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The Collective Synthesis of Natural Products via Organocascade Catalysis

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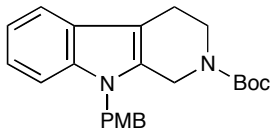
Supplementary Information

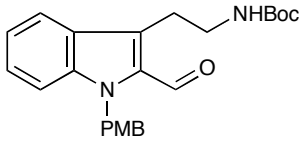
Materials and Methods. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego[1]. All solvents were purified according to the method of Grubbs[2]. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an acetone-dry ice bath. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still[3]. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching or *p*-anisaldehyde or ceric ammonium molybdate staining. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 (500 and 125 MHz) instrument, and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at d 7.27 and 77.0 ppm respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. High Performance Liquid Chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series chromatograph using a chiral column

(25 cm) and guard column (5 cm) as noted.

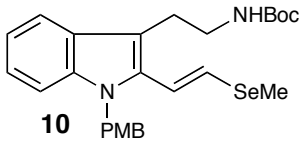


***tert*-Butyl 9-(4-methoxybenzyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate.** To a stirred solution of *tert*-butyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate **9** (3.49 g, 12.8 mmol, 1.00 equiv.) in DMF (20 mL) at 0 °C was added sodium hydride (60 wt. %, 1.03 g, 25.6 mmol, 2 equiv.) portionwise over five minutes. After complete addition, the solution was warmed to rt for 15 minutes and then recooled to 0 °C whereupon *para*-methoxybenzyl chloride (1.91 mL, 14.1 mmol, 1.1 equiv.) was added dropwise. The solution was warmed to rt for 15 minutes, recooled to 0 °C, and quenched by the cautious addition of water (3 mL). The solution was transferred to a separatory funnel, diluted with water (20 mL) and extracted with EtOAc (4×25 mL). The combined organic extracts were washed with water (3×20 mL) and brine (10 mL), dried over anhydrous magnesium sulphate, and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (gradient elution: hexanes to 30% EtOAc in hexanes) to give the title compound (4.75 g, 12.1 mmol, 94%) as a white solid. IR (film) 2971, 1693, 1613, 1513, 1464, 1416, 1365, 1306, 1240, 1173, 1108, 1035, 885, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 7.52 (d, 1H, *J* = 7.2 Hz, ArH), 7.30 (d, 1H, *J* = 8.1 Hz, ArH), 7.17 (t, 1H, *J* = 7.3 Hz, ArH), 7.12 (t, 1H, *J* = 7.3 Hz, ArH), 6.99 (d, 2H, *J* = 8.4 Hz, ArH), 6.80 (d, 2H, *J* = 8.4 Hz, ArH), 5.18 (s, 2H, PMPC$\mathbf{H_2}$N), 4.58-4.47 (m, 2H, NCC$\mathbf{H_2}$N), 3.77 (s, 3H, C$\mathbf{H_3}$O), 3.76-3.70 (m, 2H, $CH_2C\mathbf{H_2}$NBoc), 2.89-2.79 (m, 2H, C$\mathbf{H_2}CH_2$NBoc), 1.50 (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.44* (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 155.2, 136.8, 132.0, 131.8, 129.4, 127.6, 126.6, 121.4, 119.2,

117.9, 114.1, 109.2, 80.0, 55.2, 46.2, 42.4, 40.9, 28.4, 21.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{29}N_2O_3$) requires *m/z* 393.2173, found *m/z* 393.2148.



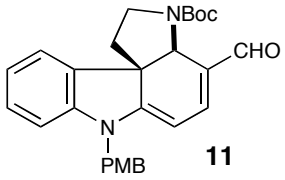
***tert*-Butyl 2-(1-(4-methoxybenzyl)-2-formyl-1*H*-indol-3-yl)ethylcarbamate.** To a stirred solution of *tert*-butyl 9-(4-methoxybenzyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (615 mg, 1.55 mmol, 1.00 equiv.) in 95:5 dioxane:water (8 mL) was added SeO_2 (344 mg, 3.10 mmol, 2.00 equiv.). The resulting solution was heated to 100 °C for five hours before being cooled to rt. After cooling to rt, the solution was filtered through a pad of celite and then the solution was transferred into a separatory funnel. EtOAc (40 mL) was added and the solution was washed with water (6×20 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The resulting brown oil was purified via flash column chromatography (gradient elution: hexanes to 40% EtOAc in hexanes) to give the title compound (550 mg, 1.35 mmol, 87%) as a white solid. IR (film) 2976, 1699, 1659, 1513, 1463, 1247, 1175, 1034, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H, C**H**O), 7.76 (d, 1H, *J* = 8.1 Hz, ArH), 7.42-7.38 (m, 2H, ArH), 7.21-7.16 (m, 1H, ArH), 7.06 (d, 2H, *J* = 8.3 Hz, ArH), 6.79 (d, 2H, *J* = 8.3 Hz, ArH), 5.75 (s, 2H, PMPC**H**$_2$), 4.66-4.58 (m, 1H, N**H**Boc), 3.75 (s, 3H, C**H**$_3$O), 3.49-3.42 (m, 2H, CH_2C**H**$_2$NHBoc), 3.34 (t, 2H, *J* = 6.6 Hz, C**H**$_2$$CH_2$NHBoc) 1.44 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 158.8, 155.9, 139.5, 132.3, 130.1, 128.2, 128.0, 127.6, 126.6, 121.4, 120.8, 113.9, 111.0, 79.5, 55.2, 47.3, 41.9, 28.4, 24.3; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{29}N_2O_4$) requires *m/z* 409.2127, found *m/z* 409.2122.



10

***tert*-Butyl 2-(1-(4-methoxybenzyl)-2-((*E*)-2-(methylselanyl)vinyl)-1*H*-indol-3-yl)ethylcarbamate (10).** Potassium hexamethyldisilazide (2.93 g, 14.7 mmol, 1.20 equiv.) and 18-crown-6 (3.88 g, 14.7 mmol, 1.20 equiv.) were added to a 250 mL flask in a glovebox. After removing from the glovebox, THF (100 mL) was added, whereupon the two reagents dissolved, and then the solution was cooled to –78 °C. Diethyl (methylselanyl)methylphosphonate (3.60 g, 14.7 mmol, 1.20 equiv.) was added dropwise via syringe and the resulting suspension stirred for one minute before adding *tert*-butyl 2-(1-(4-methoxybenzyl)-2-formyl-1*H*-indol-3-yl)ethylcarbamate (5.00 g, 12.24 mmol, 1.00 equiv.) in THF (20 mL) dropwise via syringe. The solution was removed from the cooling bath and allowed to warm to room temperature for 1.5 hours. The solution was purified directly via flash column chromatography (gradient elution: hexanes to 20% EtOAc in hexanes) to give the title compound as a separable mixture of olefin isomers (4.99 g, 9.96 mmol, 17:1 *E*:*Z*, 81%) as a white solid. *E* isomer: IR (film) 2975, 1705, 1512, 1463, 1365, 1247, 1173, 1034, 739; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J* = 7.8 Hz, ArH), 7.21 (d, 1H, *J* = 7.6 Hz, ArH), 7.19-7.15 (m, 1H, ArH), 7.14 (m, 1H, ArH), 6.98 (d, 2H, *J* = 8.6 Hz, ArH), 6.97 (d, 1H, *J* = 16.0 Hz, C**H**=CHSeCH_3), 6.82, (d, 2H, *J* = 8.6 Hz, ArH), 6.58 (d, 1H, *J* = 16.0 Hz, CH=C**H**SeCH_3), 5.30 (s, 2H, PMPC$\mathbf{H_2}$N), 4.69-4.63 (m, 1H, N**H**Boc), 3.78 (s, 3H, C$\mathbf{H_3}$O), 3.48-3.41 (m, 2H, C$\mathbf{H_2}$NHBoc), 3.05 (t, 2H, *J* = 7.0 Hz, C$\mathbf{H_2}$$CH_2$NHBoc), 2.22 (s, 3H, C$\mathbf{H_3}$Se), 1.46 (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 155.9, 137.0, 135.0, 129.9, 128.1, 127.2, 125.3, 122.3, 119.6,

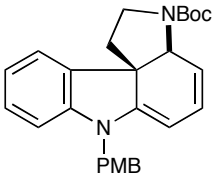
118.8, 118.7, 114.2, 110.4, 109.5, 79.1, 55.3, 46.9, 41.3, 28.5, 25.8, 5.8; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{33}N_2O_3Se$) requires *m/z* 501.1656, found *m/z* 501.1637.



11

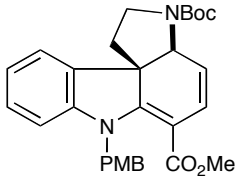
(3a*R*,11a*R*)-*tert*-Butyl 8-(4-methoxybenzyl)-11-formyl-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1(11a*H*)-carboxylate (11). A 25 mL flask was charged with *tert*-butyl 2-(1-(4-methoxybenzyl)-2-((*E*)-2-(methylselanyl)vinyl)-1*H*-indol-3-yl)ethylcarbamate (**10**) (300 mg, 0.601 mmol, 1.00 equiv.), (2*S*,5*S*)-2-*tert*-butyl-3-methyl-5-((naphthalen-1-yl)methyl)imidazolidin-4-one (**3**) (35.5 mg, 0.120 mmol, 20 mol%), and tribromoacetic acid (35.5 mg, 0.120 mmol, 20 mol%). Toluene (12 mL) was added and the resulting solution was cooled to –60 °C. Propynal (0.120 mL, 1.80 mmol) was added dropwise via syringe whereupon the flask was placed in a –40 °C bath for 13 hours. The resulting solution was allowed to warm to rt for 10 hours, concentrated, and purified via flash column chromatography (gradient elution: hexanes to 50% EtOAc in hexanes) to give the title compound (225.5 mg, 0.4918 mmol, 82%, 97% ee) as a dark orange foam. IR (film) 2974, 1686, 1662, 1627, 1606, 1513, 1479, 1462, 1397, 1364, 1248, 1171, 1087, 1033, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 9.54* (s, 1H, C**H**O), 9.52 (s, 1H, C**H**O), 7.25-7.20 (m, 3H, ArH), 7.20-7.14 (m, 2H, ArH), 7.04-7.00 (m, 2H, ArH), 7.00-6.92 (m, 1H, ArH), 6.90-6.86 (m, 2H, ArH), 6.82-6.76 (m, 1H, CHC**H**=CCHO), 5.66* (s, 1H, C**H**NHBoc), 5.53 (s, 1H, C**H**NHBoc), 5.22 (d, 1H, *J* = 6.7 Hz, C**H**CH=CCHO), 4.89-4.78 (m, 2H, PMPC$\mathbf{H_2}$N), 3.80 (s, 3H, C$\mathbf{H_3}$O), 3.72-3.64 (m, 1H,

C**H**HCH$_2$NHBoc), 3.61-3.52* (m, 1H, C**H**HCH$_2$NHBoc), 3.40-3.32 (m, 1H, CH**H**CH$_2$NHBoc), 2.60-2.49 (m, 1H, CH$_2$C**H**HNHBoc), 1.94-1.85 (m, 1H, CH$_2$CH**H**NHBoc), 1.61* (s, 9H, C(C**H$_3$**)$_3$), 1.57 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, * = minor rotamer) δ 191.2*, 190.6, 162.8*, 162.7, 159.2, 155.4, 155.0*, 144.9, 143.9, 142.9*, 134.7, 134.5*, 128.5, 128.4*, 127.9, 127.8*, 127.0*, 126.9, 124.8*, 124.3, 122.0, 121.98*, 121.93, 121.7*, 114.3, 108.2, 108.1*, 87.1, 80.2, 79.9*, 62.3, 61.4*, 55.3, 54.2, 53.5*, 46.3, 42.2*, 41.9, 40.5*, 39.7, 28.6*, 28.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{28}H_{31}N_2O_4$) requires *m/z* 459.2284, found *m/z* 459.2274; $[\alpha]_D^{23}$ = 137.7 (c = 1.00, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis using a Chiralcel OD-H (25 cm × 0.46 cm) column (20% IPA/hexane, flow = 1.0 mL/min); t_r = 15.66 min (minor) 19.45 min (major).



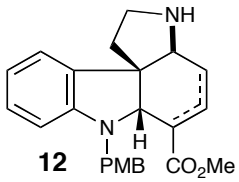
(3a*R*,11a*S*)-*tert*-Butyl 8-(4-methoxybenzyl)-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1(11a*H*)-carboxylate. A 250 mL flask was charged with (3a*R*,11a*R*)-*tert*-butyl 8-(4-methoxybenzyl)-11-formyl-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1(11a*H*)-carboxylate (**11**) (1.89 g, 4.12 mmol, 1.00 equiv.), $(Ph_3P)_3RhCl$ (3.81 g, 4.12 mmol, 1.00 equiv.), toluene (60 mL), and benzonitrile (10 mL), degassed and placed under an Ar atmosphere, and heated to 120 °C for 5.25 hours. The resulting solution was concentrated *in vacuo* at 100 °C and the residue purified via flash column chromatography (gradient elution: hexanes to 20% EtOAc in hexanes) to give the title compound (1.52 g, 3.53 mmol, 86%) as a colorless foam. IR (film) 2974, 1690, 1657, 1607, 1573, 1513, 1479,

1463, 1404, 1388, 1365, 1247, 1175, 1115, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 7.22-7.12 (m, 3H, ArH), 7.05 (d, 1H, *J* = 6.7 Hz, ArH), 7.00* (d, 1H, *J* = 6.7 Hz, ArH), 6.88-6.84 (m, 2H, ArH), 6.83-6.77 (m, 1H, ArH), 6.61 (d, 1H, *J* = 7.8 Hz, ArH), 5.92-5.87 (m, 1H, C**H**=CHCHN), 5.36* (dd, 1H, *J* = 9.6, 2.2 Hz, CH=C**H**CHN), 5.23 (dd, 1H, *J* = 9.6, 2.2 Hz, CH=C**H**CHN), 5.06-5.03* (m, 1H, C**H**NBoc), 4.94-4.92 (m, 1H, C**H**NBoc), 4.92-4.89 (m, 1H, C**H**CH=CHCHN), 4.74-4.63 (m, 2H, PMPC$\mathbf{H_2}$) 3.79 (s, 3H, C$\mathbf{H_3}$O), 3.50-3.36 (m, 2H, C$\mathbf{H_2}$NBoc), 2.58-2.47 (m, 1H, C**H**HCH_2NBoc), 1.83-1.75 (m, 1H, CH**H**CH_2NBoc), 1.57* (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.52 (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, * = minor rotamer) δ 158.8, 154.9, 154.6*, 153.8*, 153.7, 146.5*, 146.4, 134.2, 128.6*, 128.4, 128.2, 128.1*, 127.8, 123.6, 123.1*, 121.8, 121.7*, 119.4, 119.3*, 116.7, 116.4*, 114.1, 106.5, 106.4*, 86.8, 79.6, 79.5*, 62.6, 62.3*, 55.2, 52.1, 51.3*, 46.2*, 46.1, 41.8*, 41.4, 38.8*, 37.7, 28.6*, 28.6; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{27}H_{32}N_2O_3$) requires *m/z* 431.2335, found *m/z* 431.2303; $[\alpha]_D^{23} = -47.9$ (c = 0.22, $CHCl_3$).



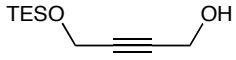
(3a*R*,11a*S*)-1-*tert*-Butyl 9-methyl 8-(4-methoxybenzyl)-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1,9(11a*H*)-dicarboxylate. A 25 mL flask was charged with (3a*R*,11a*S*)-*tert*-butyl 8-(4-methoxybenzyl)-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1(11a*H*)-carboxylate (340 mg, 0.790 mmol, 1.00 equiv.), triethylamine (0.127 mL, 0.908 mmol, 1.15 equiv.), and toluene (2.6 mL) and the resulting solution was cooled to –45 °C, whereupon phosgene (CAUTION: EXTREMELY TOXIC!) (1.92 M solution in toluene, 0.452 mL,

0.868 mmol, 1.10 equiv.) was added dropwise. The resulting solution was allowed to warm to rt over 2.5 hours and subsequently cooled to –30 °C. Triethylamine (0.127 mL, 0.908 mmol, 1.15 equiv.) and methanol (0.150 mL, 3.95 mmol, 5.00 equiv.) were added and the solution was allowed to warm to rt over 10 minutes. The resulting slurry was purified directly via flash column chromatography (gradient elution: hexanes to 20% EtOAc in hexanes) to give the title compound (340 mg, 0.696 mmol, 88%) as a bright yellow solid. IR (film) 2976, 1691, 1610, 1554, 1513, 1463, 1481, 1400, 1385, 1249, 1173, 1112, 1088, 1036, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 7.27-7.20 (m, 1H, ArH), 7.18-7.07 (m, 3H, ArH), 7.04-6.97 (m, 1H, ArH), 6.85-6.80 (m, 3H, ArH), 6.36 (dd, 1H, *J* = 9.8, 2.0 Hz, 5.34* (dd, 1H, *J* = 9.8, 2.2 Hz, C**H**=CHCHN), 5.32-5.16 (m, 2H, PMPC$\mathbf{H_2}$N), 5.22 (dd, 1H, *J* = 9.8, 2.2 Hz, C**H**=CHCHN), 5.07-5.05* (m, 1H, C**H**NBoc), 4.93-4.91 (m, 1H, C**H**NBoc), 3.78 (s, 3H, C$\mathbf{H_3}$OAr), 3.55-3.44 (m, 2H, C$\mathbf{H_2}$NBoc), 3.54 (s, 3H, C$\mathbf{H_3}$OCO), 3.53* (s, 3H, C$\mathbf{H_3}$OCO), 2.63-2.51 (m, 1H, C**H**HCH$_2$NBoc), 1.84-1.77 (m, 1H, CH**H**CH$_2$NBoc), 1.57* (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.52 (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, * = minor rotamer) δ 166.6*, 166.5, 162.2*, 161.6, 158.62, 158.60*, 154.8, 154.6*, 145.9*, 145.8, 134.5, 134.4*, 128.5, 128.4*, 128.2*, 128.1, 127.6, 127.5*, 124.9, 124.5*, 122.2, 122.1*, 121.6, 121.5*, 114.6, 114.4*, 113.94, 113.92*, 109.5*, 109.4, 93.7, 79.9, 79.8*, 63.3, 63.1*, 55.2, 54.8, 54.1*, 51.2, 51.1*, 50.2*, 49.9, 41.9*, 41.5, 40.0*, 38.8, 28.6*, 28.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{29}H_{33}N_2O_5$) requires *m/z* 489.2389, found *m/z* 489.2379; $[\alpha]_D^{23}$ = 34.3 (c = 0.25, $CHCl_3$).

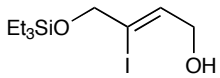


12

Inseparable mixture of **(3a*R*,8a*R*,11a*S*)-Methyl 8-(4-methoxybenzyl)-2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate** and **(3a*R*,8a*S*,11a*S*)-methyl 8-(4-methoxybenzyl)-2,3,8,8a,9,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (12).** To a solution of (3a*R*,11a*S*)-1-*tert*-butyl 9-methyl 8-(4-methoxybenzyl)-2,3-dihydro-8*H*-pyrrolo[2,3-*d*]carbazole-1,9(11a*H*)-dicarboxylate (117.5 mg, 0.2405 mmol, 1.00 equiv.) in CH_2Cl_2 (4.8 mL) at −78 °C was added neat Dibal-H (0.107 mL, 0.600 mmol, 2.5 equiv.) dropwise. The resulting solution was removed from the bath and allowed to warm to 0 °C before being recooled to −78 °C. Methanol (30 μL) and trifluoroacetic acid (2.4 mL) were sequentially added and the resulting solution was allowed to warm to rt for three hours. The solution was cooled to 0 °C and neutralized by slow addition of ammonium hydroxide solution (28 wt%, 5 mL). The resulting biphasic mixture was stirred with saturated aqueous sodium potassium tartrate (5 mL) for 30 minutes. The solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (4×10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (gradient elution: NH_3 treated SiO_2, CH_2Cl_2 to 3% MeOH in CH_2Cl_2) to give the title compound (75.9 mg, 0.194 mmol, 81%) as an inseparable mixture of epimers and olefin isomers and a colorless gum. HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{27}N_2O_3$) requires *m/z* 391.2022, found *m/z* 391.2001.

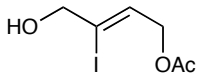


4-(triethylsilyloxy)but-2-yn-1-ol. To a mixture of butyne-1,4-diol (3.9 g, 46 mmol, 4.0 equiv.), and imidazole (1.2 g, 17 mmol, 1.5 equiv.) in DMF (70 mL) at 0 °C was added chlorotriethylsilane (1.9 mL, 11 mmol, 1.0 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature for 30 minutes before being poured into a separatory funnel and diluted with water (100 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with water (3 x 50 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude oil was purified via flash column chromatography (gradient elution: hexanes to 35% ethyl acetate in hexanes) to give the title compound (1.45 g, 7.2 mmol, 63%) as a colorless oil. IR (film) 3369, 2955, 2877, 1457, 1424, 1370, 1239, 1131, 1078, 1009, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (t, 2H, *J* = 1.7 Hz, SiOC**H**$_2$) 4.33 (dt, 2H, *J* = 6.0, 1.6 Hz, HOC**H**$_2$) 1.64 (t, 1H, *J* = 6.1 Hz, **H**O), 1.01 (t, 9H, *J* = 8.0 Hz, $SiCH_2C\mathbf{H}_3$), 0.68 (q, 6H, *J* = 8.0 Hz, $SiC\mathbf{H}_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.4, 83.0, 51.6, 51.3, 6.7, 4.4.



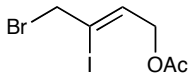
(Z)-3-iodo-4-(triethylsilyloxy)but-2-en-1-ol. To a solution of 4-(triethylsilyloxy)but-2-yn-1-ol (4.65 g, 23.2 mmol, 1.0 equiv.) in THF (116 mL, 0.2 M) at 0 °C was added Vitride (9.2 mL, 65% solution, 30 mmol, 1.3 equiv.) dropwise. The resulting mixture was allowed to stir at 0 °C for 15 minutes before I_2 (8.24 g, 32.5 mmol, 1.4 equiv.) was added portionwise and the reaction allowed to stir for an additional 15 minutes. Saturated aqueous $Na_2S_2O_3$ (25 mL) and Rochelle's salt (50 mL) were added and the biphasic mixture was allowed to stir at rt for 30 minutes before being extracted with ethyl acetate

(3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and purified via flash column chromatography (gradient elution: hexanes to 20% ethyl acetate in hexanes) to give the title compound (4.92 g, 15.0 mmol, 65%) as a colorless oil. IR (film) 3744, 2954, 2876, 1654, 1456, 1413, 1238, 1115, 1047, 1002, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (tt, 1H, *J* = 5.8, 1.5 Hz, C**H**), 4.32-4.29 (m, 2H, SiOC$\mathbf{H_2}$), 4.29-4.28 (m, 2H, HOC$\mathbf{H_2}$), 1.62 (t, 1H, *J* = 5.8 Hz, **H**O), 1.00 (t, 9H, *J* = 8.0 Hz, $SiCH_2C\mathbf{H_3}$), 0.67 (q, 6H, *J* = 8.0 Hz, $SiC\mathbf{H_2}CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.1, 107.7, 70.9, 66.6, 6.8, 4.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{10}H_{22}IO_2Si$) requires *m/z* 329.0428, found *m/z* 329.0424.



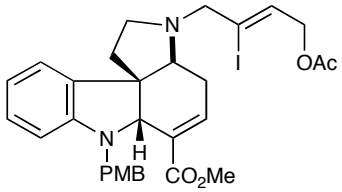
(*Z*)-4-hydroxy-3-iodobut-2-enyl acetate. To a solution of (*Z*)-3-iodo-4-(triethylsilyloxy)but-2-en-1-ol (2.15 g, 6.55 mmol, 1.0 equiv.) and triethyl amine (1.4 mL, 10 mmol, 1.5 equiv.) in CH_2Cl_2 (30 mL) at 0 °C was added acetyl chloride (0.51 mL, 7.2 mmol, 1.1 equiv.) dropwise and the resulting mixture was allowed to warm to rt for 5 minutes after which saturated aqueous sodium bicarbonate (20 mL) was added and the mixture transferred to a separatory funnel. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. To this oil was added methanol (50 mL) and para-toluenesulfonic acid hydrate (125 mg, 0.66 mmol, 0.10 equiv.) and the mixure stirred at room temperature for 20 minutes. The resulting mixture was quenched by the addition of saturate aqueous sodium bicarbonate (10 mL) and the solution extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were

washed with water (25 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and purified via flash column chromatography (gradient elution: hexanes to 50% ethyl acetate in hexanes) to give the title compound (1.44 g, 5.62 mmol, 86%) as a colorless oil. IR (film) 3414, 1720, 1378, 1224, 1083, 1074, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (tt, 1H, *J* = 5.8, 1.4 Hz, C**H**), 4.70 (d, 2H, *J* = 5.9 Hz, CHC$\mathbf{H_2}$), 4.31 (d, 2H, *J* = 5.7 Hz, HOC$\mathbf{H_2}$), 2.21 (t, 1H, *J* = 6.4 Hz, **H**O), 2.11 (s, 3H, C$\mathbf{H_3}$CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 129.6, 110.1, 71.1, 67.8, 20.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_6H_{10}IO_3$) requires *m/z* 256.9669, found *m/z* 256.9645.



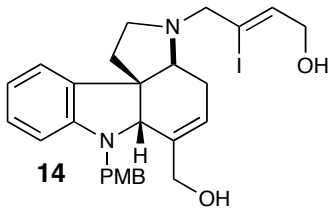
13

(*Z*)-4-bromo-3-iodobut-2-enyl acetate (13). To a solution of PPh_3 (1.62 g, 6.18 mmol, 1.10 equiv.) in CH_2Cl_2 (28 mL, 0.2 M) at 0 °C was added Br_2 (0.317 mL, 6.18 mmol, 1.10 equiv.) and triethyl amine (1.03 mL, 7.33 mmol, 1.3 equiv.) and the solution was allowed to stir at 0 °C for 10 minutes before (*Z*)-4-hydroxy-3-iodobut-2-enyl acetate (1.44 g, 5.62 mmol, 1.00 equiv.) was added as a solution in CH_2Cl_2 (5 mL). The reaction mixture was allowed to stir for 10 minutes before being directly purified via flash column chromatography (gradient elution: hexanes to 20% ethyl acetate in hexanes) to give the title compound (1.56 g, 4.89 mmol, 87%) as a colorless oil. IR (film) 1737, 1427, 1377, 1226, 1092, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (t, 1H, *J* = 5.7 Hz, C**H**), 4.57 (d, 2H, *J* = 5.7 Hz, OC$\mathbf{H_2}$), 4.27-4.26 (m, 2H, BrC$\mathbf{H_2}$), 2.03 (s, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 134.7, 103.0, 68.2, 41.8, 21.2; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_6H_9BrIO_2$) requires *m/z* 318.8825, found *m/z* 318.8821.



(3a*R*,8a*R*,11a*S*)-methyl 8-(4-methoxybenzyl)-1-((*Z*)-4-acetoxy-2-iodobut-2-enyl)-2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate. To a mixture of (3a*R*,8a*R*,11a*S*)-methyl 8-(4-methoxybenzyl)-2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate and (3a*R*,8a*S*,11a*S*)-methyl 8-(4-methoxybenzyl)-2,3,8,8a,9,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (**12**) (112.5 mg, 0.2880 mmol, 1.00 equiv.) in DMF (0.40 mL) was added sequentially 1,8-diazabicyclo[5.4.0]undec-7-ene (8 μL, 0.05 mmol, 0.2 equiv.), K_2CO_3 (119 mg, 0.862 mmol, 3.00 equiv.), (*Z*)-4-bromo-3-iodobut-2-enyl acetate (**13**) (183 mg, 0.574 mmol, 2.00 equiv.) and the resulting mixture stirred at rt for 50 minutes. The reaction mixture was directly purified via flash column chromatography (triethyl amine saturated silica gel, gradient elution: hexanes to 20% EtOAc in hexanes) to give the title compound (151.4 mg, 0.2409 mmol, 84%) as a colorless foam. IR (film) 2950, 1740, 1708, 1511, 1483, 1437, 1251, 1032, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, 1H, *J* = 7.0, 3.6 Hz, C**H**=C), 7.15 (d, 2H, *J* = 8.6 Hz, ArH), 7.11 (d, 1H, *J* = 7.3 Hz, ArH), 7.01 (t, 1H, *J* = 7.7 Hz, ArH), 6.83 (d, 2H, *J* = 8.6 Hz, ArH), 6.75 (t, 1H, *J* = 7.4 Hz, ArH), 6.30 (d, 1H, *J* = 7.8H, ArH), 6.12 (t, 1H, *J* = 5.8 Hz, C=C**H**CH_2), 4.70-4.62 (m, 2H, C**H**$_2$OAc), 4.50 (s, 1H, CH=CC**H**N), 4.24 (d, 1H, *J* = 15.8 Hz, PMPC**H**HN), 4.08 (d, 1H, *J* = 15.8 Hz, PMPCH**H**N), 3.79 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 3.51 (d, 1H, *J* = 14.7 Hz, C**H**HC=CH), 3.16 (d, 1H, *J* = 14.8 Hz), 3.10 (dd, 1H, *J* = 7.9, 7.9 Hz, C**H**HN), 2.79-2.76 (m, 1H, CH_2C**H**N), 2.57-2.50 (m, 2H, C**H**$_2$CHN), 2.50-2.44 (m, 1H, CH**H**N), 2.31 (dd,

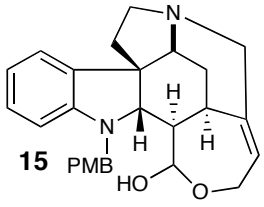
1H, *J* = 12.8, 5.6 Hz, C**H**HCH$_2$N), 2.10 (s, 3H, C**H**$_3$COO), 1.79 (ddd, 1H, *J* = 12.6, 11.1, 7.6 Hz, CH**H**CH$_2$N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 167.5, 158.4, 152.5, 145.8, 136.5, 131.4, 130.4, 129.5, 128.2, 127.8, 122.7, 118.7, 113.7, 110.1, 108.4, 72.0, 68.3, 67.6, 65.6, 55.3, 54.5, 54.0, 52.1, 51.8, 38.9, 27.1, 20.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{30}H_{34}IN_2O_5$) requires *m/z* 629.1512, found *m/z* 629.1503; $[\alpha]_D^{23}$ = –20.9 (c = 1.0, $CHCl_3$).



14

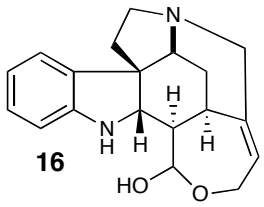
(2*Z*)-4-((3a*R*,8a*R*,11a*S*)-8-(4-methoxybenzyl)-2,3,8,8a,11,11a-hexahydro-9-(hydroxymethyl)pyrrolo[2,3-*d*]carbazol-1-yl)-3-iodobut-2-en-1-ol (14). To a solution of (3a*R*,8a*R*,11a*S*)-methyl 8-(4-methoxybenzyl)-1-((*Z*)-4-acetoxy-2-iodobut-2-enyl)-2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (91.6 mg, 0.146 mmol, 1.00 equiv.) in CH_2Cl_2 (2.9 mL) at –78 °C was added neat Dibal-H (0.156 mL, 0.875 mmol, 6.00 equiv.) dropwise. The resulting solution was stirred at –78 °C for two hours before being quenched by the addition of methanol (0.5 mL). The solution was allowed to warm to rt and diluted with CH_2Cl_2 (10 mL) and saturated aqueous sodium potassium tartrate (10 mL) and stirred for 10 minutes. The mixture was transferred to a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified via flash column chromatography (triethylamine treated silica gel, gradient elution: hexane to EtOAc) to give the title compound (73.7 mg, 0.132 mmol, 91%) as a colorless foam. IR (film) 3374, 2926, 1603,

1510, 1483, 1246, 1036, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, 2H, *J* = 8.5 Hz, ArH), 7.09 (d, 1H, *J* = 7.2 Hz, ArH), 7.04 (t, 1H, *J* = 7.5 Hz, ArH), 6.82 (d, 2H, *J* = 8.5 Hz, ArH), 6.71 (t, 1H, *J* = 7.3 Hz, ArH), 6.36 (d, 1H, *J* = 7.8 Hz, ArH), 6.21 (t, 1H, *J* = 5.4 Hz, C**H**CH_2O), 6.05-6.00 (m, 1H, C**H**=CCH_2OH), 4.39 (d, 1H, *J* =15.8 Hz, PMPC**H**HN), 4.28-4.23 (m, 2H, CI=CHC$\mathbf{H_2}$) 4.15 (d, 1H, *J* = 12.4 Hz, CHCC**H**HOH), 4.13 (d, 1H, *J* = 15.8 Hz, PMPCH**H**N), 4.05 (d, 1H, *J* = 12.4 Hz, CHCCH**H**OH), 3.92 (s, 1H, CHCC**H**N), 3.79 (s, 3H, C$\mathbf{H_3}$O), 3.53 (d, 1H, *J* = 14.7 Hz, C**H**HCl), 3.16 (d, 1H, *J* = 14.7 Hz, CH**H**Cl), 3.11 (dd, 1H, *J* = 7.7, 7.7 Hz, CH_2C**H**HN), 2.77-2.74 (m, 1H, NC**H**CH_2), 2.49 (dd, 1H, *J* = 17.0, 9.3 Hz, CH_2CH**H**N), 2.40-2.25 (m, 2H, C$\mathbf{H_2}$CHN), 2.25-2.13 (m, 1H, C**H**HCH_2N), 1.77 (ddd, 1H, *J* = 12.6, 9.4, 8.1 Hz, CH**H**CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 152.2, 137.7, 136.2, 135.3, 130.9, 128.7, 128.4, 127.9, 122.9, 118.3, 113.8, 107.7, 107.3, 71.5, 69.7, 67.0, 66.9, 65.3, 55.3, 54.6, 53.6, 52.0, 39.0, 25.3; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{27}H_{32}IN_2O_3$) requires *m/z* 559.1458, found *m/z* 559.1442; $[\alpha]_D^{23}$ = –28.5 (c = 1.0, $CHCl_3$).



PMB Wieland–Gumlich aldehyde (15). A 50 mL flask was charged with (2*Z*)-4-((3a*R*,8a*R*,11a*S*)-8-(4-methoxybenzyl)-2,3,8,8a,11,11a-hexahydro-9-(hydroxymethyl)pyrrolo[2,3-*d*]carbazol-1-yl)-3-iodobut-2-en-1-ol (**14**) (209.3 mg, 0.3748 mmol, 1.00 equiv.), $NaHCO_3$ (314 mg, 3.74 mmol, 10.0 equiv.), tetrabutyl ammonium chloride (310 mg, 1.12 mmol, 3.00 equiv.), palladium acetate (21 mg, 0.094 mmol, 0.25 equiv.), and EtOAc (21 mL) and stirred at rt for 24 hours. The resulting solution was

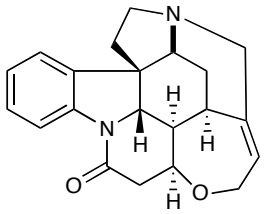
purified directly via flash column chromatography (triethylamine treated silica gel, gradient elution: CH_2Cl_2 to 7% methanol in CH_2Cl_2) to give the title compound (94.2 mg, 0.219 mmol, 58%) as a colorless powder. IR (film) 2932, 1604, 1510, 1482, 1246, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major hemiacetal diastereomer) δ 7.16 (d, 2H, *J* = 8.5 Hz, ArH), 7.08 (t, 1H, *J* = 7.6 Hz, ArH), 6.94 (d, 1H, *J* = 6.9 Hz, ArH), 6.81 (d, 2H, *J* = 8.5 Hz, ArH), 6.71 (t, 1H, *J* = 7.4 Hz, ArH), 6.53 (d, 1H, *J* = 7.8 Hz, ArH), 5.78-5.72 (m, 1H, C=C**H**CH_2), 5.41-5.38 (m, 1H, HOC**H**OCH_2), 4.82 (dd, 1H, *J* = 13.8, 2.4 Hz, C=CHC**H**HO), 4.65 (d, 1H, *J* = 15.4 Hz, PMPC**H**HN), 4.24 (d, 1H, *J* = 15.4 Hz, PMPCH**H**N), 3.98-3.91 (m, 1H, CH_2C**H**N), 3.80-3.75 (m, 1H, C=CHCH**H**O), 3.77 (s, 3H, C**H**$_3$O), 3.75-3.65 (m, 1H, NC**H**HC=CH), 3.43 (d, 1H, *J* = 10.6 Hz, NC**H**CHCHCH_2), 3.35-3.30 (m, 1H, NCHCHC**H**CH_2), 3.10 (dd, 1H, *J* = 8.6, 8.6 Hz, CH_2C**H**HN), 2.72-2.65 (m, 1H, NCH**H**C=CH), 2.65-2.58 (m, 1H, CH_2CH**H**N), 2.24-2.16 (m, 1H, CHC**H**HCHN), 1.68 (d, 1H, *J* = 10.6 Hz, C**H**CH(OH)O), 1.50 (d, 1H, *J* = 14.3 Hz, CHCH**H**CHN), 1.45-1.35 (m, 1H, C**H**HCH_2N), 1.19 (dd, 1H, *J* = 12.5, 5.9 Hz, CH**H**CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$, minor hemiacetal diastereomer included but not differentiated) δ 159.4, 158.8, 150.5, 150.2, 131.2, 131.0, 130.0, 129.1, 129.0, 128.2, 128.5, 128.4, 127.7, 123.8, 122.3, 121.8, 121.7, 118.6, 118.5, 113.82, 113.80, 109.9, 106.1, 95.5, 66.5, 64.9, 62.6, 60.1, 60.0, 59.1, 55.2, 54.5, 54.5, 53.7, 53.3, 50.9, 50.7, 46.6, 40.6, 33.0, 28.3, 26.3, 25.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{27}H_{31}N_2O_3$) requires *m/z* 431.2335, found *m/z* 431.2326; $[\alpha]_D^{23}$ = –20.9 (c = 0.22 $CHCl_3$).



16

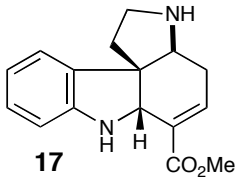
Wieland–Gumlich aldehyde (16). A vial was charged with PMB Wieland–Gumlich aldehyde (**15**) (12.2 mg, 0.0283 mmol, 1.00 equiv.), thiophenol (29 μL, 0.28 mmol, 10 equiv.), and trifluoroacetic acid (1 mL) and heated to 45 °C for 13 hours. The solution was concentrated *in vacuo* and dissolved in CH_2Cl_2 (10 mL). The solution was transferred to a separatory funnel and vigorously shaken with 1 N HCl (5 mL). The aqueous layer was washed with CH_2Cl_2 (3×5 mL) and then basified with ammonium hydroxide solution (28 wt%, 4 mL) and extracted with CH_2Cl_2(5×10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate to give the title compound (7.4 mg, 0.019 mmol, 66%) as a white powder as the monomethylene chloride adduct. IR (film) 3377, 2865, 1606, 1484, 1463, 1314, 1100, 1045, 908, 736, 600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major hemiacetal diastereomer) δ 7.04 (td, 1H, *J* = 7.6, 1.1 Hz, ArH), 6.98 (d, 1H, *J* = 7.3 Hz, ArH), 6.81 (t, 1H, *J* = 7.4 Hz, ArH), 6.73 (d, 1H, *J* = 7.8 Hz, ArH), 5.77-5.71 (m, 1H, C=C**H**CH_2), 4.95-4.92 (m, 1H, HOC**H**O), 4.64-4.60 (m, 1H, NH), 4.16 (dd, 1H, *J* = 14.2, 7.1 Hz, C=CHC**H**H), 3.86 (dd, 1H, *J* = 14.2, 5.0 Hz, C=CHCH**H**), 3.86-3.83 (m, 1H, CH_2C**H**N), 3.75 (dd, 1H, *J* = 10.5, 1.2 Hz, CHC**H**NH), 3.63 (d, 1H, *J* = 14.7 Hz, NC**H**HC=CH), 3.14 (dd, 1H, *J* = 9.8, 8.0 Hz, CH_2C**H**HN), 2.74 (ddd, 1H, *J* = 12.4, 10.1, 6.3 Hz, CH_2CH**H**N), 2.61-2.59 (m, 1H, C**H**CH_2CHN), 2.58 (d, 1H, *J* = 14.7 Hz, NCH**H**C=CH), 2.19 (ddd, 1H, *J* = 14.0 4.0, 4.0 Hz, C**H**HCHN), 1.98 (dd, 1H, *J* = 12.5, 6.3 Hz, C**H**HCH_2N), 1.75 (d, 1H, *J* = 10.7 Hz, HOCHC**H**), 1.53 (ddd, 1H, *J* = 12.5, 12.5, 7.8 Hz, CH**H**CH_2N), 1.50-1.45 (m, 1H, CH**H**CHN); ^{13}C NMR (125 MHz, $CDCl_3$, minor

hemiacetal diastereomer included but not differentiated) δ149.0, 148.2, 139.9, 132.9, 128.7, 127.0, 124.6, 121.2, 119.9, 118.0, 117.6, 112.7, 112.3, 109.2, 109.0, 104.6, 61.5, 59.5, 58.4, 58.0, 53.9, 52.7, 50.3, 50.1, 45.2, 38.1, 37.6, 31.2, 27.2, 25.3; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}N_2O_2$) requires *m/z* 311.1760, found *m/z* 311.1727; $[\alpha]_D^{23} = -112$ (c = 0.41 MeOH).



(–)-Strychnine. A flask was charged with the Wieland-Gumlich aldehyde (**16**) monomethylene chloride adduct (20.8 mg, 0.0526 mmol, 1.00 equiv.), sodium acetate (144 mg, 1.76 mmol, 33.0 equiv.), acetic anhydride (30 μL, 0.32 mmol, 6 equiv.), malonic acid (144 mg, 1.39 mmol, 26 equiv.) and acetic acid (1.5 mL) and heated to 120 °C for 2.2 hours. The resulting solution was diluted with water (10 mL) and basified with sodium hydroxide solution (50 wt%, 2 mL). The mixture was extracted with CH_2Cl_2 (4×10 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (NH_3 treated silica gel, gradient elution: CH_2Cl_2 to 6% methanol in CH_2Cl_2) to give the title compound (12.2 mg, 0.0365 mmol, 69%) as a white solid IR (film) 2924, 2857, 1667, 1597, 1477, 1389, 1289, 1108, 1096, 1048, 913, 755, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J* = 8.0 Hz, ArH), 7.26 (t, 1H, *J* = 7.2 Hz, ArH), 7.18 (d, 1H, *J* = 7.3 Hz, ArH), 7.11 (t, 1H, *J* = 7.2 Hz, ArH), 5.95-5.89 (m, 1H, C=C**H**CH_2), 4.30 (ddd, 1H, *J* = 8.2, 3.2, 3.2 Hz, OC**H**CH_2CON), 4.16 (dd, 1H, *J* = 13.8, 7.0 Hz, C=CHC**H**HO), 4.07 (dd, 1H, *J* = 13.7, 6.0 Hz, C=CHCH**H**O), 4.01-3.94 (m, 1H,

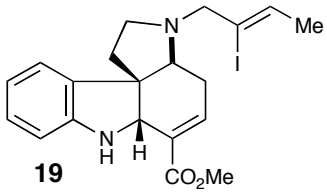
CH_2CHN), 3.87 (d, 1H, *J* = 10.5 Hz, C**H**CHN), 3.73 (d, 1H, *J* = 15.0 Hz, NC**H**HC=C), 3.26-3.20 (m, 1H, CH_2CHHN), 3.17-3.15 (m, 1H, $CHCH_2CHN$), 3.15 (dd, 1H, *J* = 17.3, 8.5 Hz, C**H**HCHO), 2.89 (dd, 1H, *J* = 18.9, 9.9 Hz, CH_2CHHN), 2.75 (d, 1H, *J* = 14.8 Hz, NCH**H**C=C), 2.68 (dd, 1H, *J* = 17.4, 3.2 Hz, CH**H**CHO), 2.39 (ddd, 1H, *J* = 14.3, 4.3, 4.3 Hz, CHC**H**HCHN), 1.94-1.92 (m, 1H, C**H**CHN), 1.92-1.89 (m, 1H, $CHHCH_2N$), 1.48 (d, 1H, *J* = 14.3 Hz, CH**H**CHN), 1.30 (ddd, 1H, *J* = 10.5, 3.2, 3.2 Hz, $CHHCH_2N$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 142.2, 140.4, 132.6, 128.7, 127.6, 124.3, 122.3, 116.3, 77.6, 64.6, 60.2, 60.1, 52.6, 51.9, 50.4, 48.2, 42.8, 42.5, 31.6, 26.8; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_2$) requires *m/z* 335.176, found *m/z* 335.1755; $[\alpha]_D^{23}$ = 118 (c = 0.30, $CHCl_3$).



17

(3a*R*,8a*R*,11a*S*)-Methyl 2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (17). A vial was charged with a mixture of (3a*R*,8a*R*,11a*S*)-methyl 8-(4-methoxybenzyl)-2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate and (3a*R*,8a*S*,11a*S*)-methyl 8-(4-methoxybenzyl)-2,3,8,8a,9,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (**12**) (100 mg, 0.256 mmol, 1.00 equiv.), thiophenol (0.262 mL, 2.56 mmol, 10.0 equiv.), and trifluoroacetic acid (4 mL) and stirred at 60 °C for 3.5 hours. The solvent was removed *in vacuo* and the resulting residue dissolved in CH_2Cl_2 (20 mL). The solution was transferred to a separatory funnel and vigorously shaken with 1 N HCl (5 mL). The CH_2Cl_2 was removed and the aqueous solution was extracted with CH_2Cl_2 (3×10 mL). The aqueous solution was basified with

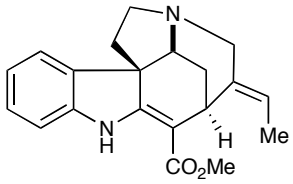
ammonium hydroxide (28 wt%, 4 mL) and extracted with CH_2Cl_2 (10×5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the pure title compound (62.8 mg, 0.232 mmol, 91%) as a colorless gum. IR (film) 3390, 2952, 1703, 1654, 1607, 1484, 1464, 1435, 1249, 1095, 1035, 741cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.01-6.94 (m, 3H, ArH, C=C**H**), 6.65 (t, 1H, *J* = 7.4 Hz, ArH), 6.52 (d, 1H, *J* = 8.0 Hz, ArH), 4.57 (s, 1H, N**H**Ar), 4.27 (s, 1H, C**H**NHAr), 3.74 (s, 3H, C**H**$_3$O), 3.38 (t, 1H, *J* = 4.6 Hz, C**H**NHCH$_2$), 3.20-3.05 (m, 2H, C**H**$_2$NH), 2.40-2.25 (m, 2H, C**H**$_2$CH=C), 2.15 (ddd, 1H, *J* = 13.0, 8.5, 4.7 Hz, C**H**HCH$_2$NH), 2.00 (ddd, 1H, *J* = 12.8, 9.6, 7.1 Hz, CH**H**CH$_2$NH); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 167.6, 150.7, 139.3, 133.1, 130.4, 128.3, 122.8, 118.7, 109.2, 60.6, 58.6, 53.8, 52.1, 43.9, 40.3, 28.3; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2O_2$) requires *m/z* 271.1477, found *m/z* 271.1441; $[\alpha]_D^{23}$ = –222.3 (c = 1.0, $CHCl_3$).



19

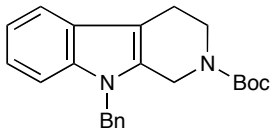
(3a*S*,8a*R*,11a*S*)-Methyl 2,3,8,8a,11,11a-hexahydro-1-((*Z*)-2-iodobut-2-enyl)-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (19). A vial was charged with (3a*R*,8a*R*,11a*S*)-methyl 2,3,8,8a,11,11a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (**17**) (11.0 mg, 0.0407 mmol, 1.00 equiv.), K_2CO_3 (28 mg, 0.20 mmol, 5.0 equiv.), DMF (0.30 mL), and (*Z*)-1-bromo-2-iodobut-2-ene (**18**) (53 mg, 0.20 mmol, 5.0 equiv.) and stirred at rt for 10 minutes. The reaction mixture was directly purified via flash column chromatography (triethylamine treated silica gel, gradient elution: hexanes to 20% EtOAc in hexanes) to give the title compound (14.0 mg, 0.0311 mmol, 76%) as a colorless gum. IR (film)

3399, 2947, 1703, 1606, 1484, 1464, 1435, 1249, 1097, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, 1H, *J* = 7.5 Hz, ArH), 7.06-7.01 (m, 2H, ArH, C**H**=C), 6.72 (t, 1H, *J* = 7.4 Hz, ArH), 6.58 (d, 1H, *J* = 7.7 Hz, ArH), 5.87 (q, 1H, *J* = 6.4 Hz, C=C**H**CH_3), 4.56 (s, 1H, NH), 4.32 (s, 1H, C**H**NH), 3.79 (s, 3H, C**H**$_3$O), 3.58 (d, 1H, *J* = 14.2 Hz, C**H**HC=CH), 3.31 (d, 1H, *J* = 14.2 Hz, CH**H**C=CH), 3.17-3.14 (m, 1H, CH_2C**H**N), 3.11 (ddd, 1H, *J* = 9.5, 8.6, 6.5 Hz, C**H**HN), 2.70 (ddd, 1H, *J* = 9.8, 9.8, 4.6 Hz, CH**H**N), 2.42-2.22 (m, 2H, C**H**$_2$CH=C), 2.16 (ddd, 1H, *J* = 12.9, 8.6, 4.8 Hz, C**H**HCH_2N), 1.98 (ddd, 1H, *J* = 12.8, 9.9, 6.6 Hz, CH**H**CH_2N), 1.78 (d, 3H, *J* = 6.4 Hz, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 150.2, 139.5, 132.7, 130.8, 129.9, 128.1, 123.3, 118.5, 109.2, 109.1, 65.3, 62.4, 61.2, 53.5, 51.8, 50.3, 37.6, 25.2, 21.7; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}IN_2O_2$) requires *m/z* 451.0882, found *m/z* 451.0877; $[\alpha]_D^{23}$ = –102.0 (c = 1.0, $CHCl_3$).



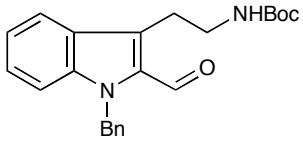
(–)-Akuammicine. A vial was charged with (3a*S*,8a*R*,11a*S*)-methyl 2,3,8,8a,11,11a-hexahydro-1-((*Z*)-2-iodobut-2-enyl)-1*H*-pyrrolo[2,3-*d*]carbazole-9-carboxylate (**19**) (9.3 mg, 0.021 mmol, 1.0 equiv.), $NaHCO_3$ (18.6 mg, 0.221 mmol, 10.0 equiv.), tetrabutylammonium chloride (18.3 mg, 0.0661 mmol, 3.00 equiv.), palladium acetate (0.9 mg, 0.004 mmol, 20 mol%) and acetonitrile (2.2 mL) and stirred at 65 °C under Ar for 4.3 hours. The resulting solution was purified directly by column chromatography (NH_3 treated silica gel, gradient elution: CH_2Cl_2 to 5% methanol CH_2Cl_2) to give the title compound (3.1 mg, 0.0096 mmol, 47%) as a colorless film. IR (film) 2951, 1671, 1602,

1464, 1434, 1237, 1099, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H, NH), 7.24 (d, 1H, *J* = 7.3 Hz, ArH), 7.15 (td, 1H, *J* = 7.6, 0.9 Hz, ArH), 6.90 (t, 1H, *J* = 7.5 Hz, ArH), 6.83 (d, 1H, *J* = 7.8 Hz, ArH), 5.34 (q, 1H, *J* = 6.7 Hz, C**H**CH_3), 4.04-4.02 (m, 1H, C**H**C=CH), 3.95-3.92 (m, 1H, C**H**N), 3.89 (d, 1H, *J* = 15.0 Hz, C**H**HC=CH), 3.81 (s, 3H, C**H**$_3$O), 3.27 (ddd, 1H, *J* = 12.6, 12.6, 5.6 Hz, C**H**HN), 3.03 (dd, 1H, *J* = 12.4, 6.7 Hz, CH**H**N), 2.95 (d, 1H, *J* = 15.1 Hz, CH**H**C=CH), 2.51 (ddd, 1H, *J* = 12.6, 12.6, 6.7 Hz, C**H**HCH_2N), 2.43 (ddd, 1H, *J* = 13.4, 3.9, 2.2 Hz, NCHC**H**H), 1.82 (dd, 1H, *J* = 12.3, 5.5 Hz, CH**H**CH_2N), 1.61 (d, 3H, *J* = 6.9 Hz, CHC**H**$_3$), 1.30 (ddd, 1H, *J* = 13.1, 2.8, 2.8 Hz, NCHCH**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 168.1, 143.4, 139.4, 137.0, 127.7, 120.9, 120.8, 120.6, 109.4, 101.2, 62.0, 57.6, 57.0, 56.4, 51.0, 46.4, 30.9, 29.8, 12.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_2O_2$) requires *m/z* 323.1760, found *m/z* 323.1757; $[\alpha]_D^{23}$ = –731 (c = 0.34, $CHCl_3$).



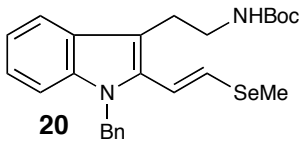
***tert*-Butyl 9-benzyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate.** To a stirred suspension of sodium hydride (3.0 g, 60 wt% mineral oil suspension, 75 mmol, 1.5 equiv.) in 100 mL of DMF, at 0 ºC, was added *tert*-butyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (**9**) (13.6 g, 50.0 mmol, 1.00 equiv.) in small portions. The resulting suspension was warmed to room temperature for 30 min and then cooled to 0 ºC after which benzyl bromide (6.24 mL, 52.5 mmol, 1.05 equiv.) was added. After stirring at ambient temperature for three hours the reaction was quenched by the cautious addition water (200 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 × 150 mL) and the combined organic extracts were washed with water (2 × 200 mL)

and brine (200 mL). Next, the solution was dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and the residue purified by flash column chromatography (silica gel, gradient elution: 5 % ethyl acetate in hexanes to 30% ethyl acetate in hexanes) to yield the title compound (17.9 g, 49.4 mmol, 99%) as a white solid. IR (film) 2975, 2924, 1692, 1454, 1413, 1359, 1306, 1234, 1164, 987, 881, 736, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 7.54 (d, 1H, *J* = 7.1 Hz, ArH), 7.31-7.24 (m, 4H, ArH), 7.18 (t, 1H, *J* = 7.4 Hz, ArH), 7.13 (t, 1H, *J* = 7.2 Hz, ArH), 7.04 (d, 2H, *J* = 7.3 Hz, ArH), 5.25 (s, 2H, PhC**H**$_2$N), 4.60-4.53 (m, 2H, NCC**H**$_2$N) 3.83-3.75 (m, 2H, CH_2C**H**$_2$NBoc), 2.90-2.80 (m, 2H, C**H**$_2CH_2$NBoc), 1.50 (s, 9H, C(C**H**$_3$)$_3$), 1.44* (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 137.3, 136.9, 132.0, 128.8, 127.4, 126.6, 126.2, 121.4, 119.3, 117.0, 109.2, 108.2, 80.0, 46.7, 42.4, 40.9, 28.4, 21.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{23}H_{27}N_2O_2$) requires *m/z* 363.2067, found *m/z* 363.2069.



***tert*-Butyl 9-benzyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate.** To a stirring solution of *tert*-butyl 9-benzyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (87.4 mg, 0.241 mmol, 1.00 equiv.) in 2.0 mL of a 95:5 dioxane:water solution was added selenium dioxide (53.4 mg, 0.482 mmol, 2.00 equiv.) The reaction mixture was then heated to 100 ºC with stirring until completion of the reaction as indicated by TLC (note: the solution turned black upon heating which confirmed formation of Se^o). After five hours the mixture was cooled to ambient temperature, concentrated *in vacuo* to remove most of the dioxane and then ethyl acetate (2.0 mL) was

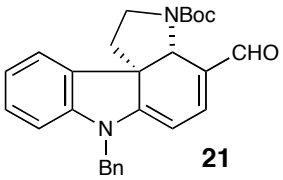
added. This organic mixture was then washed with water (2.0 mL), brine (2.0 mL), dried over anhydrous magnesium sulfate, filtered, then concentrated *in vacuo*. The resulting brown oil was purified via flash column chromatography (gradient elution: 20% EtOAc in hexanes to 100% EtOAc) to give the title compound (85.0 mg, 0.224 mmol, 93%) as a tan powder. IR (film) 3367, 2969, 1695, 1653, 1611, 1505, 1452, 1387, 1368, 1248, 1164, 1077, 1021, 906, 862, 727, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H, C**H**O), 7.79 (d, 1H, *J* = 8.0 Hz, ArH), 7.45-7.36 (m, 2H, ArH), 7.30-7.18 (m, 4H, ArH), 7.10 (d, 2H, *J* = 7.3 Hz, ArH), 5.80 (s, 2H, PhC**H**$_2$), 4.68 (br s, 1H, N**H**Boc), 3.52-3.48 (m, 2H, CH_2C**H**$_2$NHBoc), 3.39-3.36 (m, 2H, C**H**$_2$$CH_2$NHBoc) 1.46 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 155.8, 139.5, 137.9, 131.8, 131.3, 128.6, 128.1, 127.6, 127.3, 126.5, 121.4, 120.8, 110.9, 79.5, 47.8, 41.9, 28.3, 24.2; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{23}H_{27}N_2O_3$) requires *m/z* 379.2016, found *m/z* 379.2013.



20

(*E*)-*tert*-Butyl 2-(1-benzyl-2-(2-(methylselanyl)vinyl)-1*H*-indol-3-yl)ethylcarbamate (20). A 250 mL round bottom flask in an inert atmosphere glove box was charged with KHMDS (878 mg, 4.40 mmol, 1.10 equiv.) and 18-crown-6 (1.16 g, 4.40 mmol, 1.10 equiv.). The flask was capped with a septum, transferred out of the glove box and maintained under argon. The reaction mixture was dissolved in THF (30 mL) then cooled to –78 ºC. The reaction mixture was stirred vigorously then diethyl methylselanylmethylphosphonate was added at once, stirred for one minute then the aldehyde starting material was added as a THF (10 mL) suspension over two minutes. After adding the aldehyde, the flask was immediately removed from the dry ice/acetone

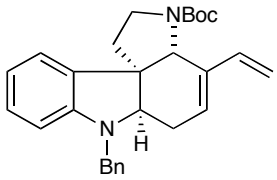
bath and the mixture was stirred vigorously at room temperature for three hours. Next, the reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic extratcts were washed with brine, dried over anhydrous magnesium sulfate filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, gradient elution: 5 % ethyl acetate in hexanes to 50% ethyl acetate) to yield the title compound (1.24 g, 26.4 mmol, 66%) as a thick pale oil that solidified upon standing. IR (film) 3428, 3352, 2977, 2926, 1699, 1593, 1494, 1462, 1451, 1363, 1249, 1168, 1082, 941, 733,; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 1H, *J* = 7.8 Hz, ArH), 7.31-7.24 (m, 3H, ArH), 7.21-7.11 (m, 3H, ArH), 7.05 (d, 2H, *J* = 7.4 Hz, ArH), 6.96 (d, 1H, *J* = 16.0 Hz, C**H**=CHSeCH$_3$), 6.56 (d, 1H, *J* = 16.1 Hz, CH=C**H**SeCH$_3$), 5.36 (s, 2H, PhC**H$_2$**N), 4.67 (br s, 1H, N**H**Boc), 3.47-3.43 (m, 2H, C**H$_2$**NHBoc), 3.07-3.04 (m, 2H, C**H$_2$**CH$_2$NHBoc), 2.20 (s, 3H, C**H$_3$**Se), 1.46 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.9, 137.0, 135.0, 128.8, 128.0, 127.3, 125.9, 125.3, 122.2, 119.6, 118.8, 118.5, 110.4, 109.5, 79.1, 47.4, 41.2, 28.4, 25.7, 5.7; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{25}H_{31}N_2O_2Se$) requires *m/z* 471.1545, found *m/z* 471.1542.



21

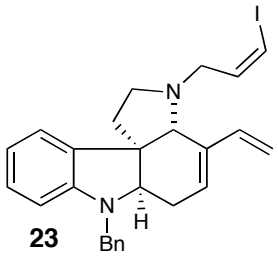
(3a*S*,11a1*S*)-*tert*-Butyl 7-benzyl-4-formyl-3a,7-dihydro-1*H*-pyrrolo[2,3-*d*]carbazole-3(2*H*)-carboxylate (21). To a stirring solution of (*E*)-*tert*-Butyl 2-(1-benzyl-2-(2-(methylselanyl)vinyl)-1*H*-indol-3-yl)ethylcarbamate (**20**), (2*R*,5*R*)-2-*tert*-butyl-3-methyl-5-(naphthalen-1-ylmethyl)imidazolidin-4-one catalyst (**ent-3**) (11.8 mg, 0.040 mmol,

0.20 equiv.), and tribromoacetic acid (11.8 mg, 0.04 mmol, 0.2 equiv.) in toluene (4 mL) at –78 ºC was added propynal (41 mL, 0.60 mmol, 3.00 equiv.). The reaction mixture was then stirred at –40 ºC for 12 hours and then allowed to stir at ambient overnight (16 hours). The dark solution was concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (silica gel, gradient elution: 20 % ethyl acetate in hexanes to 100% ethyl acetate) to yield the title compound (71 mg, 0.166 mmol, 83%, 97% ee) as an orange foam. IR (film) 2972, 2704, 1686, 1664, 1526, 1603, 1517, 1462, 1396, 1363, 1171, 1115, 1084, 1067, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, * = minor rotamer) δ 9.54* (s, 1H, C**H**O), 9.52 (s, 1H, C**H**O), 7.37-7.29 (m, 3H, ArH), 7.25-7.20 (m, 3H, ArH), 7.03-6.94 (m, 3H, ArH, CHC**H**=CCHO), 6.80-6.76 (m, 1H, ArH), 5.67* (s, 1H, C**H**NBoc), 5.54 (s, 1H, C**H**NBoc), 5.22 (d, 1H, *J* = 6.7 Hz, C**H**CH=CCHO), 4.94-4.86 (m, 2H, BnC$\mathbf{H_2}$N), 3.72-3.64 (m, 1H, CH_2C**H**HNBoc), 3.60-3.53* (m, 1H, CH_2C**H**HNBoc), 3.40-3.34 (m, 1H, CH_2CH**H**NBoc), 2.61-2.52 (m, 1H, C**H**HCH_2NBoc), 1.95-1.89 (m, 1H, CH**H**CH_2NBoc), 1.61* (s, 9H, C(C$\mathbf{H_3}$)$_3$), 1.57 (s, 9H, C(C$\mathbf{H_3}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, * = minor rotamer) δ 191.2*, 190.6, 162.6, 155.4, 155.0*, 145.0, 143.9, 142.9*, 135.1*, 135.0, 134.6, 134.4*, 129.0, 128.5 127.9, 126.5, 124.9*, 124.5, 122.1, 122.0, 121.8*, 108.2, 108.1*, 87.1, 80.2, 79.9*, 62.3, 61.4*, 54.2, 53.5*, 46.8, 42.2*, 42.0, 40.5*, 39.7, 28.6*, 28.5; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{27}H_{29}N_2O_3$) requires *m/z* 429.2173, found *m/z* 429.2174. $[\alpha]_D^{23}$ = –149.8 (c = 1.00, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis using a Chiralcel AD-H (25 cm × 0.46 cm) column (15% EtOH/hexane, flow = 1.0 mL/min); t_r = 12.82 min (major) and 16.53 min (minor).



(3a*R*,11a1*R*)-*tert*-Butyl 7-benzyl-4-vinyl-3a,6,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazole-3(2*H*)-carboxylate. (A) Preparation of the ylide solution: To a stirring suspension of methyltriphenylphosphosium iodide at 0 ºC (9.81 g, 24.3 mmol) in dry THF (46 mL) was slowly added *n*-butyl lithium (10.1 mL, 2.28 M, 23.1 mmol). The mixture was stirred at 0 ºC for 45 minutes. This gave a 0.35 M solution of the ylide which was used immediately in the next step. (B) The *tert*-Butyl 9-benzyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (**21**) (3.25 g, 7.58 mmol, 1.00 equiv.) was dissolved in dry THF (45.5 mL), cooled to 0 ºC and kept under argon. To this stirring solution was slowly added a freshly prepared ylide solution (36.4 mL, 0.350 M, 12.7 mmol, 1.68 mmol). After stirring at 0 ºC for 45 minutes was added acetic acid (21 mL) followed by immediate addition of sodium cyanoborohydride (1.9 G, 30 mmol, 4.0 equiv.) in one portion. After stirring at 0 ºC for 10 minutes the mixture was poured into a separatory funnel containing 80 mL of water and the organic extracted with diethyl ether (3 × 50 mL). Next, the combined organic extracts were washed with diluted aqueous potassium carbonate (2 × 100 mL), brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (silica gel, gradient elution: 5 % ethyl acetate, 2.5% triethylamine in hexanes to 2.5 % triethylamine in ethyl acetate) to yield the title compound (2.41 g, 5.62 mmol, 74%). IR (film) 2972, 2932, 1689, 1603, 1492, 1388, 1363, 1310, 1249, 1171, 1125, 888, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H, ArH), 7.06-7.03

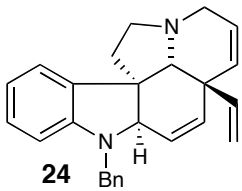
(m, 1H, ArH), 6.96 (d, 1H, *J* = 7.3 Hz, ArH), 6.66 (m, 1H, ArH), 6.41-6.34 (br m, 2H, ArH, C**H**=CH_2), 5.90 (t, 1H, *J* = 5.3 Hz, C=C**H**CH_2), 5.32 (d, 1H, *J* = 17.1 Hz, CH=C**H**H *trans*), 4.93 (d, 1H, *J* = 10.7 Hz, CH=CH**H** *cis*), 4.47 (d, 1H, *J* = 16.3 Hz, PhC**H**HN), 4.40-4.36 (m, 1H, C**H**NBoc), 4.25 (d, 1H, *J* = 16.3 Hz, PhCH**H**N), 3.90-3.82 (br m, 1H, CH_2C**H**HNBoc), 3.58 (t, 1H, *J* = 5.0 Hz, CH_2C**H**N), 3.44-3.39 (m, 1H, CH_2CH**H**NBoc), 2.44-2.24 (m, 3H, C**H**HCH_2NBoc, C**H**$_2$CH=C), 1.98-1.93 (m, 1H, CH**H**CH_2NBoc), 1.44 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 151.3, 139.9, 138.5, 136.2, 133.0, 128.53, 128.46, 127.02, 127.00, 122.8, 122.3, 117.6, 112.4, 106.4, 80.1, 67.9, 61.4, 55.4, 50.0, 45.1, 37.8, 28.5, 27.0; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{28}H_{33}N_2O_2$) requires *m/z* 429.2536, found *m/z* 429.2536. $[\alpha]_D^{23}$ = –65.3 (c = 1, $CHCl_3$).



23

(*Z*)-7-Benzyl-3-(3-iodoallyl)-4-vinyl-2,3,3a,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole (23). To a stirring solution of (3a*R*,11a1*R*)-*tert*-butyl 7-benzyl-4-vinyl-3a,6,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazole-3(2*H*)-carboxylate (2.28 g, 5.32 mmol, 1.00 equiv.) in dichloromethane (20 mL) was added trifluoroacetic acid (20 mL). Following the addition of trifluoroacetic acid, the mixture was immediately concentrated *in vacuo*. Next, potassium carbonate (7.35 g, 53.2 mmol, 10 equiv.) was added followed by *Z*-iodoallylbromide **22** (ref. 4) (3.94 g, 16.0 mmol, 3.00 equiv.) and DMF (80 mL). Next, the resulting suspension was stirred for 6 hours and then poured into a separatory funnel containing 150 mL of water and extracted with diethyl ether (3 × 80 mL). The

combined organic extracts were washed with water (150 mL), brine (150 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (silica gel, gradient elution: 5 % diethyl ether, 2.5% triethylamine in hexanes to 50% diethyl ether, 2.5% triethylamine in hexanes) to yield the title compound (2.61 g, 5.27 mmol, 99%) as a colorless gum. IR (film) 3023, 2926, 2830, 1603, 1484, 1451, 1350, 1277, 1158, 1097, 1027, 986, 900, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H, ArH), 7.26-7.22 (m, 3H, ArH), 7.13 (d, 1H, *J* = 6.51 Hz, ArH), 6.98-6.95 (m, 1H, ArH), 6.67-6.65 (m, 1H, ArH), 6.41 (dd, 1H, *J* = 11.0, 17.6 Hz, C**H**=CHI), 6.32-6.26 (m, 2H, C**H**=CH_2, CH=C**H**I), 6.18 (d, 1H, *J* = 7.8 Hz, ArH), 5.88-5.86 (m, 1H, CH_2C**H**=C), 5.21 (d, 1H, *J* = 17.6 Hz, CH=C**H**H *trans*), 4.88 (d, 1H, *J* = 11.0 Hz, CH=C**H**H *cis*), 4.31 (d, 1H, *J* = 16.6 Hz, PhC**H**$_2$N), 4.21 (d, 1H, *J* = 16.6 Hz, PhC**H**$_2$N), 3.71-3.70 (m, 1H, CH_2C**H**N), 3.38-3.34 (m, 1H, NC**H**HCH=CHI), 3.26 (s, 1H, CC**H**NCH_2), 3.17-3.15 (m, 1H, CH_2C**H**HNCH_2), 2.99-2.95 (m, 1H, NCH**H**CH=CHI), 2.77-2.74 (m, 1H, C**H**HCH=CH), 2.51-2.38 (m, 3H, CH**H**CH=CH, CH_2CH**H**NCH_2, C**H**HCH_2NCH_2), 2.08-2.02 (m, 1H, CH**H**CH_2NCH_2) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 139.1, 139.03, 139.00, 138.4, 136.0, 130.6, 128.4, 127.9, 126.8, 126.7, 122.8, 117.5, 110.4, 105.9, 82.6, 74.1, 68.7, 58.0, 54.1, 52.9, 51.0, 41.7, 25.4; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{28}IN_2$) requires *m/z* 495.1292, found *m/z* 495.1292 $[\alpha]_D^{23}$ = –82.6 (c = 1.00, $CHCl_3$).

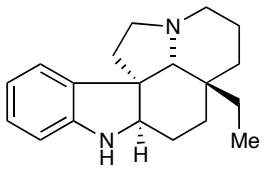


24

(3a*R*,3a1*R*,10a1*R*)-6-benzyl-3a-vinyl-3a,3a1,5a,6,11,12-hexahydro-1*H*-indolizino[8,1-

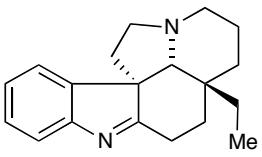
***cd*]carbazole (24).** A 500 mL round bottom flask was charged with (*Z*)-7-benzyl-3-(3-iodoallyl)-4-vinyl-2,3,3a,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole (**23**) (2.63 g, 5.32 mmol, 1.00 equiv.), palladium tetrakistriphenylphosphine (614 mg, 0.53 mmol, 0.10 equiv.), then capped with a septum. The flask was evacuated under reduced pressure then backfilled with argon (this process was performed three times) after which dry toluene (210 mL) was added followed by triethylamine (1.48 mL, 10.6 mmol, 2.00 equiv.). Next, the reaction mixture was stirred under argon at 80 ºC for 24 hours then cooled to ambient temperature and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (silica gel, gradient elution: 5 % ethyl acetate, 2.5% triethylamine in hexanes to 50 % ethyl acetate, 2.5 % triethylamine in hexanes) to yield the title compound (1.26 g, 3.44 mmol, 65%) as a white solid. IR (film) 3022, 2906, 2790, 1600, 1487, 1451, 1388, 1350, 1322, 1262, 1156, 1130, 1024, 915, 731, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H, ArH), 7.28-7.25 (m, 1H, ArH), 7.04-7.00 (m, 2H, ArH), 6.63-6.61 (m, 1H, ArH), 6.33 (d, 1H, *J* = 7.8 Hz, ArH), 5.87 (dd, 1H, *J* = 9.9, 4.1 Hz, $NCH_2C\mathbf{H}$=CHC), 5.83 (dd, 1H, *J* = 10.3, 3.3 Hz, NCHC**H**=CHC), 5.64 (d, 1H, *J* = 10.2 Hz, CC**H**=$CHCH_2N$), 5.58 (d, 1H, *J* = 9.8 Hz, CC**H**=CHCHN), 5.52 (dd, 1H, *J* = 17.4, 10.4 Hz, CC**H**=CH_2), 4.81 (d, 1H, *J* = 14.7 Hz, CH=C**H**H *trans*), 4.78 (d, 1H, *J* = 7.7 Hz, CH=CH**H** *cis*), 4.55 (d, 1H, *J* = 15.3 Hz, PhC**H**HN), 4.31 (d, 1H, *J* = 15.3 Hz, PhCH**H**N), 3.90 (d, 1H, *J* = 3.3 Hz, NC**H**CH=CH), 3.50 (dd, 1H, *J* = 16.2, 5.1 Hz, NC**H**HCH=CH), 3.33 (td, 1H, *J* = 4.5, 9.0, 9.0 Hz $CH_2C\mathbf{H}$HN), 2.90 (d, 1H, *J* = 16.2, NCH**H**CH=CH) 2.75 (s, 1H, CC**H**N), 2.49 (td, 1H, *J* = 6.6, 9.8, 9.8 Hz, $CH_2C\mathbf{H}HNCH_2$), 2.23 (ddd, 1H, *J* = 6.6, 8.6, 13.2 Hz, NC**H**HCH_2N), 1.96 (ddd, 1H, *J* = 4.5, 10.5, 13.2 Hz NCH**H**CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 143.2, 138.2, 133.8, 132.1, 131.1,

128.5, 127.8, 127.7, 127.1, 125.2, 123.7, 121.6, 117.0, 114.0 105.9, 69.9, 66.1, 52.6, 51.9, 51.1, 49.3, 44.8, 40.2; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{27}N_2$) requires *m/z* 367.2169, found *m/z* 367.2168 $[\alpha]_D^{23}$ = +13.6 (c = 1.00, $CHCl_3$).



(+)-Aspidospermidine. A 50 mL round bottom flask was charged with (3a*R*,3a1*R*,10a1*R*)-6-benzyl-3a-vinyl-3a,3a1,5a,6,11,12-hexahydro-1*H*-indolizino[8,1-*cd*]carbazole (**24**) (366 mg, 1.00 mmol) and the solid dissolved in a 1:1 methanol:ethyl acetate solution mixture (15 mL). The flask was transferred into a high pressure reactor and palladium hydroxide (1.00 g, 20% wt on carbon Degussa®) was added. The system was pressurized with hydrogen then purged five times. Next, the system was put under hydrogen (200 psi) and stirred for 72 hours. The hydrogen was then released and the mixture filtered through a celite pad to afford analytically pure (+)-aspidospermidine (276 mg, 0.980 mmol, 98%). IR (film) 3366, 2933, 2778, 1607, 1481, 1462, 1333, 1259, 1180, 1132, 1024, 905, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, 1H, *J* = 7.3 Hz, ArH), 7.02 (td, 1H, *J* = 7.6, 1.1 Hz, ArH), 6.74 (td, 1H, *J* = 7.4, 0.8 Hz, ArH), 6.65 (d, 1H, *J* = 7.7 Hz, ArH), 3.52 (dd, 1H, *J* = 11.1, 6.2 Hz, HNC**H**CH_2), 3.50 (br s, 1H, N**H**), 3.15-3.11 (m, 1H, CCH_2C**H**HN), 3.07 (d, 1H, *J* = 10.1 Hz, NC**H**HCH_2CH_2C), 2.33-2.21 (m, 2H, NCH**H**CH_2CH_2C, Alk-H), 2.23 (s, 1H, NC**H**C), 1.99-1.92 (m, 2H, CCH_2C**H**HN, HNCHC**H**HCH_2), 1.79-1.70 (m, 1H, CCH_2C**H**HCH_2N), 1.68-1.60 (m, 2H, CC**H**HCH_2CH_2N, HNCHCH_2C**H**HC), 1.54-1.45 (m, 3H, CCH**H**CH_2N, CCH_2CH**H**CH_2N, C**H**HCH_3), 1.45-1.35 (m, 1H, CCH**H**CH_2CH_2N), 1.15-1.04 (m, 2H, HNCHCH_2C**H**HC, HNCHCH**H**CH_2), 0.91-0.84 (m, 1H, CH**H**CH_3), 0.64 (t, 3H, *J* = 7.5

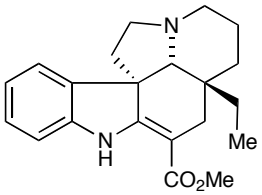
Hz, $CH_2C\mathbf{H}_3$) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 135.7, 127.0, 122.8, 119.0, 110.3, 71.3, 65.6, 53.9, 53.3, 53.0, 38.8, 35.6, 34.4, 30.0, 28.0, 22.9, 21.6, 6.8; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}N_2$) requires *m/z* 283.2169, found *m/z* 283.2168 $[\alpha]_D^{23}$ = +20.8 (c = 1.00, $CHCl_3$).



25

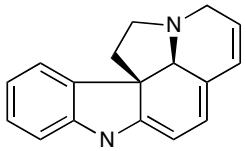
(+)-Dehydroaspidospermidine (25). To a 50 mL round bottom was added dry dichloromethane (5 mL). The flask was capped with a septum, placed under argon and cooled to –78 ºC. DMSO (192 mL, 2.70 mmol, 4.00 equiv.) followed by oxalyl chloride (88 mL, 1.01 mmol, 1.50 equiv.) were added. The resulting mixture was stirred at –78 ºC for 20 minutes then (+)-aspidospermidine (191 mg, 0.676 mmol, 1.00 equiv.) was slowly added as a 1 mL dichloromethane solution (rinsed with 0.6 mL of dichloromethane). This mixture was stirred under argon at –78 ºC, then allowed to warm to ambient temperature. Next the reaction was concentrated *in vacuo* and the residue was purifed directly by flash column chromatography (silica gel, gradient elution: 5 % ethyl acetate, 2.5% triethylamine in hexanes to 50 % ethyl acetate, 2.5 % triethylamine in hexanes) to yield the title compound (125 g, 0.446 mmol, 65%) as a clear gum. IR (film) 2935, 2776, 1576, 1454, 1323, 1248, 1193, 1123, 1013, 771, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J* = 7.6 Hz, ArH), 7.34 (d, 1H, *J* = 7.3 Hz, ArH), 7.32-7.28 (m, 1H, ArH), 7.17 (t, 1H, *J* = 7.4 Hz, ArH), 3.21-3.15 (m, 2H, $CCH_2C\mathbf{H}_2N$), 3.15-3.05 (m, 1H, $NC\mathbf{H}HCH_2CH_2C$), 2.80-2.76 (m, 1H, $NCH\mathbf{H}CH_2CH_2C$), 2.63-2.55 (m, 1H, $CC\mathbf{H}HCH_2N$), 2.50-2.42 (m, 1H, N=$CC\mathbf{H}$H), 2.40 (s, 1H, $NC\mathbf{H}C$), 2.23-2.12 (m, 2H,

N=CCH**H**, CCH**H**CH_2N), 1.90-1.81 (m, 1H, NCH_2C**H**HCH_2C), 1.69-1.52 (m, 3H, CC**H**HCH_2CH_2N, NCH_2CH**H**CCH_2C, N=CCH_2C**H**H), 1.51-1.46 (m, 1H, N=CCH_2CH**H**), 1.04-0.98 (m, 1H, CCH**H**CH_2CH_2N), 0.72-0.57 (m, 2H, C**H**$_2CH_3$), 0.50 (t, 3H, J = 7.4 Hz, CH_2C**H**$_3$) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 154.4, 147.1, 127.4, 125.1, 121.1, 120.1, 79.1, 61.2, 54.6, 52.0, 36.6, 35.1, 33.1, 29.7, 27.1, 23.7, 22.0, 7.3; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{19}H_{25}N_2$) requires m/z 281.2012, found m/z 281.2012 $[\alpha]_D^{23}$ = +205.9 (c = 1.00, $CHCl_3$).



(+)-Vincadifformine. To a stirring solution of (+)-dehydroaspidospermidine (**25**) (46 mg, 0.164 mmol, 1.00 equiv.) in dry THF (1 mL) at –78 ºC was added *n*-butyl lithium (115 mL, 2.31 M, 0.262 mmol, 1.60 equiv.). The mixture was stirred under argon at –78 ºC for 30 minutes then methyl cyanoformate (21 μL, 0.262 mmol, 1.60 equiv.) was slowly added. The resulting mixture was stirred at –78 ºC for 30 min then allowed warm to ambient temperature. This solution mixture was next concentrated *in vacuo* then purified by preparative TLC (20% diethyl ether in petroleum ether with 2.5 % triethylamine) to afford (+)-vincadifformine (31.8 mg, 0.094 mmol, 57%). IR (film) 3361, 2930, 2768, 1673, 1605, 1477, 1460, 1435, 1278, 1253, 1206, 1236, 1155, 1124, 1110, 1043, 747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91, (br s, 1H, NH), 7.19 (d, 1H, J = 7.3 Hz, ArH), 7.13 (td, 1H, J = 7.7, 1.0 Hz, ArH), 6.86 (t, 1H, J = 7.5 Hz, ArH), 6.80 (d, 1H, J = 7.7 Hz, ArH), 3.77 (s, 3H, OC**H**$_3$), 3.16-3.13 (m, 1H, CCH_2C**H**HN), 2.95-2.92 (m, 1H, NC**H**HCH_2CH_2C), 2.73 (d, 1H, J = 15.0 Hz,C=CC**H**H), 2.59-2.56 (m, 1H,

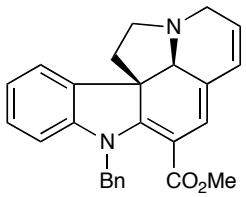
NCH**H**CH_2CH_2C), 2.45 (s, 1H, NC**H**C), 2.43-2.37 (m, 1H, CCH_2CH**H**N), 2.28 (d, 1H, *J* = 15.0 Hz,C=CCH**H**) 2.09-2.02 (m, 1H, CC**H**HCH_2N), 1.88-1.80 (m, 2H, CC**H**HCH_2CH_2N, NCH_2C**H**HCCH_2C), 1.74-1.68 (m, 1H, CCH**H**CH_2N), 1.61-1.55 (m, 1H, CCH_2CH**H**CH_2N), 1.29-1.23 (m, 1H, CCH**H**CH_2CH_2N), 1.01-0.96 (m, 1H, C**H**HCH_3), 0.66-0.57 (m, 4H, CH**H**CH_3, CH_2C**H**$_3$) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 167.8, 143.2, 137.9, 127.4, 121.0, 120.4, 109.3, 92.6, 72.7, 55.4, 51.7, 51.0, 50.7, 45.2, 38.1, 32.9, 29.3, 25.4, 22.2, 7.1; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}N_2$) requires *m/z* 339.2067, found *m/z* 339.2068. $[\alpha]_D^{23}$ = +480.0 (c = 1, $CHCl_3$).



26

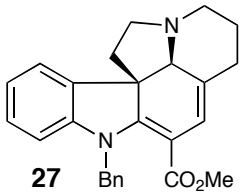
(3a^1*S*,10a^1*R*)-6-Benzyl-3a^1,6,11,12-tetrahydro-1*H*-indolizino[8,1-*cd*]carbazole (26). To a stirred solution of (3a*R*,11a1*R*)-*tert*-butyl 7-benzyl-4-formyl-3a,7-dihydro-1*H*-pyrrolo[2,3-*d*]carbazole-3(2*H*)-carboxylate (**ent-21**) (101 mg, 0.234 mmol, 1.00 equiv.) and triethylamine (165 μL, 1.17 mmol, 5.00 equiv.) in CH_2Cl_2 (1.2 mL) at 0 °C was added iodotrimethylsilane (135 μL, 0.945 mmol, 4.00 equiv.) dropwise. The mixture was stirred at 0 °C for 30 minutes after which MeOH (1.2 mL) and vinyltriphenylphosphonium bromide (224 mg, 0.607 mmol, 2.60 equiv.) were added and the mixture heated to 40 °C for 2.5 hours. After addition of toluene (1 mL), the solvent was removed *in vacuo* followed by the addition of CH_2Cl_2 (1.0 mL) and THF (5 mL). The mixture was cooled to 0 °C and potassium *tert*-butoxide (264 mg, 2.35 mmol, 10.0 equiv.) was added in one portion. The reaction was stirred for 10 minutes and then passed directly through a plug of silica gel (triethylamine treated silica gel, gradient elution:

hexanes to 20% EtOAc in hexanes) and then concentrated *in vacuo*. The residue was purified via flash column chromatography (triethylamine treated silica gel, gradient elution: hexanes to 10% EtOAc in hexanes) to give the title compound (45.9 mg, 0.135 mmol, 58%) as a yellow film. IR (film) 3012, 2833, 1644, 1600, 1557, 1478, 1461, 1365, 1350, 1195, 1162, 1066, 783, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, 1H, *J* = 7.4 Hz, 0.9, ArH), 7.24-7.09 (m, 6H, ArH), 6.87 (td, 1H *J* = 7.4 Hz, 0.6, ArH), 6.36 (d, 1H, *J* = 7.9 Hz, ArH), 6.31 (d, 1H, *J* = 9.9 Hz, C=C**H**), 5.77 (d, 1H, J = 5.7 Hz, C=C**H**), 5.30 (ddd, 1H, *J* = 9.9, 4.3, 2.2 Hz, 1H, C=C**H**CH_2), 4.88 (d, 1H, *J* = 5.8 Hz, C=C**H**), 4.37-4.27 (m, 3H, PhC**H**$_2$), 3.90 (d, 1H, *J* = 18.8, NC**H**HC=C), 3.29 (dd, 1H, *J* = 19.0, 4.3 Hz, NC**H**HC=C), 3.07 (dt, 1H, *J* = 18.4, 9.2 Hz, CH_2CH**H**N), 2.92 (ddd, 1H, *J* = 11.0, 8.1, 5.4 Hz, CH_2CH**H**N), 2.59 (td, 1H, *J* = 11.6, 5.0 Hz, C**H**HCH_2N), 1.91 (ddd, 1H, *J* = 12.3, 9.1, 5.4 Hz, C**H**HCH_2N).); ^{13}C NMR (125 MHz, C_6D_6) δ 155.6, 147.2, 137.8, 137.3, 128.9, 127.9, 127.4, 126.9, 126.8, 124.2, 122.7, 121.5, 121.1, 120.4, 106.6, 88.7, 65.8, 53.4, 48.9, 48.8, 46.7, 41.7; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{23}N_2$) requires *m/z* 339.1861, found *m/z* 339.1866. $[\alpha]_D^{23}$ = –68.7 (c = 0.500, PhH).



(3a^1*S*,10a^1*R*)-methyl-6-benzyl-3a^1,6,11,12-tetrahydro-1*H*-indolizino[8,1-*cd*]carbazole -5-carboxylate. Charged carbomethoxylation precursor (3a^1*S*,10a^1*R*)-6-Benzyl-3a^1,6,11,12-tetrahydro-1*H*-indolizino[8,1-*cd*]carbazole (**26**) (72.0 mg, 0.212 mmol, 1.00 equiv.) and dry toluene (700 μL) into an oven dried 8 mL vial with teflon cap and placed under N_2. Cooled to –45 °C and added triethyl amine (33.7 μl, 0.244 mmol, 1.15 equiv.)

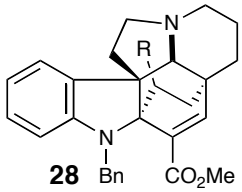
followed by a 20% solution of phosgene in toluene (115 μl, 0.233 mmol, 1.10 equiv.). The reaction mixture was slowly allowed to warm to room temperature over 1.5 hours then cooled to –30°C at which point additional triethylamine (33.7 μl, 0.244 mmol, 1.15 equiv.) was added dropwise followed by anhydrous methanol (~50 μL). The mixture was immediately allowed to warm to room and then directly purified by flash column chromatography (basic alumina, gradient elution: 5% ethyl acetate in hexanes to 20% ethyl acetate) to yield the title compound (64.0 mg, 26.4 mmol, 76%) as a yellow foam. IR (film) 3027, 2946,1681, 1597, 1540, 1434, 1350, 1216, 1192, 1161, 1128, 1083, 746 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.92 (dd, 1H, *J* = 7.3, 1.1 Hz, ArH), 7.12 (d, 2H, *J* = 7.6, ArH), 7.05 (t, 2H, *J* = 7.6, ArH), 6.99-6.94. (m, 2H, ArH), 6.91 (td, 1H, *J* = 7.5, 0.9 Hz, ArH), 6.52, (s, 1H, C=C**H**), 6.49 (d, 1H, *J* = 7.6 Hz, ArH) 6.29 (d, 1H, *J* = 9.9 Hz, C=C**H**), 5.33 (d, 1H, *J* = 16.7 Hz, PhC**H**H), 5.26 (ddd, 1H, *J* = 9.9, 4.1, 2.0 Hz, C=C**H**), 5.12 (d, 1H, *J* = 16.7 Hz, PhC**H**H), 4.08 (s, 1H, CHN), 3.78 (d, 1H, *J* = 18.9 Hz, C=CCH**H**N), 3.31 (s, 1H, CO_2CH_3), 3.20 (dd, 1H, *J* = 18.9, 4.0 Hz, C=CCH**H**N), 2.97 (td, 1H, *J* = 8.7, 5.0 Hz, CH_2CH_2CHHN), 2.80 (ddd, 1H, *J* = 11.0, 8.3, 5.4 Hz, CH_2CH_2CHHN), 2.50 (td, 1H, *J* = 11.7, 5.0 Hz, CC**H**HCH_2N), 1.79 (ddd, 1H, *J* = 12.5, 9.1, 5.2 Hz, CCH**H**CH_2N), ^{13}C NMR (125 MHz, C_6D_6) δ 167.1, 163.4, 147.2, 138.3, 137.8, 129.0, 128.7, 128.5,127.5, 127.2, 126.8, 124.7, 124.4, 123.0, 122.5, 119.1, 109.7, 96.3, 66.0, 56.6, 50.9, 48.7, 48.6, 41.8; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{25}N_2O_2$) requires *m/z* 397.1916, found *m/z* 397.1920. $[\alpha]_D^{23}$ = +118.4 (c = 1.85, PhH).



27

(8*S*,10b*R*)-methyl 6-benzyl-2,3,6,8,11,12-hexahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (27). A vigorously stirring solution of triene (3a[1]*S*,10a[1]*R*)-methyl-6-benzyl-3a[1],6,11,12-tetrahydro-1*H*-indolizino[8,1-*cd*]carbazole -5-carboxylate (100 mg, 0.252 mmol, 1.00 equiv.) and 10% Pd/C (200 mg, 200 wt%) in 5:1 EtOAc/EtOH (17 mL) at 0°C was placed under vacuum and backfilled with hydrogen (1 atm, balloon). The ice bath was removed immediately and the reaction mixture was allowed to warm to room temperature over 5 minutes until the reaction was complete by TLC (30% EtOAc/hexanes). *Note: reaction must be very carefully monitored by TLC to avoid overreduction.* The reaction mixture was then filtered through a celite plug. The plug was further washed with 25:25:1 EtOAc/EtOH/Et_3N (50 mL). The combined organics were then passed through filter paper and concentrated to give the analytically pure title compound (91.0 mg, 0.229 mmol, 91%) as a colorless oil that solidifies upon standing. IR (film) 2925, 2853, 1686, 1565, 1463, 1183, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 1H, *J* = 7.3 Hz, ArH), 7.35-7.10 (m, 6H, ArH), 7.00 (t, 1H, *J* = 7.4 Hz, ArH), 6.75 (d, 1H, *J* = 7.4 Hz, ArH), 6.11 (s, 1H, NC=CC**H**), 5.26 (s, 2H, PhC$\mathbf{H}_2$), 3.85 (s, 1H, CHN), 3.45 (s, 3H, CH_3O), 3.20-3.10 (m, 2H, $CH_2CH_2C\mathbf{H}_2N$), 2.95 (t, 1H, *J* = 7.9 Hz, $CCH_2C\mathbf{H}N$), 2.50 (d, 1H, *J* = 13.7 Hz, $CCH_2CH\mathbf{H}N$), 2.38 (td, 1H, *J* = 11.7, 7.0 Hz, $CCH\mathbf{H}CH_2N$), 2.10 (t, 1H, *J* = 10.8 Hz, $CCH\mathbf{H}CH_2N$), 1.95-185 (m, 2H, $CC\mathbf{H}_2CH_2N$), 1.85-1.75 (m, 2H, $CH\mathbf{H}CH_2CH_2N$), 1.55-1.45 (m, 1H, $CH_2C\mathbf{H}HCH_2N$), 0.95-0.85 (m, 1H, $CH_2CH\mathbf{H}CH_2N$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 162.3, 146.1, 137.1, 136.9,

128.5, 127.7, 126.9, 126.4, 123.8, 123.0, 122.1, 118.7, 108.8, 93.4, 67.5, 56.3, 51.0, 50.8, 47.6, 46.4, 42.6, 31.7, 20.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{26}H_{27}N_2O_2$) requires *m/z* 399.2073, found *m/z* 399.2068. $[\alpha]_D^{23} = -11.6$ (c = 0.300 EtOH).

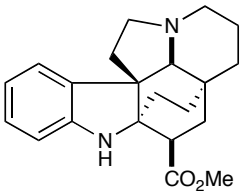


28

R= SO_2Ph

***N*[a]-Benzyl-16,17-dehydro-18-(phenylsulfonyl)kopsinine (28).** Phenyl vinyl sulfone (246 mg, 1.46 mmol, 8.00 equiv.) was heated with (8*S*,10b*R*)-methyl 6-benzyl-2,3,6,8,11,12-hexahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate (**27**) (72.5 mg, 0.182 mmol, 1.00 equiv.) in benzene (750 μL) at 100 °C under N_2. After 48 h TLC (10% MeOH, CH_2Cl_2) showed that the starting material had been consumed and a new product had formed. The reaction mixture was concentrated and directly purified by flash column chromatography (basic alumina, gradient elution: 10 to 20 % ethyl acetate in hexane, then 100% ethyl acetate, then 50% ethyl acetate in acetone) to yield the title compound (89.0 mg, 0.157 mmol, 86%) as a white foam. IR (film) 2927, 2853, 1722, 1606, 1478, 1445, 1306, 1276, 1142, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_6$) δ 7.73-7.68 (m, 2H, ArH), 7.62-7.58 (m, 1H, ArH), 7.52-7.45 (m, 2H, ArH), 7.39-7.35 (m, 2H, ArH), 7.31-7.27 (m, 2H, ArH), 7.23-7.16 (m, 2H, ArH), 7.10 (s, 1H, C**H**=CCO_2Me), 7.07-7.01 (m, 1H, ArH), 6.77 (t, 1H, *J* = 7.4 Hz, ArH), 6.27 (d, 1H, *J* = 7.8 Hz, ArH), 5.18 (d, 1H, *J* = 17.6 Hz, PhC**H**H), 4.90 (d, 1H, *J* = 17.6 Hz, PhCH**H**), 3.91 (t, 1H, *J* = 8.4 Hz, $CHSO_2Ph$), 3.29 (s, 3H, CH_3O), 3.27 (s, 1H, CHN), 3.10-2.95 (m, 2H, $CH_2CH_2C\mathbf{H_2}N$), 2.87 (dd, 1H, *J* = 13.8, 7.1 Hz, $CCH_2C\mathbf{H}HN$), 2.84-2.75 (m, 1H, $CCH_2CH\mathbf{H}N$), 2.68-2.58 (m, 1H, $CC\mathbf{H}HCH_2N$), 1.98-1.94 (m, 1H, $CCH\mathbf{H}CH_2N$), 1.94-1.84 (m, 2H, $CH_2C\mathbf{H_2}CH_2N$), 1.36-

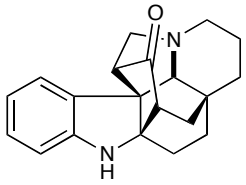
1.24 (m, 2H, C**H**$_2$CH$_2$CH$_2$N), 1.14-1.08 (m, 2H, C**H**$_2$CHSO$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 148.9, 144.8, 140.0, 139.7, 135.3, 133.4, 129.1, 128.2, 128.1, 128.0, 127.7, 126.6, 125.9, 120.9, 118.5, 109.6, 78.8, 67.5, 66.2, 60.2, 51.8, 51.7, 49.8, 46.9, 38.6, 37.1, 37.0, 33.3, 29.7; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{34}H_{35}N_2O_4S$) requires *m/z* 567.2318, found *m/z* 567.2306. $[\alpha]_D^{23}$ = –47.9 (c = 0.700 $CHCl_3$).



(–)-kopsinine

(–)-Kopsinine. Sulfone **28** (65.0 mg, 0.115 mmol) was charged along with ethanol (25 mL) and active Aldrich 2400 Raney nickel catalyst (~3.0 g of the nickel-water slurry) into a 50 mL round bottom flask equipped with stirbar and reflux condenser. The resulting mixture was heated at reflux under N_2 for 12 hours, at which point complete conversion the starting material and various reduction intermediates had been achieved according to LCMS. The reaction mixture was then filtered over a celite pad and then concentrated to give a colorless residue which was purified by flash column chromatography (basic alumina, gradient elution: dichloromethane to 10% methanol in dichloromethane) to yield the title compound (32.5 mg, 0.096 mmol, 83%) as a white foam. IR (film) 2926, 2858, 1728, 1608, 1477, 1460, 1335, 1205, 1180, 914, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, 1H, *J* = 7.5 Hz, ArH), 6.99 (t, 1H, *J* = 7.5 Hz, ArH), 6.75 (t, 1H, *J* = 7.5 Hz, ArH), 6.66 (d, 1H, *J* = 7.5 Hz, ArH), 3.76 (s, 3H, CO$_2$C**H**$_3$), 3.75 (br s, 1H, N**H**), 3.35 (q, 1H, *J* = 8.3 Hz, CH$_2$CH**H**N), 3.12 (ddt, 1H, *J* = 14, 4.0, 2.0 Hz, CH$_2$CH**H**N), 3.01 (d, 1H, *J* = 1.5 Hz, C$_3$C**H**N) 3.00 (m, 1H, CH$_2$CH**H**N),

2.96 (m, 1H, $CH_2CH\mathbf{H}N$), 2.89 (td, 1H, J = 9.3, 1.0 Hz, $C\mathbf{H}CO_2Me$), 2.78 (ddd, 1H, J = 14, 9.3, 3.0 Hz, $C\mathbf{H}HCHCO_2Me$), 2.64 (ddd, 1H, J = 14, 8.3, 7.6 Hz, $CH\mathbf{H}CH_2N$), 1.91 (m, 2H, $CCH\mathbf{H}CH_2C$, $CH\mathbf{H}CH_2N$), 1.61 (m, 1H, $CH\mathbf{H}CH_2CH_2N$), 1.56 (ddd, 1H, J = 14, 8.3, 7.6 Hz, $C\mathbf{H}HCH_2N$), 1.47-1.22 (m, 6H, $CH\mathbf{H}CH_2CH_2N$, $CCH\mathbf{H}CH_2C$, $CH\mathbf{H}CH_2N$) ^{13}C NMR (125 MHz, $CDCl_3$); δ 174.6, 148.9, 140.4, 126.4, 121.4, 119.5, 110.6, 68.1, 66.4, 57.7, 51.7, 50.5, 47.4, 43.6, 36.3, 34.5, 33.7, 33.6, 31.9, 31.5, 16.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{21}H_{27}N_2O_2$) requires *m/z* 339.2073, found *m/z* 339.2070. $[\alpha]_D^{23}$ = –65.8 (c = 1.13 $CHCl_3$).



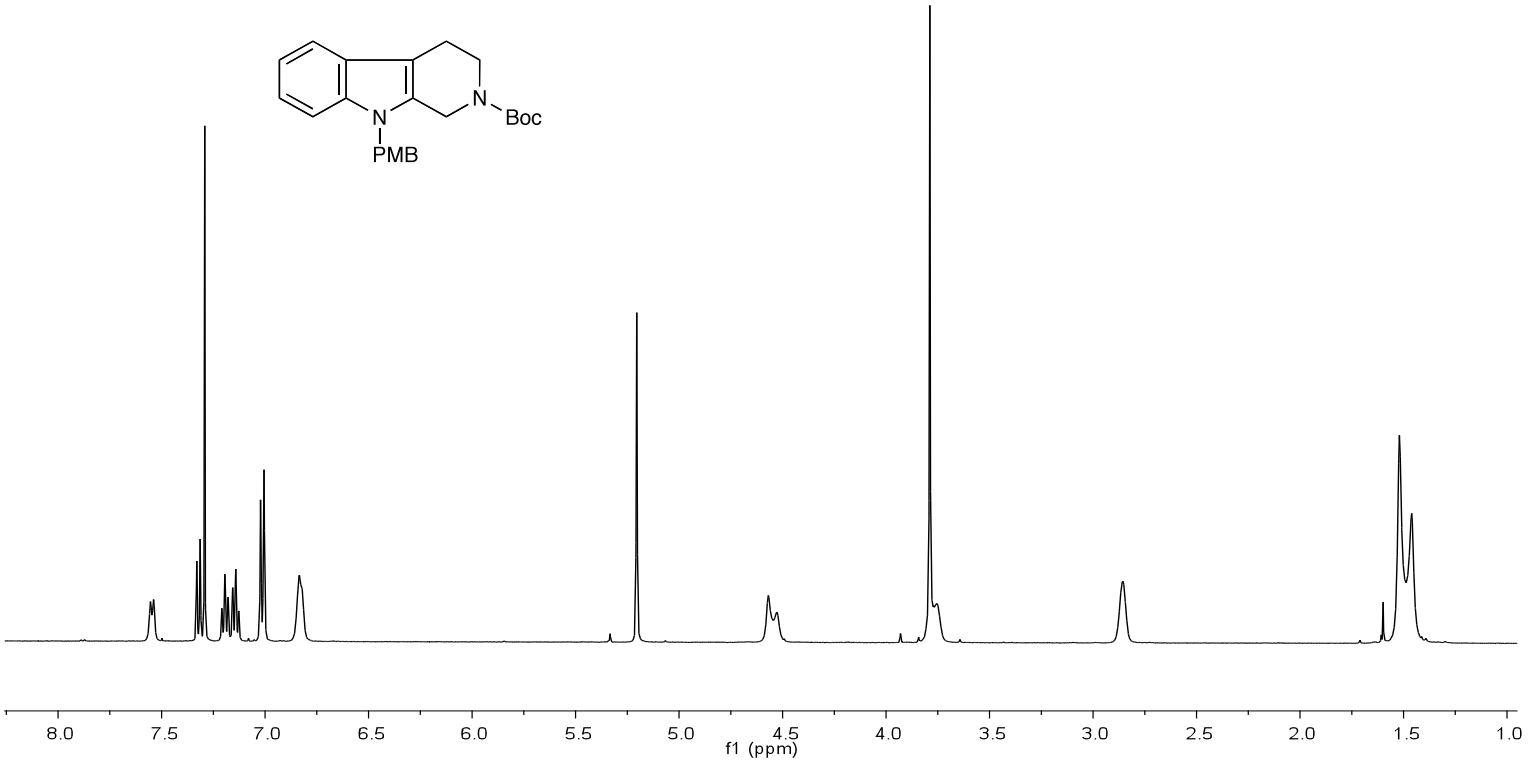
(–)-kopsanone

(–)-Kopsanone. (–)-Kopsinine (27.0 mg, 0.0798 mmol) was dissolved in 1N HCl (1 mL) and heated to 130 °C for five hours. The HCl solution was removed *in vacuo* and azeotroped with toluene (2 mL). The residue was dissolved in MeOH (1 mL) and then 28% ammonium hydroxide (50 μL) was added. The solvent was removed *in vacuo* and then dissolved in MeOH (0.1 mL). CH_2Cl_2 (2 mL) was then added to precipitate out NH_4Cl. The resulting suspension was filtered through a short pad of celite with CH_2Cl_2 (2 mL) and concentrated *in vacuo* to give mostly pure kopsinic acid (**29**) (trace amounts of NH_4Cl still present). Neat kopsinic acid (**29**) was heated under Ar at 200 °C for 15 minutes and then purified via flash column chromatography (triethylamine saturated silica gel, gradient elution: hexanes to 75% ethyl acetate in hexanes) to give the title compound (18.1 mg, 0.0591 mmol, 74%) as a white foam. IR (film) 2928, 1739, 1609, 1460, 1351, 1221, 1149, 1092, 889, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, 1H,

J = 7.3 Hz, ArH), 7.07 (td, 1H, *J* = 7.6, 1.2 Hz, ArH), 6.79 (t, 1H, *J* = 7.5 Hz, ArH), 6.67 (d, 1H, *J* = 7.8 Hz, ArH), 3.59 (br s, 1H, N**H**), 3.51 (t, 1H, *J* = 10.0 Hz, CHCH**H**N), 3.38 (s, 1H, Hz, C_3C**H**N), 3.14 (dd, 1H, *J* = 9.6, 4.7 Hz, CHCH**H**N) 3.10-2.96 (m, 2H, CH_2CH**H**N), 2.70 (d, 1H, *J* = 10.7 Hz, C**H**CO), 2.58 (dd, 1H, *J* = 10.5, 4.8 Hz, COC**H**CH_2N), 2.04 (d, 1H, *J* = 15.1 Hz, CH**H**CHCO), 1.89-1.72 (m, 2H, CH**H**CH_2N), 1.65 (m, 1H, CH**H**CHCO), 1.52 (d, 1H, *J* = 13.6 Hz, CC**H**HCH_2C), 1.40-1.35 (m, 4H, CH**H**CH_2CH_2N, CCH_2CH**H**C) 1.25 (d, 1H, *J* = 14.3 Hz, CCH**H**CH_2C); ^{13}C NMR (125 MHz, $CDCl_3$); δ 218.3, 150.8, 133.8, 127.5, 122.9, 119.6, 111.0, 70.5, 69.5, 63.1, 57.5 54.3, 52.2, 46.7, 36.3, 34.0, 33.6, 31.3, 24.2, 15.4; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_2O$) requires *m/z* 307.1810, found *m/z* 307.1807. $[\alpha]_D^{23}$ = –13.6 (c = 1.00 $CHCl_3$).

References

1. Perrin, D. D. & Armarego, W. L. F. *Purification of Laboratory Chemicals*, ed 3 (Pergamon Press, Oxford, 1988).
2. Pangborn, A. B., Giardello, M. A., Grubbs, R., Rosen, K. & Timmers, F. J. Safe and convenient procedure for solvent purification. *Organometallics* **15**, 1518 (1996).
3. Still, W. C., Kahn, M. & Mitra, A. J. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **43**, 2923 (1978).
4. Piers, E., Cook, K. L. & Rogers, C. A new cyclopentenone annulation method. *Tetrahedron Lett.* **35**, 8573 (1994).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PMB
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7.0
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5.5
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4.5
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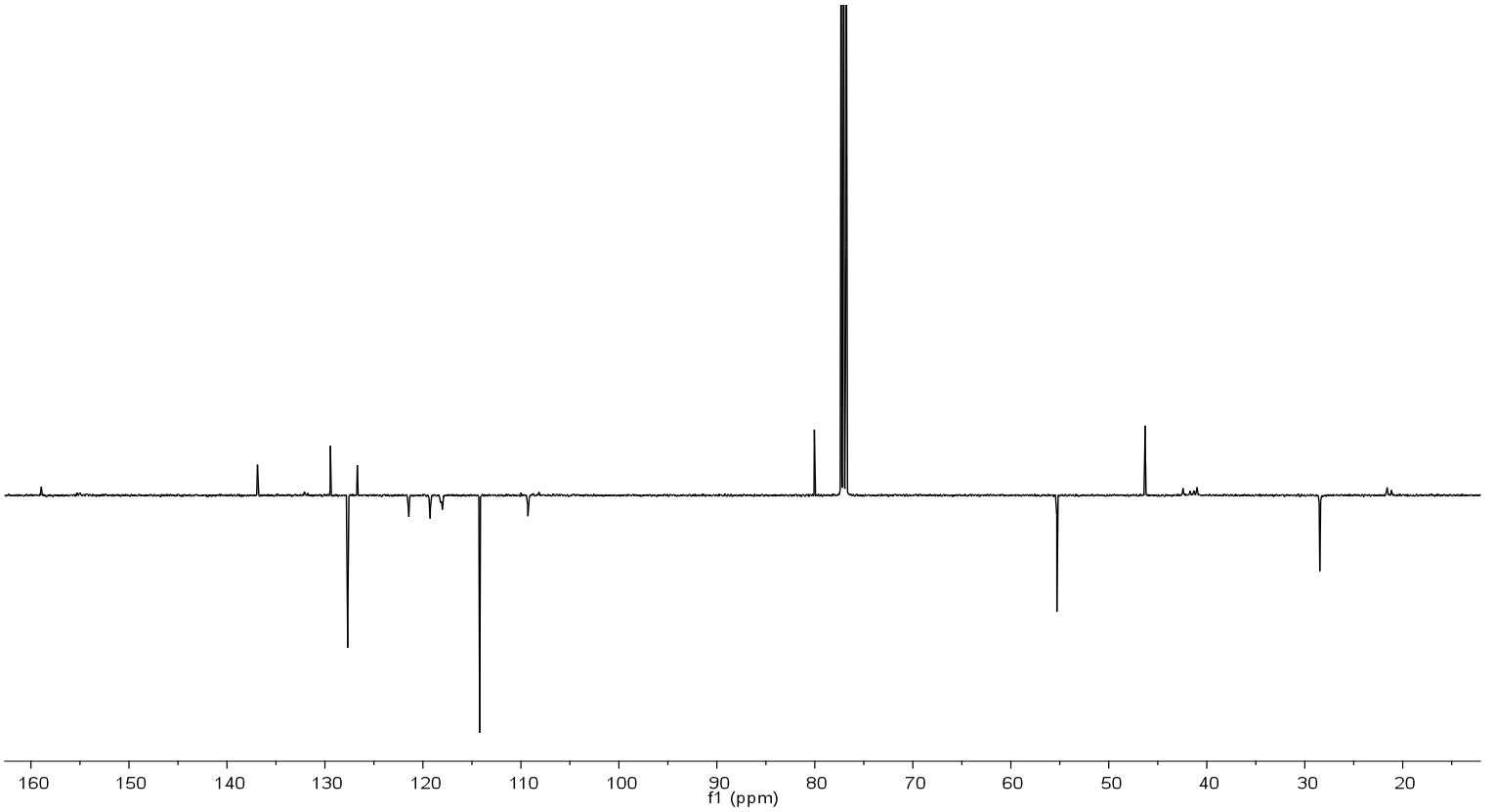
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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30
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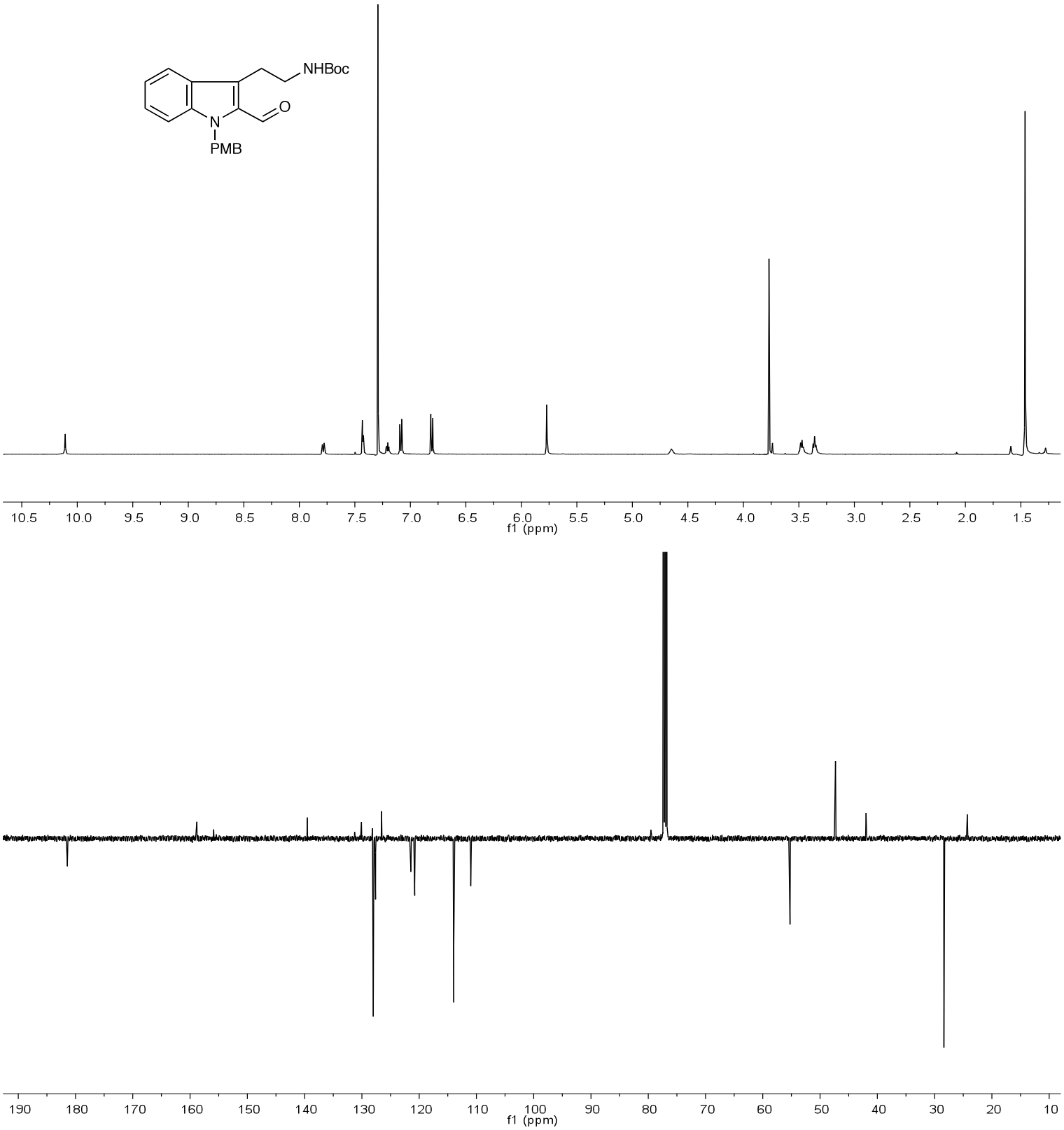
f1 (ppm)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O
N
PMB
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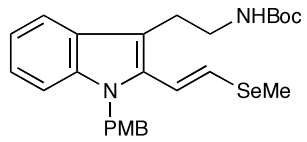
f1 (ppm)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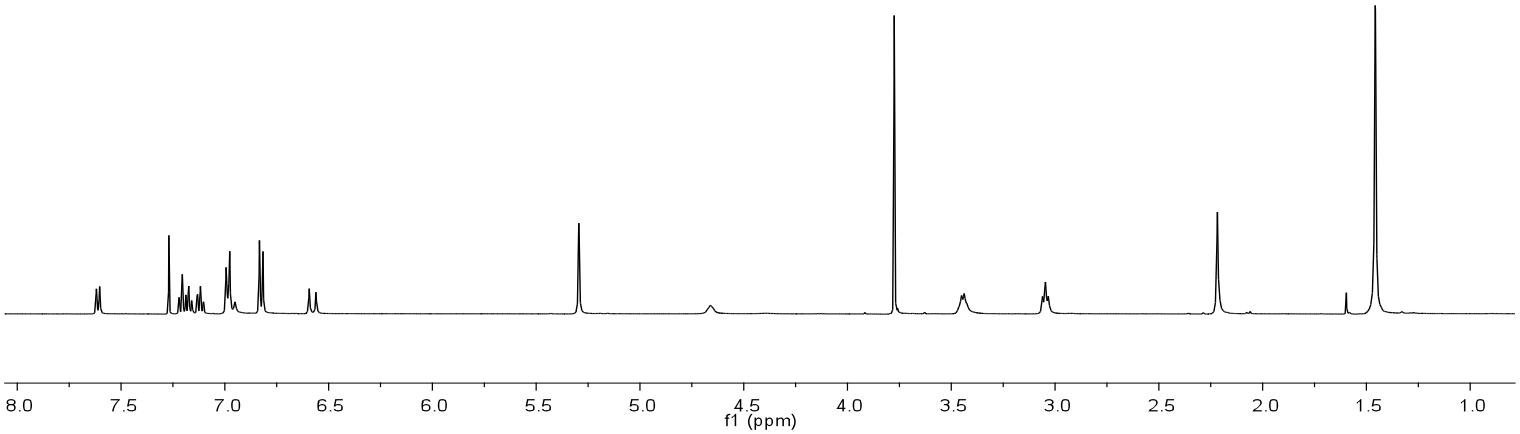
N
PMB

10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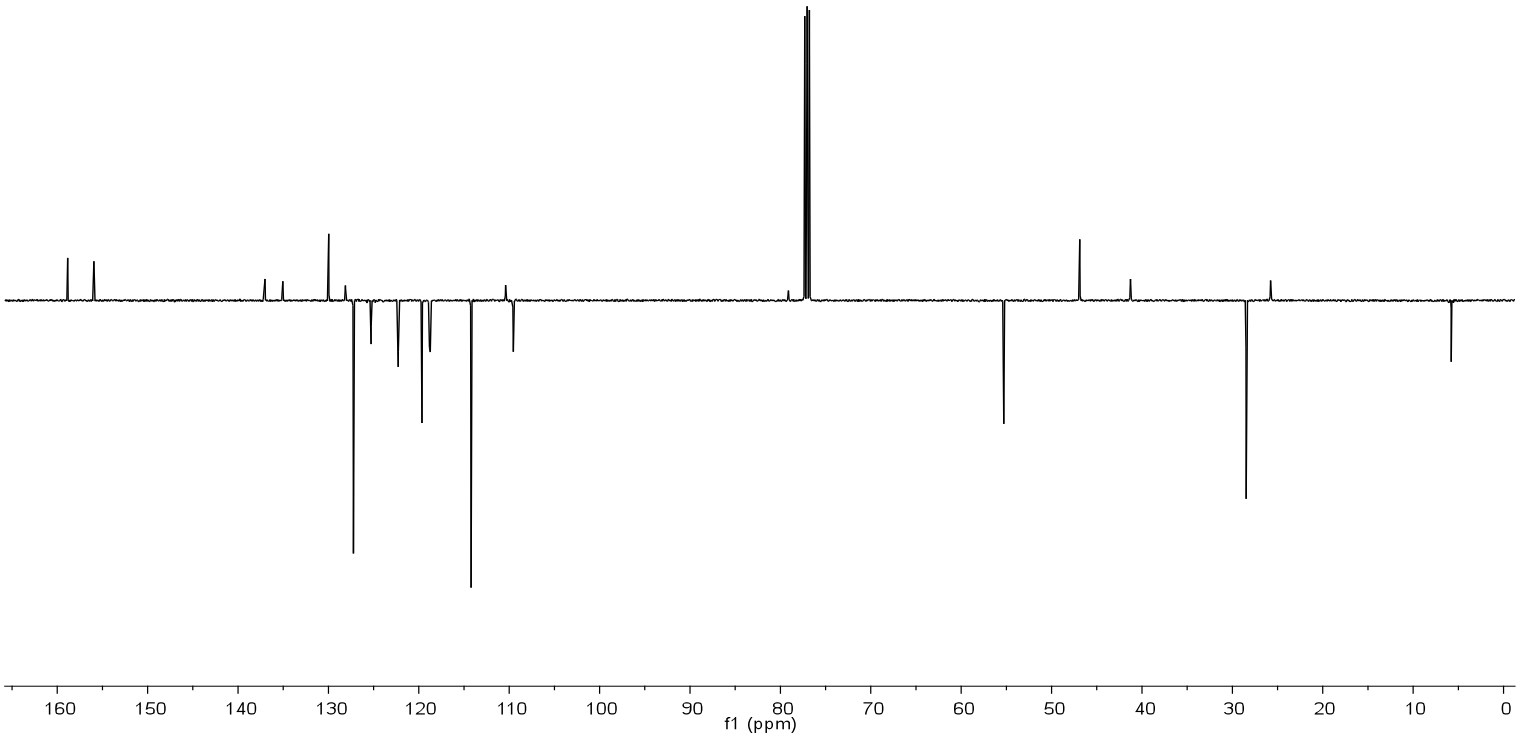
f1 (ppm)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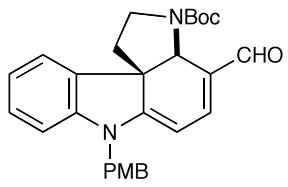
NBoc
CHO
N
PMB

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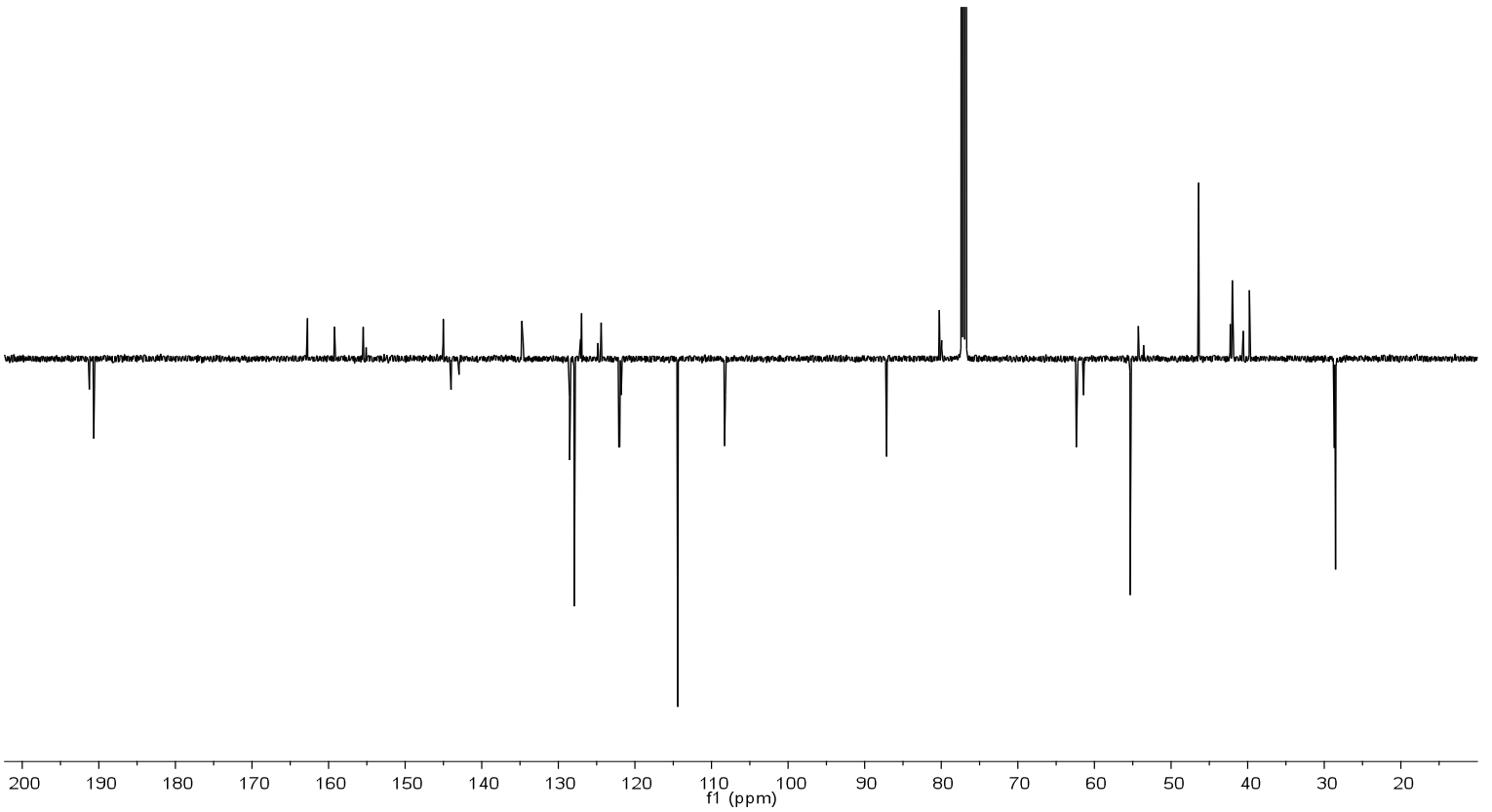
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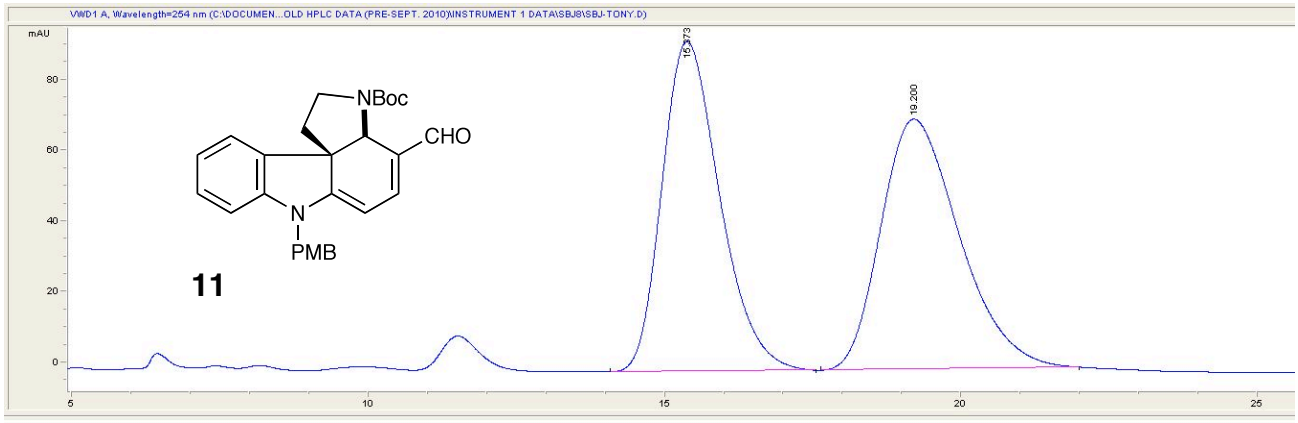

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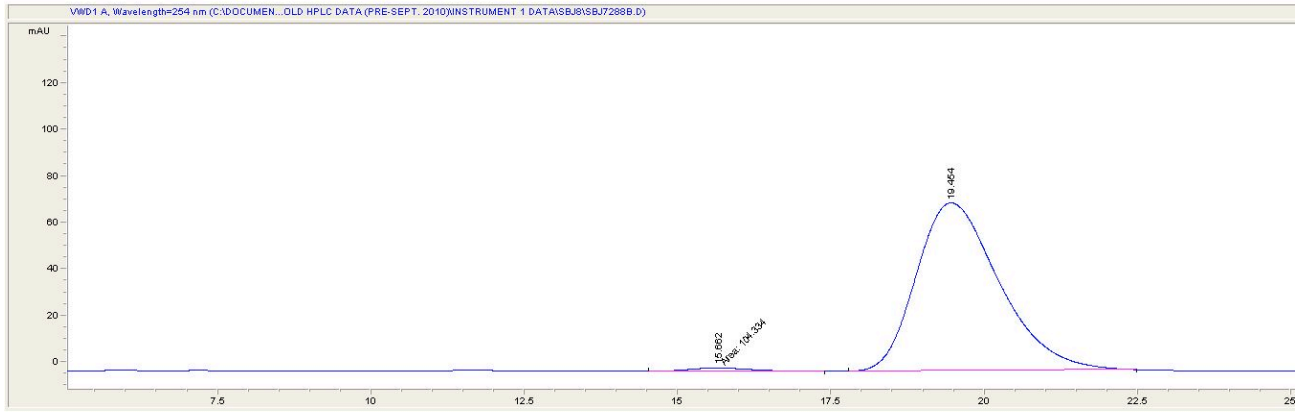

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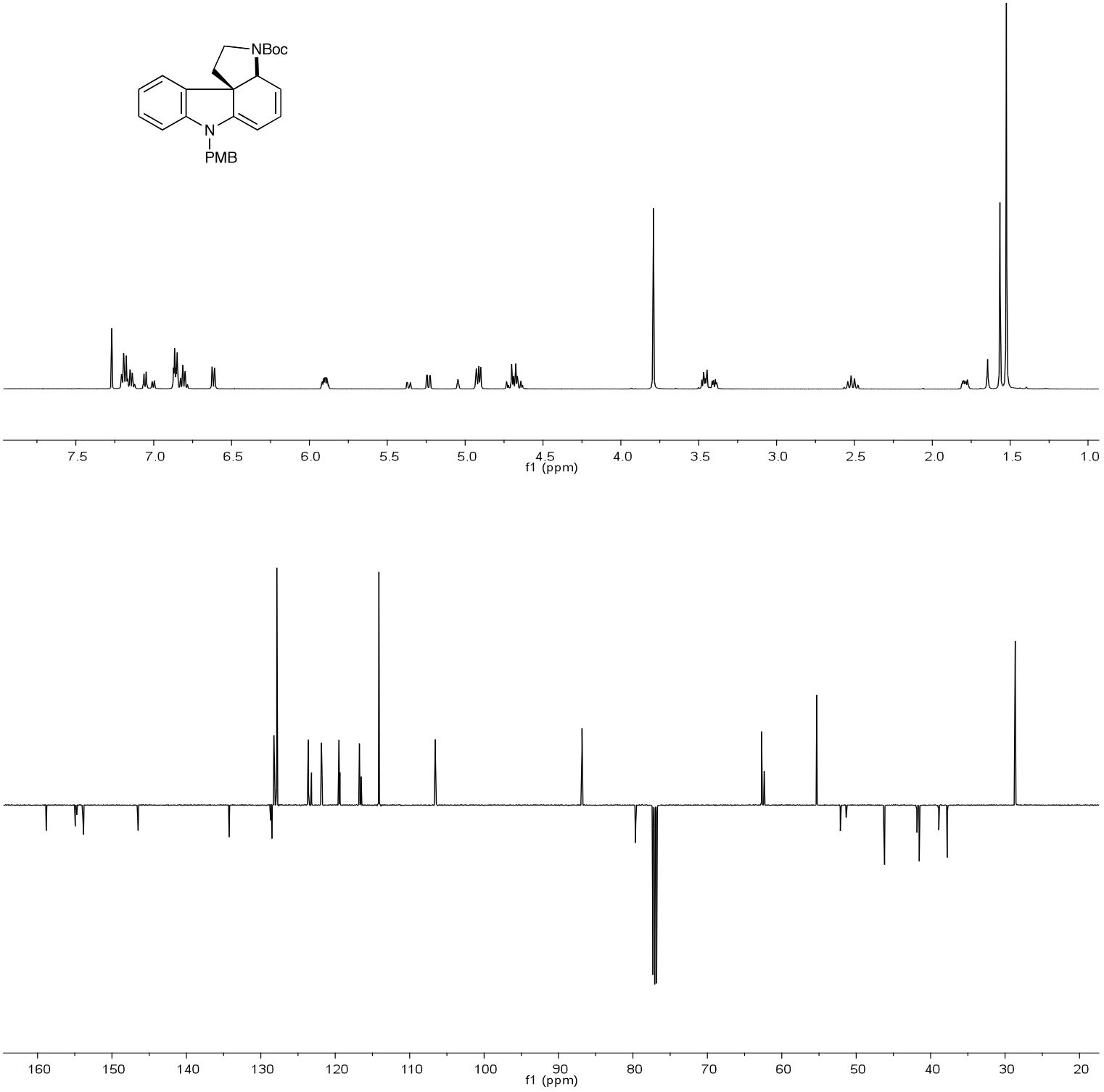
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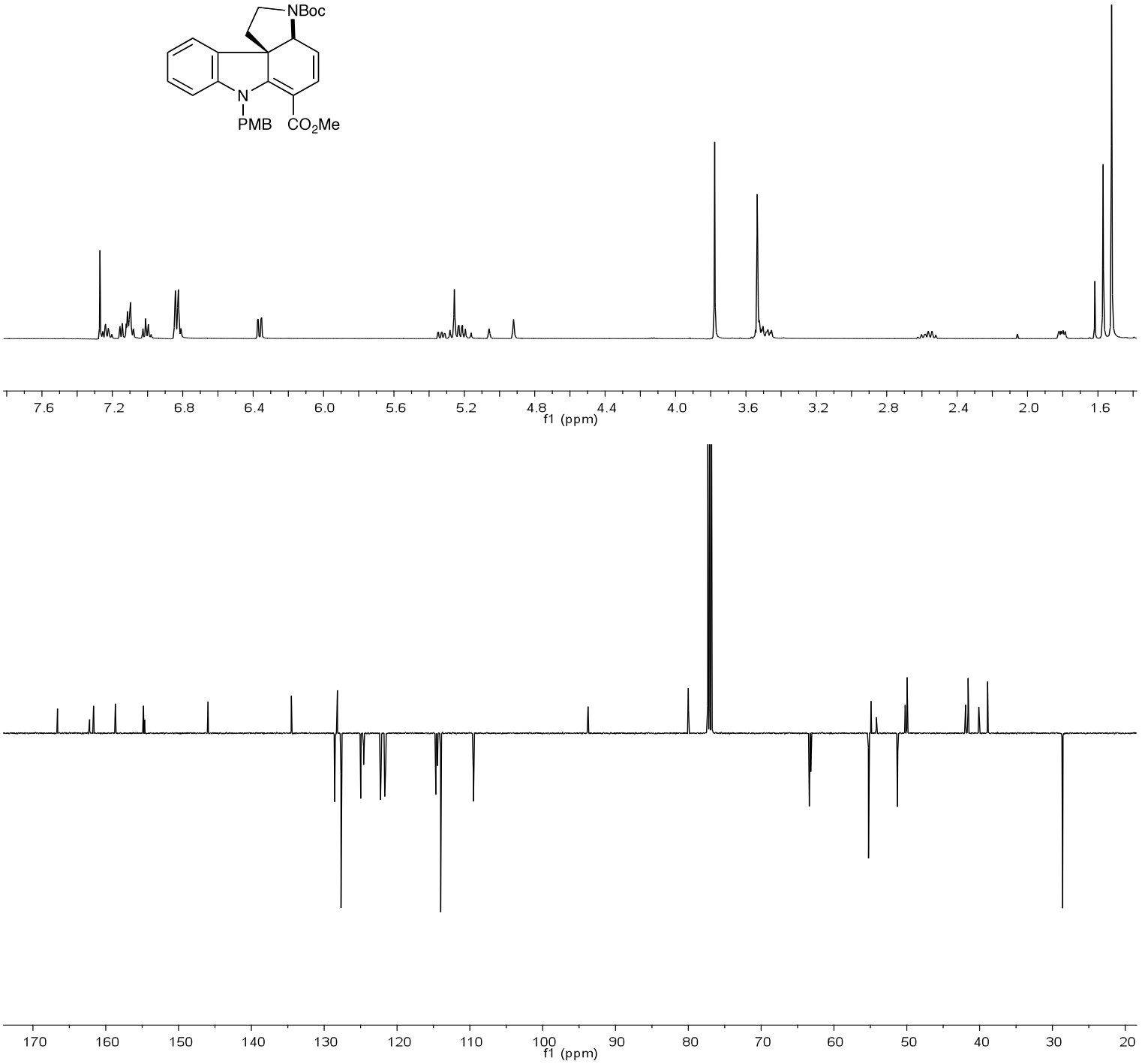
f1 (ppm)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1.6
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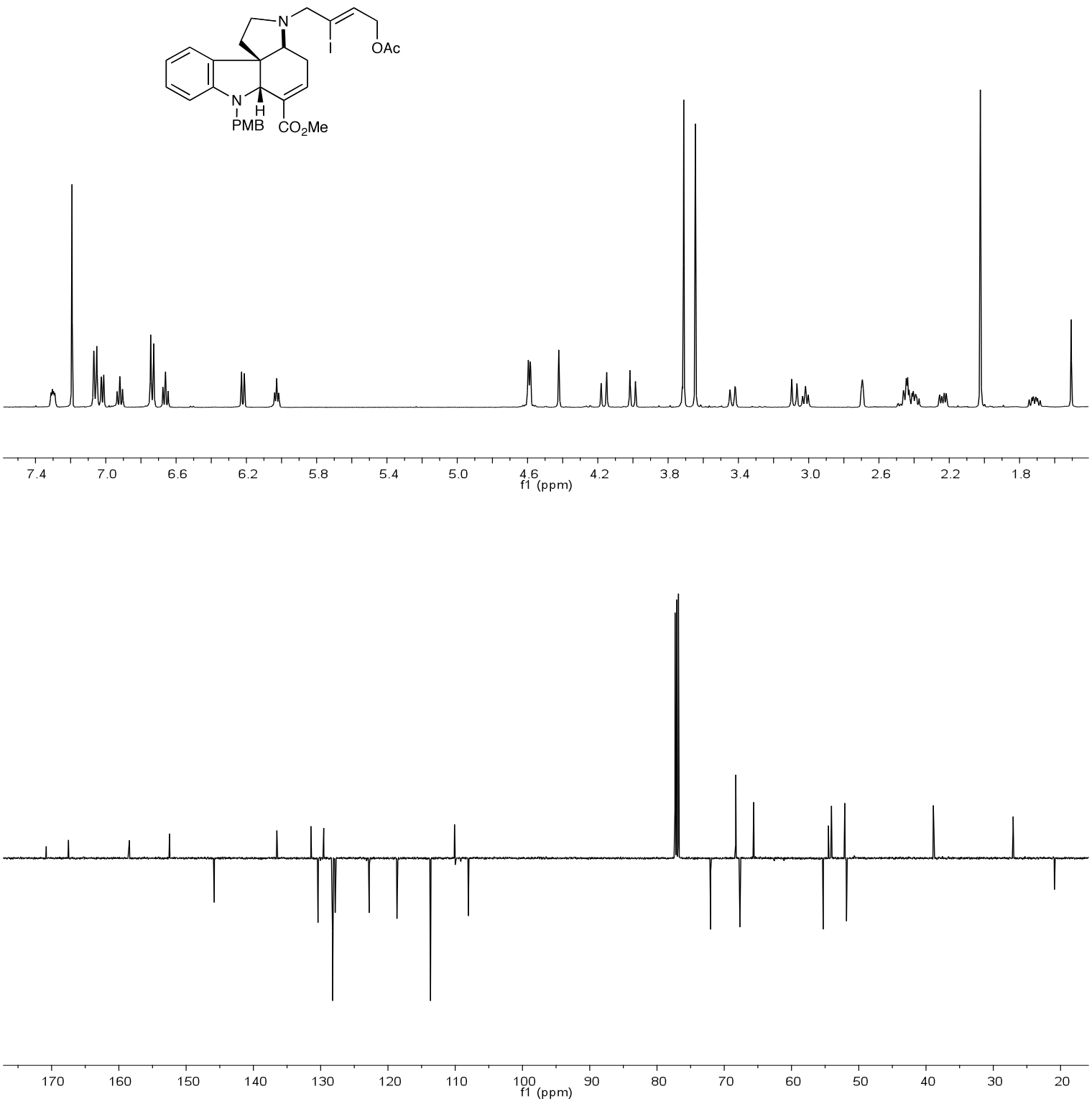
f1 (ppm)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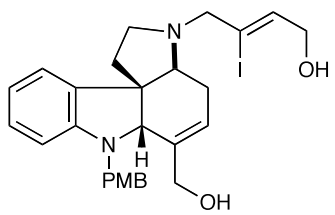
f1 (ppm)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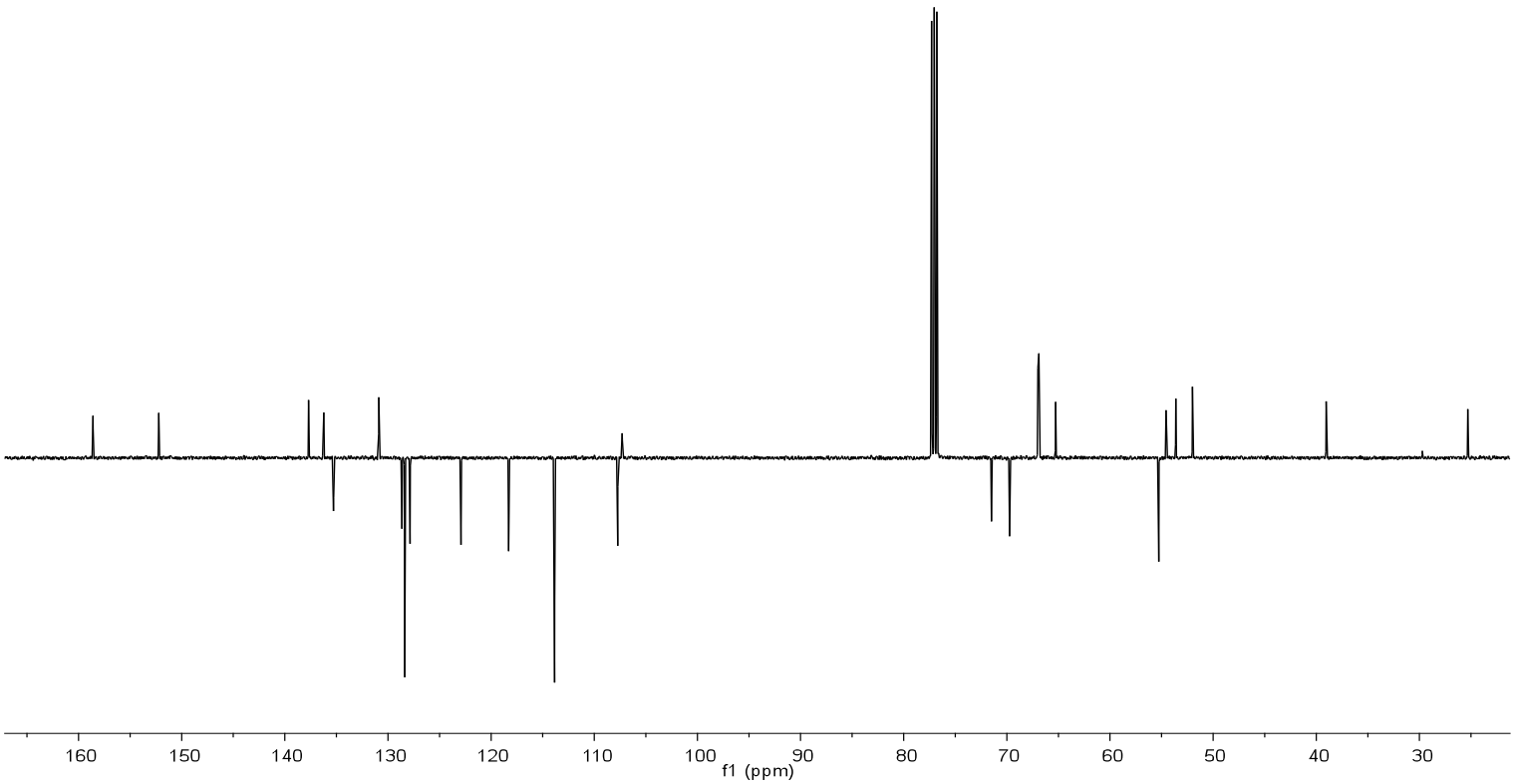
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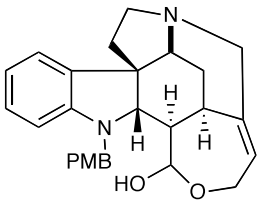
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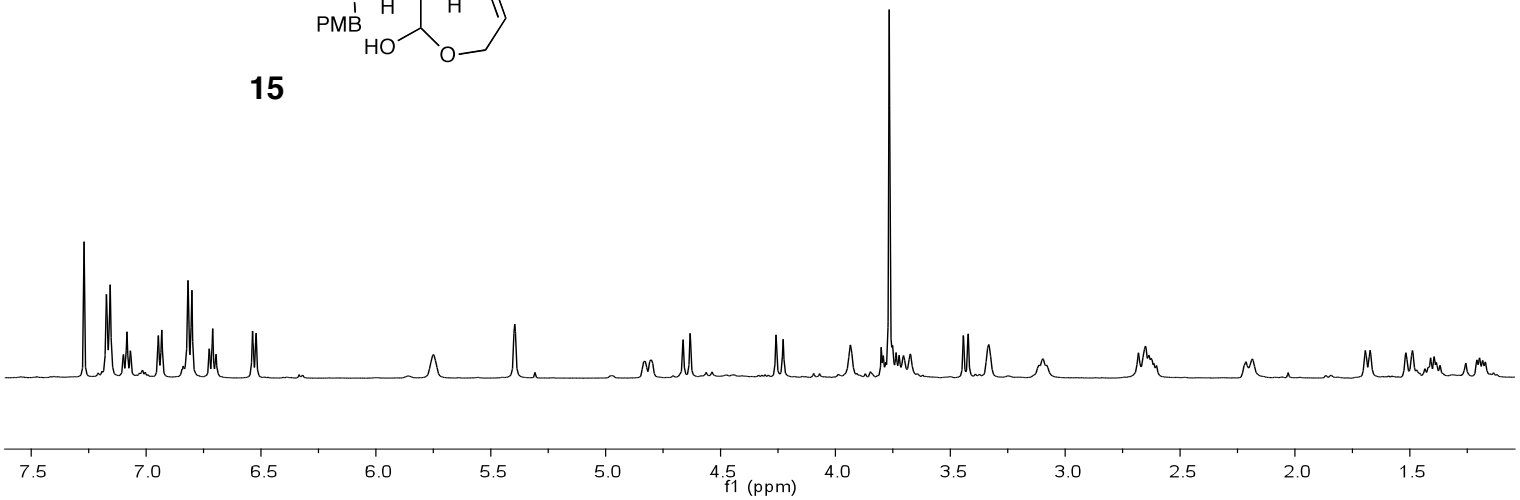
PMB
HO
O

15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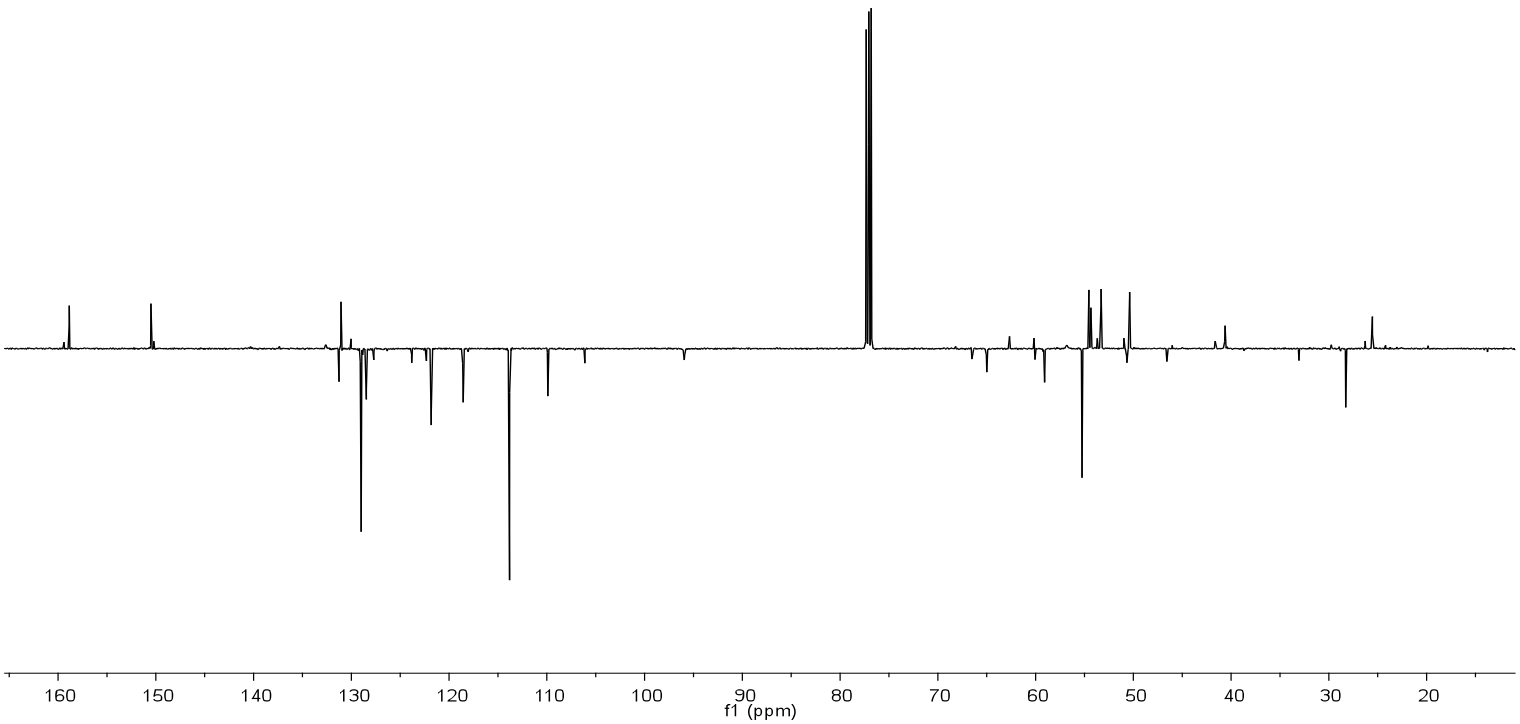
f1 (ppm)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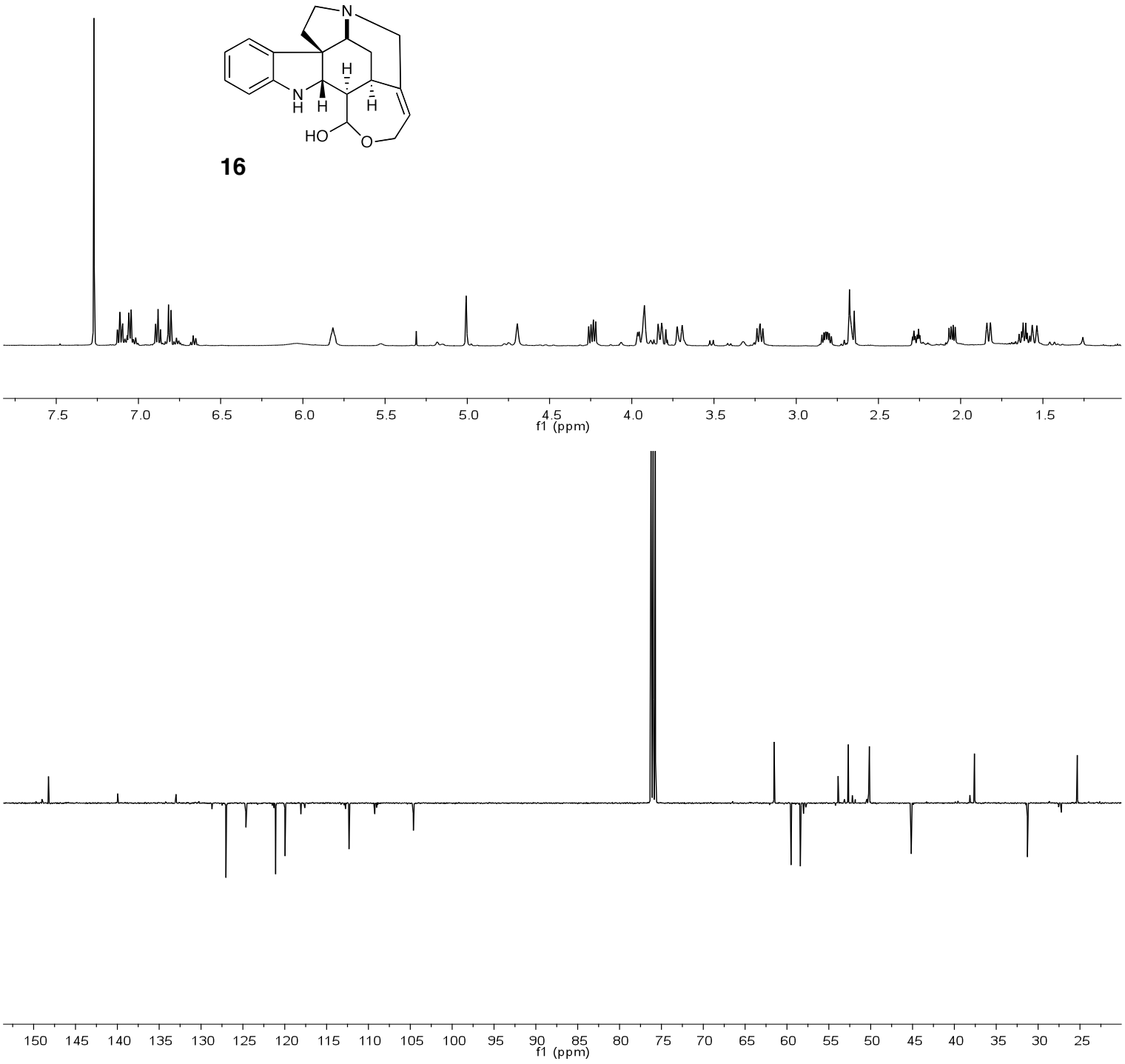
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1.5
f1 (ppm)
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140
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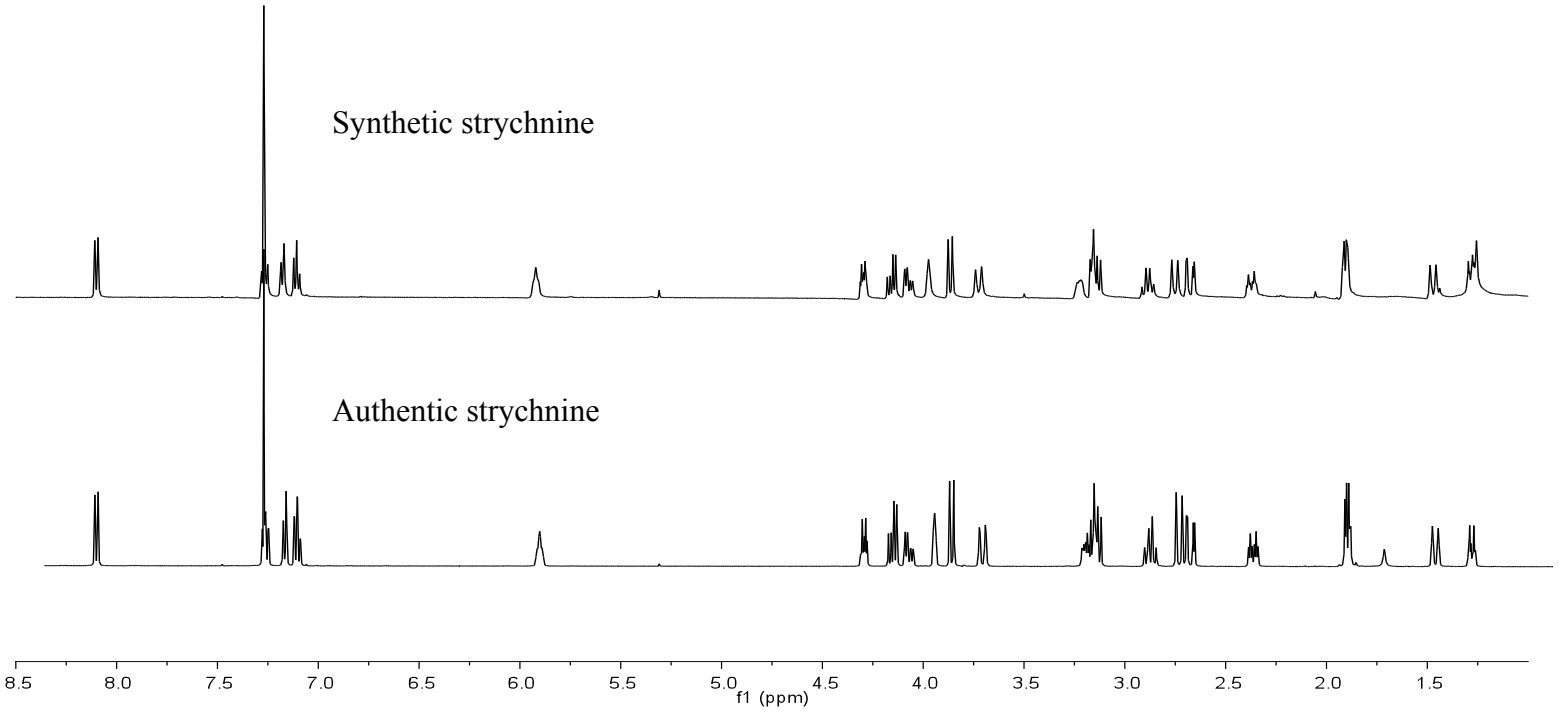
f1 (ppm)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Authentic strychnine
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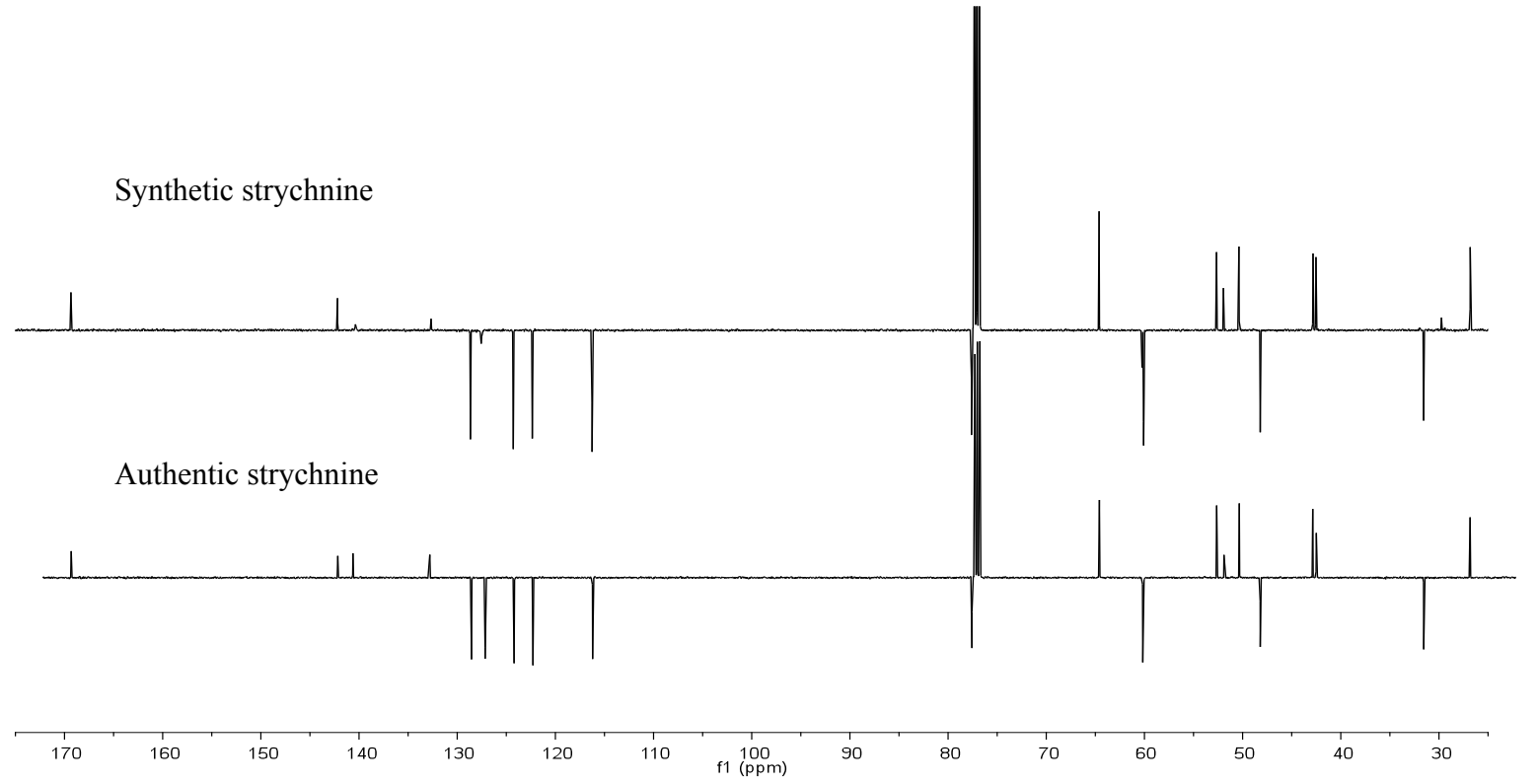
f1 (ppm)


Synthetic strychnine
Authentic strychnine
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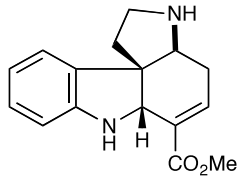
f1 (ppm)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H
H
CO2Me

17

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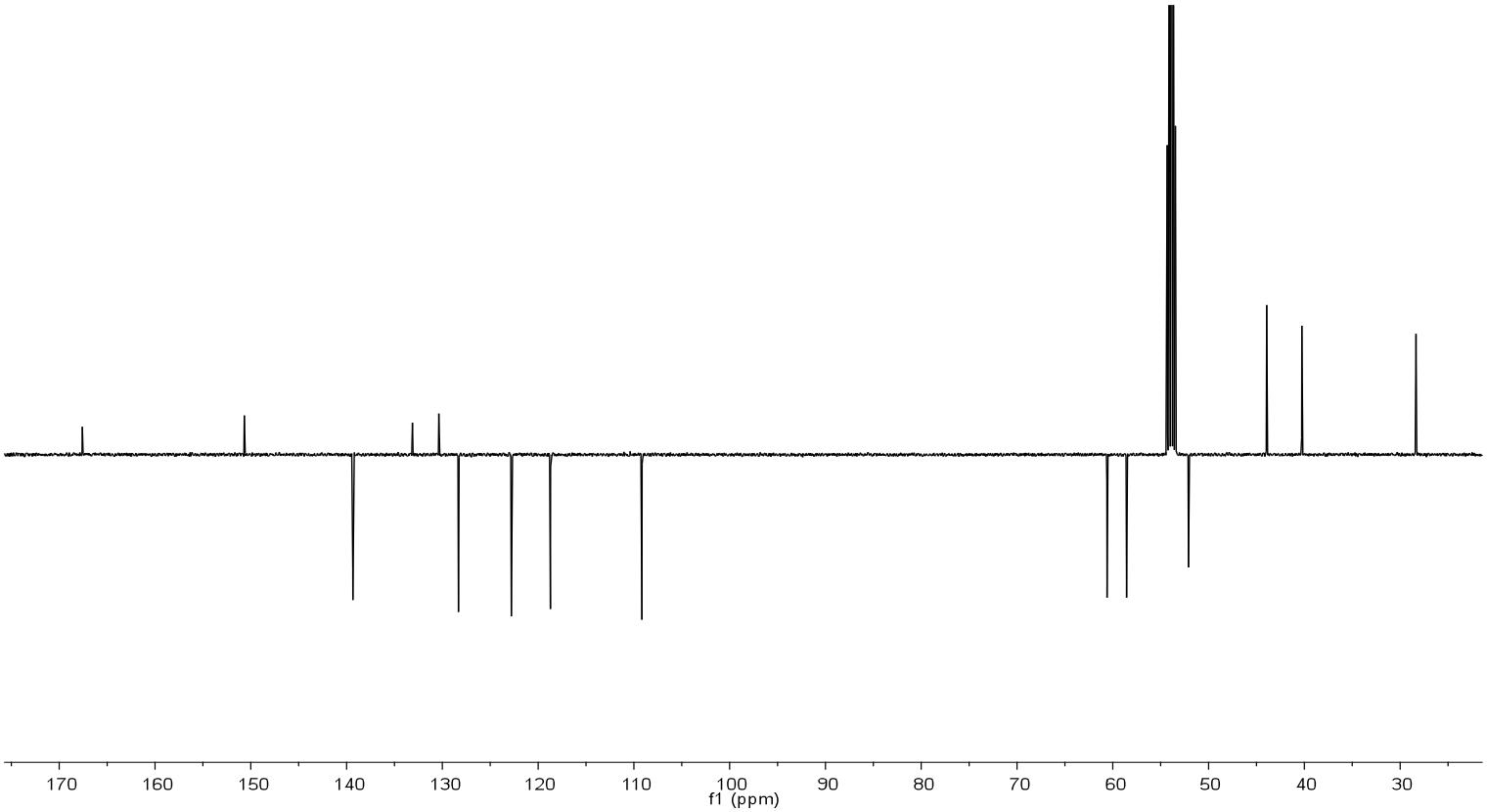
f1 (ppm)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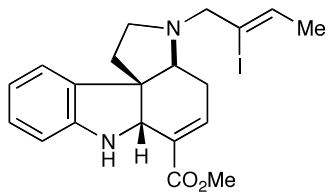
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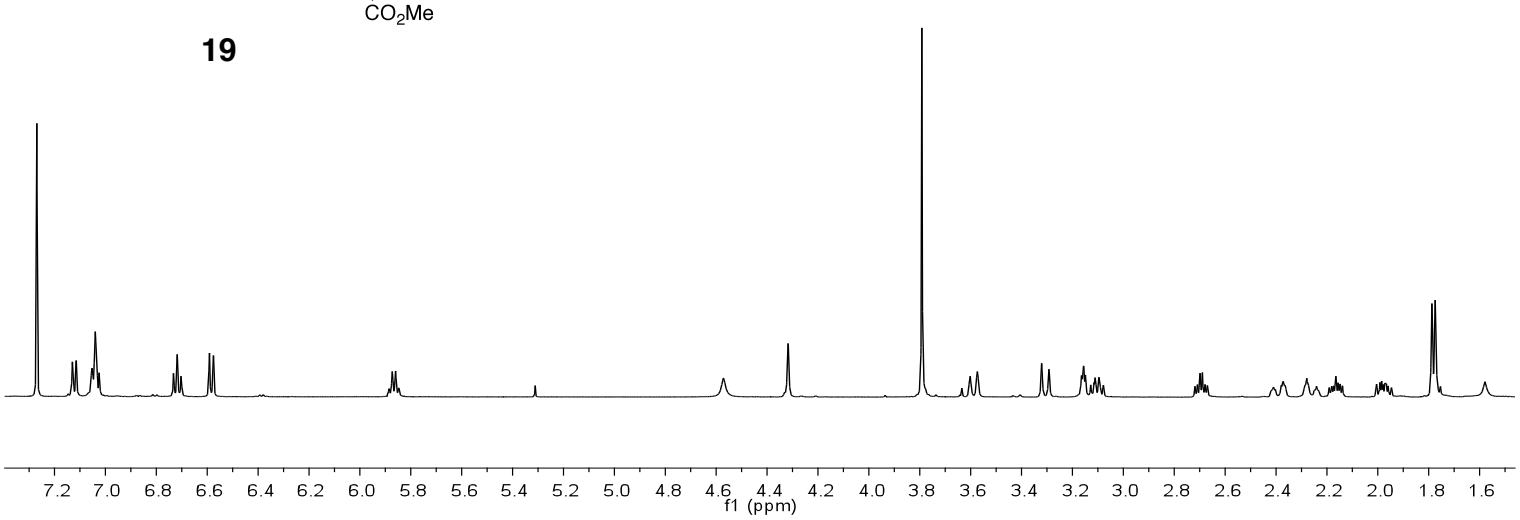
Me
I
N
H
H
CO2Me

19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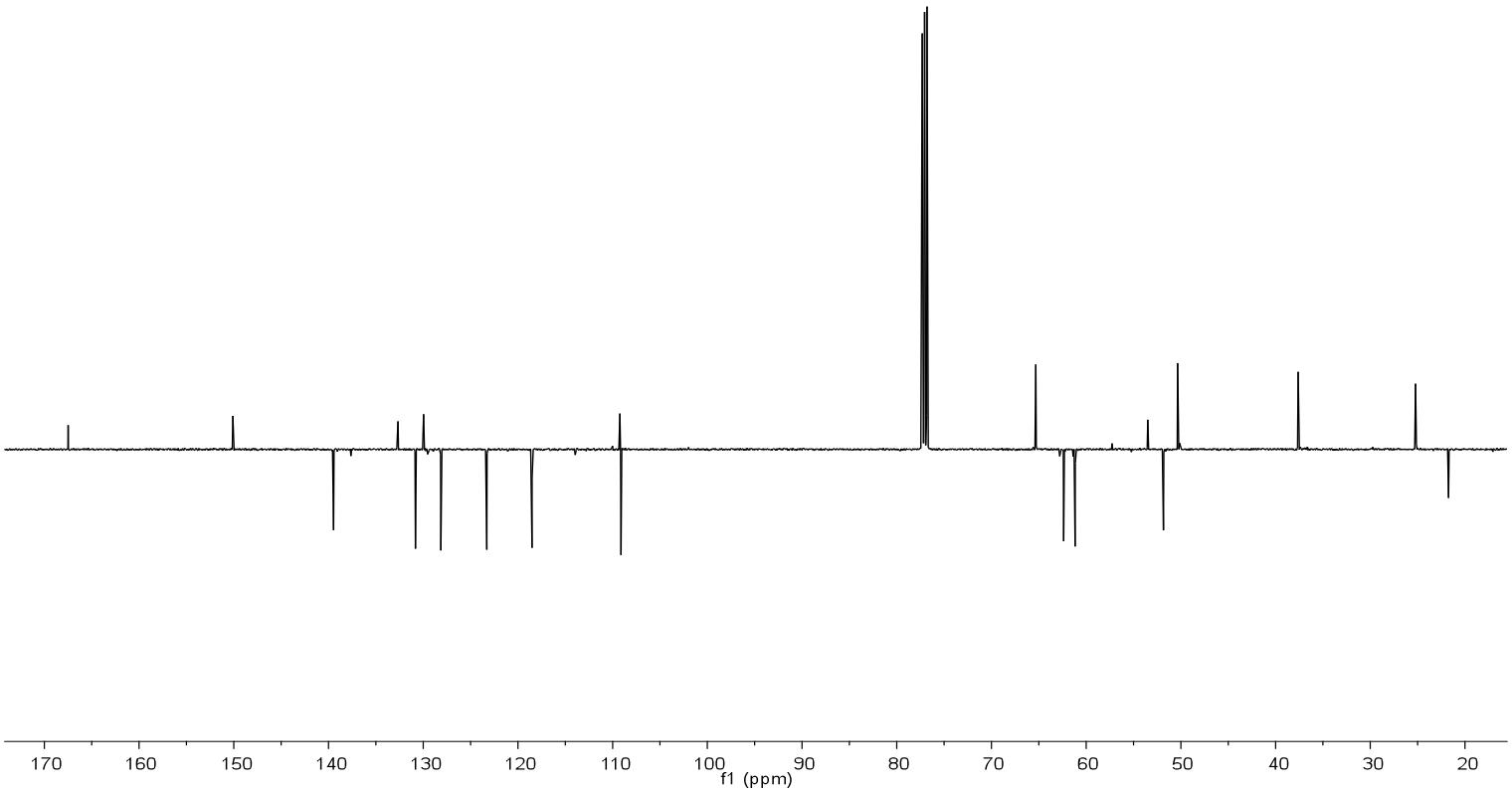
f1 (ppm)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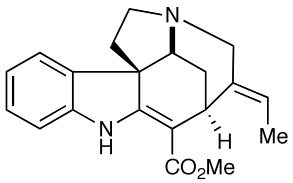
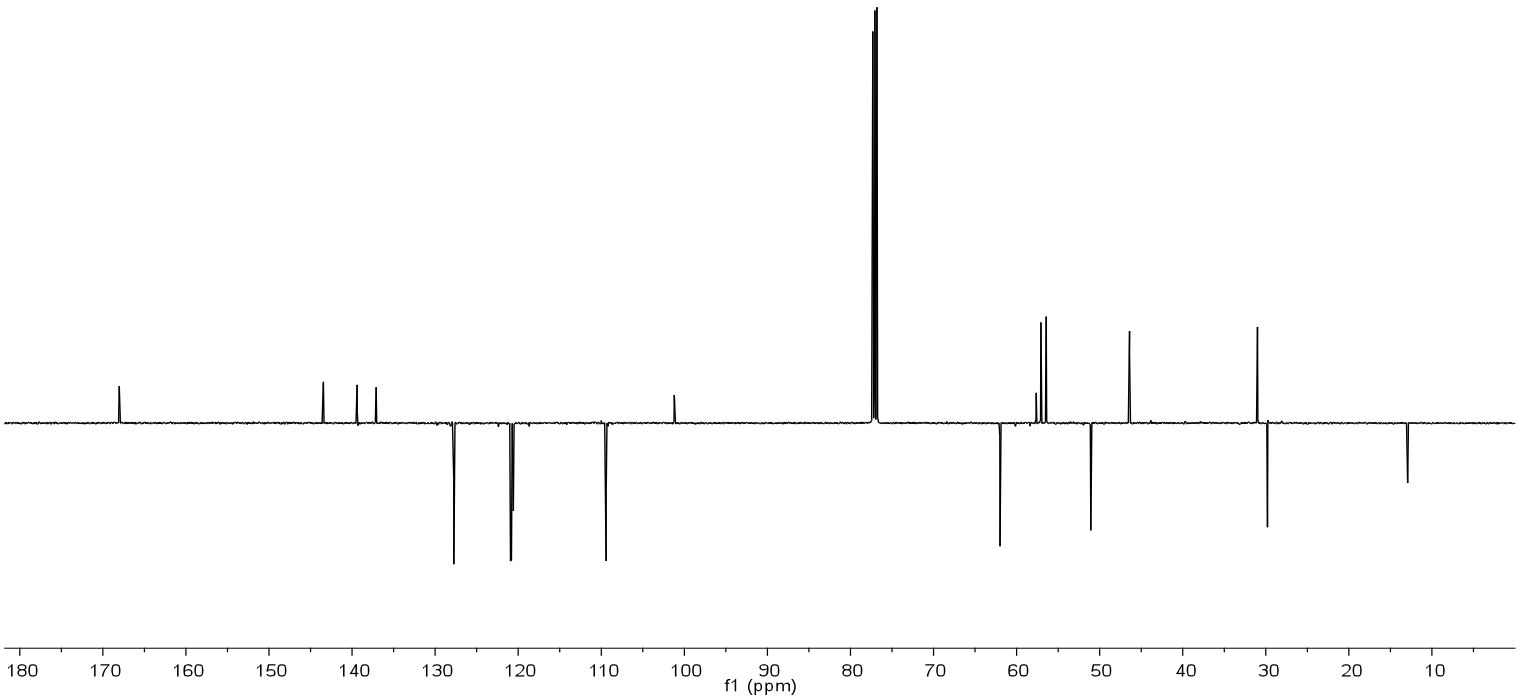
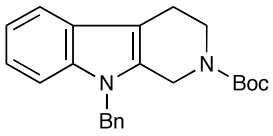


(–)-akuammicine

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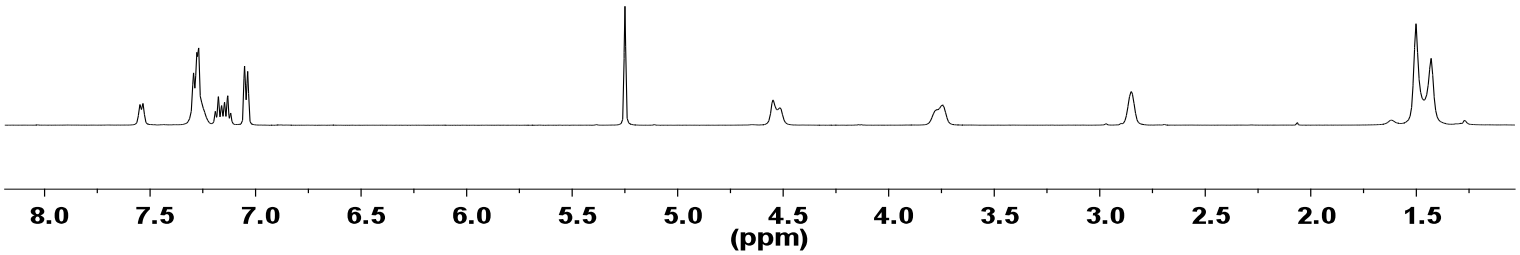
N
Bn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3.5
3.0
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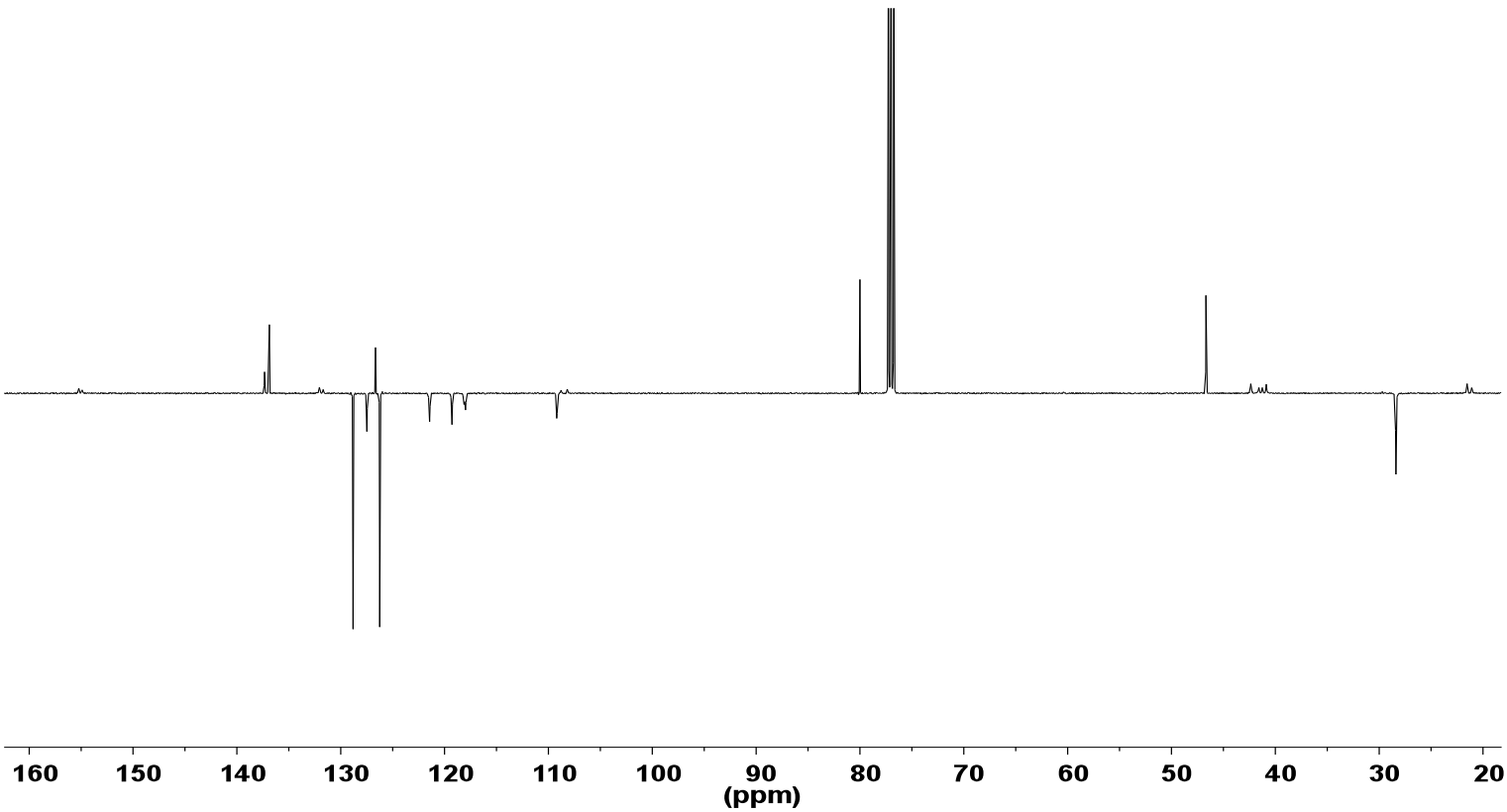
(ppm)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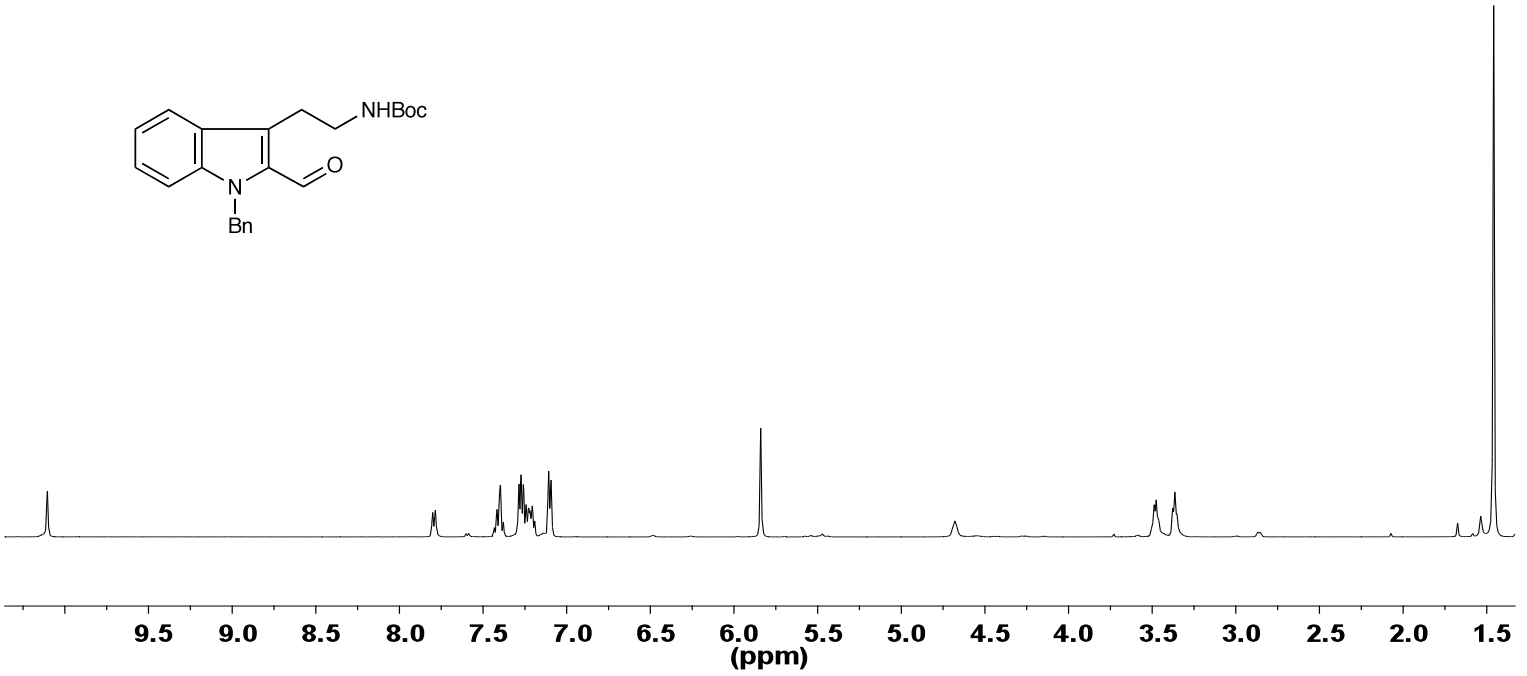
20
(ppm)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Bn
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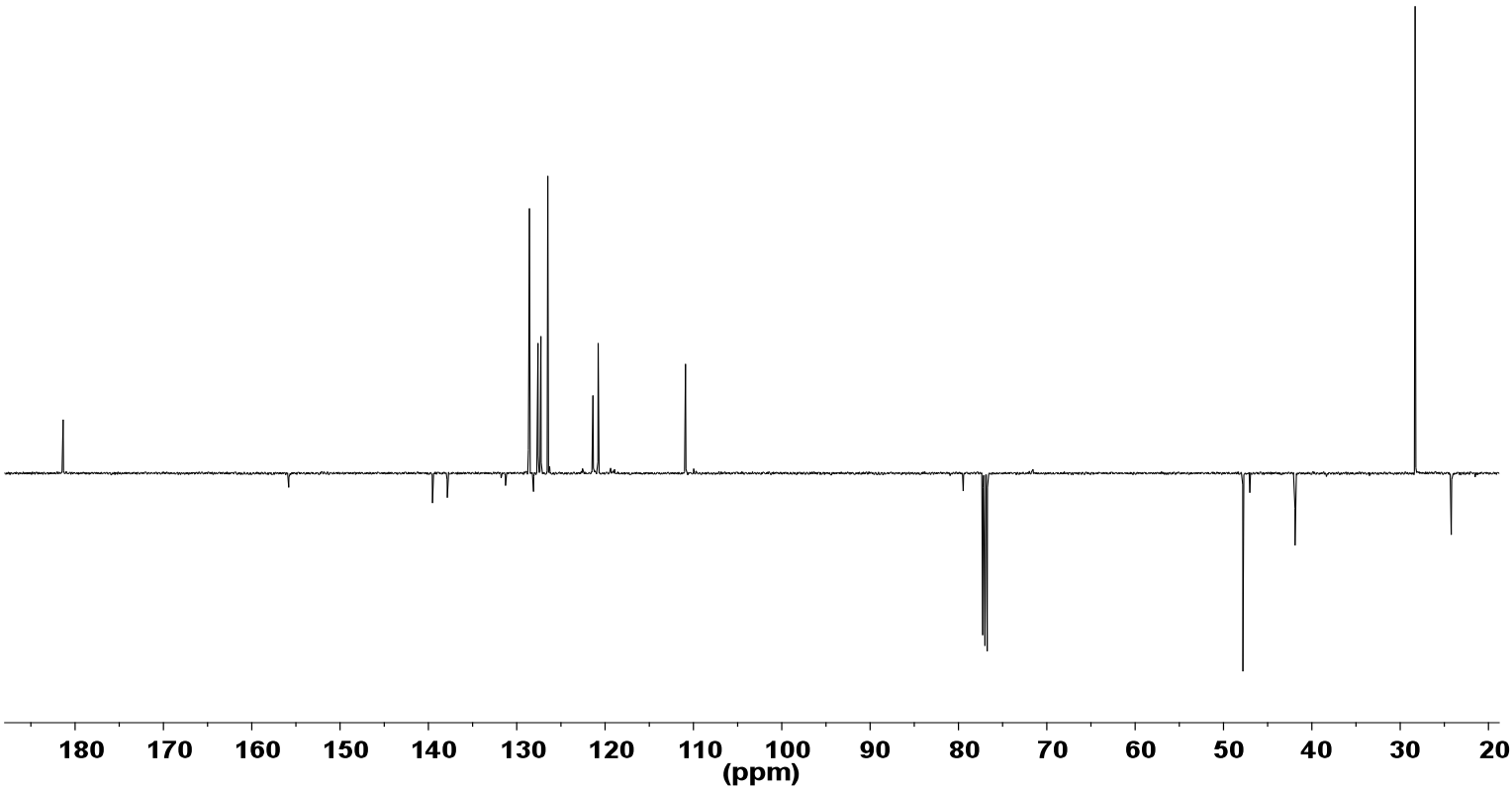
3.5
3.0
2.5
2.0
1.5
(ppm)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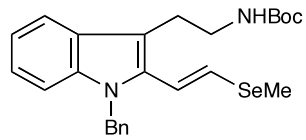
(ppm)


NHBoc
SeMe
N
Bn

20

7.5
7.0
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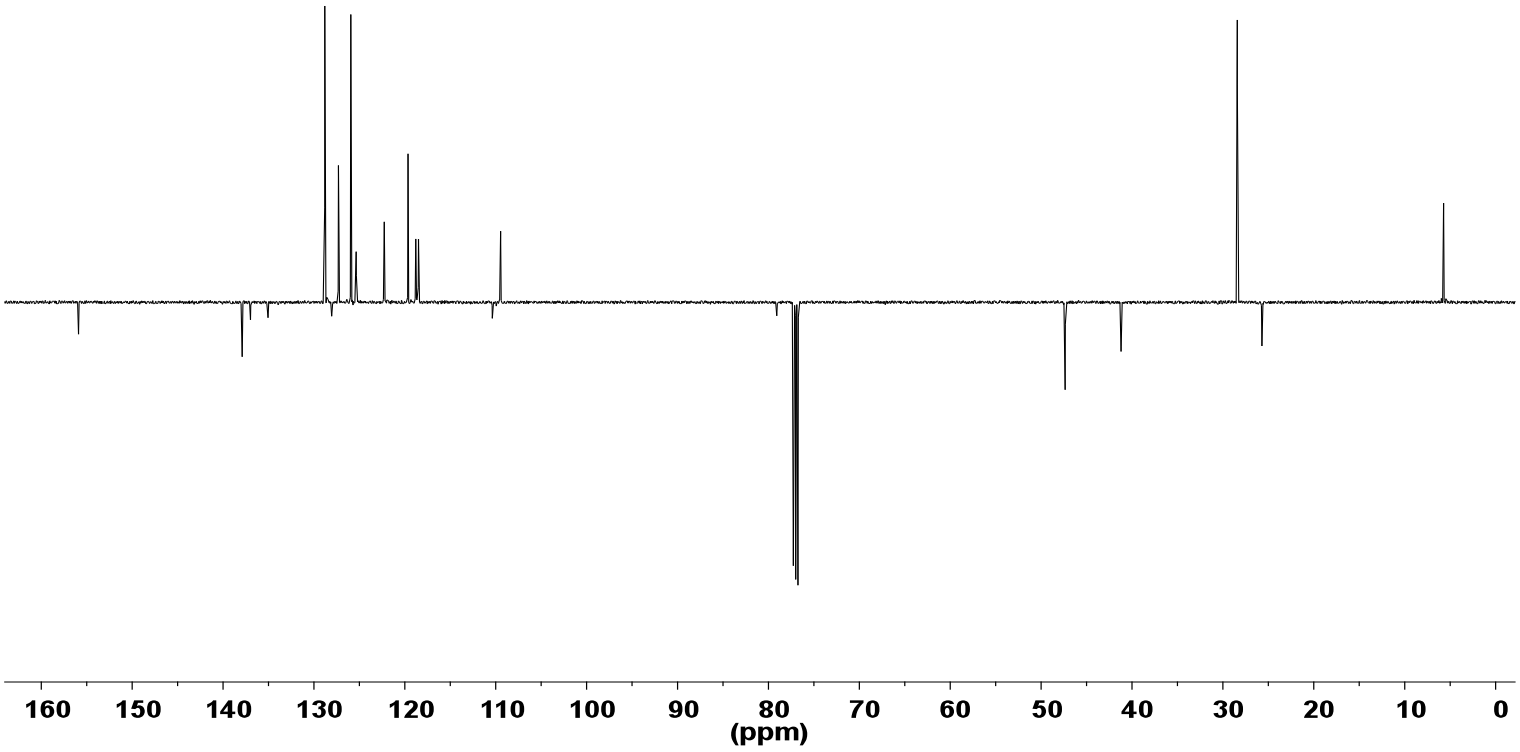
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)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120
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100
90
80
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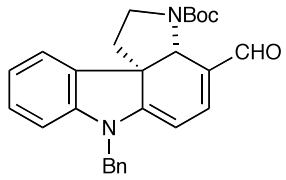
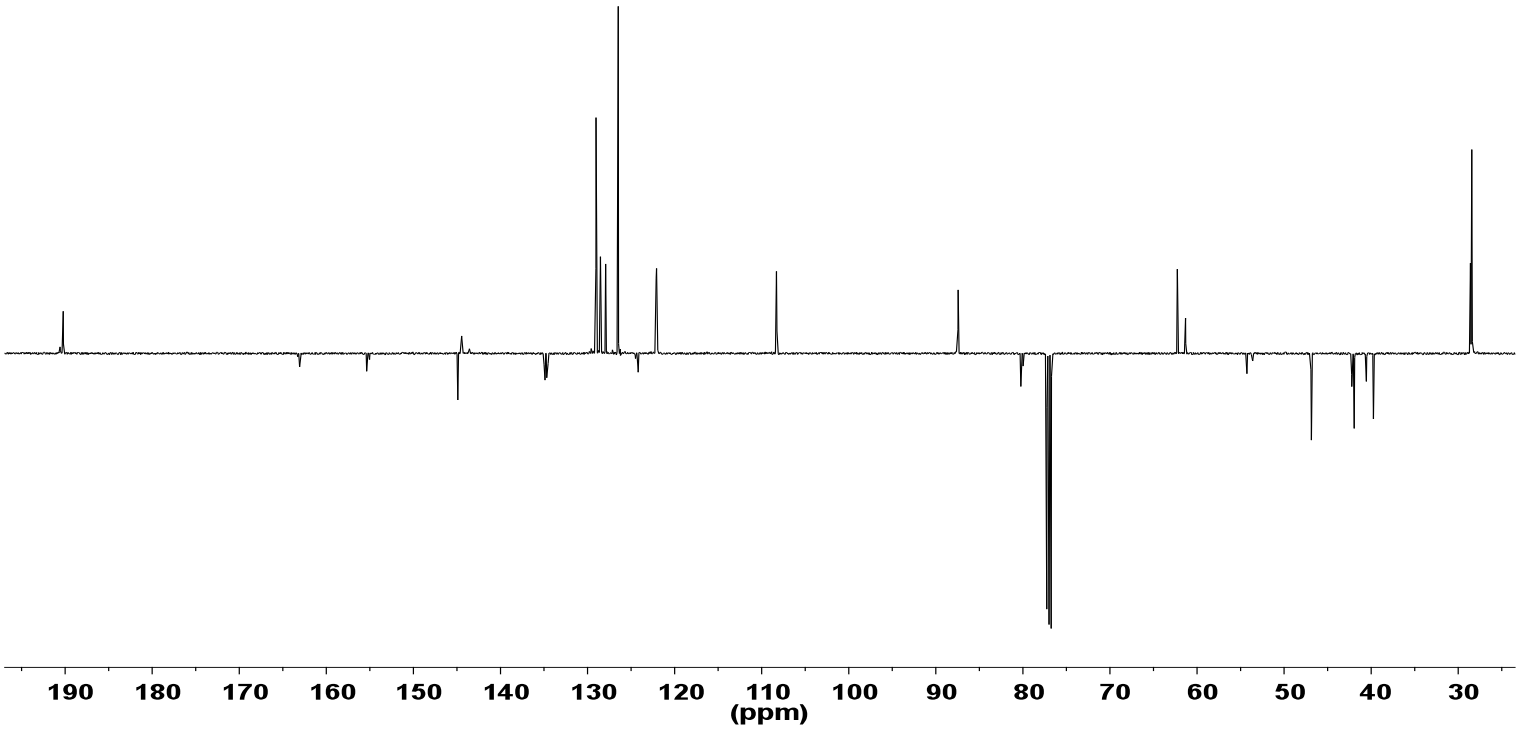
60
50
40
30
20
10
0
(ppm)


NBoc
CHO
N
Bn

21

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)


190
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150
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90
80
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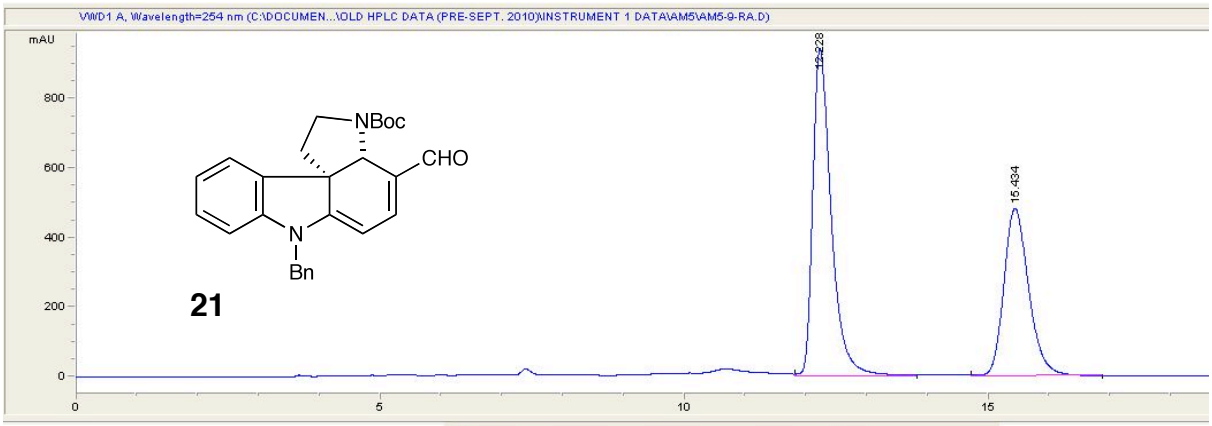
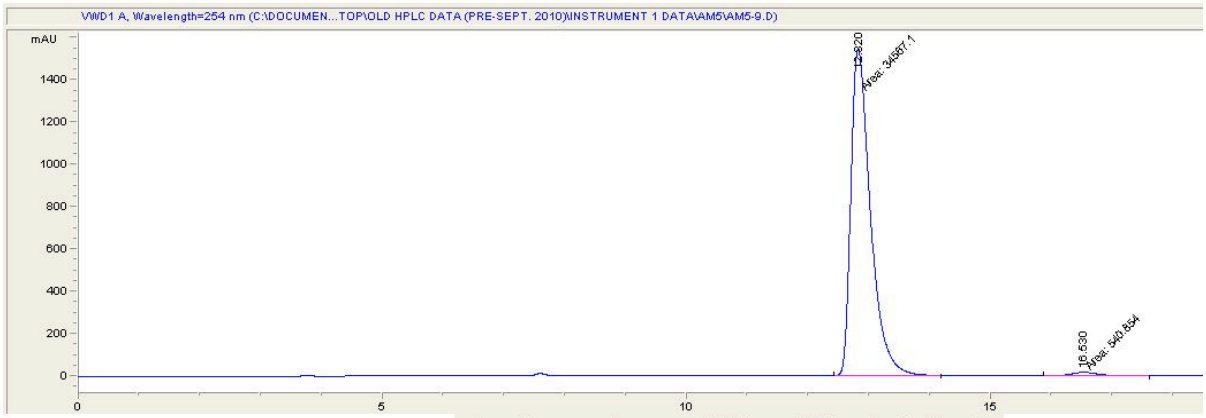
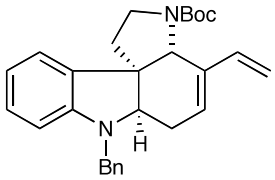
60
50
40
30
(ppm)

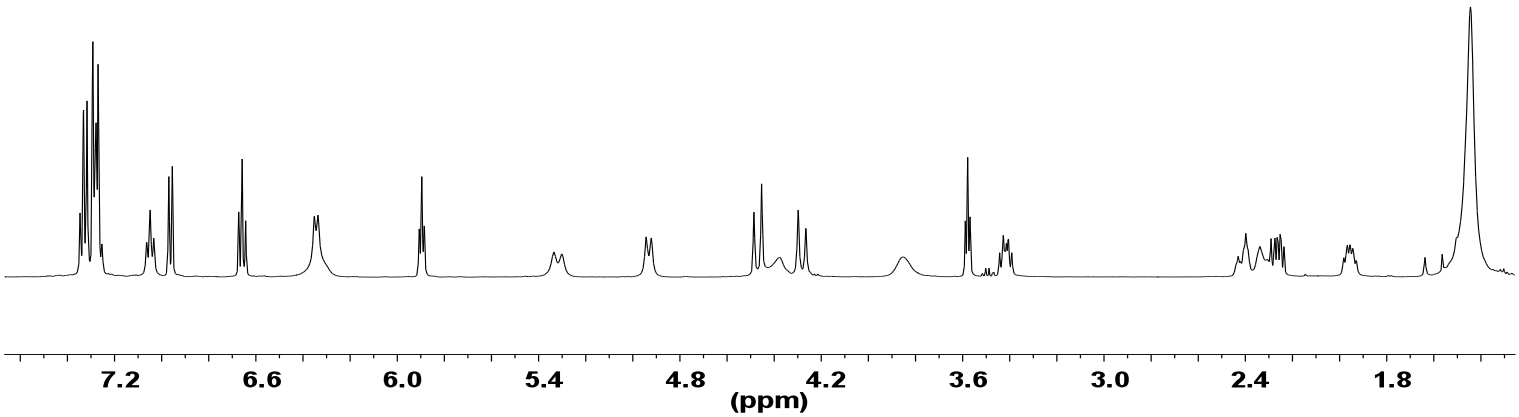


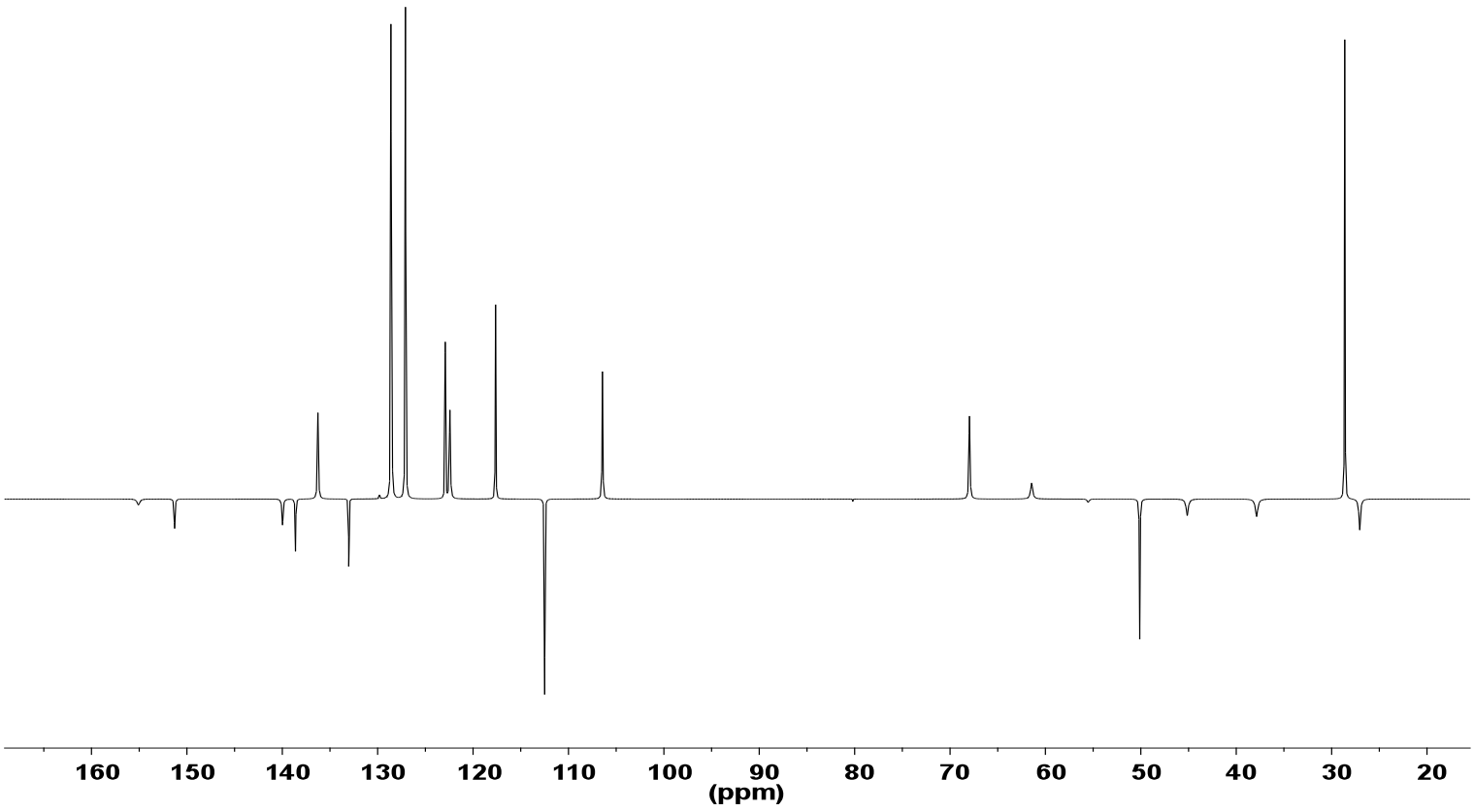
#	Time	Area	Height	Width	Area%	Symmetry
1	12.228	19988.3	941.8	0.3219	59.331	0.581
2	15.434	13701.4	482	0.4365	40.669	0.76



#	Time	Area	Height	Width	Area%	Symmetry
1	12.82	34567.1	1545.3	0.3728	98.459	0.558
2	16.53	540.9	16.9	0.5334	1.541	0.856


NBoc
N
H
Bn


7.2
6.6
6.0
5.4
4.8
4.2
3.6
3.0
2.4
1.8
(ppm)


160
150
140
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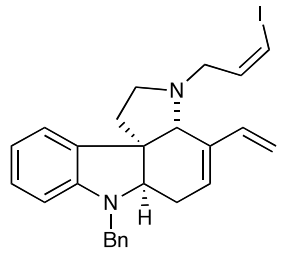
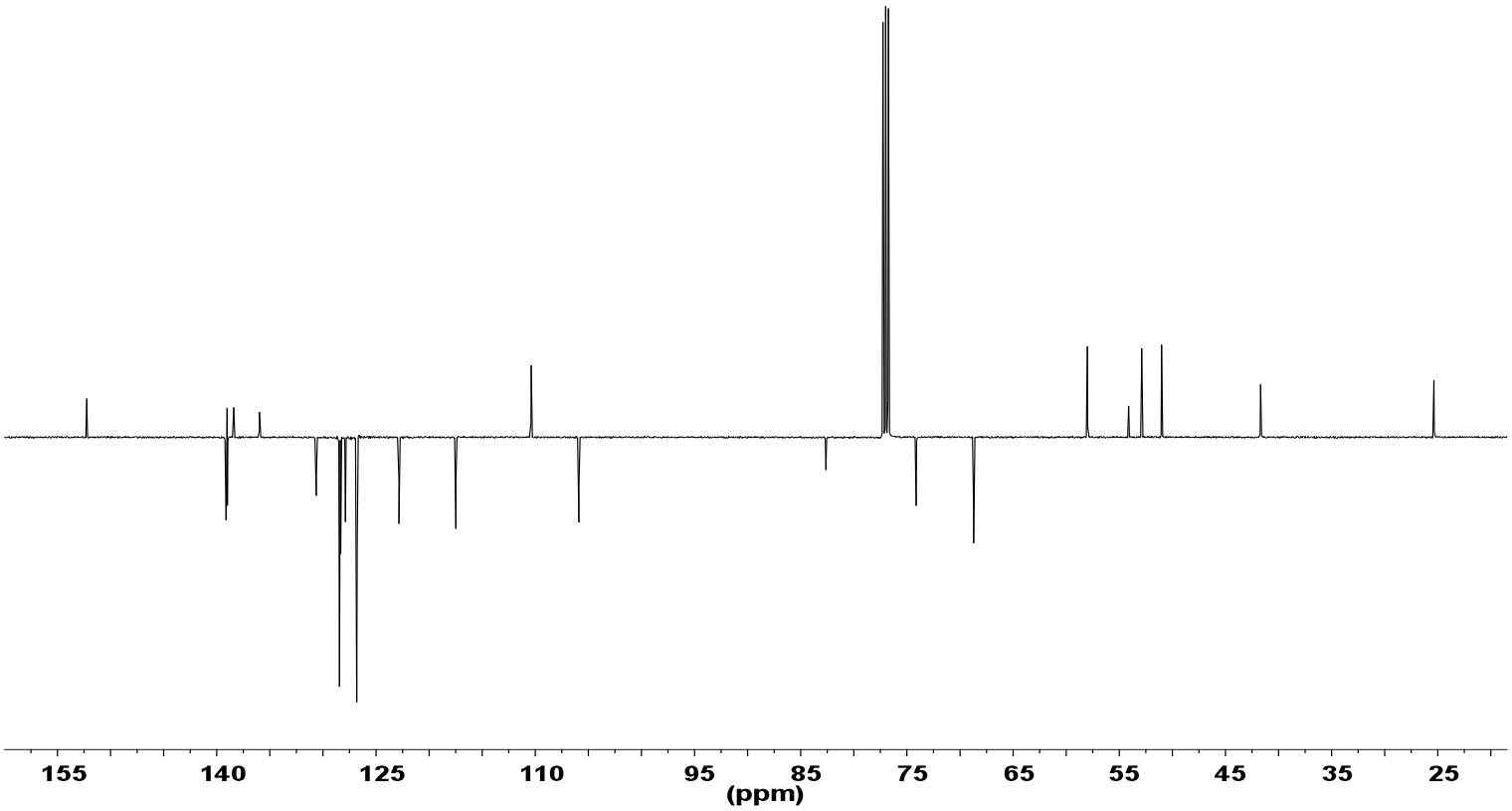
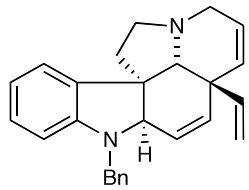
120
110
100
90
80
70
60
50
40
30
20
(ppm)


I
N
N
H
Bn

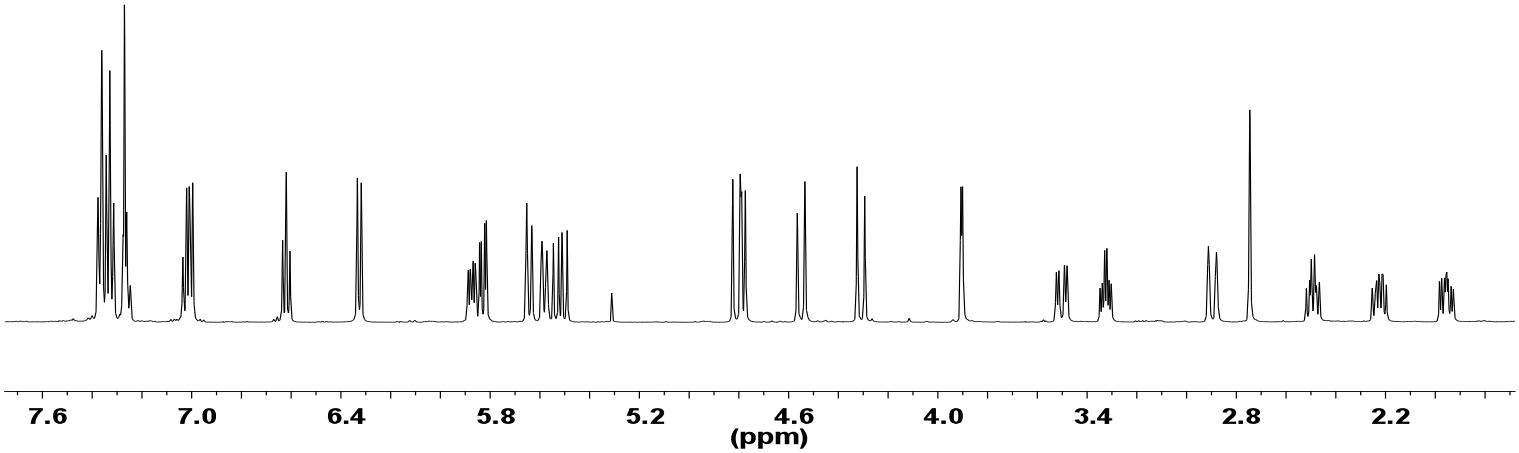
23

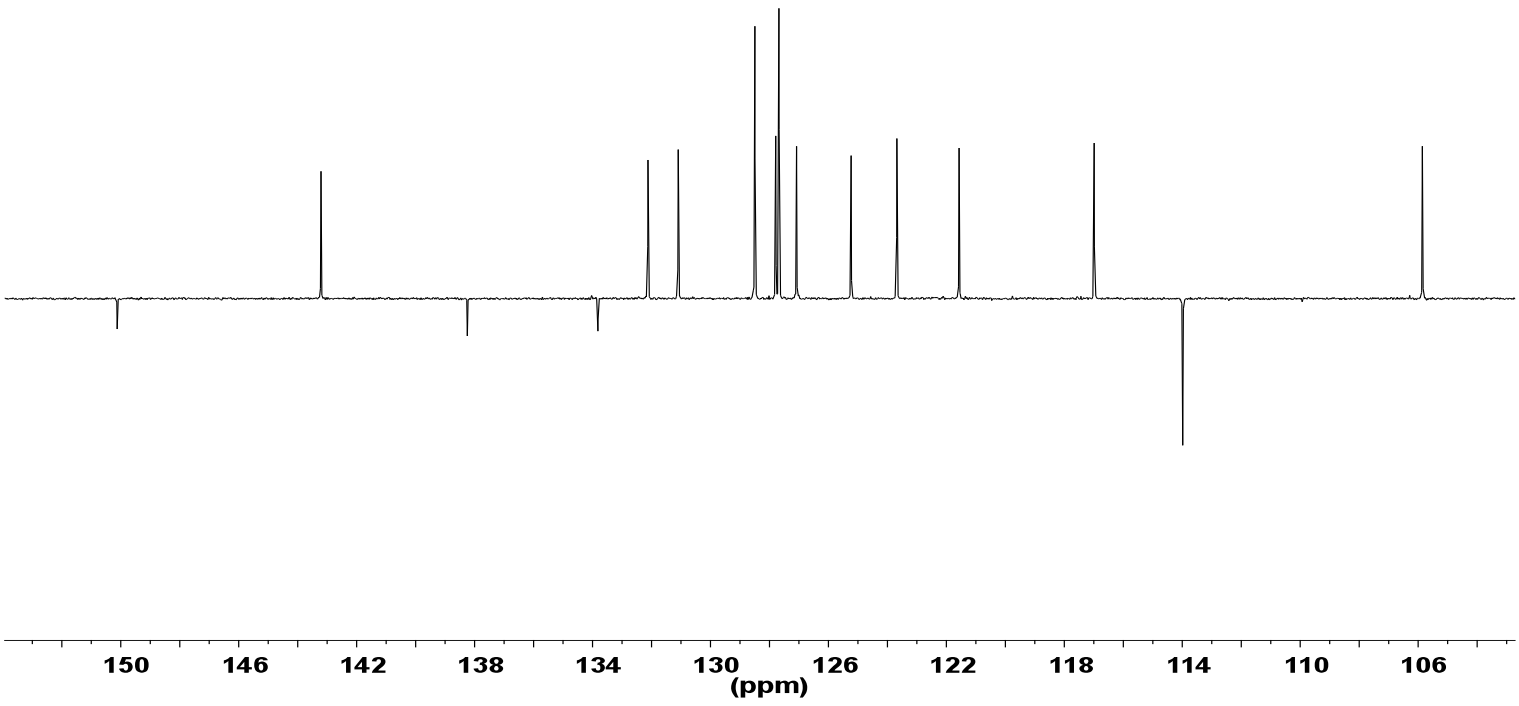
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

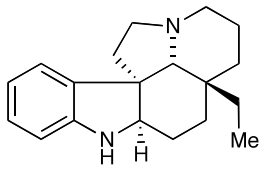

155
140
125
110
95
85
75
65
55
45
35
25
(ppm)


N
N
H
Bn

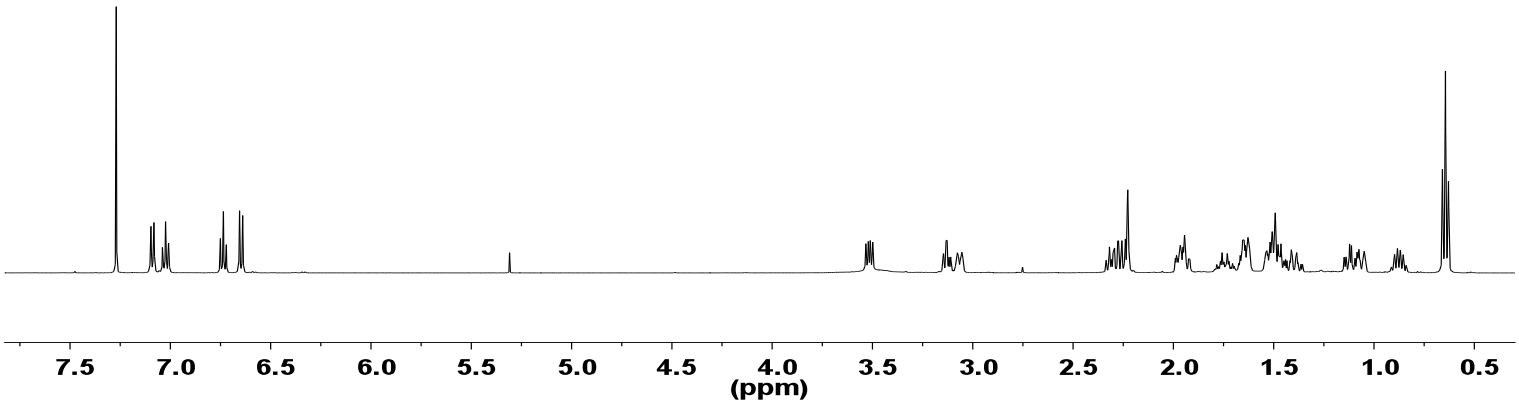
24

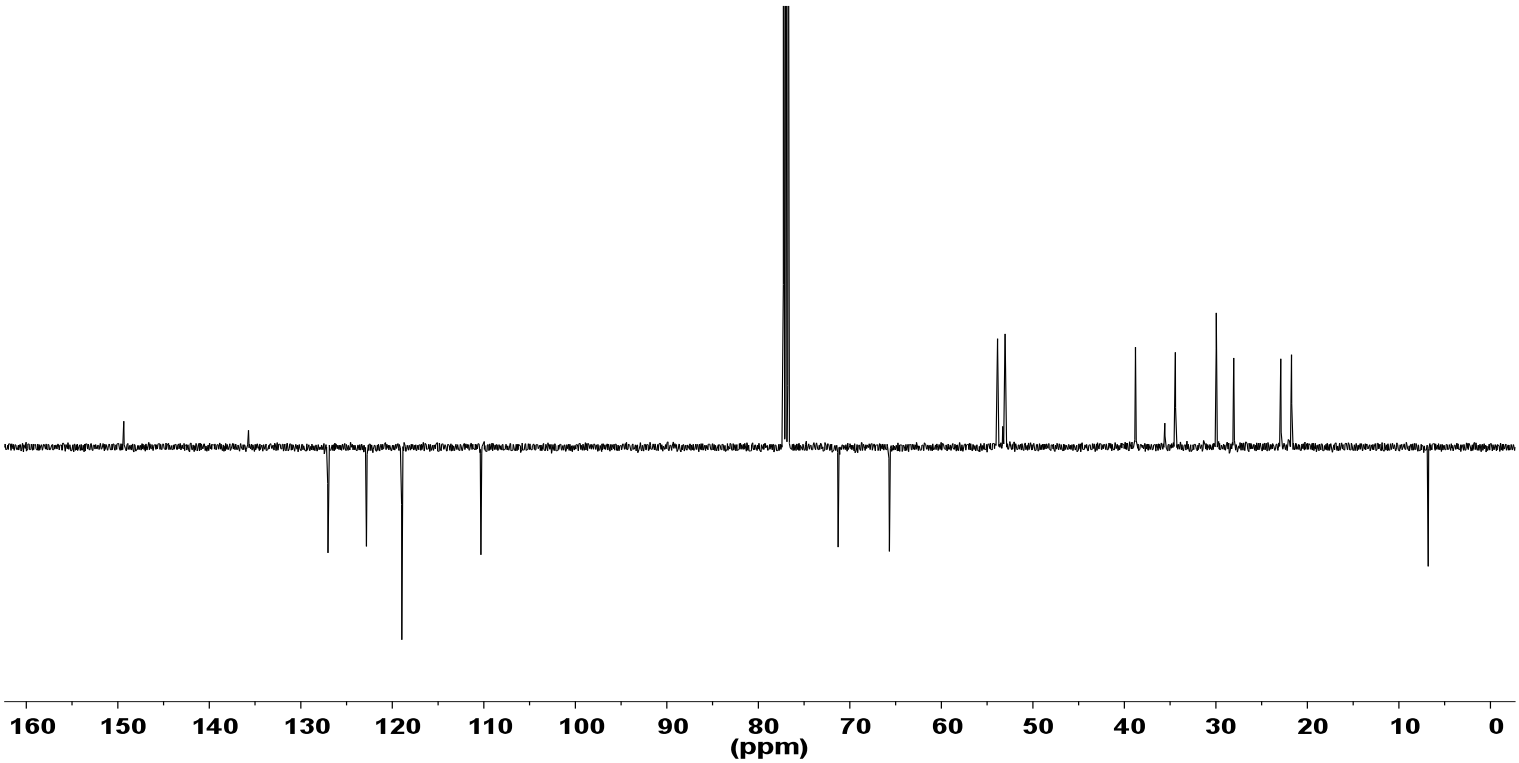

7.6
7.0
6.4
5.8
5.2
4.6
4.0
3.4
2.8
2.2
(ppm)

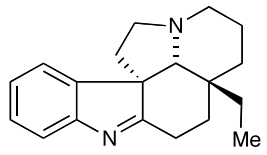

150
146
142
138
134
130
126
122
118
114
110
106
(ppm)



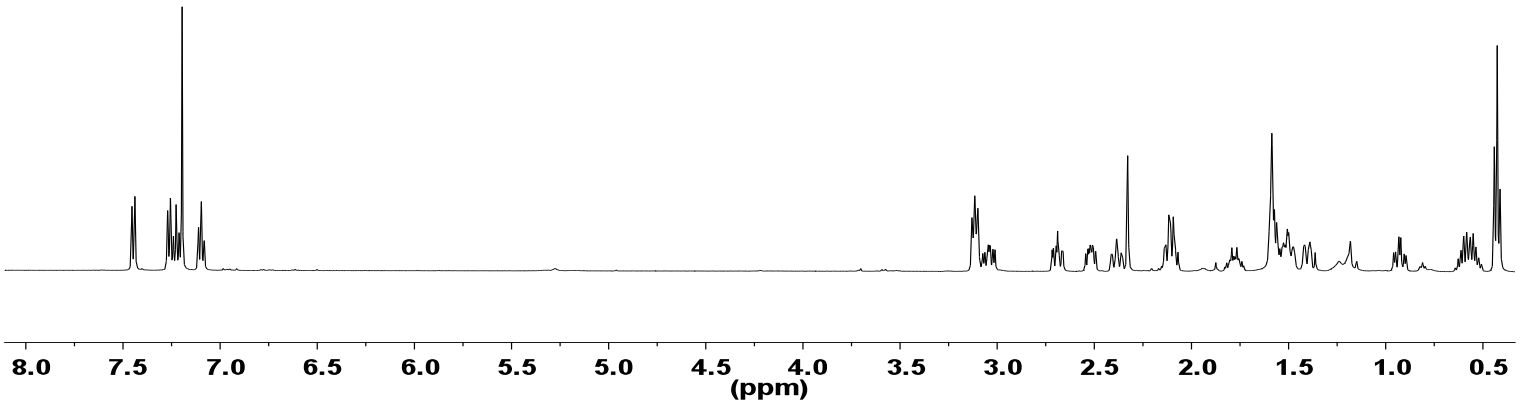
(+)-aspidospermidine

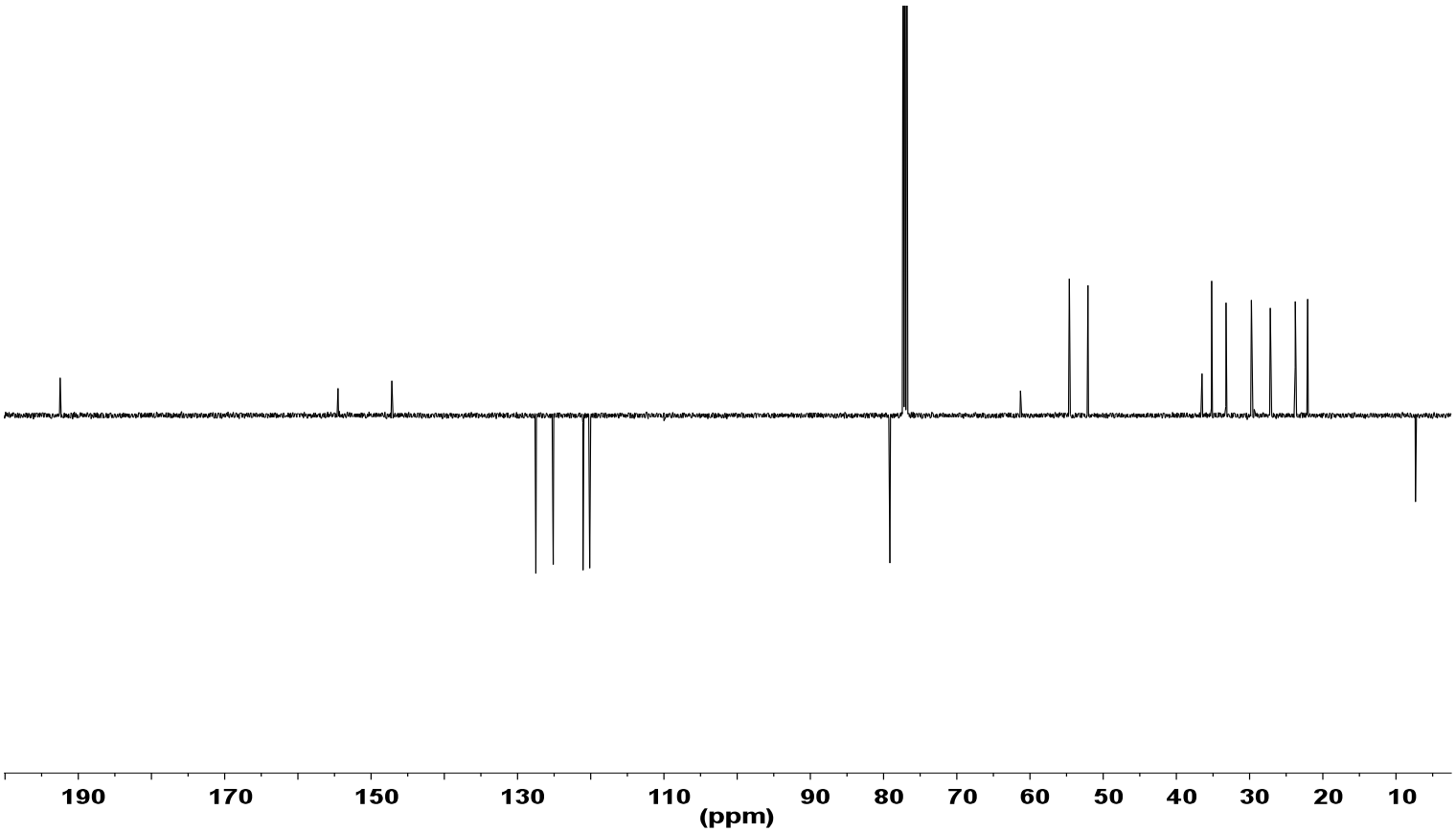


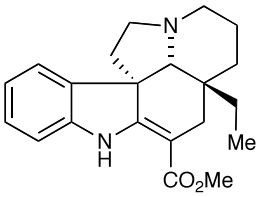



N
N
Me

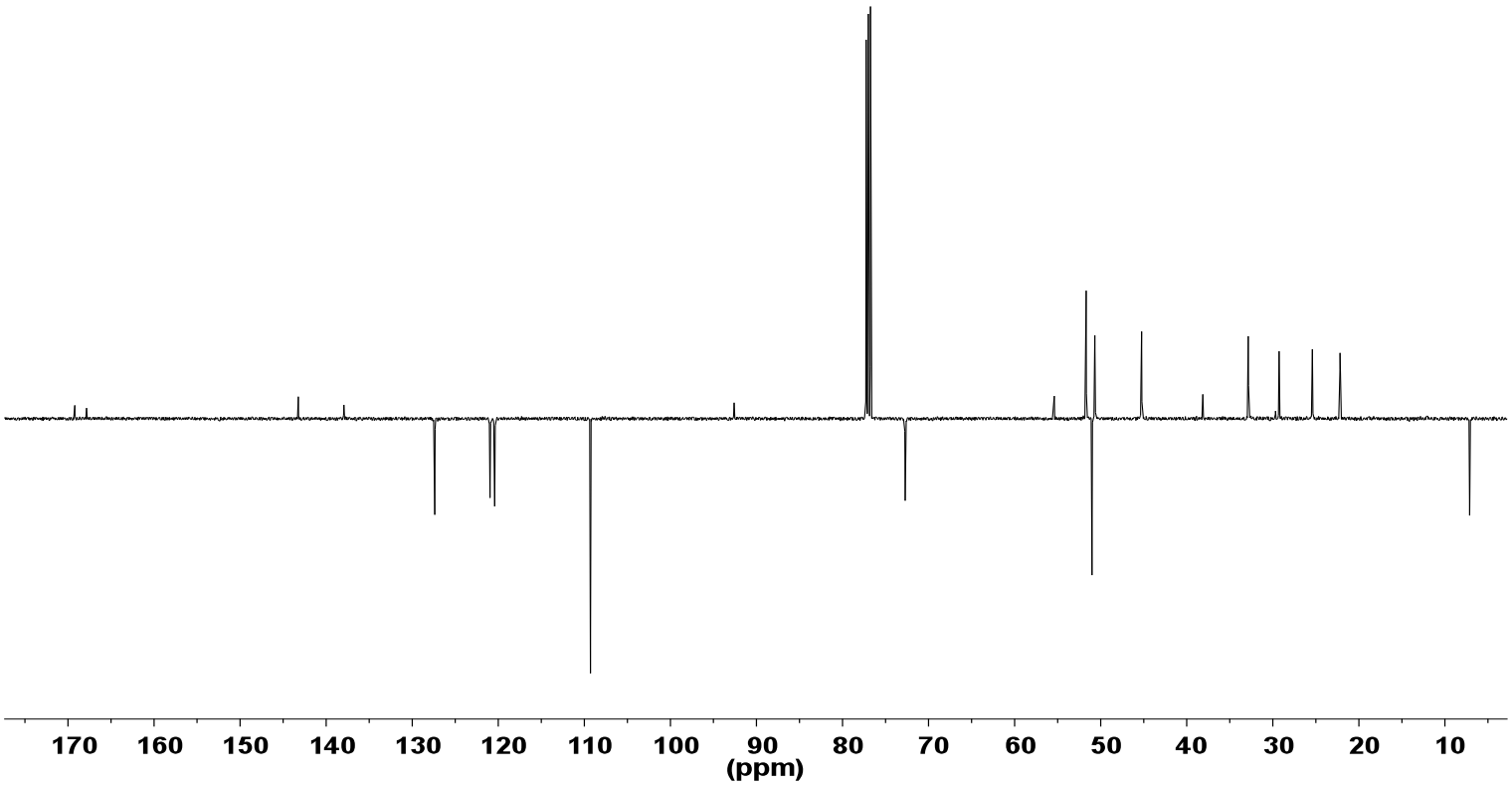
25

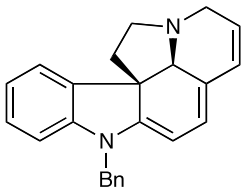

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


190
170
150
130
110
90
80
70
60
50
40
30
20
10
(ppm)

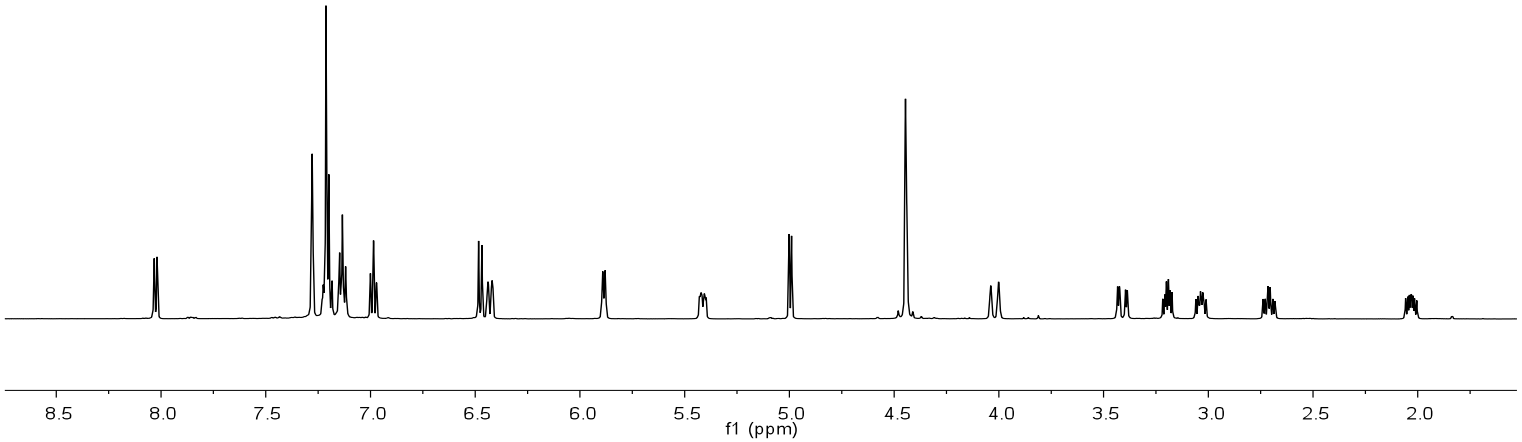


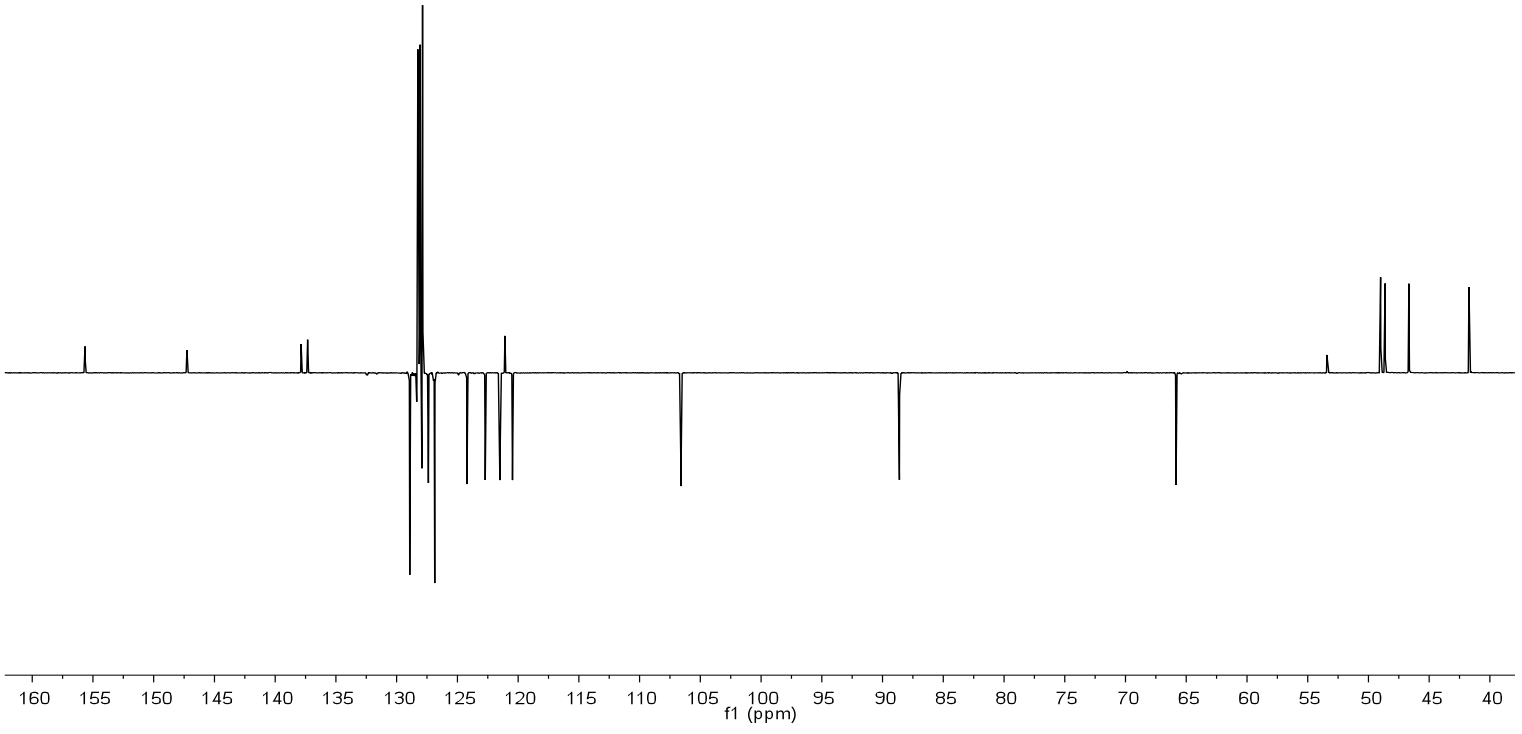
(+)-vincadifformine

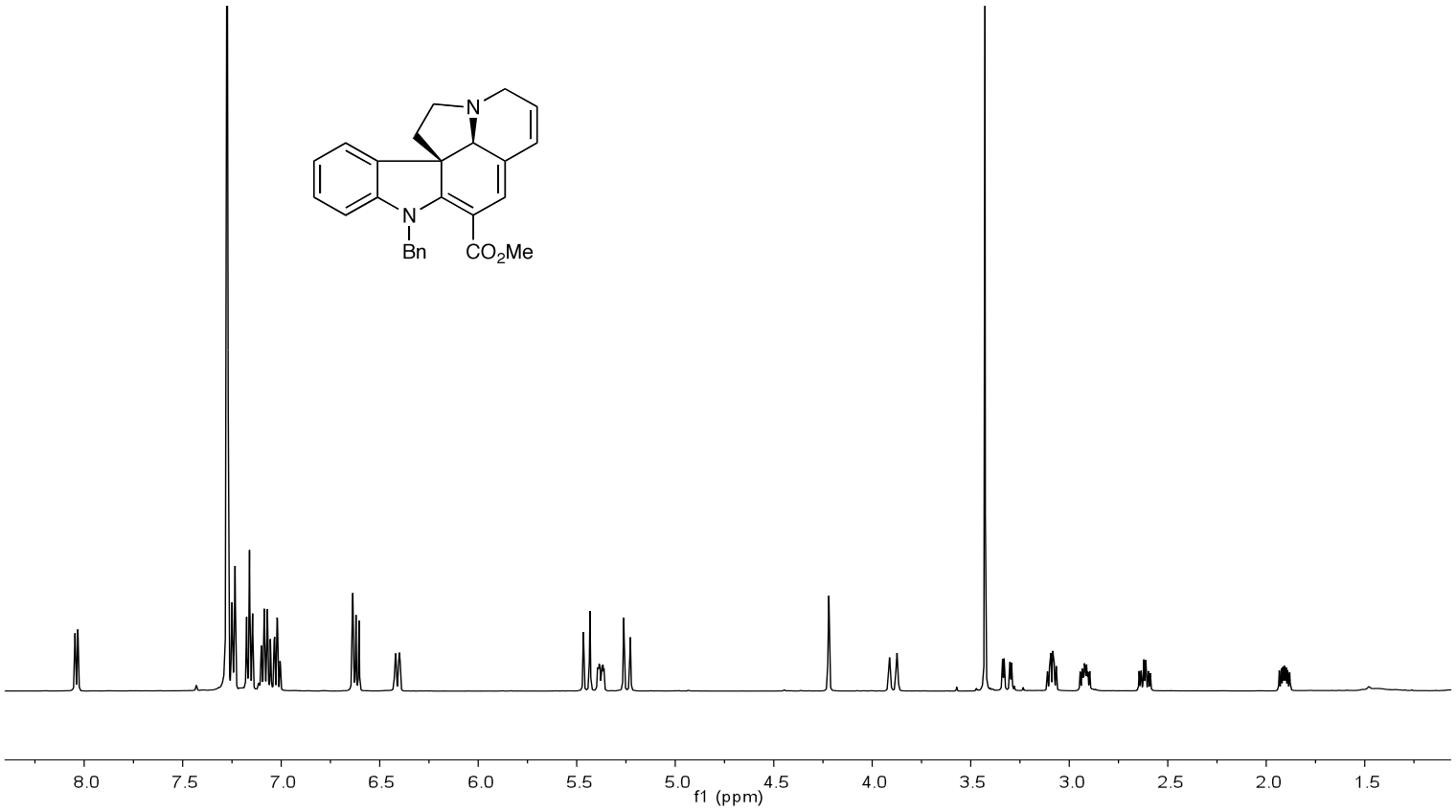


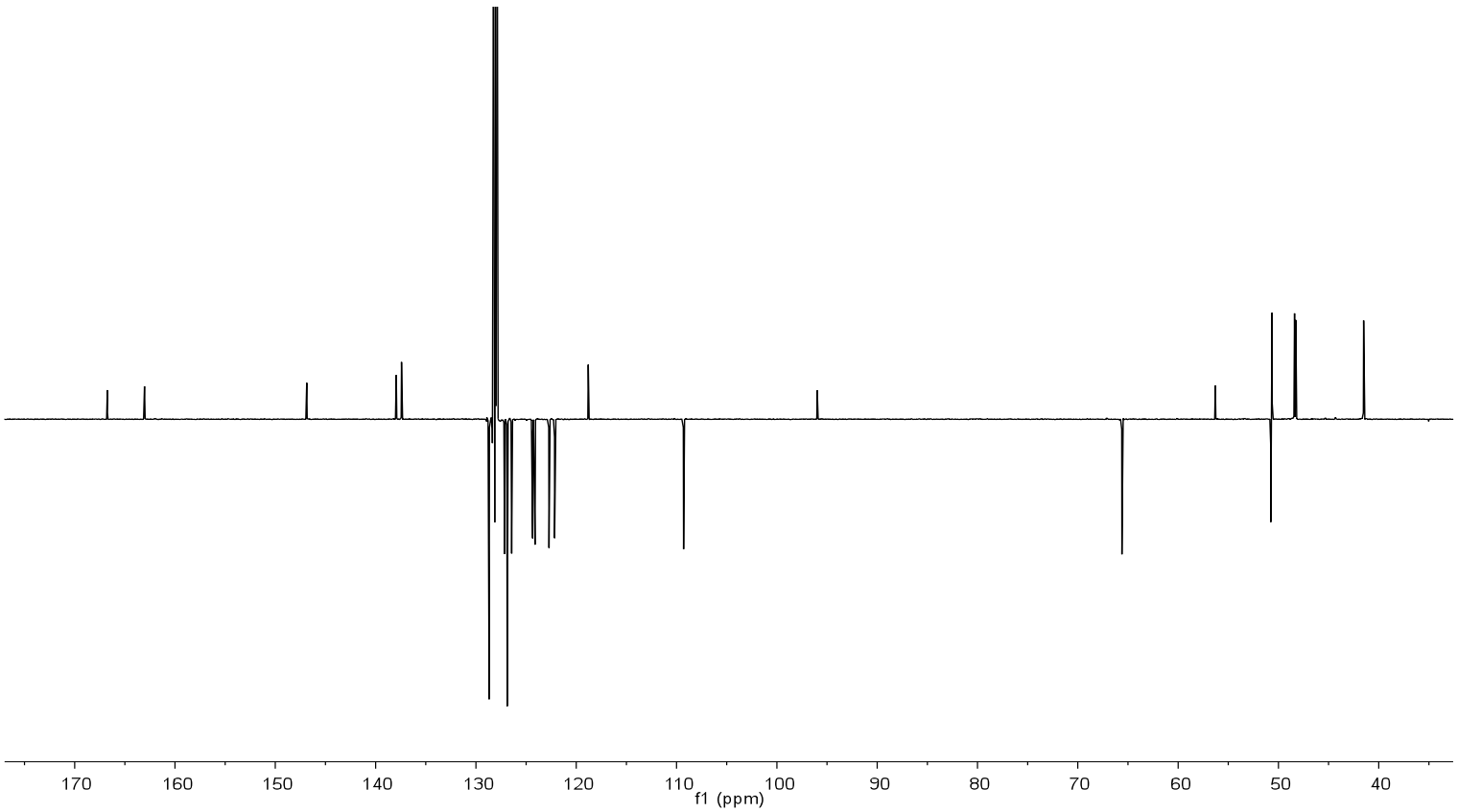

N
N
Bn

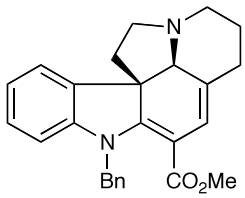
26


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

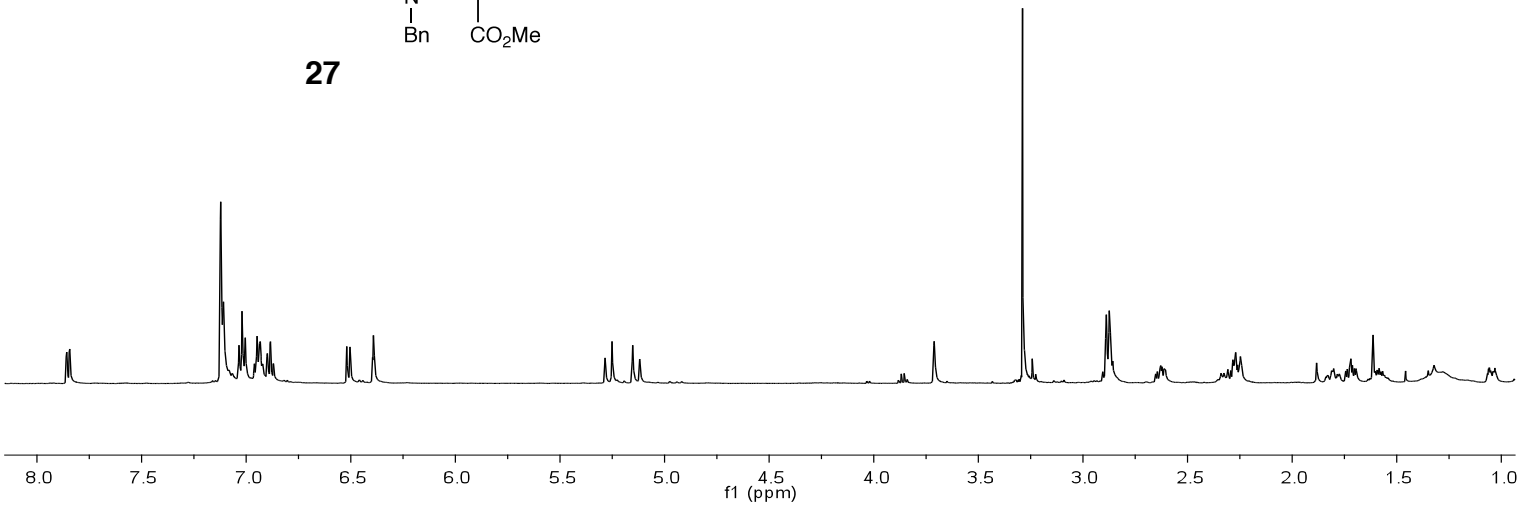

160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
f1 (ppm)

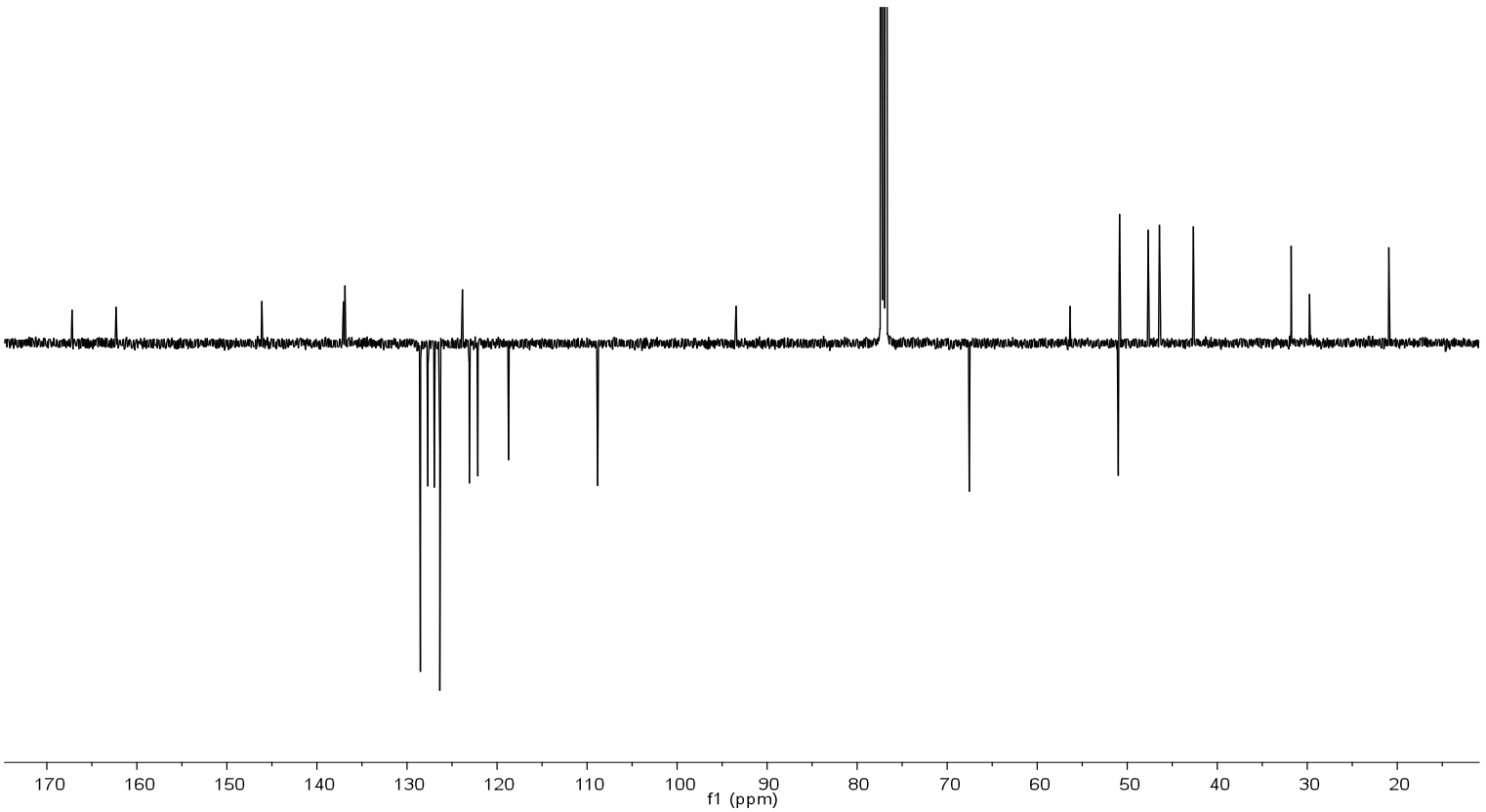

N
N
Bn
CO2Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

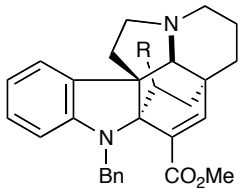

170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)


N
N
Bn
CO2Me

27

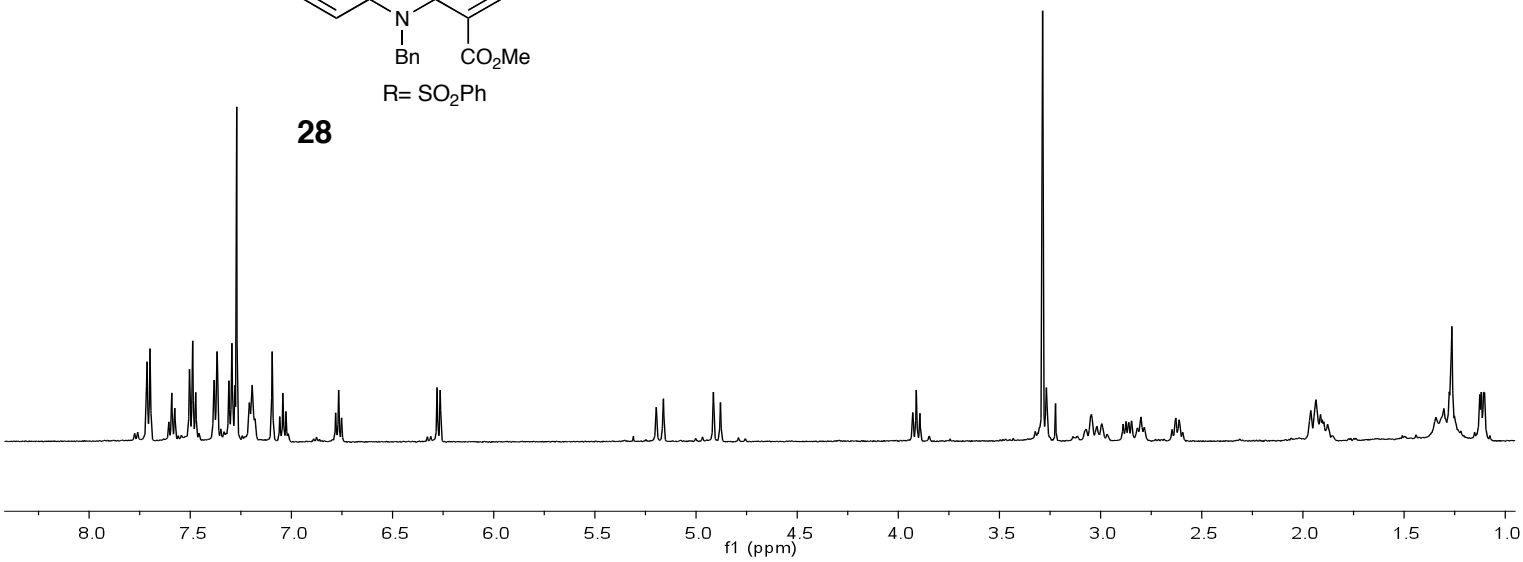

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

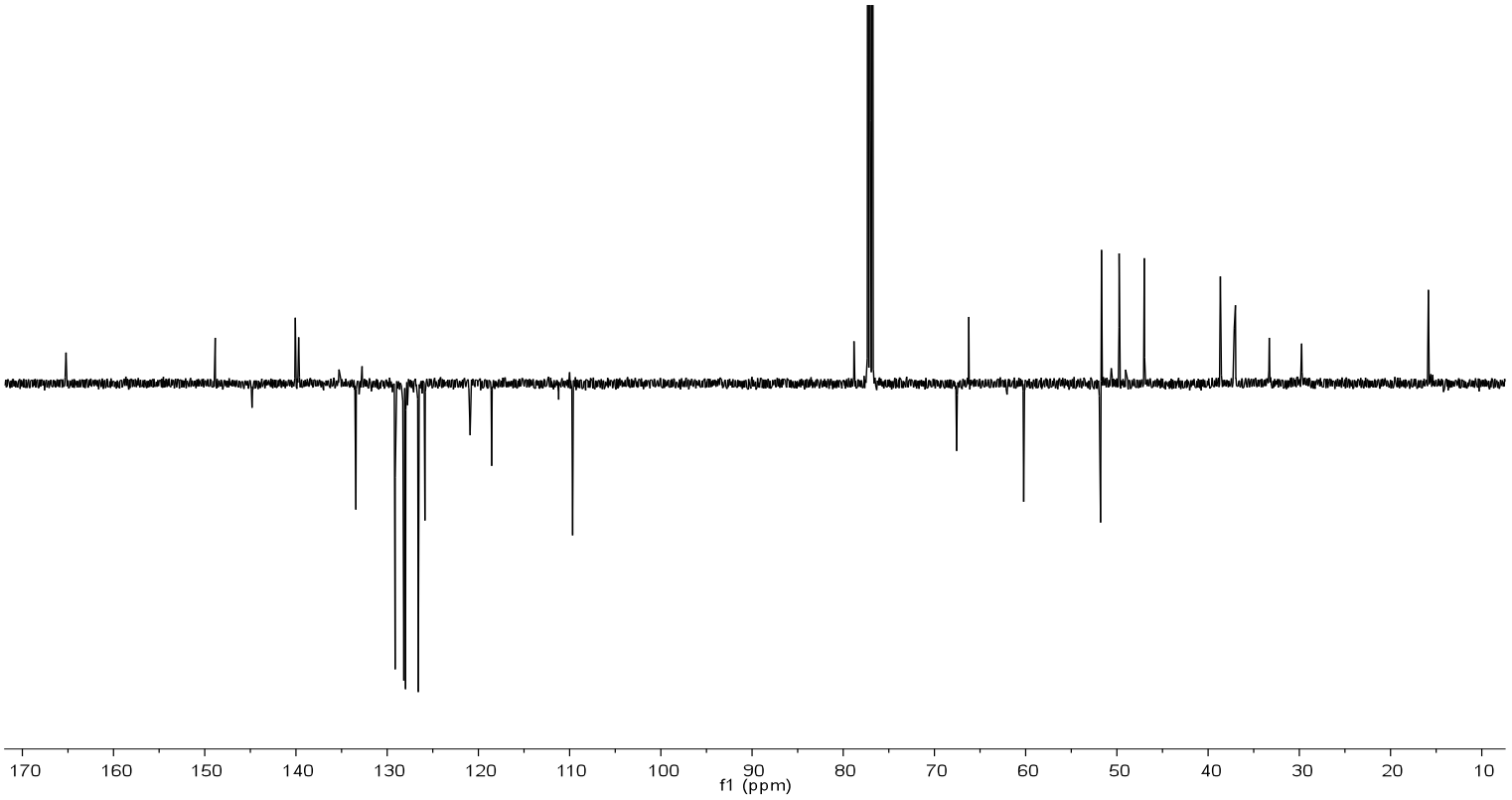

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

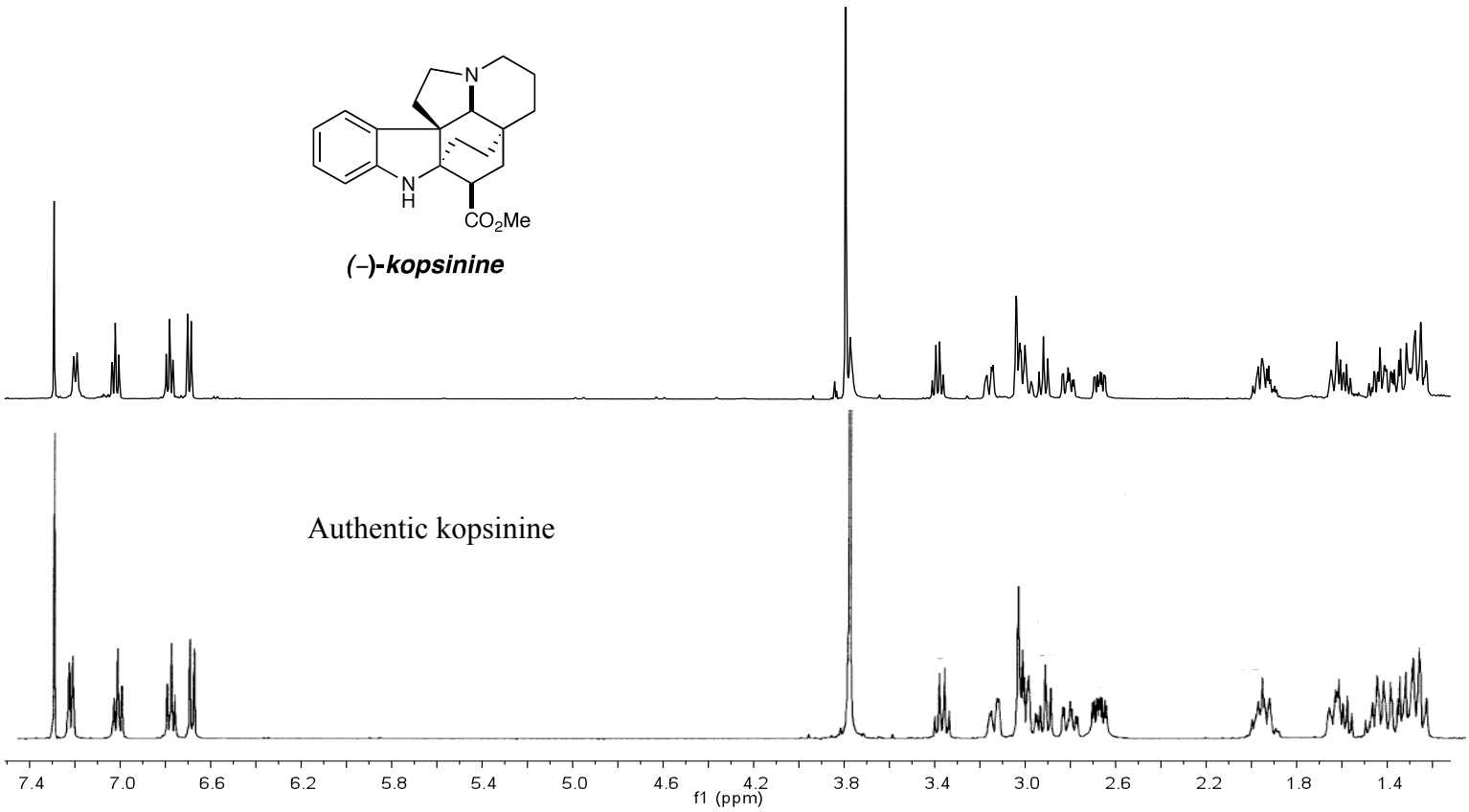

N
R
N
Bn
CO2Me

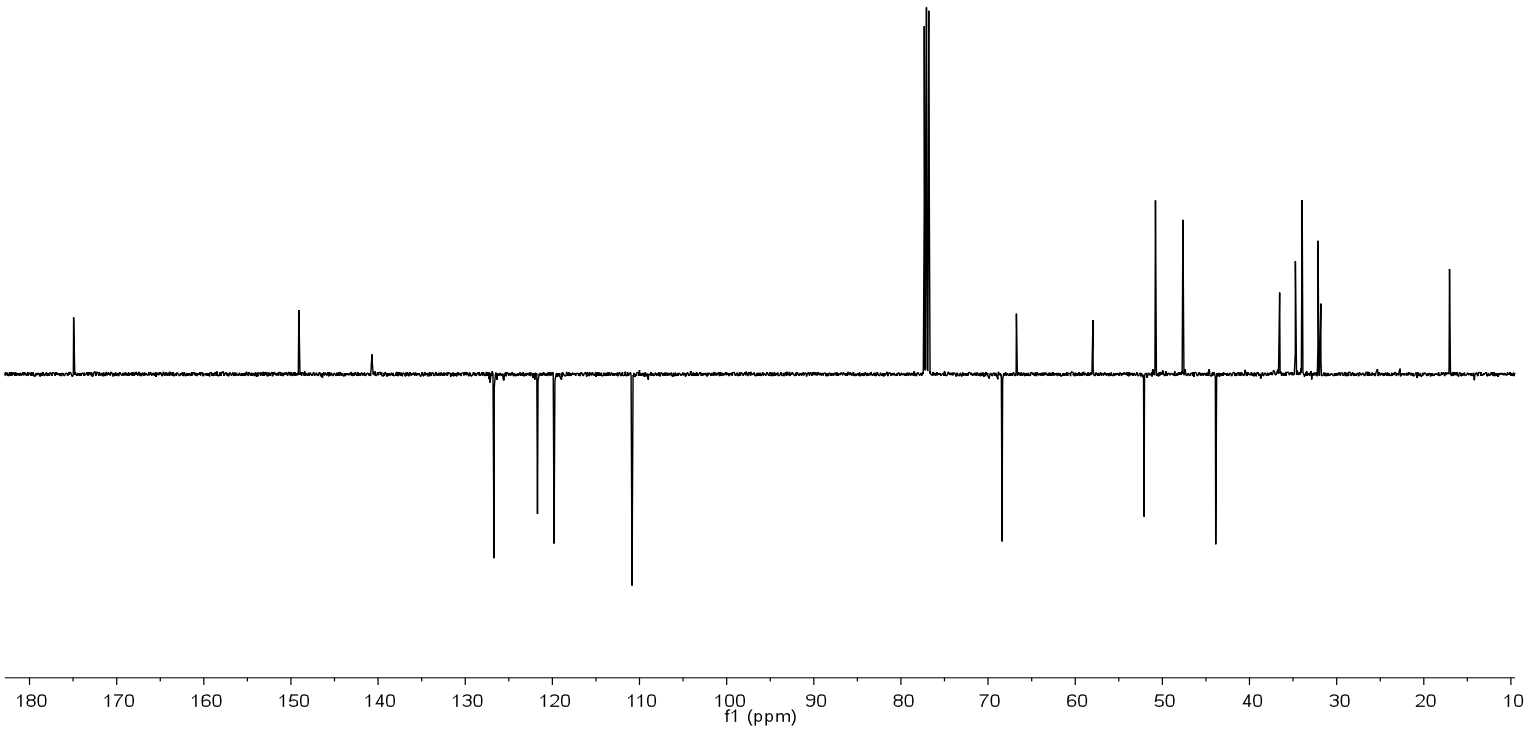
R= SO_2Ph

28


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


N
N
H
CO2Me
(–)-kopsinine
Authentic kopsinine
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2
1.8
1.4
f1 (ppm)


180
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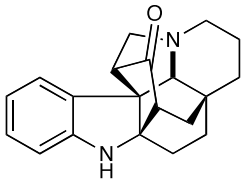
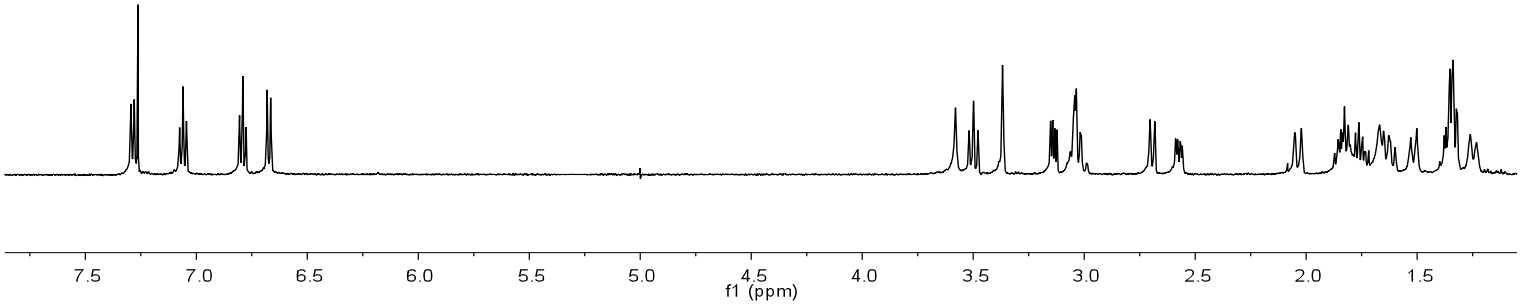
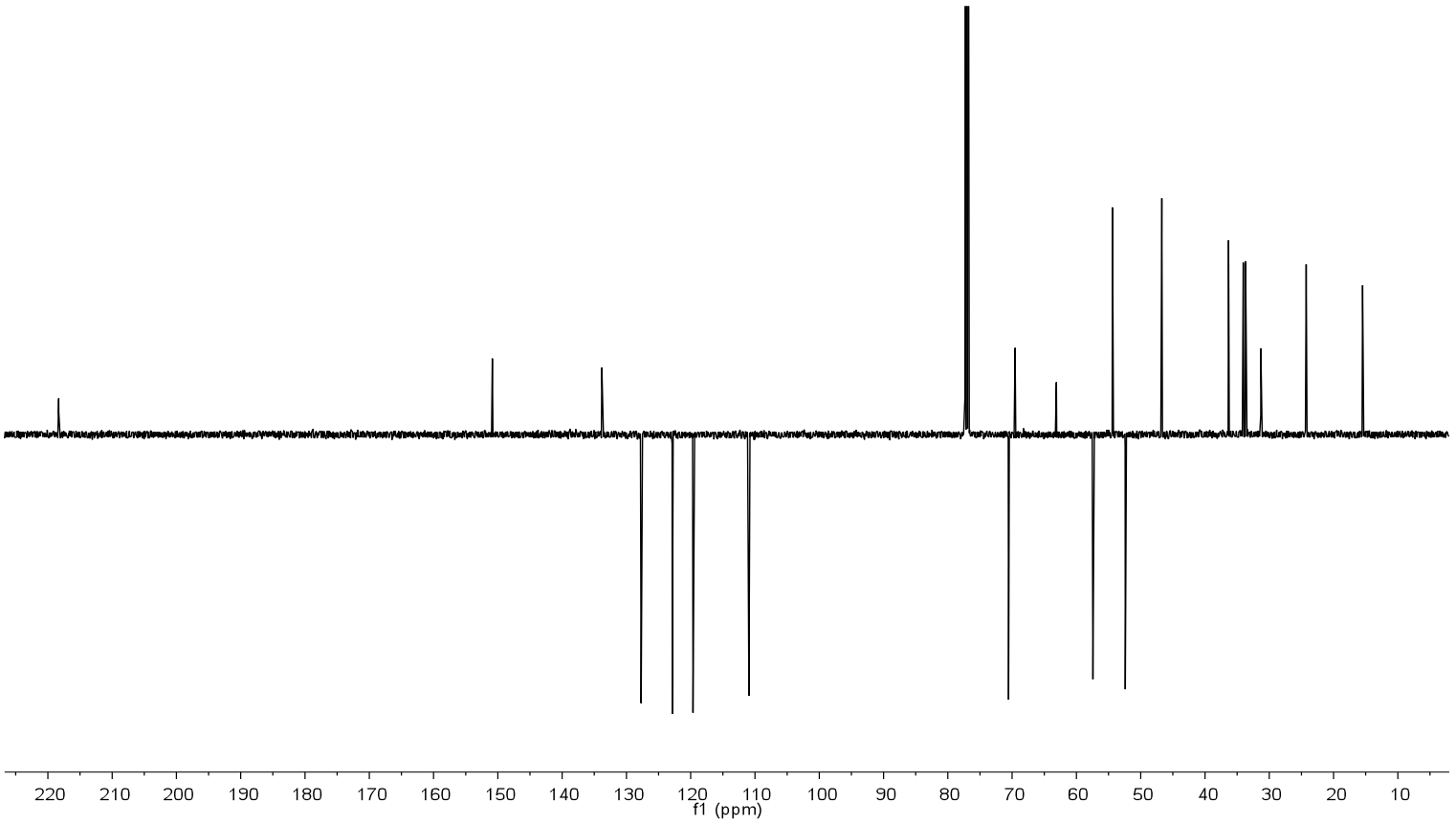
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
N
N
H

(–)-kopsanone


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)