CH₃ and CO₂CH₂CH₃), 28.5 (NCO₂C(CH₃)₃), *ca.* 30.1 (br, C-4), 35.7 (C-3), 44.6 (C-5), *ca.* 49.6 (br, NCH₂Ph), 61.9 (CO₂CH₂CH₃), 70.2 (C-2), 79.6 (NCO₂C(CH₃)₃), 127.2, *ca.* 127.5 (br) and 128.5 (ArCH × 5), 138.5 (br, ArC), *ca.* 155.8 (br, NCO₂C(CH₃)₃), 171.1 and 171.2 (CO₂CH₂CH₃); *m/z* (CI⁺) 437 ([M+H]⁺, 5 %), 337 (100); HRMS: (CI⁺) Found: [M+H]⁺ 437.2644, C₂₃H₃₇N₂O₆ requires 437.2651. *NMR analysis of this compound was complicated due to N-Boc resonance.*



N-Benzyl laccarin (18a) and 5-*epi*-N-benzyl laccarin (18b); To a solution of amine **14** (1.96 g, 4.49 mmol) in anhydrous THF (50 mL) was added diketene (419 μL, 5.50 mmol) and then DMAP (35 mg, 0.29 mmol) and the mixture was heated at 60 °C for 1 h. The mixture was then cooled to r.t., concentrated *in vacuo* and filtered through a pad of SiO₂ (eluting with EtOAc) and concentrated *in vacuo* to afford acylated intermediate **15** as a yellow oil. This residue was then dissolved in anhydrous 0.3 M NaOEt in EtOH (70 mL) and heated at 60 °C for 1.5 h. Water (14 mL) was added and heating was continued for a further 1 h. Aq. 5 M HCl (14 mL) was then added, the mixture was immediately cooled to r.t. and then extracted with CH₂Cl₂ (2 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford crude intermediate **17** (1.77 g) as an orange foam. This residue was dissolved in CH₂Cl₂ (20 mL), TFA (20 mL) was added and the

mixture was stirred at r.t. for 35 minutes. The mixture was then concentrated *in vacuo* and residual TFA was removed by azeotrope with CHCl_3 (2×20 mL). The mixture was then re-dissolved in CHCl_3 (20 mL), Et_3N (1.87 mL, 13.5 mmol) was added and the resulting solution was concentrated *in vacuo*. The brown residue thus obtained was suspended in toluene (120 mL) and heated at 80°C for 12 h. The mixture was then cooled to r.t., diluted with EtOAc (200 mL) and washed with aq. 1 M HCl (2×150 mL). The aqueous extracts were then back extracted with CH_2Cl_2 (4×100 mL). The organic extracts were combined, washed with brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. Purification by FCC (EtOAc-MeOH 14:1 - 9:1) afforded *N*-benzyl laccarin **18a** (682 mg, 53 %) and subsequently 5-*epi-N*-benzyl laccarin **18b** (195 mg, 15 %) as brown foams which were homogeneous by TLC and NMR and suitable for use in the next step without further purification. Repeated FCC failed to yield colourless material but analytical samples could be obtained by recrystallisation (EtOAc-hexanes).

Data for *N*-Benzyl laccarin **18a**; 138-139 $^\circ\text{C}$ (EtOAc-hexanes); $[\alpha]_{\text{D}}^{20} +131.2$ ($c = 1.3$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3192 (m), 2926 (m), 1668 (s), 1633 (s), 1557 (s), 1453 (m), 1342 (m), 1261 (m), 1091 (m); δ_{H} (400 MHz, CDCl_3) 1.18 (3H, d, $J = 7.0$, C10-H), 1.26-1.36 (1H, m, C4-H), 1.52-1.64 (1H, m, C3-H), 1.81-1.91 (1H, m, C3-H), 2.50 (3H, s, C12-H), 3.27-3.42 (2H, m, C2-H), 3.64 (1H, d, $J = 10.5$, C5-H), 4.97 (1H, d, $J = 15.0$, NCH₂Ph), 5.23 (1H, d, $J = 15.0$, NCH₂Ph), 6.06 (1H, br s, NH), 7.14-7.18 (2H, m, ArCH), 7.24-7.35 (3H, m, ArCH); δ_{C} (100 MHz, CDCl_3) 19.9 (C-10), 27.2 (C-3), 30.2 (C-12), 31.7 (C-4), 47.8 (C-2), 58.6 (NCH₂Ph), 59.2 (C-5), 101.5 (C-7), 127.7 (2 signals) and 128.7 (ArCH $\times 5$), 136.5 (ArC), 168.1 (C-6), 174.2 (C-8), 195.6 (C-11); HRMS: (ESI⁺) Found: $[\text{M}+\text{H}]^+$ 285.1609, $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2$ requires 285.1598.

Crystal data for 18a: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$, $M = 284.35$, monoclinic, $a = 9.6357(16)$, $b = 14.869(3)$, $c = 10.9996(17)$ Å, $\beta = 103.461(5)^\circ$, $V = 1532.6(5)$ Å³, $T = 100$ K, space group $P2_1$, $Z = 4$, $\mu = 0.651$ mm⁻¹, $R_{\text{int}} = 0.0646$ (for 8214 measured reflections), $R_1 = 0.0647$ [for 3459 unique reflections with $>2\sigma(I)$], $wR_2 = 0.1783$ (for all 3909 unique reflections). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data request/cif](http://www.ccdc.cam.ac.uk/data_request/cif) (CCDC 621099).

The relative stereochemistry of **18a** was unambiguously characterised by an X-ray diffraction study. The asymmetric unit of the structure contains two molecules of identical stereochemistry that differ slightly (in the region associated with the *N*-benzyl group) due to packing forces. It was not possible to determine the absolute stereochemistry of **18a** from the diffraction data and the absolute structure was assigned based on the use of ethyl (*3R*)-hydroxybutyrate **10** (Scheme 3).

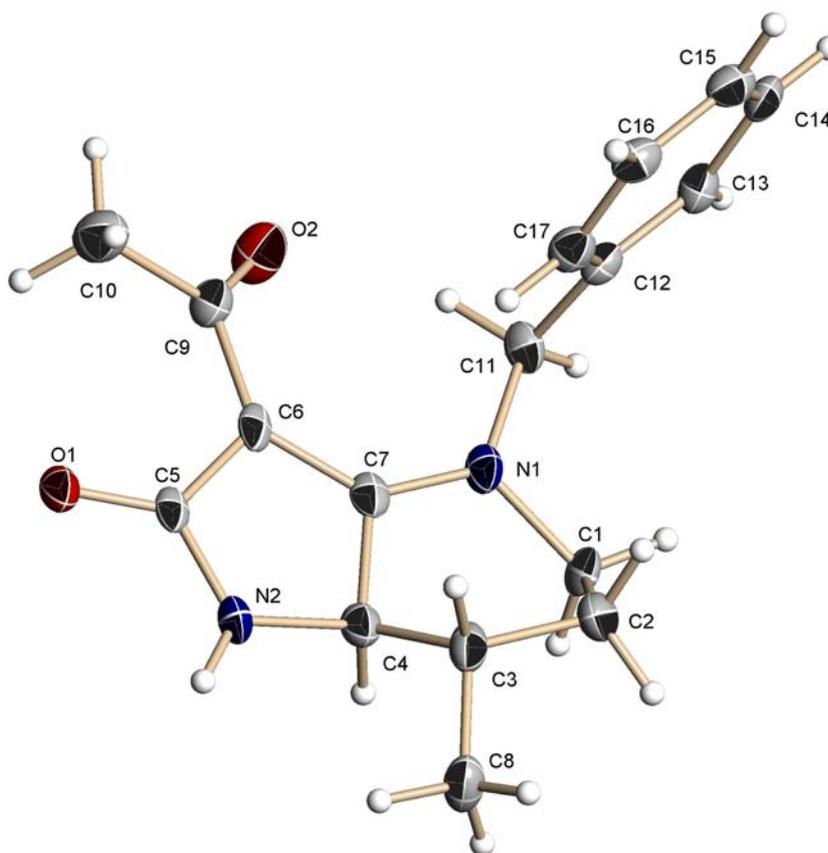
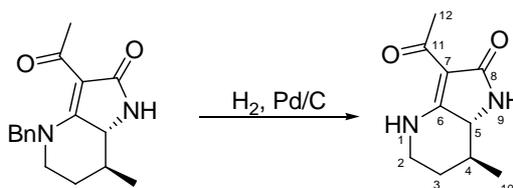


Figure 1 Molecular structure of one of the two crystallographically independent molecules of **18a** present in its crystal structure. Atomic displacement ellipsoids are drawn at the 50% probability level.

Data for 5-*epi*-*N*-benzyl laccarin **18b**; 148-151 °C (EtOAc-hexanes); $[\alpha]_D^{20}$ -83.3 ($c = 0.7$, CHCl_3); ν_{max} / cm^{-1} (film) 3238 (m), 1669 (s), 1636 (s), 1561 (s), 1454 (m); δ_{H} (400 MHz, CDCl_3) 0.79 (3H, d, $J = 7.0$, C10-H), 1.22-1.33 (1H, m, C3-H), 2.03-2.12

(1H, m, C3-H), 2.38-2.49 (1H, m, C4-H), 2.55 (3H, s, C12-H), 3.22-3.34 (2H, m, C2-H), 4.10 (1H, dd, $J = 7.0$ and 1.0 , C5-H), 5.06 (1H, d, $J = 15.0$, NCH₂Ph), 5.20 (1H, d, $J = 15.0$, NCH₂Ph), 5.92 (1H, br s, NH), 7.18-7.23 (2H, m, ArCH), 7.25-7.35 (3H, m, ArCH); δ_C (100 MHz, CDCl₃) 15.5 (C-10), 27.0 (C-4), 27.4 (C-3), 30.2 (C-12), 47.2 (C-2), 55.9 (C-5), 58.4 (NCH₂Ph), 102.3 (C-7), 127.6, 128.0 and 128.6 (ArCH \times 5), 136.6 (ArC), 167.1 (C-6), 174.7 (C-8), 194.9 (C-11); m/z (CI⁺) 285 ([M+H]⁺, 100 %); HRMS: (CI⁺) Found: [M+H]⁺ 285.1596, C₁₇H₂₁N₂O₂ requires 285.1603.



(+)-Laccarin (4); To a solution of *N*-benzyl laccarin **18a** (105 mg, 0.37 mmol) in TFA (4 mL) was added 10 % Pd/C (67 mg) and the mixture was sealed inside a hydrogenation bomb. The vessel was then purged with H₂ (6 purge cycles at a pressure of 5.5 bar) and the mixture was stirred at r.t. for 7 h. The vessel was then depressurised, the mixture was filtered through Celite ® and the residue was washed sequentially with TFA (6 mL), MeOH (6 mL) and CH₂Cl₂ (6 mL). The filtrate was concentrated *in vacuo* and the residue was purified by FCC (EtOAc-MeOH, 10:1) to afford laccarin **4** (67 mg, 93 %) as a colourless powder; m.p. > 250 °C (EtOAc-MeOH); $[\alpha]_D^{20} +176.9$ ($c = 0.5$, CHCl₃), [lit.⁸ $[\alpha]_D^{31} +188.0$ ($c = 0.5$, CHCl₃)] ; ν_{\max} /cm⁻¹ (film) 3251 (br m), 2957 (m), 1677 (s), 1626 (s), 1590 (s), 1493 (s), 1340 (s), 1205 (s), 1133 (s); δ_H (400 MHz, CDCl₃) 1.17 (3H, d, $J = 6.5$, C10-H), 1.53-1.74 (2H, m, C3-H and C4-H), 1.97-2.07 (1H, m, C3-H), 2.46 (3H, s, C12-H), 3.43-3.54 (2H, m, C2-H), 3.63 (1H, d, $J = 10.5$, C5-H), 5.94 (1H, br s, NH), 8.96 (1H, br s, NH); δ_C (100 MHz, CDCl₃) 19.0 [19.1] (C-10), 27.4 [27.5] (C-12), 28.1 [28.1] (C-3), 31.9 [31.8] (C-4), 41.2 [41.2] (C-2), 58.0 [58.3] (C-5), 100.3 [100.2] (C-7), 172.5 [172.7] (C-6), 173.3 [173.5] (C-8), 196.3 [196.2] (C-11); δ_H (400 MHz, MeOH-d₄) 1.17 (3H, d, $J = 6.0$, C10-H), 1.51-1.64 (2H, m, C3-H and C4-H), 1.93-2.05 (1H, m, C3-H), 2.37 (3H, s, C12-H), 3.42-3.57 (2H, m, C2-H), 3.75 (1H, d, $J = 10.0$, C5-H); δ_C (75 MHz, MeOH-D₄) 19.5 [19.9] (C-10), 27.2 [27.6] (C-12), 28.9 [29.2] (C-3), 33.4 [33.7] (C-4), 41.8 [42.2] (C-2), 59.5 [59.8] (C-5), 100.6 [100.9] (C-7), 175.1 [175.2]

(C-6), 176.0 [176.1] (C-8), 197.2 [197.2] (C-11); HRMS: (ESI⁺) Found: 195.1135 [M+H]⁺, C₁₀H₁₅N₂O₂ requires 195.1128. The spectroscopic properties of this compound were consistent with the data reported in the literature for laccarin.^{8,9} ¹³C NMR literature values in both CDCl₃⁸ and MeOH-d₄⁹ are quoted in [1]. Please note that ¹H NMR data for laccarin reported by Yue *et al.* are incorrectly referenced (their MeOH signal comes at *ca.* 3.15 ppm instead of 3.31 ppm).

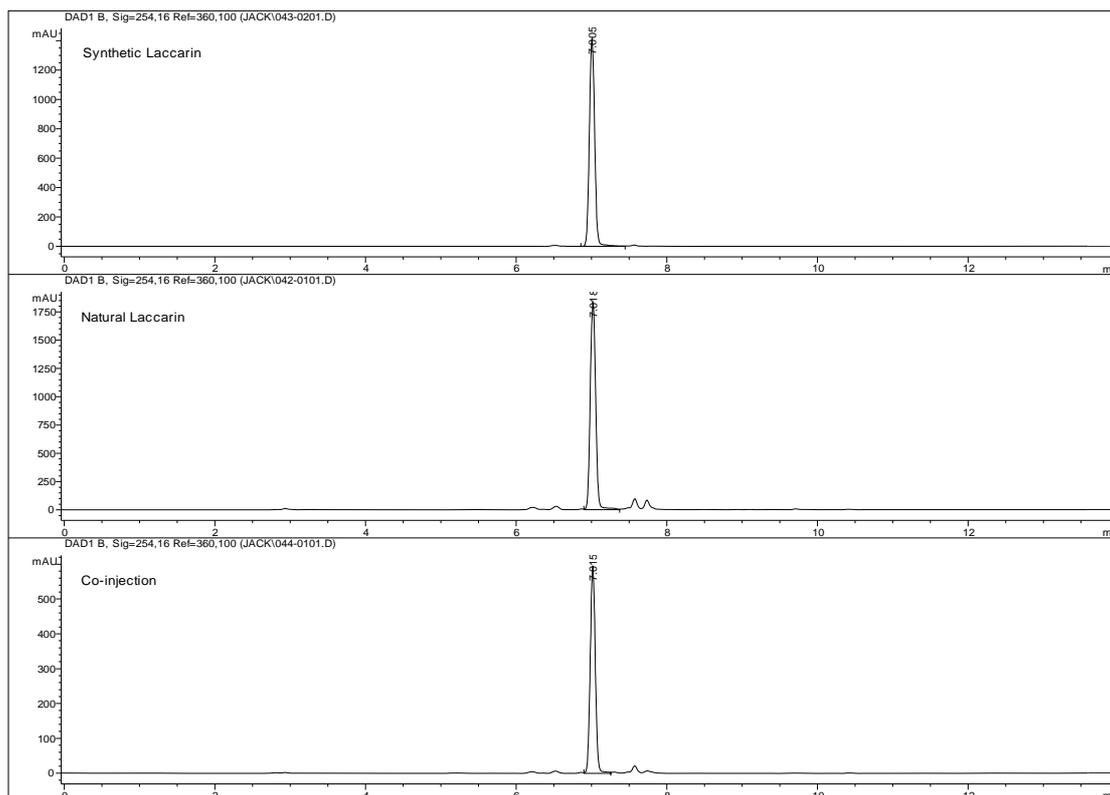


Figure 2 HPLC comparison of synthetic and natural laccarin. (HPLC conditions: Phenomenex Gemini 110 A, C18, 5 μ , 150 \times 4.6 mm column, gradient water - MeCN (+ 0.1 % TFA) 95:5 to 5:95 over 20 minutes, 1.0 mL/min, 20 °C).

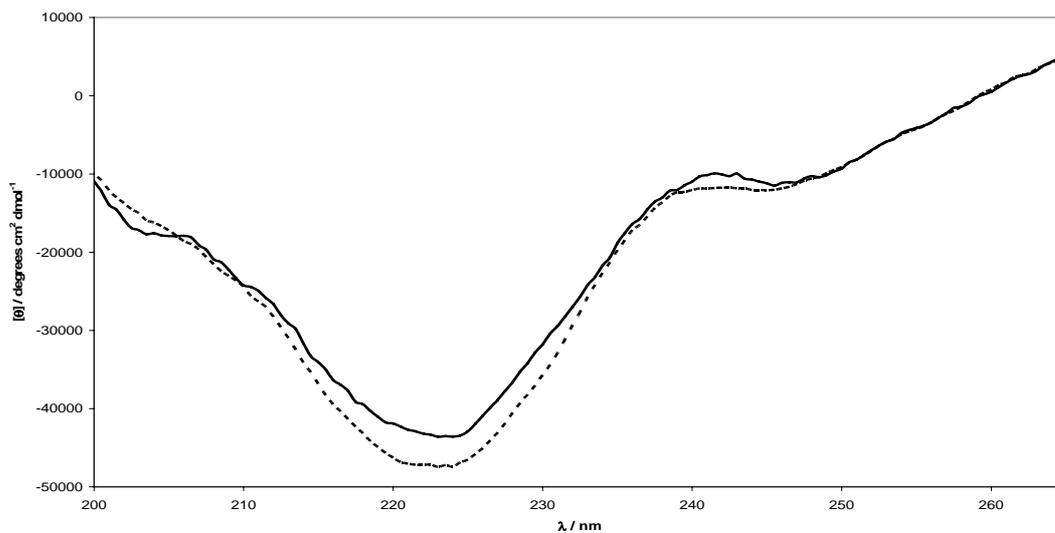
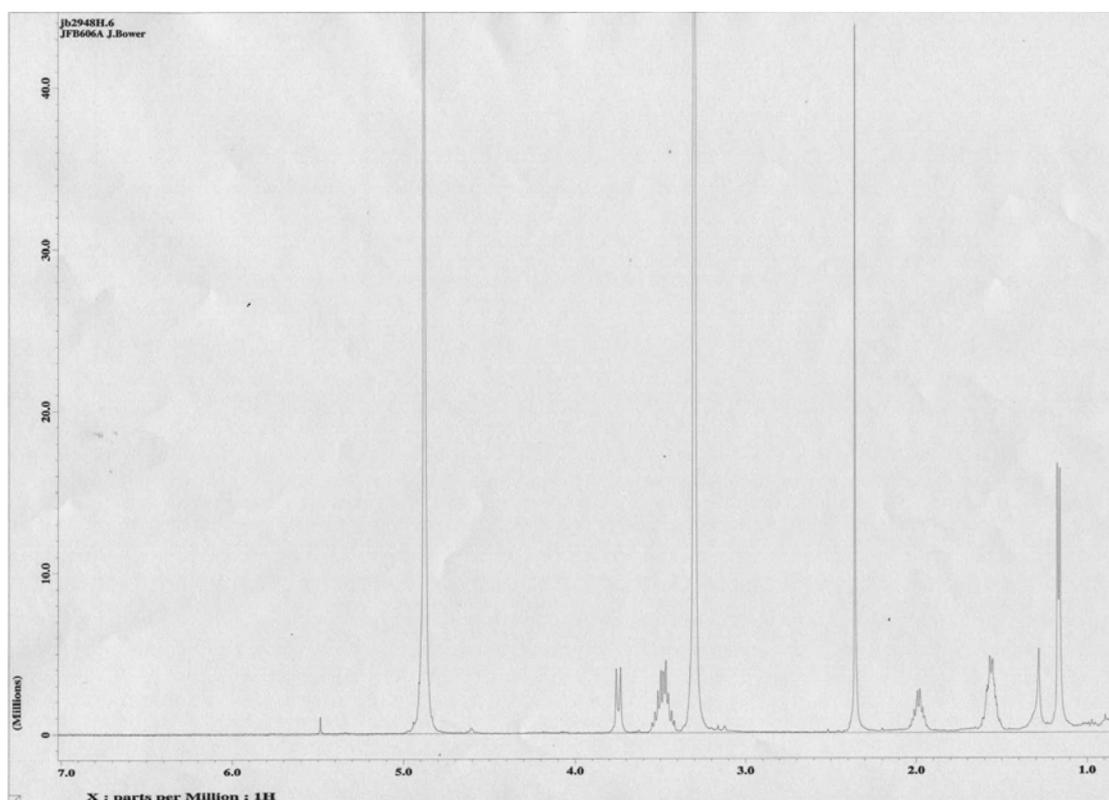
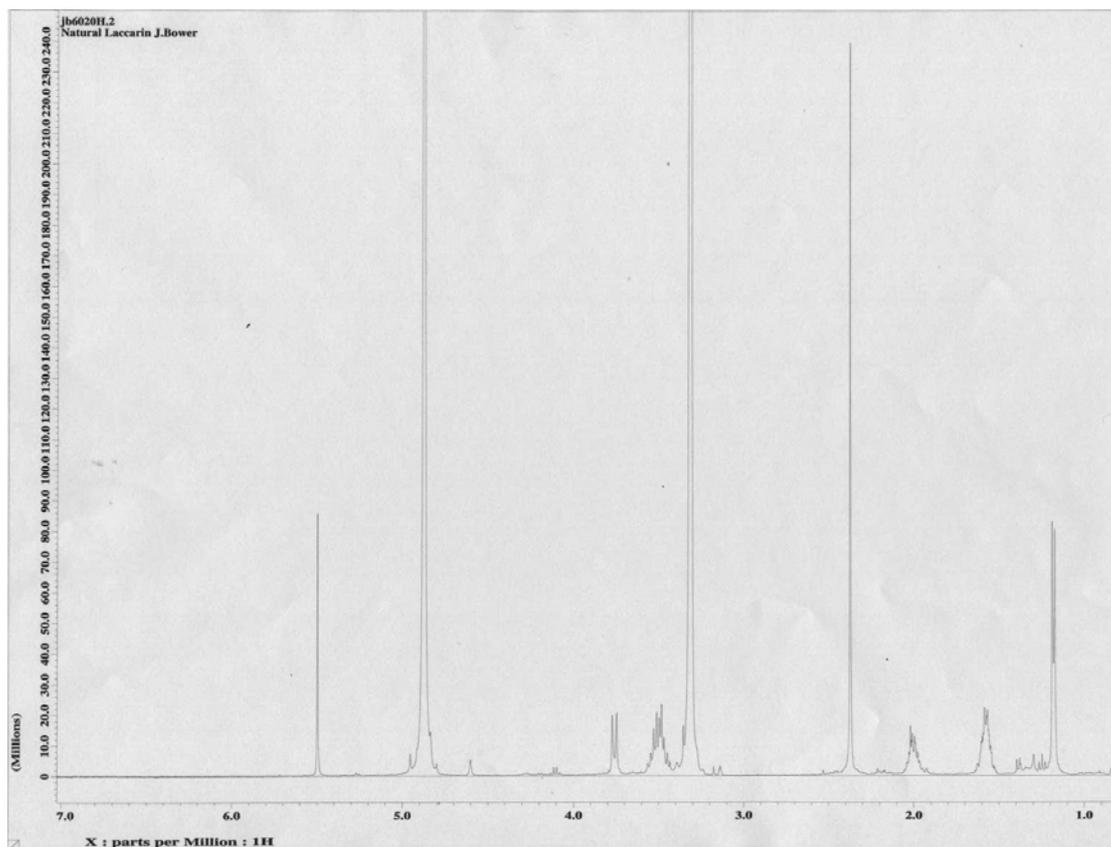


Figure 3 Circular dichroism (CD) comparison of synthetic (—) and natural (-----) laccarin (EtOH, 20 °C). $[\theta]$ = molar ellipticity. Circular Dichroism was performed on a JASCO J-810 spectropolarimeter using step scanning at 8 second intervals in 0.5 nm increments over the range 200-265 nm. Samples were recorded at 0.1 mM using a quartz cell of 1 mm path length.

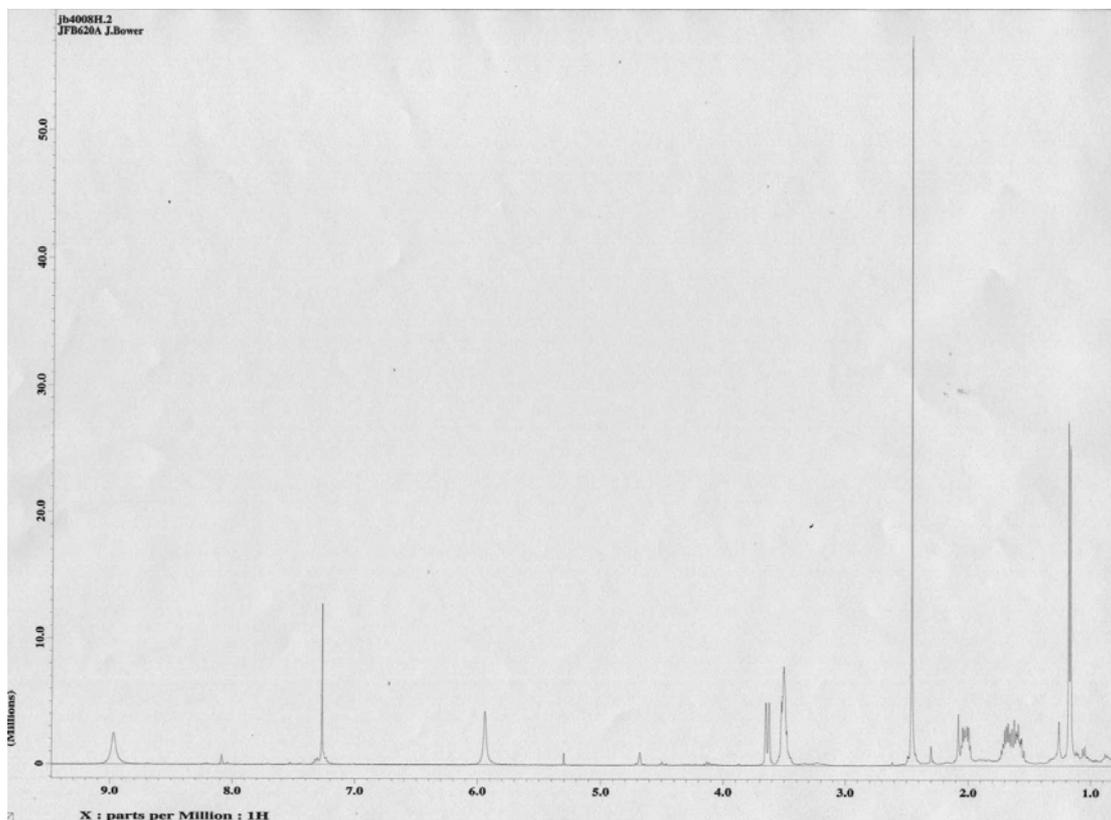
Synthetic Laccarin (400 MHz, MeOH- d_4):



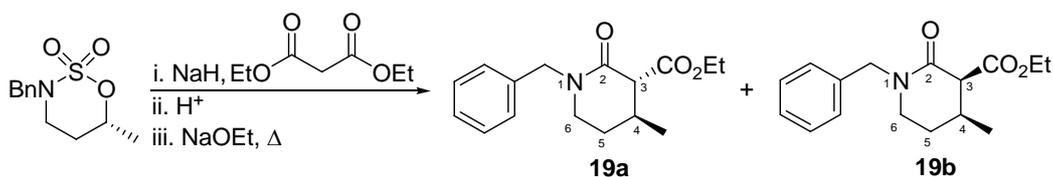
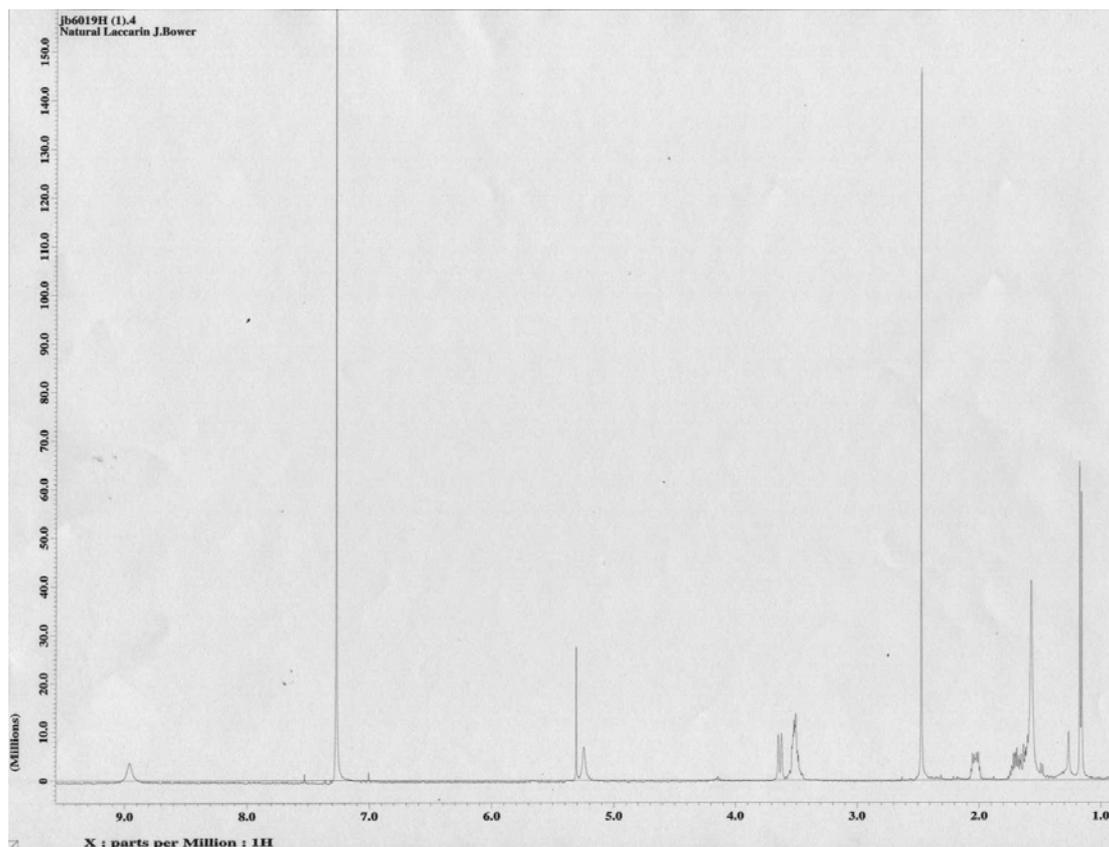
Natural Laccarin (400 MHz, MeOH-d₄):



Synthetic Laccarin (400 MHz, CDCl₃):



Natural Laccarin (400 MHz, CDCl₃):

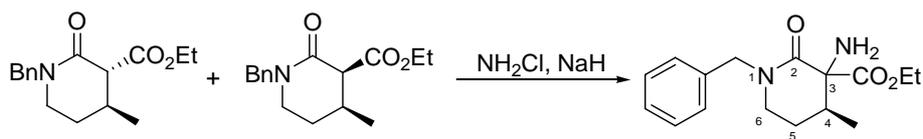


(3R,4S)-1-Benzyl-4-methyl-2-oxopiperidine-3-carboxylic acid ethyl ester (19a) and **(3S,4S)-1-Benzyl-4-methyl-2-oxopiperidine-3-carboxylic acid ethyl ester (19b)**; To a solution of diethyl malonate (1.26 mL, 8.30 mmol) in anhydrous DMF (48 mL) was added NaH (60 % dispersion in mineral oil, 324 mg, 8.09 mmol) and the resulting mixture was stirred at r.t. for 1 h. Sulfamidate **3** (1.00 g, 4.15 mmol) was added and the mixture was heated at 100 °C for 80 h. After cooling to r.t., aq. 5 M HCl (4.15 mL) was added and the mixture was stirred at r.t. for 3 h. The mixture was then neutralised with saturated aq. NaHCO₃ and extracted with CH₂Cl₂ (3 × 80 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford a brown residue which was dissolved in anhydrous 1 M NaOEt in EtOH (37

mL) 16 h. The mixture was then cooled to r.t. and concentrated *in vacuo* to leave a brown oil which was purified by FCC (hexanes-EtOAc 3:2) to afford lactam **19a/19b** (585 mg, 52 %, 13:2 d.r., > 98 % e.e.) as a colourless oil. Analytical samples of each diastereomer were isolated by careful FCC.

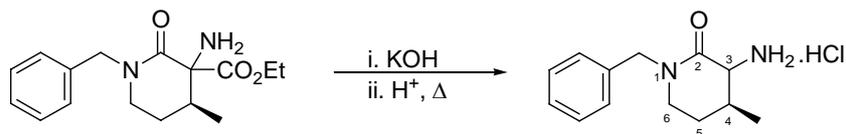
Data for *trans*-lactam **19a**: $[\alpha]_D^{20}$ -19.1 (c = 0.6, CHCl₃); ν_{\max} /cm⁻¹ (film) 2932 (m), 1734 (s), 1640 (s), 1494 (m), 1452 (m), 1158 (s), 1029 (m); δ_H (400 MHz, CDCl₃) 1.03 (3H, d, *J* = 7.0, C4-CH₃), 1.32 (3H, t, *J* = 7.0, CO₂CH₂CH₃), 1.42-1.55 (1H, m, C5-H), 1.82-1.91 (1H, m, C5-H), 2.26-2.38 (1H, m, C4-H), 3.08 (1H, d, *J* = 10.5, C3-H), 3.20 (1H, ddd, *J* = 12.0, 6.0 and 3.5, C6-H), 3.27 (1H, ddd, *J* = 12.0, 12.0 and 5.0, C6-H), 4.26 (2H, q, *J* = 7.0, CO₂CH₂CH₃), 4.52 (1H, d, *J* = 14.5, NCH₂Ph), 4.69 (1H, d, *J* = 14.5, NCH₂Ph), 7.22-7.36 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 14.1 (CO₂CH₂CH₃), 19.8 (C4-CH₃), 29.3 (C-5), 31.5 (C-4), 45.8 (C-6), 50.1 (NCH₂Ph), 57.3 (C-3), 61.1 (CO₂CH₂CH₃), 127.3, 127.9 and 128.5 (ArCH × 5), 136.7 (ArC), 165.9 and 170.6 (C-2 and CO₂CH₂CH₃); *m/z* (CI⁺) 276 ([M+H]⁺, 100 %); HRMS: (CI⁺) Found: [M+H]⁺ 276.1594, C₁₆H₂₂NO₃ requires 276.1560. The enantiomeric purity of lactam **19a** was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexane - *i*-PrOH 97:3, 1.0 mL/min, 20 °C); *t_R* (major) = 21.2 min and *t_R* (minor) = 25.9 min.

Data for *cis*-lactam **19b**: $[\alpha]_D^{20}$ -24.5 (c = 0.5, CHCl₃); ν_{\max} /cm⁻¹ (film) 2932 (m), 1734 (s), 1639 (s), 1495 (m), 1453 (m), 1157 (s), 1029 (m); δ_H (400 MHz, CDCl₃) 1.03 (3H, d, *J* = 7.0, C4-CH₃), 1.28 (3H, t, *J* = 7.5, CO₂CH₂CH₃), 1.57-1.66 (1H, m, C5-H), 1.93-2.05 (1H, m, C5-H), 2.14-2.27 (1H, m, C4-H), 3.15-3.31 (2H, m, C6-H), 3.51 (1H, d, *J* = 6.0, C3-H), 4.14-4.25 (2H, m, CO₂CH₂CH₃), 4.30 (1H, d, *J* = 15.0, NCH₂Ph), 4.93 (1H, d, *J* = 15.0, NCH₂Ph), 7.21-7.34 (5H, m, ArCH); δ_C (100 MHz, CDCl₃) 14.2 (CO₂CH₂CH₃), 17.9 (C4-CH₃), 26.6 (C-5), 30.7 (C-4), 46.3 (C-6), 50.1 (NCH₂Ph), 54.1 (C-3), 61.0 (CO₂CH₂CH₃), 127.3, 127.8 and 128.5 (ArCH × 5), 136.9 (ArC), 166.0 and 169.8 (C-2 and CO₂CH₂CH₃); *m/z* (CI⁺) 276 ([M+H]⁺, 100 %); HRMS: (CI⁺) Found: [M+H]⁺ 276.1590, C₁₆H₂₂NO₃ requires 276.1560.



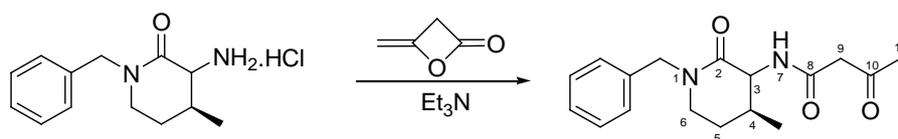
(4S)-3-Amino-1-benzyl-4-methyl-2-oxopiperidine-3-carboxylic acid ethyl ester;

To an ice-cooled (0 °C) solution of lactam **19a/19b** (410 mg, 1.49 mmol) in anhydrous THF (10 mL) was added in one portion NaH (60 % dispersion in mineral oil, 60 mg, 1.49 mmol). After 20 minutes NH₂Cl in Et₂O (*ca.* 0.15 M, 2.27 mmol) was rapidly added *via* syringe and the resulting solution was stirred at 0 °C for 1 h and subsequently at r.t. for 2 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc (20 mL) and extracted with aq. 0.5 M HCl (3 × 20 mL). The organic portion was dried (Na₂SO₄), concentrated *in vacuo* and purified by FCC (hexanes-EtOAc 3:2) to afford recovered lactam **19a/b** (123 mg, 30 %) as a colourless oil. The reserved aqueous extracts were then basified by addition of saturated aq. Na₂CO₃ and extracted with CH₂Cl₂ (3 × 40 mL). The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford aminated adduct (271 mg, 63 %, 12:1 d.r.) as a colourless oil; *NMR data is given for the major diastereomer only.* ν_{\max} /cm⁻¹ (film) 3380 (w), 2936 (m), 1736 (s), 1642 (s), 1495 (m), 1454 (m), 1200 (s), 1020 (m); δ_{H} (400 MHz, CDCl₃) 0.98 (3H, s, *J* = 7.0, C4-CH₃), 1.31 (3H, t, *J* = 7.5, CO₂CH₂CH₃), 1.61-1.68 (1H, m, C5-H), 1.98-2.17 (2H, m, C4-H and C5-H), 2.33 (2H, br s, NH₂), 3.23-3.40 (2H, m, C6-H), 4.15 (1H, d, *J* = 14.5, NCH₂Ph), 4.19-4.32 (2H, m, CO₂CH₂CH₃), 5.11 (1H, d, *J* = 14.5, NCH₂Ph), 7.23-7.37 (5H, m, ArCH); δ_{C} (100 MHz, CDCl₃) 14.2 (CO₂CH₂CH₃), 16.4 (C4-CH₃), 26.6 (C-5), 38.8 (C-4), 46.2 (C-6), 50.6 (NCH₂Ph), 61.8 (CO₂CH₂CH₃), 66.1 (C-3), 127.5, 127.8 and 128.6 (ArCH × 5), 138.9 (ArC), 169.0 and 172.6 (C-2 and CO₂CH₂CH₃); *m/z* (CI⁺) 291 ([M+H]⁺, 100 %); HRMS: (CI⁺) Found: [M+H]⁺ 291.1708, C₁₆H₂₃N₂O₃ requires 291.1709.



(4S)-3-Amino-1-benzyl-4-methylpiperidin-2-one hydrochloride; To a solution of amino ester (529 mg, 1.82 mmol) in dioxane (6 mL) and water (10 mL) was added KOH (180 mg, 3.21 mmol) and the resulting mixture was heated at reflux (*ca.* 85 °C)

for 4 h. Aq. 5 M HCl (600 μ L) was then added and heating was continued for a further 1 h. The solution was then cooled to r.t. and concentrated *in vacuo*. The residue was suspended in CH₂Cl₂ (20 mL), filtered through Celite ®, and concentrated *in vacuo* to afford the amine hydrochloride (425 mg, 92 %, 2:1 d.r. A:B) as a colourless foam; δ_{H} (400 MHz, MeOH-d₄) 0.98 (3H, d, $J = 7.5$, C4-CH₃ of B), 1.13 (3H, d, $J = 6.5$, C4-CH₃ of A), 1.56-1.95 (m), 2.01-2.22 (m) and 2.34-2.44 (m) (6H, C4-H and C5-H of A and B), 3.24-3.37 (m, C6-H of A and B and C3-H of A) *, 3.87 (1H, d, $J = 5.5$, C3-H of B), 4.47 (1H, d, $J = 14.5$, NCH₂Ph of B), 4.54 (1H, d, $J = 14.5$, NCH₂Ph of A), 4.63 (1H, d, $J = 14.5$, NCH₂Ph of A), 4.70 (1H, d, $J = 14.5$, NCH₂Ph of B), 7.21-7.36 (10H, ArCH); * (integration of these signals was not possible due to overlap with residual MeOH/MeOD). This material was used in the next stage without further purification.



(4S)-N-(1-Benzyl-4-methyl-2-oxopiperidin-3-yl)-3-oxobutanamide (20); To a solution of amine hydrochloride (200 mg, 0.79 mmol) in THF (10 mL) was added Et₃N (120 μ L, 0.86 mmol) and then diketene (67 μ L, 0.86 mmol). The mixture was stirred at r.t. 4 h and then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (30 mL), washed with aq. 1 M HCl (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford a pale yellow oil. This residue was purified by FCC (EtOAc-MeOH 9:1) to afford the title compound **20** (204 mg, 86 %, 2:1 d.r. A:B) as a colourless powder; ν_{max} /cm⁻¹ (film) 3297 (m), 2928 (m), 1716 (m), 1627 (s), 1546 (m), 1495 (m), 1453 (m), 1159 (m); δ_{H} (270 MHz, CDCl₃) 0.86 (3H, d, $J = 7.0$, C4-CH₃ of B), 1.05 (3H, d, $J = 6.5$, C4-CH₃ of A), 1.54-1.70 (2H, m, C5-H of A and B), 1.82-1.93 (1H, m, C5-H of A), 1.94-2.18 (2H, m, C5-H of B and C4-H of A), 2.28 (3H, s, C11-H of B), 2.30 (3H, s, C11-H of A), 2.69-2.81 (1H, m, C4-H of B), 3.16-3.32 (4H, m, C6-H of A and B), 3.48 (2H, s, C9-H of B), 3.51 (2H, s, C9-H of A), 4.12 (1H, d, $J = 7.5$, C3-H of A), 4.16 (1H, d, $J = 8.5$, C3-H of B), 4.45 (1H, d, $J = 14.5$, NCH₂Ph of A), 4.54 (1H, d, $J = 14.5$, NCH₂Ph of B), 4.64 (1H, d, $J = 14.5$, NCH₂Ph of B), 4.70 (1H, d, $J = 14.5$, NCH₂Ph of A), 7.21-7.37 (10H, ArCH), 7.52 (1H, d, $J = 8.5$, NH), 7.67

(¹H, d, *J* = 5.5, NH); δ_C (100 MHz, CDCl₃) 12.8 (C4-CH₃ of B), 19.0 (C4-CH₃ of A), 26.9 (C-5 of B), 28.9 (C-4 of B), 29.6 (C-5 of A), 30.4 and 30.5 (C-11), 33.6 (C-4 of A), 43.1 and 45.7 (C-6), 50.4 and 50.5 (2 × C-9 and NCH₂Ph of A), 54.6 (NCH₂Ph of B), 56.6 (2 × C-3), 127.3, 127.5, 127.8, 127.9, 128.4 and 128.5 (ArCH × 10), 136.5 and 136.6 (ArC), 165.9, 166.5, 168.5 and 168.7 (C-2 and C-8), 203.1 and 203.9 (C-10); *m/z* (CI⁺) 303 ([M+H]⁺, 100 %); HRMS: (CI⁺) Found: [M+H]⁺ 303.1702, C₁₇H₂₃N₂O₃ requires 303.1709.

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