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 °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
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 2 Cl 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 Bruker 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 (S)

This compound was prepared by adaptation of the procedure of Durst.¹ To a solution of $N,N,N'$-trimethylethylene diamine (10.19 mL, 78.4 mmol, freshly distilled from CaH$_2$) in anhydrous THF (180 mL) at -20 °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 °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 °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 °C for 30 minutes and then allowed to stand in the freezer (*ca.* -15 °C) for 24 hrs. The reaction mixture, now a deep orange solution, was cooled to -78 °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 Et₂O (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 (Na₂SO₄) 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 °C (petrol) [Lit.¹, 70-71 °C (EtOH)]; δ_H (400 MHz, CDCl₃) 3.90 (3H, s, ArOC_H₃), 6.96 (1H, ddd, J = 8.5, 3.0 and 1.0, C₅-H), 7.15 (1H, d, J = 3.0, C₃-H), 7.91 (1H, d, J = 8.5, C₆-H), 10.24 (1H, d, J = 1.0, Ar(CO)H). *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)

![Z-3-(2-Bromo-4-methoxyphenyl)-2-tert-butoxycarbonylaminoacrylic acid methyl ester (6)](image)

To solution of aldehyde 5 (512 mg, 2.38 mmol) and (+)-N-Boc-α-phosphonoglycine trimethyl ester (779 mg, 2.62 mmol) in anhydrous CH₂Cl₂ (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 CH₂Cl₂ (10 mL), washed with 10 % aq. citric acid solution (20 mL) and then saturated aq. NaHCO₃ solution (20
mL), dried (Na$_2$SO$_4$) 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; $\nu_{\text{max}} / $ cm$^{-1}$ (film) 3336 (w), 1703 (s), 1156 (s), 1026 (s); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1.36 (9H, s, NHCO$_2$C(CH$_3$)$_3$), 3.83 (3H, s, ArOCH$_3$), 3.88 (3H, s, CO$_2$CH$_3$), 6.25 (1H, br s, NHCO$_2$C(CH$_3$)$_3$), 6.83 (1H, dd, $J =$ 8.5 and 2.5, C5-H), 7.16 (1H, d, $J =$ 2.5, C3-H), 7.38 (1H, s, C7-H), 7.60 (1H, d, $J =$ 8.5, C6-H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 30.0 (NHCO$_2$C(CH$_3$)$_3$), 52.6 (ArOCH$_3$), 55.5 (CO$_2$CH$_3$), 80.7 (NHCO$_2$C(CH$_3$)$_3$), 113.6 (C-5), 117.7 (C-3), 124.3, 125.7 and 126.8 (C-1, C-2 and C-8), 127.3 (C-7), 130.3 (C-6), 152.4 (C-4), 160.1 (NHCO$_2$(CH$_3$)$_3$), 165.8 (CO$_2$CH$_3$); 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$_{20}$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$_3$); $\nu_{\text{max}} / $ cm$^{-1}$ (film) 3374 (br), 2977 (br), 1715 (s), 1495 (s), 1243 (m), 1167 (s), 1029 (m); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1.39 (9H, s, NHCO$_2$C(CH$_3$)$_3$), 3.05 (1H, dd, $J =$ 14.0 and 7.5, C7-H), 3.25 (1H, dd, $J =$ 14.0 and 6.5, C7-H), 3.73 (3H, s, CO$_2$CH$_3$), 3.79 (3H, s, ArOCH$_3$), 4.60
(1H, ddd, J = 8.0, 7.5 and 6.5, C8-H), 5.08 (1H, d, J = 8.0, NHCO2C(CH3)3), 6.81 (1H, d, 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); δC (100 MHz, CDCl3) 28.2 (NHCO2C(CH3)3), 37.7 (C-7), 52.3 (ArOCH3), 53.7 (C-8), 55.5 (CO2CH3), 80.0 (NHCO2C(CH3)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 (NHCO2C(CH3)3), 170.3 (CO2CH3); HRMS: (ESI) Found: [M+Na]⁺ 410.0570, C16H2279BrNO5 requires 410.0574; Anal. Calcd for C16H22NO5Br: 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 °C) against a racemic standard prepared under similar conditions using Wilkinson’s catalyst ((Ph3P)3RhCl, 5 mol %, 7 atm., 48 hrs); tR (major) = 9.1 min and tR (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 °C was added, dropwise via syringe, a solution of LiAlH4 in THF (1 M, 2.16 mL, 2.16 mmol) over 2 minutes. The resulting solution was stirred at 0 °C 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 CH2Cl2 (ca. 50 mL), washed with water (20 mL) and then brine (20 mL), dried (Na2SO4) and concentrated in vacuo to afford the alcohol 8 (498 mg, 96 %) as a colourless, crystalline solid; m.p. 87-90 °C (Et2O-hexanes); [α]D²⁰ +34.0 (c = 1.5, CHCl3); νmax / cm⁻¹ (film) 3394 (br m), 1689 (s), 1494 (s), 1243 (m), 1169 (m), 1028 (m); δH (270 MHz, CDCl3) 1.39 (9H, s, NHCO2C(CH3)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, ArOCH3), 4.85 (1H, br d, J = 7.5, NHCO2C(CH3)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); δc (100 MHz, CDCl3) 28.3 (NHCO2C(CH3)3), 36.5 (C-7), 36.5 (C-8 and ArOCH3), 64.4 (C-9), 79.8 (NHCO2C(CH3)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 (NHCO2(CH3)3); HRMS: (ESI) Found: [M+Na]+ 382.0621, C15H2279BrNO4 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 % qaq. NaOH solution (3 mL) and then heated at reflux (oil bath ca. 90 °C) for 2 hrs. After cooling to r.t., the mixture was diluted with brine (20 mL) and extracted with CH2Cl2 (3 × 15 mL). The combined organic extracts were dried (Na2SO4) 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; [α]D20 +20.0 (c = 0.6, CHCl3); νmax / cm⁻¹ (film) 3309 (br m), 1603 (m), 1491 (s), 1240 (s), 1026 (s); δH (400 MHz, CDCl3) 2.12 (2H, br s, NHMe and CH2OH), 2.42 (3H, s, NHCH3), 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-
(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 Et₃N (501 µL, 3.66 mmol) in anhydrous CH₂Cl₂ (15 mL) was added, dropwise, via syringe, over 5 minutes, a solution of SOCl₂ (150 µL, 2.04 mmol) in anhydrous CH₂Cl₂ (3 mL). The resulting colourless solution was stirred at 0 °C 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 CH₂Cl₂ (2 × 15 mL). The combined organic extracts were washed with water (15 mL) and then brine (15 mL), dried (Na₂SO₄) 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 NaIO₄ (69 mg, 0.32 mmol) and RuCl₃ (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 °C until careful TLC analysis showed complete consumption of starting material (ca. 0.25 hrs; TLC conditions: 1:1 Et₂O-Petrol; intermediate sulfamidite co-elutes with sulfamidate 4 but can be stained using KMnO₄ 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 (Na₂SO₄) and concentrated in vacuo to afford a brown residue which was immediately purified by FCC (Et₂O-petrol 1:1, CH₂Cl₂ loading) to afford the sulfamidate 4 (88 mg, 82 %, 99 % e.e.) as a colourless crystalline solid; m.p. 82-83 °C.
(Et₂O); [α]D²0 +8.9 (c = 0.9, CHCl₃); νmax / cm⁻¹ (film) 1605 (m), 1494 (m), 1345 (s), 1179 (s), 1028 (m), 972 (m); δH (400 MHz, CDCl₃) 2.79 (3H, s, NHCH₃), 2.88 (1H, dd, J = 14.0 and 9.0, C3-H), 3.26 (1H, dd, J = 14.0 and 5.5, C3-H), 3.75-3.85 (1H, m, C2-H), 3.80 (3H, s, Ar-OC₃), 3.80 (1H, dd, J = 8.5 and 7.0, C1-H), 4.40 (1H, dd, J = 8.5 and 6.5, C1-H), 6.84 (1H, dd, J = 8.5 and 2.5, C6-H), 7.13 (1H, d, J = 2.5, C8-H), 7.14 (1H, d, J = 8.5, C5-H); δC (100 MHz, CDCl₃) 34.0 (NCH₃), 37.4 (C-3), 55.7 and 60.5 (ArOCH₃ and C-2), 70.5 (C-1), 114.1 (C-6), 118.7 (C-8), 124.7 and 126.2 (C-4 and C-9), 132.0 (C-5), 159.7 (C-7); m/z (Cl⁻) 336 and 338 ([M+H⁺], 100 and 95%); HRMS: (Cl⁻) Found: [M+H⁺]⁺ 335.9891, C₁₁H₁₄BrNO₄S 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 °C); tR (major) = 28.3 min and tR (minor) = 31.7 min.

[(R)-5-(2-Bromo-4-methoxybenzyl)-1-methyl-2-oxypyrrolidin-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 °C to form a clear solution. After 25 minutes, sulfamidate 4 (300 mg, 0.89 mmol) was added and the reaction was stirred at 40 °C 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. NaHCO₃ solution, stirred for 12 hrs, diluted with brine (10 mL) and extracted with CH₂Cl₂ (2 × 20 mL). The organic portion was dried (Na₂SO₄) 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; $\nu_{\text{max}}$ / cm$^{-1}$ (film) 2981 (br w), 1687 (s), 1492 (m), 1240 (s), 1021 (s), 963 (m); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1.24-1.40 (12H, m, OCH$_2$CH$_3$ 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, NCH$_3$ and C2-H of A and B), 3.27 (1H, dd, $J = 13.0$ and 4.0, C5-H of B), 3.78-3.85 (1H, m, C4-H of B), 3.80 (3H, s, ArOC$_6$H$_4$ of B), 3.85-3.94 (1H, m, C4-H of A), 4.09-4.33 (8H, m, OCH$_2$ 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); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 16.3-16.7 (4C, m, OCH$_2$CH$_3$ × 4), 25.1 (d, $^2J_{\text{PC}} = 4.0$, C-3 of B), 26.1 (d, $^2J_{\text{PC}} = 3.5$, C-3 of A), 28.7 (2 signals) (NCH$_3$ of A and B), 38.6 (C-5 of A), 39.2 (C-5 of B), 40.0 (d, $^1J_{\text{PC}} = 144.5$, C-2 of A), 40.4 (d, $^1J_{\text{PC}} = 146.0$, C-2 of B), 55.6 and 55.7 (ArOC$_6$H$_4$ of A and B), 58.2 (d, $^3J_{\text{PC}} = 5.0$, C-4 of B), 58.5 (d, $^3J_{\text{PC}} = 6.0$, C-4 of B), 62.1-63.5 (4C, m, OCH$_2$CH$_3$ × 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, $^2J_{\text{PC}} = 3.5$, C-1 of B), 169.4 (d, $^2J_{\text{PC}} = 3.5$, C-1 of A); $\delta_{\text{P}}$ (121 MHz, CDCl$_3$) 25.0 (B) and 25.1 (A); HRMS: (ESI) Found: [M+Na]$^+$ 456.0545, C$_{22}$H$_{25}$BrNO$_3$P 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 $\alpha$-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$_2$SO$_4$) 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 exocyclic 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; $\delta_H$ (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, dddd, $J = 3.0$, 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); $\delta_C$ (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)

A stock solution was prepared by dissolving AIBN (42 mg, 0.26 mmol, freshly recrystallised from Et$_2$O and dried under high vacuum (r.t., 0.01 mmHg) for 4 hrs) and freshly prepared Bu$_3$SnH (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 °C (EtOAc-hexanes) [Lit.3,142-143 °C (racemate, no recrystallisation solvent quoted)]; [α]D20 -20.0 (c = 1.2, CHCl3); νmax / cm\(^{-1}\) (film) 2934 (m), 1695 (s), 1289 (m), 1244 (m), 1040 (m); δH (400 MHz, CDCl3) 1.55 (3H, s, C2-CH3), 2.03 (1H, d, J = 10.5, C3-H), 2.18 (1H, dd, J = 10.5 and 5.5, C3-H), 2.83 (3H, s, NCH3), 2.87-3.00 (2H, m, C5-H), 3.78 (3H, s, ArOC-H3), 3.84 (1H, dt, J = 5.5 and 2.5, C4-H), 6.74 (1H, dd, J = 8.5 and 3.0, C8-H), 6.84 (1H, d, J = 3.0, C10-H), 6.99 (1H, d, J = 8.5, C7-H); δC (100 MHz, CDCl3) 17.5 (C2-CH3), 27.6 (NCH3), 30.0 (C-5), 40.7 (C-3), 45.2 (C-2), 54.9 and 55.3 (ArOCH3 and C-4), 110.1 (C-10), 112.8 (C-8), 124.4 (C-6), 130.7 (C-7), 141.5 (C-11), 158.1 (C-9), 177.1 (C-1); m/z (CI+) 232 ([M+H]+, 100 %); HRMS: (CI+) Found: [M+H]+ 232.1331, C14H18NO2 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; νmax / cm\(^{-1}\) (film) 2924 (br), 1685 (s), 1513 (m), 1248 (m), 1035 (w); δH (400 MHz, CDCl3) 1.84 (3H, t, J = 1.5, C10-H), 2.51 (1H, dd, J = 13.5 and 9.0, C5-H), 3.01 (3H, s, NCH3), 3.11 (2H, dd, J = 13.5 and 5.0, C5-H), 3.80 (3H, s, ArOCH3), 3.94-4.01 (1H, m C4-H), 6.50 (1H, t, J = 1.5, C3-H), 6.84 (2H, d, J = 9.0, C8-H), 7.07 (2H, d, J = 9.0 C7-H); δC (100 MHz, CDCl3) 11.2 (C-10), 27.7 (NCH3), 37.0 (C-5), 55.3 (ArOCH3), 63.4 (C-4), 114.0 (C-8), 128.4 and 135.3 (C-2 and C-6), 130.1 (C-9), 139.5 (C-3), 158.5 (C-9), 172.0 (C-1); m/z (CI+) 232 ([M+H]+, 100 %); HRMS: (CI+) Found: [M+H]+ 232.1335, C14H18NO2 requires 232.1338.

Preparation of Bu3SnH
This was prepared according to the procedure of Hayashi et al.4 Thus, (Bu3Sn)2O (1.7 mL, 3.36 mmol) was added via syringe to a N2 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 °C, 0.1 mmHg) to afford Bu3SnH as a colourless oil (N.B. An initial
minor fraction (b.p. ca. 65 °C, 0.1 mmHg) was discarded). This material was generally prepared immediately prior to use but, if desired, could be stored under N₂ at 5 °C for up to 48 hrs without any evidence (cloudiness) of decomposition.

(+)-O-Methyl aphanorphine (13)

[Chemical structure image]

Lactam 12 was converted to (+)-O-methyl aphanorphine 13 using the procedure described by Funk;³ [α]⁺Dₒ +8.3 (c = 0.5, CHCl₃); lit. [α]⁺D₂₀ +8.1 (c 1.2, CHCl₃),⁵ [α]⁺D₀ +9.4 (c 0.3, CHCl₃),⁶ [α]⁺D₀ +8.7 (c 1.06, CHCl₃);⁷ δH (400 MHz, CDCl₃) 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); δC (125 MHz, CDCl₃) 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
(C) References