Cyclic sulfamidates as lactam precursors. An efficient asymmetric synthesis of (-)-aphanorphine

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Supplementary Information

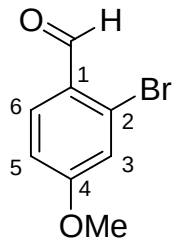
(A) General experimental details

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 ^{o}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 ^{o}C) for at least 2 hrs 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 60F_{254} aluminium backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence, acidic $KMnO_4$ 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 CH_2Cl_2 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); ^{1}H 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 ^{1}H 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.

(B) Experimental Procedures

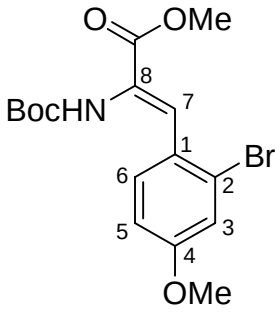
2-Bromo-4-methoxybenzaldehyde (5)



This compound was prepared by adaptation of the procedure of Durst.[1] To a solution of *N*,*N*,*N*'-trimethylethylenediamine (10.19 mL, 78.4 mmol, freshly distilled from CaH_2) in anhydrous THF (180 mL) at -20 ^{o}C was added, *via* syringe, *n*-BuLi (30.3 mL, 75.8 mmol, 2.5 M in hexanes) over two minutes and the resulting pale yellow mixture was stirred at -20 ^{o}C for 15 minutes. *p*-Anisaldehyde (8.94 mL, 73.4 mmol)

was added *via* syringe in one portion and the resulting mixture was stirred at -20 ^{o}C for 20 minutes. *n*-BuLi (88.1 mL, 220.2 mmol, 2.5 M in hexanes) was added *via* syringe and the mixture was stirred at -20 ^{o}C for 30 minutes and then allowed to stand in the freezer (*ca.* -15 ^{o}C) for 24 hrs. The reaction mixture, now a deep orange solution, was cooled to -78 ^{o}C and, with vigorous stirring, a solution of carbon tetrabromide (68.5 g, 207 mmol) in anhydrous THF (30 mL) was added dropwise, *via* syringe, over 15 minutes (**Caution**: slow addition of the quench is required to moderate the reaction exotherm). The resulting brown suspension was then poured into stirred, ice cold aq. 3 M HCl (500 mL) and extracted with Et_2O (2 × 500 mL). The combined organic portions were concentrated to *ca.* 150 mL, washed with saturated aq. sodium thiosulfate solution (5 × 100 mL), water (100 mL) and then brine (100 mL), dried (Na_2SO_4) and then concentrated *in vacuo* to afford a brown oil (*ca.* 46 g). This was pre-adsorbed onto silica (*ca.* 120 g) and purified by FCC (hexanes-EtOAc 12:1) to yield a crude product which was then recrystallised from petrol (2 crops) to afford **5** (9.81 g, 62 %) as pale yellow needles; m.p. 77.5 - 79 ^{o}C (petrol) [Lit.[1],70-71 ^{o}C (EtOH)]; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, ArOC<u>H</u>$_3$), 6.96 (1H, ddd, *J* = 8.5, 3.0 and 1.0, C5-<u>H</u>), 7.15 (1H, d, *J* = 3.0, C3-<u>H</u>), 7.91 (1H, d, *J* = 8.5, C6-<u>H</u>), 10.24 (1H, d, *J* = 1.0, Ar(CO)<u>H</u>). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[1]

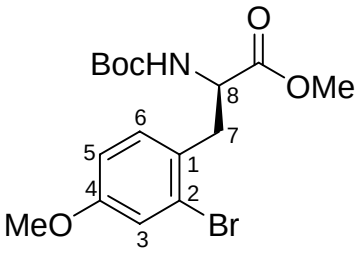
(Z)-3-(2-Bromo-4-methoxyphenyl)-2-*tert*-butoxycarbonylaminoacrylic acid methyl ester (6)



To solution of aldehyde **5** (512 mg, 2.38 mmol) and (±)-*N*-Boc-α-phosphonoglycine trimethyl ester (779 mg, 2.62 mmol) in anhydrous CH_2Cl_2 (11 mL) was added tetramethylguanidine (448 μL, 3.57 mmol) and the resulting solution was stirred at r.t. for 18 hrs. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with 10 % aq. citric acid solution (20 mL) and then saturated aq. $NaHCO_3$ solution (20

mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil. This was then purified by FCC (hexanes-EtOAc 7:2) to afford the dehydroamino ester **6** (909 mg, 99 %) as a viscous, colourless oil; ν_{max} / cm^{-1} (film) 3336 (w), 1703 (s), 1231 (s), 1156 (s), 1026 (s); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, $NHCO_2C(C\underline{H}_3)_3$), 3.83 (3H, s, $ArOC\underline{H}_3$), 3.88 (3H, s, $CO_2C\underline{H}_3$), 6.25 (1H, br s, $N\underline{H}CO_2C(CH_3)_3$), 6.83 (1H, dd, *J* = 8.5 and 2.5, C5-<u>H</u>), 7.16 (1H, d, *J* = 2.5, C3-<u>H</u>), 7.38 (1H, s, C7-<u>H</u>), 7.60 (1H, d, *J* = 8.5, C6-<u>H</u>); δ_C (100 MHz, $CDCl_3$) 30.0 ($NHCO_2C(\underline{C}H_3)_3$), 52.6 ($ArO\underline{C}H_3$), 55.5 ($CO_2\underline{C}H_3$), 80.7 ($NHCO_2\underline{C}(CH_3)_3$), 113.6 (<u>C</u>-5), 117.7 (<u>C</u>-3), 124.3, 125.7 and 126.8 (<u>C</u>-1, <u>C</u>-2 and <u>C</u>-8), 127.3 (<u>C</u>-7), 130.3 (<u>C</u>-6), 152.4 (<u>C</u>-4), 160.1 ($NH\underline{C}O_2(CH_3)_3$), 165.8 ($\underline{C}O_2CH_3$); *m/z* ($CI^+$) 388 and 386 ($[M+H]^+$, 84 and 82 %), 287 and 285 ($[M+H-Boc]^+$, 100 and 98); HRMS: (ESI) Found: $[M+Na]^+$ 408.0414, $C_{16}H_{20}{}^{79}BrNO_5$ requires 408.0417. *The stereochemistry of this compound was assigned as Z on the basis of related reactions described in the literature.*[2]

(R)-3-(2-Bromo-4-methoxyphenyl)-2-*tert*-butoxycarbonylaminopropionic acid methyl ester (7)

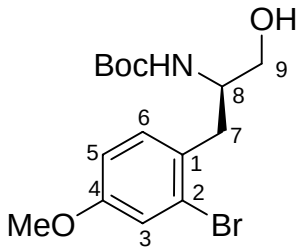


In an Aldrich Atmosbag ® (N_2 atmosphere), MeOH (13 mL, deoxygenated by passage of N_2 for 2 hrs) was added to a 25 mL r.b. flask containing dehydroamino ester **6** (436 mg, 1.13 mmol) and [((*R,R*)-Et-DuPHOS)Rh(COD)]BF_4 (11.1 mg, 1.5 mol %) and the reaction vessel was sealed inside a hydrogenation bomb. The system was then purged with H_2 (6 purge cycles at a pressure of 5 atm.) and stirred vigorously at r.t for 40 hrs. The mixture was then concentrated *in vacuo* and filtered through a pad of silica (60, 5 × 5 cm) eluting with EtOAc (*ca.* 30 mL). The eluent was concentrated *in vacuo* to afford the amino ester derivative **7** (440 mg, 100 %, 99 % e.e.) as a colourless, viscous oil; $[\alpha]_D{}^{20}$ -5.1 (c = 0.8, $CHCl_3$); ν_{max} / cm^{-1} (film) 3374 (br), 2977 (br), 1715 (s), 1495 (s), 1243 (m), 1167 (s), 1029 (m); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, $NHCO_2C(C\underline{H}_3)_3$), 3.05 (1H, dd, *J* = 14.0 and 7.5, C7-<u>H</u>), 3.25 (1H, dd, *J* = 14.0 and 6.5, C7-<u>H</u>), 3.73 (3H, s, $CO_2C\underline{H}_3$), 3.79 (3H, s, $ArOC\underline{H}_3$), 4.60

(1H, ddd, *J* = 8.0, 7.5 and 6.5, C8-H), 5.08 (1H, d, J = 8.0, NHCO$_2$C(CH$_3$)$_3$), 6.81 (1H, dd, *J* = 8.5 and 3.0, C5-H), 7.10 (1H, d, *J* = 8.5, C6-H), 7.11 (1H, d, *J* = 3.0, C3-H); δ_C (100 MHz, $CDCl_3$) 28.2 (NHCO$_2$C(CH$_3$)$_3$), 37.7 (C-7), 52.3 (ArOCH$_3$), 53.7 (C-8), 55.5 (CO$_2$CH$_3$), 80.0 (NHCO$_2$C(CH$_3$)$_3$), 113.6 (C-5), 118.0 (C-3), 125.1 and 127.8 (C-1 and C-2), 131.6 (C-6), 155.0 (C-4), 158.1 (NHCO$_2$C(CH$_3$)$_3$), 170.3 (CO$_2$CH$_3$); HRMS: (ESI) Found: $[M+Na]^+$ 410.0570, $C_{16}H_{22}{}^{79}BrNO_5$ requires 410.0574; Anal. Calcd for $C_{16}H_{22}NO_5Br$: C, 49.50; H, 5.71; N, 3.61. Found: C, 49.51; H, 5.41; N, 3.33.

The enantiomeric purity of this compound was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexane - *i*-PrOH 95:5, 1.0 mL/min, 25 ^oC) against a racemic standard prepared under similar conditions using Wilkinson's catalyst ((Ph$_3$P)$_3$RhCl, 5 mol %, 7 atm., 48 hrs); t_R (major) = 9.1 min and t_R (minor) = 12.6 min.

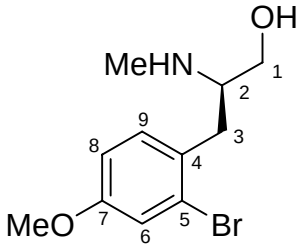
[(R)-2-(2-Bromo-4-methoxyphenyl)-1-hydroxymethylethyl]-carbamic acid *tert*-butyl ester (8)



To a solution of ester **7** (569 mg, 0.72 mmol) in anhydrous THF (10 mL) at -78 ^oC was added, dropwise *via* syringe, a solution of $LiAlH_4$ in THF (1 M, 2.16 mL, 2.16 mmol) over 2 minutes. The resulting solution was stirred at 0 ^oC for 30 minutes and then, sequentially, water (80 μL), aq. 4 M NaOH solution (80 μL) and water (240 μL) were added dropwise, *via* syringe (**Caution:** gas evolution), to form a colourless precipitate. The mixture was then filtered through Celite ®, rinsing copiously with CH_2Cl_2 (*ca.* 50 mL), washed with water (20 mL) and then brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the alcohol **8** (498 mg, 96 %) as a colourless, crystalline solid; m.p. 87-90 ^oC (Et_2O-hexanes); $[\alpha]_D^{20}$ +34.0 (c = 1.5, $CHCl_3$); ν_{max} / cm^{-1} (film) 3394 (br m), 1689 (s), 1494 (s), 1243 (m), 1169 (m), 1028 (m); δ_H (270 MHz, $CDCl_3$) 1.39 (9H, s, NHCO$_2$C(CH$_3$)$_3$), 2.50 (1H, br s, OH), 2.62-

3.01 (2H, m, C7-H), 3.54-3.95 (3H, m, C8-H and C9-H), 3.78 (3H, s, ArOCH_3), 4.85 (1H, br d, *J* = 7.5, NHCO$_2$C(CH_3)$_3$), 6.81 (1H, dd, *J* = 8.5 and 2.5, C5-H), 7.10 (1H, d, *J* = 2.5, C3-H), 7.18 (1H, d, *J* = 8.5, C6-H); δ_C (100 MHz, $CDCl_3$) 28.3 (NHCO$_2$C(CH_3)$_3$), 36.5 (C-7), 53.3 and 55.5 (C-8 and ArOCH_3), 64.4 (C-9), 79.8 (NHCO$_2$C(CH$_3$)$_3$), 114.0 (C-5), 117.9 (C-3), 124.9 and 129.4 (C-1 and C-2), 131.9 (C-6), 156.3 (C-4), 158.8 (NHCO$_2$(CH$_3$)$_3$); HRMS: (ESI) Found: $[M+Na]^+$ 382.0621, $C_{15}H_{22}{}^{79}BrNO_4$ requires 382.0624.

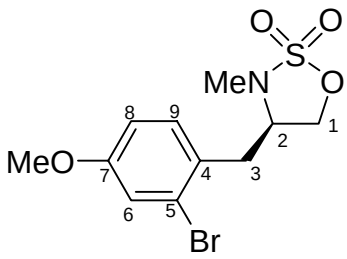
(R)-3-(2-Bromo-4-methoxyphenyl)-2-methylaminopropan-1-ol (10)



To a solution of *N*-Boc alcohol **8** (364 mg, 1.02 mmol) in anhydrous THF (12 mL) was added NaH (54.8 mg, 1.37 mmol, 60 % dispersion in mineral oil) causing immediate gas evolution. The resulting pale yellow slurry was then stirred at r.t. for 8 hrs prior to the addition of NaH (61.2 mg, 1.52 mmol, 60 % dispersion in mineral oil) and then MeI (254 μL, 4.08 mmol). After stirring for a further 1 hr excess NaH was quenched by careful addition of water (**Caution:** vigorous gas evolution) and the mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (6 mL) and 50 % aq. NaOH solution (3 mL) and then heated at reflux (oil bath *ca.* 90 ^oC) for 2 hrs. After cooling to r.t., the mixture was diluted with brine (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow solid. This was then dissolved in MeCN (20 mL), washed with hexane (2 × 10 mL) and concentrated *in vacuo* to afford essentially pure amino alcohol **10** (129 mg, 92 %) as a pale yellow wax; $[\alpha]_D^{20}$ +20.0 (c = 0.6, $CHCl_3$); ν_{max} / cm^{-1} (film) 3309 (br m), 1603 (m), 1491 (s), 1240 (s), 1026 (s); δ_H (400 MHz, $CDCl_3$) 2.12 (2H, br s, NHMe and CH_2OH), 2.42 (3H, s, NHCH_3), 2.71 (1H, dd, *J* = 13.0 and 7.0, C3-H), 2.83-2.89 (1H, m, C2-H), 2.91 (1H, dd, *J* = 13.0 and 6.5, C3-H), 3.31 (1H, dd, *J* = 11.0 and 5.0, C1-H), 3.61 (1H, dd, *J* = 11.0 and 4.0, C1-

H), 3.77 (3H, s, ArOCH$_3$), 6.80 (1H, dd, *J* = 8.5 and 2.5, C8-H), 7.09 (1H, d, *J* = 2.5, C6-H), 7.11 (1H, d, *J* = 8.5, C9-H); δ_C (100 MHz, $CDCl_3$) 33.7 (NCH$_3$), 36.9 (C-3), 55.5 (ArOCH$_3$), 60.4 (C-2), 61.8 (C-1), 113.6 (C-8), 118.1 (C-6), 124.8 and 130.0 (C-4 and C-5), 131.7 (C-9), 158.7 (C-7); HRMS: (ESI) Found: $[M+H]^+$ 274.0437, $C_{11}H_{17}{}^{79}BrNO_2$ requires 274.0437.

(R)-4-(2-Bromo-4-methoxybenzyl)-3-methyl-1,2,3-oxathiazolidine 2,2-dioxide (4)

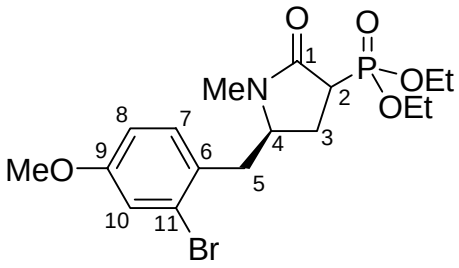


To an ice cold solution of amino alcohol **10** (468 mg, 1.7 mmol), imidazole (465 mg, 6.84 mmol) and Et_3N (501 μL, 3.66 mmol) in anhydrous CH_2Cl_2 (15 mL) was added, dropwise, *via* syringe, over 5 minutes, a solution of $SOCl_2$ (150 μL, 2.04 mmol) in anhydrous CH_2Cl_2 (3 mL). The resulting colourless solution was stirred at 0 ^oC for 2.5 hrs and then poured into aq. 1 M HCl (15 mL). The organic portion was isolated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with water (15 mL) and then brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford intermediate cyclic sulfamidite (533 mg, 98 %) as a pale yellow oil. *This material was used immediately in the next stage without further purification.* To a vigorously stirred, ice cold solution of $NaIO_4$ (69 mg, 0.32 mmol) and $RuCl_3$ (0.1 mg, 0.15 mol %) in water (2 mL) was added, in one portion, a solution of sulfamidite (100 mg, 0.32 mmol) in EtOAc (3 mL). The resulting pale brown suspension was stirred at 0 ^oC until careful TLC analysis showed complete consumption of starting material (*ca.* 0.25 hrs; TLC conditions: 1:1 Et_2O-Petrol; intermediate sulfamidite co-elutes with sulfamidate **4** but can be stained using $KMnO_4$ dip without the need for heat). The mixture was then diluted with EtOAc (10 mL) and aq. 1 M HCl (10 mL) and the organic portion was isolated, washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown residue which was immediately purified by FCC (Et_2O-petrol 1:1, CH_2Cl_2 loading) to afford the sulfamidate **4** (88 mg, 82 %, 99 % e.e.) as a colourless crystalline solid; m.p. 82-83 ^oC

(Et_2O); $[\alpha]_D^{20}$ +8.9 (c = 0.9, $CHCl_3$); ν_{max} / cm^{-1} (film) 1605 (m), 1494 (m), 1345 (s), 1179 (s), 1028 (m), 972 (m); δ_H (400 MHz, $CDCl_3$) 2.79 (3H, s, NHC<u>H</u>$_3$), 2.88 (1H, dd, *J* = 14.0 and 9.0, C3-<u>H</u>), 3.26 (1H, dd, *J* = 14.0 and 5.5, C3-<u>H</u>), 3.75-3.85 (1H, m, C2-<u>H</u>), 3.80 (3H, s, Ar-OC<u>H</u>$_3$), 4.26 (1H, dd, *J* = 8.5 and 7.0, C1-<u>H</u>), 4.40 (1H, dd, *J* = 8.5 and 6.5, C1-<u>H</u>), 6.84 (1H, dd, *J* = 8.5 and 2.5, C6-<u>H</u>), 7.13 (1H, d, *J* = 2.5, C8-<u>H</u>), 7.14 (1H, d, *J* = 8.5, C5-<u>H</u>); δ_C (100 MHz, $CDCl_3$) 34.0 (N<u>C</u>H$_3$), 37.4 (<u>C</u>-3), 55.7 and 60.5 (ArO<u>C</u>H$_3$ and <u>C</u>-2), 70.5 (<u>C</u>-1), 114.1 (<u>C</u>-6), 118.7 (<u>C</u>-8), 124.7 and 126.2 (<u>C</u>-4 and <u>C</u>-9), 132.0 (<u>C</u>-5), 159.7 (<u>C</u>-7); *m/z* (CI^+) 336 and 338 ($[M+H]^+$, 100 and 95 %); HRMS: (CI^+) Found: $[M+H]^+$ 335.9891, $C_{11}H_{14}{}^{79}BrNO_4S$ requires 335.9905. *The oxidation step could conveniently be carried out on a larger scale (up to 10 mmol) but resulted in diminished and variable yields of the product* ***4*** *(58 - 77 %).*

The enantiomeric purity of this compound was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexane - *i*-PrOH 70:30, 1.0 mL/min, 25 ^oC); t_R (major) = 28.3 min and t_R (minor) = 31.7 min.

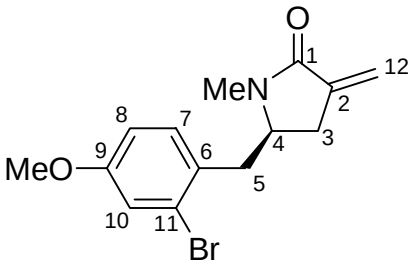
[(R)-5-(2-Bromo-4-methoxybenzyl)-1-methyl-2-oxopyrrolidin-3-yl]-phosphonic acid diethyl ester (11)



To a solution of triethyl phosphonoacetate (355 μL, 1.79 mmol) in anhydrous THF (8 mL) was added *t*-BuOK (200 mg, 1.79 mmol) and the mixture was heated at 40 ^oC to form a clear solution. After 25 minutes, sulfamidate **4** (300 mg, 0.89 mmol) was added and the reaction was stirred at 40 ^oC for a further 15 hrs. The mixture was then cooled to r.t. and treated with aq. 5 M HCl (0.89 mmol) and stirred at r.t. for 3 hrs. The mixture was neutralised by addition of saturated aq. $NaHCO_3$ solution, stirred for 12 hrs, diluted with brine (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC (EtOAc-MeOH 19:1) to yield the α-phosphono lactam **11** (311 mg,

84 %, 4:3 d.r. *A:B*) as a colourless oil; ν_{max} / cm^{-1} (film) 2981 (br w), 1687 (s), 1492 (m), 1240 (s), 1021 (s), 963 (m); δ_H (400 MHz, $CDCl_3$) 1.24-1.40 (12H, m, $OCH_2C\underline{H}_3$ *of A and B*), 1.99-2.38 (4H, m, C3-H *of A and B*), 2.54 (1H, dd, *J* = 13.0 and 9.0, C5-H *of A*), 2.79 (1H, dd, *J* = 13.0 and 10.5, C5-H *of B*), 2.56-3.01 (8H, m, $NC\underline{H}_3$ and C2-H *of A and B*), 3.27 (1H, dd, *J* = 13.0 and 4.0, C5-H *of A*), 3.37 (1H, dd, *J* = 13.0 and 4.0, C5-H *of B*), 3.78-3.85 (1H, m, C4-H *of B*), 3.79 (3H, s, $ArOC\underline{H}_3$ *of B*), 3.80 (3H, s, $ArOC\underline{H}_3$ *of A*), 3.85-3.94 (1H, m, C4-H *of A*), 4.09-4.33 (8H, m, $OC\underline{H}_2$ *of A and B*), 6.80-6.85 (2H, m, C8-H *of A and B*), 7.08 (1H, d, *J* = 8.5, C7-H *of A*), 7.11-7.15 (2H, m, C10-H *of A and B*), 7.25 (1H, d, *J* = 8.5, C7-H *of B*); δ_C (100 MHz, $CDCl_3$) 16.3-16.7 (4C, m, $OCH_2\underline{C}H_3 \times 4$), 25.1 (d, $^2J_{PC}$ = 4.0, C-3 *of B*), 26.1 (d, $^2J_{PC}$ = 3.5, C-3 *of A*), 28.7 (2 signals) ($N\underline{C}H_3$ *of A and B*), 38.6 (C-5 *of A*), 39.2 (C-5 *of B*), 40.0 (d, $^1J_{PC}$ = 144.5, C-2 *of A*), 40.4 (d, $^1J_{PC}$ = 146.0, C-2 *of B*), 55.6 and 55.7 ($ArO\underline{C}H_3$ *of A and B*), 58.2 (d, $^3J_{PC}$ = 5.0, C-4 *of B*), 58.5 (d, $^3J_{PC}$ = 6.0, C-4 *of B*), 62.1-63.5 (4C, m, $O\underline{C}H_2CH_3 \times 4$), 113.8 (C-8 of A), 114.0 (C-8 of B), 118.4 (C-10 of A), 118.5 (C-10 of B), 124.7, 125.0, 128.0 and 128.5 (C-6 and C-11 of A and B), 131.7 (C-7 of B), 132.5 (C-7 of A), 159.3 (2 signals) (C-9 of A and B), 169.3 (d, $^2J_{PC}$ = 3.5, C-1 *of B*), 169.4 (d, $^2J_{PC}$ = 3.5, C-1 *of A*); δ_P (121 MHz, $CDCl_3$) 25.0 (*B*) and 25.1 (*A*); HRMS: (ESI) Found: $[M+Na]^+$ 456.0545, $C_{22}H_{25}{}^{79}BrNO_5P$ requires 456.0546.

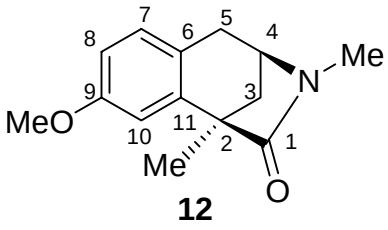
(S)-5-(2-Bromo-4-methoxybenzyl)-1-methyl-3-methylenepyrrolidin-2-one (3)



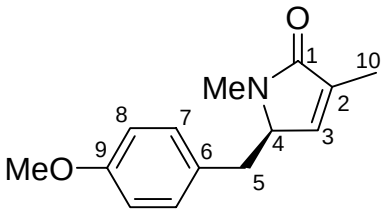
NaH (21.4 mg, 0.54 mmol, 60 % dispersion in mineral oil) was washed, *via* syringe, with anhydrous hexane (2 × 0.5 mL) and then suspended in anhydrous THF (1 mL). To this suspension was added, *via* syringe, a solution of α-phosphono lactam **11** (217 mg, 0.51 mmol) in anhydrous THF (1 mL and 0.5 mL line wash) resulting in immediate gas evolution and the formation of a brown solution. Paraformaldehyde (30.6 mg, 1.02 mmol) was added and the mixture was stirred at r.t. for 3 hrs. The

reaction was quenched by addition of aq. 1 M HCl (2 mL), then diluted with brine (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with aq. 1 M NaOH solution (20 mL) and then brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was dissolved in EtOAc and rapidly filtered through a short plug of silica (60, 2 × 2 cm) eluting with EtOAc (30 mL). Concentration of the eluent *in vacuo* afford the exocylic alkene **3** (116 mg, 74 %) as a pale yellow oil. *This material was unstable to chromatography (60 silica or neutral alumina) and so was used in the next stage without further purification;* δ_H (400 MHz, $CDCl_3$) 2.46-2.55 (2H, m, C3-H and C5-H), 2.68 (1H, dddd, *J* = 17.0, 8.0, 3.0 and 3.0, C3-H), 3.00 (3H, s, NCH_3), 3.29 (1H, dd, *J* = 13.5 and 4.5, C5-H), 3.80 (3H, s, $ArOCH_3$), 3.80-3.88 (1H, m, C4-H), 5.28 (1H, ddd, *J* = 3.0, 3.0 and 1.0, C12-H), 5.97 (1H, ddd, *J* = 3.0, 3.0 and 1.0, C12-H), 6.82 (1H, dd, *J* = 8.5 and 3.0, C8-H), 7.09 (1H, d, *J* = 8.5, C7-H), 7.13 (1H, d, *J* = 3.0, C10-H); δ_C (100 MHz, $CDCl_3$) 28.8 (NCH_3), 30.4 (C-3), 39.3 (C-5), 55.6 and 56.0 ($ArOCH_3$ and C-4), 113.8 (C-8), 115.5 (C-12), 118.5 (C-10), 125.0 and 128.3 (C-6 and C-11), 131.8 (C-7), 138.9 (C-2), 159.2 (C-9), 168.2 (C-1).

(1R,9R)-4-Methoxy-1,10-dimethyl-10-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-11-one (12) *and* (R)-5-(4-methoxybenzyl)-1,3-dimethyl-1,5-dihydropyrrol-2-one (16)



12



16

A stock solution was prepared by dissolving AIBN (42 mg, 0.26 mmol, freshly recrystallised from Et_2O and dried under high vacuum (r.t., 0.01 mmHg) for 4 hrs) and freshly prepared Bu_3SnH (200 mg, 0.57 mmol) in anhydrous benzene (32 mL, freshly distilled from sodium benzophenone ketyl and further deoxygenated by passage of N_2 for 2 hrs). To a flask containing a solution of alkene **3** (28 mg, 0.09 mmol) in refluxing benzene (8 mL, prepared as above) was added a portion of the stock solution (8 mL) over 1.5 hrs *via* syringe pump. After stirring for a further 1 hr the mixture was cooled to r.t. and concentrated *in vacuo*. The residue was dissolved in MeCN (10 mL) and washed with hexane (2 × 5 mL). The MeCN portion was then

concentrated *in vacuo* to afford a colourless oil which was purified by FCC (EtOAc-hexanes 4:1) to yield the tricycle **12** (13.0 mg, 62 %) as a colourless crystalline solid and subsequently the endocylic alkene **16** (3.7 mg, 18 %) as a colourless oil.

12: m.p. 147-148 ^{o}C (EtOAc-hexanes) [Lit.[3],142-143 ^{o}C (racemate, no recrystallisation solvent quoted)]; $[\alpha]_D^{20}$ -20.0 (c = 1.2, $CHCl_3$); ν_{max} / cm^{-1} (film) 2934 (m), 1695 (s), 1289 (m), 1244 (m), 1040 (m); δ_H (400 MHz, $CDCl_3$) 1.55 (3H, s, C2-C$\underline{H}_3$), 2.03 (1H, d, *J* = 10.5, C3-$\underline{H}$), 2.18 (1H, dd, *J* = 10.5 and 5.5, C3-$\underline{H}$), 2.83 (3H, s, NC$\underline{H}_3$), 2.87-3.00 (2H, m, C5-$\underline{H}$), 3.78 (3H, s, ArOC$\underline{H}_3$), 3.84 (1H, dt, *J* = 5.5 and 2.5, C4-$\underline{H}$), 6.74 (1H, dd, *J* = 8.5 and 3.0, C8-$\underline{H}$), 6.84 (1H, d, *J* = 3.0, C10-$\underline{H}$), 6.99 (1H, d, *J* = 8.5, C7-$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 17.5 (C2-$\underline{C}H_3$), 27.6 (N$\underline{C}H_3$), 30.0 ($\underline{C}$-5), 40.7 ($\underline{C}$-3), 45.2 ($\underline{C}$-2), 54.9 and 55.3 (ArO$\underline{C}H_3$ and $\underline{C}$-4), 110.1 ($\underline{C}$-10), 112.8 ($\underline{C}$-8), 124.4 ($\underline{C}$-6), 130.7 ($\underline{C}$-7), 141.5 ($\underline{C}$-11), 158.1 ($\underline{C}$-9), 177.1 ($\underline{C}$-1); *m/z* (CI^+) 232 ($[M+H]^+$, 100 %); HRMS: (CI^+) Found: $[M+H]^+$ 232.1331, $C_{14}H_{18}NO_2$ requires 232.1338. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[3]

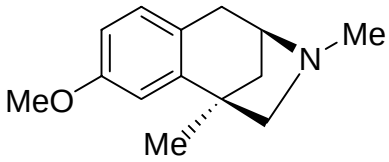
16: *This material was contaminated with ca. 5 % of* ***16*** *as judged by* ^{1}*H NMR*; ν_{max} / cm^{-1} (film) 2924 (br), 1685 (s), 1513 (m), 1248 (m), 1035 (w); δ_H (400 MHz, $CDCl_3$) 1.84 (3H, t, *J* = 1.5, C10-$\underline{H}$), 2.51 (1H, dd, *J* = 13.5 and 9.0, C5-$\underline{H}$), 3.01 (3H, s, NC$\underline{H}_3$), 3.11 (2H, dd, *J* = 13.5 and 5.0, C5-$\underline{H}$), 3.80 (3H, s, ArOC$\underline{H}_3$), 3.94-4.01 (1H, m C4-$\underline{H}$), 6.50 (1H, t, *J* = 1.5, C3-$\underline{H}$), 6.84 (2H, d, *J* = 9.0, C8-*H*), 7.07 (2H, d, *J* = 9.0 C7-$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 11.2 ($\underline{C}$-10), 27.7 (N$\underline{C}H_3$), 37.0 ($\underline{C}$-5), 55.3 (ArO$\underline{C}H_3$), 63.4 ($\underline{C}$-4), 114.0 ($\underline{C}$-8), 128.4 and 135.3 ($\underline{C}$-2 and $\underline{C}$-6), 130.1 ($\underline{C}$-9), 139.5 ($\underline{C}$-3), 158.5 ($\underline{C}$-9), 172.0 ($\underline{C}$-1); *m/z* (CI^+) 232 ($[M+H]^+$, 100 %); HRMS: (CI^+) Found: $[M+H]^+$ 232.1335, $C_{14}H_{18}NO_2$ requires 232.1338.

Preparation of Bu_3SnH

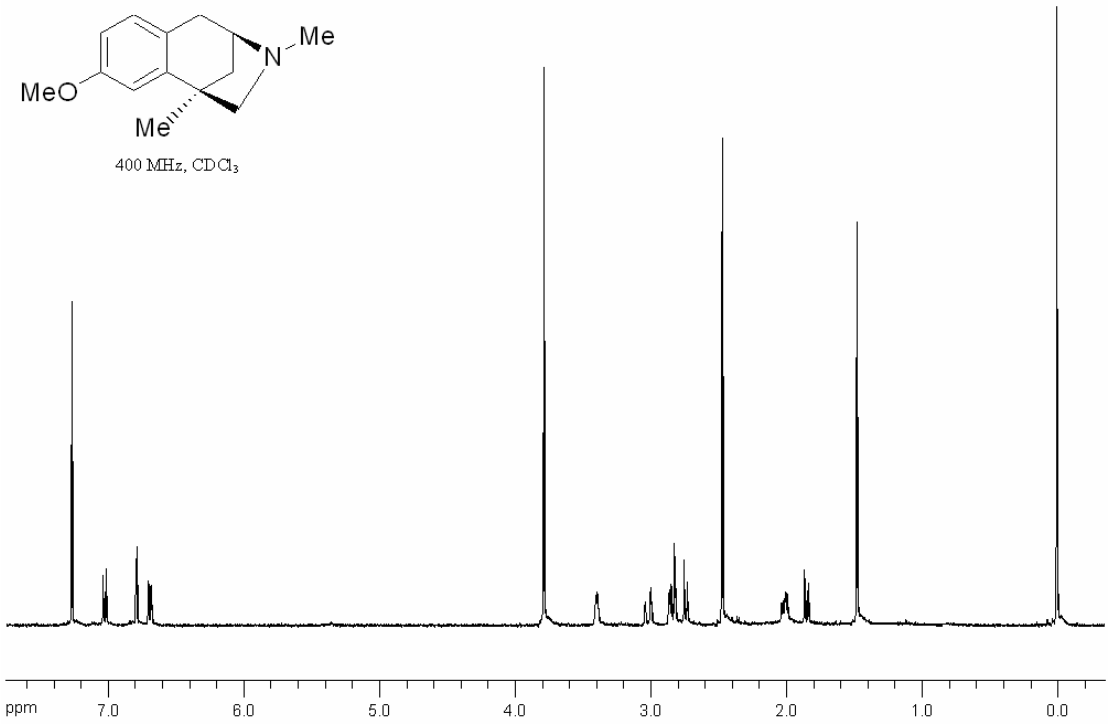
This was prepared according to the procedure of Hayashi *et al*.[4] Thus, $(Bu_3Sn)_2O$ (1.7 mL, 3.36 mmol) was added *via* syringe to a N_2 purged flask containing poly(methylhydrosiloxane) (401 μL, 6.72 mmol) causing a mild exotherm. The mixture was stirred at r.t. for 1 hr (until no further exotherm was observed) and then distilled (*ca.* 85 ^{o}C, 0.1 mmHg) to afford Bu_3SnH as a colourless oil (*N.B.* An initial

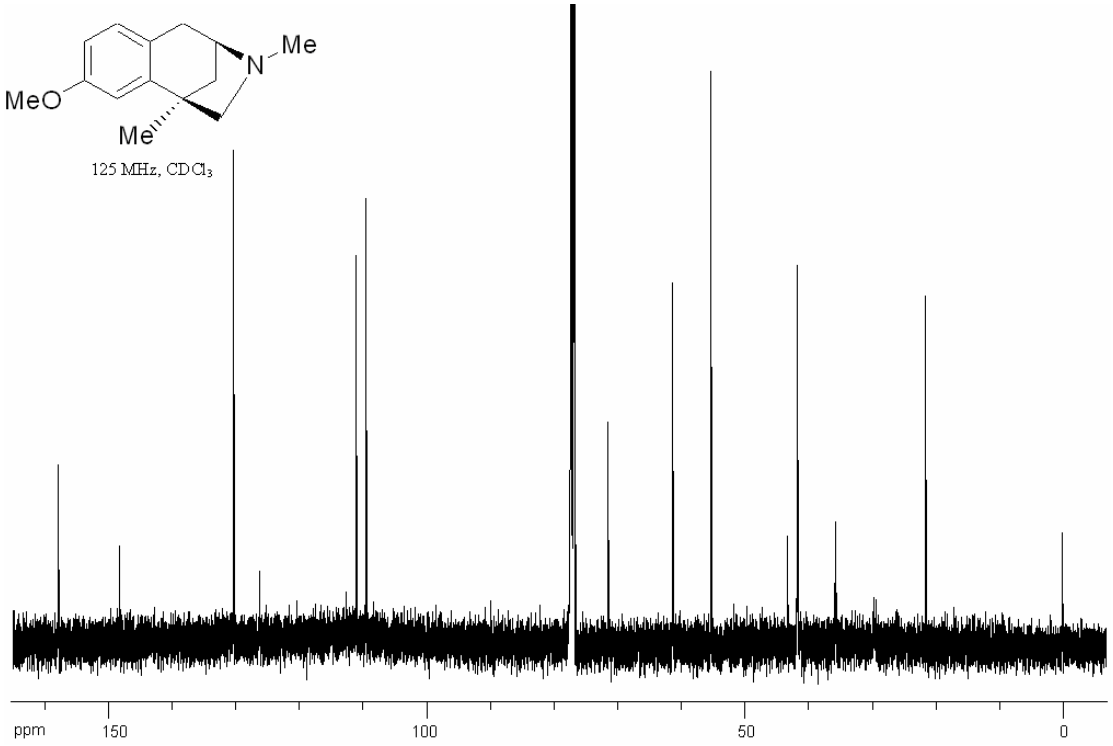
minor fraction (b.p. *ca.* 65 ^{o}C, 0.1 mmHg) was discarded). *This material was generally prepared immediately prior to use but, if desired, could be stored under N_2 at 5 ^{o}C for up to 48 hrs without any evidence (cloudiness) of decomposition.*

(+)-*O*-Methyl aphanorphine (13)



Lactam **12** was converted to (+)-*O*-methyl aphanorphine **13** using the procedure described by Funk;[3] $[\alpha]_D^{20}$ +8.3 (c = 0.5, $CHCl_3$); lit. $[\alpha]^{28}_D$ +8.1 (c 1.2, $CHCl_3$),[5] $[\alpha]^{20}_D$ +9.4 (c 0.3, $CHCl_3$),[6] $[\alpha]^{20}_D$ +8.7 (c 1.06, $CHCl_3$);[7] δ_H (400 MHz, $CDCl_3$) 1.48 (3H, s), 1.84 (1H, d, *J* = 11.0), 2.01 (1H, ddd, *J* = 11.0, 5.5 and 1.0), 2.47 (3H, s), 2.73 (1H, d, *J* = 9.0), 2.80-2.87 (2H, m), 3.01 (1H, d, *J* = 17.0), 3.39 (1H, ddd, *J* = 5.5, 3.0 and 3.0), 3.78 (3H, s), 6.68 (1H, dd, *J* = 8.5 and 2.5), 6.78 (1H, d, *J* = 2.5), 7.02 (1H, d, *J* = 8.5); δ_C (125 MHz, $CDCl_3$) 21.5, 35.7, 41.6, 41.7, 43.2, 55.3, 61.3, 71.3, 109.4, 110.9, 126.1, 130.2, 148.1, 157.7 . *The spectroscopic properties of this compound were consistent with the data available in the literature.*[8]





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