General remarks

$^1$H-NMR spectra: These were recorded on Bruker DPX-250 (250 MHz); Bruker DRX-400 (400 MHz) and Bruker DRX-500 (500 MHz) spectrometers using deuterochloroform as an internal deuterium lock. The chemical shift are quoted in ppm relative to tetramethylsilane ($\delta_H = 0.00$ ppm). The multiplicity of the signal is indicated as: s - singlet, d - doublet, t - triplet, q - quartet, qn - quintet, br - broad, m - multiplet, dd - doublet of doublets, dt - doublet of triplets etc. Coupling constants ($J$) are quoted in Hz.

Two dimensional (2D) spectra were recorded on Bruker DRX-500 (500 MHz) spectrometers, fitted with gradient coils. Double Quantum Filtered (DQF) and magnitude COSY spectra were typically acquired with 256 slices in $F_1$ and 2048 points in $F_2$ (acquisition time approximately 20 min).

$^{13}$C-NMR spectra: These were recorded on Bruker DPX-250 (62.5 MHz) and Bruker DRX-400 (100 MHz) instruments using an internal deuterium lock and proton decoupling. The chemical shift are quoted in ppm relative to tetramethylsilane ($\delta_H = 0.00$ ppm). The attached proton tests (APT) were used to assign signals in particular cases.

Infrared spectra: These were recorded on a Perkin-Elmer 1600 series FTIR spectrometer (nujol, film, CHCl$_3$). Relative intensities are indicated as s, strong; m, medium; w, weak; br, broad.

Mass spectra: These were recorded by the EPSRC Mass Spectrometry Service Centre, University of Swansea or the University of Cambridge. In Swansea, Electron Impact (EI) and Chemical Ionisation (CI) low resolution spectra were carried out on a VG model 12-253 under ACE conditions and a Quattro II low resolution triple quadrupole MS. Accurate mass measurements for EI and CI were performed on a +VG ZAB-E and Finnigan MAT 900 XLT instruments. In Cambridge, FAB, EI and CI low resolution and accurate mass spectra were performed on a Kratos MS-890 and on a Micromass Q-TOF instrument. Electrospay spectra were determined with an ES Bruker FTICR. All CI measurements were performed with NH$_3$ as the carrier gas.

Melting Points: Melting points were determined using a Büchi 510 melting point apparatus, and are uncorrected.

Kugelrohr bulb-to-bulb distillations: These were carried out using a Büchi GKR-51 machine. Boiling points are the actual oven temperatures.

Chromatography: Flash chromatography was carried out on silica gel [Merck 9385 Kieselgel 60 (230-400 ASTM)].$^1$ TLC was performed on 0.25 mm thick plates precoated with Merck Kieselgel 60 F$_{254}$ silica gel.

Solvents: Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other solvents were purified by standard techniques.$^2$ Ether refers to diethyl ether. Dioxane refers to 1, 4-dioxane. Brine refers to a saturated solution of sodium chloride in water.
EXPERIMENTAL
Investigations into the regiochemical outcome of the intramolecular nitrone dipolar cycloaddition reaction.
Model studies: formation of the nitrone by direct hydroxylamine-alkyne cyclisation

4-Benzylxybutan-1-ol, 14.
Sodium hydride (50% dispersion in mineral oil; 7.3 g, 150 mmol, 1.3 eq) was dissolved in dry dioxane (54 mL) and the mixture cooled to 0 °C under nitrogen. Butan-1,4-diyl (16.0 g, 180 mmol, 1.5 eq) was added dropwise over 40 min and the reaction mixture warmed to 25 °C and stirred for 3 h. Benzyl chloride (13.5 mL, 18 mmol, 1 eq) was added dropwise over 35 min and the reaction heated at reflux for 1.5 h. The reaction mixture was cooled to 25 °C, washed with brine (40 mL) and water (40 mL) and the combined aqueous extracted with dichloromethane (3 x 60 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo yielding a yellow oil. The compound was purified by flash column chromatography (1:1 hexane:EtOAc) yielding the monobenzylated product 14 (17.0 g, 80%) as a light yellow oil; Rf 0.38 (1:1 hexane:EtOAc); δH (250 MHz; CDCl₃) 7.35-7.22 (5H, m, aromatics), 4.52 (2H, s, PhCH₂O), 3.66 (2H, q, J 5.1, CH₂OH), 3.55 (2H, t, J 7.1, BnOC₂H), 2.18-2.10 (1H, t, J 5.1, OH) and 1.87-1.60 (4H, m, 2 x CH₂); data identical to literature values.

4-Benzylxy-1-iodobutane, 15.
4-Benzylxybutan-1-ol 14 (17.0 g, 94 mmol, 1 eq) was dissolved in dichloromethane (76 mL) and DMAP (115 mg, 0.94 mmol, 0.01 eq) and triethylamine (19.7 mL, 140 mmol, 1.5 eq) were added. The mixture was stirred at 25 °C under nitrogen and a solution of para-toluenesulfonyl chloride (18.0 g, 94 mmol, 1 eq) in dichloromethane (59 mL) was added dropwise over 30 min. The mixture was stirred for 16 h and then poured into water (70 mL). The organics were separated and washed with aqueous hydrochloric acid (2 M; 2 x 50 mL) and the combined aqueous extracted with dichloromethane (3 x 50 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo yielding the crude tosylate as a yellow oil. The crude tosylate was dissolved in acetone (150 mL) and sodium iodide (21.2 g, 140 mmol, 1.5 eq) added. The mixture was stirred for 16 h under nitrogen with the exclusion of light and then poured into a mixture of water (150 mL) and ether (150 mL). The aqueous was separated and extracted with ether (2 x 50 mL) and the combined organics were dried (MgSO₄) and concentrated in vacuo yielding an orange oil. The compound was purified by flash column chromatography (19:1 hexane:EtOAc), with the exclusion of light, yielding the iodide 15 (24.0 g, 88%) as a pale yellow oil; Rf 0.46 (9:1 hexane:EtOAc); δH (250 MHz; CDCl₃) 7.35-7.23 (5H, m, aromatics), 4.50 (2H, s, PhCH₂O), 3.52 (2H, t, J 10.1, BnOCH₂), 3.32 (2H, t, J 10.2, CH₂I), 2.00-1.90 (2H, m, CH₂) and 1.80-1.78 (2H, m, CH₂); data identical to literature values.
2-(Pent-4yny1-yloxy)tetrahydropyran, 17.

Pent-4-yn-1-ol 16 (10.0 g, 0.119 mol) and 3,4-dihydropyran (10.0 g, 0.119 mol) were dissolved in dichloromethane (100 mL). Amberlyst® 15 acidic ion exchange resin (1.0 g) was added, and the reaction monitored by tlc (1 : 1 hexane : ether). The mixture was stirred under nitrogen at rt for 24 h, filtered and the solvent was removed in vacuo to give the crude product as a brown oil. The crude product was further purified by flash column chromatography eluting with 10 : 3 hexane : EtOAc. The product was further purified by Kugelrohr bulb-to-bulb distillation to yield the THP ether 17 (19.2 g, 96%) as a colourless oil; Rf 0.57 (1 : 1 hexane : ether) and 0.38 (10 : 3 hexane : EtOAc); bp 180 °C, 20 mmHg (lit.6 60 °C, 1.5 mmHg); νmax (film) 3297, 2942, 2871, 2119, 1441, 1137 and 1121 cm⁻¹; δH (CDCl₃, 200 MHz) 4.59 (1H, td, J 3.6 and 1.2, CHO₂), 3.90 - 3.70 (2H, m, CH₂OTHP), 3.50 - 3.40 (2H, m, CH₂O), 2.32 (2H, tdd, J 7.3, 2.7 and 0.5, CH₂C≡C), 1.94 (1H, t, J 2.7, C≡CH) and 1.90 - 1.50 (8H, m, 4 x -CH₂-).

2-(9-Benzylxynon-4-yn-1-yloxy)tetrahydropyran, 18.

n-Butyllithium (1.5 M in hexane; 9.68 mL, 14.5 mmol) was added slowly dropwise to a stirred solution of 2-(pent-4-ynyl-1-oxy)tetrahydropyran 17 (2.22 g, 13.2 mmol) in dry THF (25 mL) at −10 °C under nitrogen. After 10 min. dry DMPU (8.25 mL) was added, and the mixture stirred for a further 10 min. A solution of the 4-benzyloxy-1-iodobutane 15 (3.83 g, 13.2 mmol) in dry THF (10 mL) was added at –10 °C. The mixture was stirred for 1 h at –10 °C, and was then warmed to 25 °C and stirred for 45 h. The mixture was poured into brine (120 mL) and extracted with dichloromethane (240 mL, 2 x 120 mL). The combined organic extracts were dried (MgSO₄) and the solvent was removed in vacuo. The crude product was purified by flash column chromatography eluting with 19 : 1 hexane/EtOAc to give the crude product 18. The crude product was further purified by flash column chromatography eluting with 19 : 1 hexane/EtOAc to yield the pure alkyne 18 (2.51 g, 88%) as a colourless oil; Rf 0.45 (hexane/EtOAc, 9:1) and 0.09 (hexane/EtOAc, 1:9); FTIR νmax (KBr) 2944, 2865, 1495, 1451, 1358, 1200, 1119, 1080, 1026 cm⁻¹; δH (CDCl₃, 250 MHz) 7.39-7.21 (5H, m, aromatics), 4.59 (1H, t, J 3.5, CHO₂), 4.50 (2H, s, PhCH₂O), 3.93 - 3.75 (2H, m, CH₂O), 3.55-3.41 (2H, m, CH₂OTHP), 3.49 (2H, t, J 6.5, CH₂OBn), 2.26 (2H, tt, J 7.0 and 2.5, CH₂C≡C), 2.17 (2H, tt, J 7.0 and 2.5, C≡CCH₂), 1.83-1.45 (12H, m, 6 x CH₂); δC (CDCl₃, 63 MHz) 138.6, 128.3, 127.6, 127.5, 98.7, 80.1, 79.8, 72.9, 69.9, 66.1, 62.1, 30.7, 29.3, 28.9, 25.8, 25.5, 19.5, 18.6, 15.6; HRMS (CI) m/z calcd for C₂₃H₂₄O₃ (M-H): 329.2117, found 329.2139; MS (CI, NH₃) m/z 331 (16%), 330 (18), 329 (48), 295 (8), 281 (32), 267 (14), 247 (24), 223 (14), 221 (36), 207 (40), 191 (16), 167 (19), 147 (100), 136 (49), 123 (54), 108 (81).
9-Benzylxynon-4-yn-1-ol, 19.

2-(9-Benzylxynon-4-ynyl-1-oxy)tetrahydropyran 18 (2.75 g, 8.32 mmol) was dissolved in methanol (50 mL). Amberlyst\textsuperscript{a} 15 acid ion exchange resin (1.50 g) was added and the mixture stirred at 25 °C for 23 h. The mixture was filtered and the product purified by flash column chromatography eluting with 1:1 hexane/EtOAc to give the alcohol 19 (1.98 g, 97%) as a colourless oil; \(R_f 0.39\) (hexane/EtOAc, 1:1); (Found: C, 77.60; H, 9.02; \(C_{18}H_{22}O_2\) requires C, 78.01; H, 9.00%). FTIR \(v_{\text{max}}\) (KBr) 3388, 3030, 2941, 2864, 1496, 1454, 1362, 1105, 1075, 773 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 7.36-7.24 (5H, m, aromatics), 4.49 (2H, s, PhCH\(_2\)O), 3.72 (2H, t, \(J 6.0\), CH\(_2\)OH), 3.47 (2H, t, \(J 6.5\), CH\(_2\)OBn), 2.25 (2H, tt, \(J 7.0\) and 2.5, CH\(_2\)C≡C), 2.16 (2H, tt, \(J 7.0\) and 2.5, C≡CCH\(_2\)), 1.83-1.65 (5H, m, 2 x CH\(_2\), OH), 1.62 - 1.51 (2H, m, CH\(_2\)); \(\delta_C\) (CDCl\(_3\), 100 MHz) 138.6, 128.4, 127.7, 127.8, 80.7, 79.7, 72.9, 69.9, 62.0, 31.6, 28.9, 25.8, 18.6, 15.4; HRMS (CI) \(m/z\) calc'd for \(C_{18}H_{23}O_2\) (M+H\(^+\)): 247.1698, found: 247.1720; MS (CI, NH\(_3\)) \(m/z\) 245 \([M+OH]^+\), 243 (16), 137 (12), 105 (12), 91 (100), 71 (20), 58 (43), 43 (33).

9-Benzylxynon-4-ynal, 20.

A solution of oxalyl chloride (0.48 mL, 704 mg, 5.55 mmol) in dry dichloromethane (50 mL) was cooled to \(-78^\circ\)C under argon. A solution of dry DMSO (0.79 mL, 866 mg, 11.1 mmol) in dry dichloromethane (5 mL) was added slowly dropwise maintaining the temperature below \(-65^\circ\)C, and the resulting white precipitate stirred for 30 min. A solution of dry triethylamine (1.9 mL, 1.4 g, 13.9 mmol) in dry dichloromethane (5 mL) was added slowly dropwise and the mixture allowed to warm to 25 °C over 1 h. The mixture was poured into water and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL) and the combined organic extracts were washed with saturated brine (50 mL) and dried (MgSO\(_4\)). The solvent was removed in vacuo to give the crude product as a yellow oil which was purified by flash column chromatography eluting with 7:3 hexane/EtOAc to yield the aldehyde 20 (554 mg, 90%) as a pale yellow oil; \(R_f 0.13\) (hexane/EtOAc, 9:1) and 0.44 (hexane/EtOAc, 7:3); FTIR \(v_{\text{max}}\) (KBr) 3030, 2940.5, 2912, 2862, 2727, 1728, 1496, 1454, 1360, 1206, 1106, 877 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\), 400 MHz) 9.77 (1H, t, \(J 1.5\), CHO), 7.36-7.24 (5H, m, aromatics), 4.49 (2H, s, PhCH\(_2\)O), 3.47 (2H, t, \(J 6.5\), CH\(_2\)OBn), 2.60 (2H, t, \(J 7.0\), CH\(_2\)CHO), 2.46 (2H, ttd, \(J 7.0\), 2.5 and 0.5, C≡CCH\(_2\)CH\(_2\)CHO), 2.15 (2H, t, \(J 7.0\) and 2.5, CH\(_2\)C≡C), 1.73-1.61 (2H, m, CH\(_2\)), 1.59-1.50 (2H, m, CH\(_2\)); \(\delta_C\) (CDCl\(_3\), 100 MHz) 201.2, 138.6, 128.4, 127.6, 127.5, 81.2, 78.1, 72.9, 69.9, 43.0, 28.9, 25.6, 18.5, 12.2; MS (Cl, NH\(_3\)) \(m/z\) 261 \([M+OH]^+\), 47\%; 245 \([M+H]^+\), 12\%; 243 (14), 225 (10), 201 (16), 187 (26), 169 (15), 157 (14), 139 (14), 129 (12), 109 (10).
(Z)-11-Benzylxyundec-2-en-6-yenitrile, 21.

Trimethylsilylacetonitrile (239 mg, 2.11 mmol) was dissolved in dry THF (4.2 mL) and cooled to –78 °C under argon. n-Butyllithium (1.5 M in hexane; 1.4 mL, 2.11 mmol) was added slowly dropwise and the mixture stirred for 20 min. Triisopropyl borate (0.49 mL, 2.11 mmol) was added and the mixture stirred for a further 10 min. A solution of 9-benzyloxynon-4-ynal 20 (516 mg, 2.11 mmol) in dry THF (1.7 mL) was added and after 2 min. dry HMPA (0.84 mL) was added. The mixture was stirred at –78 °C for 50 min., during which time the reaction was monitored by TLC (hexane/EtOAc, 7:3). Water (6 mL) was added and the mixture allowed to warm to 25 °C. The mixture was poured into saturated aqueous sodium hydrogen carbonate solution (50 mL) and extracted with ether (3 x 75 mL). The combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo to give the crude product as a yellow oil which was purified by flash column chromatography eluting with 4:1 hexane/EtOAc to yield the pure nitrile 21 (332 mg, 64%; 1:6.8 E:Z) as a pale yellow oil; Rf 0.47 (hexane/EtOAc, 7:3); FTIR ʋmax (KBr) 3031, 2916, 2850, 2221, 1496, 1454, 1435, 1365, 1332, 1028, 773, 698 cm⁻¹; ʋ(C=CN) 2222, 1435, 1332, 1105, 1059, 1031, 773.5 cm⁻¹; ʋ(CH₃) 2939, 2866, 2222, 1435, 1332, 1059, 1031, 773.5 cm⁻¹; ʋ(CH₃) 2939, 2866, 2222, 1435, 1332, 1059, 1031, 773.5 cm⁻¹; ʋ(CH₃) 2939, 2866, 2222, 1435, 1332, 1059, 1031, 773.5 cm⁻¹; ʋ(CH₂) 153.2, 138.6, 128.4, 127.6, 127.5, 115.8, 100.6, 81.8, 77.9, 72.9, 69.9, 31.6, 28.9, 25.6, 18.5, 17.9; HRMS (CI) m/z calcd for C₁₉H₂₁NO (M+H)⁺: 268.1701, found 268.1709; MS (Cl, NH₃) 267 [(M+H)⁺, 100%], 208 (10), 154 (45), 106 (59).

(Z)-11-Hydroxyundec-2-en-6-yenitrile, 22.

(Z)-11-Benzylxyundec-2-en-6-yenitrile 21 (330 mg, 1.23 mmol) was dissolved in dry dichloromethane (20 mL) under nitrogen. Boron trichloride-methyl sulfide complex (1.0 M in dichloromethane; 1.23 mL, 2.5 mmol) was added and the mixture stirred for 90 min. The reaction was monitored by TLC (hexane/EtOAc, 1:1). Further boron trichloride-methyl sulfide complex (1.0 M in dichloromethane; 0.62 mL, 1.23 mmol) was added and the mixture stirred for another 75 min. The mixture was poured into saturated aqueous sodium hydrogen carbonate solution (50 mL) and extracted with ether (3 x 75 mL). The combined organic extracts were dried (MgSO₄) and the solvents removed in vacuo to give the crude product as a pale yellow oil. The product was purified by flash column chromatography eluting with 1:1 hexane/EtOAc to yield the pure alcohol 22 (164 mg, 76%) as a pale yellow oil; Rf 0.23 (hexane/EtOAc, 1:1); FTIR ʋmax (KBr) 3401, 3067, 2939, 2866, 2222, 1435, 1332, 1059, 1031, 773.5 cm⁻¹; ʋ(CH₃) (CDCl₃, 400 MHz) 6.55 (1H, dt, J 11.0 and 7.5, CH₃=CHCN), 5.38 (1H, dt, J 11.0 and 1.5, CH₃=CHCN), 3.64 (2H, td, J 6.5 and 2.0, CH₂OH), 2.55 (2H, q, J 7.5, CH₂CH=CHCN), 2.32 (2H, tt, J 7.0 and 2.5, CH₂C≡C), 2.17 (2H, tt, J 7.0 and 2.5, C≡CCH₂), 1.69-1.58 (3H, m, CH₃, CH₂OH), 1.58-1.49 (2H, m, CH₂); ʋ(CH₃) (CDCl₃, 100 MHz) 153.3, 115.9, 100.6, 81.8, 78.0, 62.4, 31.8, 31.2, 25.1, 18.5, 17.9; HRMS (Cl) m/z calcd for C₁₉H₂₃NO (M+H)⁺: 283.1618, found: 283.1623; MS (Cl, NH₃) m/z: 195 (40%), 178 (100), 160 (36), 149 (10), 132 (22), 121 (12), 111 (14), 91 (22), 77 (12), 65 (13), 55 (9).
(Z)-10-Cyanodec-9-en-5-ynal, 23.

(Z)-11-Hydroxyundec-6-yn-2-enenitrile 22 (120 mg, 0.677 mmol) was dissolved in dry dichloromethane (6 mL) and cooled to 0 °C. Activated 4 Å MS were added and the mixture stirred under nitrogen. NMO (350 mg, 2.99 mmol) was added and the mixture brought to 25 °C. TPAP (14.0 mg, 4 mol%) was added and the mixture stirred for 55 min., with monitoring by TLC (hexane/EtOAc, 1:1). The mixture was filtered through silica (SiO₂, Merck 9385) and the solvent removed in vacuo to yield the aldehyde 23 (111 mg, 94%) as a pale yellow oil; Rf 0.58 (hexane/EtOAc, 1:1); FTIR v_max (KBr) 3415, 3263, 2925, 2857, 2222, 1733, 1605, 1435, 1333, 881, 467 cm⁻¹; δ_H (CDCl₃, 400 MHz) 9.79 (1H, t, J 1.5, CHO), 6.55 (1H, dt, J 11.0 and 7.5, CH=C=CHCN), 5.39 (1H, dt, J 11.0 and 1.5, CH=CHCN), 2.63-2.53 (4H, m, CH₂CH=CHCN, CH₂CHO), 2.33 (2H, tt, J 7.0 and 2.5, CH₂C=NOH), 2.22 (2H, tt, J 7.0 and 2.5, C=CH₂), 1.81 (2H, qn, J 7.0, CH₂); δ_C (CDCl₃, 100 MHz) 202.1, 153.0, 115.8, 100.8, 80.7, 78.9, 42.8, 31.1, 21.3, 18.1, 17.9; HRMS (CI) m/z calc for C₁₁H₁₂NO (M-H): 174.0919, found: 174.0923; MS (CI, NH₃) m/z: 193 (30%), 176 (19), 174 (50), 146 (13), 132 (30), 116 (55), 84 (27), 49 (100).


To a solution of (Z)-10-cyanodec-5-yn-9-enal 23 (100 mg, 0.635 mmol) in EtOH (5 mL) was added a solution of hydroxylammonium chloride (119 mg, 1.71 mmol) and sodium acetate (140 mg, 1.71 mmol) in water (1.8 mL). The mixture was stirred at 25 °C for 30 min., with TLC monitoring (hexane/EtOAc, 1:1). The mixture was poured into water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na₂SO₄) and filtered through silica (SiO₂, Merck 9385). The solvent was removed in vacuo to yield the oxime 24 (114 mg, 94%) as a 1:1 ratio of stereoisomers (which were not separated) as a colourless oil; Rf 0.38 and 0.44 (hexane/EtOAc, 1:1); FTIR v_max (KBr) 3415, 3263, 2925, 2857, 2222, 1733, 1605, 1435, 1333, 881, 467 cm⁻¹; δ_H (CDCl₃, 400 MHz) 8.05 (0.5H, br s, OH), 7.77 (0.5H, br s, OH), 7.43 (0.5H, t, J 6.0, CH=NOH), 6.73 (0.5H, t, J 5.5, CH=NOH), 6.57 (0.5H, dt, J 11.0 and 7.5, CH=CHCN), 6.56 (0.5H, dt, J 11.0 and 7.5, CH=CHCN), 5.39 (1H, dt, J 11.0 and 1.5, CH=CHCN), 2.59 (2H, q, J 7.0, CH₂CH=CHCN), 2.47 (1H, td, J 7.5 and 5.5, CH₂CH=NOH), 2.44-2.27 (3H, m, CH₂CH=NOH, CH₂C=NOH), 2.25-1.18 (2H, m, C=CH₂), 1.68 (approx. 1H, qn, J 7.0, CH₂), 1.68 (approx. 1H, qn, J 7.5, CH₂); δ_C (CDCl₃, 100 MHz) 153.1, 152.1, 151.5, 115.8, 100.7, 81.0, 78.6, 31.1, 29.0, 25.7, 25.4, 24.2, 18.6, 18.2, 17.9; HRMS (CI) m/z calc for C₁₁H₁₂N₂O (M+H)+: 191.1184, found: 191.1173; MS (CI, NH₃) m/z: 191 (8%), 83 (60), 64 (10), 49 (100).
(1R*,5R*,6R*)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0\(^1\)5]dodecane, 29,
(1R*,5R*,6S*)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0\(^1\)5]dodecane, 30,
(1R*,8S*,12S*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^4\)1]dodecane, 27
and (1R*,8S*,12R*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^4\)1]dodecane, 28.

**Method 1:**

To a solution of (Z)-10-cyoundec-9-en-5-ynal oxime 24 (62.4 mg, 328 µmol) in MeOH (15 mL) under argon was added sodium cyanoborohydride (44.0 mg, 656 µmol). Methyl orange indicator (2 drops) was added and the mixture cooled to –10 °C. Hydrochloric acid (6 M in MeOH) was added dropwise so as just to keep the solution pink (pH 3). After 10 min. sodium hydroxide (10% in MeOH; 6 mL) was added, and the mixture poured into saturated brine (20 mL) and extracted with dichloromethane (4 x 20 mL). The combined organic extracts were dried (MgSO\(_4\)) and the solvent removed in vacuo. The crude hydroxylamine 25 was dissolved in dry toluene (20 mL) and heated under reflux for 26 h. The solvent was removed in vacuo, and the products were separated by preparative TLC (fourfold elution, hexane/EtOAc, 9:1) to give the adduct 30 (1.2 mg, 2%). \(R_f\) 0.54 (hexane/EtOAc, 1:1); \(\delta\)\(_H\) (CDCl\(_3\), 500 MHz) 4.24 (1H, d, J 5.3, CH(O)CN), 3.20-2.80 (2H, m, CH\(_2\)N), 2.60-2.40 (1H, m, CHCH(O)CN), 2.40-0.5 (12H, m, 6 x CH\(_2\)). Further elution gave the adduct 29 (2.2 mg, 4%) as a white glassy solid, \(R_f\) 0.38 (4 x hexane/EtOAc, 9:1). An inseparable mixture was obtained on further elution, which appeared to contain the other regioisomers 27 and 28 (3 mg, ~5%; 1:1.3 27 : 28) with key diagnostic data as follows; \(R_f\) 0.24 (hexane/EtOAc, 1:1); \(\delta\)\(_H\) (500 MHz, CDCl\(_3\)) 4.83 (1H, d, J 4.7, 28-CHO), 2.84 (1H, s, 28-CHCN).

**Method 2:**

The \(\alpha,\beta\)-unsaturated nitrile 39 (20 mg, 0.07 mmol) was dissolved in ether and added to a high pressure reaction tube. The ether was removed under a flow of nitrogen and the flask evacuated and refilled three times. Toluene (8 mL) was added and the solution was freeze-thaw degassed (3 times). The suba seal was then exchanged quickly for the screw cap and the tube heated at 100 °C for 2 h and then heated at 160 °C for 3 h under argon. The solvent was then removed in vacuo.

The residue was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the 6,5,5-adduct 29 (3 mg, 15%) as a white crystalline solid which was recrystallised from CH\(_2\)Cl\(_2\):pentane; mp 70-72 °C (from CH\(_2\)Cl\(_2\):pentane); \(R_f\) 0.24
(4:1 hexane:EtOAc; ν<sub>max</sub> (film) 2932, 2855, 2162 and 1446 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz; CDC<sub>3</sub>) 4.92 (1H, d, J 9.0, CH(O)CN), 3.37 (1H, dt, J 14.6 and 4.1, CHHN), 3.09 (1H, ddd, J 4.1, 11.7 and 14.6, CHHN), 2.75 (1H, dt, J 9.0 and 3.3, CHCH(O)CN), 2.09-2.01 (2H, m, CH<sub>2</sub>), 1.96-1.91 (1H, m, CH), 1.87-1.78 (3H, m, CH and CH<sub>2</sub>), 1.70-1.60 (2H, m, CH<sub>2</sub>) and 1.53-1.30 (4H, m, 2 x CH<sub>2</sub>); δ<sub>C</sub> (125 MHz; CDC<sub>3</sub>) 117.6, 74.0, 69.5, 57.4, 49.0, 35.2, 31.8, 29.1, 26.3, 21.5 and 21.5; HRMS (ES) m/z calcd for C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 193.1341, found: 193.1346; MS (ES) m/z 193 [(M+H)<sup>+</sup>], 177 (40) and 90 (35); followed by the starting material 39 (16 mg, 77%) as a colourless oil.

**Method 3:**

![Chemical Structure](image)

The α,β-unsaturated nitrile 39 (44.0 mg, 0.15 mmol) was dissolved in diethyl ether and added to a high pressure reaction tube. The ether was removed under a flow of nitrogen and the flask evacuated and refilled three times. Toluene (15 mL) was added and the solution was freeze-thaw degassed (3 times). The suba seal was then exchanged quickly for the screw cap and the tube heated at 185 °C for 3 h under argon. The solvent was then removed <i>in vacuo</i>. The residue was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the 6,5,5-adducts 29 and 30 (2.6 mg, 8%; 6:1 29:30) as an inseparable mixture with key diagnostic data as follows: R<sub>f</sub> 0.24 (4:1 hexane:EtOAc); δ<sub>H</sub> (250 MHz; CDC<sub>3</sub>) 4.92 (0.85H, d, J 9.0, CH(O)CN), 4.24 (0.15H, d, J 5.3, CH(O)CN).

Further elution yielded a third spot which, on NMR analysis was found to be a mixture of three compounds. Repurification by flash column chromatography (9:1 hexane:EtOAc) yielded the 6,6,5-adduct 27 (7.8 mg, 27%) as a colourless oil; R<sub>f</sub> 0.13 (4:1 hexane:EtOAc); ν<sub>max</sub> (film) 2940, 2864, 2238 and 1448 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz; CDC<sub>3</sub>) 4.74 (1H, ddd, J 2.6, 3.1 and 6.2 CHO), 3.46 (1H, dd, J 2.3 and 6.0, CHCN), 3.40 (1H, ddt, J 1.8, 11.0 and 3.4, CHHN-equatorial), 2.50 (1H, ddd, J 3.2, 11.0 and 13.6, CHHN-axial), 2.16 (1H, ddt, J 6.4, 14.4 and 3.2, CHF), 2.01-1.94 (1H, m, CHH), 1.85 (1H, dt, J 6.0 and 13.5, CHH), 1.78-1.75 (2H, m, CH<sub>2</sub>), 1.72-1.53 (5H, 2 x CH<sub>2</sub> and CH) and 1.31-1.24 (2H, m, CH<sub>2</sub>); δ<sub>C</sub> (125 MHz; CDC<sub>3</sub>) 117.8, 76.0, 64.9, 55.6, 37.5, 35.9, 31.9, 27.1, 24.5, 19.4 and 17.6; HRMS (ES) m/z C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>O calcd for (M+H)<sup>+</sup>: 193.1341, found: 193.1332; MS (ES) m/z 193 [(M+H)<sup>+</sup>], 177 (40) , 152 (30) and 136 (35); followed by an inseparable mixture of adduct 27 and adduct 28 (2.4 mg, 6%) with key diagnostic data as follows; δ<sub>H</sub> (250 MHz; CDC<sub>3</sub>) 4.83 (1H, d, J 4.7, CHO) and 2.84 (1H, s, CHCN); and starting material 39 (2.4 mg, 6%); data consistent with those reported previously.7
Microwave reactions

(1R*,8S*,12S*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^{1,6}\)]dodecane, 27 and (1R*,8S*,12R*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^{1,6}\)]dodecane, 28.

Method A:
The \(\alpha,\beta\)-unsaturated nitrile 39 (5 mg, 0.017 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (1.7 mL) was added and the mixture was then subjected to microwave irradiation at 150 °C for 30 min. The solvent was then removed in vacuo.

The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding a 6:1 mixture of the adducts 27 and 28 (3 mg, 60%) as a colourless oil; data identical to those reported previously.

Method B:
The \(\alpha,\beta\)-unsaturated nitrile 39 (3 mg, 0.010 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (1.0 mL) was added and the mixture was then subjected to microwave irradiation at 140 °C for 20 min. The solvent was then removed in vacuo.

The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding a 6:1 mixture of the adducts 27 and 28 (3 mg, 60%) as a colourless oil; data identical to those reported previously.

(1R*,5R*,6R*)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0\(^{1,5}\)]dodecane, 29,
(1R*,5R*,6S*)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0\(^{1,5}\)]dodecane, 30,
(1R*,8S*,12S*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^{1,6}\)]dodecane, 27
and (1R*,8S*,12R*)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0\(^{1,6}\)]dodecane, 28.

The \(\alpha,\beta\)-unsaturated nitrile 39 (3 mg, 0.017 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (1.0 mL) was added and the mixture was then subjected to microwave irradiation at 140 °C for 15 min. The solvent was then removed in vacuo.

The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding a 4:1:12:2 mixture of the adducts 29, 30, 27 and 28 and the starting material 39 (2 mg overall) as a colourless oil; data identical to those reported previously.
Investigations into the regiochemical outcome of the intramolecular nitrone dipolar cycloaddition reaction.

Model studies: formation of the nitrone by dipolar cycloreversion

![Nitrone structure]

1-(tert-Butyldiphenylsilanyloxy)-pent-4-yne, 31. †

Pent-4-yn-1-ol 16 (10.0 g, 120 mmol, 1 eq) and chloro-tert-butyldiphenylsilane (31.0 mL, 120 mmol, 1 eq) were dissolved in dichloromethane (100 mL) under nitrogen. A solution of imidazole (12.2 g, 180 mmol, 1.5 eq) in dichloromethane (160 mL) was added dropwise over 30 min and the reaction mixture stirred for 16 h. The reaction mixture was poured into aqueous hydrochloric acid (2 M; 200 mL) and the aqueous extracted with dichloromethane (3 x 100 mL). The combined organics were dried (MgSO₄) and the solvent was removed in vacuo yielding a yellow oil. The compound was purified by flash column chromatography (9:1 hexane:ether) yielding the protected alcohol 31 (32.8 g, 85%) as a colourless oil; Rf 0.61 (9:1 hexane:EtOAc); δH (250 MHz; CDCl₃) 7.69-7.66 (4H, m, aromatics), 7.44-7.36 (6H, m, aromatics), 3.76 (2H, t, J 7.5, CH₂OSi), 2.36 (2H, dt, J 1.0 and 7.5, CH₂C=C), 1.92 (1H, d, J 1.0, C=CH), 1.79 (2H, qn, J 7.5, CH₂) and 1.06 (9H, s, C(CH₃)₃); data identical to literature values.⁸

1-(tert-Butyldiphenylsilanyloxy)-9-benzyloxynon-4-yne, 32

1-(tert-Butyldiphenylsilanyloxy)pent-4-yne 31 (12.4 g, 39 mmol, 1 eq) was dissolved in THF (63 mL) and cooled to –78 °C under nitrogen. n-Butyllithium (1.6 M in hexane; 24.1 mL, 39 mmol, 1 eq) was added dropwise and the mixture stirred for 1 h at –78 °C. A solution of 4-benzyloxy-1-iodobutane 15 (10.0 g, 35 mmol, 1 eq) in THF (25 mL) was added and the mixture heated at 50 °C for 36 h. Satd. aqueous NH₄Cl (90 mL) was added and the organics separated. The aqueous was further extracted with ether (2 x 45 mL) and the combined organics dried (MgSO₄) and concentrated in vacuo yielding a yellow oil. The compound was purified by flash column chromatography (3:1 → 2:1 hexane:CH₂Cl₂) to yield the nonyne 32 (15.0 g, 88%) as a colourless oil; Rf 0.12 (4:1 hexane:CH₂Cl₂); (Found: C, 79.5; H, 8.3%. C₃₂H₃₄O₂Si requires C, 79.3; H, 8.3%); νmax (film) 3068, 2930, 1958, 1888, 1821, 1588, and 1494 cm⁻¹; δH (250 MHz; CDCl₃) 7.76-7.72 (4H, m, aromatics), 7.47-7.38 (11H, m, aromatics), 4.55 (2H, s, PhCH₂O), 3.81 (2H, t, J 5.8, CH₂O), 3.53 (2H, t, J 8.3, BnOCH₂), 2.36-2.35 (2H, m, CH₂C=C), 2.22-2.20 (2H, m, C=CCCH₂), 1.82-1.62 (6H, m, 3 x CH₂) and 1.12 (9H, s, C(CH₃)₃); δC (62.5 MHz; CDCl₃) 138.7, 135.6, 134.0, 129.6, 128.4, 127.7, 127.5, 80.1, 80.0, 72.9, 70.0, 62.6, 32.1, 29.0, 26.9, 25.9, 19.3, 18.7 and 15.4; HRMS (ES) m/z calcd for C₃₂H₂₄O₂Si (M+H)⁺: 485.2876, found: 485.2879; MS (ES) m/z 502 [(M+NH₄), 100%] and 108 (30).
The benzyl ether 32 (1.4 g, 2.9 mmol, 1 eq) was dissolved in dichloromethane (14 mL) and cooled to 0 °C under nitrogen. Boron trichloride-dimethyl sulfide complex (2.0 M in CH₂Cl₂; 2.2 mL, 4.3 mmol, 1.5 eq) was added dropwise over 30 min. The reaction was allowed to warm to 25 °C and stirred for 16 h. The mixture was cooled to 0 °C and stirred vigorously during the portionwise addition of satd. aqueous NaHCO₃ (14 mL). The mixture was stirred for a further 10 min and the organics separated. The aqueous was extracted with dichloromethane (3 x 15 mL) and the combined organics dried (MgSO₄) and concentrated in vacuo before further drying by azeotroping with toluene (3 x 10 mL) yielding a yellow oil. The compound was purified by flash column chromatography (1:1 hexane:ether) to yield the title compound (1.1 g, 91%) as a light yellow oil; Rₜ 0.22 (1:1 hexane:ether); (Found: C, 76.1; H, 8.7%; C₄₉H₃₈O₃Si requires 76.1; H, 8.7%); v_{max}(film) 3553, 3070, 2931, 1959, 1890, 1825, 1589, 1471 and 1428 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.71-7.66 (4H, m, aromatics), 7.48-7.26 (6H, m, aromatics), 3.75 (2H, t, J₂₁,₂₂ 8.7 Hz), 3.64 (2H, q, J₂₁,₂₂ 7.7 Hz), 2.52 (2H, dt, J₁₃,₁₄ 7.3 Hz, CH₂CHO), 2.31-2.30 (2H, m, CH₂C=C), 1.79-1.73 (4H, m, 2 x CH₂) and 1.06 (9H, s, C(CH₃)₃); δ_C (125 MHz; CDCl₃) 159.7, 134.0, 129.5, 127.6, 80.1, 80.0, 62.5, 62.5, 32.0, 31.9, 26.9 (q), 25.3, 19.2, 15.5 and 15.3; HRMS (ES) m/z calc for C₄₉H₃₈O₃Si (M+H)^+: 765.2406, found: 765.2402; MS (ES) m/z 412 [(M+NH₄)^+, 20%], 317 (100) and 239 (30).

**9-(tert-Butyldiphenylsilyloxy)-non-5-yn-1-ol.**

Oxalyl chloride (3.0 mL, 34 mmol, 3 eq) was dissolved in dichloromethane (207 mL) and cooled to –78 °C under nitrogen. A solution of DMSO (3.6 mL, 50 mmol, 4.4 eq) in dichloromethane (20 mL) was added dropwise and the solution stirred for 1.25 h at –78 °C. A solution of 9-(tert-butyldiphenylsilyloxy)-non-5-yn-1-ol (4.5 g, 11 mmol, 1 eq) in dichloromethane (62 mL) was added and the reaction mixture stirred for a further 1.25 h. Triethylamine (8.7 mL, 63 mmol, 5.5 eq) in dichloromethane (10 mL) was added and the reaction warmed to 25 °C and stirred for 20 min. The solvent was removed in vacuo and the residue taken up in EtOAc. The salts were removed by filtration and the organics concentrated in vacuo yielding a yellow oil. The compound was purified by passing through a short plug of silica (3:1 hexane:EtOAc) yielding the title compound (4.4 g, 97%) as a light yellow oil; Rₜ 0.63 (1:1 hexane:EtOAc); (Found: C, 76.6; H, 8.2%. C₄₉H₃₈O₃Si requires C, 76.5; H, 8.2%); v_{max}(film) 3070, 2930, 2718, 1960, 1889, 1726, 1589, 1471 and 1427 cm⁻¹; δ_H (500 MHz; CDCl₃) 9.76 (1H, br s, CHO), 7.69-7.67 (4H, m, aromatics), 7.44-7.37 (6H, m, aromatics), 3.74 (2H, t, J₆.₀, CH₂OSi), 2.52 (2H, dt, J₁.₃ and 7.3, CH₂CHO), 2.31-2.30 (2H, m, CH₂C=C), 2.21-2.19 (2H, m, C≡CCH₂), 1.79-1.73 (4H, m, 2 x CH₂) and 1.06 (9H, s, C(CH₃)₃); δ_C (125 MHz; CDCl₃) 202.0, 135.6, 133.9, 129.6, 127.6, 81.0,
The aldehyde 9-(tert-butyldiphenylsilyloxy)-non-5-ynal (0.35 g, 0.88 mmol, 1 eq) was dissolved in THF (0.9 mL) and a solution of hydroxylamine-hydrochloride (0.18 g, 2.64 mmol, 3 eq) and sodium acetate trihydrate (0.36 g, 2.64 mmol, 3 eq) in water (0.9 mL) was added and the reaction mixture stirred for 10 min at 25 °C. The reaction mixture was diluted with water (10 mL) and ether (10 mL) and the organics separated. The aqueous was extracted with ether (2 x 10 mL) and the combined organics dried (MgSO₄) and concentrated in vacuo yielding a light yellow oil. The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the title compound (0.34 g, 96%), a colourless oil, as an inseparable 1:1 mixture of geometrical isomers; Rf 0.39 (3:2 hexane:EtOAc); (Found: C, 74.0; H, 8.3; N, 3.6%; C₂₅H₃₃NO₄Si requires C, 73.7; H, 8.2; N, 3.4%); ν max (film) 3258, 3070, 2928, 1659, 1588, 1471 and 1427 cm⁻¹; δH (500 MHz; CDCl₃) 7.70-7.69 (4H, m, aromatics), 7.46-7.38 (6.5H, m, CHNOH and aromatics), 6.74 (0.5H, t, J 5.4, CHNOH), 3.76 (2H, t, J 6.5, CH₂OSi), 2.46 (1H, dt, J 7.3 and 5.4, CH₃CHNOH), 2.34-2.27 (3H, m, CH₃CHNOH and CH₂C≡C), 2.24-2.16 (2H, tt, J 2.2 and 7.3, C≡CCH₂), 1.75 (2H, qn, J 6.5, CH₂CH₂C≡C), 1.64 (2H, qn, J 7.3, C≡CCH₂CH₂) and 1.07 (9H, s, C(CH₃)₃); δC (62.5 MHz; CDCl₃) 151.5, 152.0, 135.6, 134.0, 129.5, 127.6, 81.0, 79.8, 62.6, 32.0, 26.9 (q), 25.9, 25.6, 24.3, 19.2, 18.6, 18.3 and 15.3; HRMS (ES) m/z calc/ for C₂₅H₃₃NO₄Si (M+H)^+: 408.2359, found: 408.2363; MS (ES) m/z 407 [M⁺, 100%], 392 (90) and 314 (40).
and 1.05 (9H, s, C(CH$_3$)$_3$); δC (62.5 MHz; CDCl$_3$) 135.6, 134.0, 129.5, 127.6, 80.1, 79.8, 62.6, 53.4, 32.0, 26.9 (q), 26.7, 26.3, 19.3, 18.7 and 15.3; HRMS (ES) m/z calecd for C$_{25}$H$_{38}$NO$_2$Si (M+H)$^+$: 410.2515, found: 410.2517; MS (ES) m/z 410 [(M+H)$^+$, 25%], 394 (100), 138 (20) and 84 (25).

6-[4-(tert-Butyldiphenylsilyloxy)-butyl]-2,3,4,5-tetrahydro-pyridine-1-oxide, 34

The hydroxylamine 33 (100 mg, 0.24 mmol) was dissolved in toluene (12 mL) and heated to 85 °C for 5 h under nitrogen. The toluene was removed in vacuo yielding a yellow oil. The compound was purified by passing through a plug of silica (EtOAc/MeOH, 5:1) yielding the nitrone 34 (63 mg, 63%) as a light yellow oil; R$_f$ 0.21 (EtOAc/MeOH, 5:1); δH (CDCl$_3$, 500 MHz) 7.66-7.64 (4H, m, aromatics), 7.43-7.26 (6H, m, aromatics), 3.81-3.79 (2H, t, CH$_2$O, J 6.0), 3.70-3.69 (2H, m, CH$_2$N), 2.55-2.54 (2H, t, CH$_2$J 6.0), 2.40-2.38 (2H, t, CH$_2$J 6.0), 1.94-1.89 (2H, tt, CH$_2$J 6.0 and 6.0), 1.74-1.67 (2H, tt, CH$_2$J 6.5 and 6.5), 1.63-1.62 (4H, m, 2 x CH$_2$J), 1.04 (9H, s, C(CH$_3$)$_3$).

6R*,8R*)-6-(4'- tert-Butyldiphenylsilanyloxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 35 and (6R*,8S*)-6-(4'- tert-Butyldiphenylsilanyloxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 36.

The hydroxylamine 33 (1.85 g, 4.54 mmol) was dissolved in toluene (220 mL) and heated at 80 °C for 4.5 h under nitrogen. The solvent was removed in vacuo and the residue immediately dissolved in neat styrene, quinol (10 mg) was added and the mixture heated at 80 °C for 16 h under nitrogen. The styrene was removed in vacuo yielding a yellow oil. The compound was purified by flash column chromatography (9:1 hexane:EtOAc) yielding the adduct 35 (1.70 g, 73%) as a colourless oil; R$_f$ 0.25 (9:1 hexane:EtOAc); (Found: C, 77.2; H, 8.5; N, 2.9%. C$_{33}$H$_{42}$NO$_2$Si requires C, 77.1; H, 8.4, N, 2.8%); ν$_{max}$ (film) 3069, 2834, 1589 and 1471 cm$^{-1}$; δH (250 MHz; CDCl$_3$) 7.72-7.67 (4H, m, aromatics), 7.47-7.23 (11H, m, aromatics), 5.31 (1H, dd, J 9.0 and 6.4, CH(O)Ph), 3.65 (2H, t, J 6.2, CH$_2$OSi), 3.22-3.14 (2H, m, CH$_2$N), 2.55 (1H, dd, J 9.0 and 12.1, CH/CH(0)Ph), 2.08 (1H, dd, J 6.4 and 12.1, CH/CH(O)Ph), 1.87-1.24 (12H, m, 6 x CH$_2$) and 1.07 (9H, s, C(CH$_3$)$_3$); δC (125 MHz; CDCl$_3$) 143.7, 135.6, 134.1, 129.6, 128.4, 127.6, 127.0, 125.8, 76.6, 65.4, 63.7, 49.2, 46.7, 37.7, 33.2, 28.9, 26.9 (q), 21.5, 20.9, 20.0 and 19.3; HRMS (ES) m/z calecd for C$_{33}$H$_{42}$NO$_2$Si (M+H)$^+$: 514.3141, found: 514.3141; MS (ES) m/z 514 [(M+H)$^+$, 100%], 394 (20) and 138 (100), 98 (35); followed by the adduct 36 (0.17 g, 7%) as a light yellow oil; R$_f$ 0.21 (hexane:EtOAc); (Found: C, 76.8; H, 8.5; N, 3.1%. C$_{33}$H$_{42}$NO$_2$Si requires C, 77.1; H, 8.4, N, 2.8%); ν$_{max}$ (film) 2934, 2857, 1654, 1471 and 1427 cm$^{-1}$; δH (500 MHz; CDCl$_3$) 7.31-7.69 (4H, m, aromatics), 7.47-7.26 (11H, m, aromatics), 5.15 (1H, t, J 8.5, CH(O)Ph), 3.76 (2H, t, J 6.2, CH$_2$OSi), 3.19-3.13 (2H, m, CH$_2$N), 2.51 (1H, dd, J 8.5 and 12.0, CH/CH(0)Ph), 2.12 (1H, dd, J 8.5 and 12.0, CH/CH(O)Ph), 1.88-1.78 (2H, m, CH$_2$), 1.66-1.46 (10H, m, 5 x CH$_2$) and 1.08 (9H, s, C(CH$_3$)$_3$); δC (125 MHz; CDCl$_3$) 142.9, 135.6, 134.1, 129.5, 128.3, 127.6, 127.0, 127.8, 78.5, 65.2, 63.7, 50.6, 45.7, 36.5, 33.2, 29.9, 26.9 (q), 22.0 20.8, 20.0 and 19.2; HRMS (ES) m/z
calcd for C_{33}H_{42}NO_{2}Si (M+H)^+: 514.3141, found: 514.3146; MS (ES) m/z 514 [(M+H)^+, 100%], 394 (100), 202 (20) and 138 (25), 98 (20).

(6R*,8R*)-6-(4'-Butyldiphenylsilanyloxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane hydrochloride, 37.

The styrene adduct 35 (10 mg, 0.019 mmol, 1 eq) was dissolved in MeOH (1 mL) and methanolic HCl (1 M; 19 µL, 1 eq) was added and the mixture stirred for 1 h. The solvent was removed in vacuo to give the hydrochloride salt 37 (7 mg, 67%) as a colourless oil which slowly crystallised on standing at –20 ºC; mp 102-104 ºC (from MeOH); νmax (film) 3068.3, 2931.2, 2857.3, 1471.6 and 1427.9 cm⁻¹; δ_H (400 MHz; MeOD) 7.62-7.59 (4H, m, aromatics), 7.40-7.15 (11H, m, aromatics), 5.32 (1H, dd, J 6.5 and 9.0, CH(O)Ph), 3.76 (2H, t, J 6.2, CH₂OSi), 3.12-3.01 (2H, m, CH₂Si); δ_C (125 MHz; MeOD) 144.1, 136.6, 135.0, 130.8, 129.4, 128.7, 128.2, 126.8, 78.4, 67.3, 64.6, 50.4, 45.8, 38.8, 34.1, 30.3, 27.4 (q), 23.0, 21.8, 20.7 and 20.0; HRMS (ES) m/z calcd for C_{33}H_{42}ClNO_{2}Si (M-Cl)^+: 514.3146, found: 514.3140.

(6R*,8R*)-6-(4'-Hydroxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane.

The styrene adduct 35 (50.0 mg, 0.10 mmol, 1 eq) was dissolved in THF (7.5 mL) and cooled to 0 ºC under nitrogen. Tetra-n-butylammonium fluoride (1 M in THF; 0.49 mL, 0.49 m mol, 5 eq) was added and the reaction mixture stirred for 5 min at 0 ºC and then 25 ºC for 1.5 h. The reaction mixture was poured into water (10 mL) and extracted with ether (3 x 10 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo yielding a light yellow oil. The compound was purified by flash column chromatography (2:1 EtOAc:CH₂Cl₂) yielding the title compound (24.4 mg, 92%) as a colourless oil; R_f 0.17 (2:1 EtOAc:CH₂Cl₂); (Found: C, 74.2; H, 9.0; N, 5.0%). C_{33}H_{42}NO_{2} requires C, 74.1; H, 9.2, N, 5.1%); νmax (film) 3385, 3032, 2937, 2862, 2862, 1603, 1494 and 1449 cm⁻¹; δ_H (500 MHz; CDCl₃) 7.39-7.21 (5H, m, aromatics), 5.33 (1H, dd, J 6.2 and 9.2, CH(O)Ph), 3.58-3.55 (2H, m, CH₂OH), 3.14-3.12 (2H, m, CH₂N), 2.59 (1H, dd, J 9.2 and 12.2, CHCH(O)Ph), 2.04 (1H, dd, J 6.2 and 12.2, CHCH(O)Ph) and 1.81-1.76 (13H, m, 6 x CH₂ and OH); δ_C (62.5 MHz; CDCl₃) 143.4, 128.4, 127.0, 125.7, 76.7, 65.7, 62.3, 49.5, 45.9, 37.4, 33.1, 29.2, 21.9, 20.5 and 20.0; HRMS (ES) m/z calcd for C_{33}H_{39}NO_{2} (M+H)^+: 276.1963, found: 276.1966; MS (ES) m/z 276 [(M+H)^+, 70%], 258 (20), 156 (100) and 138 (70).
Method A:

(6R*,8R*)-6-(4’-Hydroxybut-1’-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (100 mg, 0.36 mmol, 1 eq) was dissolved in dichloromethane (20 mL) under nitrogen and powdered 4 Å molecular sieves and N-methylmorpholine-N-oxide (190 mg, 1.60 mmol, 4.4 eq) were added. The reaction mixture was stirred for 30 min and tetra-n-propylammonium perruthenate (5 mg, 0.02 mmol, 0.04 eq) was added. The mixture was stirred at 25 ºC for 45 min. The mixture was filtered through a plug of silica (EtOAc) and the solvent removed in vacuo. The compound was purified by passing through a short plug of silica (1:1 hexane:EtOAc) yielding the aldehyde [38 (94 mg, 95%)] as a colourless oil.

Method B:

(6R*,8R*)-6-(4’-Hydroxybut-1’-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (42 mg, 0.15 mmol, 1 eq) was dissolved in DMSO (14.3 mL) and IBX (60 mg, 0.21 mmol, 1.4 eq) was added and the reaction mixture stirred at 25 ºC for 16 h under nitrogen. Water (4 mL) was added and the residue extracted with ether (3 x 15 mL). The combined organics were washed with water (25 mL), dried (MgSO₄) and concentrated in vacuo. The compound was purified by passing through a short plug of silica (1:1 hexane:EtOAc) yielding the aldehyde [38 (26 mg, 63 %) as a colourless oil; R₁ 0.27 (1:1 hexane:EtOAc); νmax (film) 2936, 1721 and 1450 cm⁻¹; δH (500 MHz; CDCl₃) 7.38-7.21 (5H, m, aromatics), 5.34 (1H, dd, J 6.1 and 9.3, CH(O)Ph), 3.15-3.12 (2H, m, C=CH), 2.05 (1H, dd, J 6.1 and 12.1, CHHC(O)Ph) and 1.81-1.76 (12H, m, 5 x C(CH₃)₃); δC (62.5 MHz; CDCl₃) 154.7, 143.3, 128.4, 127.0, 125.7, 115.9, 109.9, 77.2, 65.5, 49.5, 45.8, 44.2, 37.4, 29.2, 22.0 and 19.9; HRMS (ES) m/z 297 [(M+H)⁺, 5%], 245 (15), 202 (100) and 113 (40).

(6R*,8R*)-(4’Z)-6-(5’-Cyanopent-4’-en-1’-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 39

Trimethylsilylacetonitrile (49 µL, 0.36 mmol, 1.7 eq) was dissolved in THF (0.7 mL) and cooled to –78 °C under nitrogen. n-Butyllithium (1.6 M in hexane; 215 µL, 0.34 mmol, 1.6 eq) was added dropwise and the reaction mixture was stirred at –78 °C for a further 20 min. The reaction was quenched by the addition of wet THF (1:1 THF:water; 0.5 mL) and the mixture was warmed to 25 ºC. A solution of the aldehyde [38 (59 mg, 0.21 mmol, 1 eq) in THF (0.9 mL)] and washed with water and ether and the organics separated. The aqueous was extracted with ether (3 x 5 mL) and the combined organics washed with water (10 mL) and brine (10 mL). The combined organics were dried (MgSO₄) and concentrated in vacuo yielding a light yellow oil. The compound was purified by flash column chromatography (2:1 hexane:EtOAc) yielding a 9:1 Z:E inseparable mixture of the α,β-unsaturated nitrile [39 (47 mg, 76%)] as a colourless oil; R₁ 0.36 (1:1 hexane:EtOAc); νmax (film) 2937, 2861, 2217, 1618, 1493 and 1449 cm⁻¹; δH (250 MHz; CDCl₃) 7.40-7.20 (5H, m, aromatics), 6.36 (1H, dt, J 10.9 and 7.4, CH₂CH=CH), 5.35 (1H, dd, J 6.0 and 9.4, CH(O)Ph), 5.26 (1H, dt, J 10.9 and 1.3, CH=CHCN), 3.18-3.14 (2H, m, CH₂N), 2.63 (1H, dd, J 9.4 and 12.2, CHHCH(O)Ph), 2.38 (2H, q, J 7.4, CH₂CH=CH), 2.05 (1H, dd, J 6.0 and 12.2, CHHCH(O)Ph) and 1.84-1.26 (10H, m, 5 x CH₂); δC (62.5 MHz; CDCl₃) 154.7, 143.3, 128.4, 127.0, 125.7, 115.9, 99.8, 77.2, 65.5, 49.6, 45.6, 37.3, 32.1, 29.4, 23.1, 22.0 and 19.9; HRMS (ES) m/z calcd for C₁₇H₂₂N₂O (M+H)⁺: 297.1967, found: 297.1963; MS (ES) m/z 297 [(M+H)⁺, 35%], 177 (100) and 138 (20). The inseparable (E)-isomer had...
key diagnostic data as follows; 6.61 (0.09H, dt, J 16.3 and 6.9, CH$_2$CH=CH) and 5.26 (1H, dt, J 16.3 and 1.6, CH=CHCN).

![Chemical structure](image)

(6R*,8R*)-6-(Pent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 40.

Methyltriphenylphosphonium bromide (110 mg, 0.31 mmol, 2.1 eq) was dried in a Schlenk tube under argon, dissolved in THF (4.5 mL) and cooled to −78 °C. n-Butyllithium (1.6 M in hexane; 0.17 mL, 0.28 mmol, 1.9 eq) was added dropwise. After 5 min at −78 °C the solution was allowed to warm to 25 °C, stirred for 30 min at 25 °C and then recooled to −78 °C. A solution of the aldehyde 38 (40 mg, 0.15 mmol, 1 eq) in THF (1.5 mL) was added and the reaction mixture was allowed to warm to 25 °C and stirred for 1 h. The reaction was quenched by the addition of satd. aqueous NH$_4$Cl (6 mL) and the mixture extracted with ether (3 x 10 mL). The combined organics were dried (MgSO$_4$) and concentrated in vacuo.

The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the alkene 40 (36 mg, 91%) as a colourless oil; R$_f$ 0.42 (3:1 hexane:EtOAc); (Found: C, 79.8; H, 9.4; N, 5.3%. C$_{18}$H$_{23}$NO requires C, 79.7; H, 9.3; N, 5.2%). ν$_{max}$(film) 2969, 2860, 1640, 1604, 1494 and 1449 cm$^{-1}$; δ$_H$ (500 MHz; CDCl$_3$) 7.48-7.21 (5H, m, aromatics), 5.73 (1H, ddt, J 10.2, 17.1 and 6.6, CH$_2$CH=CH$_2$), 5.29 (1H, dd, J 6.4 and 9.0, CH(O)Ph), 4.97 (1H, dd, J 1.0 and 17.1, CH=CHH-Z), 4.92 (1H, dd, J 1.0 and 10.2, CH=CHH-E), 3.17-3.14 (2H, m, CH$_2$N), 2.55 (1H, dd, J 9.0 and 12.2, CH=CHCH(O)Ph), 2.04 (1H, dd, J 6.4 and 12.2, CHH=CH(O)Ph), 2.02-1.97 (2H, m, CH$_2$) and 1.87-1.27 (10H, m, 5 x CH$_3$); δ$_C$ (125 MHz; CDCl$_3$) 143.6, 138.6, 128.3, 125.9, 125.7, 114.6, 76.6, 65.3, 49.2, 46.5, 37.0, 34.2, 29.0, 23.9, 21.5 and 20.0; HRMS (ES) m/z calcd for C$_{18}$H$_{23}$NO (M+H)$^+$: 272.2014, found: 272.2013; MS (ES) m/z 272 [(M+H)$^+$, 50%], 152 (100), 138 (55), 98 (30) and 90 (35).

![Chemical structure](image)

(6R*,8R*)-6-(5'-Methoxycarbonylpent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 41

18-Crown-6 (0.45 g, 1.70 mmol, 10 eq) was dissolved in THF (6 mL) and the mixture freeze-thaw degassed (3 times). The mixture was stirred at 25 °C before the dropwise addition of bis[(2,2,2-trifluoroethyl)methoxycarbonylmethyl]phosphonate (82 µL, 0.39 mmol, 2.3 eq). The mixture was cooled to −78 °C under argon and KHMDS (0.5 M in toluene; 0.77 µL, 0.39 mmol, 2.3 eq) was added dropwise. The mixture was stirred for 30 min and the aldehyde 38 (46 mg, 0.17 mmol, 1 eq) in THF 1 mL was added dropwise. The reaction was stirred for 2 h at −78 °C and the reaction was quenched by the addition of satd. aqueous NH$_4$Cl (2 mL). The aqueous was extracted ether (4 x 15 mL), dried (MgSO$_4$) and the solvent removed in vacuo yielding a yellow oil.

The product was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the (Z)-o,β-unsaturated ester 41 (14 mg, 25%) as a colourless oil; R$_f$ 0.15 (4:1 hexane:EtOAc); ν$_{max}$(film) 2928, 2851, 1722.8, 1644 and 1440 cm$^{-1}$; δ$_H$ (500 MHz; CDCl$_3$) 7.40 (2H, br d, J 7.6, CH-ortho), 7.34 (2H, t J 7.6, CH-meta), 7.25 (1H, tt, J 1.3 and 7.6, CH-para).
6.13 (1H, dt, J 11.4 and 7.6, CH=CHCO₂), 5.75 (1H, dt, J 11.4 and 1.9, CH=CHCO₂), 5.33 (1H, dd, J 6.0 and 9.1, CH(O)Ph), 3.70 (3H, s, CH₃), 3.21 (2H, m, CH₂N), 2.63 (2H, dq, J 1.9 and 7.6, CH₂CH=C), 2.58 (1H, dd, J 9.1 and 12.3, CHHCH(O)Ph), 2.07 (1H, dd, J 6.0 and 12.3, CHHCH(O)Ph), 1.88-1.78 (2H, m, CH₂), 1.71 (1H, m, CH), 1.63-1.49 (5H, 2 x CH₂ and CH), and 1.43-1.32 (2H, CH₂);

δC (125 MHz; CDCl₃) 166.8, 150.3, 143.4, 128.4, 127.0, 125.7, 119.5, 76.8, 65.4, 51.0 (q), 49.3, 46.1, 37.2, 29.7, 29.2, 23.9, 21.7 and 19.9; HRMS (CI) m/z calcd for C₂₀H₂₈NO₃ (M+H)⁺: 330.2064, found: 330.2068; MS (EI) m/z 330 [(M+H)⁺, 100%], 210 (70) and 135 (20); further elution yielded the (E)-α,β-unsaturated ester (5 mg, 9%) as a colourless oil; Rf 0.11 (4:1 hexane:EtOAc); νmax (film) 2938, 2856, 1724, 1656 and 1437 cm⁻¹;

δH (400 MHz; CDCl₃) 7.37 (2H, br d, J 7.5, CH ortho), 7.32 (2H, t, J 7.5, CH meta), 7.23 (1H, t, J 7.5, CH para), 6.91 (1H, dt, J 15.7 and 7.0, CH=CHCO₂), 5.79 (1H, dt, J 15.7 and 1.6, CH=CHCO₂), 5.32 (1H, dd, J 6.4 and 9.1, CH(O)Ph), 3.72 (3H, s, CH₃), 3.14 (2H, br t, J 5.4, CH₂N), 2.58 (1H, dd, J 9.1 and 12.2, CHHCH(O)Ph), 2.15 (2H, br q, J 7.0, CH₂CH=C), 2.03 (1H, dd, J 6.4 and 12.2, CHHCH(O)Ph), 1.83-1.78 (2H, m, CH₂) and 1.70-1.35 (12H, m, 6 x CH₂); data identical to literature values.⁹

Method A:
The alkene 40 (11 mg, 0.04 mmol) was dissolved in ether and added to a high pressure reaction tube. The ether was removed under a flow of nitrogen and the flask evacuated and refilled three times with argon. Toluene (5 mL) was added and the solution was freeze-thaw degassed (3 times). The suba seal was then exchanged quickly for the screw cap and the tube heated at 160 °C for 5 h under argon. The solvent was then removed in vacuo.

The residue was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the adduct 42 (5 mg, 72%) as a colourless oil; Rf 0.37 (4:1 hexane:EtOAc); δH (500 MHz; CDCl₃) 4.27 (1H, br t, J 8.2, CHO-cis), 3.45 (1H, dd, J 5.1 and 8.2, CHO-trans), 3.09-3.05 (1H, m, CHHN), 2.87-2.82 (1H, m, CHHN), 2.63-2.59 (1H, m, CHCH₂O) and 1.94-1.35 (12H, m, 6 x CH₂); data identical to literature values.⁹

Method B:
The alkene 40 (11 mg, 0.04 mmol) was dissolved in ether and added to a high pressure reaction tube. The ether was removed under a flow of nitrogen and the flask evacuated and refilled three times with argon. Toluene (5 mL) was added and the solution was freeze-thaw degassed (3 times). The suba seal was then exchanged quickly for the screw cap and the tube heated at 190 °C under argon. After 16 h only baseline material was present.

Method C:
The alkene 40 (6 mg, 0.021 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (2.0 mL) was added and the mixture was then subjected to microwave irradiation at 140 °C for 2 h. The solvent was then removed in vacuo.

(1R*,S,R*)-8-Aza-7-oxatricyclo[6.4.0.0₁²⁵]dodecane, 42.
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the adduct 42 (2 mg, 62%) and the starting material (2 mg, 33%) as a colourless oil.

**Method D:**
The alkene 40 (6 mg, 0.021 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (2.0 mL) was added and the mixture was then subjected to microwave irradiation at 180 °C for 20 min. The solvent was then removed *in vacuo.*
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the adduct 42 (1 mg, 30%) as a colourless oil; data identical to those reported previously.

\[
\text{N} \quad \text{O} \\
\text{CO}_2\text{Me}
\]

\((1R^*,5R^*,6R^*)-6\text{-Methoxycarbonyl-8-aza-7-oxatricyclo[6.4.0.0}^{3,5}]\text{dodecane, 43.}

**Method A:**
The \((Z)-\alpha,\beta\)-unsaturated ester 41 (5 mg, 0.015 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (1.5 mL) was added and the mixture was then subjected to microwave irradiation at 140 °C for 1.6 h. The solvent was then removed *in vacuo.*
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the starting material (2 mg, 33%) followed by the adduct 43 (2 mg, 62%) as a colourless oil.

**Method B:**
The \((Z)-\alpha,\beta\)-unsaturated ester 41 (4 mg, 0.017 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (1.2 mL) was added and the mixture was then subjected to microwave irradiation at 180 °C for 30 min. The solvent was then removed *in vacuo.*
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the adduct 43 (3 mg, 59%) as a colourless oil; \(R_f\) 0.25 (1:1 hexane:EtOAc); \(\delta^1\mathrm{H}\) (400 MHz; CDCl3) 4.74 (1H, d, \(J\ 9.0\ \text{CHO})\), 3.76 ( 3H, s, CH₃), 3.25 (1H, dt, \(J\ 14.3\) and 3.8, CHHN), 3.03 (1H, ddd, \(J\ 10.0\) and 14.3, CHHN), 2.85 (1H, dt, \(J\ 9.0\) and 7.0, CHCH(O)CO₂) and 1.91-1.28 (12H, m, 6 x CH₂); data identical to literature values.¹⁰
Investigations into the regiochemical outcome of the intramolecular nitrene dipolar cycloaddition reaction. 

Model studies: histrionicotoxin precursors

(2S, 6R, 8R)-2-(Benzyloxymethyl)-6-(4'-hydroxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane. 

(2S, 6R, 8R)-2-(Benzyloxymethyl)-6-[4'-(tert-butyldiphenylsilyloxy)but-1'-yl]-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (300 mg, 0.50 mmol) was dissolved in distilled acetonitrile (20 mL) and hydrofluoric acid (40% aq; 0.25 mL) added, giving a 0.5% solution. The mixture was stirred overnight, triethylamine (0.1 mL) added and the mixture filtered through a short column of silica. The solvent was removed and the residue purified by flash chromatography (hexane/EtOAc, 1:1) to afford the pure product (172 mg, 91%) as a colourless oil which solidified to a powdered activated 4 Å MS, NMO (72 mg, 612 µmol, 4.4 equiv.) and TPAP (2.0 mg, 5.6 µmol, 4 mol%). After 20 min. oxabicyclo[4.4.0]decane (55 mg, 139 µmol) in dry dichloromethane (10 mL) under nitrogen at 0 °C were added.

(25,6R,8R)-2-(Benzyloxymethyl)-6-(3'-formylprop-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 44.

Method A:

To a stirred solution of (2S, 6R, 8R)-2-(benzyloxymethyl)-6-(4'-hydroxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (55 mg, 139 µmol) in dry dichloromethane (10 mL) under nitrogen at 0 °C were added powdered activated 4 Å MS, NMO (72 mg, 612 µmol, 4.4 equiv.) and TPAP (2.0 mg, 5.6 µmol, 4 mol%). After 20 min. at 0 °C the solution was warmed to 25 °C and stirred for a further 25 min. The volume of the solvent was reduced to ~2.5 mL under a stream of nitrogen and the mixture loaded directly onto a small pre-packed silica column and eluted with 2:1 hexane/EtOAc, affording the pure aldehyde 44 (54 mg, 100%) as a colourless oil; Rf 0.31 (hexane/EtOAc, 2:1); [α]D 31.8 (c 2.24 in CHCl3); FTIR νmax (film) 3028, 2939, 2863, 2719, 1722, 1603, 1469, 1100, 754 and 600 cm⁻¹; δH (CDCl3, 250 MHz) 9.67 (1H, t, J 1.5, CHO), 7.36-7.21 (10H, m, aromatics), 5.45 (1H, dd, J 10.5 and 5.0, CH(O)Ph), 4.55 (s, 2H, PhCH₂O), 3.94 (1H, dd, J 9.0 and 3.0, CHHOBn), 3.43 (1H, t, J 9.0, CHHOBn), 3.02 (1H, dddd, J 11.5, 9.0, 3.0 and 3.0, CHN), 2.69 (1H, dd, J 12.5 and 10.5, CHHCH(O)Ph), 2.45-2.08 (2H, m, CH₃C=O), 2.12 (1H, m, CH₂), 2.00 (1H, dd, J 12.5 and 5.0, CH/CH(O)Ph), 1.86-1.13 (10H, m, 5 x CH₃); δC (CDCl3, 63 MHz) 202.5, 141.5, 138.6, 128.4, 128.3, 127.7, 127.5, 127.2, 125.9, 77.1, 73.5, 73.3, 67.7, 59.2, 44.2, 42.3, 41.4, 30.9, 28.3, 19.2, 16.6; HRMS (CI) m/z
calcd for C_{29}H_{32}O_{2}N (M+H)^+: 394.2382; found: 394.2394; MS (CI, NH_{3}) m/z 394 [(M+H)^+, 7%], 304 (1), 281 (4), 272 (7), 166 (11), 138 (62), 121 (67), 108 (70), 106 (76), 105 (75), 94 (62), 91 (53), 78 (70), 72 (42), 60 (38), 58 (100).

**Method B:**
To a stirred solution of (25, 6R, 8R)-2-(benzyloxymethyl)-6-(4'-hydroxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (120 mg, 353.3 μmol) in dry DMSO (6 mL) was added IBX (297 mg, 1.06 mmol) and the flask stoppered. The mixture was stirred at 25 °C for 17 h and then poured into water (100 mL) and extracted with ether (3 x 100 mL). The ethereal extracts were washed with brine (100 mL) using the 3 funnel extraction method, combined and dried (MgSO_{4}). The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (hexane/EtOAc, 1:1), to give the pure aldehyde 44 (105 mg, 89%, 100% rec.) as a colourless oil, followed by recovered alcohol 3,41 (13 mg, 11%).

![Chemical Structure](attachment:image.png)

(Z)-(2S, 6R, 8R)-2-(Benzyloxymethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 11.
A solution of trimethylsilylacetonitrile (31 mg, 0.27 mmol) in dry THF (1 mL) was cooled to −78 °C under nitrogen. n-Butyllithium (1.55 M in hexane; 0.17 mL, 0.27 mmol) was introduced in a dropwise manner and the resulting solution stirred for 15 min. at this temperature. Triisopropylborate (50 mg, 0.27 mmol) was then added and after stirring a further 15 min, a solution of aldehyde 44 (80 mg, 0.20 mmol) in dry THF (0.5 mL, 0.5 mL wash) was slowly added *via* cannula. The resulting solution was stirred at −78 °C for 30 min. Whereupon water (0.1 mL) was added and the mixture brought to 25 °C. The solution was filtered through a short plug of silica (SiO_{2}, Merck 9385) and the solvent removed to afford a residue that was purified by flash chromatography (hexane/EtOAc, 4:1) to afford the nitrile 11 (70 mg, 84%; 9:1:1 Z:E); R_{f} 0.47 (hexane/EtOAc, 2:1); [α]^{25}_{D} +31.2 (c 1.29 in CHCl_{3}); (Found: C, 77.9; H, 7.9; N, 6.9; C_{27}H_{32}N_{2}O_{2} requires C, 77.9; H, 7.7; N, 6.7%); FTIR ν_{max}(film) 3029, 2938, 2864, 2218, 1620, 1604, 1495 and 1106 cm⁻¹; δ_{H} (CDCl_{3}, 250 MHz) 7.37-7.27 (10H, m, aromatics), 6.29 (1H, ddd, J 11.0, 7.5 and 7.5, CH=CHCN), 5.45 (1H, dd, J 10.5 and 5.0, CH(O)Ph), 5.20 (1H, ddd, J 11.0, 1.0 and 1.0, CH=CHCN), 4.56 (1H, s, PhCH_{2}O), 3.95 (1H, td, J 9.0 and 3.0, CHHOBn), 3.43 (1H, t, J 9.0, CHHOBn), 3.02 (1H, dddd, J 11.5, 9.0, 3.0 and 3.0, CNH), 2.69 (1H, dd, J 12.5 and 10.5, CNHICN(O)Ph), 2.39-2.27 (2H, m, CH_{2}CH=), 2.17-1.18 (11H, m, 5 x CH_{2}, CHCHCH(O)Ph); δ_{C} (CDCl_{3}, 63 MHz) 154.9, 141.5, 138.4, 128.3, 128.2, 127.6, 127.4, 127.1, 125.8, 115.9, 99.4, 77.0, 73.4, 73.2, 67.5, 59.1, 41.9, 41.0, 31.9, 30.9, 28.3, 22.5, 19.1; HRMS (EI) m/z calcd for C_{27}H_{32}N_{2}O_{2} (M+H)^+: 417.2542, found: 417.2525; MS (El) m/z 417 [(M+H)^+, 16%], 307 (100), 289 (45).

![Chemical Structure](attachment:image.png)

(E)-(2S,6R,8R)-2-(Benzyloxymethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 54
NaHMD (1.0 M in THF; 0.20 mL, 0.20 mmol) was added to dry THF (2.5 mL) under nitrogen at −78 °C with stirring. A solution of diethyl cyanomethylphosphonate (0.33 μl, 36 mg, 0.20 mmol) in dry THF (2.0 mL, 0.5 mL wash) was
added dropwise via cannula and the mixture stirred at −78 °C for 20 min. The mixture was warmed to rt and stirred for 2 h before cooling to −78 °C and stirring for a further 1.5 h. A solution of aldehyde 44 (20 mg, 0.05 mmol) in dry THF (1.0 mL) was added and the mixture warmed to rt. After 15 h, TLC showed no starting material to be present, and the solvent was removed in vacuo. Water (5.0 mL) was added, and the product extracted with ether (3 x 5.0 mL). The combined organic extracts were dried (Na₂SO₄) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (1 : 1 hexane : EtOAc) to give the enenitrile 54 (19.5 mg, 93%; Z/E 1 : 2) as a colourless oil; Rf 0.59 (3 : 2 hexane : EtOAc); FTIR νmax (KBr) 3062, 3030, 2937, 2865, 2211, 1632, 1604, 1585, 1495, 1454, 1362, 1247, 1207, 1100, 1028, 967, 912, 813, 749, 699 and 476 cm⁻¹; δH (250 MHz) 7.40-7.25 (10H, m, aromatics), 6.58 (1H, d, J 16.3 and 6.9, CH=CHCN), 5.46 (1H, dd, J 10.2 and 4.95, CH(O)Ph), 5.24 (1H, dt, J 16.3 and 1.6, =CHCN), 4.56 (2H, s, PhCH₂O), 3.95 (1H, dd, J 9.1 and 3.2, CHHOBn), 3.44 (1H, dd, J 9.1 and 8.7, CHHOBn), 3.02 (1H, dddd, J 11.3, 8.7, 3.3 and 3.2, CHN), 2.70 (1H, dd, J 12.6 and 10.2, CHHCH(O)Ph) and 2.38 - 1.19 (13H, m, 6 x -CH₂- and CHHCH(O)Ph); δC (62.5 MHz) 155.7, 141.7, 138.6, 128.5, 128.3, 127.7, 127.5, 125.9, 117.5, 99.9, 77.2, 73.5, 73.3, 67.6, 59.3, 42.3, 41.1, 33.5, 31.0, 28.4, 22.0 and 19.3; HRMS (ES) m/z found: 417.2526; MS (ES) m/z 417 [(M+H)+, 100%], 394 (8), 366 (6), 342 (7) and 313 (10).

(1R, 5S, 8S, 12R)-8-(Benzyloxyethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1.0₁⁴⁻₅⁻₀]undecane 13

and

(1R, 5S, 8S, 12S)-8-(Benzyloxyethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1.0₁⁴⁻₅⁻₀]undecane 48.

Method 1:

(Z)-(2S, 6R, 8R)-2-(Benzyloxyethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 11 (9.1:1 Z:E; 375 mg, 0.9 mmol) was transferred as an ethereal solution to a thick-walled glass tube equipped with a magnetic stirrer. The solvent was then evaporated under a stream of nitrogen and the residual oil dried thoroughly in vacuo. The vacuum was quenched with nitrogen, dry distilled toluene (20 mL) introduced and the tube sealed under a stream of dry nitrogen. The apparatus was transferred carefully to an oil bath at 190 °C and the gently refluxing solution was stirred for 3.5 h at this temperature before being removed from the bath and allowed to cool. TLC analysis of the faintly yellow solution (2 elutions in hexane/EtOAc, 4:1) established that the reaction was complete. After removal of the solvent, the residual yellow oil was purified by flash chromatography (hexane/EtOAc, 4:1) to afford the tricycle 13 (230 mg, 82%) as a colourless oil; Rf 0.42 (hexane/EtOAc, 4:1; 2 elutions); [α]D²¹ = −185.5 (c 1.5 in CHCl₃); νmax(film) 3028, 2939, 2863, 2239, 1453, 1096, 738 and 698 cm⁻¹; δH (CDCl₃, 250 MHz) 7.38-7.29 (5H, m, aromatics), 4.71 (1H, m, CH(O)CHCN), 4.54 (2H, s, PhCH₂O), 3.80 (1H, dd, J 9.0 and 3.0, BnOCH), 3.42 (1H, dd, J 6.5 and 2.0, CHCN), 3.39 (1H, dd, J 9.0 and 7.5, BnOCH/H), 2.67 (1H, dddd, J 11.5, 7.5, 3.0 and 3.0, CHN), 2.19 (1H, m, 10-H), 2.04 (1H, m, 9-H), 1.98-1.92 (1H, m, 3-H), 1.90-1.83 (1H, m, 2-H), 1.79-1.72 (2H, m, 4-H), 1.67-1.50 (4H, m, 2-H, 3-H, 10-H and 11-H), 1.39-1.16 (2H, m, 9-H and 11-H); δC (CDCl₃, 63 MHz) 138.4, 127.8, 127.7, 127.6, 117.7, 75.8, 73.5, 72.4, 65.4, 65.0, 38.1, 35.9, 32.2, 28.5, 27.1, 18.7, 17.5; HRMS (Cl) m/z found for C₂₃H₂₃N₂O₂ (M+H)+: 313.1916, 313.1916; MS (Cl, NH₃) m/z 313 [(M+H)+, 100%], 191 (42), 108 (15), 91 (18).
Further elution of the column afforded the tricycle 48 (20 mg, 7%) as a white crystalline solid; Rf 0.45 (hexane/EtOAc, 1:1); mp 114 °C dec. (from hexane/EtOAc, 4:1); [α]D20.5 = −156.7 (c 0.425 in CDCl3); FTIR νmax (KBr) 2945, 2858, 2237, 1496, 1454, 1303, 1190, 1095, 979, 913, 808, 743 and 699 cm−1; δH (CDCl3, 500 MHz) 7.35-7.25 (5H, m, aromatics), 5.46 (1H, dd, J 10.0 and 5.0, CH=H2), 5.00-4.91 (1H, m, =CHH), 4.93-4.88 (2H, m, =CHH, CH(O)Ph), 4.57 (2H, s, PhCH2O), 3.98 (1H, dd, J 9.0 and 3.0, CHHOBn), 3.95 (1H, dd, J 9.0 and 9.0, CHHOBn), 3.04 (1H, ddd, J 11.5, 9.0, 3.0 and 3.0, CHN), 2.65 (1H, dd, J 12.5 and 10.0, CHCH(O)Ph), 2.17-1.16 (13H, m, 6 x CH2, CHH(O)Ph); δC (CDCl3, 125 MHz) 146.8, 138.7, 138.6, 128.3, 128.3, 127.7, 127.1, 126.1, 114.5, 77.3, 73.4, 73.4, 67.8, 59.2, 41.8, 41.7, 34.0, 31.3, 28.4, 23.2, 19.3; HRMS (Cl) m/z calcd for C36H34N2O2 (M+H)⁺: 587.2589, found: 587.2590; MS (Cl, NH3) m/z 392 [(M+H)⁺, 83%], 378 (14), 274 (31), 272 (100), 270 (32), 138 (27).

Method 2:

(E)-(2S,6R,8R)-2-(Benzyloxymethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 54 (Z/E 1 : 2; 18.0 mg, 43.2 μmol) was transferred to a thick-walled glass tube as an ethereal solution and the solvent removed under a stream of nitrogen and then in vacuo. Toluene (2 mL) was added and the tube sealed under a nitrogen atmosphere. The solution was heated at 190 °C with stirring for 2.5 h and the solvent removed in vacuo. Separation of the mixture by flash column chromatography afforded the tricycle 13 (2.0 mg, 15%) as a colourless oil, starting material 54 (2.6 mg, 15%) as a colourless oil and the tricycle 48 (4.7 mg, 35%) as a white crystalline solid. All data are as reported previously.

(2S, 6S, 8R)-2-(Benzyloxymethyl)-6-(4'-penten-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 45.

A suspension of recrystallised, powdered and dried methyltriphenylphosphonium iodide (117 mg, 0.29 mmol) was suspended in dry THF (4 mL) under argon and cooled to −30 °C. n-Butyllithium (1.5 M in hexane; 0.22 mL, 0.35 mmol) was added dropwise to the suspension which over the space of 1 h was observed almost completely to dissolve giving a bright yellow solution. This was then cooled to −78 °C and a solution of (2S, 6R, 8R)-2-(benzyloxymethyl)-6-(3'-formylprop-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 44 (103 mg, 0.26 mol) in THF (1 mL, 1 mL wash) was slowly added to give an almost colourless solution. The reaction was allowed to warm to rt, quenched by the addition of water (0.2 mL), dried (MgSO4), and the solvent was removed in vacuo. The crude residue was purified by flash chromatography to afford the alkene 45 (81 mg, 85%) as a colourless oil; Rf 0.65 (hexane/EtOAc, 4:1); [α]D20.5 = −30.9 (c 1.49 in CHCl3); (Found: C, 79.65; H, 8.45; N, 3.58%); νmax (film) 3029, 2936, 2863, 1640, 1604, 1495, 1101, 910, 752 and 699 cm−1; δH (CDCl3, 250 MHz) 7.42-7.22 (10H, m, aromatics), 5.46 (1H, dd, J 10.0 and 5.0, CH=H2), 5.00-4.91 (1H, m, =CHH), 4.93-4.88 (2H, m, =CHH, CH(O)Ph), 4.57 (2H, s, PhCH2O), 3.98 (1H, dd, J 9.0 and 3.0, CHHOBn), 3.95 (1H, dd, J 9.0 and 9.0, CHHOBn), 3.04 (1H, ddd, J 11.5, 9.0, 3.0 and 3.0, CHN), 2.65 (1H, dd, J 12.5 and 10.0, CHCH(O)Ph), 2.17-1.16 (13H, m, 6 x CH2, CHH(O)Ph); δC (CDCl3, 125 MHz) 146.8, 138.7, 138.6, 128.3, 128.3, 127.7, 127.1, 126.1, 114.5, 77.3, 73.4, 73.4, 67.8, 59.2, 41.8, 41.7, 34.0, 31.3, 28.4, 23.2, 19.3; HRMS (CI) m/z calcd for C36H34N2O2 (M+H)⁺: 587.2589, found: 587.2590; MS (Cl, NH3) m/z 392 [(M+H)⁺, 83%], 378 (14), 274 (31), 272 (100), 270 (32), 138 (27).
An ethereal solution of (2S, 8R)-2-(benzylxymethyl)-6-(4'-penten-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 45 (3.3 mg, 8.43 µmol) was transferred to a thick walled glass tube and the solvent removed under a stream of nitrogen and then in vacuo. Toluene (0.8 mL) was added and the tube sealed under nitrogen. The solution was heated with stirring at 190 °C for 9 h, cooled, and the solvent was removed in vacuo. Purification by flash column chromatography (hexane/EtOAc, 4:1) gave the tricycle 49 (2.4 mg, 100%) as a colourless oil; Rf 0.25 (hexane/EtOAc, 4:1); [α]D22 86.9 (c 0.74 in CHCl3); νmax (film) 3029, 2941, 2863, 1495, 1099, 736 and 698 cm⁻¹; δ_H (CDCl3, 500 MHz) 7.33-7.24 (5H, m, aromatics), 4.52 (2H, s, PhC=O), 4.27 (1H, dd, J 8.5 and 8.5, CHHON), 3.80 (1H, dd, J 9.0 and 3.0, CHHOBn), 3.43 (1H, dd, J 8.5 and 4.0, CHHON), 3.37 (1H, dd, J 9.0 and 9.0, CHHOBn), 2.70 (1H, dddd, J 11.0, 9.0, 3.0 and 3.0, CHN), 2.65 (1H, m, CHCH3ON), 2.07-1.23 (12H, m, 6 x Cα), 8.5 and 3.0, C18H32NO2 (M+H)+: 288.1964, found: 288.1952; MS (ES) m/z 288 [M+H]+, 100%.

(Z)-(2S, 8R)-2-(Benzylxymethyl)-6-(5'-methoxycarbonylpent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 46.

Method A.
Carbon monoxide gas was bubbled through a stirred solution of (Z)-(2S, 6R, 8R)-2-(benzylxymethyl)-6-(5'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0] nonane (12.0 mg, 23.3 µmol), dry distilled MeOH (8.2 µl, 6.5 mg, 203 µmol) and dry distilled triethylamine (2.5 µl, 1.9 mg, 18.5 µmol) in dry distilled acetonitrile (1 mL) for 5 min. Tetrakis(triphenylphosphine)palladium(0) (1.3 mg, 1.2 µmol) was added and the reaction stirred with exclusion of light at 60 °C under an atmosphere of carbon monoxide (balloon) with TLC monitoring for 20 h, after which time the reaction appeared to have stopped. Fresh acetonitrile (0.5 mL) was added as the solvent had boiled dry, followed by MeOH (8.2 µl, 6.5 mg, 203 µmol) and triethylamine (2.5 µl, 1.9 mg, 18.5 µmol) and stirring was continued for a further 60 h. The carbon monoxide was vented and the flask flushed with nitrogen, before the solvent was removed under a steady stream of nitrogen. The crude brown residue was purified by flash column chromatography (hexane/EtOAc, 7:3). Mixed fractions were purified by a second round of flash column chromatography (hexane/EtOAc, 4:1) affording recovered starting material (1.9 mg, 16%) followed by the methyl ester 46 (7.0 mg, 67%, 80% rec.; 6.45:1 Z:E) as a pale orange oil; Rf 0.30 (hexane/ether, 13:7); [α]D23 10.7 (c 0.23 in CDCl3); νmax (KBr) 3030, 2958, 2925, 2851.5, 1717, 1651.5, 1445, 1267, 1265, 1173, 1100, 1021, 907, 824, 749 and 694.5 cm⁻¹; δ_H (CDCl3, 400 MHz) 7.38-7.23 (10H, m, aromatics), 6.05 (1H, dt, J 11.5 and 7.5, CH=CHCO2Me), 5.68 (1H, dt, J 11.5 and 1.5, =CHCO2Me), 5.44 (1H, dd, J 10.0 and 5.0, CH(O)Ph), 4.55 (2H, s, PhCH2O), 3.95 (1H, dd, J 8.5 and 3.0, CHHOBn), 3.67 (3H, s, CO2CH3), 3.41 (1H, dd, J 8.5 and
8.5, CHHOBn), 3.01 (1H, dddd, J 11.5, 8.5, 3.0 and 3.0, CHN), 2.65 (1H, dd, J 12.5 and 10.0, CHHCH(O)Ph), 2.58-2.55 (2H, m, CH₂CH=), 2.18-2.10 (1H, m, -CHNH-), 2.05 (1H, dd, J 12.5 and 5.0, CHHCH(O)Ph), 1.90-0.80 (9H, m, -CH₂H-, 4 x -CH₂-);  δ(CDCls, 100 MHz) 166.8, 150.6, 141.6, 138.0, 128.6, 128.4, 127.5, 127.5, 127.2, 126.0, 119.3, 77.2, 73.5, 73.4, 67.8, 59.2, 51.0, 41.8, 41.6, 31.8, 31.2, 28.4, 23.3, 19.3; HRMS (CI) m/z calcd for C₂₇H₂₈N₄O₅ (M+H)+: 450.2617, found: 450.2618; MS (ES) m/z 450 [(M+H)+, 100%].

Also visible was the following data corresponding to the E-isomer: δH (CDCl₃, 400 MHz) 5.75 (1H, dt, J 15.5 and 1.5, =CHCO₂Me), 3.71 (3H, s, CO₂CH₂). Analysis of the integrals of either of these peaks gave the E:Z ratio reported above.

**Method B.**

18-Crown-6 (250 mg, 0.95 mmol) was dissolved in dry THF (2.5 mL) under argon with stirring. Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (40 μL, 61 mg, 0.19 mmol) was added and the mixture cooled to –78 °C. Potassium bis(trimethylsilylamide) (0.5 M in PhMe; 0.38 ml, 0.19 mmol) was added, and the mixture stirred for 30 min. A solution of (2S, 6R, 8R)-2-(benzyloxymethyl)-6-(3’-formylprop-1’-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 44 (75 mg, 0.19 mmol) in dry THF (2.5 mL, 2.5 mL rinse) was added and the mixture stirred for a further 50 min. at –78 °C. Saturated aqueous ammonium chloride solution (25 mL) was added and the mixture warmed to 25 °C, poured into further saturated aqueous ammonium chloride solution (50 mL) and extracted with ether (3 x 100 mL). The combined organic extracts were dried (MgSO₄), and baseline was material removed by filtration through a short silica plug, eluting with 7:3 hexane/ether, to give the methyl ester 46 (60 mg, 70%; 87% rec.; 44:1 Z:E) as a colourless oil, followed by unreacted starting material (15 mg, 20%).

![Chemical Structure](image)

(1R, 5S, 8S, 12S)-8-(Benzyloxymethyl)-12-methoxycarbonyl-7-aza-6-oxatricycle [5.4.1.15,0]undecane 50

and

(1S, 5S, 6R, 9S)-9-(Benzyloxymethyl)-6-methoxycarbonyl-8-aza-7-oxatricycle [6.4.0.15,5]undecane 51.

The methyl ester 46 (44:1 Z:E; 50 mg, 0.11 mmol) was transferred to a thick walled glass vessel as a solution in ether and the ether removed first under a stream of nitrogen and then in vacuo. A magnetic stirrer bar and dry distilled toluene (10 mL) were added, and the vessel was sealed under an atmosphere of nitrogen. The solution was heated at 190 °C for 4 h and allowed to cool to 25 °C.

The solvent was removed in vacuo, and the mixture separated by flash column chromatography (hexane/ether, 7:3) affording the 6,6,5-adduct 52 (20.4 mg, 53%) as a colourless oil which slowly undergoes N-inversion; Rf 0.28 (hexane/EtOAc, 3:1); [α]⁺D 24.5 = 7.5 (c 0.08 in CDCl₃); νmax(KBr) 3088, 3063, 3030, 2936, 2862, 2799, 1760, 1732, 1604, 1586, 1496, 1454, 1205, 1066, 1028, 950 and 699 cm⁻¹; δH (CDCl₃, 500 MHz) 7.35-7.26 (5H, m, aromatics), 4.71 (approx. 0.5H, dd, J 5.5 and 5.5, CHO) 4.59-4.54 (approx. 2.5H, m, PhCH₂O, CHO), 3.85 (1H, m, BrNCHΗ), 3.72 (3H, s, OCH₃), 3.57 (approx. 0.5H, dd, J 8.5 and 8.5, BrNCHΗ) 3.45 (approx 0.5H, br d, J 6.5, CHCO₂Me). 3.39 (approx. 0.5H, dd, J 8.5 and 8.5, BrNCHΗ), 3.16-3.08 (approx. 0.5H, m, CHN), 2.86-2.77 (approx. 1H, m, CHN, CHCO₂Me), 2.40-2.30 (approx 0.5H, m, CHH), 2.08-1.15 (approx. 11.5H, m, 5 x CH₂, CHH); δ(13C, 100 MHz) 170.5, 138.8, 138.6, 128.4, 128.3, 127.7, 127.6, 127.5, 127.4, 77.2, 76.3, 73.4, 73.4, 73.0, 64.4, 63.9, 57.9, 51.6, 51.5, 48.9, 34.8, 32.6,
29.0, 28.1, 26.6, 21.7, 18.7, 17.7; HRMS (ES) m/z calcd for C_{20}H_{17}NNaO_{4} (M+Na)^+: 368.1838, found: 368.1867; MS (ES) m/z 368 [(M+Na)^+] 4%, 346 (100), 258 (5), 238 (3); followed by the 6,5,5-adduct 51 (8 mg, 21%) as a pale yellow oil; R_{f} 0.15 (hexane/ethyl acetate, 3:1); [alpha]_{D}^{24.5}^{20} = 16.7 (c 0.06 in CDCl_{3}); v_{max} (KBr) 3088, 3064, 3030, 2950, 2865, 2798, 1750, 1732, 1496, 1454, 1029 and 699 cm\(^{-1}\); \delta_{H} (CDCl_{3}, 500 MHz) 7.34-7.24 (5H, m, aromatics), 4.82 (1H, d, J 9.5, CH(O)CO_{2}Me), 4.51 (2H, s, PhCH_{2}O), 3.85 (1H, dd, J 9.0 and 3.0, BnOCH_{2}H), 3.78 (3H, s, OC\(^{(N+Na)}\)), 3.0 (1H, dt, J 9.0 and 3.0, C\(^{(H)}\)).

(Z)-(2S, 6R, 8R)-2-(Benzyloxymethyl)-6-(5'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane.

Iodomethyltriphenylphosphonium iodide (28.0 mg, 52.9 \mu mol) was suspended in dry THF (0.5 mL) and cooled to 0 °C under nitrogen. NaHMDS (1.0 M in THF; 55 \mu l, 55 \mu mol) was added dropwise and the mixture stirred for 10 min., during which time a dark orange solution formed. The mixture was cooled to –85 °C and a precooled solution (–85 °C) of (2S, 6R, 8R)-2-(benzyloxymethyl)-6-(3'-formylprop-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 44 (16.0 mg, 40.7 \mu mol) in dry THF (1.0 mL, 0.7 mL wash) was added dropwise. After 1 h TLC (hexane/EtOAc, 2:1) analysis showed the reaction to have stopped. The reaction was quenched by the addition of water (0.05 mL) and the solvents were reduced in vacuo. The crude mixture was loaded directly onto a pre-packed silica column (SiO\(_{2}\), Merck 9385) and purified by slow gravity chromatography (eluting hexane/EtOAc, 4:1) to afford the corresponding vinyl iodide (16 mg, 76%, rec. 87%, 92:8 Z:E) as a pale yellow oil; R_{f} 0.6 (hexane/EtOAc, 2:1); [alpha]_{D}^{22}^{20} = -12.4 (c 1.5 in CDCl_{3}); v_{max} (film) 3027, 1604, 1494, 1452, 1099, 1027, 735, 697 cm\(^{-1}\); \delta_{H} (CDCl_{3}, 400 MHz) 7.38-7.22 (10H, m, aromatics), 6.11 (1H, dt, J 6.5 and 1.0, =CHI), 6.01 (1H, q, J 6.5, CH=CHI), 5.45 (1H, dd, J 10.0 and 5.0, CH(O)Ph), 4.55 (2H, s, OCH_{2}Ph), 3.95 (1H, dt, J 9.0 and 3.0, CHHOBn), 3.43 (1H, t, J 9.0, CHHOBn), 3.02 (1H, ddt, J 11.5, 8.5 and 3.0, CHN), 2.66 (1H, m, CHHCH(O)Ph), 2.10-0.80 (13H, m, CHCHCH(O)Ph, 6 x CH_{2}); \delta_{C} (CDCl_{3}, 100 MHz) 153.1, 141.0, 138.6, 128.4, 128.3, 127.7, 127.5, 127.2, 126.1, 82.4, 77.2, 73.5, 73.4, 67.8, 59.2, 41.8, 41.4, 31.2, 29.7, 28.4, 22.4, 19.3; HRMS (ES) m/z calcd for C_{25}H_{25}INO_{2} (M+H)^+: 518.1556, found: 518.1554; MS (Cl, NH\(_{3}\)) m/z 518 [(M+H)^+, 100%], 414 (12). Further elution of the column afforded unreacted aldehyde 38 (2.0 mg, 13%).

(Z)-(2S, 6R, 8R)-2-(Benzyloxymethyl)-6-[7'(trimethylsilyl)-hept-4'-en-6'-yn-1'-yl]-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 47.
Recrystallised copper(I) iodide (5.0 mg; cat.) was suspended in distilled diethylenimine (1.0 mL) under argon with the exclusion of light and trimethylsilylacetylene (17.3 µl, 12.0 mg, 122 µmol) added. The resulting pale pink solution was stirred for 5 min.

Meanwhile, in a separate flask, tetrakis(triphenylphosphine)palladium(0) (5.0 mg; cat.) was added to a stirred solution of (Z)-(2S, 6R, 8R)-2-(benzoxymethyl)-6-(7'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (21.0 mg, 40.8 µmol) in distilled diethylenimine (1.0 mL), and light was excluded. After 5 min., the solution of the copper acetylide prepared above was added by cannula and the reaction monitored by TLC (hexane/EtOAc, 3:1). After 30 min. the reaction was deemed complete and the solvent removed under a stream of nitrogen. The crude product was loaded onto a flash column and eluted with 4:1 petroleum ether-40-60/EtOAc affording the pure enyne 47 (20 mg, 100%, > 50:1 Z:E) as a yellow oil; \( R_f \) 0.11 (hexane/EtOAc, 95:5) and 0.52 (hexane/EtOAc, 3:1); \( [\alpha]_D^{22} \) -11.7 (c 2.0 in CDCl3) v \( \text{max} \) (KBr) 2148, 1459, 1366, 1252, 1099, 1034, 846, 754, 695 cm \(^{-1}\); \( \delta_H \) (CDCl3, 250 MHz) 7.46-7.19 (10H, m, aromatics), 5.80 (1H, dt, J 11.0 and 7.5, CH=CHC=), 3.95 (1H, dd, J 9.0 and 3.0, CHCH(O)Ph), 3.43 (1H, dd, J 9.0 and 9.0, CH(O)Ar), 2.35-2.05 (2H, m, C(CH\( \equiv \)C)), 2.01 (1H, dd, J 12.5 and 5.0, CHHCH(O)Ar), 1.90-0.75 (1H, m, 5 x CH;), 0.17 (9H, s, Si(CH\( \equiv \)C)) \( \delta_C \) (CDCl3, 63 MHz) 145.2, 141.7, 138.6, 128.4, 128.3, 127.7, 127.5, 127.2, 126.1, 109.2, 102.1, 93.0, 77.3, 73.5, 73.4, 67.8, 59.2, 41.9, 41.8, 31.2, 29.7, 1.0; HRMS (ESI) \( m/z \) calcd for C\( \text{H}_2\text{O}_3\text{N}_2\)Si(M+H)+: 488.2985, found: 488.2990; MS (ESI) \( m/z \) 488 [(M+H)+, 100%], 384 (3).

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\text{Recrystallised copper(I) iodide (5.0 mg; cat.) was suspended in distilled diethylenimine (1.0 mL) under argon with the exclusion of light and trimethylsilylacetylene (17.3 µl, 12.0 mg, 122 µmol) added. The resulting pale pink solution was stirred for 5 min.}
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\text{Meanwhile, in a separate flask, tetrakis(triphenylphosphine)palladium(0) (5.0 mg; cat.) was added to a stirred solution of (Z)-(2S, 6R, 8R)-2-(benzoxymethyl)-6-(7'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (21.0 mg, 40.8 µmol) in distilled diethylenimine (1.0 mL), and light was excluded. After 5 min., the solution of the copper acetylide prepared above was added by cannula and the reaction monitored by TLC (hexane/EtOAc, 3:1). After 30 min. the reaction was deemed complete and the solvent removed under a stream of nitrogen. The crude product was loaded onto a flash column and eluted with 4:1 petroleum ether-40-60/EtOAc affording the pure enyne 47 (20 mg, 100%, > 50:1 Z:E) as a yellow oil; \( R_f \) 0.11 (hexane/EtOAc, 95:5) and 0.52 (hexane/EtOAc, 3:1); \( [\alpha]_D^{22} \) -11.7 (c 2.0 in CDCl3) v \( \text{max} \) (KBr) 2148, 1459, 1366, 1252, 1099, 1034, 846, 754, 695 cm \(^{-1}\); \( \delta_H \) (CDCl3, 250 MHz) 7.46-7.19 (10H, m, aromatics), 5.80 (1H, dt, J 11.0 and 7.5, CH=CHC=), 3.95 (1H, dd, J 9.0 and 3.0, CHCH(O)Ph), 3.43 (1H, dd, J 9.0 and 9.0, CH(O)Ar), 2.35-2.05 (2H, m, C(CH\( \equiv \)C)), 2.01 (1H, dd, J 12.5 and 5.0, CHHCH(O)Ar), 1.90-0.75 (1H, m, 5 x CH;), 0.17 (9H, s, Si(CH\( \equiv \)C)) \( \delta_C \) (CDCl3, 63 MHz) 145.2, 141.7, 138.6, 128.4, 128.3, 127.7, 127.5, 127.2, 126.1, 109.2, 102.1, 93.0, 77.3, 73.5, 73.4, 67.8, 59.2, 41.9, 41.8, 31.2, 29.7, 1.0; HRMS (ESI) \( m/z \) calcd for C\( \text{H}_2\text{O}_3\text{N}_2\)Si(M+H)+: 488.2985, found: 488.2990; MS (ESI) \( m/z \) 488 [(M+H)+, 100%], 384 (3).}

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(1R, 5S, 8S, 12S)-8-(Benzoxymethyl)-12-(trimethylsilylthynyl)-7-aza-6-oxatricyclo[5.4.1.0\]^{2,5}\]undecane 54 and

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(1S, 5S, 6R, 9S)-9-(Benzoxymethyl)-6-(trimethylsilylthynyl)-8-aza-7-oxatricyclo[6.4.0.0\]^{2,5}\]undecane 53.

Separation of the mixture by gravity chromatography eluting with 95:5 hexane/EtOAc yielded the tricycle 54 (0.6 mg, 9%, 16% rec.) as a colourless oil; \( R_f \) 0.16 (hexane/EtOAc, 95:5); \( [\alpha]_D^{22.5} \) -40.5 (c 0.06 in CH\( \text{Cl}_2\)) v \( \text{max} \) (KBr) 2958, 2928, 2876, 2361, 2341, 1462, 1286, 1122, 913, 844 and 743.5 cm \(^{-1}\); \( \delta_H \) (CDCl3, 500 MHz) 7.36-7.24 (5H, m, aromatics), 4.68-
4.54 (1H, m, CHO), 4.56 (2H, s, PhCH$_2$O), 3.77 (1H, dd, $J$ 9.5 and 4.5, BnOCH), 3.48 (1H, dd, $J$ 9.5 and 7.0, BnOCH$_2$H), 3.09 (1H, m, C$_2$H$_{11}$N), 2.54 (1H, m, CH$_3$C≡CTMS), 2.00-0.87 (12H, m, 6 x C$_2$H$_2$), 0.15 (9H, s, Si(C$_3$H$_3$)$_3$); HRMS (ES) $m$/z calc for C$_{23}$H$_{34}$NO$_2$Si (M+H)$^+$: 384.2359, found: 384.2359; MS $m$/z 384 [(M+H)$^+$, 100%].

Further elution of the column afforded recovered starting material 47 (3.5 mg; 43%) followed by the tricycle 53 (2.1 mg, 33%, 57% rec.) as a colourless oil; $R_f$ 0.05 (hexane/EtOAc, 95:5); $[\alpha]_D^{25}$ –30.5 (c 0.21 in CDCl$_3$); $v$$_{max}$ (KBr) 3031, 2952, 2911, 2846, 2354, 2174, 1497, 1464, 1339, 1252, 1094, 1026, 841, 741 and 694.5 cm$^{-1}$; $\delta$$_H$ (CDCl$_3$, 750 MHz) 7.33-7.12 (5H, m, aromatics), 5.02 (1H, d, $J$ 9.0, C$_6$H$_2$(O)C≡C), 4.51 (2H, s, PhCH$_2$O), 3.85 (1H, dd, $J$ 9.0 and 3.0, C$_4$H$_2$OBn), 3.38 (1H, dd, $J$ 9.0 and 8.5, CH$_2$HOBn), 2.67 (1H, dddd, $J$ 11.0, 8.5, 3.0 and 3.0, C$_6$H$_2$N), 2.62 (1H, dd, $J$ 9.0 and 7.0, CHCH(O)C≡C), 2.16 (1H, dd, $J$ 13.5 and 8.5, 4-H), 2.08-2.04 (1H, m, 10-H$_{eq}$), 2.03-1.99 (1H, m, 2-H), 1.89 (1H, dd, $J$ 14.5 and 3.0, 11-H$_{eq}$), 1.84-1.80 (1H, m, 3-H), 1.75 (1H, ddd, $J$ 14.5, 12.5 and 4.0, 11-H$_{ax}$), 1.72-1.67 (1H, m, 3'-H), 1.63-1.52 (3H, m, 12-H$_{eq}$, 4'-H, 2'-H), 1.32-1.27 (2H, m, 12-H$_{ax}$, 10-H$_{eq}$), 0.18 (9H, s, Si(CH$_3$)$_3$); $\delta$$_C$ (CDCl$_3$, 100 MHz) 138.5, 128.3, 127.8, 127.5, 100.9, 94.5, 78.3, 73.5, 73.1, 70.2, 60.5, 49.9, 41.2, 34.3, 28.6, 28.4, 23.1, 20.6, -0.2; HRMS (CI) $m$/z calc for C$_{23}$H$_{34}$NO$_2$Si (M+H)$^+$: 384.2359, found: 384.2358; MS (EI) $m$/z 384 [(M+H)$^+$, 100%].

Thermal Equilibration Experiments

General Procedure

The substrate was dissolved in ether and transferred to a thick walled glass tube and the solvent removed first under a stream of nitrogen and then in vacuo. The substrate was re-dissolved in dry distilled toluene to give a 0.4 mg mL$^{-1}$ solution and the tube sealed under an atmosphere of nitrogen. The sealed tube was heated to 190 °C and the reaction monitored by TLC.

Thermal equilibration of (1$R$, 5$S$, 8$S$, 12$S$)-8-(benzyloxymethyl)-12-(trimethylsilylethynyl)-7-aza-6-oxatricyclo[5.4.1.1,5,0]undecane 54.

(1$R$, 5$S$, 8$S$, 12$S$)-8-(Benzyloxymethyl)-12-(trimethylsilylthethyl)-7-aza-6-oxatricyclo[5.4.1.1,5,0]undecane 54 (0.3 mg, 0.78 µmol) was treated according to the above procedure. After 4.5 h, TLC analysis showed the mixture to be almost entirely the 6,5,5-tricycle 53, along with a significant amount of baseline material.

Thermal equilibration of (1$S$, 5$S$, 6$R$, 9$S$)-9-(benzyloxymethyl)-6-(trimethylsilylthethyl)-8-aza-7-oxatricyclo[6.4.0.0$^{1,5}$]undecane 53.

(1$S$, 5$S$, 6$R$, 9$S$)-9-(Benzyloxymethyl)-6-(trimethylsilylthethyl)-8-aza-7-oxatricyclo[6.4.0.0$^{1,5}$]undecane 53 (1.0 mg, 2.6 µmol) was treated according to the above procedure. After 4.5 h, TLC analysis showed only starting material 53, along with a significant amount of baseline material. After 24 h, only baseline material was present.
Synthesis of the “unsymmetrical” histrionicotoxins

Total synthesis of HTX-259A

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\text{HO} \quad \text{CN}
\]

(2S, 6R, 7R, 8S)-2-(Hydroxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane. †

(2S, 6R, 7R, 8S)-2-(Benzoyloxymethoxy)methyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane\[11\] S7 (53.9 mg, 0.15 mmol) was dissolved in methanol (20 mL) and Amberlyst-15™ resin (10 mg) added, after which the reaction mixture was stirred at 25 °C overnight. NEt3 (4 mL) was added and the reaction stirred for a further 1 h. The solution was filtered to remove the resin and the filtrate was concentrated in vacuo. The crude alcohol was purified by flash column chromatography (EtOAc) to yield the alcohol as a white crystalline solid which was recrystallised from a hexane/ether mix (97%); Rf 0.32 (EtOAc); mp 93-94 °C (from hexane/ether); [α]D\[^{0}\] -121.2 (c 0.61 in CHCl₃); δH (250 MHz; CDCl₃) 4.74 (1H, ddd, J 3.0, 3.0 and 0.0, CHO ring), 3.77 (1H, ddd, J 11.0, 5.0 and 3.5, CHCHOH, 3.63-3.54 (1H, m, CHCHOH), 3.42 (1H, dd, J 5.0 and 2.0, CHCN), 2.65 (1H, dddd, J 11.5, 3.5, 3.5 and 3.5, CHN), 2.49 (1H, dd, J 5.0 and 5.0, OH), 2.20 (1H, dm, J 11.0, CH) and 2.03-1.25 (11H, m, 5 x CH₂ and CH); all data identical to literature values.\[11\]

\[
\text{MsO} \quad \text{CN}
\]

(2S, 6R, 7R, 8S)-2-(Methanesulfonyloxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane. †

(2S, 6R, 7R, 8S)-2-(Hydroxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane (6.0 mg, 0.027 mmol), DMAP (2 mg, cat.) and NEt₃ (7.5 µL, 0.054 mmol, 2 eq) were dissolved in dry CH₂Cl₂ (1.5 mL) and a solution of methanesulfonyl chloride (2.3 µL, 0.029 mmol, 1.1 eq) in dry CH₂Cl₂ (0.3 mL) was added dropwise, after which the reaction mixture was stirred for 1 h. The CH₂Cl₂ was removed in vacuo and the residue taken up in EtOAc (2 mL) and washed with brine (2 x 1 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo to leave a pale yellow oil. Purification of the crude residue by flash column chromatography (3:1 EtOAc:hexane) yielded the mesylate (100%); Rf 0.61 (EtOAc); [α]D\[^{11}\] -143.0 (c 0.18 in CHCl₃); δH (250 MHz; CDCl₃) 4.77-4.72 (1H, m, CHO ring), 4.35 (1H, dd, J 10.5 and 3.0, CHHOMs), 4.25 (1H, dd, J 10.5 and 5.5, CHHOMs), 3.39 (1H, dd, J 6.5 and 1.5, CHCN), 3.06 (3H, s, CH₃SO₂), 2.80-2.71 (1H, m, CHN), 2.22 (1H, m, CH) and 1.92-1.25 (11H, m, 5 x CH₂ and CH); all data identical to literature values.\[11\]

\[
\text{NC} \quad \text{CN}
\]

(2S, 6R, 7R, 8S)-2-(Cyanomethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane, 56. †

To a mixture of (2S, 6R, 7R, 8S)-2-(methanesulfonyloxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1.0\text{6,8}]undecane (31.5 mg, 0.11 mmol) and powdered molecular sieves (4 Å) was added dry DMSO (3 mL) followed by NaCN (102.9 mg, 2.09
mmol, 20 eq) and the mixture was stirred at 50 °C for 4 days. The reaction vessel was allowed to cool to 25 °C before the addition of a 1:1 mixture of ether and water (6 mL). The organic layer was separated and the aqueous layer was further extracted with ether (5 x µ6 mL). The combined organic phases were washed with water (5 x 5 mL) and brine (5 x 5 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the crude residue by flash column chromatography (1:1 hexane:EtOAc) yielded the bis-nitrile 56 (69%); Rf 0.45 (1:1 hexane:EtOAc); mp 115-116 °C (from hexane:EtOAc); [α]D⁰ 248.5 (c 0.35 in CHCl₃); δH (250 MHz; CDCl₃) 4.73 (1H, ddd, J 6.0, 3.0 and 3.0, CHO ring), 3.36 (1H, d, J 6.0, CHCN), 2.76 (1H, dd, J 17.0 and 3.0, CHHCN), 2.80-2.71 (1H, m, CHN), 2.55 (1H, dd, J 17.0 and 8.0, CHHCN), 2.22 (1H, dm, J 13.0, CH) and 2.05-1.35 (11H, m, 5 x CH₂ and CH); all data identical to literature values.

![Chemical structure](image)

(2S, 6R, 7S, 8S)-2-(Oxo-1'-ethyl)-7-formyl-1-aza-12-oxatricyclo[5.4.1.0³⁸.⁰]undecane, 59. †
The bis-nitrile 55 (17.1 mg, 0.074 mmol) was dissolved in dry toluene (2 mL) and cooled to -78 °C under nitrogen. Dibal-H (1.5 M in toluene; 123 µL, 0.185 mmol, 2.5 eq) was added dropwise and the reaction stirred for 0.5 h. The reaction was quenched by the addition of wet MeOH (1 mL) and warmed to 25 °C. The mixture was diluted with EtOAc (5 mL) and Rochelle’s salt was added (2 mL) together with a few drops of HCl (2 M aq.) in order to lower the pH to 5, after which the reaction mixture was stirred at 25 °C overnight. The aqueous layer was separated, neutralised by the addition of NaHCO₃ (aq.), and extracted with EtOAc (2 x 5 mL). The organic phases were washed with brine (2 x 2 mL), combined, dried (MgSO₄) and concentrated in vacuo to yield the crude aldehyde. Purification by flash column chromatography (1:1 hexane:EtOAc) through a short plug yielded the bis-aldehyde (100%); Rf 0.19 (1:1 hexane:EtOAc); [α]D⁰ 130.7 (c 0.17 in CHCl₃); δH (250 MHz; CDCl₃) 10.01 (1H, d, J 2.5, CHO), 9.83 (1H, dd, J 9.0, 6.5 and 3.0, CHN), 2.86 (1H, ddd, J 16.5, 5.0 and 2.0, CHHCHO), 2.51 (1H, ddd, J 16.5, 6.5 and 2.0, CHHCHO), 2.18-1.96 (2H, m, CH₂) and 1.81-1.72 (10H, m, 5 x CH₃); all data identical to literature values.¹¹

![Chemical structure](image)

(2S, 6R, 7S, 8S)-2-(2'-Oxo-ethyl)-7-(2''-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1.0³⁸.⁰]undecane, 61.*

and

(2S, 6R, 7S, 8S)-2-(3'-Iodoprop-2'-enyl)-7-(2''-iodoethenyl)-1-aza-12-oxatricyclo [5.4.1.0³⁸.⁰]undecane, 60. †

Dry recrystallised iodomethyltriphenylphosphonium iodide (215.0 mg, 0.41 mmol) was suspended in degassed THF (2.0 mL) under argon and cooled to -30 °C. KHMDS (0.5 M in toluene; 780 µL, 0.39 mmol, 0.96 eq) was added dropwise with rapid stirring and the solution was stirred at -30 °C for 0.5 h. The solution was cooled further to -78 °C and stirring stopped allowing the salts to settle.
The bis-aldehyde 59 (7.7 mg, 0.032 mmol) was dissolved in degassed THF (1.5 mL) and cooled to -78 °C under argon. The supernatant from the ylide formation (334 µL, 0.048 mmol, 1.5 eq) was added quickly and the reaction mixture was stirred for a further 0.5 h. The reaction was quenched by the addition of wet THF (1:1 THF:H2O; 2 mL) and warmed to 25 °C. Ether (4 mL) and satd. NH4Cl (4 mL) were added and the organic layer separated. The aqueous layer was further extracted with ether (3 x 4 mL) and the organic phases were combined, dried (MgSO4) and concentrated in vacuo. Purification via flash column chromatography (3:1 hexane:ether) yielded the bis-vinyl iodide 60 (1.5 mg, 10%); Rf 0.60 (1:1 hexane:EtOAc); [α]D20 30° -35.9 (c 0.07 in CHCl3); δH (250 MHz; CDCl3) 6.54 (1H, d, J 7.5, =CHI), 6.38-6.29 (3H, m, =CHCH2, =CH and =CHI), 4.56 (1H, ddd, J 6.0, 6.0 and 0.0, CHO ring), 3.53 (1H, m, =CHCH2), 2.94 (1H, ddd, J 12.0, 8.0 and 3.0, CHN), 2.67 (1H, dm, J 14.0, CHHCH=), 2.45-2.33 (1H, ddd, J 12.0, 8.0 and 7.5, CHHCH=), 2.05-1.21 (12H, m, 6 x CH2); all data identical to literature values. Further purification provided the mono-vinyl iodide 61 (7.0 mg, 60%) as a colourless oil; Rf 0.32 (1:1 hexane:EtOAc); [α]D20 30° -62.9 (c 0.31 in CHCl3); νmax(CHCl3) cm⁻¹ 2941s (C-H), 2874s (C-H), 1722s (C=O), 1220m, 1210s and 926w; δH (250 MHz; CDCl3) 9.88 (1H, t, J 2.5, CHO), 6.55 (1H, d, J 7.5, =CHI), 6.35 (1H, dd, J 9.0 and 7.5, CH=CHI), 4.54 (1H, ddd, J 5.5, 5.5 and 0.0, CHO ring), 3.56 (1H, m, CHCH=CHI), 3.42-3.30 (1H, ddd, J 12.0, 6.0, 5.0 an 2.5, CHN), 2.88 (1H, ddd, J 16.0, 5.0 and 2.5, CHH/CHO), 2.53 (1H, ddd, J 16.0, 6.0 and 2.5, CHICCHO) and 2.05-1.21 (12H, m, 6 x CH2); δδ (63 MHz, APT; CDCl3) 202.6, 136.1, 86.5, 77.0, 65.4, 60.7, 50.7, 49.6, 35.0, 32.1, 31.0, 25.7, 20.1 and 17.8; HRMS (EI) m/z calcd for C19H19O2NI (M+H)+: 361.0539, found: 361.0546; MS (CI) m/z 362 [(M+H)+, 80%], 235 (81), 192 (46) and 176 (100).12

Method A13

A solution of the aldehyde 61 (2.7 mg, 0.008 mmol) and DMAP (1.3 mg, 0.011 mmol, 1.3 eq) in THF (1 mL) was freeze-thaw degassed (three cycles) before being cooled down to -50 °C. Tebbe reagent (0.5 M in toluene; 21 µL, 0.011 mmol, 1.3 eq) was added dropwise and the resultant orange solution was allowed to warm to 20 °C over 1.5 h. The solution was recooled to -20 °C and an aqueous solution of NaOH (0.98 M; 21 µL, 0.011 mmol, 1.3 eq) was added dropwise and the resultant orange solution was allowed to warm to 20 °C over 1.5 h. The reaction mixture was allowed to warm to 20 °C over 1 h. The quenched reaction mixture was poured into ether (2 mL) over Na2SO4 before filtration through a short plug of Celite™. The filtrate was concentrated in vacuo. Purification of the crude residue via flash column chromatography (2:1 hexane:EtOAc) furnished the alkene 62 (1.7 mg, 63%) as a colourless oil.

Method B14

The aldehyde 61 (9.4 mg, 0.026 mmol) was dissolved in dry toluene (6 mL) and Petasis' reagent 4.41 (127 mg/mL; 64 µL, 0.039 mmol, 1.5 eq) added dropwise and the reaction mixture was stirred at reflux in the absence of light for 1.5 h. The mixture was concentrated in vacuo and the crude residue was preabsorbed onto silica (CH2Cl2) and purified by flash column chromatography (3:1 hexane:EtOAc; 1% NEt3) to yield the alkene 62 (7.8 mg, 83%) as a colourless oil; Rf 0.60

![Image](2S, 6R, 7S, 8S)-2-(Prop-2'-eny1)-7-(2''-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1.06,9]undecane, 62.
(1:1 hexane:EtOAc); \([\alpha]_D^{20} +23.5\ (c\ 0.17\ in\ CHCl_3);\ \nu_{\text{max}}(\text{thin film})\ 3070, 2932, 2864, 1639, 1604, 1446, 1302, 1279, 1263, 1081 and 923 cm\(^{-1}\); \(\delta\_H(500\ \text{MHz};\ \text{CDCl}_3) 6.52\ (1\H,\ d,\ J\ 7.5,\ =CHI),\ 6.35\ (1\H,\ dd,\ J\ 9.0\ and\ 7.5,\ CH=CHI),\ 5.86\ (1\H,\ dddd,\ J\ 17.0,\ 10.5,\ 10.0\ and\ 6.5,\ CH=CH_2),\ 5.08\ (1\H,\ d,\ J\ 17.0,\ CH=CHH\ trans),\ 5.04\ (1\H,\ d,\ J\ 10.0,\ CH=CHH\ cis),\ 4.55\ (1\H,\ ddd,\ J\ 6.0,\ 6.0\ and\ 0.0,\ CHO\ ring),\ 3.54\ (1\H,\ dd,\ J\ 7.5,\ and\ 6.0,\ CHCH=CHI),\ 2.79\ (1\H,\ dddd,\ J\ 12.0,\ 9.0,\ 3.0\ and\ 3.0,\ CHN),\ 2.82-2.71\ (1\H,\ m,\ CHHCH=CH_2),\ 2.10\ (1\H,\ ddd,\ J\ 13.5,\ 6.5\ and\ 6.5,\ CHH),\ 2.02\ (1\H,\ m,\ CHHCH=CH_2),\ 1.77\ (2\H,\ tm,\ J\ 13.5,\ CH_2),\ 1.66\ (1\H,\ m,\ CHH),\ 1.60-1.40\ (7\H,\ m,\ 3\times\ CH_2\ and\ CHH)\ and\ 1.13\ (1\H,\ m,\ CHH); \(\delta\_C(63\ \text{MHz};\ \text{CDCl}_3)\ 136.5, 136.0, 116.6, 86.1, 77.2, 65.3, 64.3, 50.8, 39.3, 35.2, 32.5, 29.6, 25.8, 20.1\ and\ 17.9;\ HRMS\ (CI)\ m/z\ \text{calcd}\ for\ C_{12}H_{20}NOI\ (M+H)^+:\ 360.0824,\ \text{found:}\ 360.0827;\ MS\ (CI)\ m/z\ 360\ [(M+H)^+,\ 76\%],\ 279\ (47),\ 234\ (65),\ 218\ (75),\ 130\ (79)\ and\ 102\ (100).

\[ \text{TIPS} \]

(2S, 6R, 7S, 8S)-2-(Prop-2'-enyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxa tricyclo[5.4.1\(^{48}\).0\]undecane, 63.

Copper iodide (4 mg, cat.) was dissolved in HNEt\(_2\) (1.0 mL) under nitrogen and TIPS-acetylene (9.7 µL, 0.043 mmol, 2 eq) was added, after which the reaction mixture was stirred in the absence of light for 0.25 h. The mono-vinyl iodide 62 (7.8 mg, 0.022mmol) was dissolved in HNEt\(_2\) (1.5 mL) under nitrogen in the absence of light and then Pd(PPh\(_3\)_4 (5 mg, cat.) was added. After the reaction mixture was stirred for 5 min., the Cu/TIPS acetylene mix was added, and the reaction mixture was again stirred for 17 h at 25 °C in the absence of light.

The reaction mixture was diluted with the addition of EtOAc (6 mL) and reduced to virtual dryness under vacuum. This process was repeated twice. The crude residue was purified by flash column chromatography (9:1 hexane:EtOAc; 1% NEt\(_3\)) to yield the triisopropylsilyl acetylene 63 (7.3 mg, 81%) as a colourless oil; R\(_f\) 0.70 (1:1 hexane:EtOAc); \([\alpha]_D^{20} +0.40\ (c\ 0.58\ in\ CHCl_3);\ \nu_{\text{max}}(\text{thin film})\ 2941s (C-H),\ 2865, 2146, 2063, 1640, 1462, 1007 and 951cm\(^{-1}\); \(\delta\_H(500\ \text{MHz};\ \text{CDCl}_3)\ 6.06\ (1\H,\ dd,\ J\ 10.5\ and\ 10.5,\ CH=CHC\equiv\text{CTIPS}),\ 5.82-5.73\ (1\H,\ m,\ CH=CH_2),\ 5.76\ (1\H,\ d,\ J\ 10.5,\ CH=CHC\equiv\text{CTIPS}),\ 5.05\ (1\H,\ d,\ J\ 19.5,\ CH=CHH\ trans),\ 5.02\ (1\H,\ d,\ J\ 11.0,\ CH=CHH\ cis),\ 4.53\ (1\H,\ ddd,\ J\ 6.5,\ 6.0\ and\ 0.0,\ CHO\ ring),\ 3.98\ (1\H,\ dd,\ J\ 10.5\ and\ 6.5,\ CHCH=CHC\equiv\text{CTIPS}),\ 2.79-2.75\ (2\H,\ m,\ CHN\ and\ CHHCH=CH_2),\ 2.07-1.95\ (2\H,\ m,\ CHHCH=CH_2\ and\ CHH),\ 1.79-1.72\ (2\H,\ tm,\ J\ 15.5,\ CH_2),\ 1.63-1.37\ (8\H,\ m,\ 4\times\ CH_2),\ 1.09\ (21\H,\ s,\ Si(\text{Pr}_3)),\ 1.09\ (1\H,\ m,\ CH);\ \delta\_C(63\ \text{MHz};\ \text{APT};\ \text{CDCl}_3)\ 138.7, 135.9, 116.5, 113.6, 103.4, 96.5, 77.7, 65.7, 64.2, 46.4, 39.2, 34.5, 32.6, 29.6, 25.4, 19.6, 18.6 (q),\ 17.9\ and\ 11.3;\ HRMS\ (ES)\ m/z\ \text{calcd}\ for\ C_{26}H_{46}NOSi\ (M+H)^+:\ 414.3192,\ \text{found:}\ 414.3189;\ MS\ (CI)\ m/z\ 414\ [(M+H)^+,\ 100\%],\ 174\ (25)\ and\ 98\ (16).
(−)-Triisopropylsilylhistirionicotoxin 259A, 64.

The isoxazolidine 63 (3.8 mg, 0.009 mmol) was dissolved in glacial acetic acid (1 mL) under nitrogen and activated zinc dust (7.0 mg, 13 eq) added in one portion. After vigorous stirring at 25 °C for 0.75 h, the reaction was quenched by the addition of a solution of satd. aqueous NaOAc and EtOAc (1:1; 4 mL) and stirring was continued for a further 1 h. The aqueous layer was separated, neutralised (satd. NaHCO₃) and extracted further with EtOAc (2 x 5 mL). The combined organic phases were washed with water (3 x 5 mL) then brine (3 x 5 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the crude residue via flash column chromatography (1:9 MeOH:CH₂Cl₂) yielded TIPS-hiristrionicotoxin 4 (3.4 mg, 89%) as a colourless oil; Rf 0.10 (1:9 MeOH:CH₂Cl₂); [α]D²⁵ -31.1 (c 0.18 in CHCl₃); νmax (thin film) 3233, 2939, 2864, 1642, 1462, 1070 and 996 cm⁻¹; δH (500 MHz; CDCl₃) 5.71 (1H, dd, J 10.5 and 10.0, CH=CH=CH₂, 2H, d, J 10.0, CH=CHH cis); 3.01 (1H, bs, CH₂O); 2.83 (1H, br d, J 14.0, CH); 1.85 (1H, br d, J 13.5, CH₂), 1.77 (1H, br d, J 13.5, CH), 1.67-1.54 (8H, m, 4 x CH₂) and 1.10 (21H, s, Si(Pr)₃); HRMS (ES) m/z calcd for C₂₈H₄₀NOSi (M+H)⁺: 416.3348, found: 416.3344; MS (Cl) m/z 416 [(M+H)⁺, 100%], 98 (28) and 90 (35).

(--)-Histirionicotoxin 259A, 2.

Triisopropylsilylhistirionicotoxin-259A 64 (6.6 mg, 0.016 mmol) was dissolved in THF (3 mL) and a solution of TBAF (1.0 M in THF; 32 µL, 0.032 mmol, 2 eq) was added with stirring. After the reaction mixture was stirred at 25 °C for 0.75 h the reaction was deemed complete as judged by TLC analysis. The reaction mixture was concentrated under a stream of nitrogen and purified via flash column chromatography (1:9 MeOH:CH₂Cl₂) to furnish (−)-HTX-259A 2 as a colourless oil; Rf 0.28 (1:9 MeOH:CH₂Cl₂); δH (500 MHz; CDCl₃) 5.83 (1H, dd, J 10.5 and 10.5, H-15), 5.83-5.75 (1H, m, H-13), 5.62 (1H, d, J 10.5, H-16), 5.25 (1H, d, J 17.5, H-14 trans), 5.15 (1H, d, J 10.0, H-14 cis), 3.97 (1H, br s, CHOH), 3.71 (1H, d, J 10.0, CHNH), 3.22 (2H, br m, H-7 and H-18), 2.50-2.33 (2H, br m, H-12 x 2), 2.09-2.00 (2H, m, CH₂) and 1.80-0.80 (10H, m, 5 x CH₂).
(–)-Histrionicotoxin 259A Hydrochloride.

(–)-Histrionicotoxin 259A 2 was dissolved in dry methanol (1 mL) and a solution of methanolic HCl (0.3 M; 54 µL, ≈ 1 eq) was added. After the mixture was stirred for 0.5 h, the solvent was removed in vacuo furnishing (–)-HTX-259A hydrochloride (3.9 mg, 82%) as a colourless oil; Rf 0.28 (1:9 MeOH:CH2Cl2); [α]25.5D -54.0 (c 0.2 in EtOH); δH (500 MHz; MeOH) 6.00 (1H, dd, J 10.5 and 10.5, H-15), 5.85-5.75 (1H, m, H-13), 5.78 (1H, d, J 10.5, H-16), 5.27 (1H, d, J 15.5, H-14 trans), 5.25 (1H, d, J 8.0, H-14 cis), 3.99 (1H, s, CHO), 3.78 (1H, s, H-18), 3.63 (1H, m, H-7), 3.55-3.49 (1H, br m, CHNH), 2.55-2.49 (1H, m, H-12), 2.34 (1H, ddd, J 14.0, 9.0 and 9.0, H-12), 2.04-1.87 (3H, m, CH2 and CH), 1.76-1.68 (6H, m, 3 x CH2) and 1.37-1.29 (3H, m, CH2 and CH); δC (100 MHz; MeOH) 137.8, 132.0, 119.3, 112.7, 84.5, 78.6, 70.0, 59.9, 51.4, 40.8, 38.3, 33.9, 32.4, 28.2, 26.8, 17.4 and 14.0; HRMS (ES) m/z calcd for C17H26NOCl (M-Cl)+: 260.2014, found: 260.2015; MS (Cl) m/z 260 [(M-Cl)+, 100%], 186 (52).
Synthesis of the “unsymmetrical” histrionicotoxins

(2S, 6R, 7S, 8S)-2-(Benzyloxyethyl)methyl)-7-formyl-1-aza-12-oxatricyclo[5.4.16.8.0]undecane, 69.

(2S, 6R, 7S, 8S)-2-(Benzyloxyethyl)methyl)-7-cyano-1-aza-12-oxatricyclo[5.4.16.8.0]undecane 57 (185.1 mg, 0.541 mmol) was dissolved in dry toluene (21 mL) and cooled to -78 °C under nitrogen. DIBAL-H (1.5 M in toluene; 0.72 mL, 1.1 mmol, 2 eq) was added dropwise and the reaction mixture was stirred for 0.75 h.

The reaction was quenched by the addition of wet MeOH (1.5 mL) and warmed to 25 °C. The reaction mixture was diluted with EtOAc (15 mL) and Rochelle’s salt was added (6 mL), together with a few drops of HCl (2 M aq.) in order to dissolve the salts to settle. The solution was stirred at -30 ˚C for 0.5 h. The solution was cooled further to -78 ˚C and stirring was stopped, allowing the salts to settle. THF (30 mL) under argon and cooled to -30 °C. KHMD S (0.5 M in toluene; 3.26 mL, 1.63 mmol, 3 eq) was added and the reaction was quenched by the addition of wet THF (1:1 THF:H2O; 10 mL) and warmed to 25 °C. Ether (30 mL) and satd. NH4Cl (4 mL) were added and the organic layer was separated. The aqueous layer was further extracted with ether (3 x 30 mL), the organic phases were combined, dried (MgSO4) and concentrated in vacuo. Purification via flash column chromatography (1:1 hexane:EtOAc) yielded the aldehyde 69 (187.2 mg, 100%) as a clear oil; Rf 0.34 (1:1 hexane:EtOAc); [α]25D -93.7 (c 0.62 in CHCl3); νmax (thin film) 3030, 2937, 2867, 1710, 1496, 1453, 1160, 1105, 1050 and 925 cm⁻¹; δH (500 MHz; CDCl3) 9.99 (1H, d, J 2.5, CHO), 7.35-7.24 (5H, m, aromatics), 4.79 (1H, d, J 7.0, OCHHO), 4.77 (1H, d, J 7.0, OCHHO), 4.79-4.74 (1H, m, CHO ring), 4.61 (1H, d, J 12.0, OCHHP), 4.58 (1H, d, J 12.0, OCHHP), 3.87 (1H, dd, J 9.5 and 3.0, CHHOBOM), 3.60 (1H, dd, J 9.5 and 7.5, CHHOBOM), 3.25 (1H, m, CHCHO), 2.74 (1H, dddd, J 11.5, 7.5, 3.0 and 3.0, CHN), 2.13-2.00 (2H, m, CH2), 1.92 (1H, dm, J 13.5, CH), 1.79-1.52 (7H, m, 3 x CH2 and CH) and 1.46-1.26 (2H, m, CH2); δC (125 MHz, APT; CDCl3) 201.1, 138.0, 128.3, 127.8, 127.6, 95.0, 75.9, 70.1, 69.3, 65.4, 64.5, 56.3, 35.9, 32.5, 28.4, 26.6, 18.8 and 18.1; HRMS (CI) m/z calcd for C30H28NO4 (M+H)⁺: 346.2018, found: 346.2021; MS (EI) m/z 346 [(M+H)+, 100%], 330 (16), 286 (20) 194 (23) and 106 (17).

(2S, 6R, 7S, 8S)-(1Z)-2-(Benzyloxyethyl)methyl)-7-(2’-iodoethenyl)-1-aza-12-oxatricyclo[5.4.16.8.0]undecane.

Dry recrystallised iodomethyltriphenylphosphonium iodide (900.7 mg, 1.69 mmol, 3.1 eq) was suspended in degassed THF (30 mL) under argon and cooled to -30 °C. KHMDS (0.5 M in toluene; 3.26 mL, 1.63 mmol, 3 eq) was added and the solution was stirred at -30 °C for 0.5 h. The solution was cooled further to -78 °C and stirring was stopped, allowing the salts to settle.

The aldehyde 5,53 (187.2 mg, 0.541 mmol) was dissolved in degassed THF (15 mL) and cooled to -78 °C under argon. The supernatant from the ylide formation (16.6 mL, 0.85 mmol, 1.5 eq) was added quickly and the reaction mixture was stirred for a further 0.5 h.

The reaction was quenched by the addition of wet THF (1:1 THF:H2O; 10 mL) and warmed to 25 °C. Ether (30 mL) and satd. NH4Cl (4 mL) were added and the organic layer was separated. The aqueous layer was further extracted with ether (3 x 30 mL), the organic phases were combined, dried (MgSO4) and concentrated in vacuo. Purification via flash column chromatography (3:1 hexane:EtOAc) yielded the title compound (203.4 mg, 81%) as a colourless oil; Rf 0.32 (2:1...
hexane:EtOAc); [α]D 21.5 \degree -48.8 (c 1.26 in CHCl₃); (Found: C, 54.8; H, 6.1; N, 3.1%. C₂₂H₂₃NO₄I requires C, 54.7; H, 6.0; N, 3.0%). νmax (thin film) 2932, 2865, 1456, 1300, 1278, 1159, 1108 and 1050 cm⁻¹; δH (500 MHz; CDCl₃) 7.37-7.26 (5H, m, aromatics), 6.53 (1H, d, J 7.5, =CHI), 6.34 (1H, dd, J 9.0 and 7.5, CH=CHI), 4.82 (1H, d, J 6.5, OCHHO), 4.80 (1H, d, J 6.5, OCHHO), 4.62 (2H, s, OCH₂Bn), 4.55 (1H, ddd, J 5.5, 5.5 and 0.0, CHO), 3.95 (1H, dd, J 9.5 and 3.0, CHHOBOM), 3.63 (1H, dd, J 9.5 and 7.5, CHHOBOM), 3.55 (1H, br dd, J 9.0 and 5.5, CHCH=CHI), 3.00 (1H, dddd, J 12.0, 7.5, 3.0 and 3.0, CHN), 2.04-1.95 (2H, m, CHJCH), 1.77 (1H, dd, J 14.0 and 2.5, CH), 1.67-1.42 (8H, m, 4 x CH₂J and 1.31 (1H, ddt, J 13.0, 13.0 and 3.0, CH); δc (125 MHz; CDCl₃) 138.1, 136.3, 128.4, 127.9, 127.6, 95.1, 86.4, 76.9, 70.5, 69.3, 65.2, 64.3, 50.7, 35.0, 32.4, 28.6, 25.8, 19.7 and 17.8; HRMS (ES) m/z: C₂₂H₂₃NO₄I (M+H)⁺: 470.1192, found: 470.1196; MS (CI) m/z: C₂₂H₂₃NO₄I (M+H)⁺, 85%; 391 (53), 344 (100), 328 (36), 106 (42) and 58 (44).

(2S, 6R, 7S, 8S)-(1’Z)-2-(Benzylxoxymethoxymethyl)-7-(4’-trimethylsilyl-but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0₁⁸]undecane. 70.

Copper iodide (9 mg, cat.) was dissolved in HNEt₂ (5 mL) under nitrogen and TMS-acetylene (46 µL, 0.32 mmol, 1.5 eq) was added after which the mixture was stirred in the dark for 0.25 h. Meanwhile, (2S, 6R, 7S, 8S)-(1’Z)-2-(benzylxoxymethoxymethyl)-7-(2’-idoethenyl)-1-aza-12-oxatricyclo[5.4.1.0₁⁸]undecane (101.7 mg, 0.216 mmol) was dissolved in HNEt₂ (8 mL) under nitrogen and Pd(PPh₃)₄ (8 mg, cat) added. The reaction mixture was stirred for 5 min., after which the Cu/TMS acetylene mix was added rapidly and the reaction stirred for 1 h.

The reaction mixture was diluted by the addition of EtOAc (10 mL) and reduced to virtual dryness in vacuo. This process was repeated twice. The resulting crude residue was purified by flash column chromatography (4:1 hexane:EtOAc; 1% NEt₃) to yield the trimethylsilyl-enzyme 70 (90.2 mg, 95%) as a pale yellow oil; Rf 0.64 (2:1 hexane:EtOAc); [α]D ¹⁹ \degree -11.7 (c 0.40 in CHCl₃); νmax (thin film) 3030, 2935, 2869, 2148, 1603, 1496, 1450, 1379, 1290, 1050 and 844 cm⁻¹; δH (500 MHz; CDCl₃) 7.37-7.26 (5H, m, aromatics), 6.05 (1H, dd, J 10.5 and 10.0, CH=CH₂=CTMS), 5.73 (1H, d, J 10.5, CH=CH₂=CT), 4.81 (1H, d, J 6.5, OCHHO), 4.79 (1H, d, J 6.5, OCHHO), 4.63 (1H, d, J 12.0, PhCHHO), 4.60 (1H, d, J 12.0, PhCHHO), 4.52 (1H, ddd, J 6.5, 5.5 and 0.0, CHO), 3.93 (1H, dd, J 9.5 and 3.0, CHHOBOM), 3.89 (1H, dd, J 10.0 and 6.5, CHCH=CH), 3.64 (1H, dd, J 9.5 and 7.0, CHHOBOM), 2.97 (1H, dddd, J 12.0, 7.0, 3.5 and 3.0, CHN), 2.05-1.93 (1H, m, CH), 1.93 (1H, ddd, J 13.5, 2.5 and 2.5, CH), 1.83-1.80 (1H, m, CH), 1.72-1.26 (9H, m, 4 x CH₂J and CH) and 0.20 (9H, s, Si(CHJ₃)); δc (63 MHz; CDCl₃) 139.1, 138.1, 128.3, 127.9, 127.6, 113.2, 101.9, 100.0, 94.9, 77.7, 70.4, 69.2, 65.9, 64.4, 46.3, 34.5, 32.4, 28.6, 25.3, 19.6, 17.9 and -0.1; HRMS (CI) m/z: C₂₂H₂₃NO₄Si (M+H)⁺: 440.2621, found: 440.2615; MS (CI) m/z: 440 [(M+H)⁺, 100%], 288 (13), 279 (26) and 90 (15).
The benzyloxymethyl ether 70 (52.3 mg, 0.119 mmol) was dissolved in methanol (20 mL) and Amberlyst-15™ resin (10 mg) was added, followed by stirring at 25 °C overnight. NEt₃ (2.0 mL) was added and the reaction mixture was stirred for a further 1 h.

The solution was filtered to remove the catalyst and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (1:1 hexane:EtOAc; 1% NEt₃) to yield the alcohol 71 (38.0 mg, 99%) as a colourless oil; R_f 0.43 (EtOAc); [α]_D²¹ +25.5 (c 0.42 in CHCl₃); ν_max (CHCl₃) 3417, 2935, 2861, 2148, 1599, 1448, 1250, 1009, 922, 843 and 759 cm⁻¹; δ_H (500 MHz; CDCl₃) 6.04 (1H, dd, J 10.5 and 10.0, C=H=CHC≡C), 5.73 (1H, d, J 10.5, CH=CHC≡C), 4.54 (1H, dd, J 6.5, 5.5 and 0.0, CHO), 3.86 (1H, dd, J 10.0 and 6.5, C_H=CH), 3.78 (1H, ddd, J 10.5, 5.0 and 3.5, CHHOH), 3.62 (1H, ddd, J 10.5, 6.5 and 5.0, CHHOH), 3.03 (1H, dd, J 5.0 and 5.0, O_H), 2.94 (1H, dddd, J 12.5, 6.5, 3.5 and 0.0, CHN), 2.06-1.94 (1H, m, C_H), 1.81 (1H, ddd, J 14.0, 3.0 and 2.5, CH), 1.73-1.48 (7H, m, 3 x C_H₂ and CH), 1.42-1.33 (3H, m, C_H₂ and C_H) and 0.20 (9H, s, Si(C₃H₃)₃); δ_C (63 MHz, APT; CDCl₃) 138.7, 113.4, 101.7, 100.1, 78.0, 66.3, 66.0, 65.0, 46.7, 34.5, 32.1, 27.5, 25.2, 19.5, 17.9 and -0.1 (q); HRMS (ES) m/z calcd for C₁₈H₃₀NO₂Si (M+H)^+ : 320.2046, found: 320.2043; MS (ES) m/z 320 [(M+H)^+, 86%], 166 (20), 90 (100), 82 (28) and 72 (22).

The alcohol 71 (14.5 mg, 0.045 mmol), NEt₃ (12.7 µL, 0.091 mmol, 2 eq) and DMAP (4 mg, cat.) were dissolved in dry CH₂Cl₂ (1 mL) and a solution of methanesulfonyl chloride (3.9 µL, 0.05 mmol, 1.1 eq) in dry CH₂Cl₂ (2 mL) was added dropwise. The reaction was stirred at 25 °C for 1 h.

The solvent was removed in vacuo and the residue was taken up in EtOAc (2 mL) and washed with brine (2 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 3 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo to leave a pale yellow oil. Purification by flash column chromatography (1:1 hexane:EtOAc) furnished the mesylate 72 (13.5 mg, 85%) as a colourless oil; R_f 0.58 (EtOAc); [α]_D¹⁸ -2.3 (c 0.22 in CHCl₃); ν_max(thin film) 2954, 2149, 1602, 1461, 1409, 1356, 1250, 1176, 844 and 759 cm⁻¹; δ_H(500 MHz; CDCl₃) 6.03 (1H, dd, J 10.5 and 10.0, C=H=CHC≡C), 5.74 (1H, d, J 10.5, CH=CHC≡C), 4.53 (1H, ddd, J 6.5, 5.5 and 0.0, CHO), 4.39 (1H, dd, J 10.5 and 3.0, CHHOMs), 4.35 (1H, dd, J 10.5 and 5.5, CHHOMs), 3.01 (1H, dddd, J 15.0, 5.5, 3.0 and 3.0, CHN), 1.92-1.81 (3H, m, CH₂ and CH), 1.71-1.48 (6H, m, 3 x CH₃), 1.43-1.29 (3H, m, CH₂ and CH) and 0.20 (9H, s, Si(CH₃)₃); δ_C(125 MHz; CDCl₃)
138.4, 113.6, 101.6, 100.3, 77.8, 72.0, 65.9, 63.5, 46.3, 37.1, 34.5, 32.2, 27.7, 25.2, 19.2, 18.0 and -0.2; HRMS (ES) m/z calcld for C_{18}H_{22}NO_{4}SiS (M+H)^{+}: 398.1821, found: 398.1824; MS (Cl) m/z 398 [(M+H)^{+}, 100 %], 304 (35), 90 (21), 72 (21) and 61 (21).

(2S, 6R, 7S, 8S)-(1’Z)-2-Cyanomethyl-7-(but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.6,8.0]undecane, 73.
The mesylate 72 (33.4 mg, 0.095 mmol) was dissolved in dry DMSO (2 mL) and NaCN (93.6 mg, 1.91 mmol, 20 eq) and powdered molecular sieves (4 Å) were added. The reaction mixture was stirred at 55 °C for 2 days. The reaction vessel was allowed to cool to 25 °C before the addition of ether and water (1:1; 4 mL). The organic layer was separated and the aqueous layer was further extracted with ether (2 x 5 mL). The combined organic phases were washed with water (2 x 5 mL) and brine (2 x 5 mL), dried (MgSO_{4}) and concentrated in vacuo. Purification of the crude residue by flash column chromatography (3:1 hexane:EtOAc) yielded the nitrile 73 (15.2 mg, 62%) as a colourless oil; R_{f} 0.57 (1:1 hexane:EtOAc); [α]_{D}^{21} +14.3 (c 0.70 in CHCl_{3}); ν_{max} (thin film) 3280, 2938, 2869, 2248, 2077, 1448, 1095, 916 and 781 cm^{-1}; δ_{c} (500 MHz; CDCl_{3}) 6.09 (1H, dd, J 10.5 and 10.5, CH=CHC=CH), 5.72 (1H, dd, J 10.5 and 2.0, CH=C=CH), 4.52 (1H, ddd, J 5.5, 5.5 and 0.0, CHO), 3.77 (1H, dd, J 10.5 and 5.5, CHCH=CH), 3.18 (1H, d, J 2.0, C≡CH), 3.05 (1H, dddd, J 12.0, 8.5, 3.5 and 3.5, CHN), 2.86 (1H, dd, J 16.5 and 3.5, CHHCN), 2.50 (1H, dd, J 16.5 and 8.5, CHHCN), 1.97-1.92 (2H, m, CH_{2}), 1.83 (1H, ddt, J 14.0, 3.0 and 3.0, CH) and 1.63-1.30 (9H, m, 4 x CH_{2} and CH); δ_{c} (125 MHz; CDCl_{3}) 139.2, 118.5, 112.6, 82.9, 80.1, 77.9, 66.0, 61.4, 46.2, 34.4, 32.1, 29.9, 25.2, 23.2, 19.3 and 17.8; HRMS (ES) m/z calcld for C_{18}H_{22}N_{2}O (M+H)^{+}: 257.1654, found: 257.1654; MS (Cl) m/z 257 [(M+H)^{+}, 100 %] and 58 (13).

(2S, 6R, 7S, 8S)-(1’Z)-2-(Benzylxoxyethoxymethyl)-7-(4’-triisopropylsilyl-but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.6,8.0]undecane, 74.
Copper iodide (9 mg, cat.) was dissolved in HNEt_{2} (3 mL) under nitrogen and TIPS-acetylene (96 μL, 0.43 mmol, 2.0 eq) was added after which the mixture was stirred in the dark for 0.25 h. Meanwhile, (2S, 6R, 7S, 8S)-(1’Z)-2-(benzylxoxyethoxymethyl)-7-(2’-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1.6,8.0]undecane (101.7 mg, 0.22 mmol) was dissolved in HNEt_{2} (8 mL) under nitrogen and Pd(PPh_{3})_{4} (8 mg, cat.) was added. After stirring for 5 min., the Cul/TIPS acetylene mix was added rapidly and the reaction was stirred overnight. The reaction mixture was diluted by the addition of EtOAc (11 mL) and reduced to virtual dryness in vacuo. This process was repeated twice. The crude residue resulting was purified by flash column chromatography (3:1 hexane:EtOAc; 1% NEt_{3}) to yield the triisopropylsilyl-enzyme 74 (112.9 mg, 100%) as a colourless oil; R_{f} 0.32 (3:1
The benzyloxymethyl ether 74 (66.1 mg, 0.126 mmol) was dissolved in methanol (30 mL) and Amberlyst-15™ resin (15 mg) was added followed by stirring at 25 °C overnight. NEt₃ (10 mL) was added and the reaction mixture was stirred for a further 3 h. The solution was filtered to remove the catalyst, the catalyst was washed further with methanol (3 x 10 mL), and the combined organic phases concentrated in vacuo. Purification of the crude residue by flash column chromatography (EtOAc) yielded the alcohol 75 (42.9 mg, 84%) as a white crystalline solid; Rf 0.37 (EtOAc); mp 48-49.5 °C (from hexane:EtOAc); [α]D²⁸ +21.1 (c 1.40 in CHCl₃); (Found: C, 71.5; H, 10.2; N, 3.5%. C₂₄H₄₁NO₂Si requires C, 71.4; H, 10.2; N, 3.5%); νmax (thin film) 3445, 2940, 2864, 2144, 1461 and 1007 cm⁻¹; δH (500 MHz; CDCl₃) 6.03 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.79 (1H, d, J 10.5, CH=CHC≡C), 4.56 (1H, dd, J 6.0, 5.5 and 0.0, CHO), 3.91 (1H, dd, J 10.0 and 6.0, CHCH=CH), 3.77 (1H, ddd, J 10.5, 3.5 and 3.5, CHOH), 3.57 (1H, ddd, J 10.5, 5.0 and 5.0, CHOH), 2.97 - 2.91 (2H, m, CH₂ and OH), 2.04-1.97 (1H, m, CH), 1.80 (1H, dm, J 14.0, CH), 1.65-1.34 (10H, m, 5 x CH₂) and 1.09 (21H, s, Si(iPr)₃); δC (125 MHz; CDCl₃) 138.0, 113.8, 103.2, 96.8, 78.1, 66.1, 65.6, 64.6, 46.8, 34.4, 32.2, 27.4, 25.3, 19.1, 18.6, 17.9 and 11.3; HRMS (ES) m/z calcd for C₂₃H₃₉NO₂Si (M+H)^+: 404.2985, found: 404.2989; MS (CI) m/z 404 [(M+H)^+, 32%], 374 (32), 143 (100), 112 (50) and 96 (50).

(2S, 6R, 7S, 8S)-(1’Z)-2-(Hydroxymethyl)-7-(4’-trisopropylsilyl-but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.6,8.0]undecane, 75.
(2S, 6R, 7S, 8S)-(1’Z)-2-(Methanesulfonyloxymethyl)-7-(4’-triisopropylsilyl-but-1’-en-3'-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0]undecane.

The alcohol 75 (27.8 mg, 0.069 mmol), NEt3 (19.2 µL, 0.14 mmol, 2 eq) and DMAP (10 mg, cat.) were dissolved in dry CH2Cl2 (6 mL), and a solution of methanesulfonyl chloride (11.8 µL, 0.10 mmol, 1.5 eq) in dry CH2Cl2 (1 mL) was added dropwise. The reaction was stirred at 25 °C for 1 h.

The reaction mixture was concentrated in vacuo and the residue was preabsorbed onto silica (CH2Cl2:EtOAc; 2:1) and 1% NEt3 to yield the title compound (27.5 mg, 97%) as a colourless oil which slowly crystallised on standing in the freezer; Rf 0.63 (EtOAc); [α]D28 -5.8 (c 0.32 in CHCl3); vmax (thin film) 2940, 2864, 2144, 1460, 1356, 1176, 950 and 883 cm⁻¹; δd (500 MHz; CDCl3) 6.02 (1H, dd, J 3.0, 12.5, 4.0 and 3.5, CHN), 6.02 (1H, dd, J 3.0, 6.5 and 0.0, CH=N), 5.78 (1H, d, J 10.5, CH=CH=CH=C), 4.54 (1H, ddd, J 6.0, 5.5 and 0.0, CH=N), 4.35 (2H, d, J 4.0, CH2OMs), 3.89 (1H, dd, J 10.0 and 6.0, CHCH=CH=CH), 3.09 (3H, s, CH3SO2), 3.00 (1H, ddd, J 12.5, 4.0 and 3.5, CHN), 1.92-1.85 (1H, m, CH), 1.80 (2H, br d, J 14.0, CH2), 1.60-1.33 (9H, m, 4 x CH2 and CH) and 1.09 (21H, s, Si(Pr)3); δc (125 MHz; CDCl3) 137.8, 114.0, 103.1, 96.9, 77.9, 71.9, 65.5, 63.3, 46.3, 37.1, 34.3, 32.2, 27.6, 25.3, 18.9, 18.6, 18.0 and 11.3; HRMS (ES) m/z calcd for C25H34NO3Si (M+H)+: 482.2760, found: 482.2758; MS (CI) m/z 482 [(M+H)+, 100%], 388 (26), 174 (52), 112 (53), 98 (60), 84 (59) and 62 (67).

(2S, 6R, 7S, 8S)-(1’Z)-2-(Cyanomethyl)-7-(4’-triisopropylsilyl-but-1’-en-3'-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0]undecane, 76.

(2S, 6R, 7S, 8S)-(1’Z)-2-(Methanesulfonyloxymethyl)-7-(4’-triisopropylsilyl-but-1’-en-3'-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0]undecane (39.1 mg, 0.081 mmol) was dissolved in dry DMSO (4 mL) and NaN3 (80 mg, 1.62 mmol, 20 eq) and powdered molecular sieves (4 Å) were added. The reaction mixture was stirred at 55 °C for 4 days.

The reaction vessel was allowed to cool to 25 °C before the addition of ether and water (1:1; 8 mL). The organic layer was separated and the aqueous layer was further extracted with ether (5 x 5 mL). The combined organic phases were washed with water (6 x 5 mL) and brine (6 x 5 mL), dried (MgSO4) and concentrated in vacuo. Purification of the crude residue by flash column chromatography (2:1 hexane:ether; 1% NEt3) yielded the nitrile 76 (18.7 mg, 66%) as a colourless oil which slowly crystallised on standing in the freezer; Rf 0.50 (2:1 hexane:EtOAc); mp 48.5-49.5 °C; [α]D4 2.3 (c 0.75 in CHCl3); vmax (thin film) 2940, 2864, 2243, 2144, 1459, 1007 and 918 cm⁻¹; δd (500 MHz; CDCl3) 6.02 (1H, dd, J 10.5 and 10.0, CH=N), 5.79 (1H, d, J 10.5, CH=CH=CH=C), 4.53 (1H, ddd, J 6.0, 5.5 and 0.0, CHO), 3.89 (1H, dd, J 10.0 and 6.0, CHCH=CH=CH), 3.03 (1H, ddd, J 12.0, 8.5, 3.0 and 3.0, CHN), 2.86 (1H, dd, J 16.5 and 3.0, CHHCN), 2.48 (1H, dd, J 16.5 and 8.5, CHHHCN), 1.98-1.87 (1H, m, CH), 1.90 (1H, br d, J 14.0, CH), 1.82 (1H, br d, J 14.0, CH), 1.68-1.22 (9H, m, 4 x CH2 and CH) and 1.10 (21H, s, Si(Pr)3); δc (125 MHz; CDCl3) 137.7, 118.2, 114.1, 103.1, 97.0, 93, 87, 63, 51, 48, 43, 37, 32, 26, 24, 17, 14, 13, 12, 11, 9, 8, 6, 5, 4, 3, 2, 1.
78.0, 65.8, 61.3, 46.4, 34.2, 32.1, 29.9, 25.3, 23.2, 19.1, 18.6, 17.8 and 11.3; HRMS (ES) m/z calcd for C₂₃H₄₁N₂O₅Si (M+H)⁺: 413.2988, found: 413.2985; MS (Cl m/z 413 [(M+H)⁺, 36%], 162 (100), 91 (50), 58 (49) and 49 (79). Further elution of the column furnished recovered mesylate (9.7 mg, 25%).

(2S, 6R, 7S, 8S)-(1''Z)-2-(2''-Oxo-1''-ethyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1.0²,8]undecane.
The nitrile 76 (6.1 mg, 0.015 mmol) was dissolved in dry toluene (0.7 mL) under argon and cooled to -78 °C. DIBAL-H (1.5 M in toluene; 14.8 µL; 0.022 mmol, 1.5 eq) was added dropwise and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of wet MeOH (0.5 mL) and warmed to 25 °C. The mixture was diluted with EtOAc (4 mL) and Rochelle's salt was added (1 mL), together with a few drops of HCl (2 M aq.) in order to lower the pH to 5. Stirring was then continued overnight. The aqueous layer was separated and neutralised by the addition of NaHCO₃ (aq.), and extracted with EtOAc (2 x 3 mL). The combined organic phases were washed with brine (2 x 3 mL), dried (MgSO₄ to 5.0) and concentrated in vacuo to yield the title compound (6.0 mg, 100%) as a colourless oil; Rf 0.25 (1:1 hexane:ether); [α]D²⁰ -23.0 (c 0.33 in CHCl₃); νmax (thin film) 2940, 2864, 2722, 2145, 1725, 1461, 1250, 1007, 920 and 883 cm⁻¹; δH (500 MHz; CDCl₃) 9.81 (1H, dd, J 2.0, CHO), 6.04 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.78 (1H, d, J 10.5, CH=CHC≡C), 4.54 (1H, dd, J 6.5, 5.5 and 0.0, CHO), 3.98 (1H, dd, J 10.0 and 6.5, CHCH=CH), 3.34 (1H, m, CHN), 2.85 (1H, dd, J 16.0, 5.0 and 2.0, CHHCHO), 2.47 (1H, dd, J 16.0, 6.5 and 2.0, CHHCHO), 2.02-1.93 (1H, m, CH), 1.81 (1H, dm, J 14.0, CH), 1.69 (1H, dm, J 14.0, CH), 1.64-1.36 (8H, m, 3 x CH₂ and 2 x CH), 1.27 (1H, ddt, J 13.0, 13.0 and 3.0, CH) and 1.11 (21H, s, Si(Pr)₃); δC (125 MHz; CDCl₃) 202.2, 138.1, 113.8, 103.2, 96.8, 78.0, 65.7, 60.3, 49.7, 46.3, 34.4, 32.2, 31.1, 25.3, 19.5, 18.6, 17.9 and 11.3; HRMS (Cl m/z calcd for C₂₃H₄₁N₂O₅Si (M+H)⁺: 416.2985, found: 416.2986; MS (Cl m/z 416 [(M+H)⁺, 100%], 249 (9) and 221 (12).

(2S, 6R, 7S, 8S)-(1''Z, 2''Z)-2-(3''-Iodoprop-2''-enyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1.0²,8]undecane, 77.
Dry recrystallised iodomethyltriphenylphosphonium iodide (55.7 mg, 0.105 mmol, 7.5 eq) was suspended in freeze-thawed degassed THF (3.0 mL) (three cycles) under argon and was cooled to -30 °C. KHMS (0.5 M in toluene; 0.20 mL, 0.10 mmol, 7.1 eq) was added and the solution was stirred at -30 °C for 0.5 h. The solution was cooled further to -78 °C and the stirring was stopped, allowing the salts to settle. (2S, 6R, 7S, 8S)-(1''Z)-2-(2''-Oxo-1''-ethyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1{6,8,0}undecane (6.0 mg, 0.014 mmol) was dissolved in THF (2.0 mL), thoroughly degassed and cooled to
-78 °C under argon. The supernatant from the ylide formation (0.64 mL, 0.021 mmol, 1.5 eq) was added quickly and the reaction mixture was stirred for a further 0.5 h. The reaction was quenched by the addition of wet THF (1:1 THF:H2O; 1.5 mL) and warmed to 25 °C. EtOAc (4 mL) and satd. NH4Cl (4 mL) were added and the organic layer separated. The aqueous layer was further extracted with EtOAc (3 x 5 mL) and the organic phases were combined, dried (MgSO4) and concentrated in vacuo. Purification via flash column chromatography (6:1 hexane:EtOAc; 1% NEt3) yielded the vinyl iodide 77 (6.4 mg, 82%) as a colourless oil; Rf 0.60 (4:1 hexane:EtOAc); [α]D^25 -10.6 (c 0.18 in CHCl3); νmax (thin film) 2938, 2863, 2145, 1461, 1366, 1306, 1260, 1076, 1008 and 921 cm⁻¹; δH (500 MHz; CDCl3) 6.30-6.24 (2H, m, CH=CHI and CH=CHII), 6.05 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.77 (1H, d, J 10.5, CH=CHCH≡C=), 4.54 (1H, dd, J 6.0, 5.5 and 0.0, CHO), 3.95 (1H, dd, J 10.0 and 6.0, CHCH=CH), 2.91-2.87 (1H, br d, J 11.5 and 9.0, CHN), 2.67 (1H, dm, J 14.5, CHHCH=CHI), 2.34 (1H, ddd, J 14.5, 7.5 and 7.5, CHH/CH=CHI), 2.04-1.96 (1H, m, CH), 1.78 (1H, br d, J 13.0, CH), 1.66-1.37 (8H, m, 4 x CH2), 1.28-1.19 (2H, m, CH2) and 1.09 (21H, s, Si(Pr)3); δc (63 MHz, APT; CDCl3) 138.9, 138.6, 113.6, 103.4, 96.5, 83.6, 77.8, 65.7, 63.6, 46.4, 39.8, 34.5, 32.5, 29.9, 25.4, 19.6, 18.6 (q), 17.9 and 11.3; HRMS (ESi) m/z calcd for C49H43NOSi (M+H)+: 540.2158, found: 540.2166; MS (Cl) m/z 540 [(M+H)+, 5%], 414 (19), 372 (38), 153 (41) and 96 (79).

(PdCl₂(MeCN)₂) (2 mg, cat.) was dissolved in dry DMF (0.4 mL) under nitrogen and the mixture was stirred. A solution of the vinyl iodide 77 (10.4 mg, 0.019 mmol) in dry DMF (0.4 mL) was added dropwise, followed by a solution of tributylinyl vinyl tin (8.5 μL, 0.029 mmol, 1.5 eq) in dry DMF (0.4 mL) under nitrogen. After complete addition the colour of the reaction mixture turned instantaneously from orange to black, and, after 5 min. the reaction was deemed complete by TLC analysis.

The reaction was quenched by the addition of ammonia solution (10%; 2 mL) and diluted with hexane (2 mL) followed by vigorous stirring overnight. The organic layer was separated and the aqueous layer was further extracted with hexane (2 x 4 mL). The organic phases were washed with H2O (2 x 4 mL) then brine (2 x 4 mL), dried (MgSO4) and concentrated in vacuo. Purification via flash column chromatography (6:1 hexane:ether; 1% NEt3) yielded the (Z)-diene 78 (6.8 mg, 80%) as a colourless oil; Rf 0.49 (4:1 hexane:EtOAc); [α]D^28 -20.0 (c 0.15 in CHCl3); νmax (thin film) 2940, 2864, 2145, 1461, 1004, 950 and 921 cm⁻¹; δH (500 MHz; CDCl3) 6.68 (1H, ddd, J 17.0, 10.5 and 10.5, H-15), 6.08 (1H, dd, J 11.0 and 10.5, H-14), 6.05 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.76 (1H, d, J 10.5, CH=CHC≡C), 5.44 (1H, ddd, J 11.0, 9.0 and 9.0, H-13), 5.18 (1H, d, J 17.0, H-16 trans), 5.09 (1H, d, J 10.5, H-16 cis), 4.54 (1H, ddd, J 6.5, 6.0 and 0.0, CHO), 3.97 (1H, dd, J 10.0 and 6.5, CHCH=CH), 2.82-2.76 (2H, m, CHN and CHHCH=CH), 2.27 (1H, ddd, J 14.0, 9.0 and 9.0, CHHCH=CH), 2.09-1.98 (1H, m, CH), 1.78 (1H, dm, J 13.5, CH), 1.70 (1H, dm, J 13.5, CH), 1.60-0.82 (9H, m, 4 x CH2 and CH) and 1.09 (21H, s, Si(Pr)3); δc (100 MHz; CDCl3) 138.6, 132.6, 131.0, 129.4, 117.1, 113.6, 103.4, 96.5, 77.8, 65.7, 64.7, 46.4, 34.5, 33.0, 32.6, 29.8, 25.4, 19.6, 18.6 (q), 18.0 and 11.3; HRMS (ESi) m/z calcd for C39H46NOSi (M+H)+: 440.3348, found: 440.3348; MS (Cl) m/z 440 [(M+H)+, 13%], 372 (56), 174 (100) and 150 (43).
(−)-Triisopropylsilylhistrionicotoxin 285E.

The isoxazolidine 5,49 (2.2 mg, 0.005 mmol) was dissolved in acetic acid (1 mL) and activated zinc dust (3 mg) was added in one portion with rapid stirring. After 0.25 h, the reaction was quenched by the addition of an aqueous solution of sodium acetate (satd.; 3 mL) and stirred for a further 0.25 h. The aqueous layer was extracted into EtOAc (3 x 3 mL) and the organic phases were washed with water (3 x 3 mL) then brine (3 x 3 mL). The combined organic phases were dried (MgSO₄), concentrated in vacuo and azeotroped in toluene. Purification of the crude residue via flash column chromatography (9:1 CH₂Cl₂:MeOH) yielded the title compound (2.0 mg, 91%) as a colourless oil; Rᶠ 0.17 (9:1 CH₂Cl₂:MeOH); [α]D⁰ 20° -65.7 (c 0.14 in CHCl₃); νmax(thin film) 3500-2800, 3227, 2940, 2864, 2145, 1630, 1461, 1261, 1095, 1071, 998, 906, 883 and 751 cm⁻¹; δH(500 MHz; CDCl₃) 6.71 (1H, ddd, J 16.0, 11.0 and 10.0, H-15), 6.14 (1H, dd, J 11.0 and 11.0, H-14), 5.77 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.66 (1H, d, J 10.5, CH=CHC≡C), 5.39 (1H, m, H-13), 5.23 (1H, d, J 16.0, H-16 trans), 5.17 (1H, d, J 10.0, H-16 cis), 3.93 (1H, br m, CHO), 3.81 (1H, br d, J 10.0, CHCH=CH), 3.21 (1H, br m, CHNH), 2.49 (2H, br m, CH₂CHN), 2.05 (2H, dm, J 14.0, H₃), 1.78-1.20 (10H, m, 5 x CH₃) and 1.10 (21H, s, Si(Pr)₃); HRMS (ES) m/z 442 [M+H]⁺, 444 (87), 154 (100), 115 (38), 98 (100), 90 (46), 81 (61) and 72 (35).

(−)-Histrionicotoxin 285E, 4.*

Triisopropylsilylhistrionicotoxin 285E (5.2 mg, 0.012 mmol) was dissolved in THF (2.5 mL) and TBAF (1.0 M in THF; 24 µL, 0.024 mmol, 2 eq) was added with stirring. After the reaction mixture was stirred at 25 °C for 1 h the reaction was deemed complete by TLC analysis. The reaction mixture was concentrated under a stream of nitrogen and purified via flash column chromatography (1.9 MeOH:CH₂Cl₂) to furnish (−)-HTX-285E 4 (2.8 mg, 84%) as a colourless oil; Rᶠ 0.57 (3:1 CH₂Cl₂:MeOH) [lit.¹⁵ 0.52 (9:1:0.08 CH₂Cl₂/PrOH/aq. NH₃)]; [α]D²⁷ 20° -23.8 (c 0.08 in CHCl₃); νmax(thin film) 3350-2400, 3299, 2931, 2848, 2092, 1728, 1556, 1454, 1260, 1092, 1018, 912, 798 and 757 cm⁻¹; δH(500 MHz; CDCl₃) 6.73 (1H, ddd, J 16.5, 10.5 and 10.5, H-15), 6.16 (1H, dd, J 11.0 and 10.5, H-14), 5.83 (1H, dd, J 11.0 and 10.5, H-17), 5.61 (1H, dd, J 11.0 and 2.0, H-18), 5.46 (1H, dt, J 11.0 and 8.0, H-13), 5.24 (1H, d, J 16.5, H-16 trans), 5.18 (1H, d, J 10.5, H-16 cis), 4.96 (1H, br m, CHO), 3.71 (1H, br d, J 10.5, H-7), 3.22 (2H, br m, CHNH and H-20), 2.52 (2H, br m, 2 x H-12), 2.04 (1H, br m, CH), 1.79 (2H, br t, J 12.0, CH₂) and 1.69-1.20 (9H, m, 4 x CH₂ and CH); HRMS (ES) m/z calcd for C₂₃H₂₅NO (M+H)⁺: 386.1871, found: 386.1871; MS (CI) m/z 286 [(M+H)⁺, 15%], 180 (87), 154 (100), 115 (82) and 98 (92).¹²
(–)-Histrionicotoxin 285E Hydrochloride.*

(–)-Histrionicotoxin-285E 4 (2.0 mg, 0.007 mmol) was dissolved in dry methanol (1 mL) and methanolic HCl (0.3 M; 35 µL, 0.011 mmol, ≈1.5 eq) was added. After the solution was stirred for 1 h, the solvent was removed in vacuo to furnish (–)-HTX-285E hydrochloride as a colourless oil which slowly crystallised on standing (1.9 mg, 84%); mp 231-235 °C; R\(_f\) 0.28 (9:1 CH\(_2\)Cl\(_2\):MeOH); \([\alpha]_D^{27.5}\) -38.5 (c 0.18 in EtOH) [lit.\(^{16}\) \([\alpha]_D^{25}\) -122 (c 1.0 in EtOH)]; \(\delta_H\) (500 MHz; MeOH) 6.72 (1H, ddd, \(J\) 16.5, 11.0 and 10.5, \(H\)-15), 6.27 (1H, dd, \(J\) 11.0 and 10.0, \(H\)-14), 6.00 (1H, dd, \(J\) 11.0 and 10.5, \(H\)-17), 5.61 (1H, dd, \(J\) 11.0 and 2.0, \(H\)-18), 5.45 (1H, dt, \(J\) 11.0 and 8.0, \(H\)-13), 5.33 (1H, d, \(J\) 16.5, \(H\)-16 trans), 5.25 (1H, d, \(J\) 10.5, \(H\)-16 cis), 3.99 (1H, br d, CHO), 3.78 (2H, m, \(H\)-7 and \(H\)-20), 3.56-3.50 (1H, m, CHNH), 2.65 (1H, m, \(H\)-12), 2.50 (1H, m, \(H\)-12), 2.04-1.85 (3H, m, \(CH_2\) and \(CH\)), 1.75-1.65 (6H, m, 3 x \(CH_2\)) and 1.42-1.26 (3H, m, \(CH_2\) and \(CH\)); \(\delta_C\) (100 MHz; MeOH) 137.8, 133.5, 131.1, 124.1, 118.8, 112.7, 84.5, 78.6, 70.0, 60.1, 52.5, 40.8, 33.7, 32.3, 31.8, 28.0, 26.9, 17.5 and 14.0; HRMS (ES) \(m/z\) calcd for C\(_{19}\)H\(_{28}\)NO (M-Cl): 286.2171, found: 286.2161; MS (ES) \(m/z\) 286 [(M-Cl), 100%].\(^{12}\)
Synthesis of the “unsymmetrical” histrionicotoxins

Total synthesis of HTX-285C

(2S, 6R, 7S, 8S)-(1’Z)-2-(para-Toluenesulfonylomethyl)-7-(4’-trimethylsilyl-but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0]undecane, 79.

The alcohol 71 (8.1 mg, 0.025 mmol) was dissolved in dry CH2Cl2 (1 mL) under nitrogen and DMAP (2 mg, cat.), triethylamine (5.3 µL, 0.038 mmol, 1.5 eq) and p-toluenesulfonyl chloride (5.8 mg, 0.030 mmol, 1.2 eq) were added, after which time the solution was stirred at 25 °C for 3 h.

The reaction was quenched by the addition of water (1 mL) and extracted with CH2Cl2 (3 x 3 mL). The combined organic phases were washed with HCl (2.0 M aq.; 3 x 3 mL), dried (MgSO4) and concentrated in vacuo. The crude residue was purified by flash column chromatography (3:1 hexane:EtOAc) to yield the tosylate 79 (5.9 mg, 53%) as a colourless oil; Rf 0.51 (1:1 hexane:EtOAc); [α]D 23.6 (c 0.28 in CHCl3); vmax (thin film) 2939, 2147, 1598, 1448, 1360, 1250, 1177, 975, 950, 843 and 762 cm−1; δH (500 MHz; CDCl3) 7.81 (2H, d, J 8.0, aromatic), 7.33 (2H, d, J 8.0, aromatic), 6.00 (1H, dd, J 11.0 and 10.0, CH=CH=C), 5.72 (1H, d, J 11.0, CH=CH=C), 4.46 (1H, ddd, J 6.0, 5.0 and 0.0, CHO), 4.37 (1H, dd, J 9.0 and 3.0, CHHOTs), 3.86 (1H, dd, J 9.0 and 9.0, CHHOTs), 3.77 (1H, dd, J 10.0 and 6.0, CHCH=CH), 3.00 (1H, dddd, J 12.0, 9.0, 3.0 and 3.0, CHF), 2.44 (3H, s, CH3), 1.95-1.77 (3H, m, CH2 and CH), 1.65-1.25 (8H, m, 4 x CH2), 1.15 (1H, ddt, J 13.5, 13.5 and 3.0, CH) and 0.21 (9H, s, Si(CH3)3); δc(125 MHz and DEPT; CDCl3) 144.5, 138.4, 133.0, 129.7, 128.1, 113.5, 101.4, 100.4, 77.8, 72.3, 65.9, 63.2, 46.1, 34.4, 32.2, 27.9, 25.1, 21.6 (q). 19.0, 17.8 and -0.1 (q); HRMS (ES) m/z calcld for C23H18NO3SiS (M+H)+: 474.2134, found: 474.2134; MS (Cl) m/z 474 [(M+H)+, 100%]. Further elution of the column furnished recovered alcohol 71 (2.8 mg, 35%).

(2S, 6R, 7S, 8S)-(1’Z)-2-(Trifluoromethanesulfonylomethyl)-7-(4’-triisopropyl silyl-but-1’-en-3’-yn-1’-yl)-1-aza-12-oxatricyclo[5.4.1.0]undecane, 80.

To a solution of the alcohol 75 (7.5 mg, 0.019 mmol) in CH2Cl2 (0.5 mL) under nitrogen and cooled to 0 °C was added triethylamine (3.2 µL, 0.023 mmol, 1.25 eq) and DMAP (1 mg, cat.). Triflic anhydride (3.4 µL, 0.02 mmol, 1.1 eq) was added dropwise and the reaction mixture was allowed to warm to 25 °C and stirred for 1 h.

The reaction was concentrated in vacuo, the residue was diluted with EtOAc (2 mL) and washed with HCl (2 M; 1 mL). The aqueous layer was separated and further extracted with EtOAc (2 x 2 mL), and the organic phases were washed with brine (3 x 2 mL). The combined organic phases were dried (MgSO4), concentrated in vacuo and purified by flash column chromatography to furnish the triflate 80 (6.5 mg, 69%) as a colourless oil; Rf 0.63 (1:1 hexane:EtOAc); δH (500 MHz; CDCl3) 6.03 (1H, dd, J 10.5 and 10.0, CH=CH=C), 5.79 (1H, d, J 10.5, CH=CH=C), 4.68 (1H, dd, J 10.5 and 3.0, CHHOTf), 4.55 (1H, ddd, J 6.0, 6.0 and 0.0, CHO), 4.27 (1H, dd, J 10.5 and 8.0, CHHOTf), 3.94 (1H, dd, J 10.0
and 6.0, CHCH=CH), 3.09 (1H, dddd, J 11.5, 8.0, 4.0 and 4.0, CHN), 2.01-1.90 (1H, m, CH), 1.81 (1H, dm, J 14.0, CH), 1.63-1.20 (10H, m, 5 x CH₂) and 1.09 (21H, s, Si(Pr)₃); Further characterisation was not carried out owing to the failure of later reactions.

The alcohol 71 (4.3 mg, 0.014 mmol) was dissolved in anhydrous DMSO (2 mL) and IBX¹¹⁰ (5.5 mg, 0.019 mmol, 1.4 eq) was added in one portion and the reaction mixture was stirred at 25 °C overnight.

The reaction was quenched by the addition of water (2 mL) and the residue was extracted into ether (6 x 4 mL). The organic phases were washed with water (6 x 4 mL), then brine (6 x 4 mL) before being combined and dried (MgSO₄).

After evaporation of the organic phase, purification of the crude residue by flash column chromatography (1:1 hexane:ether) yielded the aldehyde 86 (4.2 mg, 100%) as a colourless oil; Rf 0.41 (1:1 hexane:ether); [α]²³ -28.9 (c 0.37 in CHCl₃); νmax (thin film) 2940, 2869, 2149, 1733, 1447, 1250, 1007, 918 and 844 cm⁻¹; δ(500 MHz; CDCl₃) 9.78 (1H, d, J 2.5, CHO), 6.04 (1H, dd, J 10.5 and 10.0, CH=CH=C), 5.75 (1H, d, J 10.5, CH=CH=C), 4.58 (1H, ddd, J 6.5, 5.5 and 0.0, CHO), 3.80 (1H, dd, J 10.0 and 6.5, CHCH=CH), 3.33 (1H, ddd, J 12.5, 2.5 and 2.5, CHN), 2.12-2.02 (1H, m, CH), 1.87 (1H, dm, J 14.0, CH), 1.82 (1H, dm, J 13.5, CH), 1.75-1.53 (6H, m, 3 x CH₂), 1.48-1.38 (3H, m, CH₂ and CH) and 0.20 (9H, s, Si(CH₃)₃); δc (63 MHz; CDCl₃) 203.7, 138.2, 113.8, 101.5, 100.5, 78.5, 72.8, 65.6, 46.5, 34.4, 31.9, 25.9, 25.2, 19.2, 17.9 and -0.1; HRMS (ES) m/z calcd for C₁₉H₂₈NO₂Si (M+H)⁺: 318.1889, found: 318.1893; MS (CI) m/z 318 [(M+H)⁺, 100%], 222 (12), 98 (21) and 90 (68).

Magnetism turnings (11.3 mg, 0.47 mmol, 15 eq) were placed in a two-necked round-bottomed flask equipped with a reflux condenser and a suba seal. The flask was evacuated and refilled with nitrogen (3 cycles) before being charged with THF (0.5 mL). Dibromoethane (1 drop) was added and the reaction mixture was observed to warm, indicating that the reaction had been initiated. A solution of butynyl bromide 91 (32.3 mg, 0.15 mmol, 5 eq) in THF (1.5 mL) was

(2S, 6R, 7S, 8S)-(1’Z)-2-(5’-Trimethylsilyl-1’-hydroxypent-4’-ynyl)-7-(4”-trimethylsilyl-but-1”-en-3”-yn-1”-yl)-1-aza-12-oxatricyclo[5.4.1⁸.₀]undecane, 87 (S).*

and

(2S, 6R, 7S, 8S, 1’S)-(1’Z)-2-(5’-Trimethylsilyl-1’-hydroxypent-4’-ynyl)-7-(4”-trimethylsilyl-but-1”-en-3”-yn-1”-yl)-1-aza-12-oxatricyclo[5.4.1⁸.₀]undecane, 88 (S).*
added dropwise via cannula over a period of 0.25 h followed by stirring at 40 °C for 0.5 h, after which time a pale yellow solution of the Grignard reagent 92 was observed to have formed.

The precipitated salts from the Grignard reagent were allowed to settle and the clear solution (1 mL, 0.45 (1:1 hexane:ether); 0.1 (q); HRMS (ESI) 138.7, 113.4, 107.9, 101.8, 100.2, 84.3, 77.9, 74.3, 67.1, 66.2, 47.2, 34.6, 34.2, 32.2, 27.9, 25.2, 19.2, 17.9, 16.7, 0.2 (q) 842 and 759 cm⁻¹; δν(500 MHz; CDCl₃) 6.05 (1H, dd, J 10.5, 4.0 and 4.0, CHO), 3.82 (1H, br d, J 4.0, OH), 3.67 (1H, dddd, J 4.0, 4.0, 4.0 and 0.0, CHO), 2.82 (1H, ddd, J 12.5, 4.0 and 4.0, CHN), 2.41 (2H, m, CH₂), 1.82-1.46 (10H, m, 5 x CH₃), 1.38-1.30 (3H, m, CH₂ and CH), 0.21 (9H, s, Si(CH₃)₃) and 0.14 (9H, s, Si(CH₃)₃); δν(C) (63 MHz, APT; CDCl₃) 138.7, 113.4, 107.9, 101.8, 100.2, 84.3, 77.9, 74.3, 67.1, 66.2, 47.2, 34.6, 34.2, 32.2, 27.9, 25.2, 19.2, 17.9, 16.7, 0.2 (q) and -0.1 (q); HRMS (ESI) m/z calcd for C₂₅H₃₅NO₂Si₂ (M+H)+: 444.2754, found: 444.2755; MS (CI) m/z 444 [(M+H)+, 63%], 290 (100), 249 (12), 221 (20), 172 (18), 155 (11) and 90 (13). Further elution of the column yielded the diastereomeric alcohol 88 (R) (4.6 mg, 33%) also as a colourless oil; δν(1H NMR spectra). 464 [(M+H)+, 63%], 290 (52), 222 (24), 172 (80), 155 (72) and 90 (100). The assignment of the stereochemistry of the 1'-hydroxy functionality is tentative and based on observed coupling constants in the 'H NMR spectra.

Further elution of the column yielded the diastereomeric alcohol 88 (R) (4.6 mg, 33%) also as a colourless oil; Rf 0.23 (1:1 hexane:ether); [α]D²⁰ +7.5 (c 0.22 in CHCl₃); vmax (thin film) 3469, 2954, 2860, 2174, 1449, 1249, 1089, 1009, 842 and 759 cm⁻¹; δν(500 MHz; CDCl₃) 6.05 (1H, dd, J 10.5 and 10.0, CH=CH=CH), 3.95 (1H, ddd, J 9.5, 5.0 and 2.5, CH), 3.82 (1H, br d, J 4.0, OH), 3.67 (1H, dddd, J 4.0, 4.0, 4.0 and 0.0, CHO), 2.82 (1H, ddd, J 12.5, 4.0 and 4.0, CHN), 2.41 (2H, m, CH₂), 1.82-1.46 (10H, m, 5 x CH₃), 1.38-1.30 (3H, m, CH₂ and CH), 0.21 (9H, s, Si(CH₃)₃) and 0.14 (9H, s, Si(CH₃)₃); δν(C) (63 MHz, APT; CDCl₃) 138.7, 113.4, 107.9, 101.8, 100.2, 84.3, 77.9, 74.3, 67.1, 66.2, 47.2, 34.6, 34.2, 32.2, 27.9, 25.2, 19.2, 17.9, 16.7, 0.2 (q) and -0.1 (q); HRMS (ESI) m/z calcd for C₂₅H₃₅NO₂Si₂ (M+H)+: 444.2754, found: 444.2755; MS (CI) m/z 444 [(M+H)+, 63%], 290 (100), 249 (12), 221 (20), 172 (18), 155 (11) and 90 (13). The assignment of the stereochemistry of the 1'-hydroxy functionality is tentative and based on observed coupling constants in the 'H NMR spectra.

(2S, 6R, 7S, 8S, 1'S)-(1''Z)-2-[5''-Trimethylsilylpent-4''-yn-1''-(5''-methylthio carboxy)]-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo [5.4.1.0²]undecane, 89 (S).

To a solution of the alcohol 87 S (5.8 mg, 0.045 mmol) in THF (1.5 mL) cooled to 0 °C was added NaH (60% dispersion in mineral oil; 5.3 mg, 0.13 mmol, 10 eq). The reaction mixture was allowed to warm to 25 °C and stirred for 1.5 h. CS₂ (8.6 µL, 0.14 mmol, 11 eq) was added dropwise and the reaction mixture was stirred for a further 1 h. MeI (8.9 µL, 0.063 mmol, 11 eq) was added dropwise and the reaction mixture was stirred for a final 1.5 h.
The reaction was quenched by the addition of water (2 mL) and extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with water (3 x 4 mL) followed by brine (3 x 4 mL), dried (MgSO₄) and concentrated in vacuo. Purification of the crude residue by flash column chromatography (4:1 hexane:ether; 1% NEt₃) yielded the xanthate 88 S (5.8 mg, 83%) as a colourless oil; Rₜ 0.55 (4:1 hexane:ether); [α]₁⁰ D –48.3 (c 0.21 in CHCl₃); vₘₐₓ (thin film) 2954, 2868, 2176, 2150, 1448, 1249, 1217, 1193, 1063, 1011, 842 and 759 cm⁻¹; δₜ (500 MHz; CDCl₃) 6.14 (1H, ddd, J 10.0, 3.0 and 3.0, CHOSSMe), 6.06 (1H, dd, J 10.5 and 10.0, CH=CHCH=C), 5.69 (1H, d, J 10.5, CH=CHCH=C), 4.52 (1H, ddd, J 6.0, 5.5 and 0.0, CHO), 3.86 (1H, dd, J 10.0 and 6.0, CHCH=CH), 3.24 (1H, ddd, J 12.5, 3.0 and 3.0, CHN), 2.53 (3H, s, SCH₃), 2.43-2.35 (3H, m, CH₂ and CH), 2.04-1.88 (2H, m, CH₂), 1.79 (1H, dm, J 12.0, CH), 1.69 (1H, dm, J 13.5, CH), 1.62-1.25 (9H, m, 4 x CH₃ and CH₂), 0.17 (9H, s, Si(CH₃)₃) and 0.15 (9H, s, Si(CH₃)₃); δₑ (63 MHz; CDCl₃) 215.1, 139.3, 113.3, 107.0, 101.9, 100.0, 84.5, 83.3, 77.2, 66.1, 64.6, 64.5, 34.7, 32.5, 27.9, 25.3, 24.4, 19.6, 18.9, 18.1, 17.3, 0.1 and -0.2; HRMS (ES m/z calculated for C₂₅H₂₄NO₂S₂Si₂ (M+H)⁺: 534.2352, found: 534.2349; MS (CI) m/z 534 [(M+H)⁺, 100%], 428 (45), 340 (25), 308 (30), 290 (33), 272 (76) and 255 (22).

\[(2S, 6R, 7S, 8S, 1'\text{R})-1''-\text{en-3''-yn-1''-yl})-1-aza-12-oxatricyclo[5.4.1.0^{12.0}]-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1'')-7-(5''-trimethylsilylpent-4'-yn-1''-(S-methylidithio carboxy))-12-oxatricyclo[5.4.1.0^{12.0}]undecane\]

Procedure as for (2S, 6R, 7S, 8S, 1'S)-(1''Z)-2-[5''-trimethylsilylpent-4'-yn-1'-{(S-methylidithiocarboxy)]-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1'')-1-aza-12-oxatricyclo[5.4.1.0^{12.0}] undecane 89 (66%); Rₜ 0.62 (1:1 hexane:ether); [α]₁⁰ D +2.0 (c 0.14 in CHCl₃); vₘₐₓ (thin film) 2924, 2863, 2176, 2150, 1458, 1249, 1217, 1055, 842 and 759 cm⁻¹; δₜ (500 MHz; CDCl₃) 6.05 (1H, dd, J 10.5 and 10.0, CH=CHCH=C), 5.91 (1H, dm, J 7.0, CHOSSMe), 5.70 (1H, d, J 10.5, CH=CHCH=C), 4.48 (1H, ddd, J 6.5, 3.5 and 3.0, CHO), 3.75 (1H, dd, J 10.0 and 6.5, CHCH=CH), 3.12 (1H, dm, J 12.0, CHN), 2.56 (3H, s, SCH₃), 2.44-2.22 (3H, m, CH₂ and CH), 1.97 (2H, m, CH₂), 1.82 (2H, tm, J 17.0, CH₂), 1.68-0.81 (9H, m, 4 x CH₂ and CH), 0.21 (9H, s, Si(CH₃)₃) and 0.14 (9H, s, Si(CH₃)₃); δₑ (100 MHz; CDCl₃) 215.8, 139.3, 113.0, 106.6, 101.9, 100.0, 85.0, 84.9, 66.0, 65.8, 53.4, 46.8, 34.9, 32.3, 29.7, 26.5, 25.3, 19.5, 18.8, 18.1, 16.8, 0.1 and -0.1; HRMS (ES m/z calculated for C₂₅H₂₄NO₂S₂Si₂ (M+H)⁺: 534.2352, found: 534.2349; MS (CI) m/z 534 [(M+H)⁺, 100%] and 428 (60).
and

$$\textit{N}-\textit{ethyl-1,2,3,5,8-pentamethyldihydro-2H-benzo[d][1,3,2]dioxaborine}$$

The xanthate \textit{88} (S) (3.2 mg, 5.9 \(\mu\)mol) was dissolved in dry toluene (1 mL) under nitrogen and AIBN (0.5 mg, cat) was added, followed by \textit{Bu}_3\text{SnH} (8.1 \(\mu\)L, 0.03 mmol, 5 eq) and the mixture was then stirred at 110 °C for 10 minutes.

The mixture was concentrated \textit{in vacuo} and the crude residue was purified by flash column chromatography (9:1 hexane:ether; 1% \textit{NEt}_3) to yield the (\textit{Z})-isomer of \textit{zoaxazolidine} \textit{89} (1.5 mg, 57%) as a colourless oil; \(R_f\) 0.20 (4:1 hexane:ether); \(\alpha_b^3\) -15.3 (c 0.15 in CHCl_3); \(\nu_{max}\) (thin film) 2929, 2853, 2174, 2150, 1458, 1249, 1081, 1012, 842 and 782 cm\(^{-1}\); \(\delta_b\) (400 MHz; CDCl_3) 6.07 (1H, dd, \(J\) 10.5 and 10.0, \(CH=CH\equiv C\)), 5.71 (1H, d, \(J\) 10.5, \(CH=CH\equiv C\)), 4.49 (1H, ddd, \(J\) 6.5, 5.5 and 0.0, \(CHO\)), 3.89 (1H, dd, \(J\) 10.0 and 6.5, \(CHCH=CH\)), 2.71 (1H, m, \(CH\)), 2.25 (2H, dt, \(J\) 7.0 and 7.0, \(CH_2\)), 2.02-1.91 (2H, m, \(CH_2\)), 1.76 (2H, tt, \(J\) 13.0 and 3.0, \(CH_2\)), 1.70-1.26 (10H, m, 5 \(x\) \(CH_2\)), 1.15 (1H, ddt, \(J\) 12.5, 12.5 and 2.5, \(CH\)), 0.92 (1H, m, \(CH\)), 0.21 (9H, s, Si(CH_3)_3) and 0.14 (9H, s, Si(CH_3)_3); \(\delta_c\) (125 MHz; CDCI_3) 85.5, 113.0, 107.7, 101.9, 99.8, 84.2, 65.9, 64.4, 46.3, 34.6, 34.1, 32.4, 29.9, 29.6, 25.5, 25.2, 20.2, 19.9, 17.9, 0.1 and -0.2; HRMS (ESI) \(m/z\) calcd for C_{25}H_{14}NO_2Si: (M+H)^+: 428.2805, found: 428.2807; MS (CI) \(m/z\) 428 [(M+H)^+], 63%; 222 (23), 98 (40), 90 (100) and 72 (35).

Further elution of the column furnished the (\textit{E})-isomer of \textit{zoaxazolidine} (0.9 mg, 37%) also as a colourless oil; \(R_f\) 0.27 (4:1 hexane:ether); \(\alpha_b^3\) -127.9 (c 0.28 in CHCl_3); \(\nu_{max}\) (thin film) 2933, 2865, 2173, 1458, 1249, 1056, 957, 842 and 759 cm\(^{-1}\); \(\delta_b\) (400 MHz; CDCl_3) 6.29 (1H, dd, \(J\) 15.5 and 9.5, \(CH=CH\equiv C\)), 5.65 (1H, d, \(J\) 15.5, \(CH=CH\equiv C\)), 4.40 (1H, m, \(CHO\)), 3.15 (1H, dd, \(J\) 9.5 and 6.5, \(CHCH=CH\)), 2.63 (1H, dddd, \(J\) 11.5, 8.0, 3.5 and 3.5, \(CHN\)), 2.23 (2H, dt, \(J\) 7.0 and 4.0, \(CH_2\)), 2.01-1.88 (2H, m, \(CH_2\)), 1.83-1.72 (2H, m, \(CH_2\)), 1.69-0.88 (11H, m, 5 \(x\) \(CH_2\) and \(CH\)), 1.13 (1H, ddt, \(J\) 12.5, 12.5 and 2.5, \(CH\)), 0.20 (9H, s, Si(CH_3)_3) and 0.14 (9H, s, Si(CH_3)_3); \(\delta_c\) (63 MHz; CDCl_3) 140.2, 113.7, 107.8, 103.3, 84.2, 78.1, 65.4, 64.2, 49.4, 34.6, 34.2, 32.2, 29.8, 25.4, 25.3, 20.3, 19.2, 18.0, 13.7, 0.2 and -0.1; HRMS (ESI) \(m/z\) calcd for C_{25}H_{16}NO_2Si: (M+H)^+: 428.2805, found: 428.2796; MS (CI) \(m/z\) 428 [(M+H)^+], 43% and 90 (100).

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16,20-Bis(trimethylsilyl)histrionicotoxin 285C.

The \textit{zoaxazolidine} \textit{89} (5.6 mg, 0.013 mmol) was dissolved in acetic acid (3 mL) and activated zinc dust (9 mg) was added in one portion with rapid stirring. After 0.5H, the reaction was quenched by the addition of an aqueous solution of sodium acetate (satd; 3 mL) and EtOAc (3 mL) and it was then stirred for a further 0.5 h. The aqueous layer was
extracted into EtOAc (3 x 6 mL) and the organic phases were washed with water (3 x 3 mL) then brine (3 x 3 mL). The combined organic phases were dried (MgSO₄), concentrated in vacuo and azeotroped in toluene. Purification of the crude residue via flash column chromatography (93:7 CH₂Cl₂:MeOH) furnished 16,20-bis-(trimethylsilyl)histrionicotoxin 285C (5.5 mg, 97%) as a colourless oil; Rf 0.09 (9:1 CH₂Cl₂:MeOH); [α]D²⁵ ⁰ -8.5 (c 0.14 in CHCl₃); νmax (thin film) 3062, 2954, 2648, 2173, 2150, 1525, 1250, 757 cm⁻¹; δH (500 MHz; CDCl₃) 5.74 (1H, dd, J 10.5 and 10.0, CH=CHC≡C), 5.68 (1H, d, J 10.5, CH=CHC≡C), 4.09 (1H, br m, CHOH), 3.79 (1H, br d, J 10.0, CHCH≡CH), 3.28 (1H, br m, CHNH), 2.35-2.22 (1H, m, CH₂), 2.28 (2H, dt, J 7.5 and 7.5, CH₂), 2.11 (1H, m, CH₂), 2.02-1.40 (14H, m, 7 x CH₂), 0.23 (9H, s, Si(CH₃)₃) and 0.14 (9H, s, Si(CH₃)₃); δC (63 MHz; CDCl₃) 138.2, 113.9, 106.3, 101.6, 100.9, 85.3, 71.0, 59.2, 52.2, 40.6, 34.6, 33.2, 33.0, 28.6, 27.8, 24.5, 19.4, 18.5, 14.9, 0.2 and -0.1; HRMS (ES) ≈ (M+H)+: 430.2961, found: 430.2955; MS (CI) +: 286.2171, found: 286.2180; MS (CI) -: 49.2, 52.2, 40.6, 34.6, 33.2, 33.0, 28.6, 27.8, 24.5, 19.4, 18.5, 14.9, 0.2 and -0.1; 96 (18) and 52 (67).

16,20-Bis(trimethylsilyl)histrionicotoxin 285C (5.0 mg, 0.012 mmol) was dissolved in dry methanol (5 mL) and potassium carbonate (32 mg, 0.23 mmol, 20 eq) was added in one portion. After vigorous stirring at 25 °C for 17H, the solvent was removed in vacuo to virtual dryness and the residue was taken up in EtOAc (2 mL) and water (2 mL) was added. The aqueous layer was separated and extracted further with EtOAc (2 x 2 mL) and the organic phases washed with brine (2 x 2 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. Purification of the crude residue via flash column chromatography (1:9 MeOH:CH₂Cl₂) yielded (−)-HTX-285C 3 as a colourless oil (2.9 mg, 88%); Rf 0.18 (9:1 CH₂Cl₂:MeOH); [α]D⁻¹⁸ -43.3 (c 0.12 in CHCl₃); νmax (thin film) 3301, 3218, 2935, 2125, 2092, 1665, 1553, 1452, 1261, 1097 and 961 cm⁻¹; δH (500 MHz; CDCl₃) 5.84 (1H, dd, J 10.5 and 10.0, H-17), 5.61 (1H, d, J 10.5, H-18), 3.96 (1H, br s, CHOH), 3.71 (1H, d, J 10.0, CHCH≡CH), 3.21 (1H, s, H-20), 3.17 (1H, br m, CHNH), 2.24 (2H, br m, CH₂), 2.08 (1H, br m, CH), 1.96 (1H, s, H-16) and 1.82-1.13 (15H, m, 7 x CH₂ and CH); HRMS (ES) m/z calcd for C₁₉H₂₃NO (M+H)+: 286.2171, found: 286.2180; MS (EI) m/z 286 [(M+H)+, 100%] and 52 (67).

(−)-Histrionicotoxin 285C, 3.

(−)-Histrionicotoxin 285C 3 (2.5 mg, 0.009 mmol) was dissolved in dry methanol (1 mL) and methanolic HCl (0.3 M; 44 µL, ≈1.5 eq) was added. After stirring for 0.5H, the solvent was removed in vacuo furnishing (−)-HTX-285C hydrochloride as a colourless oil which slowly crystallised on standing at -20 °C (2.5 mg, 88%); mp 244.5-246.5 °C (lit.¹⁷ 247-250 °C); Rf 0.15 (9:1 CH₂Cl₂:MeOH); [α]D⁻¹⁸ -44.6 (c 0.12 in EtOH) [lit.¹⁷ [α]D⁻¹⁸ -43.4 (c 1.18 in EtOH)]; δH (500 MHz; MeOD) 6.00 (1H, dd, J 10.5 and 10.0, H-17), 5.78 (1H, dd, J 10.5 and 2.0, H-18), 4.01 (1H, s, CHOH), 3.79 (1H, m, H-7), 3.79 (1H, d, J 2.0, H-20), 3.63 (2H, m, NH₂), 3.54-3.45 (1H, m, CHNH), 2.30-2.27 (3H, m, CH₂ and H-
1.05-1.94 (3H, m, CH₂ and CH₃), 1.81-1.62 (9H, m, 4 x CH₂ and CH₃) and 1.35-1.26 (4H, m, 2 x CH₂); δ_C (100 MHz; MeOD) 137.9, 112.7, 84.5, 82.5, 78.6, 72.2, 69.1, 60.8, 60.0, 52.3, 40.8, 33.8, 32.8, 32.3, 28.1, 26.9, 23.8, 17.4 and 14.0; HRMS (ES) m/z calcd for C₁₉H₂₈NO (M-Cl): 286.2171, found: 286.2169; MS (Cl) m/z 286 [(M-Cl)⁺, 100%], and 268 (33).¹²


*These experimental procedures were previously published in the Electronic Supplementary Information for the following paper: C. J. Smith, A. B. Holmes and N. J. Press, Chem. Commun., 2002, 1214-1215.
NMR DATA
(1R,5S,8S,12R)-8-(Benzylxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1.5.0]undecane 13

$^1H$ NMR (250 MHz; CDCl$_3$)

$^{13}$C NMR (62.5 MHz; CDCl$_3$)
COSY (500 MHz; CDCl₃)

HMOC (500 MHz; CDCl₃)
(1R,5S,8S,12S)-8-(Benzyloxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1.1\(^1\).5\(^0\)]undecane 54

\(^1\)H NMR & NOEs (500 MHz; CDCl\(_3\))

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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**COSY (500 MHz; CDCl₃)**

![COSY spectrum image]

**HMQC (500 MHz; CDCl₃)**

![HMQC spectrum image]
(1S,5S,9S)-9-Benzylxymethyl-8-aza-7-oxatricyclo[6.4.1.0^1,5]undecane 49

$^1H$ NMR (500 MHz; CDCl$_3$)

$^{13}C$ NMR (62.5 MHz; CDCl$_3$)
(1R,5S,8S,12S)-8-(Benzyloxymethyl)-12-(trimethylsilylthynyl)-7-aza-6-oxatricyclo[5.4.1.1^5.0]undecane

$^1H$ NMR (500 MHz; CDCl$_3$)

COSY (600 MHz; CDCl$_3$)
**TOCSY (600 MHz; CDCl₃)**

![TOCSY NMR Spectrum](image)

**HMQC (600 MHz; CDCl₃)**

![HMQC NMR Spectrum](image)
(15S,5S,6R,9S)-9-(Benzyloxymethyl)-6-(trimethylsilylethynyl)-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]undecane

$^1$H NMR & NOEs (750 MHz; CDCl$_3$)

$^{13}$C NMR (100 MHz; CDCl$_3$)
**COSY (750 MHz; CDCl₃)**

**TOCSY (750 MHz; CDCl₃)**
$(1R,5S,8S,12S)-8$-(Benzyloxymethyl)-$12$-methoxycarbonyl-$7$-aza-6-oxatricyclo[5.4.1.0$^{1,5}$]undecane 50

$^1$H NMR (500 MHz; CDCl$_3$)

$^1$C NMR (100 MHz; CDCl$_3$)
COSY (500 MHz; CDCl₃)
(1S,5S,6R,9S)-9-(Benzyloxymethyl)-6-methoxycarbonyl-8-aza-7-oxatricyclo[6.4.0.0²1,5]undecane 51

$^1H$ NMR (500 MHz; CDCl₃)

$^{13}C$ NMR (100 MHz; CDCl₃)
HMOC (500 MHz; CDCl₃)
HTX-259A Hydrochloride

$^1$H NMR (500MHz, MeOD)

$^{13}$C NMR (100 MHz, MeOD)
HTX-285C Hydrochloride

$^1$H NMR (500MHz, MeOD)

$^{13}$C NMR (100 MHz, MeOD)
**HTX-285E Hydrochloride**

**$^1$H NMR (500MHz, MeOD)**

**$^{13}$C NMR (100 MHz, MeOD)**
CRYSTALLOGRAPHIC STRUCTURES

Crystal Data for 37. C_{33}H_{44}ClNO_{2}Si, M = 550.23, triclinic, a = 11.7549(6), b = 13.7175(9), c = 20.1662(13) Å, \( \alpha = 84.294(3) \), \( \beta = 75.250(4) \), \( \gamma = 89.894(4) \)°, \( U = 3128.1(3) \) Å\(^3\), \( T = 180(2) \) K, space group \( P-1 \), \( Z = 4 \), \( \mu(\text{Mo K\( \alpha \)}) = 0.189 \) mm\(^{-1}\), 26 871 reflections collected, 10 742 unique (\( R_{\text{int}} = 0.0510 \), \( R1 = 0.0729 \), \( wR2[I > 2\sigma(I)] = 0.1828 \), CCDC deposition number 620201.

Crystal Data for 75. C_{24}H_{41}NO_{2}Si, M = 403.67, monoclinic, a = 7.7031(3), b = 9.8991(6), c = 15.8805(8) Å, \( \beta = 98.831(3) \)°, \( U = 1196.59(11) \) Å\(^3\), \( T = 180(2) \) K, space group \( P2_1 \), \( Z = 2 \), \( \mu(\text{Mo K\( \alpha \)}) = 0.890 \) mm\(^{-1}\), 7454 reflections collected, 4564 unique (\( R_{\text{int}} = 0.0432 \), \( R1 = 0.0439 \), \( wR2[I > 2\sigma(I)] = 0.1107 \), CCDC deposition number 865489.

Crystal Data for 29. C_{11}H_{16}N_{2}O, M = 192.26, orthorhombic, a = 9.6609(9), b = 11.5354(11), c = 9.1360(5) Å, \( U = 1018.14(15) \) Å\(^3\), \( T = 180(2) \) K, space group \( Pcc2_1 \), \( Z = 4 \), \( \mu(\text{Mo K\( \alpha \)}) = 0.082 \) mm\(^{-1}\), 5693 reflections collected, 1705 unique (\( R_{\text{int}} = 0.0974 \), \( R1 = 0.0401 \), \( wR2[I > 2\sigma(I)] = 0.0878 \), CCDC deposition number 881632.

Crystal Data for 48. C_{19}H_{24}N_{2}O_{2}, M = 312.40, monoclinic, a = 8.4675(15), b = 11.662(2), c = 8.6820(16) Å, \( U = 834.4(3) \) Å\(^3\), \( T = 150(2) \) K, space group \( P2_1 \), \( Z = 2 \), \( \lambda = 0.6885 \) Å (SRS Daresbury), \( \mu = 0.081 \) mm\(^{-1}\), 7499 reflections collected, 3867 unique (\( R_{\text{int}} = 0.0575 \), \( R1[I > 2\sigma(I)] = 0.0643 \), \( wR2(\text{all data}) = 0.1555 \), CCDC deposition number 885212.
Molecular structure of 29 with displacement ellipsoids at the 50% probability level for non-H atoms.

Asymmetric unit for 37 with displacement ellipsoids at the 50% probability level for non-H atoms. Atom labels are shown only for one independent molecule. The other molecule is labelled in an analogous way.
Molecular structure of \textbf{48} with displacement ellipsoids at the 50% probability level for non-H atoms.

Molecular structure of \textbf{75} with displacement ellipsoids at the 50% probability level for non-H atoms.
REFERENCES