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 (δ_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 appoximately 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 (δ_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. Electrospray 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.

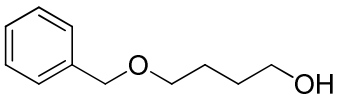
Kugelrohr bulb-to-bulb distillations: These were carried out using a Büchi GKR-51 machine. Boiling points are the actual oven temperatures.

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.

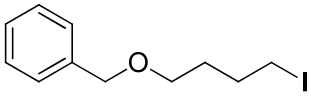
EXPERIMENTAL

Investigations into the regiochemical outcome of the intramolecular nitrone dipolar cycloaddition reaction. Model studies: formation of the nitrone by direct hydroxylamine-alkyne cyclisation



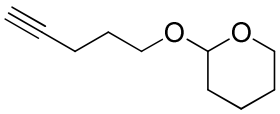
4-Benzyloxybutan-1-ol, 14.[3]

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-diol (16.0 g, 180 mmol, 1.5 eq) was added dropwise over 40 min and the reaction mixture warmed to 25 ºC 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 ºC, 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 ($MgSO_4$) 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; R_f 0.38 (1:1 hexane:EtOAc); δ_H (250 MHz; $CDCl_3$) 7.35-7.22 (5H, m, aromatics), 4.52 (2H, s, PhCH_2O), 3.66 (2H, q, *J* 5.1, CH_2OH), 3.55 (2H, t, *J* 7.1, BnOCH_2), 2.18-2.10 (1H, t, *J* 5.1, OH) and 1.87-1.60 (4H, m, 2 x CH_2); data identical to literature values.[3]



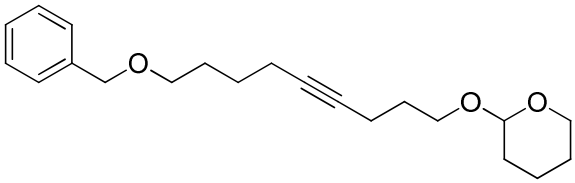
4-Benzyloxy-1-iodobutane, 15.[4]

4-Benzyloxybutan-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 ºC 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 ($MgSO_4$) 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 ($MgSO_4$) 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; R_f 0.46 (9:1 hexane:EtOAc); δ_H (250 MHz; $CDCl_3$) 7.35-7.23 (5H, m, aromatics), 4.50 (2H, s, PhCH_2O), 3.52 (2H, t, *J* 10.1, BnOCH_2), 3.32 (2H, t, *J* 10.2, CH_2I), 2.00-1.90 (2H, m, CH_2) and 1.80-1.78 (2H, m, CH_2); data identical to literature values.[5]



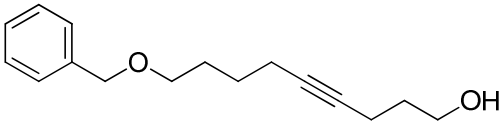
2-(Pent-4-yn-1-yloxy)tetrahydropyran, 17.

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 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; R_f 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); ν_{max} (film) 3297, 2942, 2871, 2119, 1441, 1137 and 1121 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 4.59 (1H, td, *J* 3.6 and 1.2, C*H*O_2), 3.90 - 3.70 (2H, m, CH_2OTHP), 3.50 - 3.40 (2H, m, CH_2O), 2.32 (2H, tdd, *J* 7.3, 2.7 and 0.5, CH_2C≡C), 1.94 (1H, t, *J* 2.7, C≡C*H*) and 1.90 - 1.50 (8H, m, 4 x -CH_2-).



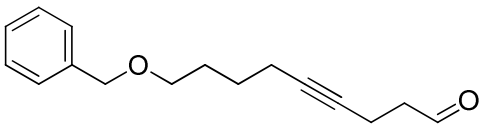
2-(9-Benzyloxynon-4-yn-1-yloxy)tetrahydropyran, 18.

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 ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was 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; R_f 0.45 (hexane/EtOAc, 9:1) and 0.09 (hexane/EtOAc, 19:1); FTIR ν_{max} (KBr) 2944, 2865, 1495, 1451, 1358, 1200, 1119, 1080, 1026 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.39-7.21 (5H, m, aromatics), 4.59 (1H, t, *J* 3.5, C*H*O_2), 4.50 (2H, s, PhCH_2O), 3.93 - 3.75 (2H, m, CH_2O), 3.55-3.41 (2H, m, CH_2OTHP), 3.49 (2H, t, *J* 6.5, CH_2OBn), 2.26 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C,), 2.17 (2H, tt, *J* 7.0 and 2.5, C≡CCH_2), 1.83-1.45 (12H, m, 6 x CH_2); δ_C ($CDCl_3$, 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 $C_{21}H_{29}O_3$ $(M-H)^-$: 329.2117, found 329.2139; MS (CI, NH_3) *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).



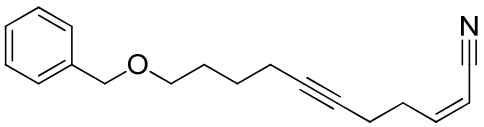
9-Benzyloxynon-4-yn-1-ol, 19.

2-(9-Benzyloxynon-4-ynyl-1-oxy)tetrahydropyran **18** (2.75 g, 8.32 mmol) was dissolved in methanol (50 mL). Amberlyst® 15 acidic 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; $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%); FTIR ν_{max} (KBr) 3388, 3030, 2941, 2864, 1496, 1454, 1362, 1105, 1075, 773 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.36-7.24 (5H, m, aromatics), 4.49 (2H, s, PhCH_2O), 3.72 (2H, t, *J* 6.0, CH_2OH), 3.47 (2H, t, *J* 6.5, CH_2OBn), 2.25 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.16 (2H, tt, *J* 7.0 and 2.5, C≡CCH_2), 1.83-1.65 (5H, m, 2 x CH_2, O*H*), 1.62 - 1.51 (2H, m, CH_2); δ_C ($CDCl_3$, 100 MHz) 138.6, 128.4, 127.7, 127, 80.7, 79.7, 72.9, 69.9, 62.0, 31.6, 28.9, 25.8, 18.6, 15.4; HRMS (CI) *m/z* calcd for $C_{16}H_{23}O_2$ $(M+H)^+$: 247.1698, found: 247.1720; MS (CI, NH_3) 247 [$(M+H)^+$, 55%], 232 (11), 187 (7), 155 (16), 137 (12), 105 (12), 91 (100), 71 (20), 58 (43), 43 (33).



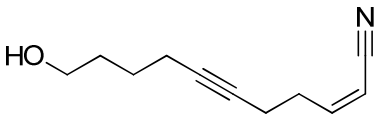
9-Benzyloxynon-4-ynal, 20.

A solution of oxalyl chloride (0.48 mL, 704 mg, 5.55 mmol) in dry dichloromethane (50 mL) was cooled to –78 °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 °C, and the resulting white precipitate stirred for 30 min. A solution of 9-benzyloxynon-4-yn-1-ol **19** (621 mg, 2.52 mmol) in dry dichloromethane (5 mL) was added slowly dropwise and the mixture stirred for 1 h at –78 °C. 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 ν_{max} (KBr) 3030, 2940.5, 2912, 2862, 2727, 1728, 1496, 1454, 1360, 1206, 1106, 877 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 9.77 (1H, t, *J* 1.5, C*H*O), 7.36-7.24 (5H, m, aromatics), 4.49 (2H, s, PhCH_2O), 3.47 (2H, t, *J* 6.5, CH_2OBn), 2.60 (2H, t, *J* 7.0, CH_2CHO), 2.46 (2H, ttd, *J* 7.0, 2.5 and 0.5, C≡CCH_2CH$_2$CHO), 2.15 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C), 1.73-1.61 (2H, m, CH_2), 1.59-1.50 (2H, m, CH_2); δ_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 (CI, NH_3) *m/z*: 261 [$(M+OH)^+$, 47%], 245 [$(M+H)^+$, 12], 243 (14), 225 (10), 201 (16), 187 (26), 169 (15), 151 (21), 139 (13), 123 (17), 108 (22), 91 (100).



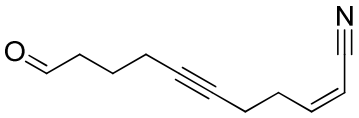
(*Z*)-11-Benzyloxyundec-2-en-6-ynenitrile, 21.

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 water (50 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) 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; R_f 0.47 (hexane/EtOAc, 7:3), 0.31 (hexane/EtOAc, 4:1) and 0.21 (hexane/EtOAc, 9:1); FTIR ν_{max} (KBr) 3031, 2916, 2850, 2221, 1496, 1454, 1435, 1365, 1332, 1105, 1028, 773, 698 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.36-7.25 (5H, m, aromatics), 6.56 (1H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 5.36 (1H, dt, *J* 11.0 and 1.5, CH=C*H*CN), 4.49 (2H, s, PhCH_2O), 3.48 (2H, t, *J* 6.5, CH_2OBn), 2.58 (2H, qd, *J* 7.5 and 1.5, CH_2CH=CHCN), 2.32 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.17 (2H, tt, *J* 7.0 and 2.5, C≡CCH_2), 1.74-1.64 (2H, m, CH_2), 1.61-1.52 (2H, m, CH_2); δ_C ($CDCl_3$, 100 MHz) 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 $C_{18}H_{22}NO$ $(M+H)^+$: 268.1701, found 268.1709; MS (CI, NH_3) 267 [$(M+H)^+$, 100%], 208 (10), 154 (45), 106 (59).



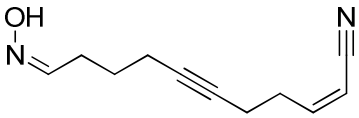
(*Z*)-11-Hydroxyundec-2-en-6-ynenitrile, 22.

(*Z*)-11-Benzyloxyundec-2-en-6-ynenitrile **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 ($MgSO_4$) 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; R_f 0.23 (hexane/EtOAc, 1:1); FTIR ν_{max} (KBr) 3401, 3067, 2939, 2866, 2222, 1435, 1332, 1059, 1031, 773.5 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 6.55 (1H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 5.38 (1H, dt, *J* 11.0 and 1.5, CH=C*H*CN), 3.64 (2H, td, *J* 6.5 and 2.0, CH_2OH), 2.55 (2H, q, *J* 7.5, CH_2CH=CHCN), 2.32 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.17 (2H, tt, *J* 7.0 and 2.5, C≡CCH_2), 1.69-1.58 (3H, m, CH_2, CH$_2$O*H*), 1.58-1.49 (2H, m, CH_2); δ_C ($CDCl_3$, 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 (CI) *m/z* calcd for $C_{11}H_{16}NO$ $(M+H)^+$: 178.1232, found: 178.1231; MS (CI, NH_3) *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 (SiO_2, Merck 9385) and the solvent removed *in vacuo* to yield the *aldehyde* **23** (111 mg, 94%) as a pale yellow oil; R_f 0.58 (hexane/EtOAc, 1:1); FTIR ν_{max} (KBr) 2929, 2849, 2727, 2221, 1723, 1436, 1391, 1333, 1261, 1087, 1021, 773 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 9.79 (1H, t, *J* 1.5, C*H*O), 6.55 (1H, dt, *J* 11.0 and 7.5, C*H*C=CHCN), 5.39 (1H, dt, *J* 11.0 and 1.5, CH=C*H*CN), 2.63-2.53 (4H, m, CH_2CH=CHCN, CH_2CHO), 2.33 (2H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.22 (2H, tt, *J* 7.0 and 2.5, C≡CCH_2), 1.81 (2H, qn, *J* 7.0, CH_2); δ_C ($CDCl_3$, 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* calcd for $C_{11}H_{12}NO$ $(M-H)^-$: 174.0919, found: 174.0923; MS (CI, NH_3) *m/z*: 193 (30%), 176 (19), 174 (50), 146 (13), 132 (30), 116 (55), 84 (27), 49 (100).



(*Z*)-10-Cyanodec-9-en-5-ynal oxime, 24.

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 (Na_2SO_4) and filtered through silica (SiO_2, 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; R_f 0.38 and 0.44 (hexane/EtOAc, 1:1); FTIR ν_{max} (KBr) 3415, 3263, 2925, 2857, 2222, 1733, 1605, 1435, 1333, 881, 467 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 8.05 (0.5H, br s, O*H*), 7.77 (0.5H, br s, O*H*), 7.43 (0.5H, t, *J* 6.0, C*H*=NOH), 6.73 (0.5H, t, *J* 5.5, C*H*=NOH), 6.57 (0.5H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 6.56 (0.5H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 5.39 (1H, dt, *J* 11.0 and 1.5, CH=C*H*CN), 2.59 (2H, q, *J* 7.0, CH_2CH=CHCN,), 2.47 (1H, td, *J* 7.5 and 5.5, CH_2CH=NOH), 2.44-2.27 (3H, m, CH_2CH=NOH, CH_2C≡C), 2.25-1.18 (2H, m, C≡CCH_2), 1.68 (approx. 1H, qn, *J* 7.0, CH_2), 1.68 (approx. 1H, qn, *J* 7.5, CH_2); δ_C ($CDCl_3$, 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* calcd for $C_{11}H_{15}N_2O$ $(M+H)^+$: 191.1184, found: 191.1173; MS (CI, NH_3) *m/z*: 191 (8%), 83 (60), 64 (10), 49 (100).

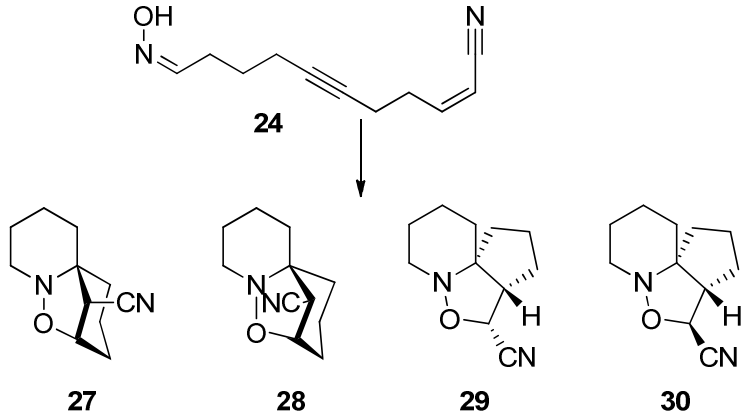
(1*R,5*R**,6*R**)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]dodecane, 29,**

(1*R,5*R**,6*S**)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]dodecane, 30,**

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

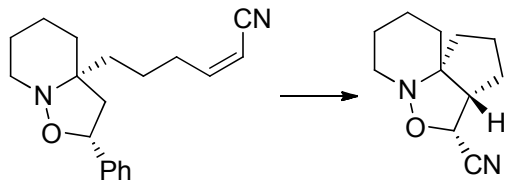
and (1*R,8*S**,12*R**)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0^{1,6}]dodecane, 28.**

Method 1:



To a solution of (*Z*)-10-cyanoundec-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); δ_H ($CDCl_3$, 500 MHz) 4.24 (1H, d, *J* 5.3, C*H*(O)CN), 3.20-2.80 (2H, m, CH_2N), 2.60-2.40 (1H, m, C*H*CH(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); δ_H (500 MHz, $CDCl_3$) 4.83 (1H, d, *J* 4.7, **28**-CHO), 2.84 (1H, s, **28**-CHCN).

Method 2:

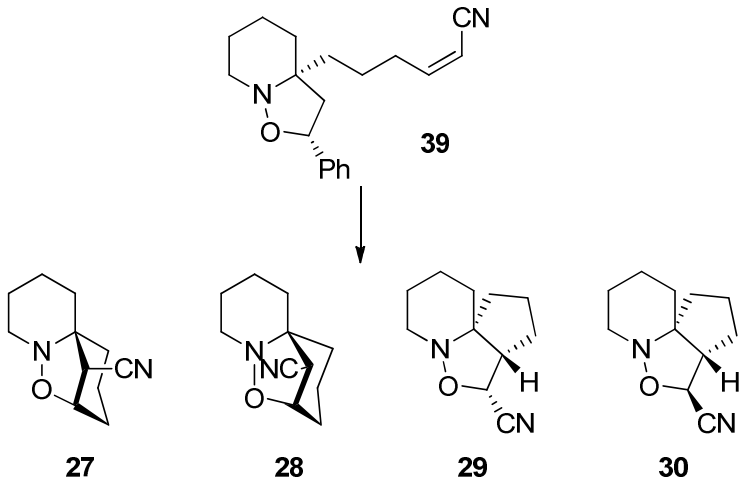


The *α,β-unsaturated nitrile* **39** (20 mg, 0.07 mmol) was dissolved in ether and added to a high pressure reaction tube. The ether was removed under a flow of nitrogen and the flask evacuated and refilled three times. Toluene (8 mL) was added and the solution was freeze-thaw degassed (3 times). The suba seal was then exchanged quickly for the screw cap and the tube heated at 100 ºC for 2 h and then heated at 160 ºC 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_2Cl_2:pentane; mp 70-72 ºC (from CH_2Cl_2:pentane); R_f 0.24

(4:1 hexane:EtOAc); ν_{max} (film) 2932, 2855, 2162 and 1446 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 4.92 (1H, d, *J* 9.0, C*H*(O)CN), 3.37 (1H, dt, *J* 14.6 and 4.1, C*H*HN), 3.09 (1H, ddd, *J* 4.1, 11.7 and 14.6, C*H*HN), 2.75 (1H, dt, *J* 9.0 and 3.3, C*H*CH(O)CN), 2.09-2.01 (2H, m, CH_2), 1.96-1.91 (1H, m, C*H*), 1.87-1.78 (3H, m, C*H* and CH_2), 1.70-1.60 (2H, m, CH_2) and 1.53-1.30 (4H, m, 2 x CH_2); δ_C (125 MHz; $CDCl_3$) 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 $C_{11}H_{17}N_2O$ $(M+H)^+$: 193.1341, found: 193.1346; MS (ES) *m/z* 193 [$(M+H)^+$, 100%], 177 (40) and 90 (35); followed by the starting material **39** (16 mg, 77%) as a colourless oil.

Method 3:



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 ºC 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-adducts* **29** and **30** (2.6 mg, 8%; 6:1 **29**:**30**) as an inseparable mixture with key diagnostic data as follows: R_f 0.24 (4:1 hexane:EtOAc); δ_H (250 MHz; $CDCl_3$) 4.92 (0.85H, d, *J* 9.0, C*H*(O)CN), 4.24 (0.15H, d, *J* 5.3, C*H*(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_f 0.13 (4:1 hexane:EtOAc); ν_{max} (film) 2940, 2864, 2238 and 1448 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 4.74 (1H, ddd, *J* 2.6, 3.1 and 6.2 C*H*O), 3.46 (1H, dd, *J* 2.3 and 6.0, C*H*CN), 3.40 (1H, ddt, *J* 1.8, 11.0 and 3.4, C*H*HN-equatorial), 2.50 (1H, ddd, *J* 3.2, 11.0 and 13.6, CH*H*N-axial), 2.16 (1H, ddt, *J* 6.4, 14.4 and 3.2, CH*H*), 2.01-1.94 (1H, m, CH*H*), 1.85 (1H, dt, *J* 6.0 and 13.5, CH*H*), 1.78-1.75 (2H, m, CH_2), 1.72-1.53 (5H, 2 x CH_2 and C*H*) and 1.31-1.24 (2H, m, CH_2); δ_C (125 MHz; $CDCl_3$) 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* $C_{11}H_{17}N_2O$ calcd for $(M+H)^+$: 193.1341, found: 193.1332; MS (ES) *m/z* 193 [$(M+H)^+$, 100%], 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_H (250 MHz; $CDCl_3$) 4.83 (1H, d, *J* 4.7, C*H*O) and 2.84 (1H, s, C*H*CN); and starting material **39** (2.4 mg, 6%); data consistent with those reported previously.[7]

Microwave reactions

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

Method A:

The *α,β-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 ^{o}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 *α,β-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 ^{o}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.

(1*R,5*R**,6*R**)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]dodecane, 29,**

(1*R,5*R**,6*S**)-6-Cyano-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]dodecane, 30,**

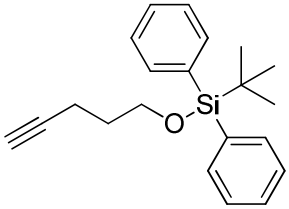
(1*R,8*S**,12*S**)-12-Cyano-7-aza-6-oxatricyclo[6.3.1.0^{1,6}]dodecane, 27**

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

The *α,β*-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 ^{o}C for 15 min. The solvent was then removed *in vacuo*.

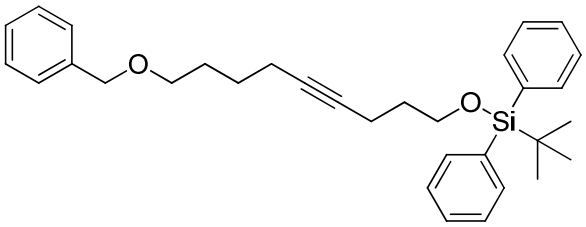
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding a 4:1:12:2 mixture of the adducts **29**, **30**, **27** and **28** and the starting material **39** (2 mg overall) as a colourless oil; data identical to those reported previously.

Investigations into the regiochemical outcome of the intramolecular nitrone dipolar cycloaddition reaction.
Model studies: formation of the nitrone by dipolar cycloreversion



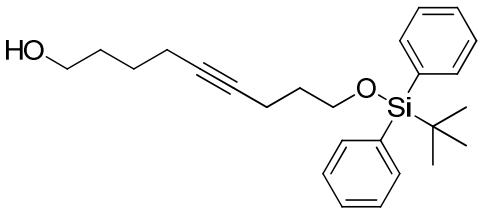
1-(*tert*-Butyldiphenylsilanyloxy)-pent-4-yne, 31. †

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 ($MgSO_4$) 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; R_f 0.61 (9:1 hexane:EtOAc); δ_H (250 MHz; $CDCl_3$) 7.69-7.66 (4H, m, aromatics), 7.44-7.36 (6H, m, aromatics), 3.76 (2H, t, *J* 7.5, C*H*$_2$OSi), 2.36 (2H, dt, *J* 1.0 and 7.5, C*H*$_2$C≡C), 1.92 (1H, d, *J* 1.0, C≡C*H*), 1.79 (2H, qn, *J* 7.5, C*H*$_2$) and 1.06 (9H, s, C(C*H*$_3$)$_3$); data identical to literature values.[8]



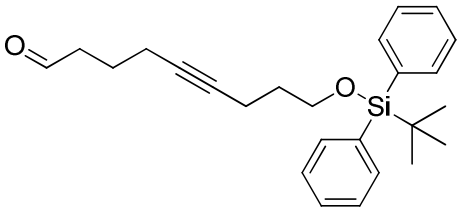
1-(*tert*-Butyldiphenylsilanyloxy)-9-benzyloxynon-4-yne, 32

1-(*tert*-Butyldiphenylsilanyloxy)pent-4-yne **31** (12.4 g, 39 mmol, 1.1 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, 1.1 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 NH_4Cl (90 mL) was added and the organics separated. The aqueous was further extracted with ether (2 x 45 mL) and the combined organics dried ($MgSO_4$) and concentrated *in vacuo* yielding a yellow oil. The compound was purified by flash column chromatography (3:1 → 2:1 hexane: CH_2Cl_2) to yield the *nonyne* **32** (15.0 g, 88%) as a colourless oil; R_f 0.12 (4:1 hexane: CH_2Cl_2); (Found: C, 79.5; H, 8.3%. $C_{32}H_{40}O_2Si$ requires C, 79.3; H, 8.3%); ν_{max} (film) 3068, 2930, 1958, 1888, 1821, 1588, 1494, and 1427 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.76-7.72 (4H, m, aromatics), 7.47-7.38 (11H, m, aromatics), 4.55 (2H, s, PhC*H*$_2$O), 3.81 (2H, t, *J* 5.8, C*H*$_2$OSi), 3.53 (2H, t, *J* 8.3, BnOC*H*$_2$), 2.36-2.35 (2H, m, C*H*$_2$C≡C), 2.22-2.20 (2H, m, C≡CC*H*$_2$), 1.82-1.62 (6H, m, 3 x C*H*$_2$) and 1.12 (9H, s, C(C*H*$_3$)$_3$); δ_C (62.5 MHz; $CDCl_3$) 138.7, 135.6, 134.0, 129.6, 128.4, 127.7, 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 $C_{32}H_{41}O_2Si$ $(M+H)^+$: 485.2876, found: 485.2879; MS (ES) *m/z* 502 [$(M+NH_4)$, 100%] and 108 (30).



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

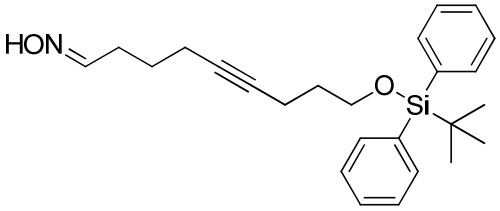
The benzyl ether **32** (1.4 g, 2.9 mmol, 1 eq) was dissolved in dichloromethane (14 mL) and cooled to 0 °C under nitrogen. Boron trichloride-dimethyl sulfide complex (2.0 M in CH_2Cl_2; 2.2 mL, 4.3 mmol, 1.5 eq) was added dropwise over 30 min. The reaction was allowed to warm to 25 ºC and stirred for 16 h. The mixture was cooled to 0 °C and stirred vigorously during the portionwise addition of satd. aqueous $NaHCO_3$ (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 ($MgSO_4$) 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; R_f 0.22 (1:1 hexane:ether); (Found: C, 76.1; H, 8.7%; $C_{25}H_{34}O_2Si$ requires 76.1; H, 8.7%); ν_{max}(film) 3353, 3070, 2931, 1959, 1890, 1825, 1589, 1471 and 1428 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.71-7.66 (4H, m, aromatics), 7.48-7.26 (6H, m, aromatics), 3.75 (2H, t, *J* 6.1, C*H*$_2$OSi), 3.64 (2H, q, *J* 5.9, HOC*H*$_2$), 2.34-2.27 (2H, m, C*H*$_2$C≡C), 2.21-2.15 (2H, m, C≡CC*H*$_2$), 1.76 (2H, qn, *J* 6.4, C*H*$_2$), 1.70-1.44 (5H, m, 2 x C*H*$_2$ and O*H*) and 1.06 (9H, s, C(C*H*$_3$)$_3$); δ_C (62.5 MHz; $CDCl_3$) 135.6, 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* calcd for $C_{25}H_{35}O_2Si$ $(M+H)^+$: 395.2406, found: 395.2402; MS (ES) *m/z* 412 [$(M+NH_4)^+$, 20%], 317 (100) and 239 (30).



9-(*tert*-Butyldiphenylsilanyloxy)-non-5-ynal.

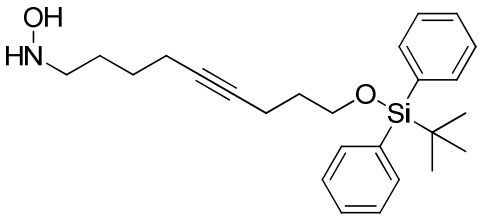
Oxalyl chloride (3.0 mL, 34 mmol, 3 eq) was dissolved in dichloromethane (207 mL) and cooled to –78 °C under nitrogen. A solution of DMSO (3.6 mL, 50 mmol, 4.4 eq) in dichloromethane (20 mL) was added dropwise and the solution stirred for 1.25 h at –78 °C. A solution of 9-(*tert*-butyldiphenylsilanyloxy)non-5-yn-1-ol (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 ºC 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; R_f 0.63 (1:1 hexane:EtOAc); (Found: C, 76.6; H, 8.2%. $C_{25}H_{32}O_2Si$ requires C, 76.5; H, 8.2%); ν_{max}(film) 3070, 2930, 2718, 1960, 1889, 1726, 1589, 1471 and 1427 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 9.76 (1H, br s, C*H*O), 7.69-7.67 (4H, m, aromatics), 7.44-7.37 (6H, m, aromatics), 3.74 (2H, t, *J* 6.0, C*H*$_2$OSi), 2.52 (2H, dt, *J* 1.3 and 7.3, C*H*$_2$CHO), 2.31-2.30 (2H, m, C*H*$_2$C≡C), 2.21-2.19 (2H, m, C≡CC*H*$_2$), 1.79-1.73 (4H, m, 2 x C*H*$_2$) and 1.06 (9H, s, C(C*H*$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 202.0, 135.6, 133.9, 129.6, 127.6, 81.0,

78.9, 65.5, 42.8, 31.9, 26.8 (q), 21.5, 19.2, 18.2 and 15.2; HRMS (ES) *m/z* calcd for $C_{25}H_{33}O_2Si$ $(M+H)^+$: 393.2250, found: 393.2258; MS (ES) *m/z* 410 [$(M+NH_4)^+$, 40%], 315 (20), 137 (100) and 121 (35).



9-(*tert*-Butyldiphenylsilanyloxy)non-5-ynal oxime.

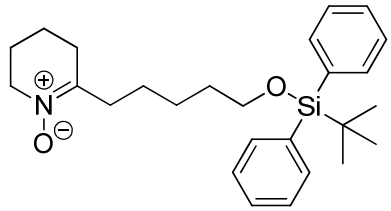
The aldehyde 9-(*tert*-butyldiphenylsilanyloxy)-non-5-ynal (0.35 g, 0.88 mmol, 1 eq) was dissolved in THF (0.9 mL) and a solution of hydroxylamine-hydrochloride (0.18 g, 2.64 mmol, 3 eq) and sodium acetate trihydrate (0.36 g, 2.64 mmol, 3 eq) in water (0.9 mL) was added and the reaction mixture stirred for 10 min at 25 ºC. 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 ($MgSO_4$) 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; R_f 0.39 (3:2 hexane:EtOAc); (Found: C, 74.0; H, 8.3; N, 3.6%. $C_{25}H_{33}NO_2Si$ requires C, 73.7; H, 8.2; N, 3.4%); ν_{max} (film) 3258, 3070, 2928, 1659, 1588, 1471 and 1427 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.70-7.69 (4H, m, aromatics), 7.46-7.38 (6.5H, m, C*H*NOH and aromatics), 6.74 (0.5H, t, *J* 5.4, C*H*NOH), 3.76 (2H, t, *J* 6.5, CH_2OSi), 2.46 (1H, dt, *J* 7.3 and 5.4, CH_2CHNOH), 2.34-2.27 (3H, m, CH_2CHNOH and CH_2C≡C), 2.24-2.16 (2H, tt, *J* 2.2 and 7.3, C≡CCH_2), 1.75 (2H, qn, *J* 6.5, CH_2CH$_2$C≡C), 1.64 (2H, qn, *J* 7.3, C≡CCH$_2$CH_2) and 1.07 (9H, s, C(CH_3)$_3$); δ_C (62.5 MHz; $CDCl_3$) 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* calcd for $C_{25}H_{34}NO_2Si$ $(M+H)^+$: 408.2359, found: 408.2363; MS (ES) *m/z* 407 [M^+, 100%], 392 (90) and 314 (40).



9-(*tert*-Butyldiphenylsilanyloxy)non-5-yn-1-hydroxylamine, 33.

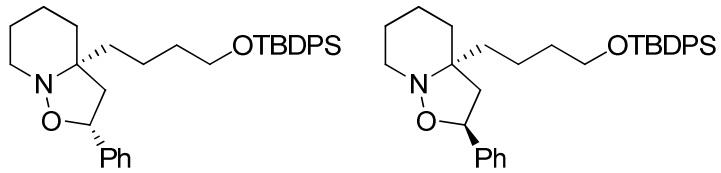
9-(*tert*-Butyldiphenylsilanyloxy)non-5-ynal oxime (1.9 g, 4.7 mmol, 1 eq) was dissolved in MeOH (125 mL) and cooled to –10 °C under nitrogen. Sodium cyanoborohydride (0.6 g, 9.3 mmol, 2 eq) and methyl orange (2 drops) were added. The solution was stirred at –10 °C and methanolic hydrochloric acid (6 M in MeOH) was added dropwise to keep the pH below 3. After 2 h the solution was neutralised with sodium hydroxide solution (20%) and the suspension poured into brine (60 mL) containing ice. The suspension was extracted with dichloromethane (4 x 50 mL) and the combined organics dried (Na_2SO_4) and concentrated *in vacuo* yielding a yellow oil. The compound was purified by passing through a short plug of silica (EtOAc → 9:1 EtOAc:MeOH; 1% NEt_3) yielding the *hydroxylamine* **33** (1.7 g, 90%) as a colourless oil; R_f 0.36 (EtOAc); ν_{max} (film) 3243, 2932, 1589, 1504 and 1472 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.68-7.67 (4H, m, aromatics), 7.47-7.36 (6H, m, aromatics), 3.74 (2H, t, *J* 6.3, CH_2OSi), 2.92 (2H, t, *J* 7.2, NCH_2), 2.31-2.28 (2H, m, CH_2C≡C), 2.17-2.16 (2H, m, C≡CCH_2), 1.73 (2H, qn, *J* 6.3, CH_2), 1.62 (2H, qn, *J* 7.2, CH_2), 1.51 (2H, qn, *J* 7.2, CH_2)

and 1.05 (9H, s, C(CH_3)$_3$); δ_C (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* calcd for $C_{25}H_{36}NO_2Si$ $(M+H)^+$: 410.2515, found: 410.2517; MS (ES) *m/z* 410 [$(M+H^+)$, 25%], 394 (100), 138 (20) and 84 (25).



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

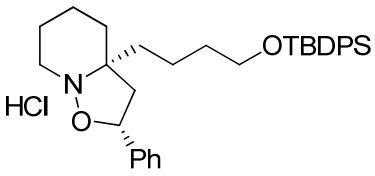
The hydroxylamine **33** (100 mg, 0.24 mmol) was dissolved in toluene (12 mL) and heated to 85 °C for 5 h under nitrogen. The toluene was removed *in vacuo* yielding a yellow oil. The compound was purified by passing through a plug of silica (EtOAc/MeOH, 5:1) yielding the *nitrone* **34** (63 mg, 63%) as a light yellow oil; R_f 0.21 (EtOAc/MeOH, 5:1); δ_H ($CDCl_3$, 500 MHz) 7.66-7.64 (4H, m, aromatics), 7.43-7.26 (6H, m, aromatics), 3.81-3.79 (2H, t, CH_2O, *J* 6.0), 3.70-3.69 (2H, m, CH_2N), 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), 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.

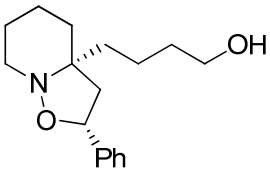
The hydroxylamine **33** (1.85 g, 4.54 mmol) was dissolved in toluene (220 mL) and heated at 80 °C for 4.5 h under nitrogen. The solvent was removed *in vacuo* and the residue immediately dissolved in neat styrene, quinol (10 mg) was added and the mixture heated at 80 °C for 16 h under nitrogen. The 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%. $C_{33}H_{43}NO_2Si$ requires C, 77.1; H, 8.4, N, 2.8%); ν_{max} (film) 3069, 2834, 1589 and 1471 cm^{-1}; δ_H (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, C*H*(O)Ph), 3.65 (2H, t, *J* 6.2, CH_2OSi), 3.22-3.14 (2H, m, CH_2N), 2.55 (1H, dd, *J* 9.0 and 12.1, CH*H*CH(O)Ph), 2.08 (1H, dd, *J* 6.4 and 12.1, C*H*HCH(O)Ph), 1.87-1.24 (12H, m, 6 x CH_2) and 1.07 (9H, s, C(CH_3)$_3$); δ_C (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* calcd for $C_{33}H_{44}NO_2Si$ $(M+H)^+$: 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%. $C_{33}H_{43}NO_2Si$ requires C, 77.1; H, 8.4, N, 2.8%); ν_{max} (film) 2934, 2857, 1654, 1471 and 1427 cm^{-1}; δ_H (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, C*H*(O)Ph), 3.76 (2H, t, *J* 6.2, CH_2OSi), 3.19-3.13 (2H, m, CH_2N), 2.51 (1H, dd, *J* 8.5 and 12.0, CH*H*CH(O)Ph), 2.12 (1H, dd, *J* 8.5 and 12.0, C*H*HCH(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)$_3$); δ_C (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 $C_{33}H_{44}NO_2Si$ $(M+H)^+$: 514.3141, found: 514.3146; MS (ES) *m/z* 514 [$(M+H)^+$, 100%], 394 (100), 202 (20) and 138 (25), 98 (20).



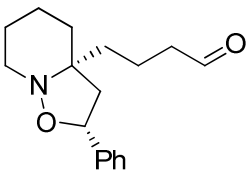
(6R*,8R*)-6-(4'-^{t}Butyldiphenylsilanyloxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane hydrochloride, 37.

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); ν_{max}(film) 3068.3, 2931.2, 2857.3, 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, C*H*(O)Ph), 3.76 (2H, t, *J* 6.2, CH_2OSi), 3.12-3.01 (2H, m, CH_2N), 2.57 (1H, dd, *J* 9.0 and 12.3, CH*H*CH(O)Ph), 2.00 (1H, dd, *J* 6.5 and 12.3, C*H*HCH(O)Ph), 1.82-1.74 (2H, m, CH_2), 1.62-1.16 (10H, m, 5 x CH_2) and 0.99 (9H, C(CH_3)$_3$; 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 $C_{33}H_{44}ClNO_2Si$ $(M-Cl)^+$: 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 °C under nitrogen. Tetra-*n*-butylammonium fluoride (1 M in THF; 0.49 mL, 0.49 mmol, 5 eq) was added and the reaction mixture stirred for 5 min at 0 °C 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 ($MgSO_4$) and concentrated *in vacuo* yielding a light yellow oil. The compound was purified by flash column chromatography (2:1 EtOAc:CH_2Cl_2) yielding the *title compound* (24.4 mg, 92%) as a colourless oil; R_f 0.17 (2:1 EtOAc:CH_2Cl_2); (Found: C, 74.2; H, 9.0; N, 5.0%. $C_{17}H_{25}NO_2$ requires C, 74.1; H, 9.2, N, 5.1%); ν_{max} (film) 3385 , 2937, 2862, 2862, 1603, 1494 and 1449 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.39-7.21 (5H, m, aromatics), 5.33 (1H, dd, *J* 6.2 and 9.2, C*H*(O)Ph), 3.58-3.55 (2H, m, CH_2OH), 3.14-3.12 (2H, m, CH_2N), 2.59 (1H, dd, *J* 9.2 and 12.2, CH*H*CH(O)Ph), 2.04 (1H, dd, *J* 6.2 and 12.2, C*H*HCH(O)Ph) and 1.81-1.76 (13H, m, 6 x CH_2 and O*H*); δ_C (62.5 MHz; $CDCl_3$) 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 $C_{17}H_{26}NO_2$ $(M+H)^+$: 276.1963, found: 276.1966; MS (ES) *m/z* 276 [$(M+H)^+$, 70%], 258 (20), 156 (100) and 138 (70).



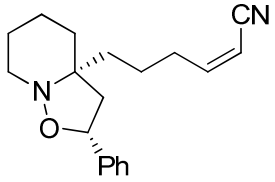
(6R*,8R*)-6-(3'-Formylprop-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 38.

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:

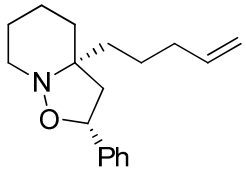
(6R*,8R*)-6-(4'-Hydroxybut-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (42 mg, 0.15 mmol, 1 eq) was dissolved in DMSO (14.3 mL) and IBX (60 mg, 0.21 mmol, 1.4 eq) was added and the reaction mixture stirred at 25 ºC for 16 h under nitrogen. Water (4 mL) was added and the residue extracted with ether (3 x 15 mL). The combined organics were washed with water (25 mL), dried ($MgSO_4$) 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; R_f 0.27 (1:1 hexane:EtOAc); ν_{max} (film) 2936, 1721 and 1450 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 9.70 (1H, s, C*H*O), 7.38-7.21 (5H, m, aromatics), 5.34 (1H, dd, *J* 6.1 and 9.3, C*H*(O)Ph), 3.15-3.12 (2H, m, CH_2N), 2.61 (1H, dd, *J* 9.3 and 12.1, CH*H*C(O)Ph), 2.05 (1H, dd, *J* 6.1 and 12.1, C*H*HC(O)Ph) and 1.81-1.76 (12H, m, 5 x CH_2); δ_C (62.5 MHz; $CDCl_3$) 202.3, 143.3, 128.4, 127.0, 125.7, 76.6, 65.5, 49.5, 45.8, 44.2, 37.4, 29.2, 22.0, 19.9 and 17.1; HRMS (EI) *m/z* calcd for $C_{17}H_{22}NO_2$ $(M+H)^+$: 273.1729, found: 273.1729; MS (EI) *m/z* 273 [$(M+H)^+$, 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 20 min. Tri-*iso*-propylborate (78 µL, 0.34 mmol, 1.6 eq) was then added and the reaction mixture stirred at –78 °C for a further 20 min. A solution of the aldehyde **38** (59 mg, 0.21 mmol, 1 eq) in THF (0.9 mL) was added and the reaction mixture was stirred at –78 °C for 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. The residue was diluted 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 ($MgSO_4$) 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; R_f 0.36 (1:1 hexane:EtOAc); ν_{max} (film) 2937, 2861, 2217, 1618, 1493 and 1449 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.40-7.20 (5H, m, aromatics), 6.36 (1H, dt, *J* 10.9 and 7.4, CH_2C*H*=CH), 5.35 (1H, dd, *J* 6.0 and 9.4, C*H*(O)Ph), 5.26 (1H, dt, *J* 10.9 and 1.3, CH=C*H*CN), 3.18-3.14 (2H, m, CH_2N), 2.63 (1H, dd, *J* 9.4 and 12.2, C*H*HCH(O)Ph), 2.38 (2H, q, *J* 7.4, CH_2CH=C), 2.05 (1H, dd, *J* 6.0 and 12.2, CH*H*CH(O)Ph) and 1.84-1.26 (10H, m, 5 x CH_2); δ_C (62.5 MHz; $CDCl_3$) 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 $C_{19}H_{25}N_2O$ $(M+H)^+$: 297.1967, found: 297.1963; MS (ES) *m/z* 297 [$(M+H)^+$, 35%], 177 (100) and 138 (20). The inseparable (*E*)-isomer had

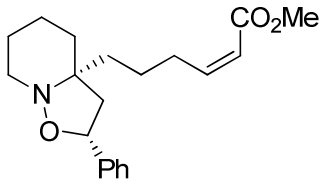
key diagnostic data as follows; 6.61 (0.09H, dt, *J* 16.3 and 6.9, C*H*$_2$C*H*=CH) and 5.26 (1H, dt, *J* 16.3 and 1.6, CH=C*H*CN).



(6*R,8*R**)-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 ºC, stirred for 30 min at 25 ºC 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 ºC and stirred for 1 h. The reaction was quenched by the addition of satd. aqueous NH_4Cl (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%. $C_{18}H_{25}NO$ 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, C*H*$_2$C*H*=CH$_2$), 5.29 (1H, dd, *J* 6.4 and 9.0, C*H*(O)Ph), 4.97 (1H, dd, *J* 1.0 and 17.1, CH=CH*H-E*), 4.92 (1H, dd, *J* 1.0 and 10.2, CH=C*H*H-*Z*), 3.17-3.14 (2H, m, C*H*$_2$N), 2.55 (1H, dd, *J* 9.0 and 12.2, C*H*HCH(O)Ph), 2.04 (1H, dd, *J* 6.4 and 12.2, CH*H*CH(O)Ph), 2.02-1.97 (2H, m, C*H*$_2$) and 1.87-1.27 (10H, m, 5 x C*H*$_2$); 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 $C_{18}H_{26}NO$ $(M+H)^+$: 272.2014, found: 272.2013; MS (ES) *m/z* 272 [$(M+H)^+$, 50%], 152 (100), 138 (55), 98 (30) and 90 (35).

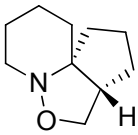


(6R*,8R*)-6-(5'-Methoxycarbonylpent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane, 41

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 ºC 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 ºC 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 ºC and the reaction was quenched by the addition of satd. aqueous NH_4Cl (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*)-*α,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, C*H-ortho*), 7.34 (2H, t *J* 7.6, C*H-meta*), 7.25 (1H, tt, *J* 1.3 and 7.6, C*H-para*),

6.13 (1H, dt, *J* 11.4 and 7.6, C*H*=CHCO$_2$), 5.75 (1H, dt, *J* 11.4 and 1.9, CH=C*H*CO$_2$), 5.33 (1H, dd, *J* 6.0 and 9.1, C*H*(O)Ph), 3.70 (3H, s, C*H*$_3$), 3.21 (2H, m, C*H*$_2$N), 2.63 (2H, dq, *J* 1.9 and 7.6, C*H*$_2$CH=C), 2.58 (1H, dd, *J* 9.1 and 12.3, C*H*HCH(O)Ph), 2.07 (1H, dd, *J* 6.0 and 12.3, CH*H*CH(O)Ph), 1.88-1.78 (2H, m, C*H*$_2$), 1.71 (1H, m, C*H*), 1.63-1.49 (5H, 2 x C*H*$_2$ and C*H*) and 1.43-1.32 (2H, C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 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 $C_{20}H_{28}NO_3$ $(M+H)^+$: 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; R_f 0.11 (4:1 hexane:EtOAc); ν_{max}(film) 2938, 2856, 1724, 1656 and 1437 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.37 (2H, br d, *J* 7.5, C*H-ortho*), 7.32 (2H, t, *J* 7.5, C*H-meta*), 7.23 (1H, t, *J* 7.5, C*H-para*), 6.91 (1H, dt, *J* 15.7 and 7.0, C*H*=CHCO$_2$), 5.79 (1H, dt, *J* 15.7 and 1.6, CH=C*H*CO$_2$), 5.32 (1H, dd, *J* 6.4 and 9.1, C*H*(O)Ph), 3.72 (3H, s, C*H*$_3$), 3.14 (2H, br t, *J* 5.4, C*H*$_2$N), 2.58 (1H, dd, *J* 9.1 and 12.2, C*H*HCH(O)Ph), 2.15 (2H, br q, *J* 7.0, C*H*$_2$CH=C), 2.03 (1H, dd, *J* 6.4 and 12.2, CH*H*CH(O)Ph), 1.83-1.78 (2H, m, C*H*$_2$) and 1.70-1.31 (8H, 4 x C*H*$_2$ and C*H*); δ_C (125 MHz; $CDCl_3$) 167.1, 149.1, 143.3, 128.4, 127.0, 125.7, 121.2, 76.6, 65.5, 51.4 (q), 49.4, 46.0, 37.5, 32.7, 29.2, 23.0, 21.9 and 20.0; HRMS (ES) *m/z* calcd for $C_{20}H_{28}NO_3$ $(M+H)^+$: 330.2064, found: 330.2066; MS (ES) *m/z* 330 [$(M+H)^+$, 80%], 210 (100) and 138 (35).



(1*R,5*R**)-8-Aza-7-oxatricyclo[6.4.0.0^{1,5}]dodecane, 42.**

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 ºC 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; R_f 0.37 (1:1 hexane:EtOAc); δ_H (500 MHz; $CDCl_3$) 4.27 (1H, br t, *J* 8.2, C*H*O-*cis*), 3.45 (1H, dd, *J* 5.1 and 8.2, C*H*O-*trans*), 3.09-3.05 (1H, m, C*H*HN), 2.87-2.82 (1H, m, CH*H*N), 2.63-2.59 (1H, m, C*H*CH$_2$O) and 1.94-1.35 (12H, m, 6 x C*H*$_2$); 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 ºC under argon. After 16 h only baseline material was present.

Method C:

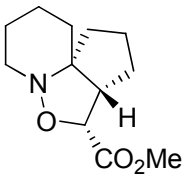
The alkene **40** (6 mg, 0.021 mmol) was dissolved in ether and transferred to a microwave tube. The ether was removed under a flow of nitrogen and the flask evacuated, refilled three times with argon and the microwave tube was sealed. Chlorobenzene (2.0 mL) was added and the mixture was then subjected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

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 ºC 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.



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

Method A:

The (*Z*)-*α,β-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 ºC for 1.6 h. The solvent was then removed *in vacuo*.

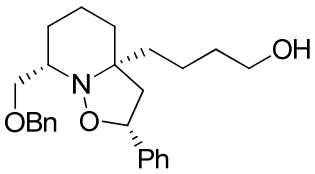
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the starting material (2 mg, 33%) followed by the adduct **43** (2 mg, 62%) as a colourless oil.

Method B:

The (*Z*)-*α,β-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 ºC for 30 min. The solvent was then removed *in vacuo*.

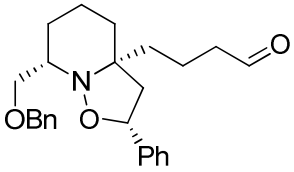
The compound was purified by flash column chromatography (4:1 hexane:EtOAc) yielding the adduct **43** (3 mg, 59%) as a colourless oil; R_f 0.25 (1:1 hexane:EtOAc); δ_H (400 MHz; $CDCl_3$) 4.74 (1H, d, *J* 9.0 C*H*O), 3.76 (3H, s, CH_3), 3.25 (1H, dt, *J* 14.3 and 3.8, C*H*HN), 3.03 (1H, ddd, *J* 3.5, 10.0 and 14.3, CH*H*N), 2.85 (1H, dt, *J* 9.0 and 7.0, C*H*CH(O)CO_2) and 1.91-1.28 (12H, m, 6 x CH_2); data identical to literature values.[10]

Investigations into the regiochemical outcome of the intramolecular nitrone dipolar cycloaddition reaction.
Model studies: histrionicotoxin precursors



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

(2*S*, 6*R*, 8*R*)-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 *title compound* (172 mg, 91%) as a colourless oil which solidified to a wax on standing; R_f 0.14 (hexane/EtOAc, 2:1); $[\alpha]_D^{22}$ –49.6 (*c* 1.09 in $CHCl_3$); (Found: C, 75.8; H, 8.4; N, 3.5; $C_{25}H_{33}NO_3$ requires C, 75.9; H, 8.4; N, 3.5%); ν_{max}(film) 3406, 3026, 2936, 2863, 1603, 1495, 753 and 699 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.41-7.22 (m, 10H, aromatics), 5.44 (1H, dd, *J* 10.0 and 5.0, C*H*(O)Ph), 4.56 (2H, s, PhCH_2O), 3.96 (1H, dd, *J* 9.0 and 3.0, C*H*HOBn), 3.53 (2H, m, CH_2OH), 3.46 (1H, t, *J* 9.0, CH*H*OBn,), 3.03 (1H, dddd, *J* 11.5, 9.0, 3.0 and 3.0, C*H*N,), 2.66 (1H, dd, *J* 12.5 and 10.0, C*H*HCH(O)Ph), 2.33 (1H, s, O*H*), 2.15-1.17 (13H, m, 6 x CH_2, CH*H*CH(O)Ph); δ_C ($CDCl_3$, 63 MHz) 141.4, 138.3, 128.1, 128.1, 127.5, 127.3, 127.0, 125.8, 77.0, 73.2, 73.0, 67.8, 61.6, 59.0, 41.7, 40.9, 32.5, 30.8, 28.1, 19.4, 19.0; HRMS (CI) *m/z* calcd for $C_{25}H_{34}NO_3$ $(M+H)^+$: 396.2539, found: 396.2542; MS (CI, NH_3) *m/z* 396 [$(M+H)^+$, 18%], 274 (10), 138 (90), 121 (92), 106 (100).



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

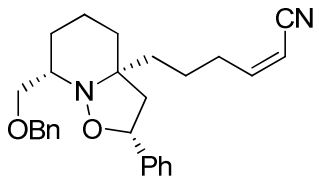
Method A:

To a stirred solution of (2*S*, 6*R*, 8*R*)-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; R_f 0.31 (hexane/EtOAc, 2:1); $[\alpha]_D^{19}$ –31.8 (*c* 2.24 in $CHCl_3$); FTIR ν_{max}(film) 3028, 2939, 2863, 2719, 1722, 1603, 1469, 1100, 754 and 600 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 9.67 (1H, t, *J* 1.5, C*H*O), 7.36-7.21 (10H, m, aromatics), 5.45 (1H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 4.55 (s, 2H, PhCH_2O), 3.94 (1H, dd, *J* 9.0 and 3.0, C*H*HOBn), 3.43 (1H, t, *J* 9.0, CH*H*OBn), 3.02 (1H, dddd, *J* 11.5, 9.0, 3.0 and 3.0, C*H*N), 2.69 (1H, dd, *J* 12.5 and 10.5, C*H*HCH(O)Ph), 2.45-2.08 (2H, m, CH_2C=O), 2.12 (1H, m, C*H*), 2.00 (1H, dd, *J* 12.5 and 5.0, CH*H*CH(O)Ph), 1.86-1.13 (10H, m, 5 x CH_2); δ_C ($CDCl_3$, 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 $C_{25}H_{32}O_3N$ $(M+H)^+$: 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).

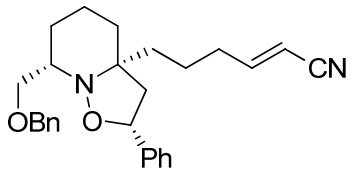
Method B:

To a stirred solution of (2*S*, 6*R*, 8*R*)-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%).



(*Z*)-(2*S*, 6*R*, 8*R*)-2-(Benzyloxymethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 11.

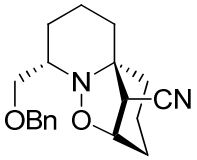
A solution of trimethylsilylacetonitrile (31 mg, 0.27 mmol) in dry THF (1 mL) was cooled to –78 °C under nitrogen. *n*-Butyllithium (1.55 M in hexane; 0.17 mL, 0.27 mmol) was introduced in a dropwise manner and the resulting solution stirred for 15 min. at this temperature. Tri*iso*propylborate (50 mg, 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); $[\alpha]_D^{21}$ –31.2 (*c* 1.29 in $CHCl_3$); (Found: C, 77.9; H, 7.9; N, 6.9; $C_{27}H_{32}N_2O_2$ 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, C*H*=CHCN), 5.45 (1H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 5.20 (1H, ddd, *J* 11.0, 1.0 and 1.0, CH=C*H*CN), 4.56 (1H, s, PhCH_2O), 3.95 (1H, td, *J* 9.0 and 3.0, C*H*HOBn), 3.43 (1H, t, *J* 9.0, CH*H*OBn), 3.02 (1H, dddd, *J* 11.5, 9.0, 3.0 and 3.0, C*H*N), 2.69 (1H, dd, *J* 12.5 and 10.5, C*H*HCH(O)Ph), 2.39-2.27 (2H, m, CH_2CH=), 2.17-1.18 (11H, m, 5 x CH_2, CH*H*CH(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 $C_{27}H_{32}N_2O_2$ $(M+H)^+$: 417.2542, found: 417.2525; MS (EI) *m/z* 417 [$(M+H)^+$, 16%], 307 (100), 289 (45).

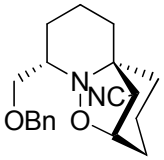


(*E*)-(2*S*,6*R*,8*R*)-2-(Benzyloxymethyl)-6-(5'-cyanopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 54

NaHMDS (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 (Na_2SO_4) 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; R_f 0.59 (3 : 2 hexane : EtOAc); FTIR ν_{max} (KBr) 3062, 3030, 2937, 2865, 2221, 1632, 1604, 1585, 1495, 1454, 1362, 1247, 1207, 1100, 1028, 967, 912, 813, 749, 699 and 476 cm^{-1}; δ_H (250 MHz) 7.40-7.25 (10H, m, aromatics), 6.58 (1H, dt, *J* 16.3 and 6.9, C*H*=CHCN), 5.46 (1H, dd, *J* 10.2 and 4.95, C*H*(O)Ph), 5.24 (1H, dt, *J* 16.3 and 1.6, =C*H*CN), 4.56 (2H, s, PhCH_2O), 3.95 (1H, dd, *J* 9.1 and 3.2, C*H*HOBn), 3.44 (1H, dd, *J* 9.1 and 8.7, CH*H*OBn), 3.02 (1H, dddd, *J* 11.3, 8.7, 3.3 and 3.2, C*H*N), 2.70 (1H, dd, *J* 12.6 and 10.2, C*H*HCH(O)Ph) and 2.38 - 1.19 (13H, m, 6 x -CH_2- and CH*H*CH(O)Ph); δ_C (62.5 MHz) 155.7, 141.7, 138.6, 128.5, 128.3, 127.7, 127.5, 127.3, 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* calcd for $C_{27}H_{33}N_2O_2$ $(M+H)^+$: 417.2542, found: 417.2526; MS (ES) *m/z* 417 [$(M+H)^+$, 100%], 394 (8), 366 (6), 342 (7) and 313 (10).





(1*R*, 5*S*, 8*S*, 12*R*)-8-(Benzyloxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1^{1,5}.0] undecane 13

and

(1*R*, 5*S*, 8*S*, 12*S*)-8-(Benzyloxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 48.

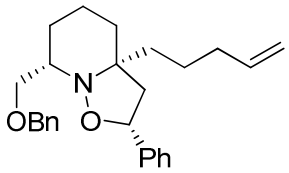
Method 1:

(*Z*)-(2*S*, 6*R*, 8*R*)-2-(Benzyloxymethyl)-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; R_f 0.42 (hexane/EtOAc, 4:1; 2 elutions); $[\alpha]_D^{21}$ –185.5 (*c* 1.5 in $CHCl_3$); ν_{max}(film) 3028, 2939, 2863, 2239, 1453, 1096, 738 and 698 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.38-7.29 (5H, m, aromatics), 4.71 (1H, m, C*H*(O)CHCN), 4.54 (2H, s, PhCH_2O), 3.80 (1H, dd, *J* 9.0 and 3.0, BnOC*H*H), 3.42 (1H, dd, *J* 6.5 and 2.0, C*H*CN), 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, C*H*N), 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); δ_C ($CDCl_3$, 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 (CI) *m/z* calcd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$: 313.1916, found: 313.1916; MS (CI, NH_3) *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; R_f 0.45 (hexane/EtOAc, 1:1); mp 114 °C dec. (from hexane/EtOAc, 4:1); $[\alpha]_D^{20.5}$ –156.7 (*c* 0.425 in $CDCl_3$); FTIR ν_{max} (KBr) 2945, 2858, 2237, 1496, 1454, 1303, 1190, 1095, 979, 913, 808, 743 and 699 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 7.35-7.25 (5H, m, aromatics), 4.80 (1H, d, *J* 5.0, C*H*O), 4.58 (2H, s, PhCH_2O), 3.80 (1H, dd, *J* 13.5 and 7.0, C*H*HOBn), 3.49-3.43 (2H, m, CH*H*OBn, C*H*N), 2.81 (1H, s, C*H*CN), 2.37 (1H, dddd, *J* 14.5, 4.0, 3.0 and 3.0, H-10_{eq}), 2.10-1.90 (3H, m, H-9_{eq}, H-11_{eq}, H-3_{eq}), 1.85 (1H, ddd, *J* 13.5, 5.5 and 5.5, H-4_{eq}), 1.76 (1H, ddd, *J* 14.5, 13.0 and 5.5, H-10_{ax}), 1.60 (1H, dd, *J* 13.5 and 7.0, H-2_{eq}), 1.60 (1H, m, 11-H_{ax}), 1.54 (1H, ddd, *J* 13.5, 5.5 and 5.5, H-3_{ax}), 1.39 (1H, ddd, *J* 13.5, 13.5 and 6.0, H-2_{ax}), 1.35 - 1.25 (1H, m, H-9_{ax}), 1.29 (1H, ddd, *J* 13.5, 13.0 and 6.0, H-4_{ax}); δ_C ($CDCl_3$, 63 MHz) 138.5, 128.4, 127.7, 127.6, 120.3, 78.8, 73.3, 72.5, 65.0, 63.7, 44.5, 41.9, 33.3, 31.4, 27.3, 18.9, 18.0; HRMS (ES) *m/z* calcd for $C_{19}H_{25}NO_2$ $(M+H)^+$: 313.1916, found: 313.1902; MS (ES) *m/z* 313 [$(M+H)^+$, 100%].

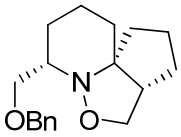
Method 2:

(*E*)-(2*S*,6*R*,8*R*)-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.



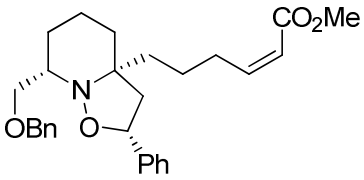
(2*S*, 6*S*, 8*R*)-2-(Benzyloxymethyl)-6-(4'-penten-1'-yl)-8-phenyl-1-aza-9-oxabicyclo [4.3.0]nonane 45.

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 (2*S*, 6*R*, 8*R*)-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 ($MgSO_4$), 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; R_f 0.65 (hexane/EtOAc, 4:1); $[\alpha]_D^{22}$ –30.9 (*c* 1.49 in $CHCl_3$); (Found: C, 79.65; H, 8.45; N, 3.7; $C_{26}H_{33}NO_2$ requires C, 79.75; H, 8.49; N, 3.58%); ν_{max} (film) 3029, 2936, 2863, 1640, 1604, 1495, 1101, 910, 752 and 699 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.42-7.22 (10H, m, aromatics), 5.46 (1H, dd, *J* 10.0 and 5.0, C*H*=CH_2), 5.00-4.91 (1H, m, =C*H*H), 4.93-4.88 (2H, m, =CH*H*, C*H*(O)Ph), 4.57 (2H, s, PhCH_2O), 3.98 (1H, dd, *J* 9.0 and 3.0, CH*H*OBn), 3.45 (1H, dd, *J* 9.0 and 9.0, C*H*HOBn), 3.04 (1H, dddd, *J* 11.5, 9.0, 3.0 and 3.0, C*H*N), 2.65 (1H, dd, *J* 12.5 and 10.0, CH*H*CH(O)Ph), 2.17-1.16 (13H, m, 6 x CH_2, C*H*HC(O)Ph); δ_C ($CDCl_3$, 63 MHz) 141.6, 138.7, 138.6, 128.3, 128.3, 127.7, 127.4, 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 $C_{26}H_{34}NO_2$ $(M+H)^+$: 392.2589, found: 392.2590; MS (CI, NH_3) *m/z* 392 [$(M+H)^+$, 83%], 378 (14), 274 (31), 272 (100), 270 (32), 138 (27).



(1*S*, 5*S*, 9*S*)-9-Benzyloxymethyl-8-aza-7-oxatricyclo[6.4.1.0^{1,5}]undecane 49.

An ethereal solution of (2*S*, 6*S*, 8*R*)-2-(benzyloxymethyl)-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; R_f 0.25 (hexane/EtOAc, 4:1); $[\alpha]_D^{22}$ –69.9 (*c* 0.74 in $CHCl_3$); ν_{max} (film) 3029, 2941, 2863, 1495, 1099, 736 and 698 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 7.33-7.24 (5H, m, aromatics), 4.52 (2H, s, PhC*H*$_2$O), 4.27 (1H, dd, *J* 8.5 and 8.5, C*H*HON), 3.80 (1H, dd, *J* 9.0 and 3.0, C*H*HOBn), 3.43 (1H, dd, *J* 8.5 and 4.0, CH*H*ON), 3.37 (1H, dd, *J* 9.0 and 9.0, CH*H*OBn), 2.70 (1H, dddd, *J* 11.0, 9.0, 3.0 and 3.0, C*H*N), 2.65 (1H, m, C*H*CH$_2$ON), 2.07-1.23 (12H, m, 6 x C*H*$_2$); δ_C ($CDCl_3$, 100 MHz) 138.6, 128.3, 127.8, 127.5, 76.9, 73.5, 73.1, 71.8, 59.8, 47.3, 41.7, 34.0, 31.5, 28.3, 22.8, 20.8; HRMS (ES) *m/z* calcd for $C_{18}H_{26}NO_2$ $(M+H)^+$: 288.1964, found: 288.1952; MS (ES) *m/z* 288 [$(M+H)^+$, 100%].



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

Method A.

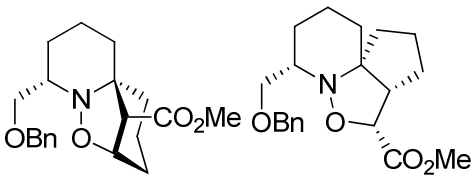
Carbon monoxide gas was bubbled through a stirred solution of (*Z*)-(2*S*, 6*R*, 8*R*)-2-(benzyloxymethyl)-6-(5'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0] nonane (12.0 mg, 23.3 µmol), dry distilled MeOH (8.2 µl, 6.5 mg, 203 µmol) and dry distilled triethylamine (2.5 µl, 1.9 mg, 18.5 µmol) 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, 19 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; R_f 0.30 (hexane/ether, 13:7); $[\alpha]_D^{23}$ –10.7 (*c* 0.23 in $CDCl_3$); ν_{max} (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 ($CDCl_3$, 400 MHz) 7.38-7.23 (10H, m, aromatics), 6.05 (1H, dt, *J* 11.5 and 7.5, C*H*=CHCO$_2$Me), 5.68 (1H, dt, *J* 11.5 and 1.5, =C*H*CO$_2$Me), 5.44 (1H, dd, *J* 10.0 and 5.0, C*H*(O)Ph), 4.55 (2H, s, PhC*H*$_2$O), 3.95 (1H, dd, *J* 8.5 and 3.0, C*H*HOBn), 3.67 (3H, s, CO$_2$C*H*$_3$), 3.41 (1H, dd, *J* 8.5 and

8.5, C*H*HOBn), 3.01 (1H, dddd, *J* 11.5, 8.5, 3.0 and 3.0, C*H*N), 2.65 (1H, dd, *J* 12.5 and 10.0, C*H*HCH(O)Ph), 2.58-2.55 (2H, m, CH_2CH=), 2.18-2.10 (1H, m, -C*H*H-), 2.05 (1H, dd, *J* 12.5 and 5.0, CH*H*CH(O)Ph), 1.90-0.80 (9H, m, -CH*H*-, 4 x -CH_2-); δ_C ($CDCl_3$, 100 MHz) 166.8, 150.6, 141.6, 138.0, 128.6, 128.4, 127.75, 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 $C_{28}H_{36}NO_4$ $(M+H)^+$: 450.2617, found: 450.2618; MS (ES) *m/z* 450 [$(M+H)^+$, 100%].

Also visible was the following data corresponding to the *E*-isomer: δ_H ($CDCl_3$, 400 MHz) 5.75 (1H, dt, *J* 15.5 and 1.5, =C*H*CO_2Me), 3.71 (3H, s, CO_2CH_3). 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 (2*S*, 6*R*, 8*R*)-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 ($MgSO_4$), 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%).



(1*R*, 5*S*, 8*S*, 12*S*)-8-(Benzyloxymethyl)-12-methoxycarbonyl-7-aza-6-oxatricyclo [5.4.1^{1,5}.0]undecane 50

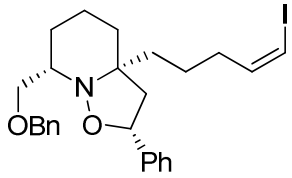
and

(1*S*, 5*S*, 6*R*, 9*S*)-9-(Benzyloxymethyl)-6-methoxycarbonyl-8-aza-7-oxatricyclo [6.4.0.0^{1,5}]undecane 51.

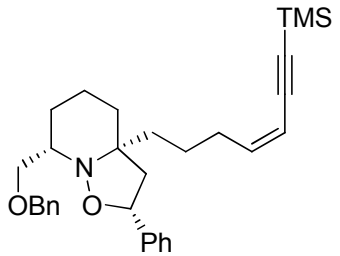
The *methyl ester* **46** (44:1 *Z*:*E*; 50 mg, 0.11 mmol) was transferred to a thick walled glass vessel as a solution in ether and the ether removed first under a stream of nitrogen and then *in vacuo*. A magnetic stirrer bar and dry distilled toluene (10 mL) were added, and the vessel was sealed under 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; R_f 0.28 (hexane/EtOAc, 3:1); $[\alpha]_D^{24.5}$ –7.5 (*c* 0.08 in $CDCl_3$); ν_{max}(KBr) 3088, 3063, 3030, 2936, 2862, 2799, 1760, 1732, 1604, 1586, 1496, 1454, 1205, 1066, 1028, 950 and 699 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 7.35-7.26 (5H, m, aromatics), 4.71 (approx. 0.5H, dd, *J* 5.5 and 5.5, C*H*O) 4.59-4.54 (approx. 2.5H, m, PhCH_2O, C*H*O), 3.85 (1H, m, BnOC*H*H), 3.72 (3H, s, OCH_3), 3.57 (approx. 0.5H, dd, *J* 8.5 and 8.5, BnOCH*H*) 3.45 (approx 0.5H, br d, *J* 6.5, C*H*CO_2Me), 3.39 (approx. 0.5H, dd, *J* 8.5 and 8.5, BnOCH*H*), 3.16-3.08 (approx. 0.5H, m, C*H*N), 2.86-2.77 (approx. 1H, m, C*H*N, C*H*CO_2Me), 2.40-2.30 (approx 0.5H, m, C*H*H), 2.08-1.15 (approx. 11.5H, m, 5 x CH_2, CH*H*); δ_C ($CDCl_3$, 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 $C_{20}H_{27}NNaO_4$ $(M+Na)^+$: 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/EtOAc, 3:1); $[\alpha]_D^{24.5}$ –16.7 (*c* 0.06 in $CDCl_3$); ν_{max}(KBr) 3088, 3064, 3030, 2950, 2865, 2798, 1750, 1732, 1496, 1454, 1029 and 699 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 7.34-7.24 (5H, m, aromatics), 4.82 (1H, d, *J* 9.5, C*H*(O)CO_2Me), 4.51 (2H, s, PhC*H*$_2$O), 3.85 (1H, dd, *J* 9.0 and 3.0, BnOC*H*H), 3.78 (3H, s, OC*H*$_3$), 3.39 (1H, dd, *J* 9.0 and 8.5, BnOCH*H*), 2.91 (1H, ddd, *J* 9.5, 7.5 and 2.0, C*H*CH(O)CO_2Me), 2.75 (1H, dddd, *J* 11.0, 8.5, 3.0 and 3.0, C*H*N), 2.17-1.24 (12H, m, 6 x C*H*$_2$); δ_C ($CDCl_3$, 100 MHz) 170.6, 138.5, 128.3, 127.7, 127.5, 78.2, 77.2, 73.5, 73.1, 60.6, 51.9, 50.8, 40.9, 33.6, 28.2, 27.8, 22.7, 20.3; HRMS (CI) *m/z* calcd for $C_{20}H_{27}NNaO_4$ $(M+Na)^+$: 368.1838, found: 368.1845.



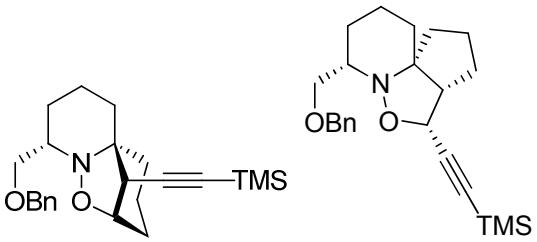
(*Z*)-(2*S*, 6*R*, 8*R*)-2-(Benzyloxymethyl)-6-(5'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane. Iodomethyltriphenylphosphonium iodide (28.0 mg, 52.9 µmol) was suspended in dry THF (0.5 mL) and cooled to 0 °C under nitrogen. NaHMDS (1.0 M in THF; 55 µl, 55 µmol) was added dropwise and 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 (2*S*, 6*R*, 8*R*)-2-(benzyloxymethyl)-6-(3'-formylprop-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane **44** (16.0 mg, 40.7 µmol) 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); $[\alpha]_D^{22}$ –12.4 (*c* 1.5 in $CDCl_3$); ν_{max} (film) 3027, 1604, 1494, 1452, 1099, 1027, 735, 697 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.38-7.22 (10H, m, aromatics), 6.11 (1H, dt, *J* 6.5 and 1.0, =C*H*I), 6.01 (1H, q, *J* 6.5, C*H*=CHI), 5.45 (1H, dd, *J* 10.0 and 5.0, C*H*(O)Ph), 4.55 (2H, s, OC*H*$_2$Ph), 3.95 (1H, dt, *J* 9.0 and 3.0, C*H*HOBn), 3.43 (1H, t, *J* 9.0, CH*H*OBn), 3.02 (1H, ddt, *J* 11.5, 8.5 and 3.0, C*H*N), 2.66 (1H, m, C*H*HCH(O)Ph), 2.10-0.80 (13H, m, CH*H*CH(O)Ph, 6 x C*H*$_2$); δ_C ($CDCl_3$, 100 MHz) 153.1, 141., 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 $C_{26}H_{33}INO_2$ $(M+H)^+$: 518.1556, found: 518.1554; MS (CI, NH_3) *m/z* 518 [$(M+H)^+$, 100%], 414 (12). Further elution of the column afforded unreacted aldehyde **38** (2.0 mg, 13%).



(*Z*)-(2*S*, 6*R*, 8*R*)-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 diethylamine (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(triphenylphoshine)palladium(0) (5.0 mg; cat.) was added to a stirred solution of (*Z*)-(2*S*, 6*R*, 8*R*)-2-(benzyloxymethyl)-6-(5'-iodopent-4'-en-1'-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane (21.0 mg, 40.8 µmol) in distilled diethylamine (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 $CDCl_3$); ν_{max} (KBr) 2148, 1459, 1366, 1252, 1099, 1034, 846, 754, 695 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.46-7.19 (10H, m, aromatics), 5.80 (1H, dt, *J* 11.0 and 7.5, C*H*=CHC≡CTMS), 5.44 (1H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 5.41 (1H, d, *J* 11.0, CH=C*H*C≡CTMS), 4.55 (2H, s, PhCH_2O), 3.95 (1H, dd, *J* 9.0 and 3.0, C*H*HOBn), 3.43 (1H, dd, *J* 9.0 and 9.0, CH*H*OBn), 3.03 (1H, ddt, *J* 11.5, 9.0 and 3.0, C*H*N), 2.65 (1H, dd, *J* 12.5 and 10.5, C*H*HCH(O)Ar), 2.35-2.05 (2H, m, CH_2CH=), 2.01 (1H, dd, *J* 12.5 and 5.0, CH*H*CH(O)Ar), 1.90-0.75 (10H, m, 5 x CH_2), 0.17 (9H, s, Si(CH_3)$_3$); δ_C ($CDCl_3$, 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 (ES) *m/z* calcd for $C_{31}H_{42}NO_2Si$ $(M+H)^+$: 488.2985, found: 488.2990; MS (ES) *m/z* 488 [$(M+H)^+$, 100%], 384 (3).



(1*R*, 5*S*, 8*S*, 12*S*)-8-(Benzyloxymethyl)-12-(trimethylsilylethynyl)-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 54

and

(1*S*, 5*S*, 6*R*, 9*S*)-9-(Benzyloxymethyl)-6-(trimethylsilylethynyl)-8-aza-7-oxatricyclo [6.4.0.0^{1,5}]undecane 53.

(*Z*)-(2*S*, 6*R*, 8*R*)-2-(Benzyloxymethyl)-6-[7'-(trimethylsilyl)-hept-4'-en-6'-yn-1'-yl]-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane **47** (8.2 mg, 16.8 µmol) was transferred to a thick-walled glass tube as a solution in ether, and the ether removed under first a stream of nitrogen and then *in vacuo*. Dry distilled toluene (3 mL) was added and the tube sealed under a stream of nitrogen and heated for a total time of 3 h with TLC monitoring (hexane/EtOAc, 9:1) as follows: the tube was removed from the heating bath and allowed to cool (~35 min.) to hand temperature. The tube was opened carefully and a TLC plate spotted. After the TLC plate had been exposed and developed the tube was re-sealed under a nitrogen atmosphere and re-immersed in the heating bath at 190 °C. This procedure was repeated at 30 - 45 min. intervals throughout the course of the reaction. TLC showed the formation of two products, and the reaction could not be driven to completion. The tube was cooled and the contents were transferred to a round bottomed flask and the solvent was removed *in vacuo* to give the crude product as a brown oil.

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_2Cl_2); ν_{max} (KBr) 2958, 2928, 2876, 2361, 2341, 1462, 1286, 1122, 913, 844 and 743.5 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 7.36-7.24 (5H, m, aromatics), 4.68-

4.54 (1H, m, C*H*O), 4.56 (2H, s, PhCH_2O), 3.77 (1H, dd, *J* 9.5 and 4.5, BnOC*H*H), 3.48 (1H, dd, *J* 9.5 and 7.0, BnOCH*H*), 3.09 (1H, m, C*H*N), 2.54 (1H, m, C*H*C≡CTMS), 2.00-0.87 (12H, m, 6 x CH_2), 0.15 (9H, s, Si(CH_3)$_3$); HRMS (ES) *m/z* calcd for $C_{23}H_{34}NO_2Si$ $(M+H)^+$: 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 $CDCl_3$); ν_{max} (KBr) 3031, 2952, 2911, 2846, 2354, 2174, 1497, 1464, 1339, 1252, 1094, 1026, 841, 741 and 694.5 cm^{-1}; δ_H ($CDCl_3$, 750 MHz) 7.33-7.12 (5H, m, aromatics), 5.02 (1H, d, *J* 9.0, C*H*(O)C≡C), 4.51 (2H, s, PhCH_2O), 3.85 (1H, dd, *J* 9.0 and 3.0, C*H*HOBn), 3.38 (1H, dd, *J* 9.0 and 8.5, CH*H*OBn), 2.67 (1H, dddd, *J* 11.0, 8.5, 3.0 and 3.0, C*H*N), 2.62 (1H, dd, *J* 9.0 and 7.0, C*H*CH(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_{ax}), 0.18 (9H, s, Si(CH_3)$_3$); δ_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* calcd for $C_{23}H_{34}NO_2Si$ $(M+H)^+$: 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 (1R, 5S, 8S, 12S)-8-(benzyloxymethyl)-12-(trimethylsilylethynyl)-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 54.

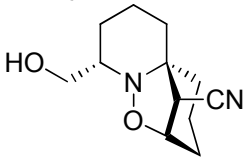
(1*R*, 5*S*, 8*S*, 12*S*)-8-(Benzyloxymethyl)-12-(trimethylsilylethynyl)-7-aza-6-oxatricyclo [5.4.1^{1,5}.0]undecane **54** (0.3 mg, 0.78 µmol) was treated according to the above procedure. After 4.5 h, TLC analysis showed the mixture to be almost entirely the *6,5,5-tricycle* **53**, along with a significant amount of baseline material.

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

(1*S*, 5*S*, 6*R*, 9*S*)-9-(Benzyloxymethyl)-6-(trimethylsilylethynyl)-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.

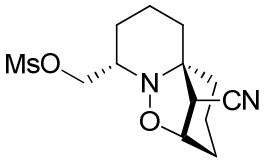
Synthesis of the "unsymmetrical" histrionicotoxins

Total synthesis of HTX-259A



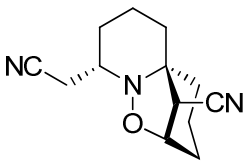
(2*S*, 6*R*, 7*R*, 8*S*)-2-(Hydroxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1^{6,8}.0] undecane. †

(2*S*, 6*R*, 7*R*, 8*S*)-2-(Benzyloxymethyloxymethyl)-7-cyano-1-aza-12-oxatricyclo [5.4.1^{6,8}.0]undecane[11] **57** (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. NEt_3 (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%); R_f 0.32 (EtOAc); mp 93-94 °C (from hexane:ether); $[\alpha]_D^{19}$ -121.2 (*c* 0.61 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 4.74 (1H, ddd, *J* 3.0, 3.0 and 0.0, C*H*O ring), 3.77 (1H, ddd, *J* 11.0, 5.0 and 3.5, C*H*HOH), 3.63-3.54 (1H, m, CH*H*OH), 3.42 (1H, dd, *J* 5.0 and 2.0, C*H*CN), 2.65 (1H, dddd, *J* 11.5, 3.5, 3.5 and 3.5, C*H*N), 2.49 (1H, dd, *J* 5.0 and 5.0, O*H)*, 2.20 (1H, dm, *J* 11.0, C*H*) and 2.03-1.25 (11H, m, 5 x CH_2 and C*H*); all data identical to literature values.[11]



(2*S*, 6*R*, 7*R*, 8*S*)-2-(Methanesulfonyloxymethyl)-7-cyano-1-aza-12-oxatricyclo [5.4.1^{6,8}.0]undecane. †

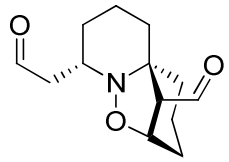
(2*S*, 6*R*, 7*R*, 8*S*)-2-(Hydroxymethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1^{6,8}.0] undecane (6.0 mg, 0.027 mmol), DMAP (2 mg, cat.) and NEt_3 (7.5 µL, 0.054 mmol, 2 eq) were dissolved in dry CH_2Cl_2 (1.5 mL) and a solution of methanesulfonyl chloride (2.3 µL, 0.029 mmol, 1.1 eq) in dry CH_2Cl_2 (0.3 mL) was added dropwise, after which the reaction mixture was stirred for 1 h. The CH_2Cl_2 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 ($MgSO_4$) 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%); R_f 0.61 (EtOAc); $[\alpha]_D^{21}$ -143.0 (*c* 0.18 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 4.77-4.72 (1H, m, C*H*O ring), 4.35 (1H, dd, *J* 10.5 and 3.0, C*H*HOMs), 4.25 (1H, dd, *J* 10.5 and 5.5, CH*H*OMs), 3.39 (1H, dd, *J* 6.5 and 1.5, C*H*CN), 3.06 (3H, s, CH_3SO_2), 2.80-2.71 (1H, m, C*H*N), 2.22 (1H, m, C*H*) and 1.92-1.25 (11H, m, 5 x CH_2 and C*H*); all data identical to literature values.[11]



(2*S*, 6*R*, 7*R*, 8*S*)-2-(Cyanomethyl)-7-cyano-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 56. †

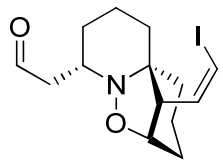
To a mixture of (2*S*, 6*R*, 7*R*, 8*S*)-2-(methanesulfonyloxymethyl)-7-cyano-1-aza-12-oxatricyclo [5.4.1^{6,8}.0]undecane (31.5 mg, 0.11 mmol) and powdered molecular sieves (4 Å) was added dry DMSO (3 mL) followed by NaCN (102.9 mg, 2.09

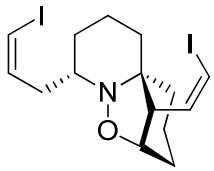
mmol, 20 eq) and the mixture was stirred at 50 ˚C for 4 days. The reaction vessel was allowed to cool to 25 °C before the addition of a 1:1 mixture of ether and water (6 mL). The organic layer was separated and the aqueous layer was further extracted with ether (5 x µ6 mL). The combined organic phases were washed with water (5 x 5 mL) and brine (5 x□5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (1:1 hexane:EtOAc) yielded the *bis-nitrile* **56** (69%); R_f 0.45 (1:1 hexane:EtOAc); mp 115-116 °C (from hexane:EtOAc); $[\alpha]_D^{16}$ -248.5 (*c* 0.35 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 4.73 (1H, ddd, *J* 6.0, 3.0 and 3.0, C*H*O ring), 3.36 (1H, d, *J* 6.0, C*H*CN), 2.76 (1H, dd, *J* 17.0 and 3.0, C*H*HCN), 2.80-2.71 (1H, m, C*H*N), 2.55 (1H, dd, *J* 17.0 and 8.0, CH*H*CN), 2.22 (1H, dm, *J* 13.0, C*H*) and 2.05-1.35 (11H, m, 5 x CH_2 and C*H*); all data identical to literature values.[11]



(2*S*, 6*R*, 7*S*, 8*S*)-2-(Oxo-1'-ethyl)-7-formyl-1-aza-12-oxatricyclo[5.4.1^{6,8}.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 $NaHCO_3$ (aq.), and extracted with EtOAc (2 x 5 mL). The organic phases were washed with brine (2 x 2 mL), combined, dried ($MgSO_4$) 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%); R_f 0.19 (1:1 hexane:EtOAc); $[\alpha]_D^{14}$ -130.7 (*c* 0.17 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 10.01 (1H, d, *J* 2.5, C*H*O), 9.83 (1H, dd, *J* 2.0 and 2.0, CH_2C*H*O), 4.78 (1H, ddd, *J* 5.5, 5.5 and 0.0, C*H*O ring), 3.32 (1H, m, C*H*CHO), 3.15 (1H, dddd, *J* 9.0, 6.5, 5.0 and 3.0, C*H*N), 2.86 (1H, ddd, *J* 16.5, 5.0 and 2.0, C*H*HCHO), 2.51 (1H, ddd, *J* 16.5, 6.5 and 2.0, CH*H*CHO), 2.18-1.96 (2H, m, CH_2) and 1.80-1.22 (10H, m, 5 x CH_2); all data identical to literature values.[11]





(2*S*, 6*R*, 7*S*, 8*S*)-2-(2'-Oxo-ethyl)-7-(2"-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0] undecane, 61.*

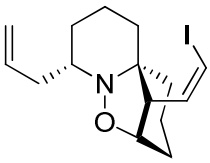
and

(2*S*, 6*R*, 7*S*, 8*S*)-2-(3'-Iodoprop-2'-enyl)-7-(2"-iodoethenyl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.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:H_2O; 2 mL) and warmed to 25 °C. Ether (4 mL) and satd. NH_4Cl (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 ($MgSO_4$) and concentrated *in vacuo*. Purification *via* flash column chromatography (3:1 hexane:ether) yielded the *bis*-vinyl iodide **60** (1.5 mg, 10%); R_f 0.60 (1:1 hexane:EtOAc); $[\alpha]_D^{19}$ -35.9 (*c* 0.07 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 6.54 (1H, d, *J* 7.5, =C*H*I), 6.38-6.29 (3H, m, =C*H*CH_2, =C*H* and =C*H*I), 4.56 (1H, ddd, *J* 6.0, 6.0 and 0.0, C*H*O ring), 3.53 (1H, m, =CHC*H*), 2.94 (1H, dddd, *J* 12.0, 8.0, 3.0 and 3.0, C*H*N), 2.67 (1H, dm, *J* 14.0, C*H*HCH=), 2.45-2.33 (1H, ddd, *J* 14.0, 8.0 and 7.5, CH*H*CH=), 2.02 (1H, m, C*H*), 1.80-1.64 (3H, m, CH_2 and C*H*), 1.60-1.40 (6H, m, 3 x CH_2) and 1.31-1.19 (2H, m, CH_2); all data identical to literature values.[11] Further elution yielded the *mono-vinyl iodide* **61** (7.0 mg, 60%) as a colourless oil; R_f 0.32 (1:1 hexane:EtOAc); $[\alpha]_D^{15}$ -62.9 (*c* 0.31 in $CHCl_3$); ν_{max}($CHCl_3$) cm^{-1} 2941s (C-H), 2874s (C-H), 1722s (C=O), 1220m, 1210s and 926w; δ_H (250 MHz; $CDCl_3$) 9.88 (1H, t, *J* 2.5, C*H*O), 6.55 (1H, d, *J* 7.5, =C*H*I), 6.35 (1H, dd, *J* 9.0 and 7.5, C*H*=CHI), 4.54 (1H, ddd, *J* 5.5, 5.5 and 0.0, C*H*O ring), 3.56 (1H, m, C*H*CH=CHI), 3.42-3.30 (1H, dddd, *J* 12.0, 6.0, 5.0 an 2.5, C*H*N), 2.88 (1H, ddd, *J* 16.0, 5.0 and 2.5, CH*H*CHO), 2.53 (1H, ddd, *J* 16.0, 6.0 and 2.5, C*H*HCHO) and 2.05-1.21 (12H, m, 6 x CH_2); δ_C(63 MHz, APT; $CDCl_3$) 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 $C_{14}H_{20}O_2NI$ $(M+H)^+$: 361.0539, found: 361.0546; MS (CI) *m/z* 362 [$(M+H)^+$, 80%], 235 (81), 192 (46) and 176 (100).[12]



(2*S*, 6*R*, 7*S*, 8*S*)-2-(Prop-2'-enyl)-7-(2"-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0] undecane, 62.

Method A[13]

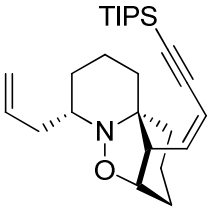
A solution of the aldehyde **61** (2.7 mg, 0.008 mmol) and DMAP (1.3 mg, 0.011 mmol, 1.3 eq) in THF (1 mL) was freeze-thaw degassed (three cycles) before being cooled down to -50 °C. Tebbe reagent (0.5 M in toluene; 21 µL, 0.011 mmol, 1.3 eq) was added dropwise and the resultant orange solution was allowed 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 and the reaction mixture was allowed to warm to 20 °C over 1 h. The quenched reaction mixture was poured into ether (2 mL) over Na_2SO_4 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 B[14]

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 (CH_2Cl_2) and purified by flash column chromatography (3:1 hexane:EtOAc; 1% NEt_3) to yield the *alkene* **62** (7.8 mg, 83%) as a colourless oil; R_f 0.60

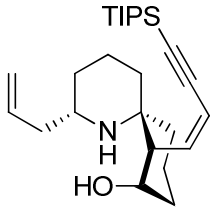
(1:1 hexane:EtOAc); $[\alpha]_D^{20}$ -23.5 (*c* 0.17 in $CHCl_3$); ν_{max}(thin film) 3070, 2932, 2864, 1639, 1604, 1446, 1302, 1279, 1263, 1081 and 923 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.52 (1H, d, *J* 7.5, =C*H*I), 6.35 (1H, dd, *J* 9.0 and 7.5, C*H*=CHI), 5.86 (1H, dddd, *J* 17.0, 10.5, 10.0 and 6.5, C*H*=CH_2), 5.08 (1H, d, *J* 17.0, CH=C*H*H *trans*), 5.04 (1H, d, *J* 10.0, CH=C*H*H *cis*), 4.55 (1H, ddd, *J* 6.0, 6.0 and 0.0, C*H*O ring), 3.54 (1H, dd, *J* 7.5, and 6.0, C*H*CH=CHI), 2.79 (1H, dddd, *J* 12.0, 9.0, 3.0 and 3.0, C*H*N), 2.82-2.71 (1H, m, CH*H*CH=CH_2), 2.10 (1H, ddd, *J* 13.5, 6.5 and 6.5, C*H*), 2.02 (1H, m, CH*H*CH=CH_2), 1.77 (2H, tm, *J* 13.5, CH_2), 1.66 (1H, m, C*H*), 1.60-1.40 (7H, m, 3 ×□□CH_2 and C*H*) and 1.13 (1H, m, C*H*); δ_C(63 MHz; $CDCl_3$) 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* calcd for $C_{15}H_{23}NOI$ $(M+H)^+$: 360.0824, found: 360.0827; MS (CI) *m/z* 360 [$(M+H)^+$, 76%], 279 (47), 234 (65), 218 (75), 130 (79) and 102 (100).



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

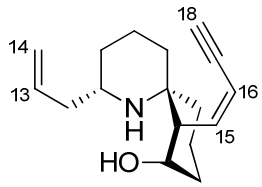
Copper iodide (4 mg, cat.) was dissolved in $HNEt_2$ (1.0 mL) under nitrogen and TIPS-acetylene (9.7 µL, 0.043 mmol, 2 eq) was added, after which the reaction mixture was stirred in the absence of light for 0.25 h. The mono-vinyl iodide **62** (7.8 mg, 0.022mmol) was dissolved in $HNEt_2$ (1.5 mL) under 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 CuI/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 by 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); $[\alpha]_D^{15}$ +0.40 (*c* 0.58 in $CHCl_3$); ν_{max}(thin film) 2941s (C-H), 2865, 2146, 2063, 1640, 1462, 1007 and 951cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.06 (1H, dd, *J* 10.5 and 10.5, C*H*=CHC≡CTIPS), 5.82-5.73 (1H, m, C*H*=CH_2), 5.76 (1H, d, *J* 10.5, CH=C*H*C≡CTIPS), 5.05 (1H, d, *J* 19.5, CH=CH*H trans*), 5.02 (1H, d, *J* 11.0, CH=CH*H cis*), 4.53 (1H, ddd, *J* 6.5, 6.0 and 0.0, C*H*O ring), 3.98 (1H, dd, *J* 10.5 and 6.5, C*H*CH=CHC≡CTIPS), 2.79-2.75 (2H, m, C*H*N and CH*H*CH=CH_2), 2.07-1.95 (2H, m, C*H*HCH=CH_2 and C*H*), 1.79-1.72 (2H, tm, *J* 15.5, CH_2), 1.63-1.37 (8H, m, 4 ×□CH_2), 1.09 (21H, s, Si(^{i}Pr)$_3$) and 1.09 (1H, m, C*H*); δ_C(63 MHz, APT; $CDCl_3$) 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* calcd for $C_{26}H_{44}NOSi$ $(M+H)^+$: 414.3192, found: 414.3189; MS (CI) *m/z* 414 [$(M+H)^+$, 100%], 174 (25) and 98 (16).



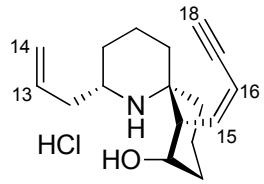
(–)-Tri*iso*propylsilylhistrionicotoxin 259A, 64.

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. $NaHCO_3$) 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 ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue *via* flash column chromatography (1:9 MeOH:CH_2Cl_2) yielded *TIPS-histrionicotoxin* **4** (3.4 mg, 89%) as a colourless oil; R_f 0.10 (1:9 MeOH:CH_2Cl_2); $[\alpha]_D^{15}$ -31.1 (*c* 0.18 in $CHCl_3$); ν_{max}(thin film) 3233, 2939, 2864, 2145, 1642, 1462, 1254, 1070 and 996 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 5.71 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡CTIPS), 5.77-5.64 (2H, m, C*H*=CH_2 and C*H*=C*H*C≡CTIPS), 5.26 (1H, d, *J* 17.0, CH=C*H*H *trans*), 5.16 (1H, d, *J* 10.0, CH=CH*H cis*), 4.04 (1H, br m, C*H*OH), 3.83 (1H, br d, *J* 10.0, C*H*CH=CH), 3.28 (1H, br m, C*H*NH), 2.52 (1H, br m, CH*H*CH=CH_2), 2.47 (1H, br m, CH*H*CH=CH_2), 2.23 (1H, br m, C*H*), 2.06 (1H, br q, *J* 14.0, C*H*), 1.85 (1H, br d, *J* 13.5, C*H*), 1.77 (1H, br d, *J* 13.5, C*H*), 1.67-1.54 (8H, m, 4 × CH_2) and 1.10 (21H, s, Si(^{i}Pr)$_3$); HRMS (ES) *m/z* calcd for $C_{26}H_{45}NOSi$ $(M+H)^+$: 416.3348, found: 416.3344; MS (CI) *m/z* 416 [$(M+H)^+$, 100%], 98 (28) and 90 (35).



(–)-Histrionicotoxin 259A, 2.

Tri*iso*propylsilylhistrionicotoxin-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:CH_2Cl_2) to furnish *(–)-HTX-259A* **2** as a colourless oil; R_f 0.28 (1:9 MeOH:CH_2Cl_2); δ_H(500 MHz; $CDCl_3$) 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, C*H*OH), 3.71 (1H, d, *J* 10.0, C*H*NH), 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, CH_2) and 1.80-0.80 (10H, m, 5 x CH_2).

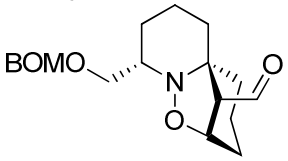


(–)-Histrionicotoxin 259A Hydrochloride.

(–)-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; R_f 0.28 (1:9 MeOH:CH_2Cl_2); $[\alpha]_D^{25.5}$ -54.0 (*c* 0.2 in EtOH); δ_H (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, C*H*OH), 3.78 (1H, s, *H*-18), 3.63 (1H, m, *H*-7), 3.55-3.49 (1H, br m, C*H*NH), 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, CH_2 and C*H*), 1.76-1.68 (6H, m, 3 x CH_2) and 1.37-1.29 (3H, m, CH_2 and C*H*); δ_C (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 $C_{17}H_{26}NOCl$ $(M\text{-}Cl)^+$: 260.2014, found: 260.2015; MS (CI) *m/z* 260 [$(M\text{-}Cl)^+$, 100%], 186 (52).[12]

Synthesis of the "unsymmetrical" histrionicotoxins

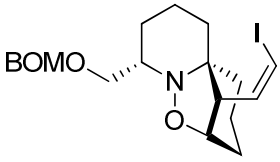
Total synthesis of HTX-285E



(2*S*, 6*R*, 7*S*, 8*S*)-2-(Benzyloxymethyloxymethyl)-7-formyl-1-aza-12-oxatricyclo [5.4.1^{6,8}.0] undecane, 69.

(2*S*, 6*R*, 7*R*, 8*S*)-2-(Benzyloxymethyloxymethyl)-7-cyano-1-aza-12-oxatricyclo [5.4.1^{6,8}.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 lower the pH to 5, followed by stirring overnight. The aqueous layer was separated and neutralised by the addition of $NaHCO_3$ (aq.) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with satd. brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude aldehyde. Purification by flash column chromatography (1:1 hexane:EtOAc) yielded the *aldehyde* **69** (187.2 mg, 100%) as a clear oil; R_f 0.34 (1:1 hexane:EtOAc); $[\alpha]_D^{25}$ -93.7 (*c* 0.62 in $CHCl_3$); ν_{max}(thin film) 3030, 2937, 2867, 1710, 1496, 1453, 1160, 1105, 1050 and 925 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 9.99 (1H, d, *J* 2.5, C*H*O), 7.35-7.24 (5H, m, aromatics), 4.79 (1H, d, *J* 7.0, OC*H*HO), 4.77 (1H, d, *J* 7.0, OCH*H*O), 4.79-4.74 (1H, m, C*H*O ring), 4.61 (1H, d, *J* 12.0, OC*H*HPh), 4.58 (1H, d, *J* 12.0, OCH*H*Ph), 3.87 (1H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.60 (1H, dd, *J* 9.5 and 7.5, CH*H*OBOM), 3.25 (1H, m, C*H*CHO), 2.74 (1H, dddd, *J* 11.5, 7.5, 3.0 and 3.0, C*H*N), 2.13-2.00 (2H, m, CH_2), 1.92 (1H, dm, *J* 13.5, C*H*), 1.79-1.52 (7H, m, 3 x CH_2 and C*H*) and 1.46-1.26 (2H, m, CH_2); δ_C (125 MHz, APT; $CDCl_3$) 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 $C_{20}H_{28}NO_4$ $(M+H)^+$: 346.2018, found: 346.2021; MS (EI) *m/z* 346 [$(M+H)^+$, 100%], 330 (16), 286 (20) 194 (23) and 106 (17).



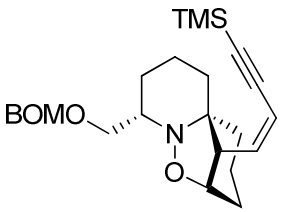
(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Benzyloxymethyloxymethyl)-7-(2'-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane.

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:H_2O; 10 mL) and warmed to 25 °C. Ether (30 mL) and satd. NH_4Cl (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 ($MgSO_4$) 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; R_f 0.32 (2:1

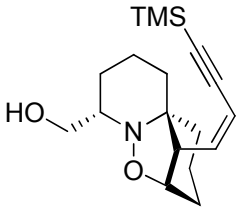
hexane:EtOAc); $[\alpha]_D^{21.5}$ -48.8 (*c* 1.26 in $CHCl_3$); (Found: C, 54.8; H, 6.1; N, 3.1%. $C_{21}H_{28}NO_3I$ requires C, 54.7; H, 6.0; N, 3.0%); ν_{max}(thin film) 2932, 2865, 1456, 1300, 1278, 1159, 1108 and 1050 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.37-7.26 (5H, m, aromatics), 6.53 (1H, d, *J* 7.5, =C*H*I), 6.34 (1H, dd, *J* 9.0 and 7.5, C*H*=CHI), 4.82 (1H, d, *J* 6.5, OC*H*HO), 4.80 (1H, d, *J* 6.5, OCH*H*O), 4.62 (2H, s, OCH_2Bn), 4.55 (1H, ddd, *J* 5.5, 5.5 and 0.0, C*H*O), 3.95 (1H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.63 (1H, dd, *J* 9.5 and 7.5, CH*H*OBOM), 3.55 (1H, br dd, *J* 9.0 and 5.5, C*H*CH=CHI), 3.00 (1H, dddd, *J* 12.0, 7.5, 3.0 and 3.0, C*H*N), 2.04-1.95 (2H, m, CH_2), 1.77 (1H, dd, *J* 14.0 and 2.5, C*H*), 1.67-1.42 (8H, m, 4 x CH_2) and 1.31 (1H, ddt, *J* 13.0, 13.0 and 3.0, C*H*); δ_C(125 MHz; $CDCl_3$) 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* calcd for $C_{21}H_{29}NO_3I$ $(M+H)^+$: 470.1192, found: 470.1196; MS (CI) *m/z* 470 [$(M+H)^+$, 85%], 391 (53), 344 (100), 328 (36), 106 (42) and 58 (44).



(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Benzyloxymethyloxymethyl)-7-(4'-trimethylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.0]undecane, 70.

Copper iodide (9 mg, cat.) was dissolved in $HNEt_2$ (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, (2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(benzyloxymethyloxymethyl)-7-(2'-iodoethenyl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane (101.7 mg, 0.216 mmol) was dissolved in $HNEt_2$ (8 mL) under nitrogen and $Pd(PPh_3)_4$ (8 mg, cat) added. The reaction mixture was stirred for 5 min., after which the CuI/TMS acetylene mix was added rapidly and the reaction stirred for 1 h.

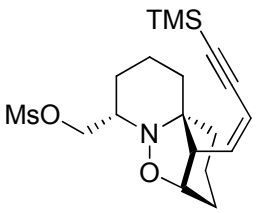
The reaction mixture was diluted by the addition of EtOAc (10 mL) and reduced to virtual dryness *in vacuo*. This process was repeated twice. The resulting crude residue was purified by flash column chromatography (4:1 hexane:EtOAc; 1% NEt_3) to yield the *trimethylsilyl-enyne* **70** (90.2 mg, 95%) as a pale yellow oil; R_f 0.64 (2:1 hexane:EtOAc); $[\alpha]_D^{19}$ -11.7 (*c* 0.40 in $CHCl_3$); ν_{max}(thin film) 3030, 2935, 2869, 2148, 1603, 1496, 1450, 1379, 1290, 1050 and 844 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 7.37-7.26 (5H, m, aromatics), 6.05 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡CTMS), 5.73 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.81 (1H, d, *J* 6.5, OC*H*HO), 4.79 (1H, d, *J* 6.5, OCH*H*O), 4.63 (1H, d, *J* 12.0, PhCH*H*O), 4.60 (1H, d, *J* 12.0, PhC*H*HO), 4.52 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.93 (1H, dd, *J* 9.5 and 3.0, CH*H*OBOM), 3.89 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.64 (1H, dd, *J* 9.5 and 7.0, C*H*HOBOM), 2.97 (1H, dddd, *J* 12.0, 7.0, 3.5 and 3.0, C*H*N), 2.05-1.93 (1H, m, C*H*), 1.93 (1H, ddd, *J* 13.5, 2.5 and 2.5, C*H*), 1.83-1.80 (1H, m, C*H*), 1.72-1.26 (9H, m, 4 x CH_2 and C*H*) and 0.20 (9H, s, Si(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 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* calcd for $C_{26}H_{38}NO_3Si$ $(M+H)^+$: 440.2621, found: 440.2615; MS (CI) *m/z* 440 [$(M+H)^+$, 100%], 288 (13), 279 (26) and 90 (15).



(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Hydroxymethyl)-7-(4'-trimethylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 71.

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. NEt_3 (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% NEt_3) to yield the *alcohol* **71** *(*38.0 mg, 99%) as a colourless oil; R_f 0.43 (EtOAc); $[\alpha]_D^{21}$ +25.5 (*c* 0.42 in $CHCl_3$); ν_{max}($CHCl_3$) 3417, 2935, 2861, 2148, 1599, 1448, 1250, 1009, 922, 843 and 759 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 6.04 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.73 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.54 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.86 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.78 (1H, ddd, *J* 10.5, 5.0 and 3.5, C*H*HOH), 3.62 (1H, ddd, *J* 10.5, 6.5 and 5.0, C*H*HOH), 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, C*H*N), 2.06-1.94 (1H, m, C*H*), 1.81 (1H, ddd, *J* 14.0, 3.0 and 2.5, C*H*), 1.73-1.48 (7H, m, 3 x CH_2 and C*H*), 1.42-1.33 (3H, m, CH_2 and C*H*) and 0.20 (9H, s, Si(CH_3)$_3$); δ_C (63 MHz, APT; $CDCl_3$) 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 $C_{18}H_{30}NO_2Si$ $(M+H)^+$: 320.2046, found: 320.2043; MS (ES) *m/z* 320 [$(M+H)^+$, 86%], 166 (20), 90 (100), 82 (28) and 72 (22).

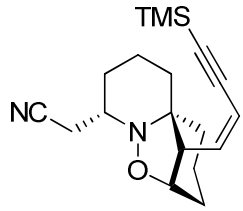


(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Methanesulfonyloxymethyl)-7-(4'-trimethylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 72.

The alcohol **71** (14.5 mg, 0.045 mmol), NEt_3 (12.7 µL, 0.091 mmol, 2 eq) and DMAP (4 mg, cat.) were dissolved in dry CH_2Cl_2 (1 mL) and a solution of methanesulfonyl chloride (3.9 µL, 0.05 mmol, 1.1 eq) in dry CH_2Cl_2 (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 ($MgSO_4$) 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); $[\alpha]_D^{18}$ -2.3 (*c* 0.22 in $CHCl_3$); ν_{max}(thin film) 2954, 2149, 1602, 1461, 1409, 1356, 1250, 1176, 844 and 759 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.03 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.74 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.53 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 4.39 (1H, dd, *J* 10.5 and 3.0, C*H*HOMs), 4.35 (1H, dd, *J* 10.5 and 5.5, CH*H*OMs), 3.82 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.10 (3H, s, CH_3SO$_2$), 3.01 (1H, dddd, *J* 15.0, 5.5, 3.0 and 3.0, C*H*N), 1.92-1.81 (3H, m, CH_2 and C*H*), 1.71-1.48 (6H, m, 3 x CH_2), 1.43-1.29 (3H, m, CH_2 and C*H*) and 0.20 (9H, s, Si(CH_3)$_3$); δ_C(125 MHz; $CDCl_3$)

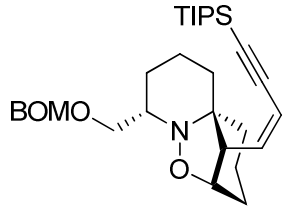
138.4, 113.6, 101.6, 100.3, 77.8, 72.0, 65.9, 63.5, 46.3, 37.1, 34.5, 32.2, 27.7, 25.2, 19.2, 18.0 and -0.2; HRMS (ES) *m/z* calcd for $C_{19}H_{32}NO_4SiS$ $(M+H)^+$: 398.1821, found: 398.1824; MS (CI) *m/z* 398 [$(M+H)^+$, 100 %], 304 (35), 90 (21), 72 (21) and 61 (21).



(2*S*, 6*R*, 7*S*, 8*S*)-(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); $[\alpha]_D^{23}$ -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_H(500 MHz; $CDCl_3$) 6.09 (1H, dd, *J* 10.5 and 10.5, C*H*=CHC≡C), 5.72 (1H, dd, *J* 10.5 and 2.0, CH=C*H*C≡C), 4.52 (1H, ddd, *J* 5.5, 5.5 and 0.0, C*H*O), 3.77 (1H, dd, *J* 10.5 and 5.5, C*H*CH=CH), 3.18 (1H, d, *J* 2.0, C≡C*H*), 3.05 (1H, dddd, *J* 12.0, 8.5, 3.5 and 3.5, C*H*N), 2.86 (1H, dd, *J* 16.5 and 3.5, C*H*HCN), 2.50 (1H, dd, *J* 16.5 and 8.5, CH*H*CN), 1.97-1.92 (2H, m, CH_2), 1.83 (1H, ddt, *J* 14.0, 3.0 and 3.0, C*H*) and 1.63-1.30 (9H, m, 4 x CH_2 and C*H*); 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* calcd for $C_{16}H_{21}N_2O$ $(M+H)^+$: 257.1654, found: 257.1654; MS (CI) *m/z* 257 [$(M+H)^+$, 100%] and 58 (13).

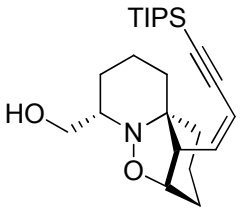


(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Benzyloxymethyloxymethyl)-7-(4'-triisopropylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo [5.4.16,8.0]undecane, 74.

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, (2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(benzyloxymethyloxymethyl)-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 CuI/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-enyne* **74** (112.9 mg, 100%) as a colourless oil; R_f 0.32 (3:1

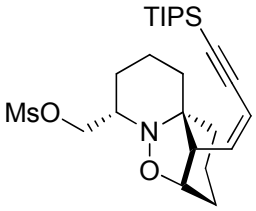
hexane:EtOAc); $[\alpha]_D^{18}$ -24.2 (*c* 0.32 in $CHCl_3$); ν_{max}(thin film) 2940, 2864, 2145, 1460, 1050 and 922 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 7.37-7.26 (5H, m, aromatics), 6.05 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.78 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.80 (1H, d, *J* 6.5, OCH*H*O), 4.78 (1H, d, *J* 6.5, OC*H*HO), 4.63 (1H, d, *J* 12.0, PhC*H*HO), 4.60 (1H, d, *J* 12.0, PhCH*H*O), 4.55 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 3.95 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.90 (1H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.63 (1H, dd, *J* 9.5 and 7.0, CH*H*OBOM), 2.97 (1H, dddd, *J* 12.0, 7.0, 3.0 and 3.0, C*H*N), 2.04-1.95 (1H, m, C*H*), 1.88 (1H, dm, *J* 13.5, C*H*), 1.80 (1H, dm, *J* 13.5, C*H*), 1.80-1.74 (1H, dm, *J* 13.5, C*H*), 1.62-1.29 (8H, m, 4 x CH_2) and 1.09 (21H, s, Si(^{i}Pr)$_3$); δ_C(63 MHz, APT; $CDCl_3$) 138.5, 138.1, 128.3, 127.9, 127.5, 113.6, 103.4, 96.6, 94.7, 77.8, 70.2, 69.1, 65.5, 64.1, 46.3, 34.4, 32.5, 28.5, 25.4, 19.3, 18.6 (q), 17.9 and 11.3; HRMS (ES) *m/z* calcd for $C_{32}H_{50}NO_3Si$ $(M+H)^+$: 524.3560, found: 524.3558; MS (CI) *m/z* 524 [$(M+H)^+$, 33%], 174 (35), 108 (100), 106 (89), 91 (87) and 60 (54).



(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Hydroxymethyl)-7-(4'-triisopropylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.0]undecane, 75.

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. NEt_3 (10 mL) was added and the reaction mixture was stirred for a further 3 h.

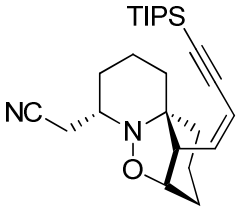
The solution was filtered to remove the catalyst, the catalyst was washed further with methanol (3 x 10 mL), and the combined organic phases concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (EtOAc) yielded the *alcohol* **75** (42.9 mg, 84%) as a white crystalline solid; R_f 0.37 (EtOAc); mp 48-49.5 °C (from hexane:EtOAc); $[\alpha]_D^{18}$ +21.1 (*c* 1.40 in $CHCl_3$); (Found: C, 71.5; H, 10.2; N, 3.5%. $C_{24}H_{41}NO_2Si$ requires C, 71.4; H, 10.2; N, 3.5%); ν_{max}(thin film) 3445, 2940, 2864, 2144, 1461 and 1007 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.03 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.79 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.56 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 3.91 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.77 (1H, ddd, *J* 10.5, 3.5 and 3.5, C*H*HOH), 3.57 (1H, ddd, *J* 10.5, 5.0 and 5.0, CH*H*OH), 2.97 - 2.91 (2H, m, C*H*N and O*H*), 2.04-1.97 (1H, m, C*H*), 1.80 (1H, dm, *J* 14.0, C*H*), 1.65-1.34 (10H, m, 5 x CH_2) and 1.09 (21H, s, Si(^{i}Pr)$_3$); δ_C(125 MHz; $CDCl_3$) 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 $C_{24}H_{42}NO_2Si$ $(M+H)^+$: 404.2985, found: 404.2989; MS (CI) 404 [$(M+H)^+$, 32%], 374 (32), 143 (100), 112 (50) and 96 (50).



(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Methanesulfonyloxymethyl)-7-(4'-triisopropylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane.

The alcohol **75** (27.8 mg, 0.069 mmol), NEt_3 (19.2 µL, 0.14 mmol, 2 eq) and DMAP (10 mg, cat.) were dissolved in dry CH_2Cl_2 (6 mL), and a solution of methanesulfonyl chloride (11.8 µL, 0.10 mmol, 1.5 eq) in dry CH_2Cl_2 (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 (CH_2Cl_2) and purified by flash column chromatography (2:1 hexane:EtOAc; 1% NEt_3) to yield the *title compound* (27.5 mg, 97%) as a colourless oil; R_f 0.63 (EtOAc); $[\alpha]_D^{18}$ -5.8 (*c* 0.32 in $CHCl_3$); ν_{max}(thin film) 2940, 2864, 2144, 1460, 1356, 1176, 950 and 883 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.02 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.78 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.54 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 4.35 (2H, d, *J* 4.0, CH_2OMs), 3.89 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.09 (3H, s, CH_3SO_2), 3.00 (1H, dtd, *J* 12.5, 4.0 and 3.5, C*H*N), 1.92-1.85 (1H, m, C*H*), 1.80 (2H, br d, *J* 14.0, CH_2), 1.60-1.33 (9H, m, 4 x CH_2 and C*H*) and 1.09 (21H, s, Si(^{i}Pr)$_3$); δ_C(125 MHz; $CDCl_3$) 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 $C_{25}H_{44}NO_4SSi$ $(M+H)^+$: 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).

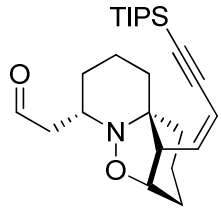


(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Cyanomethyl)-7-(4'-triisopropylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 76.

(2*S*, 6*R*, 7*S*, 8*S*)-(1'Z)-2-(Methanesulfonyloxymethyl)-7-(4'-triisopropylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane (39.1 mg, 0.081 mmol) was dissolved in dry DMSO (4 mL) and NaCN (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 ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (2:1 hexane:ether; 1% NEt_3) yielded the *nitrile* **76** (18.7 mg, 66%) as a colourless oil which slowly crystallised on standing in the freezer; R_f 0.50 (2:1 hexane:EtOAc); mp 48.5-49.5 °C; $[\alpha]_D^{14}$ -2.3 (*c* 0.75 in $CHCl_3$); ν_{max}(thin film) 2940, 2864, 2243, 2144, 1459, 1007 and 918 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.02 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.79 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.53 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 3.89 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.03 (1H, dddd, *J* 12.0, 8.5, 3.0 and 3.0, C*H*N), 2.86 (1H, dd, *J* 16.5 and 3.0, C*H*HCN), 2.48 (1H, dd, *J* 16.5 and 8.5, CH*H*CN), 1.98-1.87 (1H, m, C*H*), 1.90 (1H, br d, *J* 14.0, C*H*), 1.82 (1H, br d, *J* 14.0, C*H*), 1.68-1.22 (9H, m, 4 x CH_2 and C*H*) and 1.10 (21H, s, Si(^{i}Pr)$_3$); δ_C(125 MHz; $CDCl_3$) 137.7, 118.2, 114.1, 103.1, 97.0,

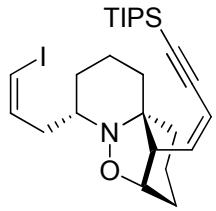
78.0, 65.8, 61.3, 46.4, 34.2, 32.1, 29.9, 25.3, 23.2, 19.1, 18.6, 17.8 and 11.3; HRMS (ES) *m/z* calcd for $C_{25}H_{41}N_2OSi$ $(M+H)^+$: 413.2988, found: 413.2985; MS (CI) *m/z* 413 [$(M+H)^+$, 36%], 162 (100), 91 (50), 58 (49) and 49 (79). Further elution of the column furnished recovered *mesylate* (9.7 mg, 25%).



(2*S*, 6*R*, 7*S*, 8*S*)-(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.

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 $NaHCO_3$ (aq.), and extracted with EtOAc (2 x 3 mL). The combined organic phases were washed with brine (2 x 3 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the *title compound* (6.0 mg, 100%) as a colourless oil; R_f 0.25 (1:1 hexane:ether); $[\alpha]_D^{19}$ -23.0 (*c* 0.33 in $CHCl_3$); ν_{max} (thin film) 2940, 2864, 2722, 2145, 1725, 1461, 1250, 1007, 920 and 883 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 9.81 (1H, dd, *J* 2.0, C*H*O), 6.04 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.78 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.54 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.98 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.34 (1H, m, C*H*N), 2.85 (1H, ddd, *J* 16.0, 5.0 and 2.0, CH*H*CHO), 2.47 (1H, ddd, *J* 16.0, 6.5 and 2.0, C*H*HCHO), 2.02-1.93 (1H, m, C*H*), 1.81 (1H, dm, *J* 14.0, C*H*), 1.69 (1H, dm, *J* 14.0, C*H*), 1.64-1.36 (8H, m, 3 x CH_2 and 2 x C*H*), 1.27 (1H, ddt, *J* 13.0, 13.0 and 3.0, C*H*) and 1.11 (21H, s, Si(^{i}Pr)$_3$); δ_C(125 MHz; $CDCl_3$) 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 (CI) *m/z* calcd for $C_{25}H_{42}NO_2Si$ $(M+H)^+$: 416.2985, found: 416.2986; MS (CI) *m/z* 416 [$(M+H)^+$, 100%], 249 (9) and 221 (12).



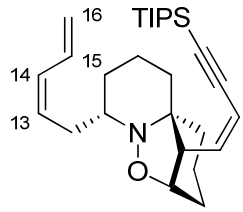
(2*S*, 6*R*, 7*S*, 8*S*)-(1"*Z*, 2'*Z*)-2-(3'-Iodoprop-2'-enyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 77.

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. KHMDS (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.

(2*S*, 6*R*, 7*S*, 8*S*)-(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.

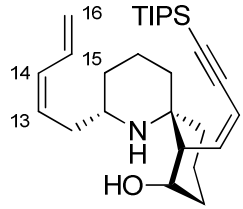
The reaction was quenched by the addition of wet THF (1:1 THF:H_2O; 1.5 mL) and warmed to 25 °C. EtOAc (4 mL) and satd. NH_4Cl (4 mL) were added and the organic layer separated. The aqueous layer was further extracted with EtOAc (3 x 5 mL) and the organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* flash column chromatography (6:1 hexane:EtOAc; 1% NEt_3) yielded the *vinyl iodide* **77** (6.4 mg, 82%) as a colourless oil; R_f 0.60 (4:1 hexane:EtOAc); $[\alpha]_D^{15}$ -10.6 (*c* 0.18 in $CHCl_3$); ν_{max} (thin film) 2938, 2863, 2145, 1461, 1366, 1306, 1260, 1076, 1008 and 921 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 6.30-6.24 (2H, m, C*H*=CHI and CH=C*H*I), 6.05 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.77 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.54 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 3.95 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 2.91-2.87 (1H, br ddm, *J* 11.5 and 9.0, C*H*N), 2.67 (1H, dm, *J* 14.5, CH*H*CH=CHI), 2.34 (1H, ddd, *J* 14.5, 7.5 and 7.5, CH*H*CH=CHI), 2.04-1.96 (1H, m, C*H*), 1.78 (1H, br d, *J* 13.0, C*H*), 1.66-1.37 (8H, m, 4 x CH_2), 1.28-1.19 (2H, m, CH_2) and 1.09 (21H, s, Si(^{i}Pr)$_3$); δ_C(63 MHz, APT; $CDCl_3$) 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 (ES) *m/z* calcd for $C_{26}H_{43}NOSiI$ $(M+H)^+$: 540.2158, found: 540.2166; MS (CI) *m/z* 540 [$(M+H)^+$, 5%], 414 (19), 372 (38), 153 (41) and 96 (79).



(2*S*, 6*R*, 7*S*, 8*S*)-(2'*Z*, 1"*Z*)-2-(Penta-2',4'-dienyl)-7-(4''-triisopropylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 78.*

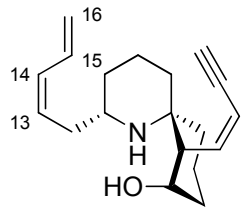
$PdCl_2(MeCN)_2$ (2 mg, cat.) was dissolved in dry DMF (0.4 mL) under nitrogen and the mixture was stirred. A solution of the vinyl iodide **77** (10.4 mg, 0.019 mmol) in dry DMF (0.4 mL) was added dropwise, followed by a solution of tributylvinyl tin (8.5 µL, 0.029 mmol, 1.5 eq) in dry DMF (0.4 mL) 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 H_2O (2 x 4 mL) then brine (2 x 4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* flash column chromatography (6:1 hexane:ether; 1% NEt_3) yielded the *(Z)-diene* **78** (6.8 mg, 80%) as a colourless oil; R_f 0.49 (4:1 hexane:EtOAc); $[\alpha]_D^{18}$ -20.0 (*c* 0.15 in $CHCl_3$); ν_{max} (thin film) 2940, 2864, 2145, 1461, 1004, 950 and 921 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 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, C*H*=CHC≡C), 5.76 (1H, d, *J* 10.5, CH=C*H*C≡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, C*H*O), 3.97 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 2.82-2.76 (2H, m, C*H*N and C*H*HCH=CH), 2.27 (1H, ddd, *J* 14.0, 9.0 and 9.0, CH*H*CH=CH), 2.09-1.98 (1H, m, C*H*), 1.78 (1H, dm, *J* 13.5, C*H*), 1.70 (1H, dm, *J* 13.5, C*H*), 1.60-0.82 (9H, m, 4 x CH_2 and C*H*) and 1.09 (21H, s, Si(^{i}Pr)$_3$); δ_C(100 MHz; $CDCl_3$) 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 (ES) *m/z* calcd for $C_{28}H_{46}NOSi$ $(M+H)^+$: 440.3348, found: 440.3348; MS (CI) *m/z* 440 [$(M+H)^+$, 13%], 372 (56), 174 (100) and 150 (43).[12]



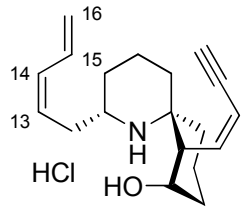
(–)-Triisopropylsilylhistrionicotoxin 285E.

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 ($MgSO_4$), concentrated *in vacuo* and azeotroped in toluene. Purification of the crude residue *via* flash column chromatography (9:1 CH_2Cl_2:MeOH) yielded the *title compound* (2.0 mg, 91%) as a colourless oil; R_f 0.17 (9:1 CH_2Cl_2:MeOH); $[\alpha]_D^{20}$ -65.7 (*c* 0.14 in $CHCl_3$); ν_{max}(thin film) 3500-2800, 3227, 2940, 2864, 2145, 1630, 1461, 1261, 1095, 1071, 998, 906, 883 and 751 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 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, C*H*=CHC≡C), 5.66 (1H, d, *J* 10.5, CH=C*H*C≡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, C*H*OH), 3.81 (1H, br d, *J* 10.0, C*H*CH=CH), 3.21 (1H, br m, C*H*NH), 2.49 (2H, br m, CH_2CHN), 2.05 (2H, dm, *J* 14.0, CH_2), 1.78-1.20 (10H, m, 5 x CH_2) and 1.10 (21H, s, Si(^{i}Pr)$_3$); HRMS (ES) *m/z* calcd for $C_{28}H_{49}NOSi$ $(M+H)^+$: 442.3505, found: 442.3503; MS (CI) *m/z* 442 [$(M+H)^+$, 64%], 358 (32), 272 (31), 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:CH_2Cl_2) to furnish *(–)-HTX-285E* **4** (2.8 mg, 84%) as a colourless oil; R_f 0.57 (3:1 CH_2Cl_2:MeOH) [lit.[15] 0.52 (9:1:0.08 CH_3Cl:^{i}PrOH:aq. NH_3)]; $[\alpha]_D^{27}$ -23.8 (*c* 0.08 in $CHCl_3$); ν_{max}(thin film) 3350-2400, 3299, 2931, 2848, 2092, 1728, 1556, 1454, 1260, 1092, 1018, 912, 798 and 757 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 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*), 3.96 (1H, br m, C*H*OH), 3.71 (1H, br d, *J* 10.5, *H*-7), 3.22 (2H, br m, C*H*NH and *H*-20), 2.52 (2H, br m, 2 x *H*-12), 2.04 (1H, br m, C*H*), 1.79 (2H, br t, *J* 12.0, CH_2) and 1.69-1.20 (9H, m, 4 x CH_2 and C*H*); HRMS (ES) *m/z* calcd for $C_{19}H_{28}NO$ $(M+H)^+$: 286.2171, found: 286.2169; MS (CI) *m/z* 286 [$(M+H)^+$, 15%], 180 (87), 154 (100), 115 (82) and 98 (92).[12]

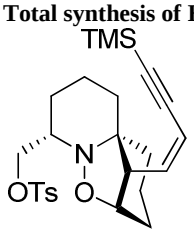


(–)-Histrionicotoxin 285E Hydrochloride.*

(–)-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_2Cl_2:MeOH); $[\alpha]_D^{27.5}$ -38.5 (*c* 0.18 in EtOH) [lit.[16] $[\alpha]_D^{25}$ -122 (*c* 1.0 in EtOH)]; δ_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, C*H*OH), 3.78 (2H, m, *H*-7 and *H*-20), 3.56-3.50 (1H, m, C*H*NH), 2.65 (1H, m, *H*-12), 2.50 (1H, m, *H*-12), 2.04-1.85 (3H, m, CH_2 and C*H*), 1.75-1.65 (6H, m, 3 x CH_2) and 1.42-1.26 (3H, m, CH_2 and C*H*); δ_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 $C_{19}H_{28}NO$ $(M\text{-}Cl)^+$: 286.2171, found: 286.2161; MS (ES) *m/z* 286 [$(M\text{-}Cl)^+$, 100%].[12]

Synthesis of the "unsymmetrical" histrionicotoxins

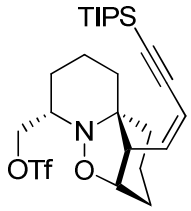
Total synthesis of HTX-285C



(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(*para*-Toluenesulfonyloxymethyl)-7-(4'-trimethylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 79.

The alcohol **71** (8.1 mg, 0.025 mmol) was dissolved in dry CH_2Cl_2 (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 CH_2Cl_2 (3 x 3 mL). The combined organic phases were washed with HCl (2.0 M aq.; 3 x 3 mL), dried ($MgSO_4$) 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; R_f 0.51 (1:1 hexane:EtOAc); $[\alpha]_D^{19}$ -23.6 (*c* 0.28 in $CHCl_3$); ν_{max} (thin film) 2939, 2147, 1598, 1448, 1360, 1250, 1177, 975, 950, 843 and 762 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 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, C*H*=CHC≡C), 5.72 (1H, d, *J* 11.0, CH=C*H*C≡C), 4.46 (1H, ddd, *J* 6.0, 5.0 and 0.0, C*H*O), 4.37 (1H, dd, *J* 9.0 and 3.0, C*H*HOTs), 3.86 (1H, dd, *J* 9.0 and 9.0, CH*H*OTs), 3.77 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.00 (1H, dddd, *J* 12.0, 9.0, 3.0 and 3.0, C*H*N), 2.44 (3H, s, CH_3), 1.95-1.77 (3H, m, CH_2 and C*H*), 1.65-1.25 (8H, m, 4 x CH_2), 1.15 (1H, ddt, *J* 13.5, 13.5 and 3.0, C*H*) and 0.21 (9H, s, Si(CH_3)$_3$); δ_C(125 MHz and DEPT; $CDCl_3$) 144.5, 138.4, 133.0, 129.7, 128.1, 113.5, 101.6, 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* calcd for $C_{25}H_{36}NO_4SiS$ $(M+H)^+$: 474.2134, found: 474.2134; MS (CI) *m/z* 474 [$(M+H)^+$, 100 %]. Further elution of the column furnished recovered alcohol 71 (2.8 mg, 35%).

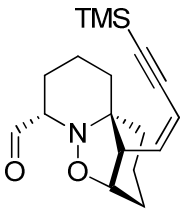


(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-(Trifluoromethanesulfonyloxymethyl)-7-(4'-triisopropyl silyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 80.

To a solution of the alcohol **75** (7.5 mg, 0.019 mmol) in CH_2Cl_2 (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 ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography to furnish the *triflate* **80** (6.5 mg, 69%) as a colourless oil; R_f 0.63 (1:1 hexane:EtOAc); δ_H (500 MHz; $CDCl_3$) 6.03 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.79 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.68 (1H, dd, *J* 10.5 and 3.0, C*H*HOTf), 4.55 (1H, ddd, *J* 6.0, 6.0 and 0.0, C*H*O), 4.27 (1H, dd, *J* 10.5 and 8.0, C*H*HOTf), 3.94 (1H, dd, *J* 10.0

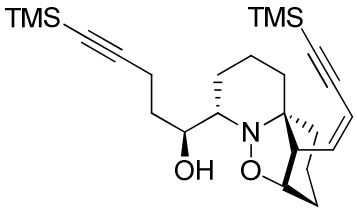
and 6.0, C*H*CH=CH), 3.09 (1H, dddd, *J* 11.5, 8.0, 4.0 and 4.0, C*H*N), 2.01-1.90 (1H, m, C*H*), 1.81 (1H, dm, *J* 14.0, C*H*), 1.63-1.20 (10H, m, 5 x CH_2) and 1.09 (21H, s, Si(^{i}Pr)$_3$); Further characterisation was not carried out owing to the failure of later reactions.

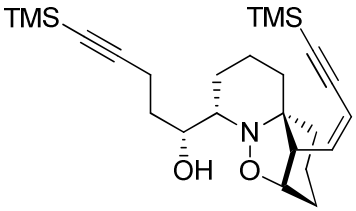


(2*S*, 6*R*, 7*S*, 8*S*)-(1'*Z*)-2-Formyl-7-(4'-trimethylsilyl-but-1'-en-3'-yn-1'-yl)-1-aza-12-oxa tricyclo[5.4.1^{6,8}.0]undecane, 86.

The alcohol **71** (4.3 mg, 0.014 mmol) was dissolved in anhydrous DMSO (2 mL) and IBX[110] (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 ($MgSO_4$). 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; R_f 0.41 (1:1 hexane:ether); $[\alpha]_D^{23}$ -28.9 (*c* 0.37 in $CHCl_3$); ν_{max}(thin film) 2940, 2869, 2149, 1733, 1447, 1250, 1007, 918 and 844 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 9.78 (1H, d, *J* 2.5, C*H*O), 6.04 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.75 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.58 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.80 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.33 (1H, ddd, *J* 12.5, 2.5 and 2.5, C*H*N), 2.12-2.02 (1H, m, C*H*), 1.87 (1H, dm, *J* 14.0, C*H*), 1.82 (1H, dm, *J* 13.5, C*H*), 1.75-1.53 (6H, m, 3 x CH_2), 1.48-1.38 (3H, m, CH_2 and C*H*) and 0.20 (9H, s, Si(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 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 $C_{18}H_{28}NO_2Si$ (M+H)$^+$: 318.1889, found: 318.1893; MS (CI) *m/z* 318 [(M+H)$^+$, 100%], 222 (12), 98 (21) and 90 (68).





(2*S*, 6*R*, 7*S*, 8*S*, 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[5.4.1^{6,8}.0]undecane, 87 (*S*).*

and

(2*S*, 6*R*, 7*S*, 8*S*, 1'*R*)-(1"*Z*)-2-(5'-Trimethylsilyl-1'-hydroxypent-4'-ynyl)-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 88 (*R*).*

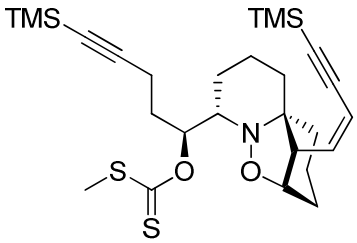
Magnesium turnings (11.3 mg, 0.47 mmol, 15 eq) were placed in a two-necked round-bottomed flask equipped with a reflux condenser and a suba seal. The flask was evacuated and refilled with nitrogen (3 cycles) before being charged with THF (0.5 mL). Dibromoethane (1 drop) was added and the reaction mixture 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

added dropwise *via* cannula over a period of 0.25 h followed by stirring at 40 °C for 0.5H, 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, ≈2.5 eq) was added dropwise *via* cannula to a solution of the aldehyde **86** (10.0 mg, 0.031 mmol) in THF (1.0 mL) and the reaction vessel was stirred at 25 °C for 5 minutes. The reaction mixture was quenched by the addition of NH_4Cl (2 mL) and extracted into EtOAc (3 x 4 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified *via* flash column chromatography (3:1 hexane:ether; 1% NEt_3) to yield the *alcohol* **87 (*S*)** (8.4 mg, 60%) as a colourless oil; R_f 0.45 (1:1 hexane:ether); $[\alpha]_D^{19}$ +8.4 (*c* 0.28 in $CHCl_3$); ν_{max} (thin film) 3423, 2954, 2860, 2173, 1448, 1249, 1081, 1009, 842 and 759 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.03 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.73 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.53 (1H, dd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.82 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.77 (1H, br d, *J* 4.0, O*H*), 3.67 (1H, dddd, *J* 4.0, 4.0, 4.0 and 0.0, C*H*OH), 2.82 (1H, ddd, *J* 12.5, 4.0 and 4.0, C*H*N), 2.41 (2H, m, CH_2), 1.82-1.46 (10H, m, 5 x CH_2), 1.38-1.30 (3H, m, CH_2 and C*H*), 0.21 (9H, s, Si(CH_3)$_3$) and 0.14 (9H, s, Si(CH_3)$_3$); δ_C (63 MHz, APT; $CDCl_3$) 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 (ES) *m/z* calcd for $C_{25}H_{42}NO_2Si_2$ $(M+H)^+$: 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).[12]

Further elution of the column yielded the diastereomeric *alcohol* **88 (*R*)** (4.6 mg, 33%) also as a colourless oil; R_f 0.23 (1:1 hexane:ether); $[\alpha]_D^{20}$ +7.5 (*c* 0.22 in $CHCl_3$); ν_{max} (thin film) 3469, 2954, 2860, 2174, 2170, 1449, 1249, 1089, 842 and 758 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.05 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.73 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.50 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.95 (1H, ddd, *J* 9.5, 5.0 and 2.5, C*H*OH), 3.83 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.31 (1H, d, *J* 1.5, O*H*), 2.80 (1H, ddd, *J* 12.0, 2.5 and 2.5, C*H*N), 2.53 (1H, ddd, *J* 17.0, 9.5 and 5.0, C*H*), 2.35 (1H, m, C*H*), 2.01-1.94 (1H, m, C*H*), 1.84-1.25 (13H, m, 6 x CH_2 and C*H*), 0.21 (9H, s, Si(CH_3)$_3$) and 0.15 (9H, s, Si(CH_3)$_3$); δ_C(100 MHz; $CDCl_3$) 138.8, 113.4, 107.6, 101.8, 100.1, 84.2, 77.6, 70.0, 67.7, 65.7, 46.9, 34.7, 32.1, 31.7, 25.3, 23.6, 19.2, 17.9, 17.3, 0.2 and -0.1; HRMS (ES) *m/z* calcd for $C_{25}H_{42}NO_2Si_2$ $(M+H)^+$: 444.2754, found: 444.2754; MS (CI) *m/z* 444 [$(M+H)^+$, 33%], 290 (52), 222 (24), 172 (80), 155 (72) and 90 (100).[12]

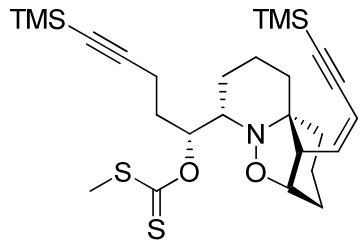
The assignment of the stereochemistry of the 1'-hydroxy functionality is tentative and based on observed coupling constants in the ^1H NMR spectra.



(2*S*, 6*R*, 7*S*, 8*S*, 1'*S*)-(1"*Z*)-2-[5'-Trimethylsilylpent-4'-yn-1'-(*S*-methyldithio carboxy)]-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.0] undecane, 89 (*S*).

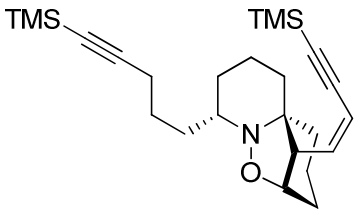
To a solution of the alcohol **87 *S*** (5.8 mg, 0.045 mmol) in THF (1.5 mL) cooled to 0 °C was added NaH (60% dispersion in mineral oil; 5.3 mg, 0.13 mmol, 10 eq). The reaction mixture was allowed to warm to 25 °C and stirred for 1.5 h. CS_2 (8.6 µL, 0.14 mmol, 11 eq) was added dropwise and the reaction 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.

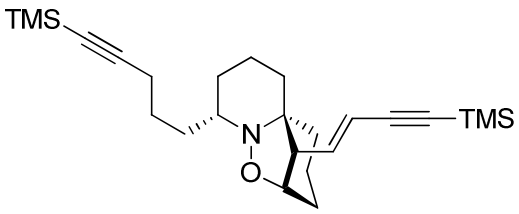
The reaction was quenched by the addition of water (2 mL) and extracted with EtOAc (3 x 4 mL). The combined organic phases were washed with water (3 x 4 mL) followed by brine (3 x 4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purication of the crude residue by flash column chromatography (4:1 hexane:ether; 1% NEt_3) yielded the *xanthate* **88** ***S*** (5.8 mg, 83%) as a colourless oil; R_f 0.55 (4:1 hexane:ether); $[\alpha]_D^{19}$ -48.3 (*c* 0.21 in $CHCl_3$); ν_{max} (thin film) 2954, 2868, 2176, 2150, 1448, 1249, 1217, 1193, 1063, 1011, 842 and 759 cm^{-1}; δ_H(500 MHz; $CDCl_3$) 6.14 (1H, ddd, *J* 10.0, 3.0 and 3.0, C*H*OCSSMe), 6.06 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.69 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.52 (1H, ddd, *J* 6.0, 5.5 and 0.0, C*H*O), 3.86 (1H, dd, *J* 10.0 and 6.0, C*H*CH=CH), 3.24 (1H, ddd, *J* 12.5, 3.0 and 3.0, C*H*N), 2.53 (3H, s, SCH_3), 2.43-2.35 (3H, m, CH_2 and C*H*), 2.04-1.88 (2H, m, CH_2), 1.79 (1H, dm, *J* 12.0, C*H*), 1.69 (1H, dm, *J* 13.5, C*H*), 1.62-1.25 (9H, m, 4 x CH_2 and C*H*), 0.17 (9H, s, Si(CH_3)$_3$) and 0.15 (9H, s, Si(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 215.1, 139.3, 113.3, 107.0, 101.9, 100.0, 84.5, 83.3, 77.2, 66.1, 64.6, 46.5, 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* calcd for $C_{27}H_{44}NO_2S_2Si_2$ $(M+H)^+$: 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).



(2*S*, 6*R*, 7*S*, 8*S*, 1'*R*)-(1"*Z*)-2-[5'-Trimethylsilylpent-4'-yn-1'-(*S*-methyldithio carboxy)]-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.0] undecane.

Procedure as for (2*S*, 6*R*, 7*S*, 8*S*, 1'*S*)-(1"*Z*)-2-[5'-trimethylsilylpent-4'-yn-1'-(*S*-methyldithiocarboxy)]-7-(4"-trimethylsilyl-but-1"-en-3"-yn-'1-yl)-1-aza-12-oxatricyclo [5.4.1^{6,8}.0] undecane **89** (66%)*;* R_f 0.62 (1:1 hexane:ether); $[\alpha]_D^{22}$ 0.0 (*c* 0.14 in $CHCl_3$); ν_{max} (thin film) 2924, 2863, 2176, 2150, 1458, 1249, 1217, 1055, 842 and 759 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 6.05 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.91 (1H, dm, *J* 7.0, C*H*OCSSMe), 5.70 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.48 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.75 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 3.12 (1H, dm, *J* 12.0, C*H*N), 2.56 (3H, s, SCH_3), 2.44-2.22 (3H, m, CH_2 and C*H*), 1.97 (2H, m, CH_2), 1.82 (2H, tm, *J* 17.0, CH_2), 1.68-0.81 (9H, m, 4 x CH_2 and C*H*), 0.21 (9H, s, Si(CH_3)$_3$) and 0.14 (9H, s, Si(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 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* calcd for $C_{27}H_{44}NO_2S_2Si_2$ $(M+H)^+$: 534.2352, found: 534.2349; MS (CI) *m/z* 534 [$(M+H)^+$, 100%] and 428 (60).





(2*S*, 6*R*, 7*S*, 8*S*)-(1"*Z*)-2-(5'-Trimethylsilylpent-4'-ynl)-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane, 90.

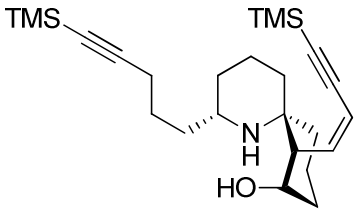
and

(2*S*, 6*R*, 7*S*, 8*S*)-(1"*E*)-2-(5'-Trimethylsilylpent-4'-ynl)-7-(4''-trimethylsilyl-but-1''-en-3''-yn-1''-yl)-1-aza-12-oxatricyclo[5.4.1^{6,8}.0]undecane.

The xanthate **88 (*S*)** (3.2 mg, 5.9 µmol) was dissolved in dry toluene (1 mL) under nitrogen and AIBN (0.5 mg, cat) was added, followed by Bu_3SnH (8.1 µL, 0.03 mmol, 5 eq) and the mixture was then stirred at 110 °C for 10 minutes.

The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (9:1 hexane:ether; 1% NEt_3) to yield the *(Z)-isomeric isoxazolidine* **89** (1.5 mg, 57%) as a colourless oil; R_f 0.20 (4:1 hexane:ether); $[\alpha]_D^{15}$ -15.3 (*c* 0.15 in $CHCl_3$); ν_{max}(thin film) 2929, 2853, 2174, 2150, 1458, 1249, 1081, 1012, 842 and 782 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 6.07 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.71 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.49 (1H, ddd, *J* 6.5, 5.5 and 0.0, C*H*O), 3.89 (1H, dd, *J* 10.0 and 6.5, C*H*CH=CH), 2.71 (1H, m, C*H*N), 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, C*H*), 0.92 (1H, m, C*H*), 0.21 (9H, s, Si(CH_3)$_3$) and 0.14 (9H, s, Si(CH_3)$_3$); δ_C (125 MHz; $CDCl_3$) 139.5, 113.0, 107.7, 101.9, 99.8, 84.1, 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 (ES) *m/z* calcd for $C_{25}H_{42}NOSi_2$ $(M+H)^+$: 428.2805, found: 428.2807; MS (CI) *m/z* 428 [$(M+H)^+$, 63%], 222 (23), 98 (40), 90 (100) and 72 (35).

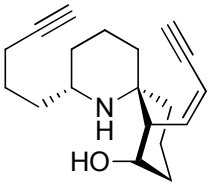
Further elution of the column furnished *(E)-isomeric isoxazolidine* (0.9 mg, 37%) also as a colourless oil; R_f 0.27 (4:1 hexane:ether); $[\alpha]_D^{23}$ -127.9 (*c* 0.28 in $CHCl_3$); ν_{max} (thin film) 2933, 2865, 2173, 1458, 1249, 1056, 957, 842 and 759 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.29 (1H, dd, *J* 15.5 and 9.5, C*H*=CHC≡C), 5.65 (1H, d, *J* 15.5, CH=C*H*C≡C), 4.40 (1H, m, C*H*O), 3.15 (1H, dd, *J* 9.5 and 6.5, C*H*CH=CH), 2.63 (1H, dddd, *J* 11.5, 8.0, 3.5 and 3.5, C*H*N), 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 C*H*), 1.13 (1H, ddt, *J* 12.5, 12.5 and 2.5, C*H*), 0.20 (9H, s, Si(CH_3)$_3$) and 0.14 (9H, s, Si(CH_3)$_3$); δ_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 (ES) *m/z* calcd for $C_{25}H_{42}NOSi_2$ $(M+H)^+$: 428.2805, found: 428.2796; MS (CI) *m/z* 428 [$(M+H)^+$, 43%] and 90 (100).



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

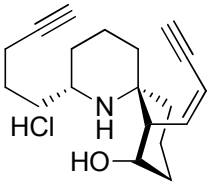
The isoxazolidine **89** (5.6 mg, 0.013 mmol) was dissolved in acetic acid (3 mL) and activated zinc dust (9 mg) was added in one portion with rapid stirring. After 0.5H, the reaction was quenched by the addition of an aqueous solution of sodium acetate (satd; 3 mL) and EtOAc (3 mL) and it was then stirred 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 ($MgSO_4$), concentrated *in vacuo* and azeotroped in toluene. Purification of the crude residue *via* flash column chromatography (93:7 CH_2Cl_2:MeOH) furnished *16,20-bis-(trimethylsilyl)histrionicotoxin 285C* (5.5 mg, 97%) as a colourless oil; R_f 0.09 (9:1 CH_2Cl_2:MeOH); $[\alpha]_D^{23}$ -8.5 (*c* 0.14 in $CHCl_3$); ν_{max} (thin film) 3062, 2954, 2648, 2173, 2150, 1552, 1451, 1250, 843 and 757 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 5.74 (1H, dd, *J* 10.5 and 10.0, C*H*=CHC≡C), 5.68 (1H, d, *J* 10.5, CH=C*H*C≡C), 4.09 (1H, br m, C*H*OH), 3.79 (1H, br d, *J* 10.0, C*H*CH=CH), 3.28 (1H, br m, C*H*NH), 2.35-2.22 (1H, m, C*H*), 2.28 (2H, dt, *J* 7.5 and 7.5, CH_2), 2.11 (1H, m, C*H*), 2.02-1.40 (14H, m, 7 x CH_2), 0.23 (9H, s, Si(CH_3)$_3$) and 0.14 (9H, s, Si(CH_3)$_3$); δ_C (63 MHz; $CDCl_3$) 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, 24.7, 19.4, 18.5, 14.9, 0.2 and -0.1; HRMS (ES) *m/z* calcd for $C_{25}H_{44}NOSi_2$ $(M+H)^+$: 430.2961, found: 430.2955; MS (CI) *m/z* 430 [$(M+H)^+$, 80%], 96 (18) and 90 (100).



(–)-Histrionicotoxin 285C, 3. *

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 ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue *via* flash column chromatography (1:9 MeOH:CH_2Cl_2) yielded *(–)-HTX-285C* **3** as a colourless oil (2.9 mg, 88%); R_f 0.18 (9:1 CH_2Cl_2:MeOH); $[\alpha]_D^{18}$ -43.3 (*c* 0.12 in $CHCl_3$); ν_{max}(thin film) 3301, 3218, 2935, 2125, 2092, 1665, 1553, 1452, 1261, 1097 and 961 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 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, C*H*OH), 3.71 (1H, d, *J* 10.0, C*H*CH=CH), 3.21 (1H, s, *H*-20), 3.17 (1H, br m, C*H*NH), 2.24 (2H, br m, CH_2), 2.08 (1H, br m, C*H*), 1.96 (1H, s, *H*-16) and 1.82-1.13 (15H, m, 7 x CH_2 and C*H*); HRMS (ES) *m/z* calcd for $C_{19}H_{28}NO$ $(M+H)^+$: 286.2171, found: 286.2180; MS (CI) *m/z* 286 [$(M+H)^+$, 100%] and 52 (67). [12]



(–)-Histrionicotoxin 285C Hydrochloride.

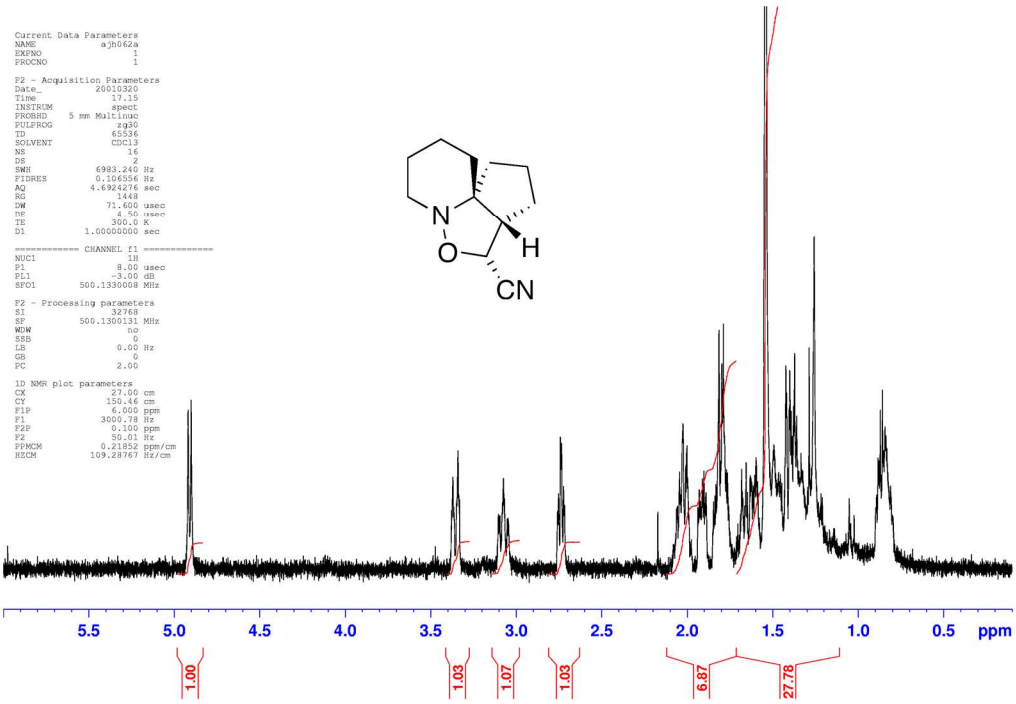
(–)-Histrionicotoxin 285C **3** (2.5 mg, 0.009 mmol) was dissolved in dry methanol (1 mL) and methanolic HCl (0.3 M; 44 µL, ≈1.5 eq) was added. After stirring for 0.5H, the solvent was removed *in vacuo* furnishing *(–)-HTX-285C hydrochloride* as a colourless oil which slowly crystallised on standing at -20 °C (2.5 mg, 88%); mp 244.5-246.5 °C (lit.[17] 247-250 °C); R_f 0.15 (9:1 CH_2Cl_2:MeOH); $[\alpha]_D^{19}$ -44.6 (*c* 0.12 in EtOH) {lit.[17] $[\alpha]_D^{25}$ -43.4 (*c* 1.18 in EtOH)}; δ_H (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, C*H*OH), 3.79 (1H, m, *H*-7), 3.79 (1H, d, *J* 2.0, *H*-20), 3.63 (2H, m, NH_2), 3.54-3.45 (1H, m, C*H*NH), 2.30-2.27 (3H, m, CH_2 and *H*-

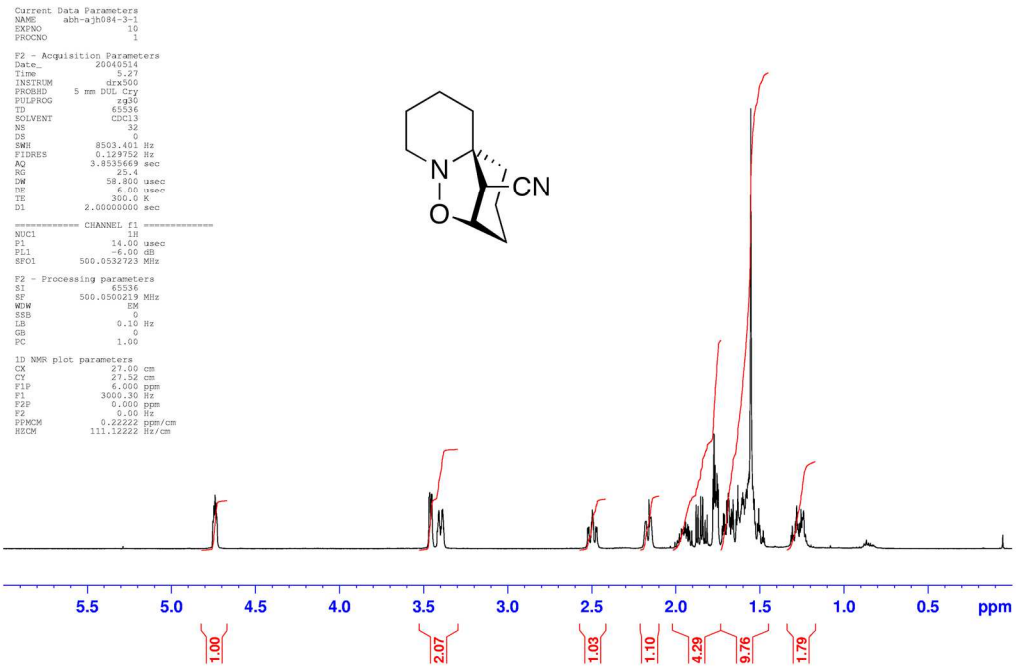
16), 2.05-1.94 (3H, m, C*H*$_2$ and C*H*), 1.81-1.62 (9H, m, 4 x C*H*$_2$ and C*H*) and 1.35-1.26 (4H, m, 2 x C*H*$_2$); δ_C (100 MHz; MeOD) 137.9, 112.7, 84.5, 82.5, 78.6, 72.2, 69.1, 60.8, 60.0, 52.3, 40.8, 33.8, 32.8, 32.3, 28.1, 26.9, 23.8, 17.4 and 14.0; HRMS (ES) *m/z* calcd for $C_{19}H_{28}NO$ $(M\text{-}Cl)^+$: 286.2171, found: 286.2169; MS (CI) *m/z* 286 [$(M\text{-}Cl)^+$, 100%], and 268 (33). [12]

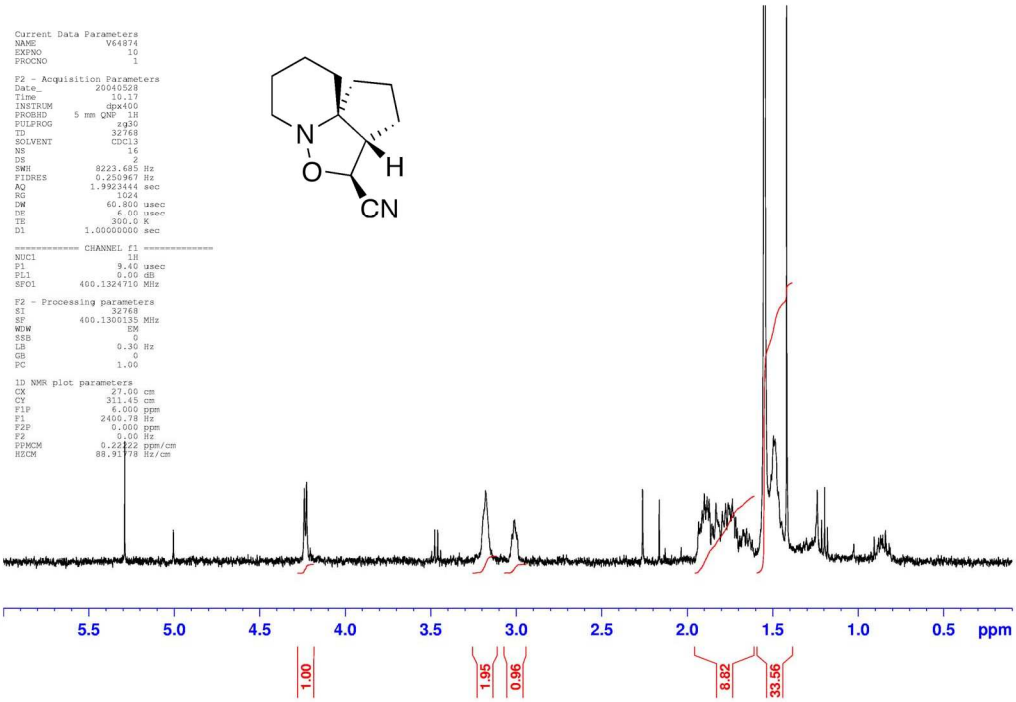
† These experimental procedures were previously published in the following paper: E. C. Davison, M. E. Fox, A. B. Holmes, S. D. Roughley, C. J. Smith, G. R. M. Williams, J. E. Davies, P. R. Raithby, J. P. Adams, I. T. Forbes, N. J. Press and M. J. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1494-1514.

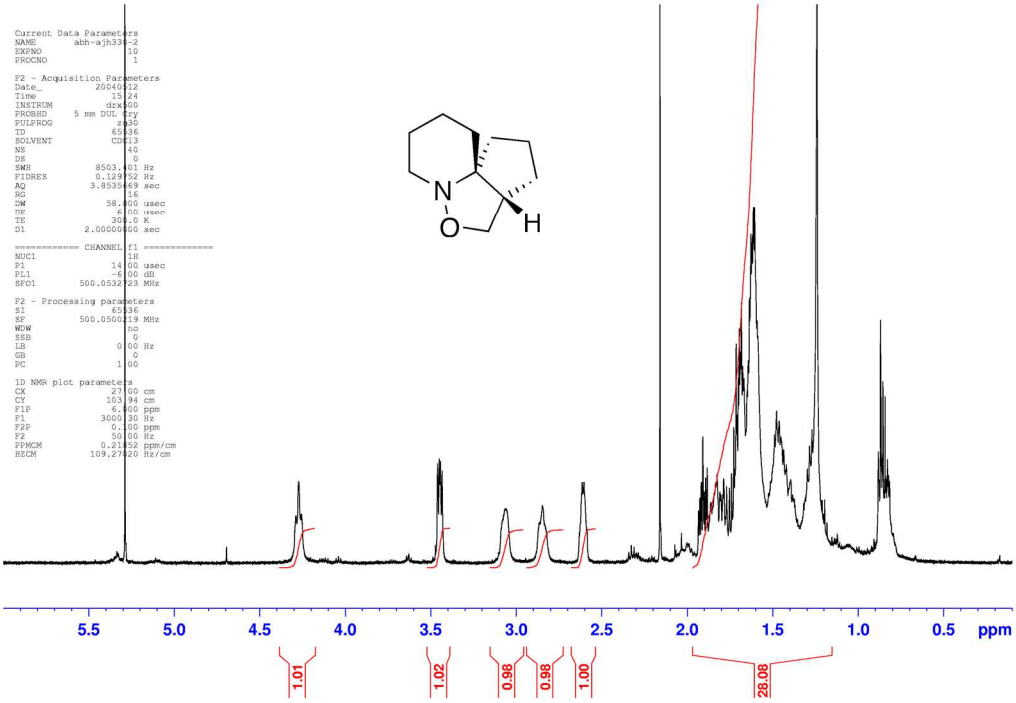
*These experimental procedures were previously published in the Electronic Supplementary Information for the following paper: C. J. Smith, A. B. Holmes and N. J. Press, *Chem. Commun.*, 2002, 1214-1215.

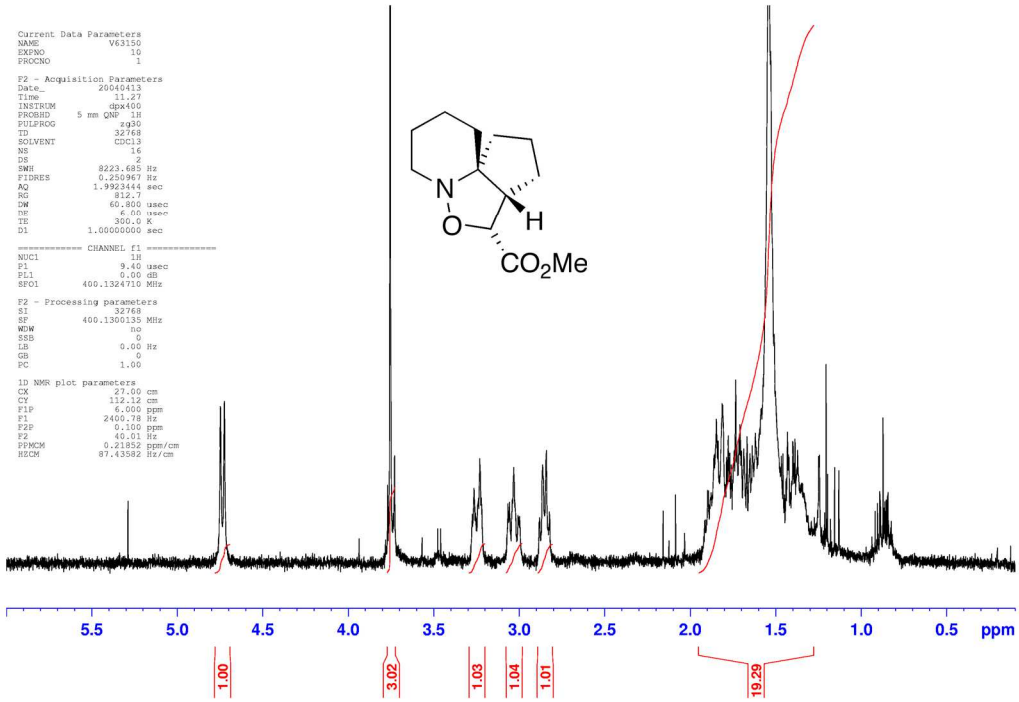
NMR DATA





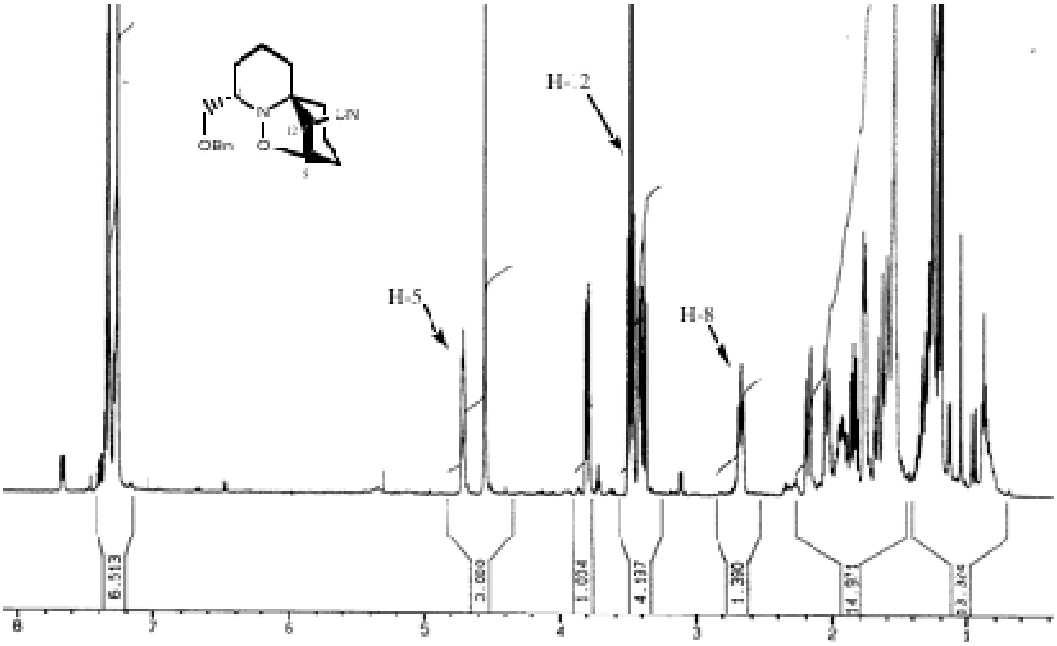




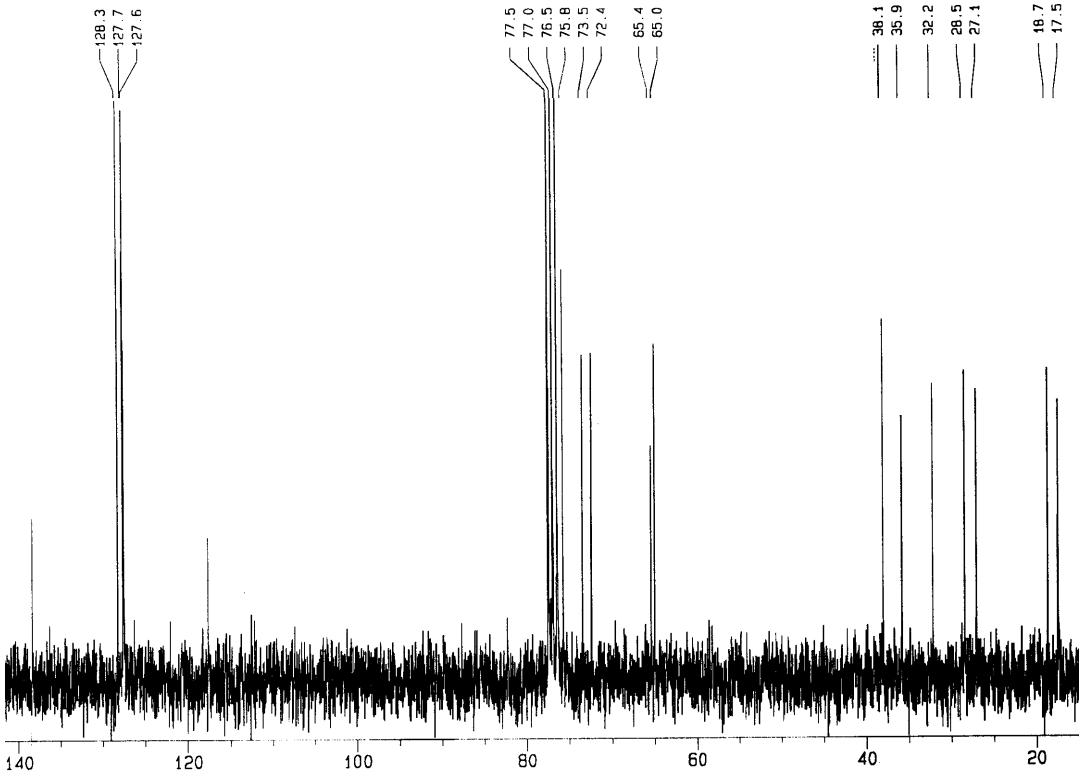


(1*R*,5*S*,8*S*,12*R*)-8-(Benzyloxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 13

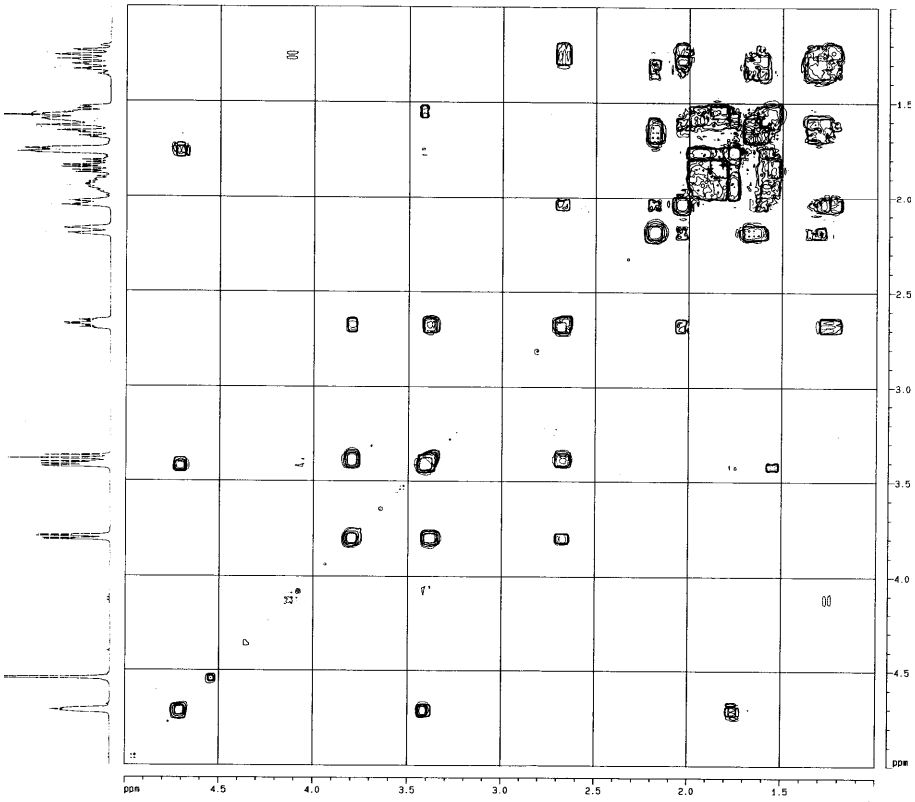
^{1}H NMR (250 MHz; $CDCl_3$)



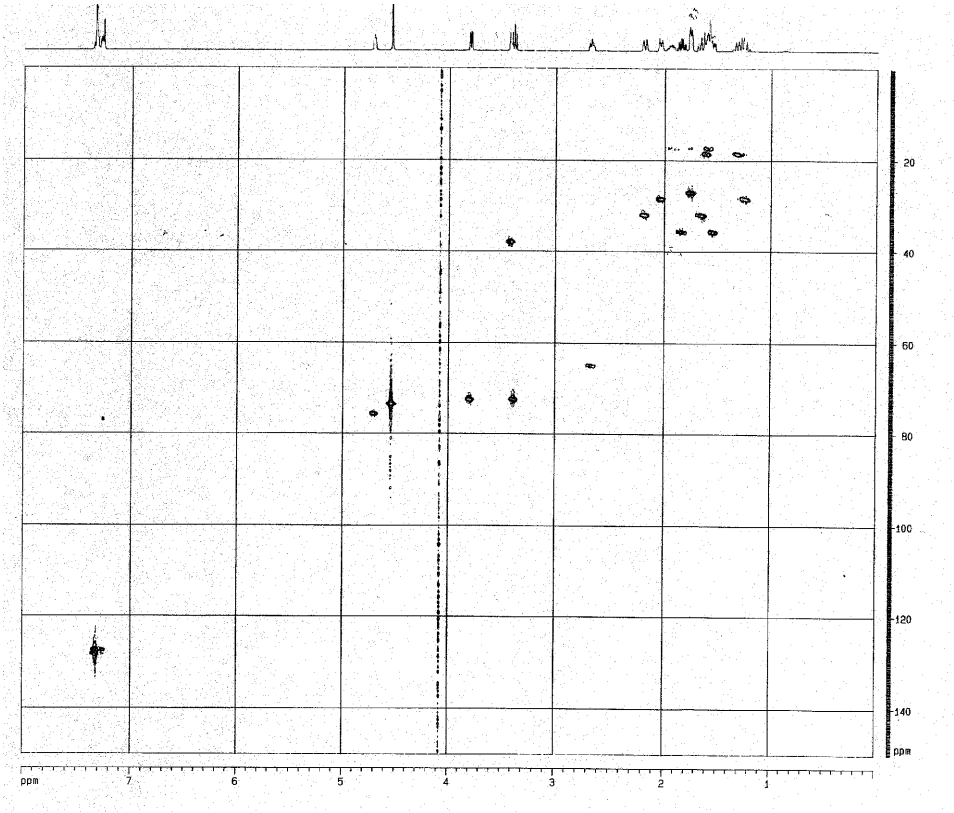
^{13}C NMR (62.5 MHz; $CDCl_3$)



COSY (500 MHz; $CDCl_3$)

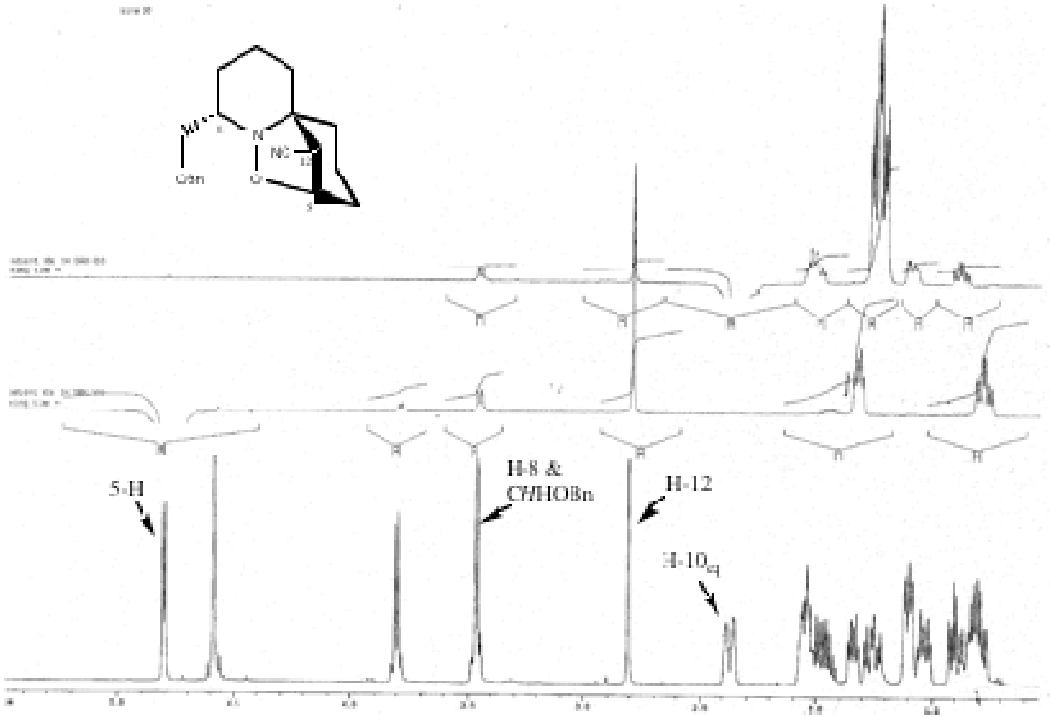


HMQC (500 MHz; $CDCl_3$)

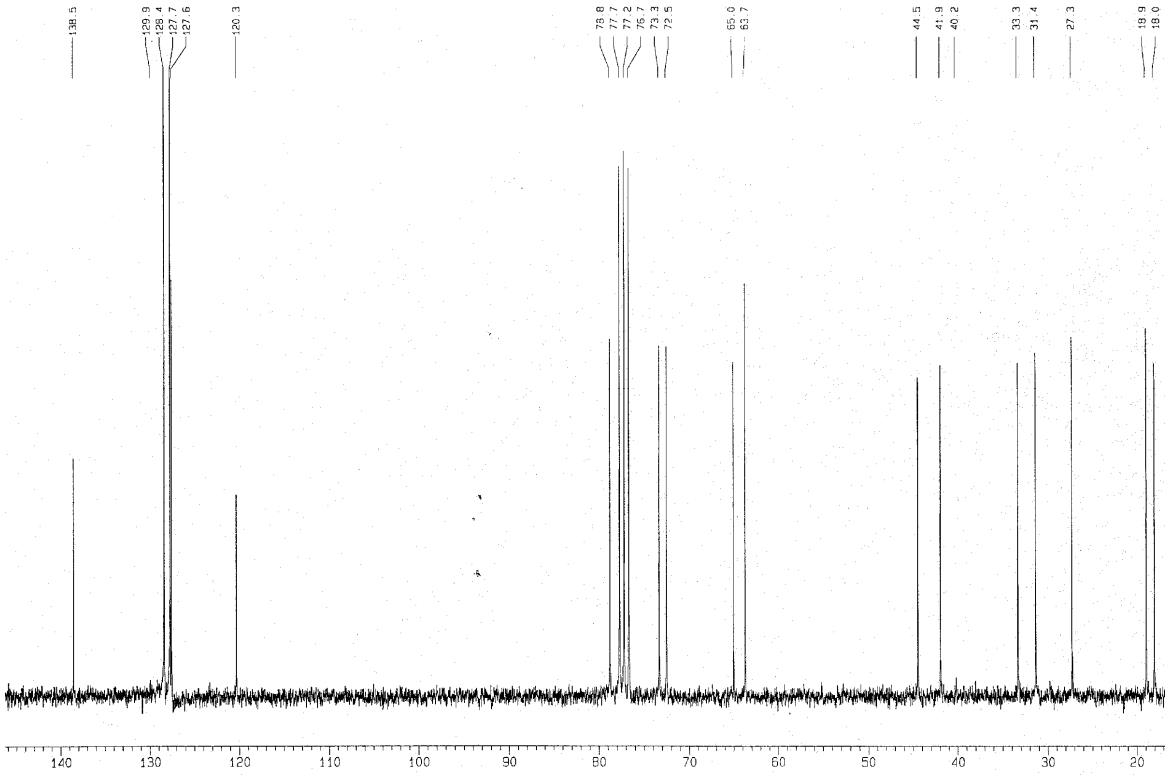


(1*R*,5*S*,8*S*,12*S*)-8-(Benzyloxymethyl)-12-cyano-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 54

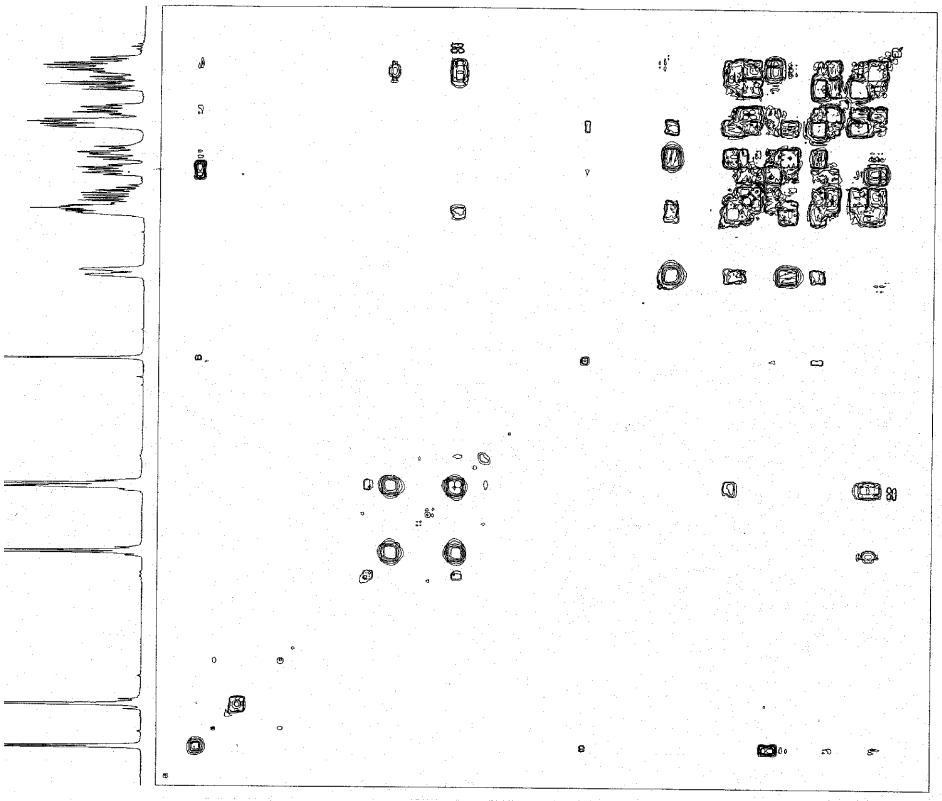
^{1}H NMR & NOEs (500 MHz; $CDCl_3$)



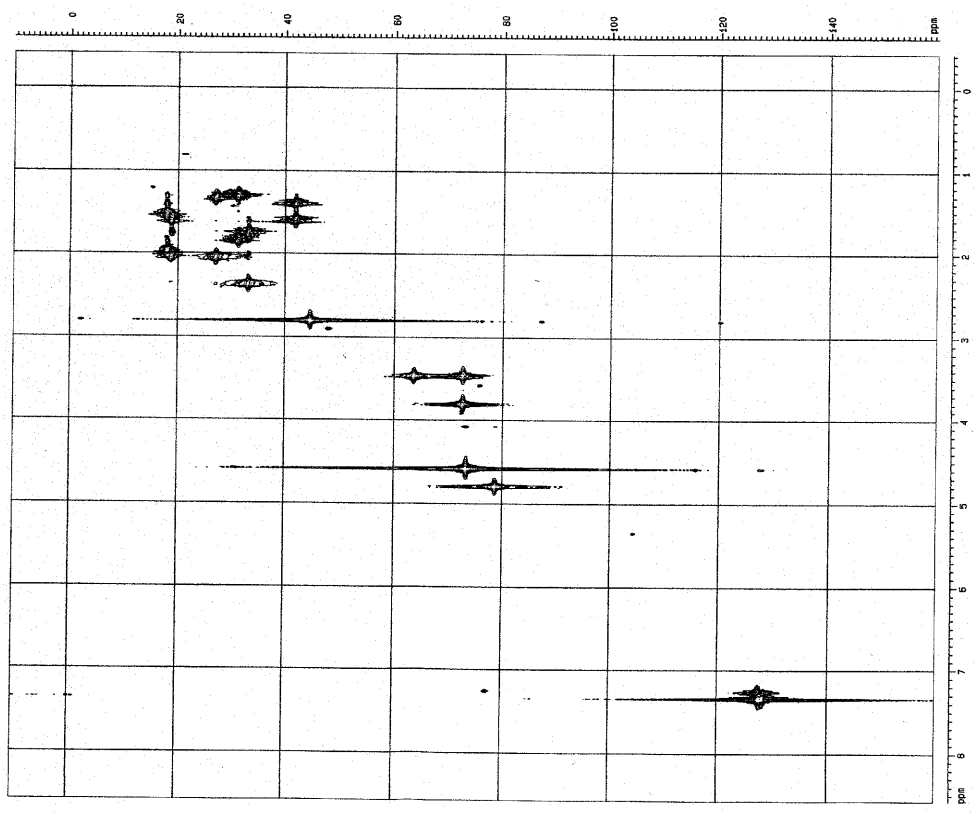
^{13}C NMR (62.5 MHz; CDCl3)



COSY (500 MHZ; $CDCl_3$)

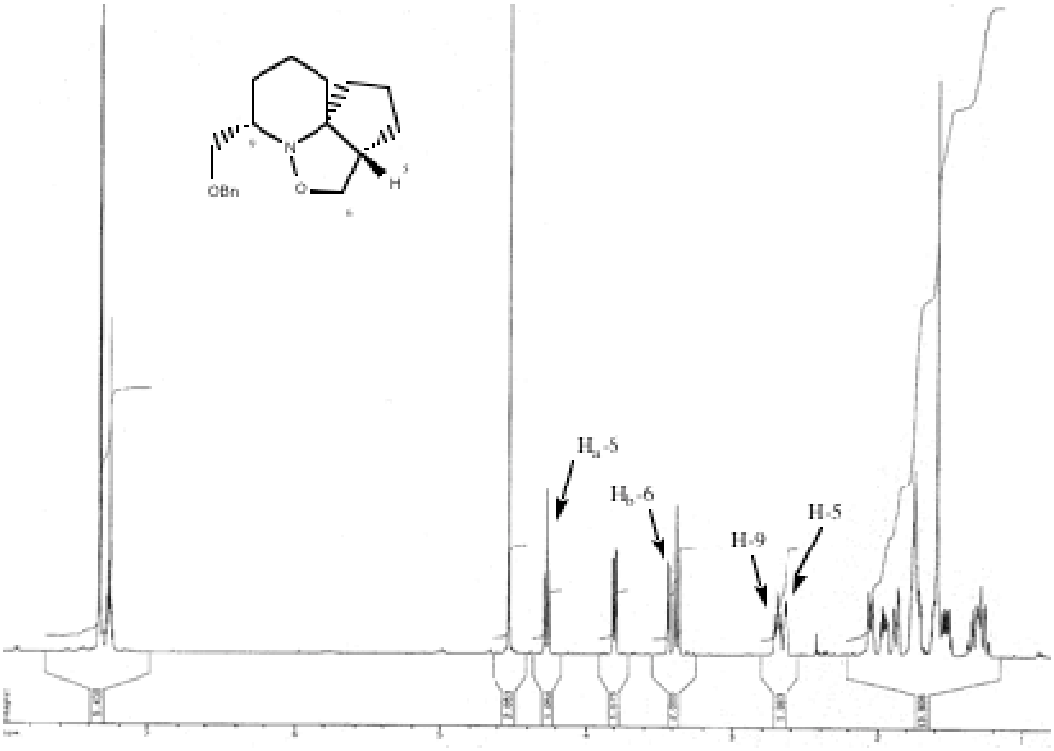


HMQC (500 MHz; $CDCl_3$)

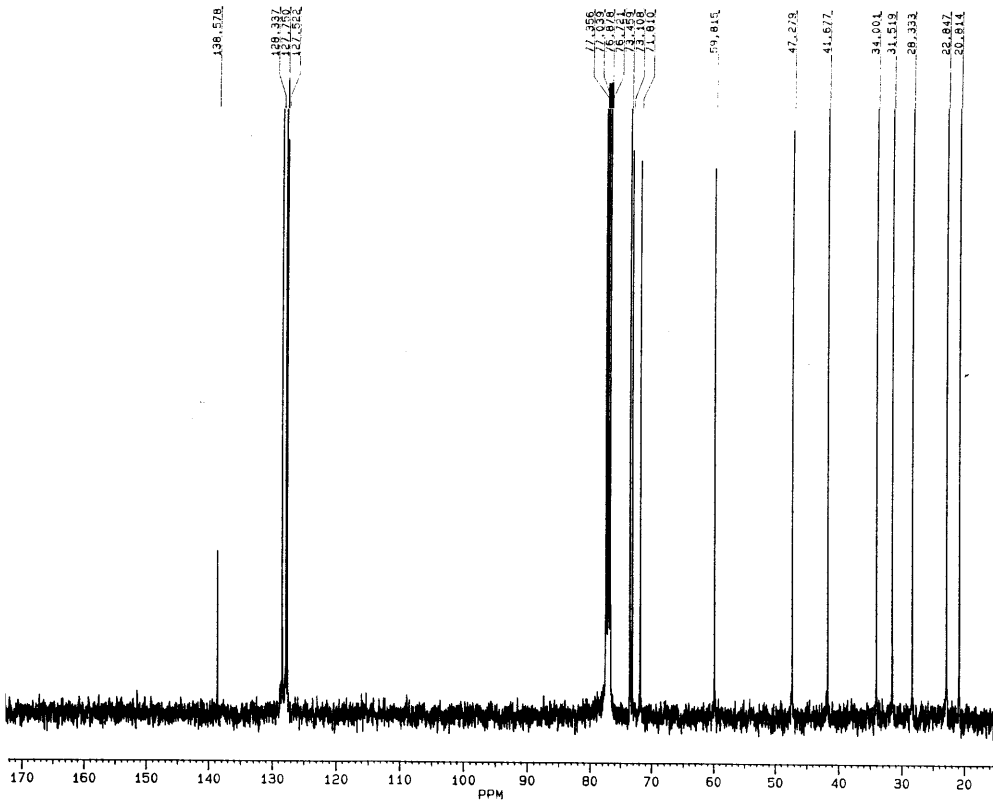


(1*S*,5*S*,9*S*)-9-Benzyloxymethyl-8-aza-7-oxatricyclo[6.4.1.0^{1,5}]undecane 49

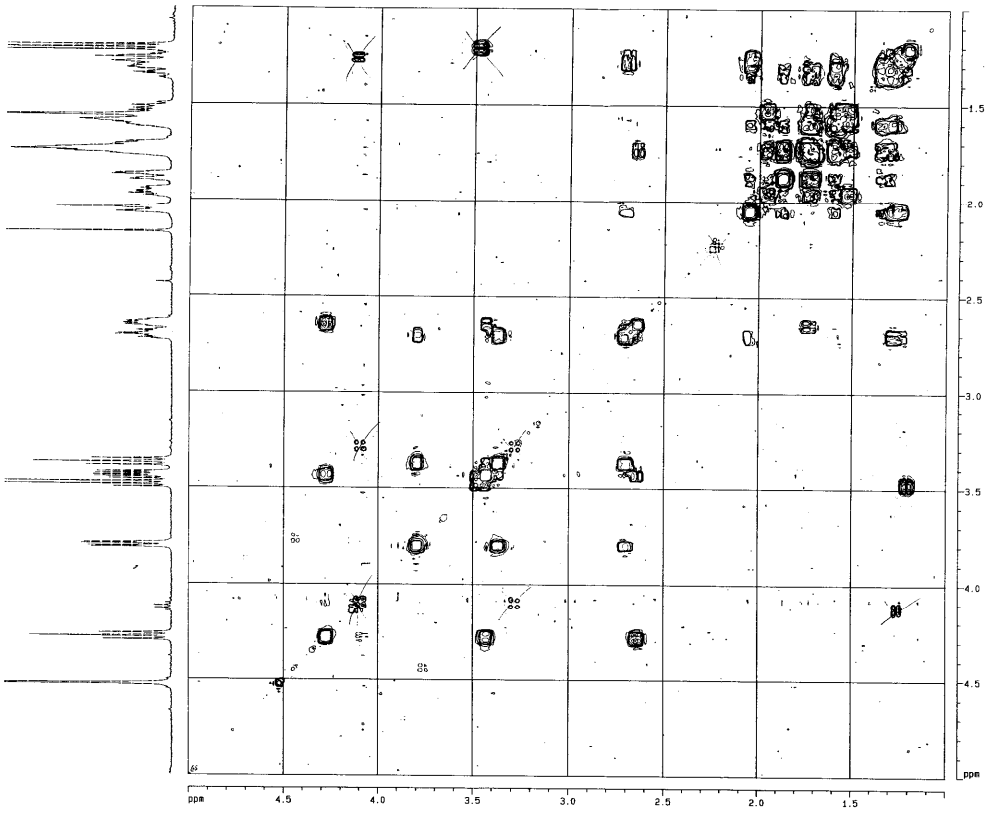
^{1}H NMR (500 MHz; $CDCl_3$)



^{13}C NMR (62.5 MHz; CDCl3)

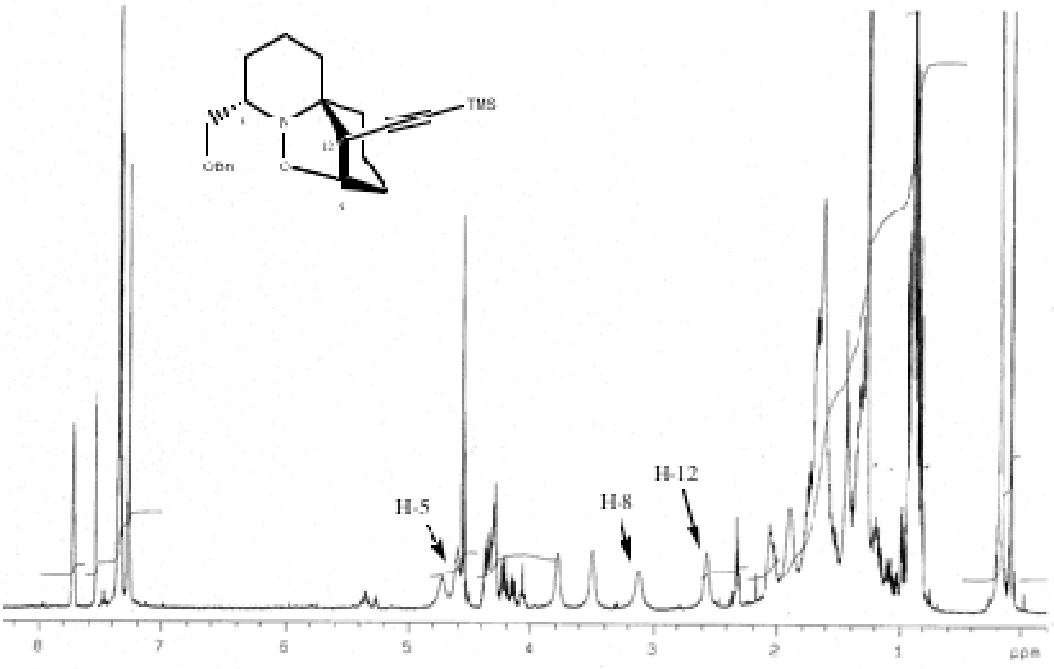


COSY (500 MHZ; $CDCl_3$)

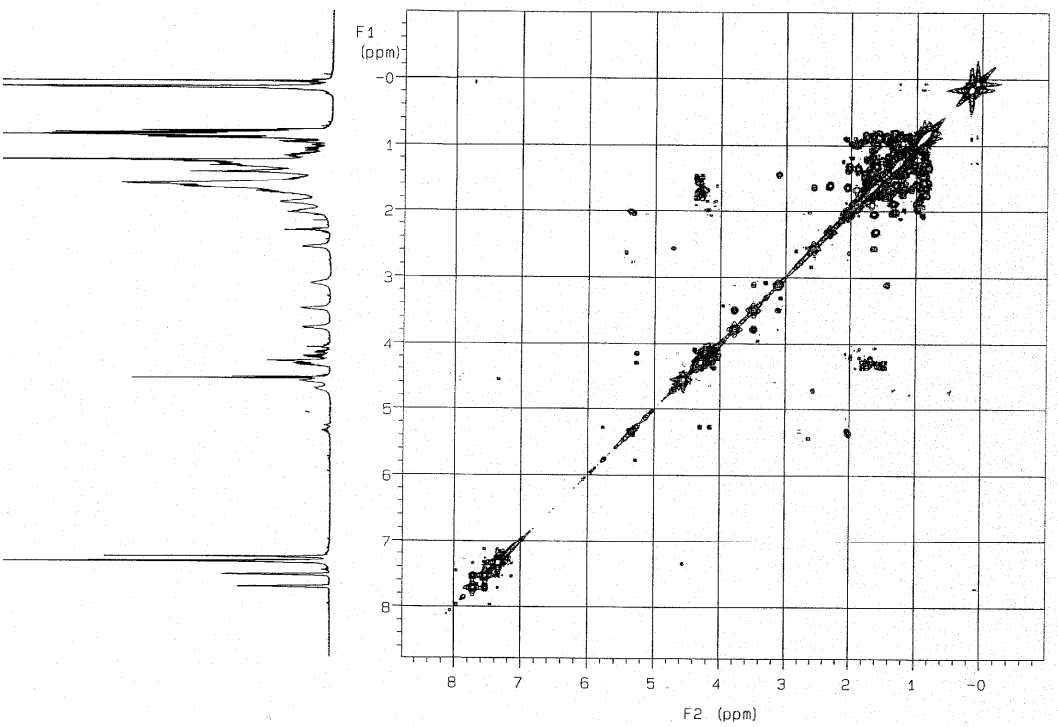


(1*R*,5*S*,8*S*,12*S*)-8-(Benzyloxymethyl)-12-(trimethylsilylethynyl)-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 52

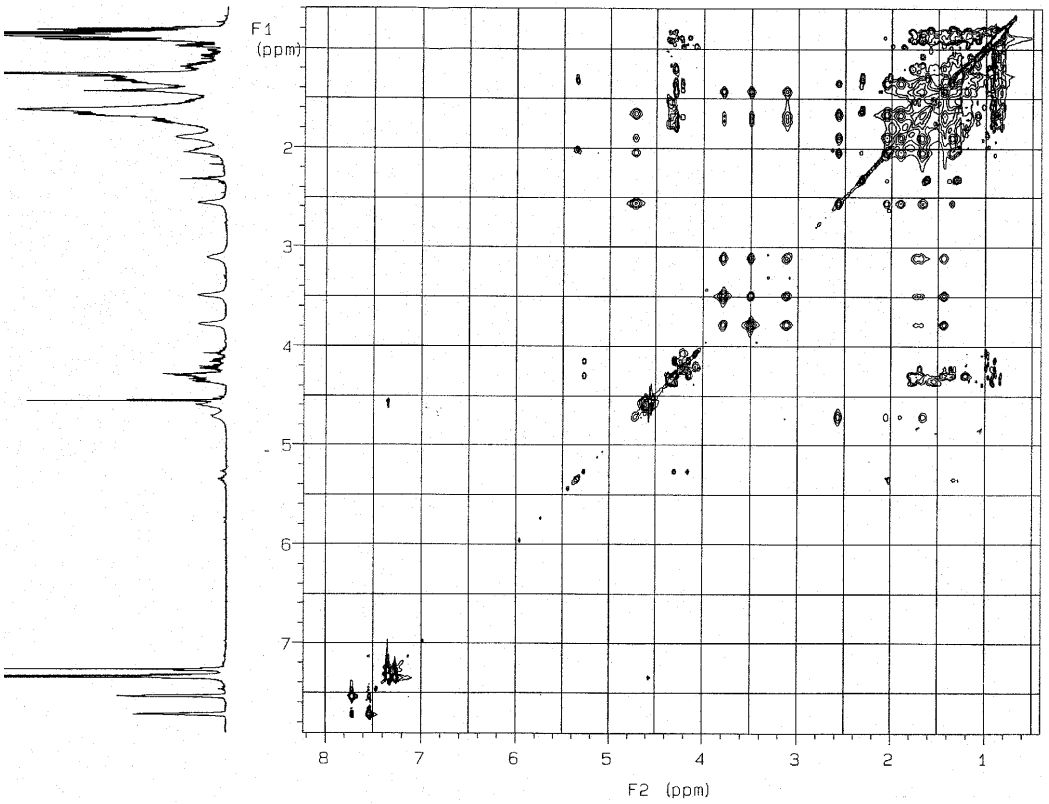
^{1}H NMR (500 MHz; CDCl3)



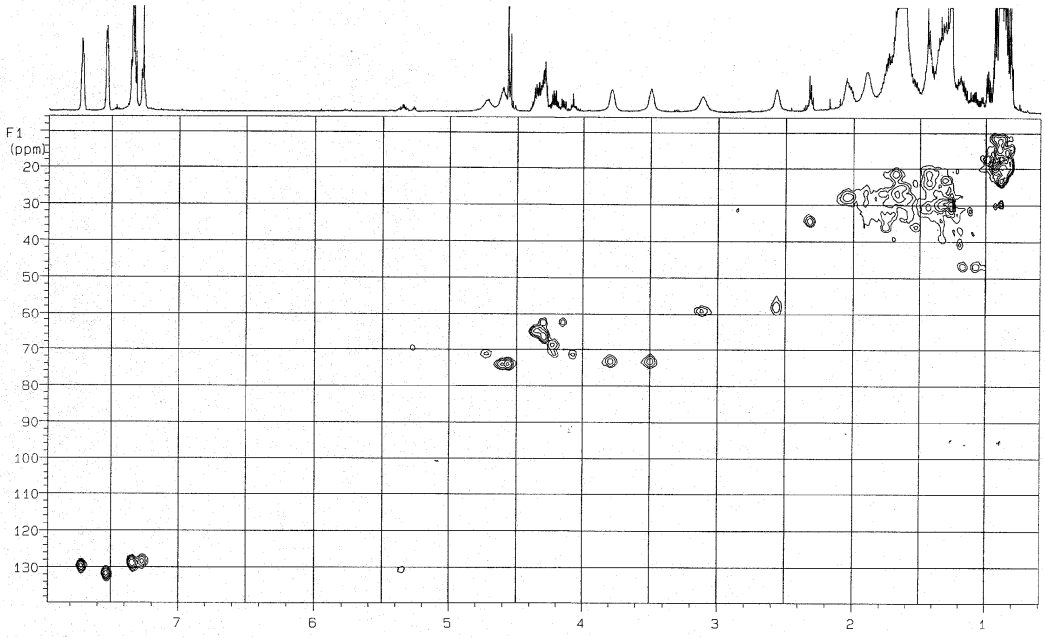
COSY (600 MHz; $CDCl_3$)



TOCSY (600 MHz; $CDCl_3$

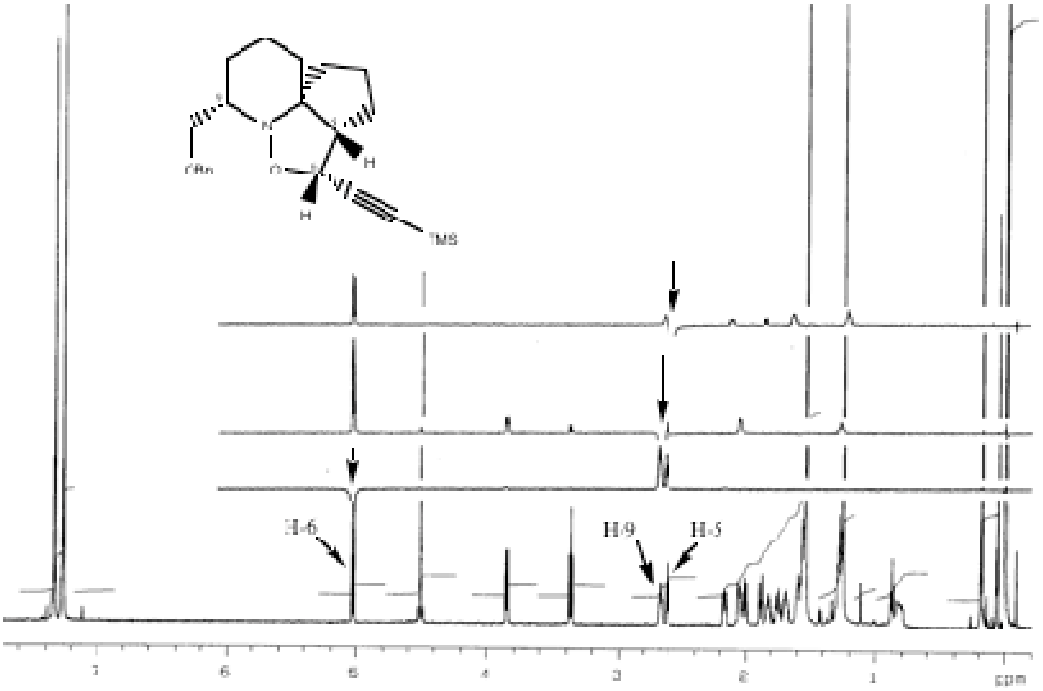


HMQC (600 MHz; $CDCl_3$)

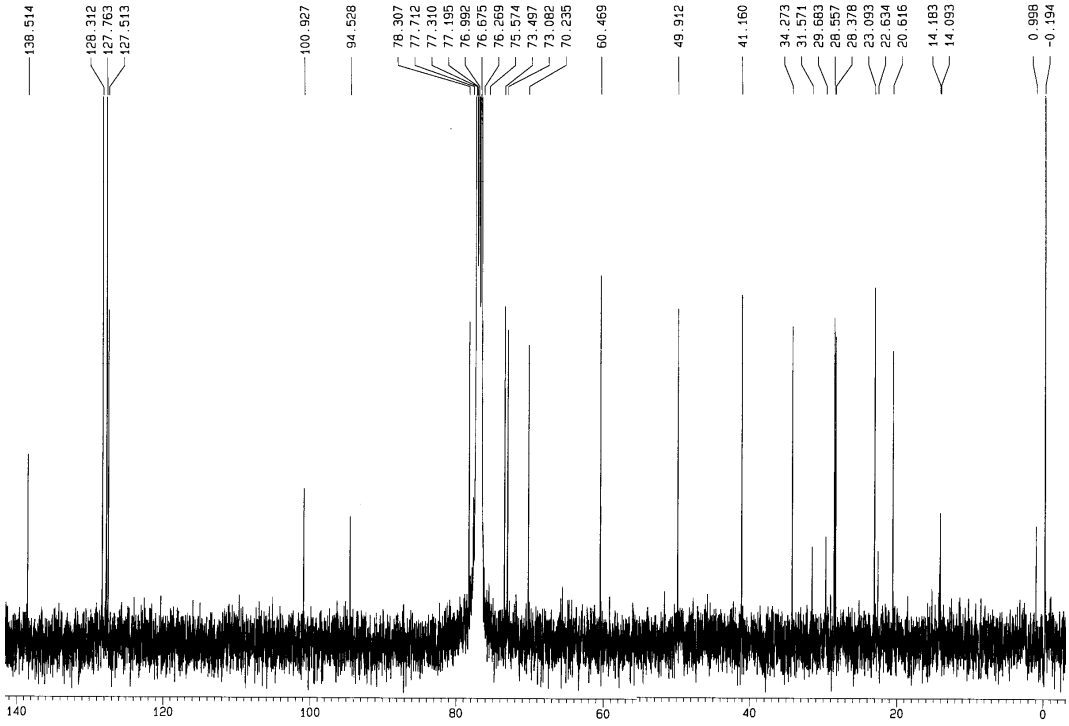


(1*S*,5*S*,6*R*,9*S*)-9-(Benzyloxymethyl)-6-(trimethylsilylethynyl)-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]undecane 53

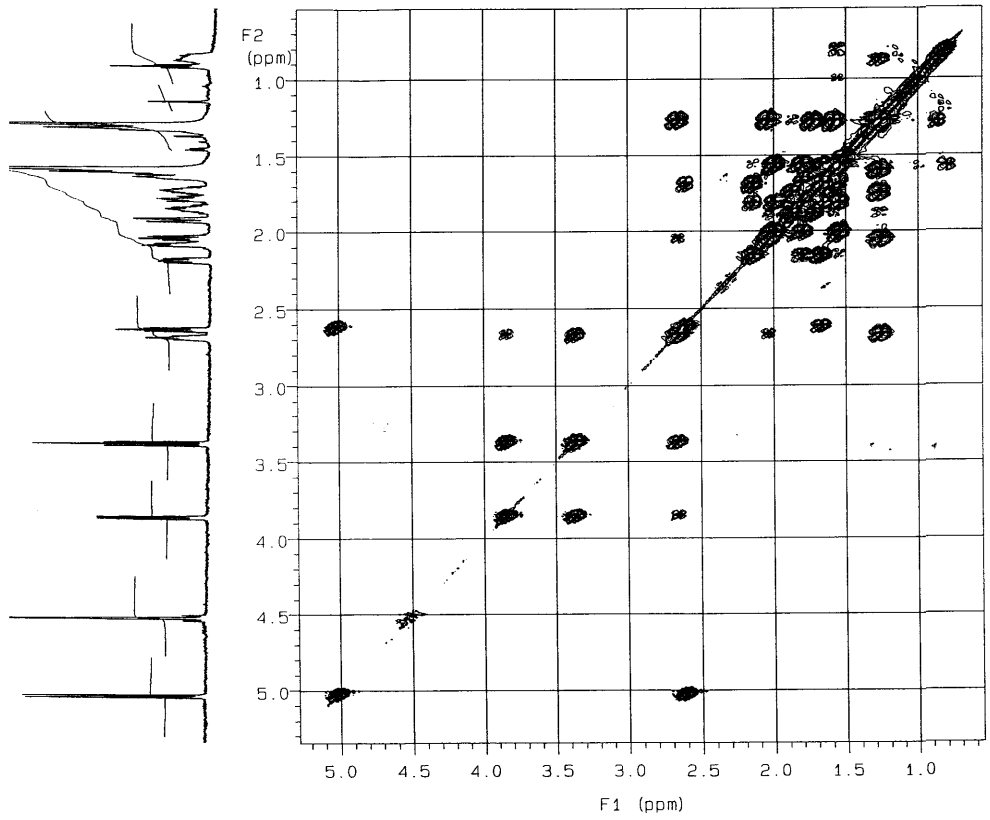
^{1}H NMR & NOEs (750 MHz; $CDCl_3$)



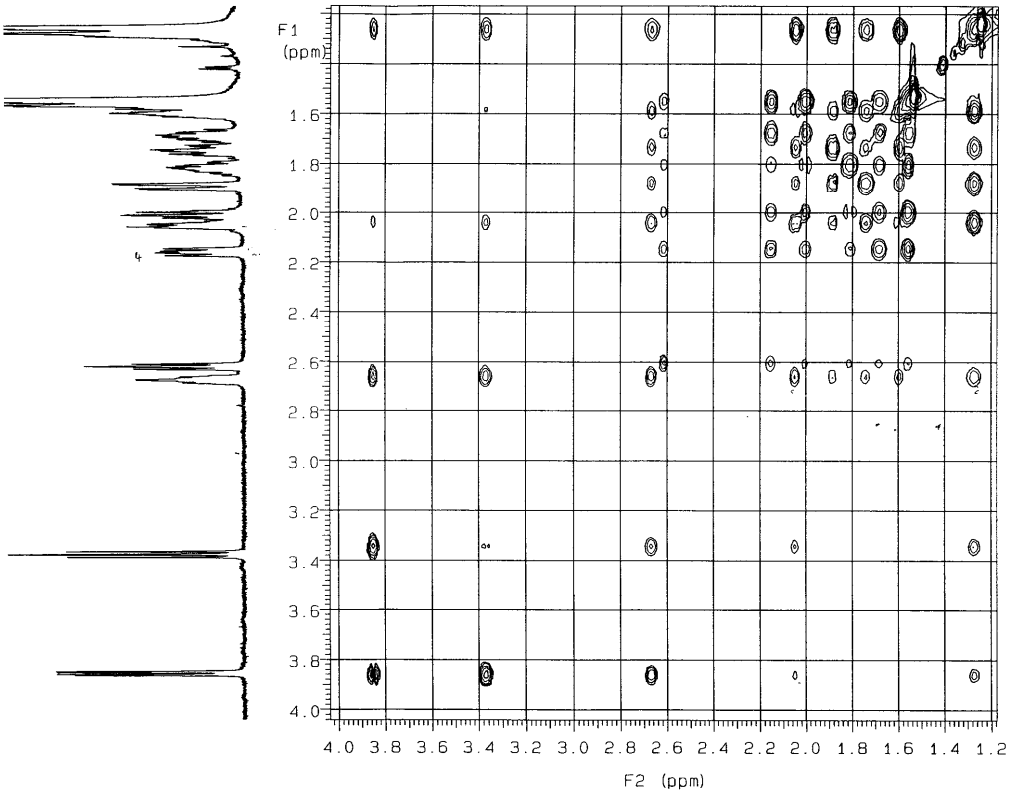
^{13}C NMR (100 MHz; $CDCl_3$)



COSY (750 MHz; $CDCl_3$)

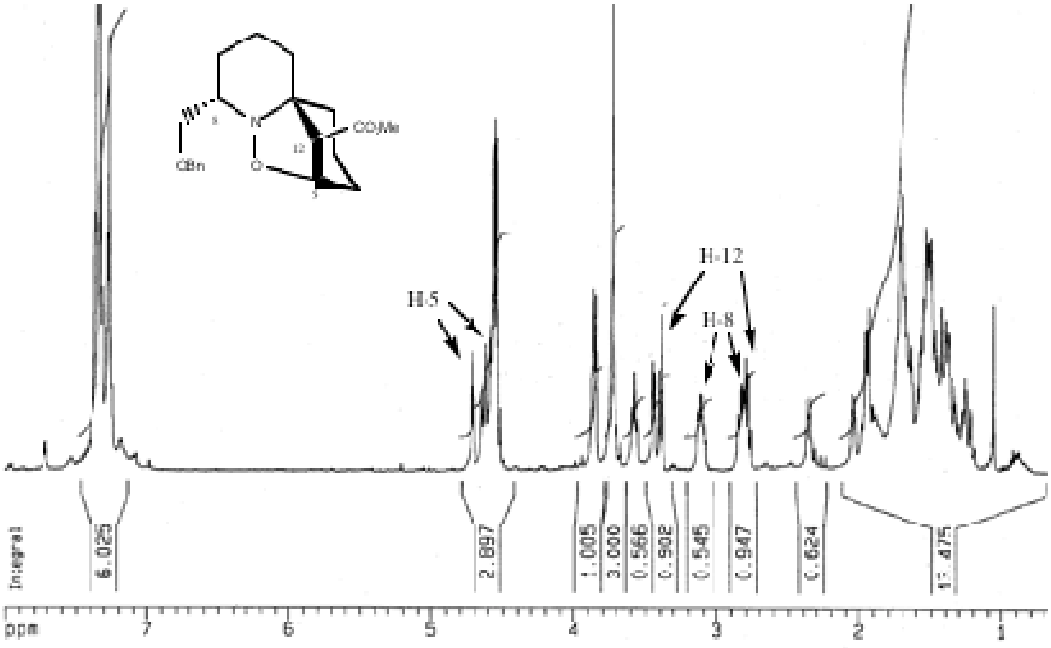


TOCSY (750 MHz; $CDCl_3$)

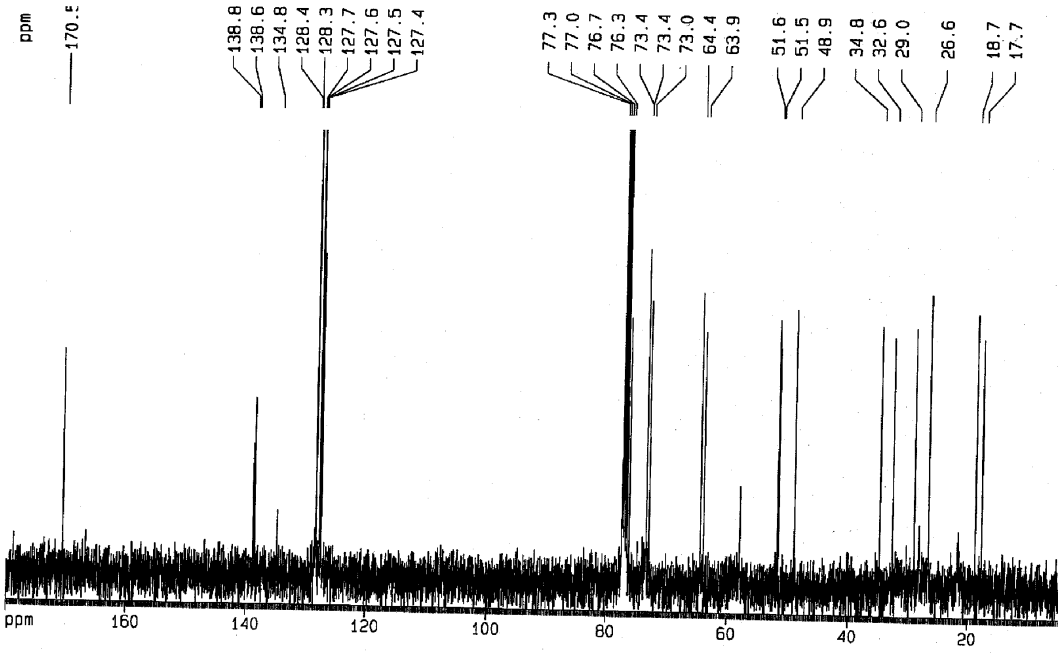


(1*R*,5*S*,8*S*,12*S*)-8-(Benzyloxymethyl)-12-methoxycarbonyl-7-aza-6-oxatricyclo[5.4.1^{1,5}.0]undecane 50

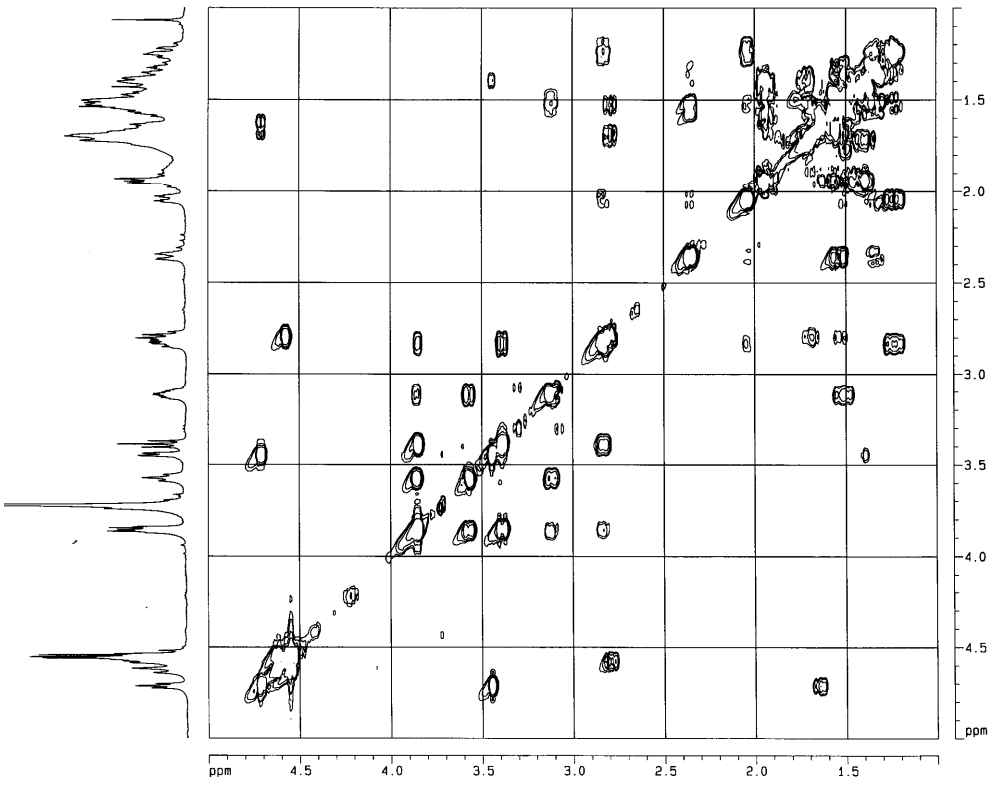
^{1}H NMR (500 MHz; $CDCl_3$)



^{13}C NMR (100 MHz; $CDCl_3$)

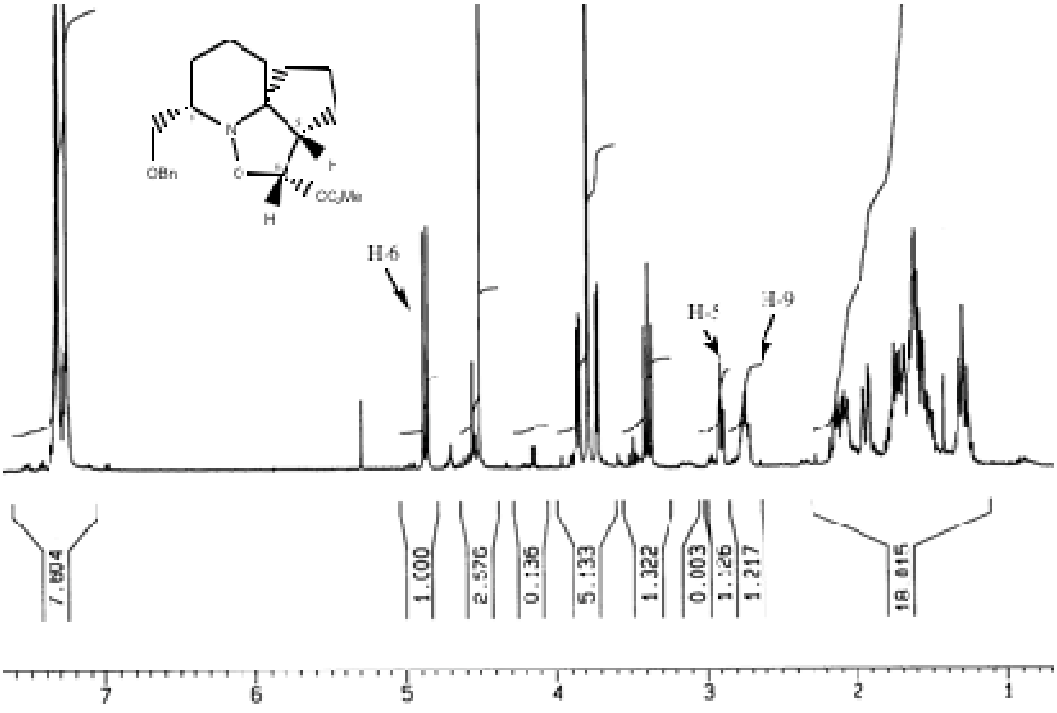


COSY (500 MHz; $CDCl_3$)

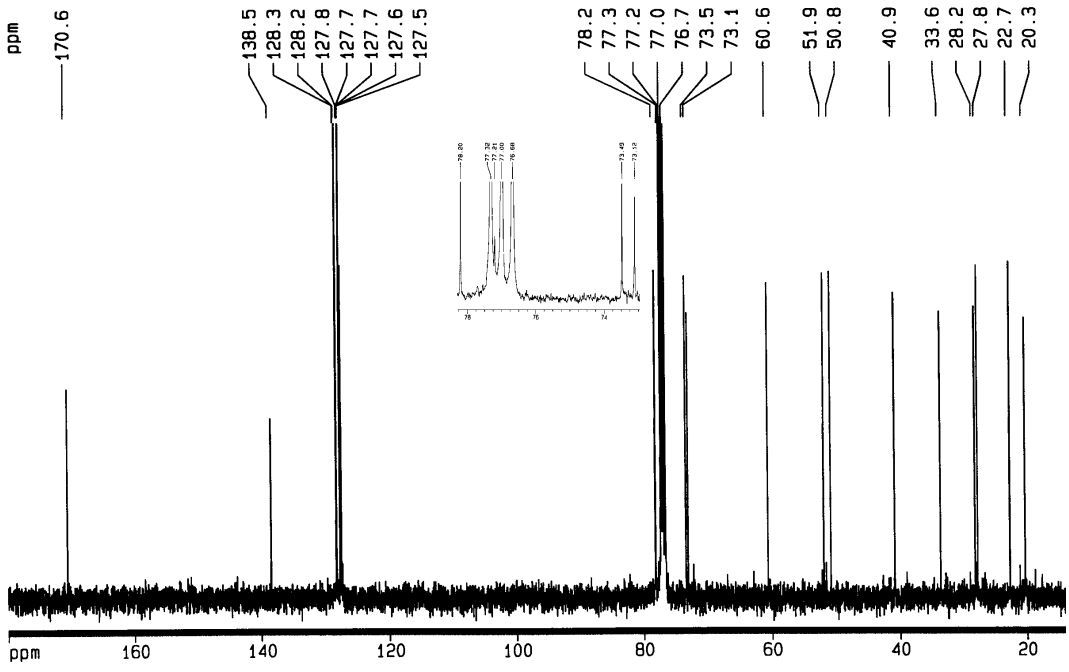


(1*S*,5*S*,6*R*,9*S*)-9-(Benzyloxymethyl)-6-methoxycarbonyl-8-aza-7-oxatricyclo[6.4.0.0^{1,5}]undecane 51

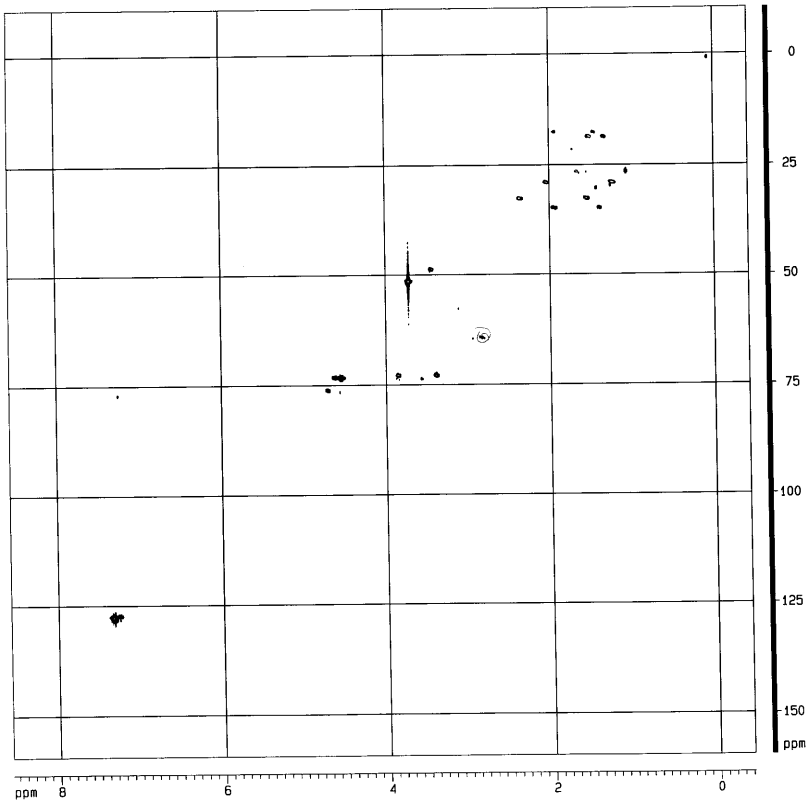
^{1}H NMR (500 MHz; $CDCl_3$)



^{13}C NMR (100 MHz; $CDCl_3$)

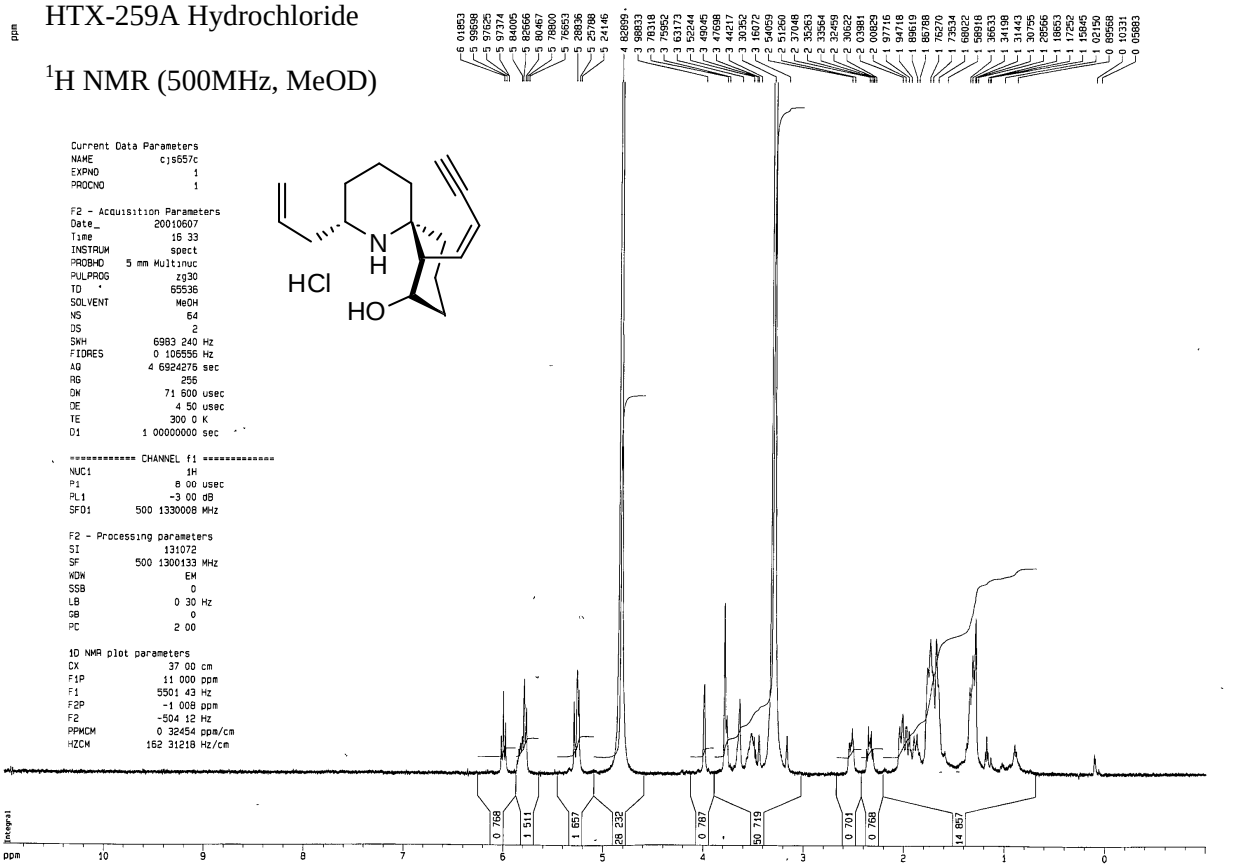


HMQC (500 MHz; $CDCl_3$)



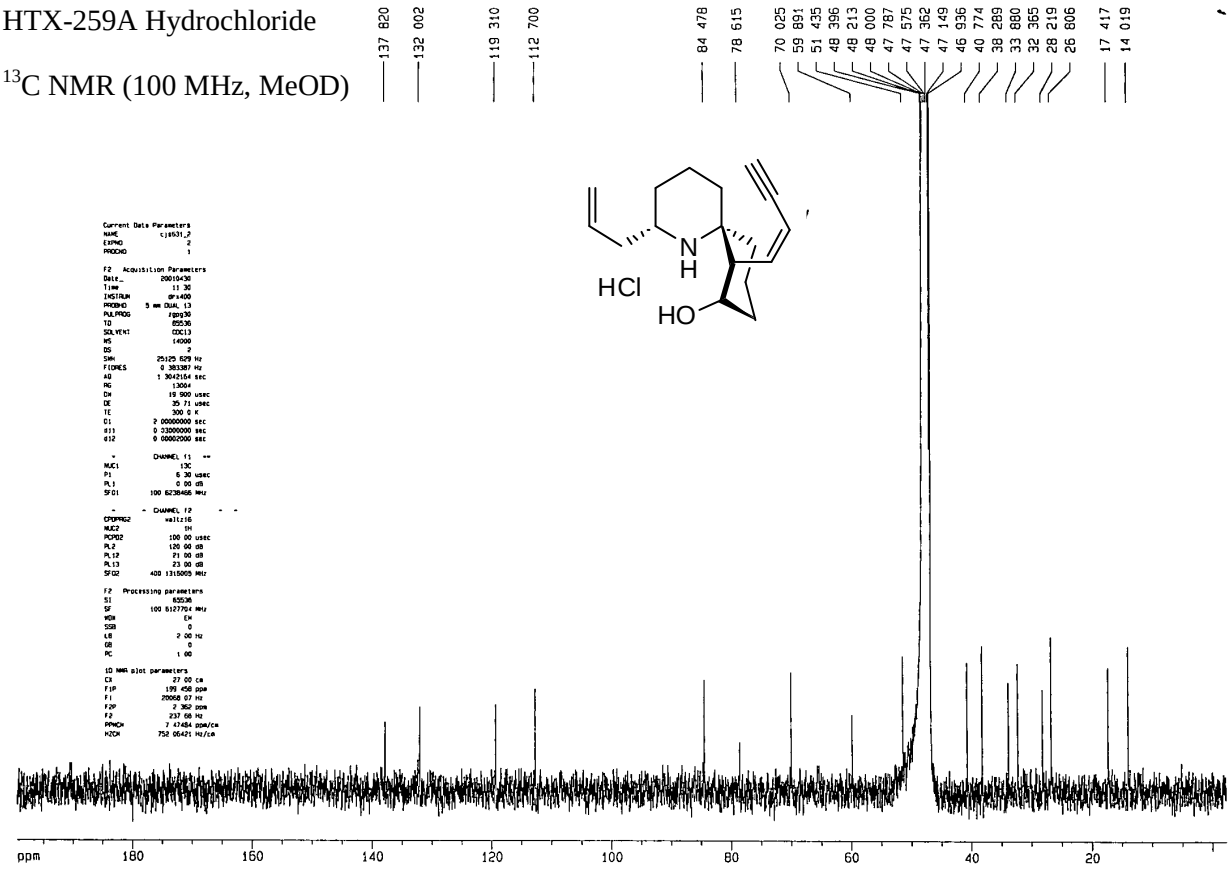
HTX-259A Hydrochloride

^{1}H NMR (500MHz, MeOD)



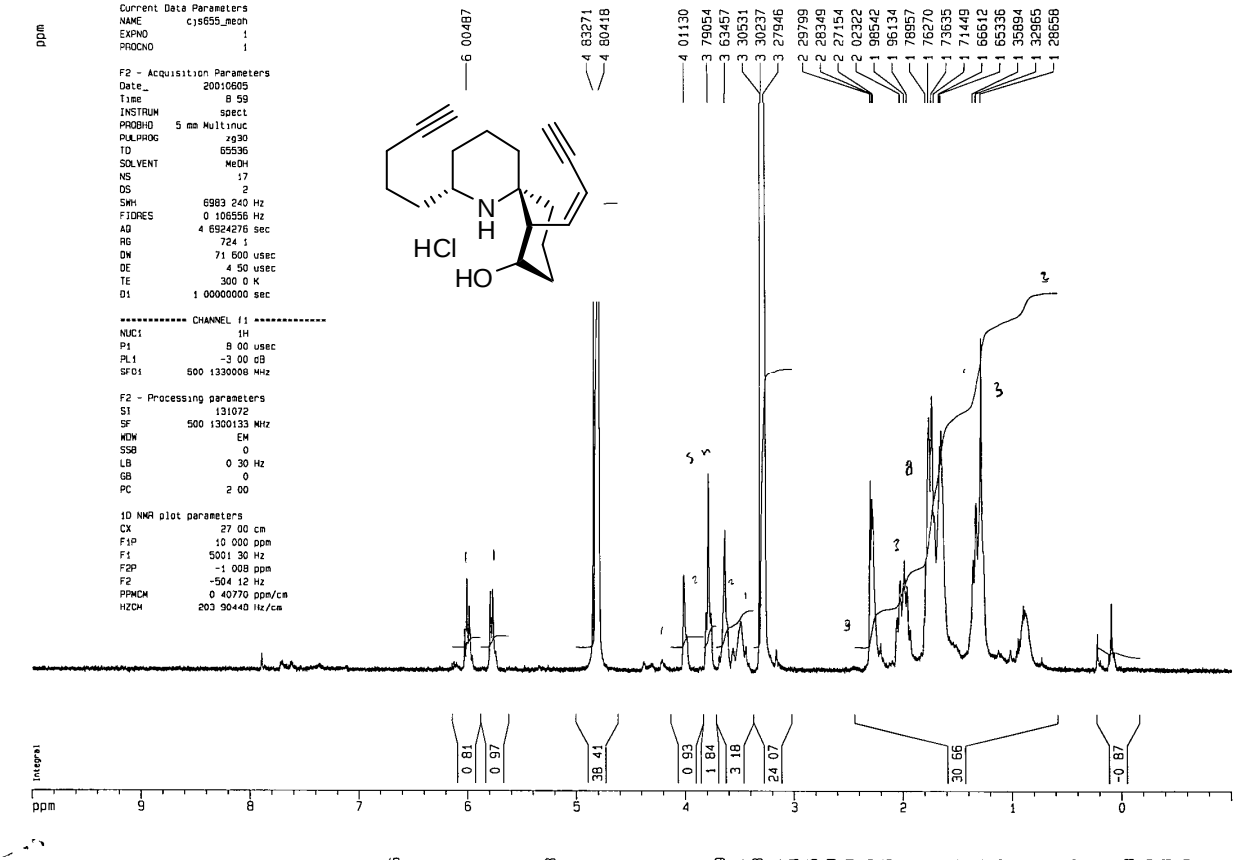
HTX-259A Hydrochloride

^{13}C NMR (100 MHz, MeOD)



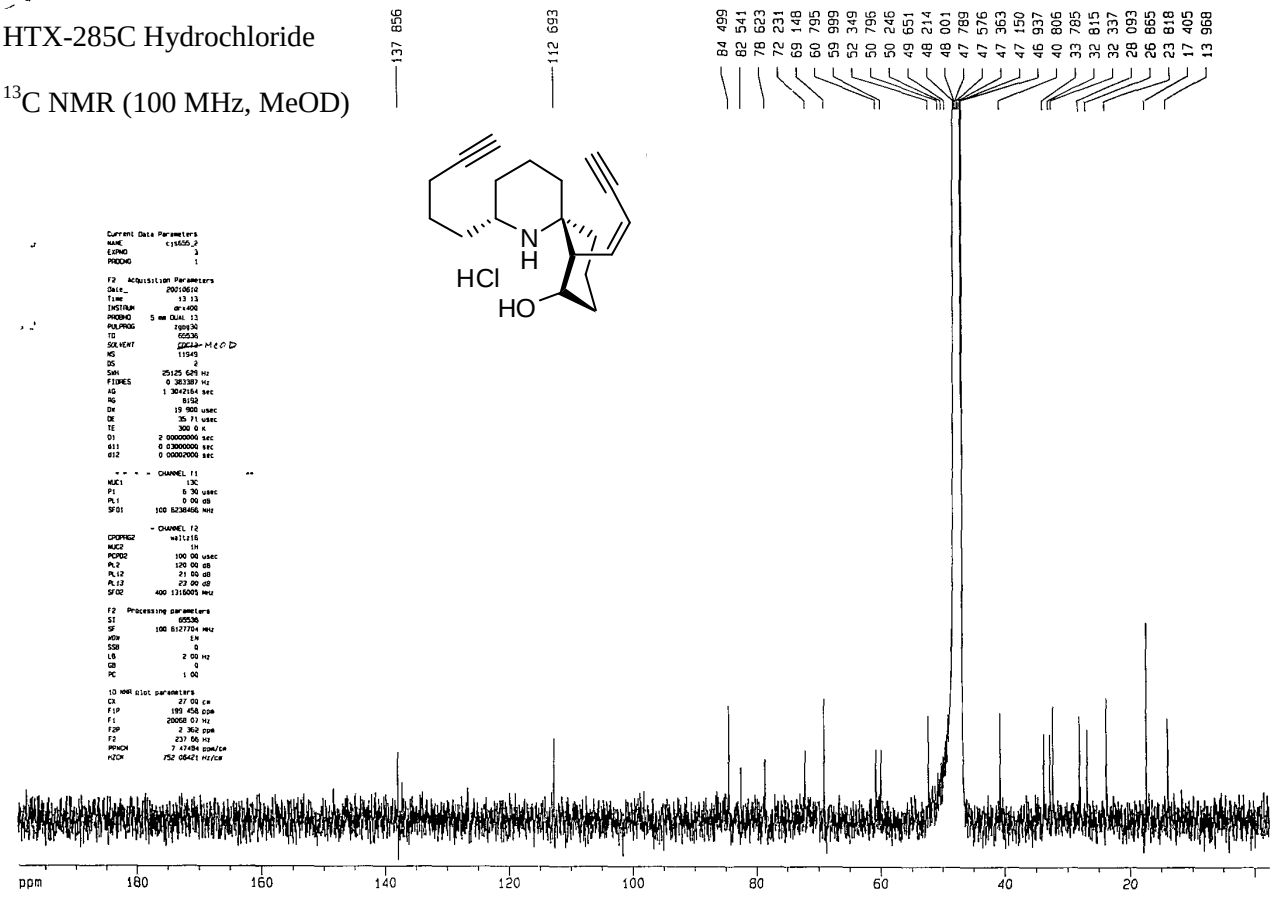
HTX-285C Hydrochloride

^{1}H NMR (500MHz, MeOD)



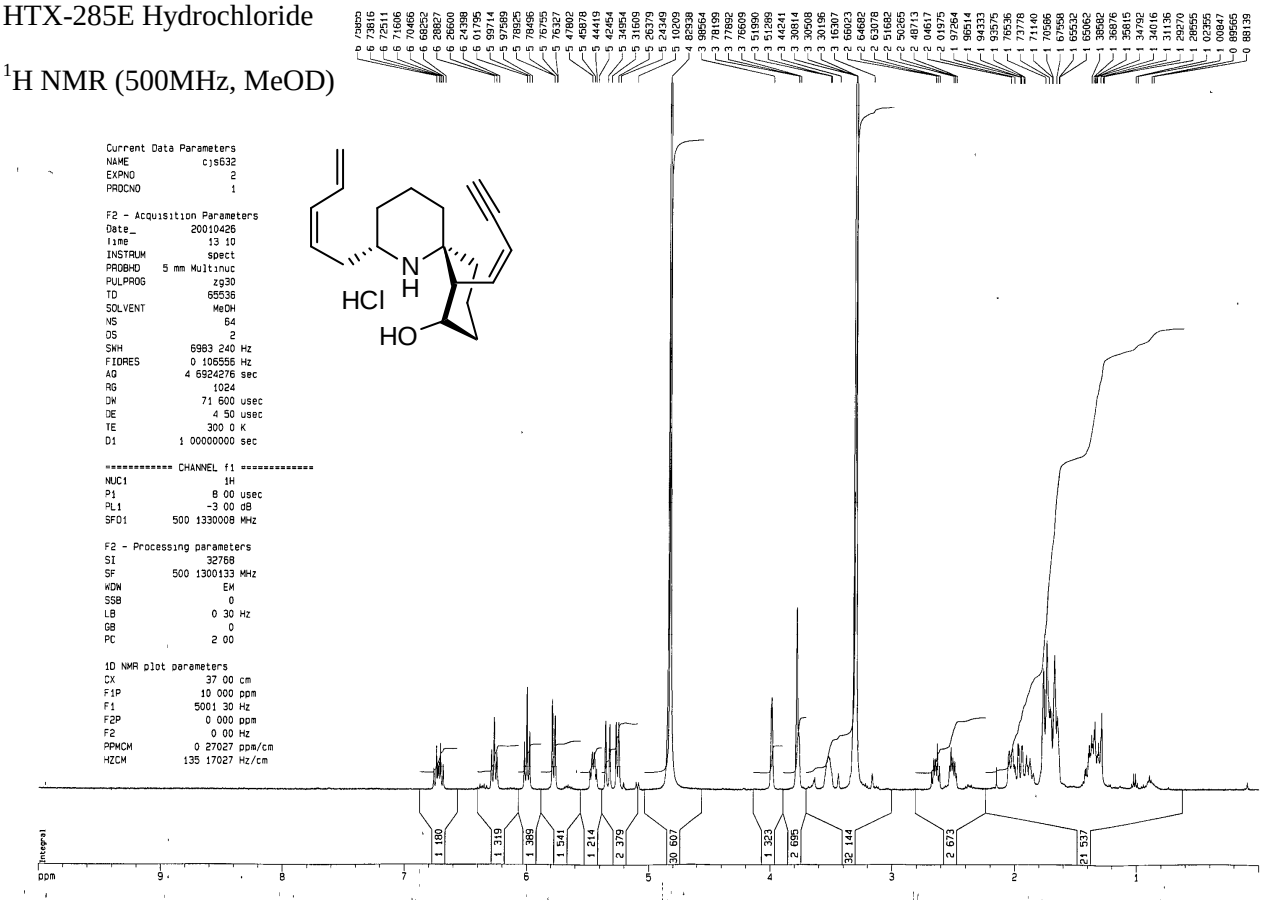
HTX-285C Hydrochloride

^{13}C NMR (100 MHz, MeOD)



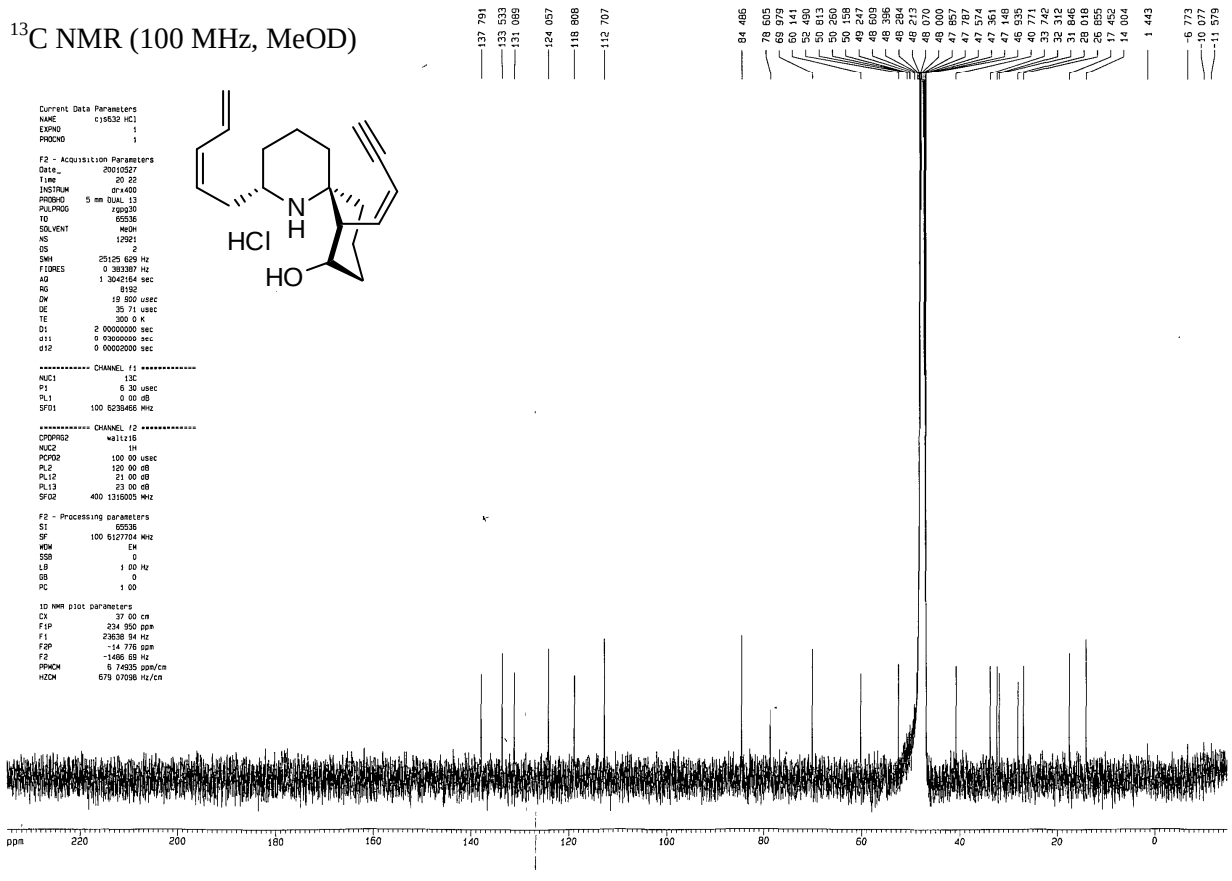
HTX-285E Hydrochloride

^{1}H NMR (500MHz, MeOD)



HTX-285E Hydrochloride

^{13}C NMR (100 MHz, MeOD)



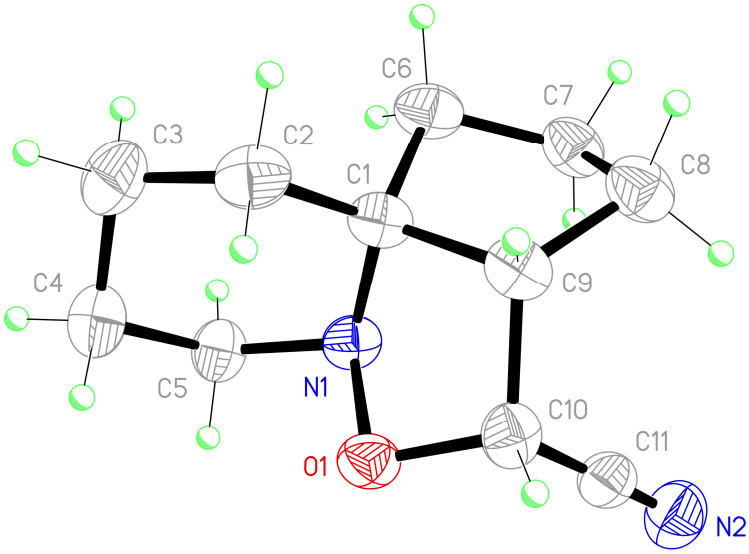
CRYSTALLOGRAPHIC STRUCTURES

Crystal Data for 37. $C_{33}H_{44}ClNO_2Si$, M = 550.23, triclinic, a = 11.7549(6), b = 13.7175(9), c = 20.1662(13) Å, α = 84.294(3), β = 75.250(4), γ = 89.894(4)°, U = 3128.1(3) Å^3, T = 180(2) K, space group P–1, Z = 4, μ(Mo Kα) = 0.189 mm^{-1}, 26 871 reflections collected, 10 742 unique (R_{int} = 0.0510), R1 = 0.0729, wR2[$I > 2\sigma(I)$] = 0.1828, CCDC deposition number 620201.

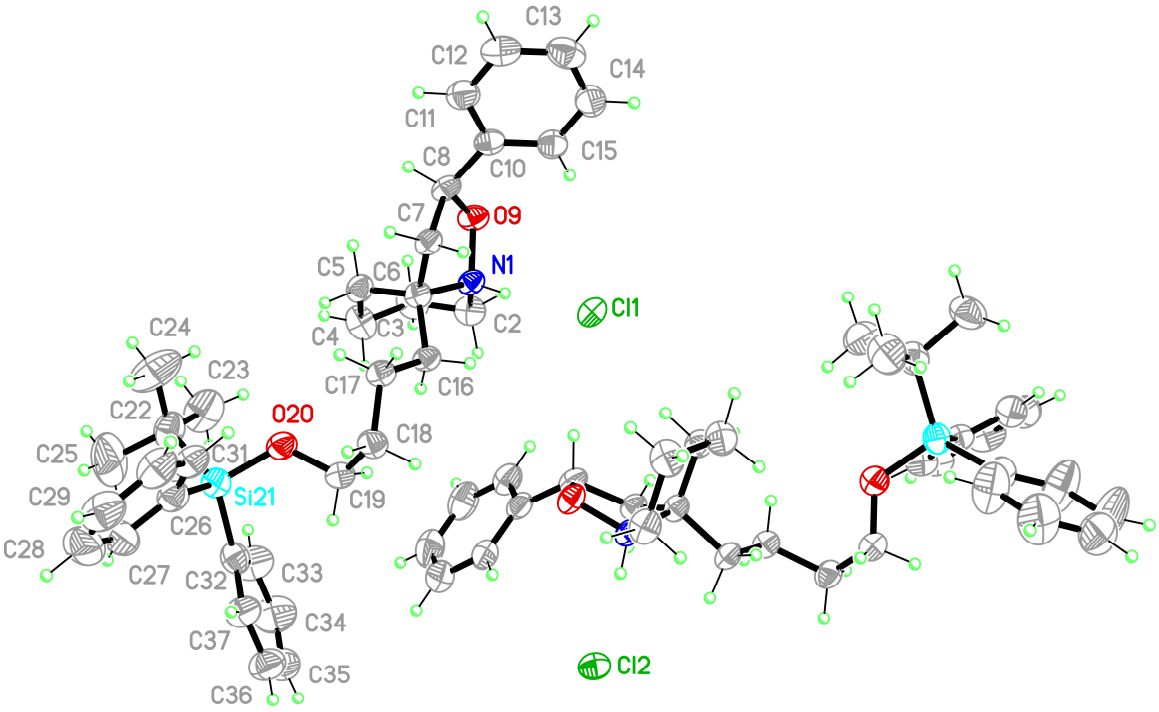
Crystal Data for 75. $C_{24}H_{41}NO_2Si$, M = 403.67, monoclinic, a = 7.7031(3), b = 9.8991(6), c = 15.8805(8) Å, β = 98.831(3)°, U = 1196.59(11) Å^3, T = 180(2) K, space group $P2_1$, Z = 2, μ(Mo Kα) = 0.890 mm^{-1}, 7454 reflections collected, 4564 unique (R_{int} = 0.0432), R1 = 0.0439, wR2[$I > 2\sigma(I)$] = 0.1107, CCDC deposition number 865489.

Crystal Data for 29. $C_{11}H_{16}N_2O$, 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 $Pca2_1$, Z = 4, μ(Mo Kα) = 0.082 mm^{-1}, 5693 reflections collected, 1705 unique (R_{int} = 0.0974), R1 = 0.0401, wR2[$I > 2\sigma(I)$] = 0.0878, CCDC deposition number 881632.

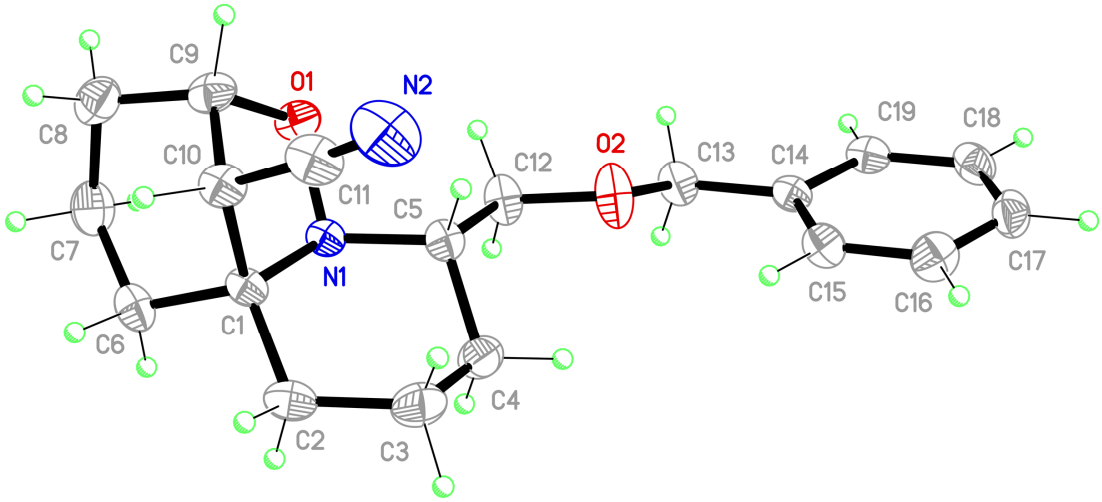
Crystal Data for 48. $C_{19}H_{24}N_2O_2$, M = 312.40, monoclinic, a = 8.4675(15), b = 11.662(2), c = 8.6820(16) Å, U = 834.4(3) Å^3, T = 150(2) K, space group $P2_1$, Z = 2, λ = 0.6885 Å (SRS Daresbury), μ = 0.081 mm^{-1}, 7499 reflections collected, 3867 unique (R_{int} = 0.0575), R1[$I > 2\sigma(I)$] = 0.0643, wR2(all data) = 0.1555, CCDC deposition number 885212.



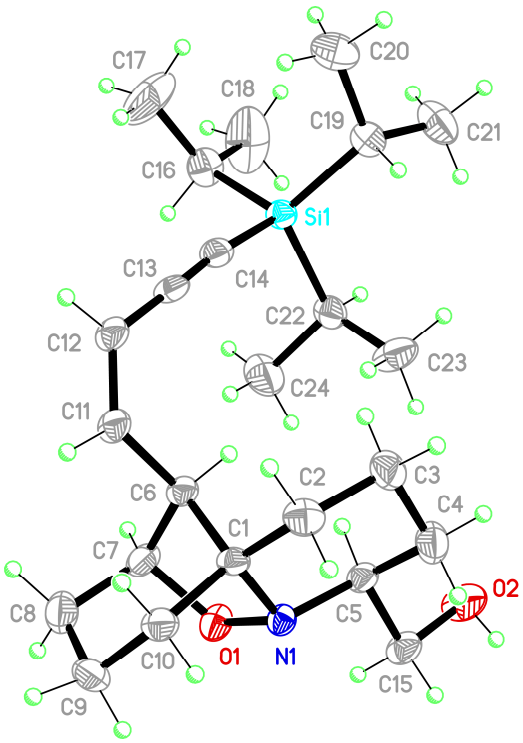
Molecular structure of **29** with displacement ellipsoids at the 50% probability level for non-H atoms.



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 **48** with displacement ellipsoids at the 50% probability level for non-H atoms.



Molecular structure of **75** with displacement ellipsoids at the 50% probability level for non-H atoms.

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