Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Rapid access to polycyclic indolines related to the stephacidin alkaloids using a radical cascade†

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General Procedures

Solution infra-red spectra were recorded using a Perkin Elmer 100-series FTIR spectrometer using chloroform as solvent. Neat infra-red spectra were also recorded using a Perkin Elmer 100-series FTIR spectrometer. Wavelengths (ν) are reported in cm^{-1}. Optical rotations were recorded as dilute solutions in the indicated solvent in a 25 mm glass cell using a JASCO DIP370 digital polarimeter at 294 nm. Mass spectra were obtained using a VG Micromass 70E or VG Micron Autospec spectrometer, using electrospray ionisation (ESI) with meta-nitrobenzyl alcohol as matrix. All ^{1}H-NMR and ^{13}C-NMR experiments were recorded using Bruker AC300, AV300, AV400 and DMX500 NMR spectrometers. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are quoted in Hz. The 7.27 ppm resonance of residual $CHCl_3$ and 77.1 ppm resonance of $CDCl_3$ were used as internal references, (MeOD signal as reference, H = 3.31 ppm, ^{13}C = 49.0 ppm, benzene-d6 signal as reference, ^{1}H = 7.16 ppm, ^{13}C = 49.0 ppm). The following abbreviations apply: (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) double doublet, etc. The chemical shifts of multiplets corresponding to a single proton are quoted as a point, representing the centre of the multiplet. When signals for two or more protons overlap, a range is quoted. Required assignments were confirmed by two-dimensional homonuclear (^{1}H-^{1}H) and heteronuclear (^{1}H-^{13}C) correlation spectroscopy on a Bruker AV400 spectrometer. Tetrahydrofuran (THF) was distilled immediately prior to use from sodium and benzophenone. All other solvents and reagents were used as received from commercial suppliers unless otherwise stated. Solvents for radical reaction were degassed for 40 minutes under a steady flow of dry nitrogen). Pet. ether refers to the fraction boiling between 40 ℃ and 60 ℃. All glassware was flame-dried under a steady flow of nitrogen or oven-dried at 100ºC overnight before use and all reactions were performed under an atmosphere of nitrogen or argon unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium or plastic plates coated with kieselgel F254 with 0.2 mm thickness. Visualisation was achieved by a combination of ultraviolet light (254 nm) and ethanolic phosphomolybdic acid (PMA), acidic potassium permanganate or anisaldehyde. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck and co.). All reaction temperatures refer to values recorded for an external bath and room temperature implies temperatures in the range 18–25 ℃.

One-pot prenylation and sulfenylation of 8 to give DKP 9a

0.8M LDA (0.27 mL, 0.218 mmol, 1.1equiv) was added to a solution of DKP **8** (100 mg, 0.20 mmol) in dry THF (5 mL) at -78℃ and the mixture was stirred for 10 min. Prenyl bromide (23 μL, 0.198 mmol, 1.0 equiv) was added and the reaction mixture was stirred for 30 min before 0.8M LDA (0.35 μL, 0.28 mmol, 1.4equiv) was added at -78℃. The mixture was stirred for additional 10 min and a solution of Ph_2S_2 (86 mg, 0.396 mmol, 2.0 equiv) in THF (3 mL) was then added. After 30 min the reaction was quenched at -78℃ by addition of 1mL of water and was allowed to warm to r.t. EtOAc (15 mL) was added and the mixture was washed with sat. NH_4Cl_{aq} (10 mL), brine (10 mL) dried over $MgSO_4$, and concentrated. The crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 2:1) to give **9a** (99 mg, 0.15 mmol, 74 %) as a light yellow solid.

R*f*: 0.58 (pet. ether/EtOAc, 1:4); m.p: 78 – 79℃; $[\alpha]_D^{18.5}$ - 26 (*c* 0.70, $CHCl_3$); FTIR (ATR) ν_{max} 2979, 2934, 1733, 1658, 1611, 1513, 1453, 1368, 1307, 1271, 1250, 1156, 1109, 1080, 1035, 1017, 853, 813, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* 8.1, 1H, H7), 7.48 (d, *J* 7.7, 1H, H4), 7.39 (d, *J* 6.7, 2H, H33), 7.28 (t, *J* 7.0, 1H, H35), 7.24 (d, *J* 7.4, 2H, H34), 7.20 (d, *J* 8.7, 2H, H27), 7.11 (t, *J* 7.5, 1H, H6), 7.04 (t, *J* 7.5, 1H, H5), 6.65 (d, *J* 8.7, 2H, H28), 6.53 (s, 1H, H2), 5.42 (d, *J* 15.2, 1H, H25a), 4.85 (d, *J* 15.2, 1H, H25b), 4.74 – 4.70 (m, 1H, H20), 3.83 (d, *J* 15.0, 1H, H10a), 3.66 (s, 3H, H30), 3.42 (ddd, *J* 12.6, 9.8, 6.9, 1H, H14a), 3.33 (d, *J* 15.0, 1H, H10b), 2.98 (ddd, *J* 12.6, 10.4, 4.2, 1H, H14b), 1.84 (dd, *J* 14.7, 8.2, 1H, H19a), 1.65 – 1.60 (m, 2H, H19b, H16a), 1.43 (s, 12H, H38, H22), 1.40 – 1.31 (m, 1H, H15a), 1.29 – 1.14 (m, 1H, H15b), 1.12 (s, 3H, H23), 0.46 – 0.37 (m, 1H,

H16b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C18) , 162.0 (C12), 158.8 (C29), 149.2 (C36), 137.4 (2C33), 134.9 (C21), 134.7 (C9), 130.6 (C8), 130.2 (C35), 130.1 (C28), 129.7 (C32), 129.7 (C26), 129.1 (2C34), 125.6 (C2), 124.2 (C6), 122.5 (C5), 120.1 (C4), 118.0 (C20), 114.6 (C7), 114.0 (C27), 113.8 (C3), 83.5 (C11), 83.3 (C37), 66.7 (C17), 55.1 (C30), 47.3 (C25), 44.8 (C14), 38.5 (C19), 32.0 (C16), 32.0 (C10), 28.0 (3C38), 25.8 (C22), 18.9 (C15), 17.5 (C23); HRMS (ESI) calculated for $C_{40}H_{45}N_3O_5NaS$ $[M+Na]^+$ 702.2978, found 702.2980.

Radical cyclisation to give indolines 11 and 12 – (Scheme 4, R = PMB)

In a two neck flask fitted with a condenser, **9a** (60 mg, 0.09 mmol) was dissolved in degassed toluene (3 mL) under an inert atmosphere. The mixture was warmed to reflux and solutions of 0.009M ACCN in degassed toluene (6.0 mg, 0.026 mmol, 0.3 equiv) and 0.044M Bu_3SnH in degassed toluene (35 μL, 0.132 mmol, 1.5 equiv) were added via a syringe pump over 8 h. After completion of the addition the mixture was allow to cooled to r.t and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 1:1) to give **11** (35 mg, 0.061 mmol, 71%) and **12** (7 mg, 0.014 mmol, 15%).

11: R*f*: 0.27 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{20.5}$ +11 (*c* 1.25, $CHCl_3$); FTIR (ATR) ν_{max} 2972, 1680, 1611, 1512, 1478, 1460, 1383, 1351, 1278, 1247, 1172, 1145, 1107, 1054, 1034, 999, 813, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* 7.4, 1H, H14), 7.30 (d, *J* 7.7, 1H, H11), 7.04 (d, *J* 8.6, 2H, H27), 7.01 (d, *J* 7.7, 1H, H12), 6.95 (d, *J* 7.4, 3.8, 1H, H13), 6.79 (d, *J* 8.6, 2H, H28), 4.85 (d, *J* 16.0, 1H, H25a), 4.24 (d, *J* 16.0, 1H, H25b), 4.06 (d, *J* 8.2, 1H, H8), 3.73 (s, 3H, H30), 3.63 (t, *J* 8.5, 1H, H16), 3.41 (ddd, *J* 11.8, 6.7, 5.4, 1H, H1a), 3.19 – 3.07 (m, 2H, H1b, H17a), 2.84 – 2.68 (m, 1H, H3a), 2.19 (dd, *J* 14.3, 9.4, 1H, H17b), 2.05 (dd, *J* 13.2, 10.6, 1H, H5a), 1.89 (dd, *J* 10.6, 5.4, 1H, H6), 1.87 – 1.82 (m, 2H, H2), 1.76 – 1.62 (m, 2H, H3b, H5b), 1.44 (s, 9H, H33), 0.83 (s, 3H, H23), 0.23 (s, 3H, H24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C22), 168.8 (C19), 159.0 (C29), 153.3 (C31), 142.6 (C10), 134.6 (C15), 130.5 (C26), 128.0 (C27), 127.0 (C12), 123.8 (C14), 123.0 (C13), 116.0 (C11), 114.4 (C28), 81.2 (C32), 67.79 (C8), 66.2 (C4), 63.5 (C18), 55.3 (C30), 49.0 (C6), 44.4 (C25), 44.3 (C1), 39.5 (C7), 38.5 (C16), 31.8 (C5), 30.3 (C3), 28.6 (C23), 28.4 (C33), 24.5 (C2), 22.3 (C17), 15.7 (C24); HRMS (ESI) calculated for $C_{34}H_{41}N_3O_5Na$ $[M+Na]^+$ 594.2944, found 594.2950.

12: R*f*: 0.20 (Pet. Ether/EtOAc, 1:1); $[\alpha]_D^{20.5}$ +100 (*c* 0.32, $CHCl_3$); FTIR (ATR) ν_{max} 2924, 1683, 1612, 1513, 1481, 1384, 1367, 1276, 1249, 1172, 11440, 1035, 752, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* 7.7, 1H, H11), 7.32 (d, *J* 7.5, 1H, H14), 7.01 (t, *J* 7.7, 1H, H12), 6.91 (d, *J* 8.6, 2H, H27), 6.84 (td, *J* 7.5, 0.9, 1H, H13), 6.74 (d, *J* 8.6, 2H, H28), 5.11 (d, *J* 15.9, 1H, H25a), 4.32 (d, *J* 9.2, 1H, H8), 4.11 (d, *J* 15.9, 1H, H25b), 3.78 (t, *J* 8.0 1H, H16), 3.70 (s, 3H, H30), 3.40 – 3.26 (m, 1H, H1a), 3.21 – 3.03 (m, 2H, H17a+1b), 2.71 (dt, *J* 12.6,

6.1, 1H, H3a), 2.30 (dd, *J* 15.5, 6.0, 1H, H17b), 1.91 – 1.78 (m, 2H, H2), 1.77 – 1.69 (m, 1H, H6), 1.68 – 1.56 (m, 2H, H5a, H3b), 1.55 – 1.49 (m, 1H, H5b), 1.46 (s, 9H, H33), 0.84 (s, 3H, H24), 0.81 (s, 3H, H23); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C22), 169.8 (19), 159.0 (C29), 153.2 (C31) 142.7 (C10), 133.6 (C15), 129.3 (C26), 128.6 (C27), 127.2 (C12), 125.6 (C14), 123.0 (C13), 115.4 (C11), 114.2 (C28), 81.2 (C32), 66.2 (C8), 65.6 (C4), 63.2 (C18), 55.3 (C30), 44.9 (C25), 44.4 (C1), 42.5 (C6), 38.0 (C7), 36.6 (C16), 30.8 (C5), 30.2 (C3), 28.5 (C33), 24.6 (C2), 23.5 (C23), 23.3 (C24), 19.4 (C17); HRMS (ESI) calculated for $C_{34}H_{41}N_3O_5Na$ $[M+Na]^+$ 594.2944, found 594.2936.

Peptide coupling and cyclisation to give DKP 10

A solution of Boc-L-Trp-OH (3.9 g, 13.0 mmol) and proline **13** (3.0 g, 13.0 mmol) in MeCN (200 mL), was cooled to 0℃ and HATU (5.4 g, 14.3 mmol, 1.1 equiv), DIPEA (5.1 mL, 28.6 mmol, 2.2 equiv) were added. After 16 h the mixture was concentrated under reduced pressure and the resulting crude oil was dissolved in EtOAc (50 mL) and washed successively with a 1N aqueous potassium hydrogenosulfate solution (15 mL), water (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was dissolved in formic acid (100 mL) stirred for 20h at r.t. and then the acid was evaporated under reduced pressure. To the residual oil, 2-butanol (150 mL) and toluene (50 mL) were added and the mixture was heated at reflux for 20h. The solvent evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (EtOAc/MeOH, 9:1) to give **10** (3.5 g, 77%) as a white solid.

R*f*: 0.37 (EtOAc/MeOH, 9:1); m.p: 182 – 183 ℃; $[\alpha]_D^{20}$ -81 (*c* 1.8, $CHCl_3$); FTI (ATR) ν_{max} 3277, 2977, 2925, 1642, 1424, 1299, 1214, 1102, 1010, 741, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, H19), 7.57 (d, *J* 7.8, 1H, H4), 7.39 (d, *J* 7.8, 1H, H7), 7.23 (t, *J* 7.4, 1H, H6), 7.13 (t, *J* 7.8, 1H, H5), 7.05 (s, 1H, H2), 5.76 (s, 1H, H1), 5.10 – 5.06 (m, 1H, H21), 4.40 (dd, *J* 11.2, 3.1, 1H, H11), 3.85 – 3.81 (m, 1H, H14a), 3.81 – 3.73 (m, 1H, H10a), 3.63 – 3.51 (m, 1H, H14b), 2.86 (dd, *J* 14.8, 11.2, 1H, H10b), 2.45 (qd, *J* 14.2, 8.3, 2H, H20), 2.13 – 2.08 (m, 2H, H16), 2.06 – 1.93 (m, 2H, H15), 1.69 (s, 3H, H24), 1.57 (s, 3H, H23); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C18), 165.5 (C12), 137.8 (C8), 136.8 (C9), 126.6 (C22), 123.6 (C2), 122.7 (C6), 119.9 (C5), 118.6 (C4), 117.2 (C21), 111.7 (C7), 109.9 (C3), 68.6 (C17), 54.5 (C11), 45.1 (C14), 36.1 (C20), 34.6 (C16), 28.2 (C10), 26.0 (C24), 20.5 (C15), 17.8 (C23); HRMS (ESI) calculated for $C_{21}H_{25}N_3O_2Na$ $[M+Na]^+$ 374.1844, found 374.1849.

Protection and sulfenylation sequence, leading to sulfide 9b from 10 (Scheme 3)

(i) Boc protection of **10** to give a doubly Boc protected DKP

$(Boc)_2O$ (5.7 g, 26.49 mmol, 3.0 equiv), 4-DMAP (336 mg, 2.65 mmol, 0.3 equiv) and TEA (3.0 mL, 22.08 mmol, 2.5 equiv) was added to a solution of **10** (3.1 g, 8.83 mmol) in DCM (70 mL) was added at r.t. After 16h stirring the crude mixture was washed with NH_4Cl_{aq} and then brine, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 1:2) gave the fully Boc protected derivative corresponding to **10** (3.4 g, 71%) as a white solid.

R*f*: 0.71 (pet. ether/EtOAc, 2:1); m.p. 107 – 108 ℃; $[\alpha]_D^{23}$ 120 (*c* 1.0, $CHCl_3$); FTI (ATR) ν_{max} 2979, 1732, 1659, 1455, 1368, 1256, 1155, 1082, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* 8.2, 1H, H7), 7.49 (d, *J* 7.8, 1H, H4), 7.33 – 7.25 (td, *J* 7.7, 1.0, 1H, H6), 7.26 (s, 1H, H2), 7.23 – 7.15 (td, *J* 7.7, 1.0, 1H, H5), 4.96 – 4.91 (m, 1H, H20), 4.84 (dd, *J* 4.8, 2.4, 1H, H11), 3.63 (ddd, *J* 12.4, 9.8, 6.0, 1H, H14a), 3.56 (dd, *J* 14.5, 2.4, 1H, H10a), 3.47 (dd, *J* 14.5, 4.8, 1H, H10b), 3.28 – 3.16 (m, 1H, H14b), 2.29 (dd, *J* 14.2, 8.5, 1H, H19a), 2.18 (dd, *J* 14.2, 7.2, 1H, H19b), 166 (s, 3H, H23), 1.65 (s, 9H, $C(CH_3)_3$), 1.63 – 1.61 (m, 1H, H15a), 1.61 – 1.59 (m, *J* 4.5, 2.8, 1H, H16a), 1.57 (s, 9H, $C(CH_3)_3$), 1.52 (s, 3H, H22), 1.27 – 1.15 (m, 1H, H15b), 0.66 – 0.51 (m, 1H, H16b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C18), 164.0 (C12), 151.0 ($CO_2C(CH_3)_3$), 149.4 ($CO_2C(CH_3)_3$), 137.4 (C21), 135.2 (C8), 130.4 (C9), 126.0 (C2), 124.7 (C6), 122.5 (C5), 119.8 (C4), 116.5 (C20), 115.0 (C7), 114.1 (C3), 83.7 ($CO_2C(CH_3)_3$), 83.6 ($CO_2C(CH_3)_3$), 69.2 (C17), 60.2 (C11), 44.20 (C14), 37.6 (C19), 33.6 (C10), 29.2 (C16), 28.2 ($CO_2C(CH_3)_3$), 28.1 ($CO_2C(CH_3)_3$), 26.1 (C22), 19.2 (C15), 17.9 (C23); HRMS (ESI) calculated for $C_{31}H_{41}N_3O_6Na$ $[M+Na]^+$ 574.2893, found 574.2886.

(ii) Sulfenylation to give **9b**

0.8M LDA (0.64 mL, 0.51 mmol, 1.4 equiv) was added to a solution of the doubly Boc-protected derivative from step (i) (200 mg, 0.36 mmol) in THF (20 mL) at -78 ℃ and the mixture was stirred for 10 min. Diphenyl disulfide (158 mg, 0.73 mmol, 2.0 equiv) in THF (7 mL) was then added to the reaction mixture and stirred for 30 min at -78 ℃. The crude mixture was quenched at -78 ℃ by addition of 1mL of water and was allowed to warm to r.t. EtOAc (15 mL) was then added and the solution was washed with sat. NH_4Cl_{aq} (10 mL), brine (10 mL) dried over $MgSO_4$, and concentrated.

The crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 1:1) to give **9b** (227 mg, 0.34 mmol, 95%) as white solid.

R*f*: 0.71 (Pet. Ether/EtOAc, 1:2); m.p. 102 – 103 ℃; $[\alpha]_D^{23}$ 118 (*c* 1.1, $CHCl_3$); FTI (ATR) ν_{max} 2978, 1733, 1659, 1453, 1364, 1252, 1148, 1080, 851, 749, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* 7.9, 1H, H7), 7.75 (d, *J* 7.4, 1H, H4), 7.64 (d, *J* 7.0, 2H, H30), 7.60 (s, 1H, H2), 7.41 – 7.33 (m, 1H, H32), 7.31 (d, *J* 7.6, 2H, H31), 7.28 – 7.22 (td, *J* 7.7, 1.0, 1H, H6), 7.20 (td, *J* 7.7, 1.0, 1H, H5), 4.53 – 4.49 (m, 1H, H20), 4.10 (d, *J* 14.4, 1H, H10a), 3.91 (d, *J* 14.4, 1H, H10b), 3.37 – 3.23 (m, 1H, H14a), 3.15 – 2.99 (m, 1H, H14b), 1.71 – 1.67 (m, 1H, H16a), 1.64 (s, 9H, OCC*H3*), 1.63 (s, 9H, OCC*H3*), 1.45 (s, 3H, H22), 1.41 – 1.29 (m, 3H, H15, H19a), 1.06 (s, 3H, H23), 0.91 (dd, *J* 14.8, 7.2, 1H, H19b), 0.86 – 0.77 (m, 1H, H16b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (C12), 162.1 (C18), 151.7 ($CO_2C(CH_3)_3$), 149.5 ($CO_2C(CH_3)_3$), 138.1 (2C30), 135.25 (C8), 134.9 (C21), 130.3 (C29), 130.1 (C32), 130.0 (C9), 128.7 (2C31), 126.5 (C2), 124.6 (C6), 122.7 (C5), 120.7 (C7), 116.9 (C20), 115.0 (C4), 114.5 (C3), 84.7 ($CO_2C(CH_3)_3$), 83.7 ($CO_2C(CH_3)_3$), 80.0 (C11), 67.5 (C17), 45.0 (C14), 36.6 (C19), 32.2 (C10), 31.0 (C16), 28.2 ($CO_2C(CH_3)_3$), 28.0 ($CO_2C(CH_3)_3$), 25.8 (C22), 18.8 (C15), 17.3 (C23); HRMS (ESI) calculated for $C_{37}H_{45}N_3O_6NaS$ $[M+Na]^+$ 682.2927, found 682.2939.

Radical cyclisation to give indolines 11 and 12 (and S1 and S2) – (Scheme 4, R = Boc)

The general procedure for radical cyclisation was followed using SPh-DKP **9b** (500 mg, 0.76 mmol) in degassed toluene (25 mL), 0.02M ACCN (93 mg, 0.38 mmol, 0.5 equiv) and 0.06M Bu_3SnH (326 μL, 1.21 mmol, 1.6 equiv) which were added via of a syringe pump over 8 h. After completion of the addition the mixture was allowed to cool to r.t. and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 1:1) to give **11** and **12** as a pale yellow foam, as an inseparable mixture (275 mg, 67%), **S1** (38 mg, 9.3%) and **S2** (13 mg, 3.0%) in 79 % total yield and ratio **11** : **12** : **S1** : **S2** =3.2 : 1.0 : 0.5 : 0.2.

Mixture 11:**12***: R*f*: 0.54 (pet. ether/EtOAc, 1:2); FTI (ATR) ν_{max} 2978, 1724, 1690, 1480, 1459, 1383, 1270, 1250, 1146, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* 7.4 Hz, 1H, H14*), 7.47 (d, *J* 7.5 Hz, 2H, H14),

7.17 – 6.97 (m, 6H, Ar, CH), 4.49 (d, *J* 9.2 Hz, 1H, H8*), 4.41 (d, *J* 8.5 Hz, 1H, H8), 3.93 (t, *J* 7.8 Hz, 2H, H16, H16*), 3.64 – 3.53 (m, 2H, H17a, H1a), 3.53 – 3.43 (m, 2H, H1a*, H17a*), 3.33 – 3.17 (m, 2H, H1b, H1b*), 2.82 – 2.74 (m, 1H, H3a), 2.74 – 2.67 (m, 1H, H3a*), 2.37 (dd, *J* 10.2, 6.4 Hz, 1H, H6), 2.22 – 2.14 (m, 4H, H5a, H5a*, H17b, H17b*), 1.98 – 1.84 (m, 5H, H2, H2*, H6*), 1.82 – 1.71 (m, 4H, H5b, H5b*, H3b, H3b*), 1.57 (s, 18H, $(CH_3)_3$, $(CH_3)_3$*,), 1.56 (s, 9H, $(CH_3)_3$,), 1.55 (s, 9H, $(CH_3)_3$, *), 1.12 (s, 3H, CH_3*), 0.99 (s, 3H, CH_3), 0.96 (s, 3H, CH_3*), 0.37 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C22, C22*), 167.2 (C19, C19*), 153.4 (*C*OC$(CH_3)_3$, *C*OC$(CH_3)_3$*), 150.8 (*C*OC$(CH_3)_3$, *C*OC$(CH_3)_3$*), 142.7 (C10,C10*), 135.1 (C15, C15*), 127.3 (C12*), 127.1 (C12), 125.4 (C14*), 123.7 (C14), 123.3 (C13), 123.1 (C13*), 16.1 (C11), 115.5 (C11*), 81.2 (**C*$(CH_3)_3$), 81.2 (*C*$(CH_3)_3$), 81.2 (*C*$(CH_3)_3$, **C*$(CH_3)_3$), 68.0 (C8*), 66.3 (C4), 66.0 (C8*), 65.7(C4*) 64.1 (C18,C18*), 48.4 (C6), 44.5 (C1), 44.4 (C1*), 41.9 (C6*), 39.4 (C7), 38.2 (C16), 38.0 (C16*), 36.9 (C7*), 31.89 (C5,C5), 30.1 (C3), 30.0 (C3*), 28.5 ($(CH_3)_3$, $(CH_3)_3$)*, CH_3, CH_3*), 28.0 ($(CH_3)_3$), 27.9 ($(CH_3)_3$), 24.4 (C2*), 24.2 (C2), 23.8 (C17), 21.8 (C17*), 15.6(CH_3, CH_3); HRMS (ESI) calculated for $C_{31}H_{41}N_3O_6Na$ $[M+Na]^+$ 574.2893, found 574.2887.

S1: R*f*: 0.32 (pet. ether/EtOAc, 1:2); $[\alpha]_D^{23}$ -80.4 (*c* 1.7, $CHCl_3$); FTI (ATR) ν_{max} 2978, 1724, 1690, 1479, 1458, 1367, 1250, 1146, 848, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* 8.0 Hz, 1H, H11), 7.17 (t, *J* 7.7 Hz, 1H, H12), 7.07 (d, *J* 7.3 Hz, 1H, H14), 6.97 (t, *J* 7.4 Hz, 1H, H13), 4.43 (d, *J* 9.3 Hz, 1H, H8), 4.05 – 3.95 (m, 1H, H16), 3.68 (ddd, *J* 11.6, 7.7, 4.0 Hz, 1H, H1a), 3.49 – 3.40 (m, 1H, H1b), 3.36 – 3.21 (m, 2H, H17), 2.77 – 2.68 (m, 1H, H3a), 2.23 (t, *J* 9.3 Hz, 1H, H6), 2.01 – 1.92 (m, 2H, H2a, H5a), 1.93 – 1.83 (m, 1H, H2b), 1.77 – 1.68 (m, 1H, H3b), 1.60 (s, 9H, $(CH_3)_3$), 1.56 (s, 9H, $(CH_3)_3$), 1.53 – 1.48 (m, 1H, H5b), 0.94 (s, 3H, H24), 0.91 (s, 3H, H23); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C22), 168.0 (C19), 153.4 (*C*OC$(CH_3)_3$), 150.4 (*C*OC$(CH_3)_3$), 143.0 (C10), 135.4 (C15), 127.6 (C12), 123.2 (C14), 122.7 (C13), 116.2 (C11), 84.8 (*C*$(CH_3)_3$), 81.3 (*C*$(CH_3)_3$), 66.2(C4), 66.1 (C8), 64.6

(C18), 46.7 (C6), 44.6 (C1), 38.0 (C16), 37.6 (C7), 32.9 (C5), 30.4 (C3), 28.4 (C(CH_3)$_3$), 28.0 (C(CH_3)$_3$), 24.2 (C2), 24.0 (C23), 23.0 (C24), 19.8 (C17); HRMS (ESI) calculated for $C_{31}H_{41}N_3O_6Na$ $[M+Na]^+$ 574.2893, found 574.2894.

Deprotection of indolines 11 and 12 to give 5 and S3

Indoline derivatives **11** and **12** (528 mg, 0.96 mmol) were diluted in 25 mL formic acid and stirred overnight at rt. Formic acid was then evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluent: pet. ether/EtOAc, 1:3) to give **5** (180 mg, 0.51 mmol, 52%), **S3** (130 mg, 0.37 mmol, 38%) as white solids.

5: R*f*: 0.18 (pet. ether/EtOAc, 1:2); m.p. 246 – 247°C; $[\alpha]_D^{23}$ -69 (*c* 1.0, $CHCl_3$); FTI (ATR) ν_{max} 2958, 1676, 1606, 1461, 1395, 1257, 1070, 1022, 746, 665;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* 7.2 Hz, 1H, H14), 7.02 (t, *J* 7.6 Hz, 1H, H12), 6.87 (s, 1H, NH, H21), 6.76 (t, *J* 7.2 Hz, 1H, H13), 6.61 (d, *J* 7.6 Hz, 1H, H11), 3.70 – 365 (m, 1H, H8), 3.64 – 3.49 (m, 2H, H16, H1a), 3.41 – 3.30 (m, 1H, H1b), 3.12 (dd, *J* 15.1, 7.8 Hz, 1H, H17a), 2.76 (brs, 1H, H3a), 2.16 – 2.04 (m, 1H, H5a), 2.06 – 1.90 (m, 3H, H2, H6), 1.86 – 1.73 (m, 2H, H3b, 17b), 1.73 – 1.62 (m, 1H, H5b), 0.94 (s, 3H, H24), 0.63 (s, 3H, H23); *NH (H9) not observed;* ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C22, C19), 150.2 (C10), 130.9 (C15), 127.7 (C14), 124.1 (C12), 118.9 (C13), 108.9 (C11), 68.7 (C8), 60.1 (C4, C18), 51.0 (C6), 44.2 (C1), 38.5 (C16), 36.5 (C7), 32.2 (C5), 29.5 (C3), 28.9 (C23), 27.3 (C17), 24.6 (C2), 16.6 (C24); HRMS (ESI) calculated for $C_{21}H_{25}N_3O_2Na$ $[M+Na]^+$ 374.1844, found 374.1836.

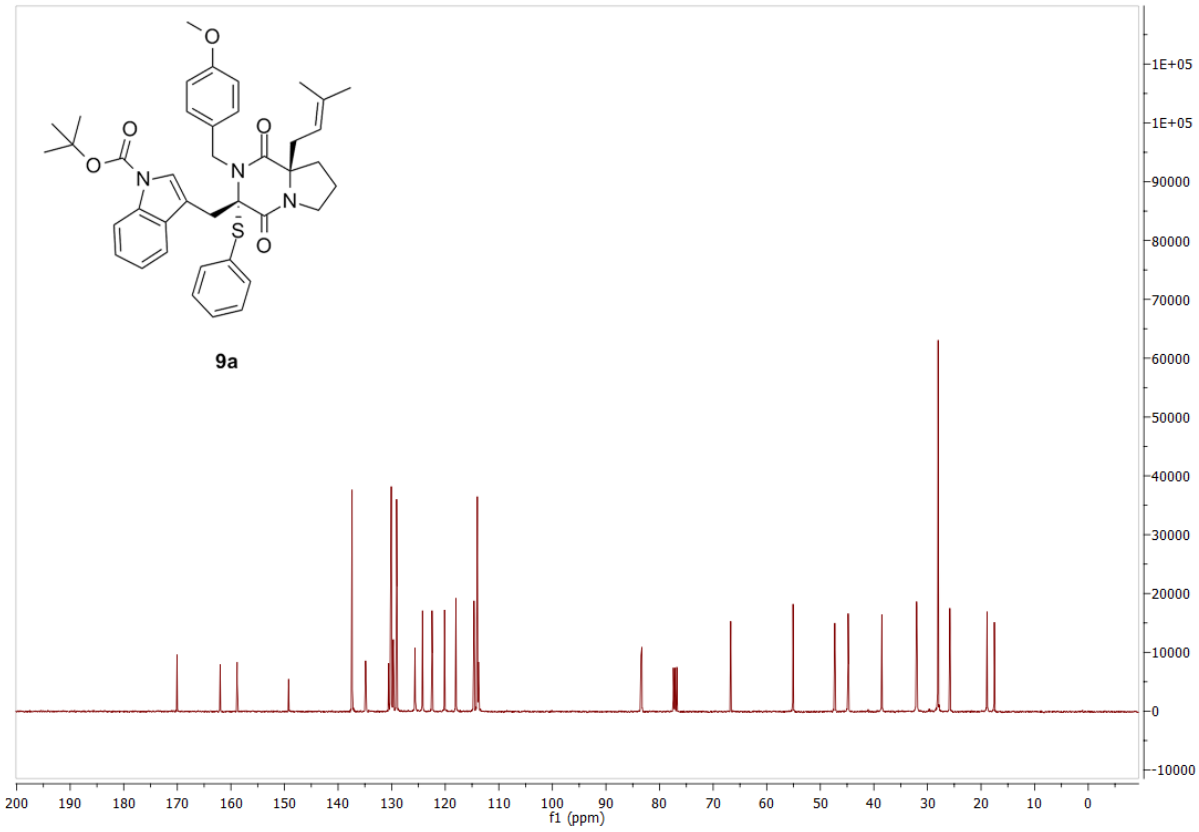
S3: R*f*: 0.18 (pet. ether/EtOAc, 1:2); m.p. 260 – 261 ℃; $[\alpha]_D^{21}$ -70 (*c* 0.3, $CHCl_3$); FTI (ATR) ν_{max} 2918, 2849, 1682, 1611, 1482, 1464, 1408, 1321, 1294, 1251, 1122, 1028, 940, 919, 744, 665, 589; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* 7.2 Hz, 1H, H14), 7.06 (td, *J* 7.7, 1.2 Hz, 1H, H12), 6.82 (s, 1H, H21), 6.77 (td, *J* 7.2, 0.9 Hz, 1H, H13), 6.70 (d, *J* 7.7 Hz, 1H, H11), 3.80 (brs, 1H, H9) 3.47 (d, *J* 6.9 Hz, 1H, H8), 3.45 (dd, *J* 6.2, 2.0 Hz, 2H, H1), 3.19 (dt, *J* 12.1, 6.1 Hz, 1H, H16), 2.78 (dt, *J* 13.1, 6.5 Hz, 1H, H3a), 2.30 (dd, *J* 10.2, 4.7 Hz, 1H, H6), 2.11 – 2.01 (m, 2H, H3b, H5a), 2.01 – 1.89 (m, 2H, H17), 1.89 – 1.80 (m, 3H, H5b, H2), 1.04 (s, 3H, H23), 1.03 (s, 3H, H24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C22), 169.5 (C19), 149.6 (C10), 134.8 (C15), 127.7 (C12), 123.7 (C14), 119.6 (C13), 110.7 (C11), 70.8 (C8), 66.8 (C4), 60.8 (C18), 53.5 (C7), 44.1 (C1), 40.4 (C6), 35.2 (C16), 32.7 (C5), 29.4 (C3), 29.2 (C2), 27.2 (C23), 24.5 (C17), 22.8 (C24). HRMS (ESI) calculated for $C_{21}H_{25}N_3O_2Na$ $[M+Na]^+$ 374.1844, found 374.1848.

Deprotection of indoline S1 to give S4 (corresponding to the isomer previously prepared by Baran and co-workers)

Indoline derivative **S1** (88 mg, 0.16 mmol) was diluted in 15 mL formic acid and stirred overnight at rt. Formic acid was then evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluent: EtOAc) to give **S4** (50 mg, 0.14 mmol, 87%) as white solid.

S4: R*f*: 0.22 (EtOAc); m.p. 210 – 211 ℃; $[\alpha]_D^{23}$ -17 (*c* 1.0, $CHCl_3$); FTI (ATR) ν_{max} 2925, 1673, 1610, 1463, 1401, 1368, 1330, 1124, 1017, 746, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* 7.5 Hz, 1H, H14), 7.06 (td, *J* 7.7, 1.2 Hz, 1H, H12), 6.77 (td, *J* 7.5, 0.8 Hz, 1H, H13), 6.72 (d, *J* 7.7 Hz, 1H, H11), 6.30 (s, 1H, H21), 3.84 (s, 1H, H9), 3.60 – 3.52 (m, 2H, H16, H1a), 3.44 – 3.32 (m, 2H, H8, H1b), 2.74 (ddd, *J* 12.7, 6.9, 5.4 Hz, 1H, H3a), 2.47 (dd, *J* 10.4, 5.8 Hz, 1H, H6), 2.38 (dd, *J* 13.0, 6.4 Hz, 1H, H17a), 2.12 (dd, *J* 13.3, 10.4 Hz, 1H, H5a), 2.07 – 1.90 (m, 2H, H2), 1.84 – 1.72 (m, 2H, H5b, H3b), 1.22 – 1.13 (m, 1H, H17b), 1.04 (s, 3H, H24), 0.90 (s, 3H, H23); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C22), 169.7 (C19), 149.2 (C10), 135.1 (C15), 127.6 (C14), 123.8 (C12), 119.7 (C13), 110.6 (C11), 70.8 (C8), 67.3 (C4), 59.7 (C18), 45.4 (C6), 43.8 (C1), 36.7 (C16), 35.4 (C7), 31.7 (C3,C5), 29.4 (C17), 26.6(C24), 24.6(C2), 20.2 (C23); HRMS (ESI) calculated for $C_{21}H_{25}N_3O_2Na$ $[M+Na]^+$ 374.1844, found 374.1851.

NMR spectra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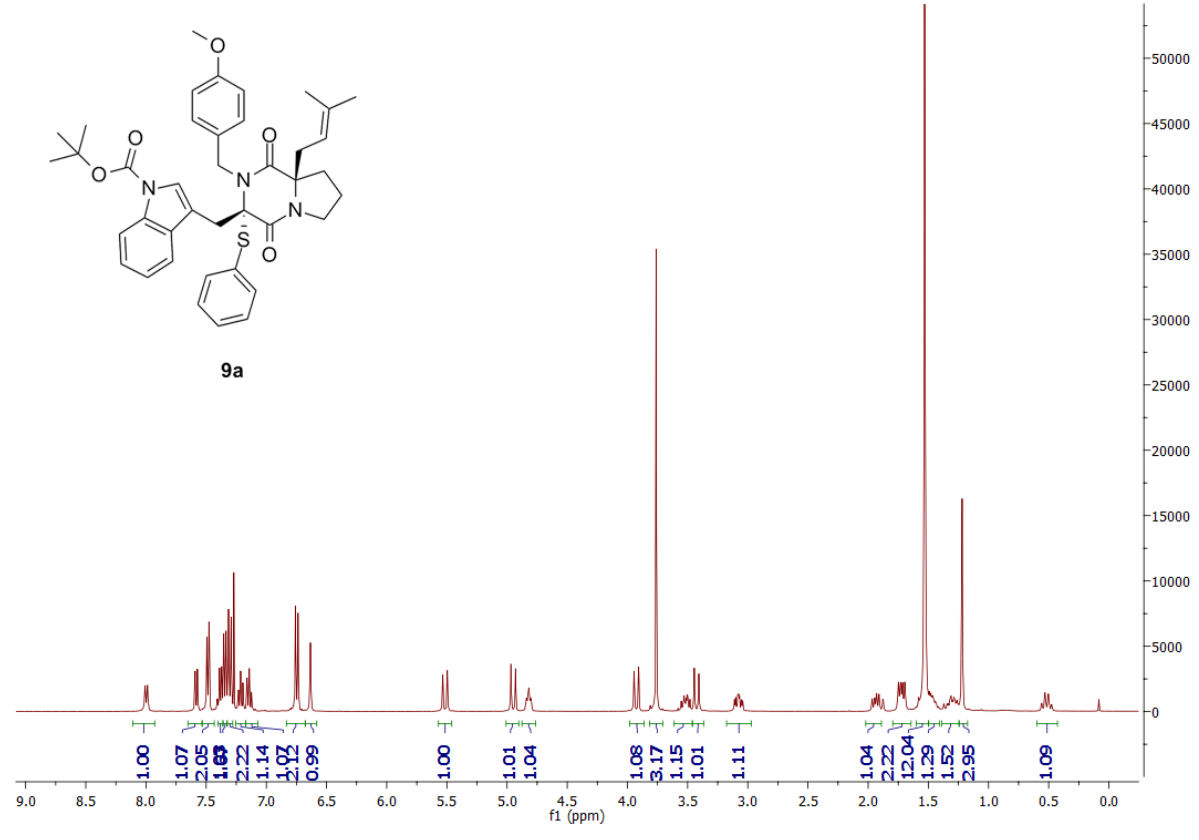
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1.04
1.08
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1.15
1.01
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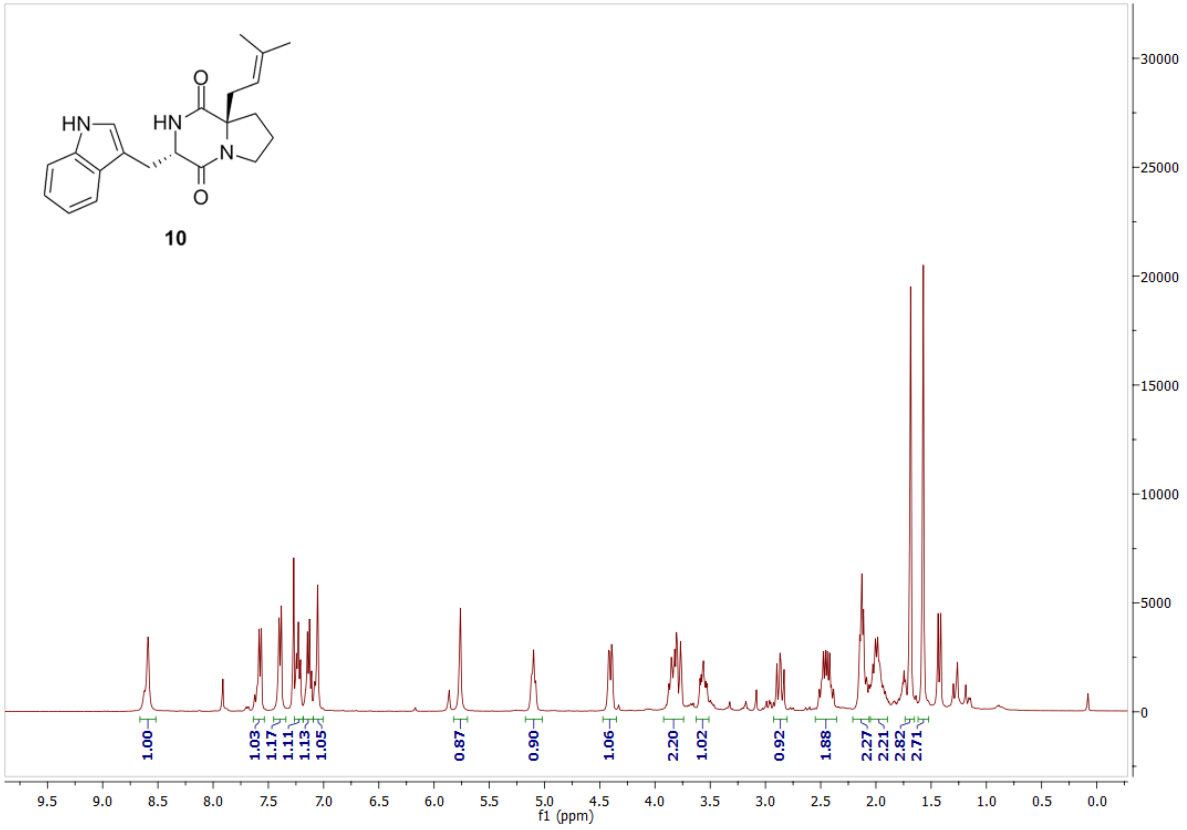
1.04
2.22
12.04
1.29
1.52
2.95
1.09
f1 (ppm)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O
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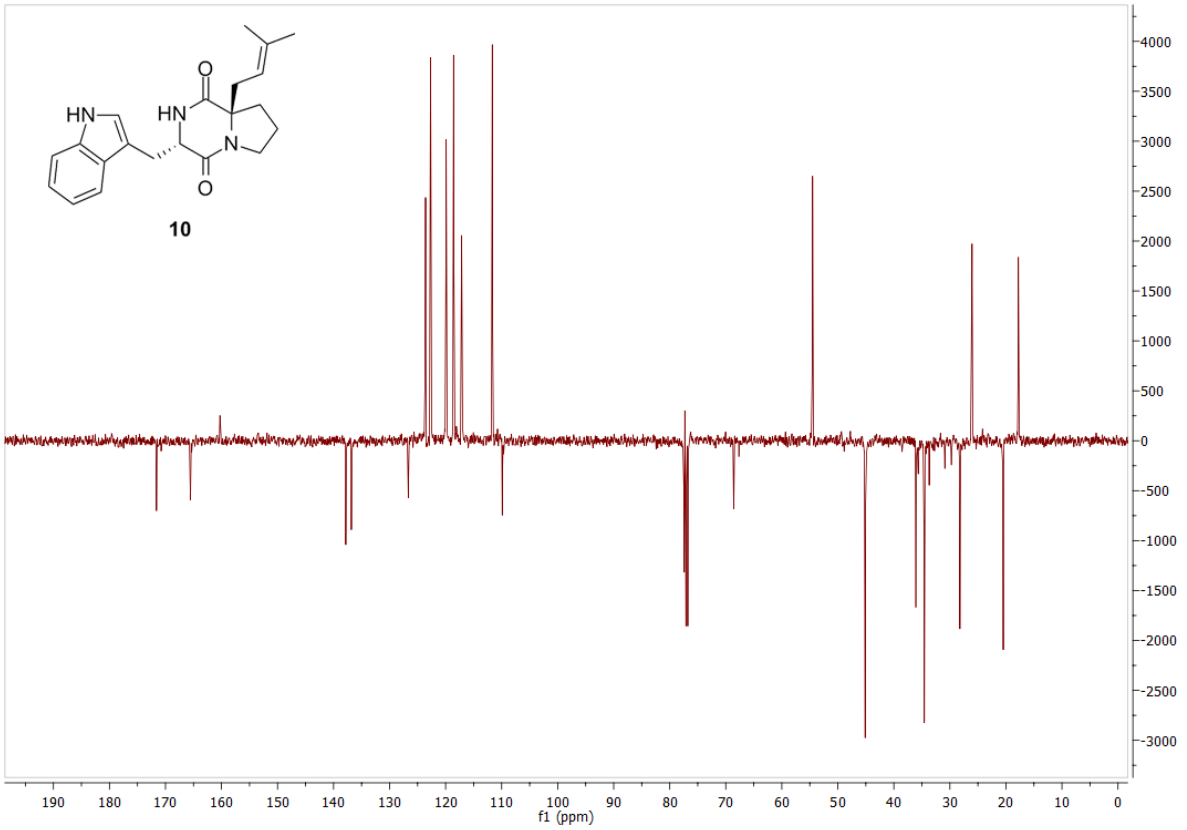
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O
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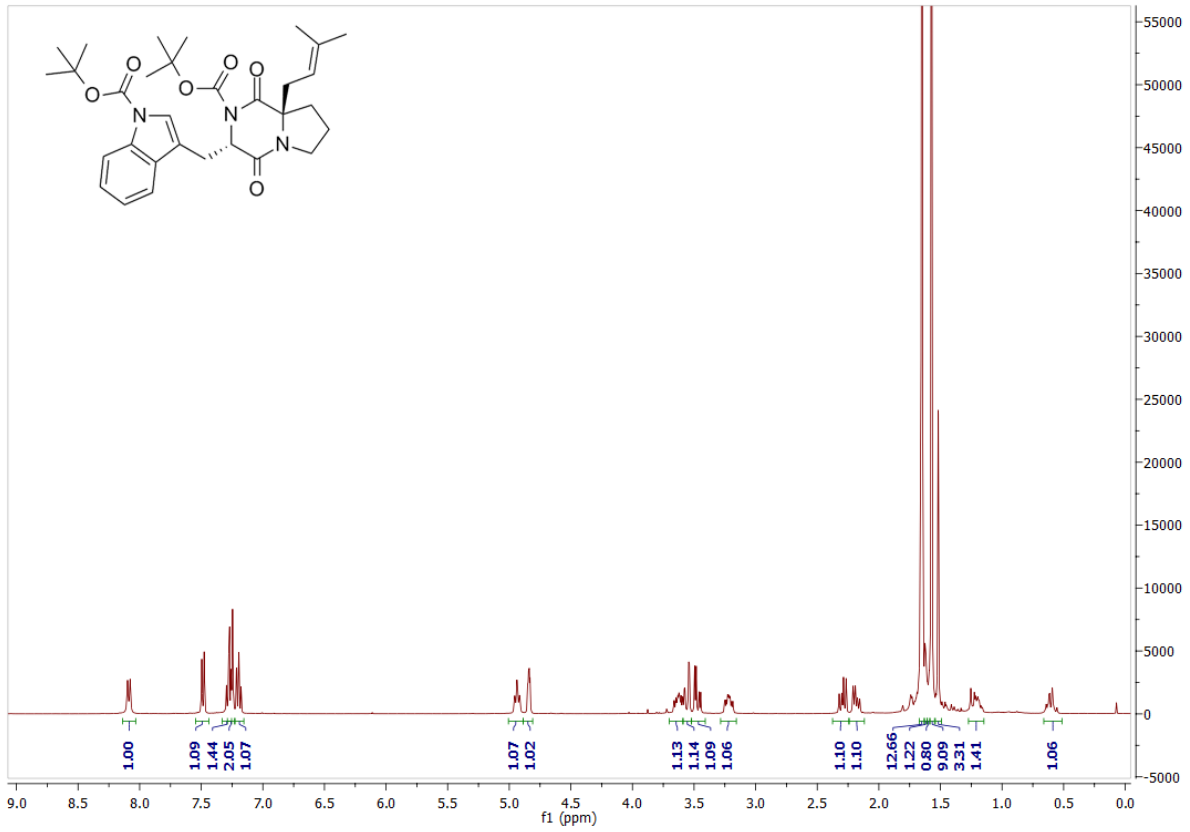

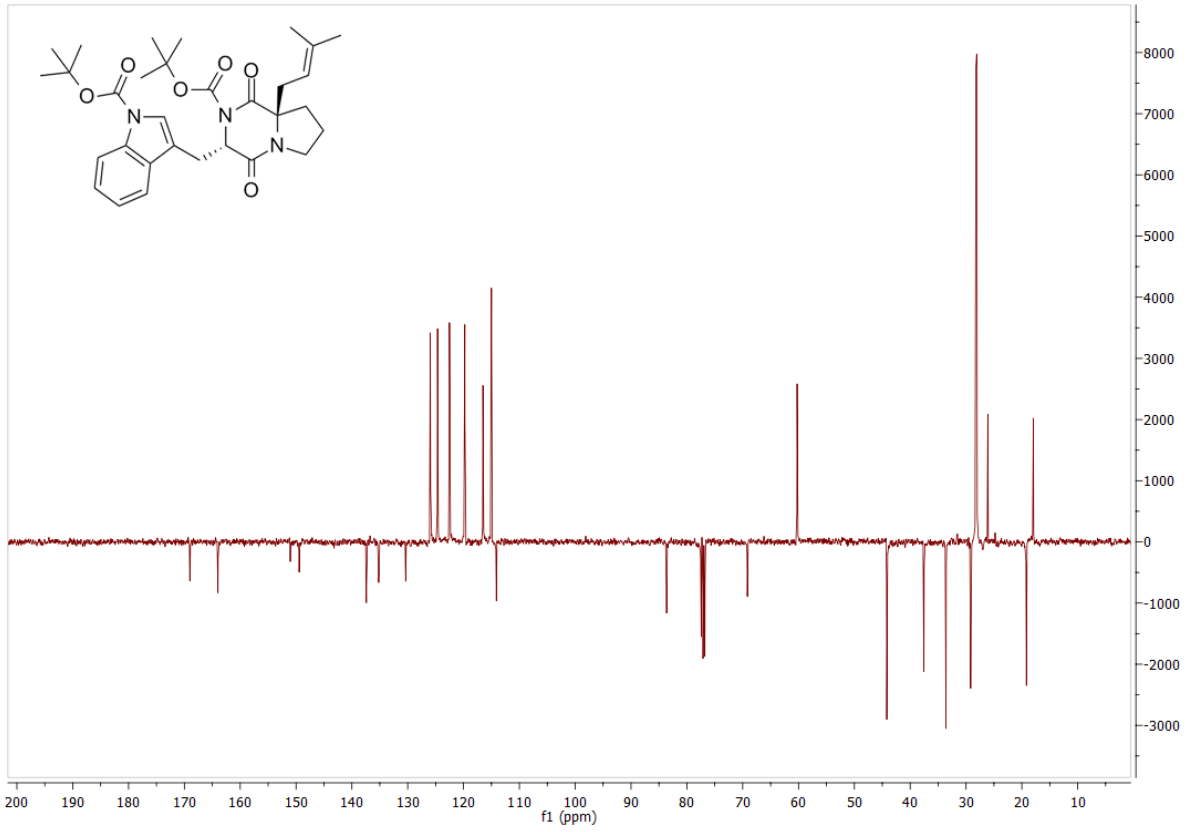

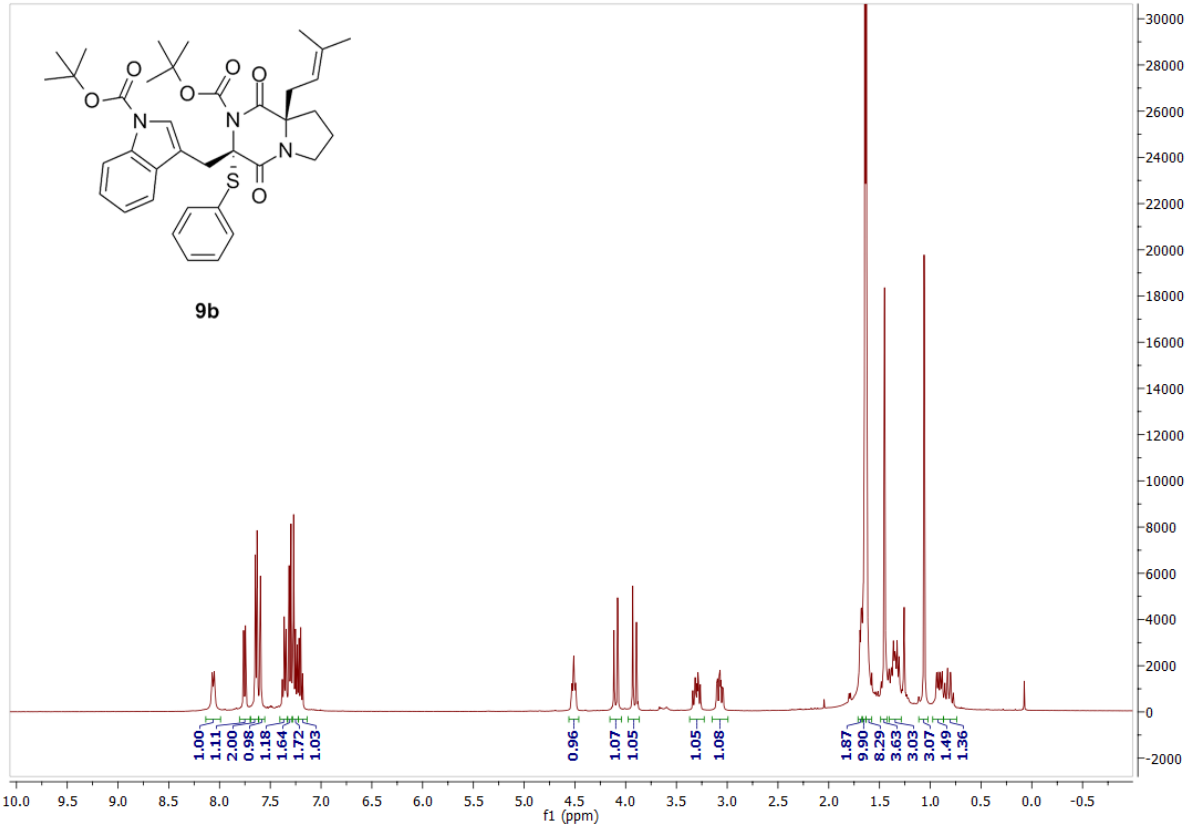
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8.29
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3.07
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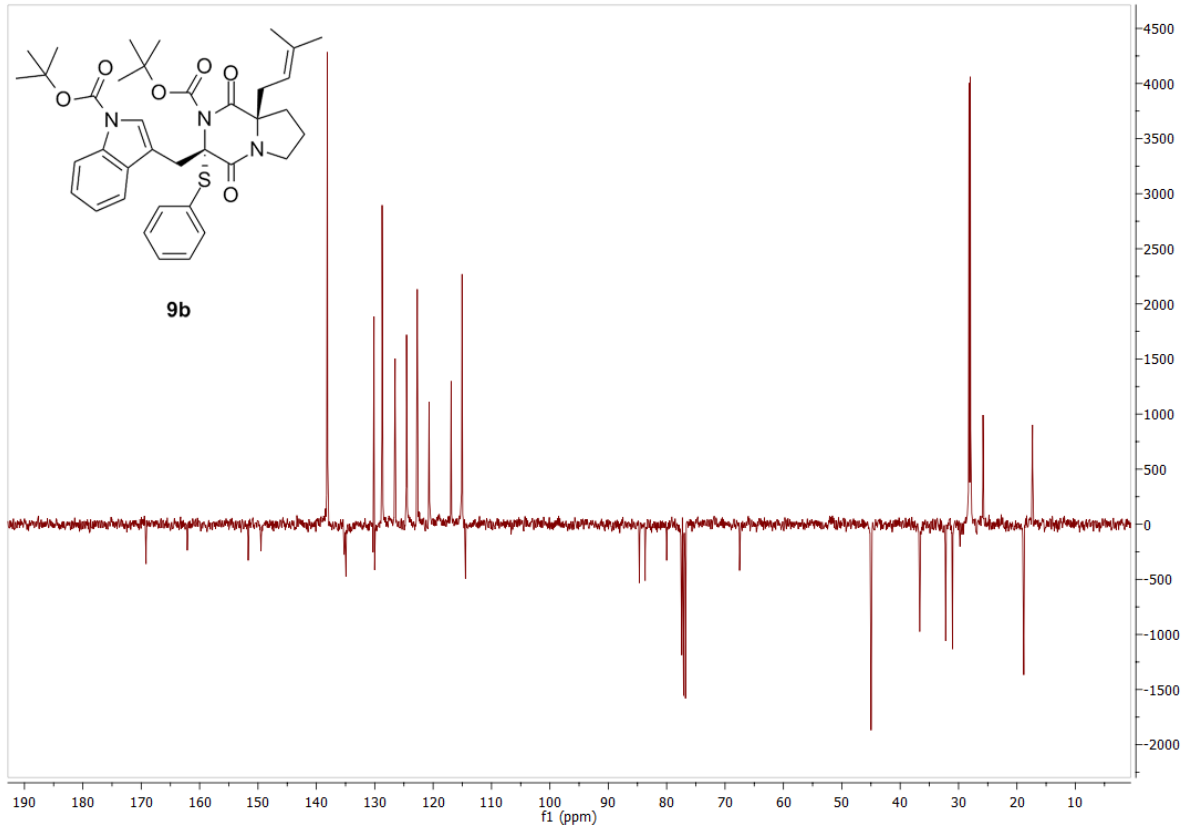
1.36
f1 (ppm)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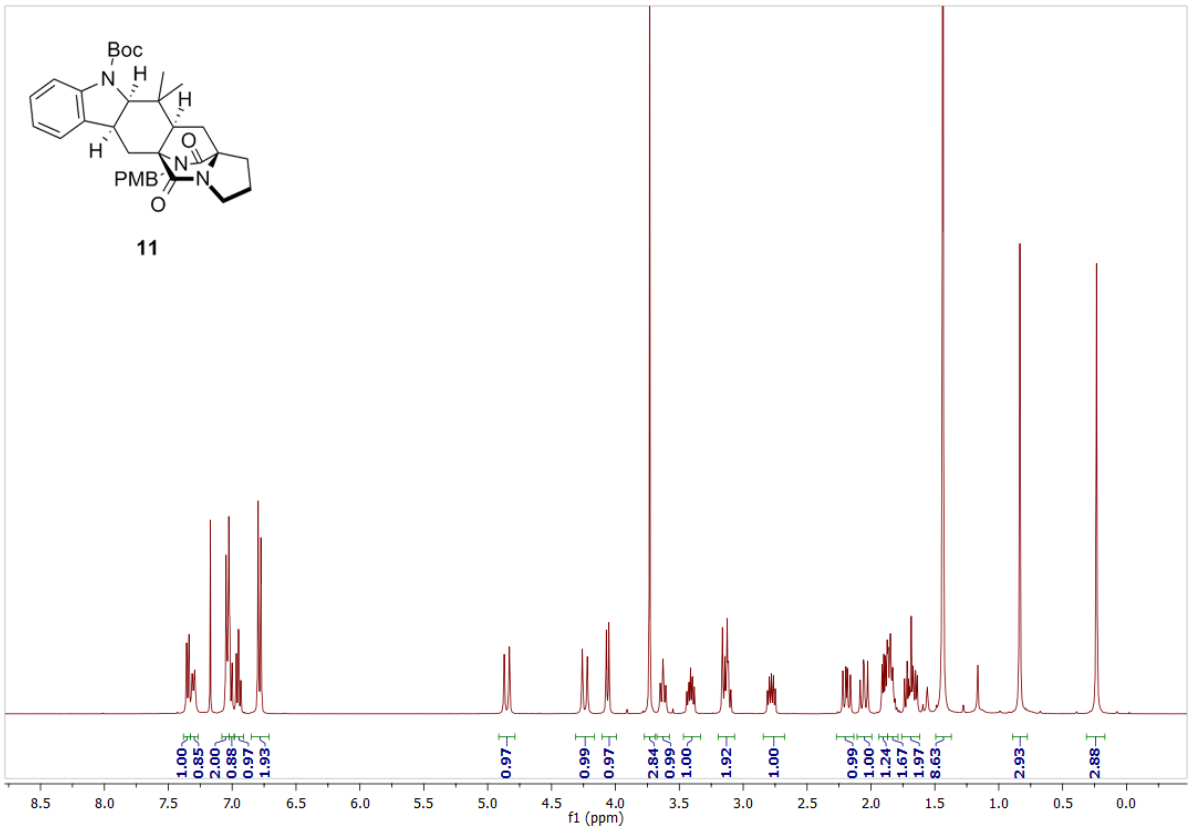
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H
H
O
N
PMB
N
O
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0.97
0.99
0.97
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0.99
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0.99
1.00
1.24
1.67
1.97
8.63
2.93
2.88
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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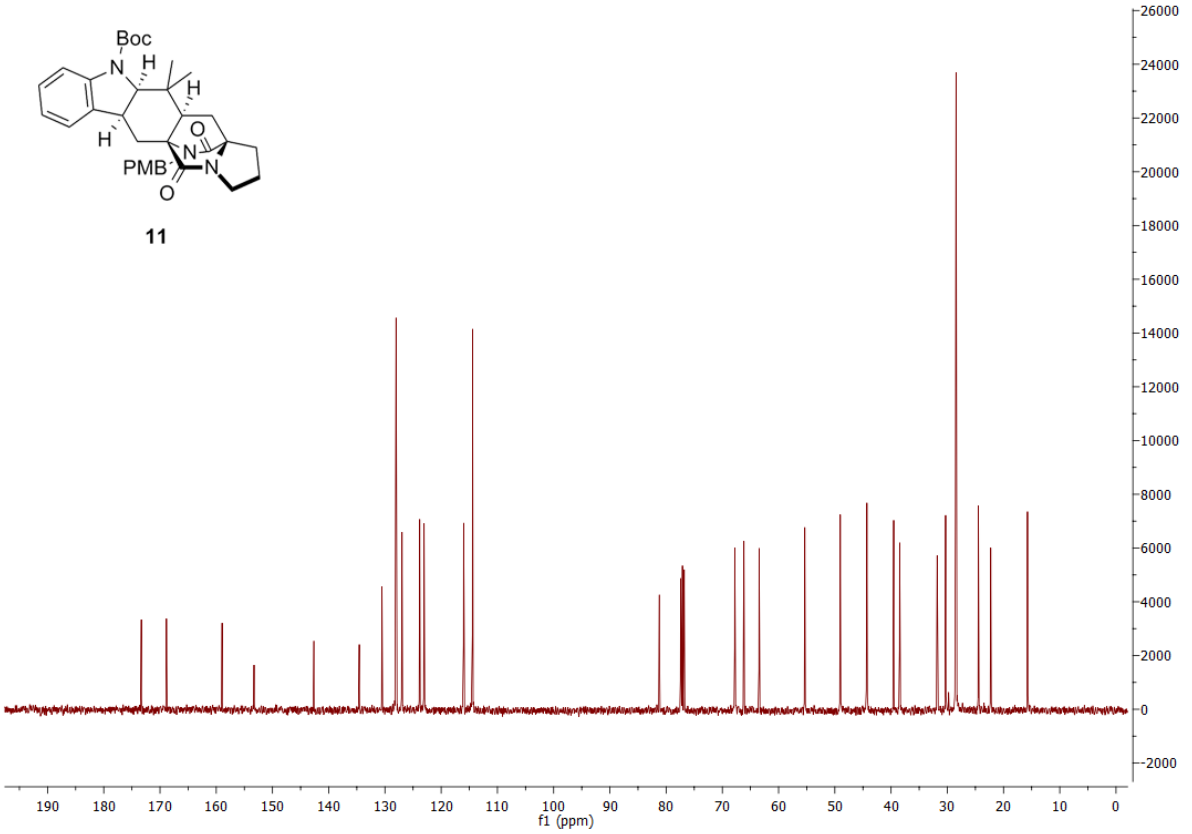
0.0
f1 (ppm)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H
H
O
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PMB
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O
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22000
20000
18000
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14000
12000
10000
8000
6000
4000
2000
0
-2000
190
180
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140
130
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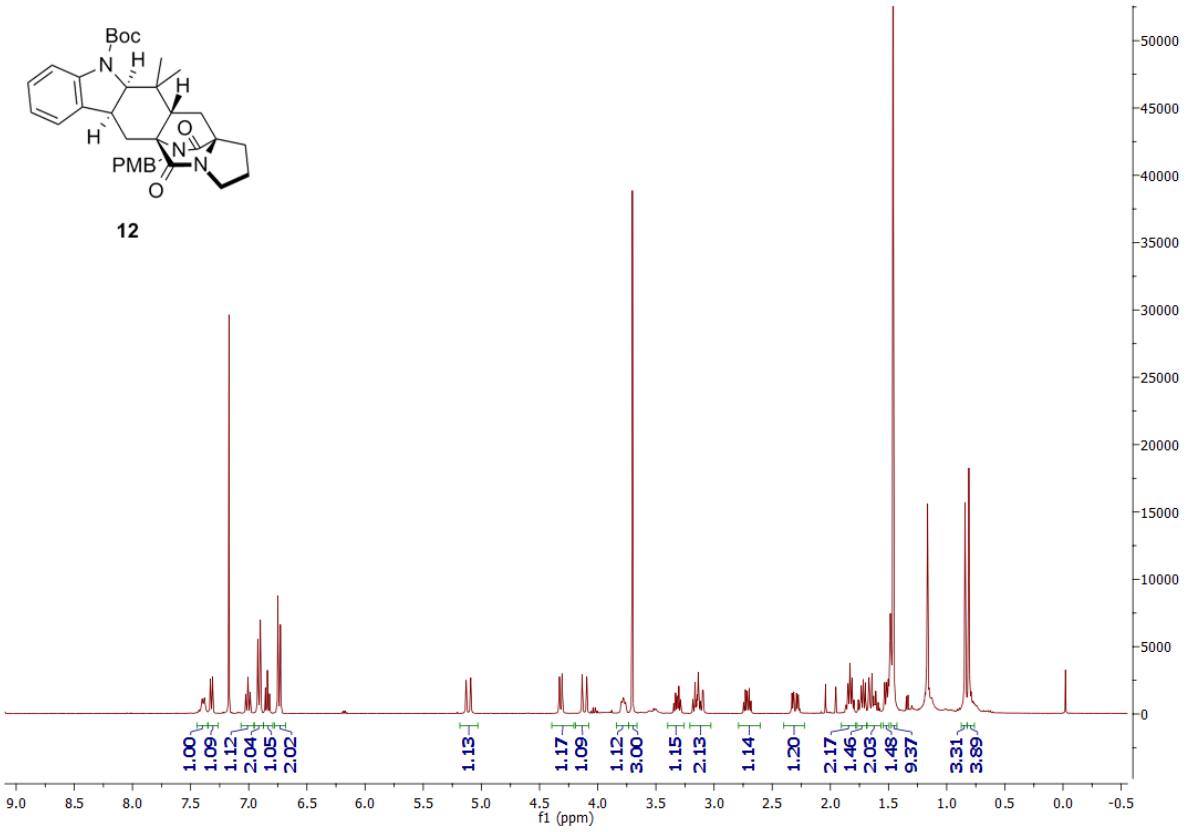
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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PMB
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2.02
1.13
1.17
1.09
1.12
3.00
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2.17
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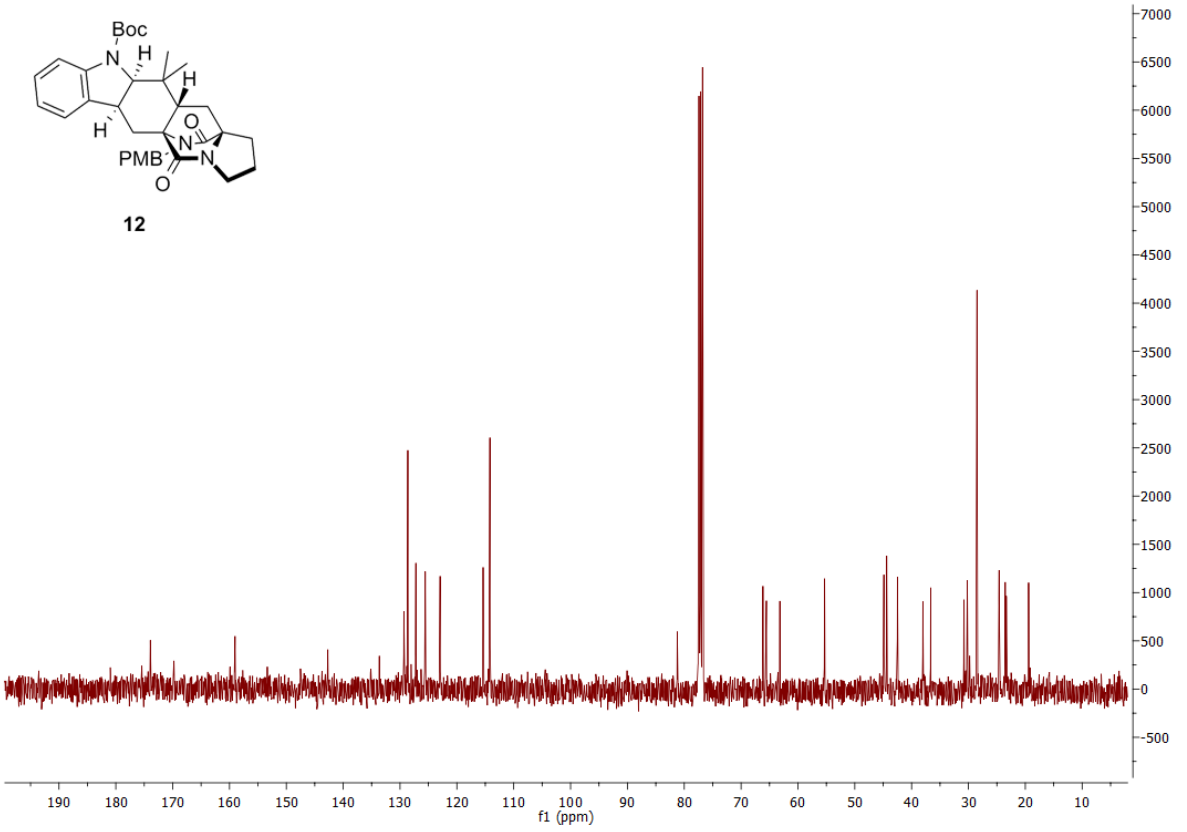
3.89
f1 (ppm)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N
PMB
N
O
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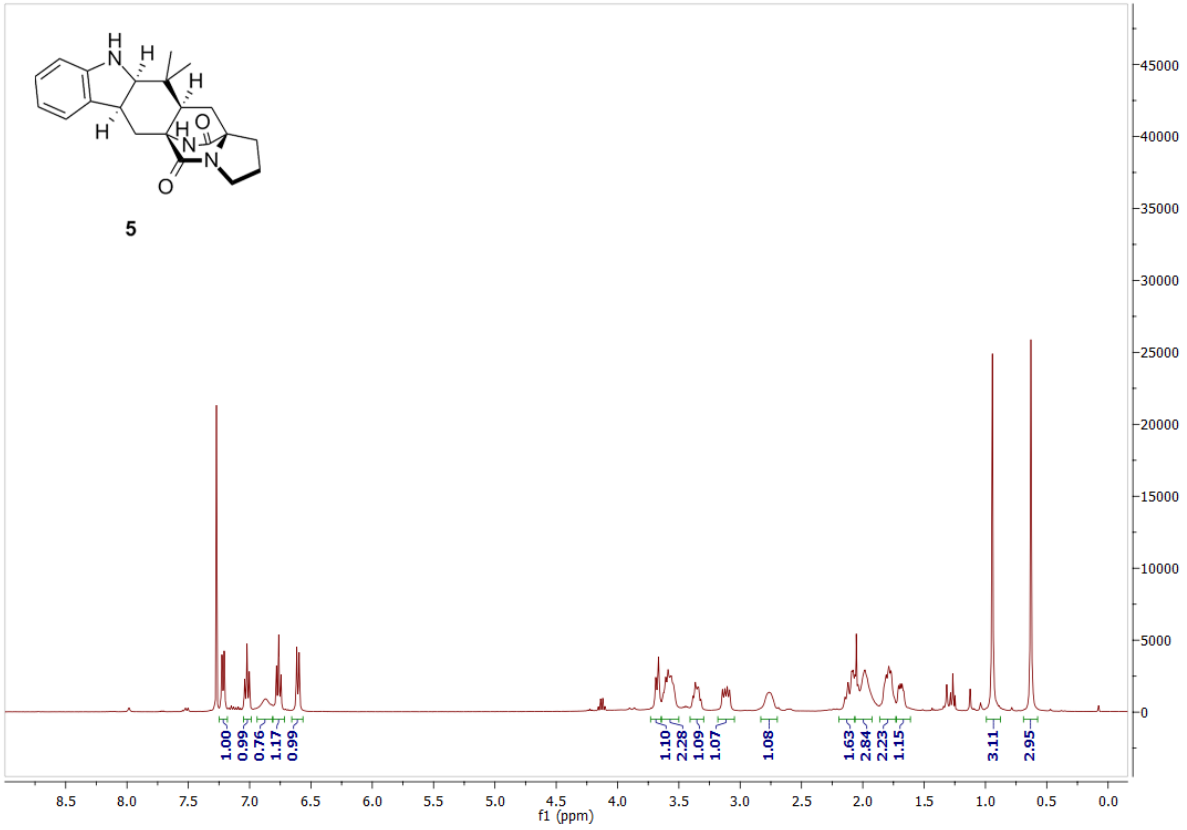
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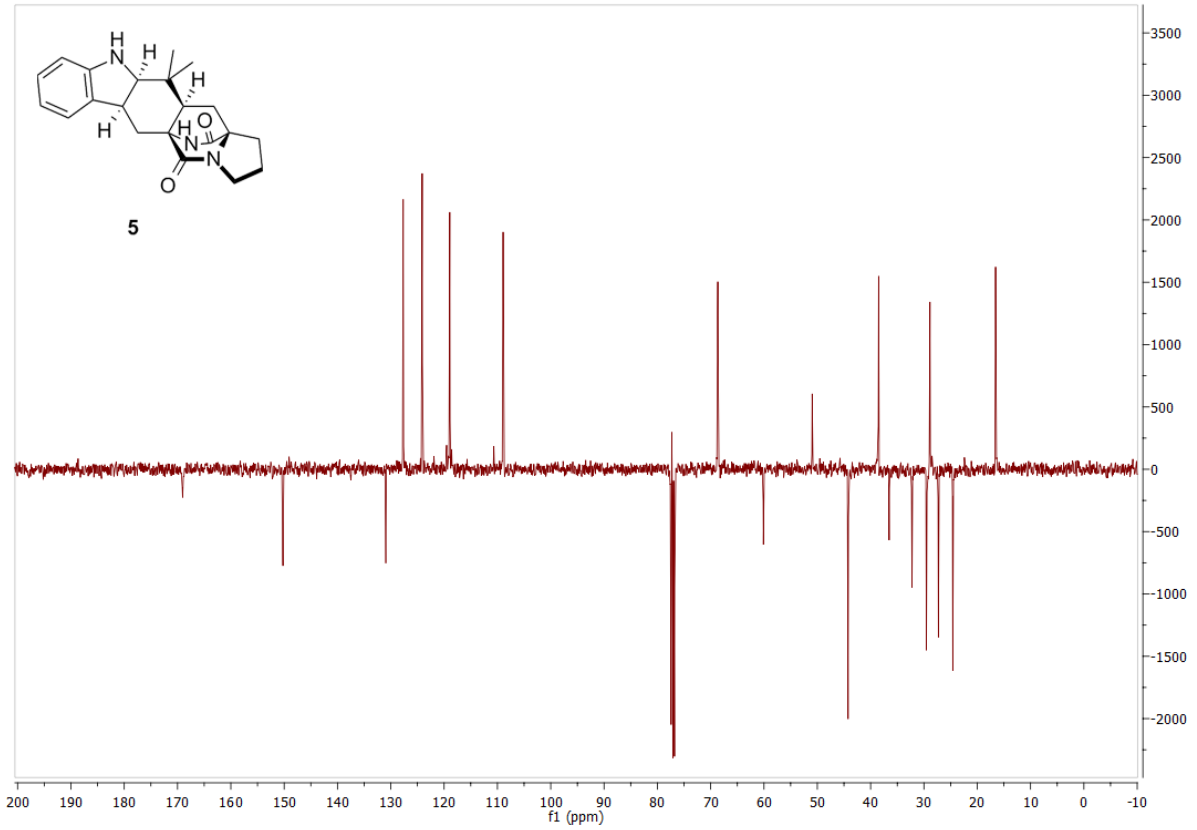
2.23
1.15
3.11
2.95
f1 (ppm)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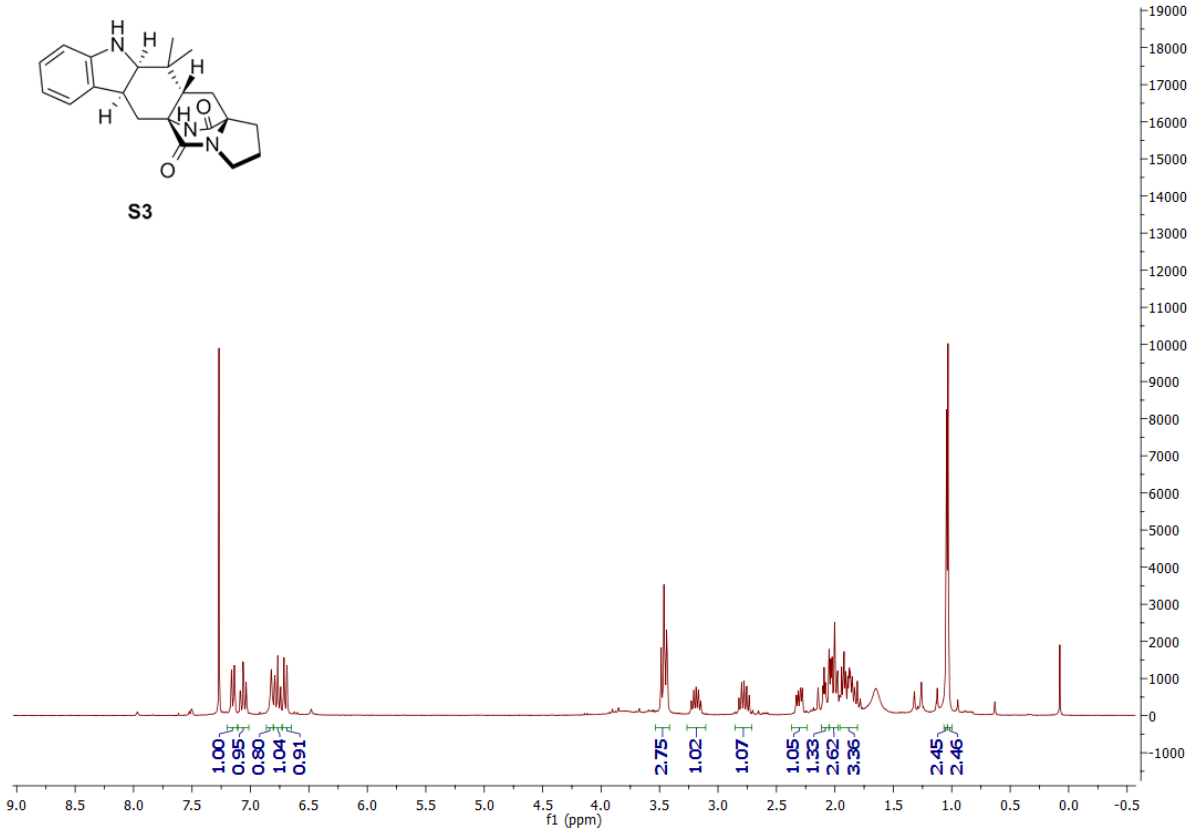
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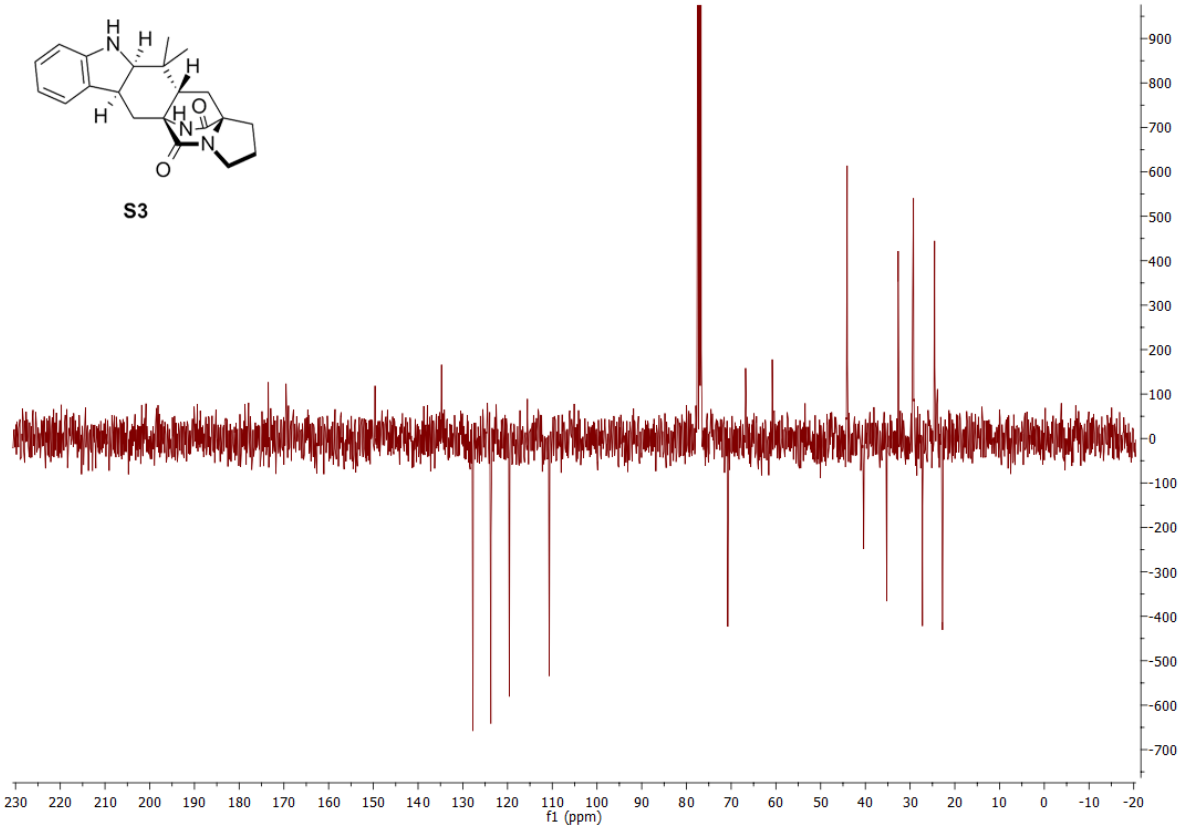
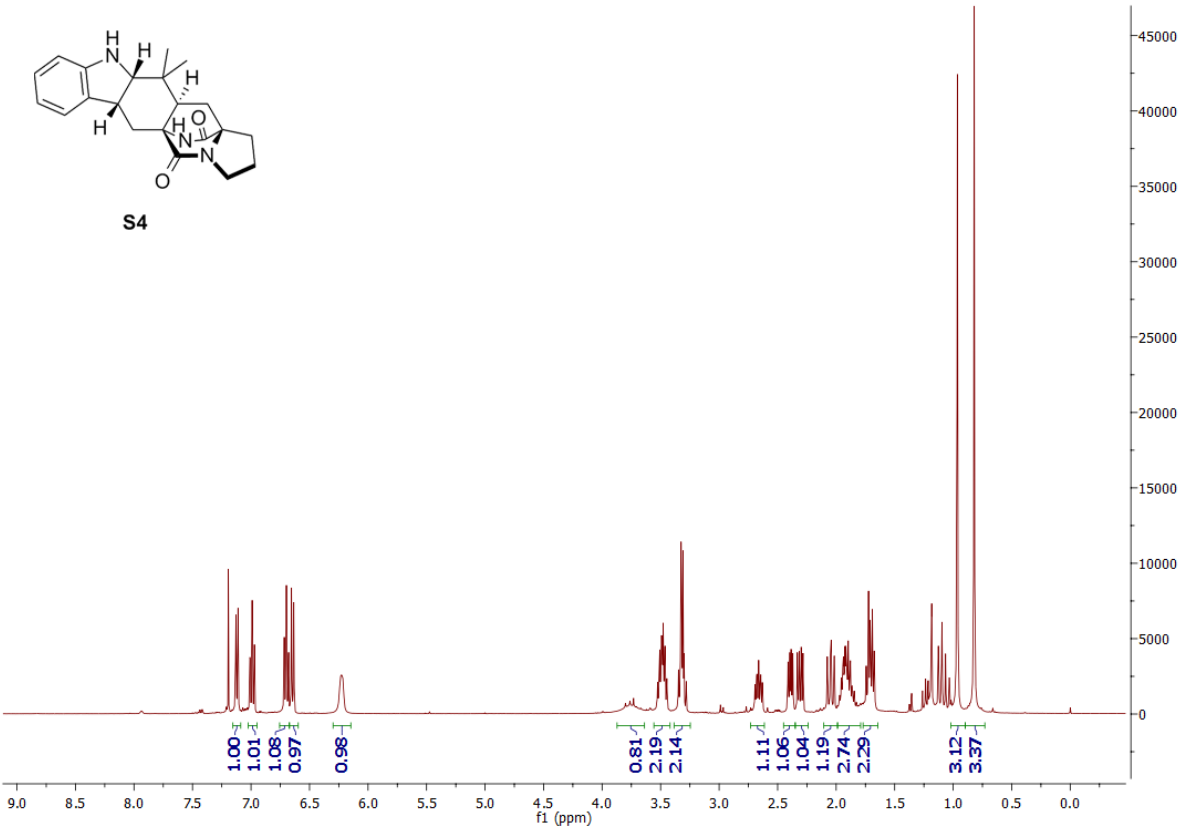
2.46
f1 (ppm)


S3
f1 (ppm)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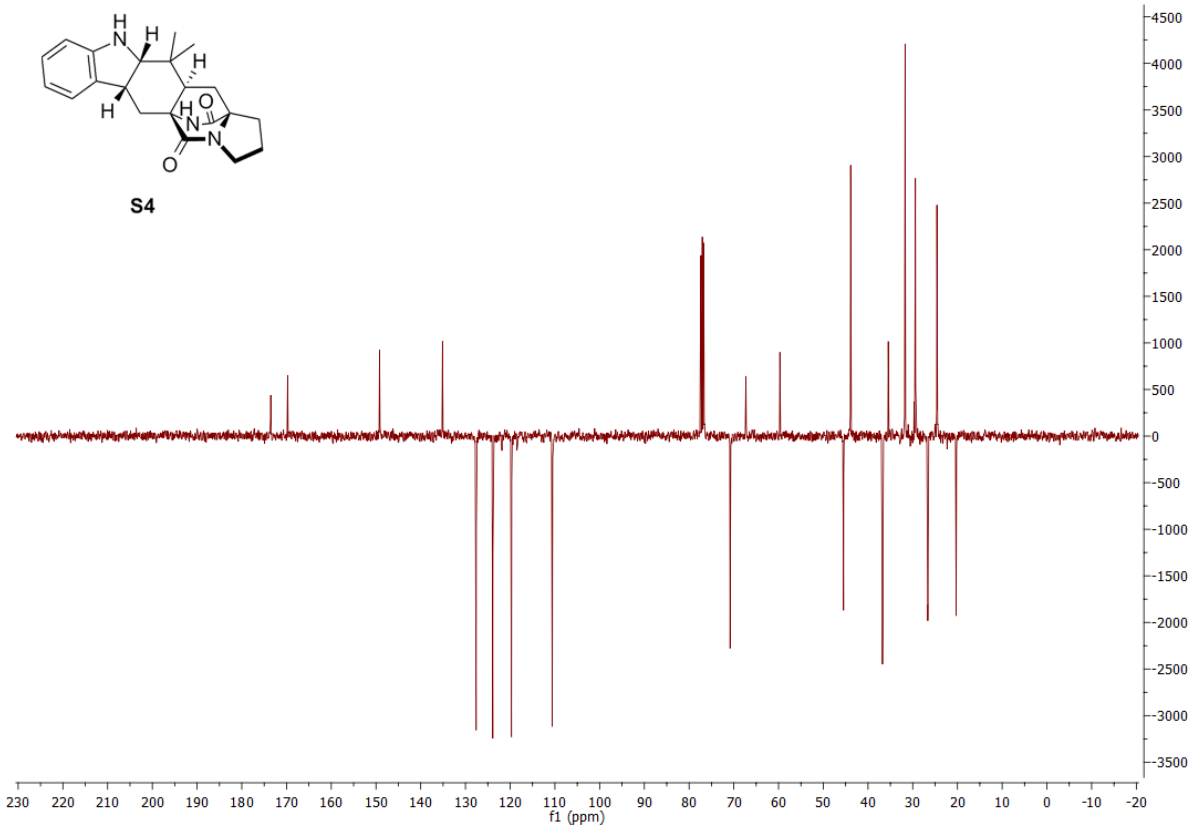
1.04
1.19
2.74
2.29
3.12
3.37
f1 (ppm)


S4
f1 (ppm)