Electronic Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Regioselective Dibromination of Methyl Indole-3-Carboxylate and Application in the Synthesis of Dibromoindoles

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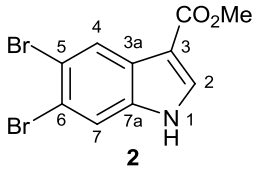


2

Methyl 1*H*-indole-3-carboxylate (6.0 g, 34.2 mMol) was suspended in acetic acid (45 mL) under an atmosphere of argon. Bromine (3.86 mL, 75.3 mMol) was added dropwise and the reaction stirred for 3 days. The fine brown precipitate which formed was removed by filtration and washed with hot ethanol (2 x 30 mL) to afford **2** (7.98 g, 70 %) as a grey solid, m.p. 238-242 °C; ν_{max} (single crystal) 3294, 2946, 1673, 1543, 1449, 1341 cm^{-1}; δ_H (400 MHz, DMSO-D_6), 3.82 (3H, s, CH_3), 7.87 (1H, s, H-7), 8.16 (1H, d, J_{NH-2} 3.0 Hz, H-2), 8.27 (1H, s, H-4), 12.15 (1H, br s, NH); δ_C (100 MHz, DMSO-D_6), 50.9 (q, CH_3), 106.0 (s, C-3), 115.9 (s, C-5/6), 116.5 (s, C-5/6), 117.2 (d, C-7), 124.4 (d, C-4), 126.5 (s, C-3a), 134.6 (d, C-2), 136.1 (s, C-7a), 164.1 (C(O)OCH_3); *m/z* (ES^-) 332 ($M\text{-}H^+$, 100%); HRMS (ES^-) calculated for $C_{10}H_6{}^{79}Br_2NO_2$ ($M\text{-}H^+$) 329.8765, found 329.8775.

1-*tert*-Butyl-3-methyl 5,6-dibromo-1*H*-indole-1,3-dicarboxylate 3

Sodium hydride (36 mg, 0.900 mMol) was dissolved in THF (1 mL) and cooled to 0 °C under an atmosphere of argon. A solution of **2** (200 mg, 0.601 mMol) in THF (2 mL) was added dropwise and the mixture stirred for 20 minutes. After this time di-*tert*-butyl dicarbonate (144 mg, 0.660 mMol) was added portionwise and the mixture stirred for 3 hours and allowed to warm to room temperature. The reaction was quenched by dropwise addition of water (1 mL) and diluted with ether (5 mL). Further water (5 mL) was added, the mixture separated and the aqueous fraction washed with ether (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 9:1) to afford **3** (250 mg, 96 %) as a white solid, m.p. 144-145 °C, ν_{max} (single crystal) 3676, 3168, 2982, 1751, 1716, 1453, 1369, 1251 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.69 (9H, s, $C(CH_3)_3$), 3.94 (3H, s, OCH_3), 8.21 (1H, s, H-2), 8.40 (1H, s, H-4), 8.52 (1H, s, H-7); δ_C (100 MHz, $CDCl_3$), 28.2 (q, $C(CH_3)_3$), 51.9 (q, OCH_3), 86.2 (s, $C(CH_3)_3$), 111.6 (s, C-3), 120.2 (s, C-5/6), 120.3 (d, C-7), 121.2 (s, C-5/6), 126.1 (d, C-4), 128.1 (s, C-3a), 133.2 (d, C-2), 135.1 (s, C-7a), 148.4 (C(O)O^{t}Bu), 164.0

(*C*(O)OCH$_3$); *m/z* (EI$^+$) 431 (M$^+$, 10), 331 ([M-(CO$_2$^{t}Bu)]$^+$, 100%); (ES$^-$) 410 ([M–(CO$_2$Me)].Cl$^-$, 100%); HRMS (EI$^+$) calculated for $C_{15}H_{15}{}^{79}Br_2NO_4$ (M$^+$) 430.9351, found 430.9368.

tert-Butyl 5,6-dibromo-3-(methoxy(methyl)carbamoyl)-1*H*-indole-1-carboxylate 4

Ester **3** (0.200 g, 0.462 mMol) and *N*,*O*-dimethylhydroxylamine hydrochloride (68 mg, 0.693 mMol) were dissolved in THF (5 mL) and cooled to 0 °C under an atmosphere of argon. Phenyl magnesium chloride (2.31 mL of a 0.6 M solution) was added dropwise and the solution stirred for 1 hour. After this time, t.l.c. analysis (hexanes:ethyl acetate, 7:3) indicated some remaining starting material. Further phenyl magnesium chloride (0.3 mL) was added and the reaction stirred for a further 10 min. After this time t.l.c. analysis indicated complete consumption of **3** (R_f 0.60) and formation of a major product (R_f 0.30). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture extracted into diethyl ether (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 7:3) to afford **4** (188 mg, 88%) as a white solid, m.p. 126-128 °C; ν_{max} (single crystal) 2982, 2938, 1747, 1634, 1542, 1440, 1370, 1347, 1237, 1153, 1118 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.70 (9H, s, C(CH$_3$)$_3$), 3.40 (3H, s, NCH$_3$), 3.73 (3H, s, OCH$_3$), 8.26 (1H, s, H-2), 8.47 (1H, s, H-4), 8.64 (1H, s, H-7); δ_C (100 MHz, $CDCl_3$), 28.0 (q, C(*C*H$_3$)$_3$), 32.9 (q, NCH$_3$), 61.1 (q, OCH$_3$), 85.8 (s, *C*(CH$_3$)$_3$), 111.6 (s, C-3), 119.6 (d, C-7), 119.7 (s, C-5/6), 120.8 (s, C-5/6), 127.0 (d, C-4), 130.0 (s, C-3a), 131.1 (d, C-2), 134.0 (s, C-7a), 148.7 (s, C(O)O^{t}Bu), 163.6 (s, C(O)N); *m/z* (ES$^+$) 517 (M.MeOH.Na$^+$, 31), 485 (MNa$^+$, 100), 461 (M$^+$, 18%); HRMS (ES$^+$) calculated for $C_{16}H_{18}{}^{79}Br^{81}BrN_2NaO_4$ (MNa$^+$) 484.9511, found 484.9512.

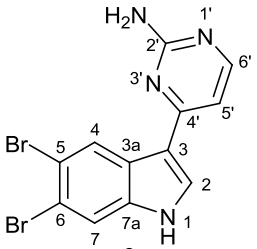
tert-Butyl 5,6-dibromo-3-propioloyl-1*H*-indole-1-carboxylate 5

Trimethylsilyl acetylene (54 μL, 0.385 mMol) was dissolved in THF (1.5 mL) and cooled to – 30 °C under an atmosphere of argon. *n*-Butyl lithium (0.36 mL of a 1.06 M solution) was added dropwise and the solution stirred for 1 hour. In a fresh flask, amide **4** (89 mg, 0.193 mMol) was dissolved in THF (1.5 mL) and cooled to 0 °C under an atmosphere of argon. The

solution of lithium trimethylsilyl acetylide was added to this dropwise over 5 minutes and stirring continued for 1 hour at 0 °C. After this time, t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of **4** (R_f 0.20) and formation of a major product (R_f 0.70). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture extracted into diethyl ether (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 5:1) to afford **5** (74 mg, 90%) as a pale yellow solid, m.p. 264-268 °C; ν_{max} (single crystal) 3248, 2096, 1749, 1627, 1540, 1443, 1356, 1259 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.73 (9H, s, $C(CH_3)_3$), 3.32 (1H, s, C≡CH), 8.36 (1H, s, H-2), 8.46 (1H, s, H-4), 8.59 (1H, s, H-7); δ_C (100 MHz, $CDCl_3$), 28.0 (q, $C(CH_3)_3$), 77.7 (d, C≡CH), 80.3 (s, C≡CH), 86.9 (s, $C(CH_3)_3$), 120.1 (d, C-7), 120.3 (s, C-3), 120.9 (s, C-5/6), 122.0 (s, C-5/6), 126.6 (d, C-4), 126.7 (s, C-3a), 135.1 (s, C-7a), 136.8 (d, C-2), 148.0 (s, C(O)O^{t}Bu), 170.8 (s, C(O)); *m/z* (ES^+) 482 ($M.MeOH.Na^+$, 94), 450 (MNa^+, 100), 426 (M^+, 24%); HRMS (ES^+) calculated for $C_{16}H_{13}{}^{79}Br^{81}BrNNaO_3$ (MNa^+) 449.9139, found 449.9141.

Meridianin F[1] 6

[4-(5,6-Dibromo-1*H*-indol-3-yl)pyrimidin-2-amine]



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meridianin F

Guanidine hydrochloride (0.50 g, 5.23 mMol) was dissolved in water (1.05 mL). Sodium hydroxide (0.209 mg, 5.23 mMol) was added and the mixture stirred for 10 minutes at room temperature. Ketone **5** (72 mg, 0.169 mMol) was dissolved in acetonitrile (1.2 mL). Sodium carbonate (18 mg, 0.169 mMol), *tert*-butanol (0.7 mL) and neutralised guanidine (84 µL of a 5 M solution, 0.421 mMol) were added sequentially to the solution of the ketone and the mixture then heated to 80 °C. After 2 hours t.l.c. analysis (ethyl acetate) indicated complete consumption of **5** (R_f 0.65) and formation of a major product (R_f 0.30). The reaction mixture

was cooled, quenched with brine (1 mL) and extracted with DCM (6 x 10 mL). The combined organic fractions were dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue purified twice by flash column chromatography (silica gel, ethyl acetate) to afford Meridianin F (29 mg, 47 %) as a yellow solid, m.p. 278-280 °C (ethyl acetate) [lit. 175 °C];[1] ν_{max} (single crystal) 3459, 3342, 3116, 3004, 2873, 1572, 1550, 1527, 1418 cm^{-1}; δ_H (300 MHz, DMSO-D_6), 6.57 (2H, br s, NH_2), 7.00 (1H, d, $J_{5',6'}$ 5.2 Hz, H-5'), 7.83 (1H, s, H-7), 8.11 (1H, d, $J_{5',6'}$ 5.2 Hz, H-6'), 8.31 (1H, s, H-2), 8.95 (1H, s, H-4), 11.93 (1H, br s, NH); δ_C (100 MHz, DMSO-D_6), 105.1 (d, C-5'), 113.2 (s, C-3), 114.9 (s, C-5/6), 116.1 (s, C-5/6), 116.5 (d, C-7), 126.1 (s, C-3a), 126.5 (d, C-4), 130.4 (d, C-2), 136.7 (s, C-7a), 157.3 (d, C-6'), 161.8 (s, C-2'/4'), 163.5 (s, C-2'/4'); *m/z* (ES^+) 369 (MH^+, 100%); HRMS (ES^+) calculated for $C_{12}H_9{}^{79}Br^{81}BrN_4$ (MH^+) 368.9173, found 368.9163.

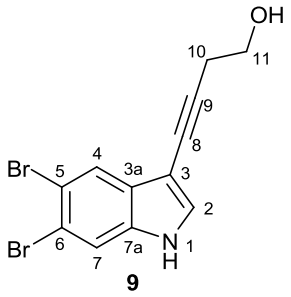
5,6-Dibromo-1*H*-indole 7

Ester **2** (0.600 g, 1.80 mMol) and potassium hydroxide (0.303 g, 5.41 mMol) were dissolved in a mixture of methanol (6 mL), THF (6 mL) and water (3 mL). The pale brown mixture was subjected to microwave irradiation (200 W, 150 °C) for 1 hour, after which time t.l.c. analysis (hexanes:ethyl acetate, 7:3) of the bright pink solution indicated complete consumption of **2** (R_f 0.40) and formation of a single product (R_f 0.50). The mixture was concentrated *in vacuo*, the residue dissolved in DCM (25 mL) and water (15 mL) and separated. The organic fraction was washed with water (15 mL) and the combined aqueous fractions extracted with DCM (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 85:15) to afford **7** (0.464 g, 94%) as a pale brown amorphous solid, m.p. 150-151 °C (toluene/hexanes); ν_{max} (single crystal) 3406, 1445, 1286 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 6.49 (1H, m, H-3), 7.22 (1H, dd, J_{NH-2} 2.5 Hz, $J_{2,3}$ 3.2 Hz, H-2), 7.70 (1H, d, $J_{3,7}$ 0.7 Hz, H-7), 7.92 (1H, s, H-4), 8.16 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$), 102.3 (d, C-3), 115.1 (s, C-5/6), 115.7 (d, C-7), 117.1 (s, C-5/6), 124.9 (d, C-4), 126.0 (d, C-2), 128.8 (s, C-3a), 135.5 (s, C-7a); *m/z* (EI^+) 275 (M^+, 100%); (ES^-) 274 ($M–H^+$, 100%); HRMS (EI^+) calculated for $C_8H_5{}^{79}Br^{81}BrN$ (M^+) 272.8789, found 272.8794.

5,6-Dibromo-3-iodo-1*H*-indole 8

5,6-Dibromo-1*H*-indole **7** (100 mg, 0.364 mMol) and potassium hydroxide (51 mg, 0.909 mMol) were dissolved in DMF (1 mL) under an atmosphere of argon. A solution of iodine (93 mg, 0.367 mMol) in DMF (1 mL) was added dropwise and the reaction mixture stirred at room temperature. After 1 hour, t.l.c. analysis (hexanes:ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.50) and formation of a major product (R_f 0.45). The reaction was quenched by addition of sodium thiosulfate (5 mL of a saturated aqueous solution), extracted into ether (2 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 4:1) to afford **8** (133 mg, 91%) as white crystals, m.p. 107-108 °C (decomposes); ν_{max} (single crystal) 3405, 1443, 1372, 1312, 1258, 1177 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 7.27 (1H, d, $J_{NH,2}$ 2.5 Hz, H-2), 7.68 (1H, s, H-7), 7.72 (1H, s, H-4), 8.32 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$), 56.6 (s, C-3), 116.1 (d, C-7), 116.5 (s, C-5/6), 118.9 (s, C-5/6), 125.7 (d, C-4), 130.4 (d, C-2), 131.0 (s, C-3a), 135.3 (s, C-7a); *m/z* (EI^+) 401 (M^+, 100%); HRMS (EI^+) calculated for $C_8H_4{}^{79}Br_2IN$ (M^+) 398.7755, found 398.7769.

4-(5,6-Dibromo-1*H*-indol-3-yl)but-3-yn-1-ol 9



9

Iodide **8** (112 mg, 0.279 mMol) and but-3-yn-1-ol (25 µL, 0.335 mMol) were dissolved in triethylamine (3 mL). The solution was degassed and put under an atmosphere of argon. Bis(triphenylphosphine) palladium (II) dichloride (7.8 mg, 11.8 nMol) and copper (I) iodide (1.1 mg, 5.6 nMol) were added and the reaction mixture stirred at room temperature. After 5 hours, t.l.c. analysis (hexanes:ethyl acetate, 3:2) indicated complete consumption of **8** (R_f 0.55) and formation of a major product (R_f 0.05). The reaction was filtered through celite®, diluted with ethyl acetate and washed with water. The organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica

gel, hexanes:ethyl acetate, 4:1 then 1:1) to afford **9** (65 mg, 68%) as a pale yellow oil; ν_{max} (single crystal) 3415, 2888, 1445, 1386, 1298, 1250 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 2.10 (1H, br s, OH), 2.76 (2H, t, *J* 6.2 Hz, CH_2), 3.87 (2H, t, *J* 6.2 Hz, CH_2), 7.29 (1H, d, $J_{NH,2}$ 2.6 Hz, H-2), 7.62 (1H, s, H-7), 7.92 (1H, s, H-4), 8.43 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$), 24.2 (t, C-10), 61.5 (t, C-11), 74.4 (s, C-8), 88.6 (s, C-9), 98.7 (s, C-3), 116.1 (s, C-5/6), 116.2 (d, C-7), 118.3 (s, C-5/6), 124.3 (d, C-4), 129.3 (d, C-2), 129.4 (s, C-3a), 134.8 (s, C-7a); *m/z* (EI^+) 343 (M^+, 100%); HRMS (EI^+) calculated for $C_{12}H_9{}^{79}Br_2NO$ (M^+) 340.9051, found 340.9061.

3,5,6-Tribromo-1*H*-indole[2] 10

5,6-Dibromo-1*H*-indole **7** (0.220 g, 0.800 mMol) was dissolved in DCM (3 mL) and the solution cooled to 0 °C under an atmosphere of argon. *N*-Bromosuccinimide (0.150 g, 0.840 mMol) was added in one portion and the reaction mixture stirred and allowed to warm to room temperature. After 1 hour, t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material and formation of a major product. Silica gel was added to the reaction mixture, the solvent removed *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 85:15) to afford **10** (0.261 g, 92%) as a white solid, m.p. 112-114 °C (decomposes) [lit. 123-124 °C];[2] ν_{max} (single crystal) 3404, 1614, 1556, 1444, 1380, 1310, 1262, 1185 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 7.23 (1H, d, $J_{NH,2}$ 2.6 Hz, H-2), 7.69 (1H, s, H-7), 7.85 (1H, d, $J < 0.5$, H-4), 8.20 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$), 91.0 (s, C-3), 116.1 (d, C-7), 116.2 (s, C-5/6), 118.7 (s, C-5/6), 123.7 (d, C-4), 125.1 (d, C-2), 127.8 (s, C-3a), 134.8 (s, C-7a); *m/z* (EI^+) 352 (M^+, 100%); HRMS (EI^+) calculated for $C_8H_4{}^{79}Br_3N$ (M^+) 350.7894, found 350.7883.

3,5,6-Tribromo-*N*-methyl-1*H*-indole[2] 11

3,5,6-Tribromo-1*H*-indole **10** (79 mg, 0.223 mMol) was dissolved in DMF (1 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (13.4 mg, 0.335 mMol) was added in one portion and the mixture stirred for 20 minutes. After this time methyl iodide (28 μL, 0.447 mMol) was added portionwise and the reaction mixture stirred for a further 1 hour at room temperature. After this time, t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.30) and formation of a single

product (R_f 0.45). The reaction was quenched by the careful addition of water (0.5 mL) and the mixture diluted with diethyl ether (20 mL). The organic fraction was washed with water (3 x 20 mL) and the combined aqueous fractions extracted with diethyl ether (2 x 20 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 5:1) to afford **11** (82 mg, 100%) as a white solid, m.p. 151-152 °C [lit. 166-168 °C];[2] ν_{max} (single crystal) 1607, 1512, 1464, 1307, 1248, 1124 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 3.74 (3H, s, CH_3), 7.06 (1H, s, H-2), 7.61 (1H, s, H-7), 7.81 (1H, s, H-4); δ_C (100 MHz, $CDCl_3$), 33.3 (q, CH_3), 88.6 (s, C-3), 114.4 (d, C-7), 115.6 (s, C-5/6), 118.2 (s, C-5/6), 123.7 (d, C-4), 128.0 (s, C-3a), 129.5 (d, C-2), 135.9 (s, C-7a); *m/z* (EI^+) 367 (M^+, 100), 288 ($M–Br^-$, 12), 207 ($M\text{-}Br_2^-$, 17%); HRMS (EI^+) calculated for $C_9H_6{}^{79}Br_3N$ (M^+) 364.8050, found 364.8064.

2,3,5,6-Tetrabromo-1*H*-indole[3] 12

3,5,6-Tribromo-1*H*-indole **10** (40 mg, 0.113 mMol) was dissolved in THF (1 mL) under an atmosphere of argon. *N*-Bromosuccinimide (26.2 mg, 0.147 mMol) was added in one portion and the reaction mixture heated to 70 °C. After 3 hours, t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material and formation of a major product. Silica gel was added to the reaction mixture, the solvent removed *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 85:15) to afford **12** (33 mg, 67%) as a pale yellow solid, m.p. 150-155 °C (decomposes) (toluene/hexane) [lit. 152.5-154 °C, 153-154 °C];[3] ν_{max} (single crystal) 3180, 1726, 1605, 1463, 1391, 1273, 1171 cm^{-1}; δ_H (300 MHz, acetone-D_6), 7.39 (1H, s, H-4), 7.98 (1H, s, H-7), 10.34 (1H, br s, NH); δ_C (100 MHz, acetone-D_6), 116.1 (s, C-3), 117.1 (d, C-7), 117.2 (s, C-5/6), 118.4 (s, C-5/6), 126.3 (s, C-2), 128.1 (s, C-3a), 131.3 (d, C-4), 131.8 (s, C-7a); *m/z* (EI^+) 431 (M^+, 100), 353 ($M–Br^-$, 18), 272 ($M\text{-}Br_2^-$, 18%); HRMS (EI^+) calculated for $C_8H_3{}^{79}Br_4N$ (M^+) 428.6999, found 428.7008.

2,3,5,6-Tetrabromo-*N*-methyl-1*H*-indole[3-4] 13

Tribromoindole **11** (0.121 g, 0.329 mMol) was dissolved in DCM (3 mL) under an atmosphere of argon. *N*-Bromosuccinimide (70.3 mg, 0.395 mMol) was added in one portion

and the reaction mixture stirred at room temperature. After 2 hours, t.l.c. (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material and formation of a major product. The reaction mixture was diluted with DCM (10 mL), washed with water (5 mL) and the organic fraction dried ($MgSO_4$). Silica gel was added, the solvent removed *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 85:15) to afford **13** (0.115 g, 78%) as a white solid, m.p. 167-169 °C (hexane) [lit. 171.5-172 °C, 168-170 °C, 170-171 °C];[3a, 4-5] ν_{max} (single crystal) 2923, 2852, 1495, 1452, 1403, 1304, 1234, 1119 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 3.75 (3H, s, CH_3), 7.57 (1H, s, H-7), 7.74 (1H, s, H-4); δ_C (100 MHz, $CDCl_3$), 32.7 (q, CH_3), 92.0 (s, C-3), 114.5 (d, C-7), 116.4 (s, C-5), 117.2 (s, C-2), 118.5 (s, C-6), 123.1 (d, C-4), 127.5 (s, C-3a), 135.8 (s, C-7a); *m/z* (EI^+) 445 (M^+, 100), 365 (M–Br^-, 11), 286 (M-Br_2^-, 15%); HRMS (EI^+) calculated for $C_9H_5{}^{79}Br_4N$ (M^+) 442.7155, found 442.7152.

5,6-Dibromo-*N*-methyl-1*H*-indole 14

5,6-Dibromo-1*H*-indole **7** (0.390 g, 1.42 mMol) was dissolved in DMF (6 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (85 mg, 2.13 mMol) was added in one portion and the mixture stirred for 20 minutes. After this time methyl iodide (0.177 mL, 2.84 mMol) was added portionwise and the reaction mixture stirred for a further 1 hour at room temperature. After this time, t.l.c. (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.40) and formation of a single product (R_f 0.45). The reaction was quenched by the careful addition of water (2 mL) and the mixture diluted with diethyl ether (20 mL). The organic fraction was washed with water (3 x 20 mL) and the combined aqueous fractions extracted with diethyl ether (2 x 20 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, hexanes:ethyl acetate, 85:15) to afford **14** (0.372 g, 91%) as a white solid, m.p. 117-118 °C; ν_{max} (single crystal) 1501, 1470, 1409, 1311, 1259, 1231 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 3.75 (3H, s, CH_3), 6.40 (1H, dd, $J_{3,7}$ 0.8 Hz, $J_{2,3}$ 3.1 Hz, H-3), 7.05 (1H, d, $J_{2,3}$ 3.1 Hz, H-2), 7.61 (1H, d, $J_{3,7}$ 0.8 Hz, H-7), 7.88 (1H, s, H-4); δ_C (100 MHz, $CDCl_3$), 33.0 (q, CH_3), 100.6 (d, C-3), 114.0 (d, C-7), 114.5 (s, C-5/6), 116.6 (s, C-5/6), 125.0 (d, C-4), 129.2 (s, C-3a), 130.7 (d, C-2), 136.5 (s, C-7a); *m/z* (EI^+) 288 (M^+, 100%); HRMS (EI^+) calculated for $C_9H_7{}^{79}Br_2N$ (M^+) 286.8945, found 286.8948.

5,6-Dibromogramine 15

[1-(5,6-dibromo-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine]

Dimethylamine (0.28 mL of a 40% aqueous solution) was cooled to 5 °C and acetic acid (1 mL) added dropwise with stirring. This was followed by the dropwise addition of formaldehyde (0.164 mL of a 37% aqueous solution). In a fresh flask 5,6-dibromo-1*H*-indole **7** (0.500 g, 1.82 mMol) was suspended in acetic acid (8 mL) and the Mannich salt solution added over 15 minutes at room temperature. The reaction mixture was stirred overnight after which time t.l.c. analysis (hexanes:ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.50) and formation of a major product (R_f 0.0). The reaction mixture was basified with sodium hydroxide (2*N*) and extracted with DCM (3 x 25 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford **15** (0.536 g, 89%) as a bronze solid, m.p. 171-173 °C (toluene/hexanes); ν_{max} (single crystal) 3108, 2978, 2942, 2858, 2817, 1541, 1439, 1406, 1313, 1296, 1258, 1237, 1169 cm^{-1}; δ_H (400 MHz, acetone-D_6), 2.18 (6H, s, $N(CH_3)_2$), 3.54 (2H, s, CH_2), 7.31 (1H, d, $J_{NH,2}$ 1.8 Hz, H-2), 7.78 (1H, s, H-7), 8.06 (1H, s, H-4), 10.35 (1H, br s, NH); δ_C (100 MHz, acetone-D_6), 45.4 (q, $N(CH_3)_2$), 55.5 (t, CH_2), 114.0 (s, C-3), 116.5 (s, C-5/6), 117.0 (s, C-5/6), 117.0 (d, C-7), 124.9 (d, C-4), 127.3 (d, C-2), 129.8 (s, C-3a), 137.6 (s, C-7a); *m/z* (ES^+) 333 (MH^+, 100); HRMS (ES^+) calculated for $C_{11}H_{13}{}^{79}Br_2N_2$ (MH^+) 330.9445, found 330.9440.

5,6-Dibromo-1-methylgramine 16

[1-(5,6-dibromo-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine]

Dimethylamine (0.12 mL of a 40% aqueous solution) was cooled to 5 °C and acetic acid (0.3 mL) added dropwise with stirring. This was followed by the dropwise addition of formaldehyde (71 µL of a 37% aqueous solution). In a fresh flask **14** (0.228 g, 0.789 mMol) was suspended in acetic acid (3 mL) and the Mannich salt solution added over 15 minutes at room temperature. The reaction mixture was stirred overnight after which time t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.45) and formation of a major product (R_f 0.0). The reaction mixture was basified with sodium hydroxide (2*N*) and extracted with DCM (3 x 15 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford **16** (0.220 g, 81%) as a very pale yellow solid,

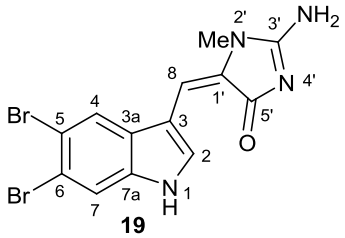
m.p. 76-77 °C; ν_{max} (single crystal) 2940, 2809, 2767, 1607, 1472, 1422, 1313, 1282, 1197 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 2.24 (6H, s, $N(CH_3)_2$), 3.51 (2H, s, CH_2), 3.71 (3H, s, CH_3), 6.96 (1H, s, H-2), 7.57 (1H, s, H-7), 7.95 (1H, s, H-4); δ_C (100 MHz, $CDCl_3$), 33.0 (q, CH_3), 45.5 (q, $N(CH_3)_2$), 54.5 (t, CH_2), 112.2 (s, C-3), 114.2 (d, C-7), 114.6 (s, C-5/6), 116.9 (s, C-5/6), 124.0 (d, C-4), 129.2 (s, C-3a), 130.0 (d, C-2), 136.9 (s, C-7a); *m/z* (ES^+) 347 (MH^+, 43), 302 (M^+–NMe_2, 100%); HRMS (ES^+) calculated for $C_{12}H_{15}{}^{79}Br_2N_2$ (MH^+) 344.9602, found 344.9596.

5,6-Dibromo-1*H*-indole-3-carbaldehyde 17

DMF (2 mL) in an oven-dried flask was cooled to 0 °C under an atmosphere of argon. Phosphorus (V) oxychloride (0.40 mL, 4.36 mMol) was added dropwise and the mixture stirred for 30 minutes. 5,6-Dibromo-1*H*-indole **7** (0.990 g, 3.60 mMol) in DMF (8 mL) was added portionwise, the solution stirred at room temperature for a further 30 minutes then warmed to 50 °C for 2 hours. After this time, t.l.c. analysis (hexanes:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.40) and formation of a single product (R_f 0.0). The mixture was allowed to cool to room temperature, ice (~ 10 g) was added and the mixture stirred vigorously. Sodium hydroxide (1M, aqueous solution) was added until the solution reached pH ~ 11, the mixture was boiled for 15 minutes, cooled and filtered. The solid was washed with water (3 x 10 mL) and dried under vacuum to afford **17** (0.883 g, 81%) as a cream solid, m.p. 278-280 °C [lit. 295-297 °C];[6] ν_{max} (single crystal) 3105, 3014, 2888, 1630, 1565, 1521, 1445, 1415, 1393, 1239, 1141 cm^{-1}; δ_H (400 MHz, DMSO-D_6), 7.91 (1H, s, H-7), 8.37 (1H, s, H-4), 8.38 (1H, s, H-2), 9.93 (1H, s, CHO), 12.30 (1H, br s, NH); δ_C (100 MHz, DMSO-D_6), 116.7 (s, C-5/6), 117.1 (s, C-5/6), 117.3 (d, C-7), 117.5 (s, C-3), 124.7 (d, C-4), 125.0 (s, C-3a), 136.7 (s, C-7a), 140.0 (d, C-2), 185.1 (d, CHO); *m/z* (EI^+) 303 (M^+, 100%); HRMS (EI^+) calculated for $C_9H_5{}^{79}Br_2NO$ (M^+) 300.8738, found 300.8748.

5,6-Dibromo-4'-demethylaplysinopsin 19

[(*E*)-2-Amino-5-((5,6-dibromo-1*H*-indol-3-yl)methylene)-1-methyl-1*H*-imidazol-4(5*H*)-one]



19

Method 1

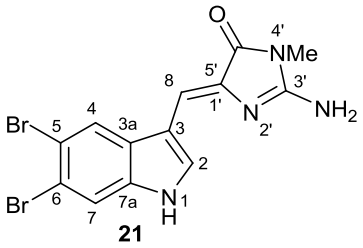
Aldehyde **17** (100 mg, 0.330 mMol) and 2-amino-1-methyl-1*H*-imidazol-4(5*H*)-one **18** (creatinine) (37 mg, 0.330 mMol) were dissolved in piperidine (1.5 mL). The pale brown solution was subjected to microwave irradiation (200 W, 150 °C) for 1 hour, after which time a yellow solid was observed in the reaction mixture. The solid was filtered, washed with acetic acid (3 x 1 mL) and diethyl ether (5 x 1 mL) and dried *in vacuo* to afford a mixture of (*E*)- and (*Z*)-5,6-dibromo-4'-demethylaplysinopsin **19** (80 mg, 61 %) in a ratio of ~ 22:1 *E*:*Z* as a yellow solid.

Method 2

Aldehyde **17** (48 mg, 0.159 mMol), Imidazolone **18** (23.3 mg, 0.206 mMol) and sodium acetate (18.2 mg, 0.222 mMol) were suspended in acetic acid (1 mL) and heated to reflux for 5 days. The resulting yellow solid was filtered, washed with acetic acid (3 x 1 mL) and diethyl ether (5 x 1 mL) and dried *in vacuo* to afford **19** as the pure *E* isomer (53 mg, 73 %) as a yellow powder, m.p. 328-330 °C (effervesces); ν_{max} (single crystal) 3106, 2908, 1691, 1631, 1557, 1505, 1409, 1376, 1218 cm^{-1}; δ_H (500 MHz, DMSO-D_6), 1.91 (3H, s, CO_2CH_3), 3.29 (3H, s, CH_3), 6.53 (1H, s, H-8), 7.82 (1H, s, H-7), 8.41 (1H, s, H-4), 9.13 (1H, d, $J_{NH,2}$ 2.4 Hz, H-2), 11.64 (1H, br d, $J_{NH,2}$ 1.2 Hz, NH); δ_C (125 MHz, DMSO-D_6), 21.0 (q, CO_2CH_3), 27.9 (q, CH_3), 103.5 (d, C-8), 109.0 (s, C-3), 113.9 (s, C-5/6), 115.5 (s, C-5/6), 116.4 (d, C-7), 122.9 (d, C-4), 128.7 (s, C-3a), 130.5 (d, C-2), 131.7 (s, C-1'), 135.3 (s, C-7a), 165.2 (s, C-3'), 172.0 (s, CO_2CH_3), 175.4 (s, C-5'); $^3J_{H8\text{-}C5'}$ 8.4 Hz; *m/z* (EI^+) 421 (MNa^+, 100%); HRMS (EI^+) calculated for $C_{13}H_{10}{}^{79}Br_2N_4NaO$ (MNa^+) 418.9120, found 418.9119.

5,6-Dibromo-2'-demethylaplysinopsin[7] 21

[(*Z*)-2-Amino-4-((5,6-dibromo-1*H*-indol-3-yl)methylene)-1-methyl-1*H*-imidazol-5(4*H*)-one]



21

Method 1

Aldehyde **17** (54 mg, 0.178 mMol), 1-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-2-aminium chloride **20** (isocreatinine hydrochloride salt) (35 mg, 0.232 mMol) and sodium acetate (20.5 mg, 0.250 mMol) were suspended in acetic acid (1 mL). The pale pink mixture was subjected to microwave irradiation (200 W, 150 °C) for 1 hour, after which time a brown solid was observed in the reaction mixture. The solid was filtered, washed with acetic acid (3 x 1 mL) and diethyl ether (5 x 1 mL) and dried *in vacuo* to afford a mixture of (*E*)- and (*Z*)-5,6-dibromo-2'-demethylaplysinopsin **21** (48 mg, 68 %) in a ratio of ~ 1:21 *E*:*Z* as a tan powder.

Method 2

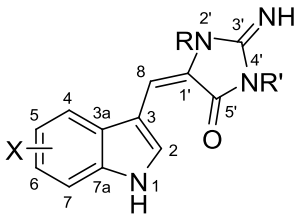
Aldehyde **17** (33 mg, 0.109 mMol), hydrochloride salt **20** (21.2 mg, 0.142 mMol) and sodium acetate (12.5 mg, 0.153 mMol) were suspended in acetic acid (1 mL) and heated to reflux for 5 days. The resulting brown solid was filtered, washed with acetic acid (3 x 1 mL) and diethyl ether (5 x 1 mL) and dried *in vacuo* to afford **21** as the pure *Z* isomer (36 mg, 83 %) as a light brown powder, m.p. > 350 °C (darkens ~ 290 °C) [lit. 79.8-82.2 °C for free base, 165-169 °C for 9:1 mixture of *Z*:*E* isomers of TFA salt][7b]; ν_{max} (single crystal) 3417, 3166, 1753, 1670, 1646, 1583, 1518, 1446, 1288, 1232 cm^{-1}; δ_H (500 MHz, DMSO-D_6), 3.18 (3H, s, CH_3), 7.30 (1H, s, H-8), 7.90 (1H, s, H-7), 8.23 (1H, d, $J_{NH,2}$ 2.8 Hz, H-2), 8.43 (1H, s, H-4), 12.33 (1H, br s, NH); δ_C (125 MHz, DMSO-D_6), 26.2 (q, CH_3), 107.8 (s, C-3), 109.6 (d, C-8), 115.3 (s, C-5/6), 116.9 (d, C-7), 117.0 (s, C-5/6), 121.5 (s, C-1'), 123.6 (d, C-4), 127.7 (s, C-3a), 130.7 (d, C-2), 135.6 (s, C-7a), 155.5 (s, C-3'), 162.7 (s, C-5'); *m/z* (ES^+) 399 (M^+, 100%); HRMS (ES^+) calculated for $C_{13}H_{11}{}^{79}Br_2N_4O$ (M^+) 396.9300, found 396.9302.

For the (*E*) isomer:

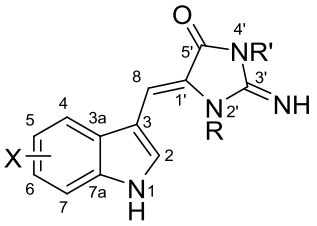
δ_H (500 MHz, DMSO-D_6), 3.18 (3H, s, CH_3), 7.34 (1H, s, H-8), 7.93 (1H, s, H-7), 8.11 (1H, s, H-4), 8.88 (1H, d, $J_{NH,2}$ 2.8 Hz, H-2), 12.17 (1H, br s, NH); δ_C (125 MHz, DMSO-D_6), 26.0 (q, CH_3), 108.1 (s, C-3), 115.0 (d, C-8), 115.3 (s, C-5/6), 116.7 (s, C-5/6), 117.2 (d, C-7), 121.5 (s, C-1'), 122.3 (d, C-4), 128.3 (s, C-3a), 132.6 (d, C-2), 135.6 (s, C-7a), 152.4 (s, C-3'), 160.8 (s, C-5').

Determination of aplysinopsin alkene geometry

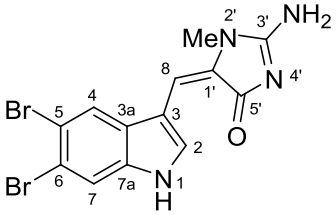
The determination of the olefinic geometry of the aplysinopsins has received some previous attention.[10-12] It has been found that when R=Me (methyl at the 2' position, as in aplysinopsin itself, and in the non-natural derivative **19**) the *E* isomer predominates due to steric factors (smaller clash between H(2) and C(5')=O than between H(2) and the N(2')-Me group). The *E*-isomer was found to be both thermodynamically and photochemically more stable than the *Z* in these cases. When R=H or lone pair (as in the natural product 5,6-dibromo-2'-demethylaplysinopsin **21**)[8] the *Z*-isomer is the thermodynamically more stable, but is also photochemically more labile than the *E*-isomer.



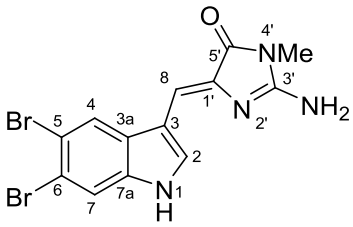
(*E*)-aplysinopsins



(*Z*)-aplysinopsins



19



21

The geometry of the double bond can be conveniently determined by NMR analysis. In the case of the *E*-isomers, H(2) is observed to be significantly deshielded due to the close proximity of the C(5')=O compared to the *Z*-isomers (typical values for *E*-isomers: 8.69-9.08; typical values for *Z*-isomers: 7.57-8.29).[10,11] It has also been observed that there is consistently a larger H(8)-C(5') heteronuclear coupling constant[13] in the *E*-isomers compared to the *Z*- (typical values for *Z*: ^{3}J(H(8)-C(5')) 4.2-5.2 Hz; typical values for *E*: ^{3}J(H(8)-C(5')) 9.8-11.0).[10] Furthermore, in the case of the compounds where R=Me (methylated at N(2')), irradiation of H(8) leads to an nOe effect on both H(4) and N(2')-Me in the *E*-isomer, while none is observed in the *Z*-isomer.

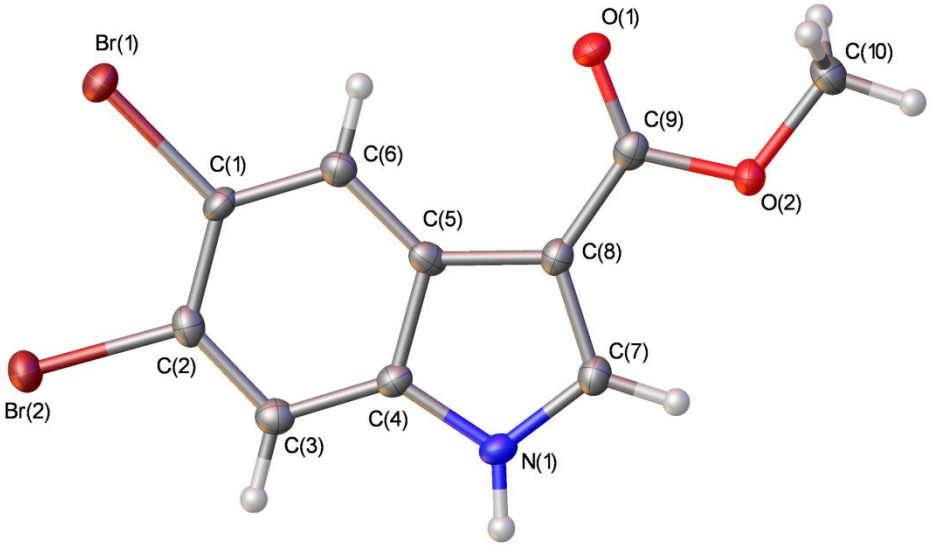
The major isomer of isolated 5,6-dibromo-2'-demethylaplysinopsin **21** was assigned as *Z* by comparison of the chemical shift of H(2) and C(8) to those of 6-bromo-2'-demethylaplysinopsin.[8] The synthetic sample of 5,6-dibromo-2'-demethylaplysinopsin **21**

matches well with the data for the *Z*-isomer, with a chemical shift for H(2) of 8.23 ppm. This is as expected for an aplysinopsin derivative where the substituent at N(2') is H. The NMR sample (in DMSO-D_6) was observed to undergo isomerisation over the course of one week to give a mixture of ~84:16 *Z*:*E*, indicating that the *Z*-isomer is photochemically labile, a result also in line with previous observations on this type of structure.[10-12] That the new isomer was the *E* was supported by the significant deshielding of $H(2)_{minor}$ of 8.88 ppm. Unfortunately the solubility of the sample was insufficient to enable us to obtain a reliable value for the H(8)-C(5') heteronuclear coupling constant. Nevertheless, our data appears to concur with the previous assignment of this compound.

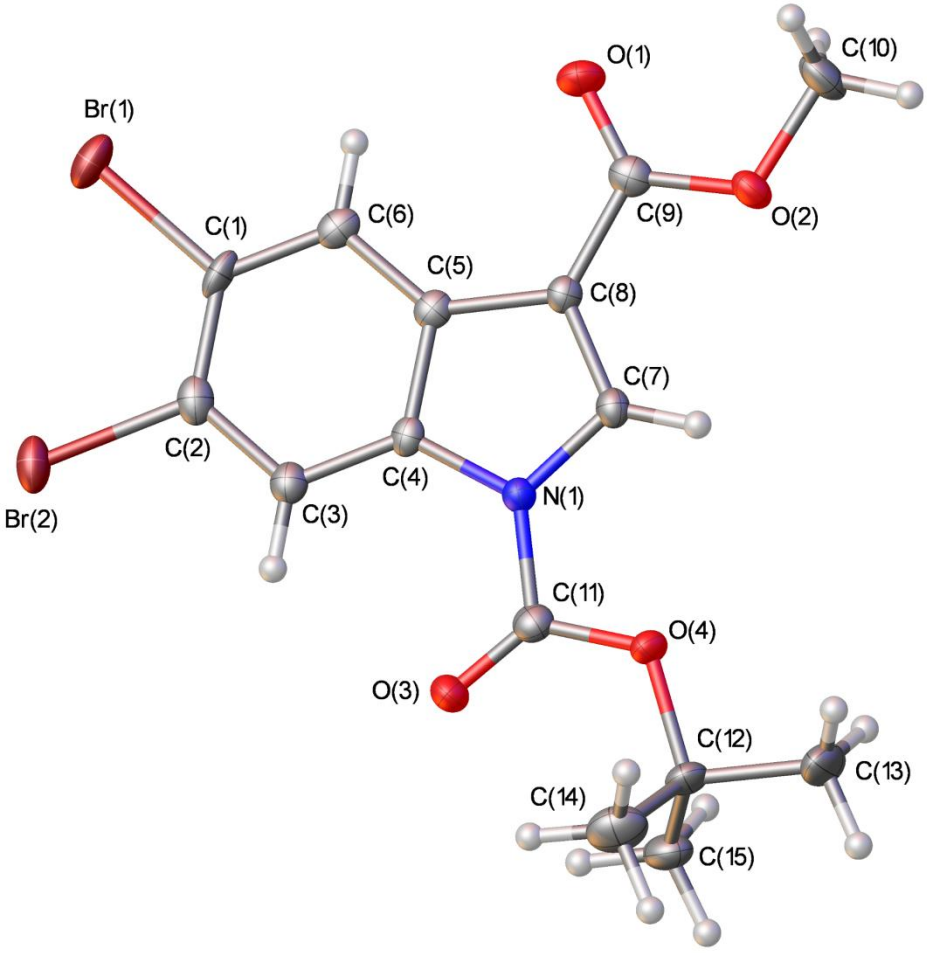
In the case of the non-natural derivative 5,6-dibromo-4'-demethylaplysinopsin **19** our data is more conclusive. In this case we expect the product to be the *E* due to the steric influence of the N(2')-Me. The large deshielding of H(2) (9.13 ppm) would appear to support this expectation. Upon irradiation of H(8), an nOe effect was observed on both H(4) and N(2')-Me. Furthermore, irradiation of the N(2')-Me protons lead to an nOe on H(8). These results are consistent with assignment as the *E*-isomer. Furthermore, in this case we were able to measure the H(8)-C(5') heteronuclear coupling constant which was found to be 8.4 Hz. Although this is slightly smaller than those previously reported for *E*-aplysinopsin derivatives, it is of the appropriate magnitude. These three pieces of evidence would appear to confirm that the geometry of the double bond is *E*, as expected. Also of note is the fact that no isomerisation to the *Z*-isomer was observed over the course of one week in DMSO-D_6, indicating that the *E*-isomer is photochemically stable.

X-ray crystallography

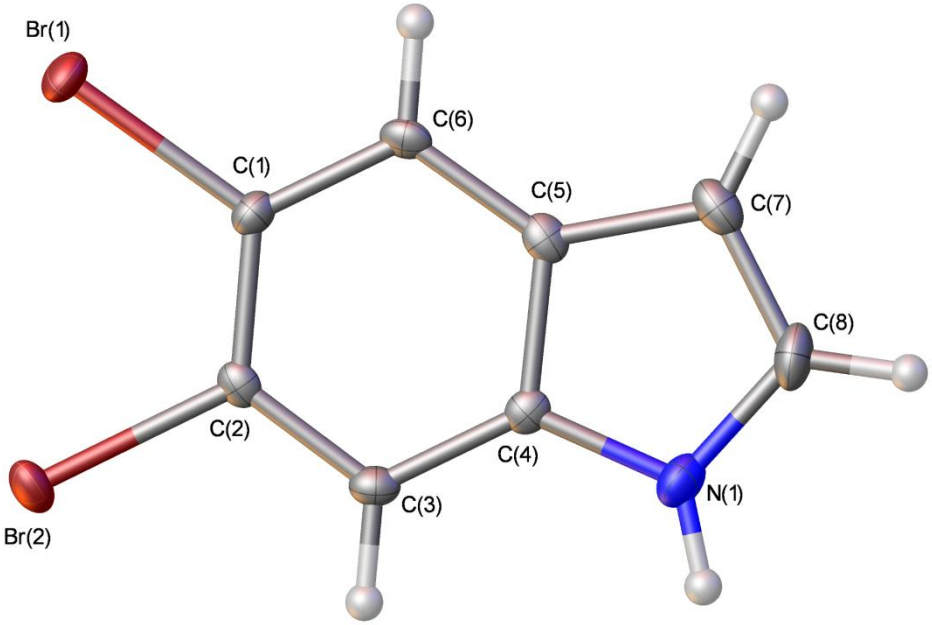
Crystal structure of **2** with ellipsoids drawn at the 50 % probability level:



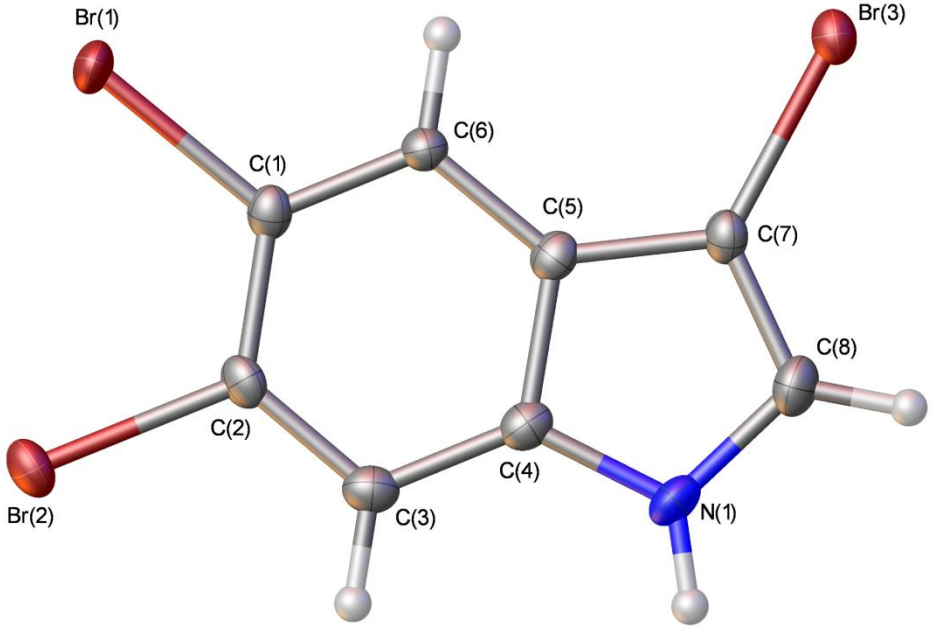
Crystal structure of **3** with ellipsoids drawn at the 50 % probability level:



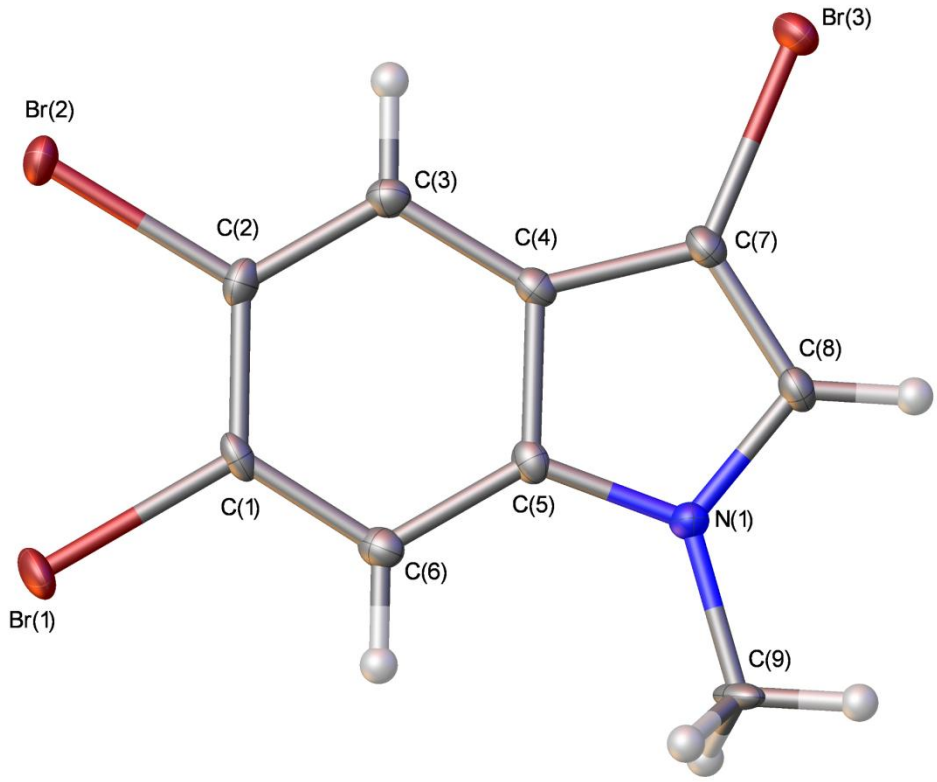
Crystal structure of **7** with ellipsoids drawn at the 50 % probability level:



Crystal structure of **10** with ellipsoids drawn at the 50 % probability level:



Crystal structure of **11** with ellipsoids drawn at the 50 % probability level:



Suitable crystals were selected and datasets were measured on a Bruker SMART 6000 diffractometer ($\lambda_{Cu\text{-}K\alpha}$ = 1.5418 Å) for **7**, **10** and **11**. Datasets were measured on a Bruker KappaCCD diffractometer for **3** and on a Bruker APEXII CCD diffractometer for **2**, both at the window of a Bruker FR591 rotating anode ($\lambda_{Mo\text{-}K\alpha}$ = 0.71073 Å). The data collections were driven by SMART[10] and processed by SAINTPLUS[11] for **7**, **10** and **11**, were driven by COLLECT[12] and were processed by DENZO[13] for **2** and **3**. Absorption corrections were applied using SADABS[14] for all compounds. The structures of **2** and **3** were solved using SIR92[15], of **7** by SIR2004[16] and of **10** and **11** by ShelXS-97[17] and all structures were refined by a full-matrix least-squares procedure on F^2 in ShelXL-97.[17] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. Figures were produced using OLEX2.[18]

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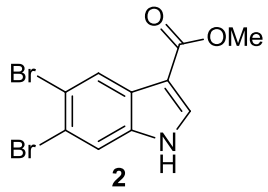
NMR Spectra

Methyl 5,6-dibromo-1*H*-indole-3-carboxylate **2**; DMSO-D_6, 400 MHz



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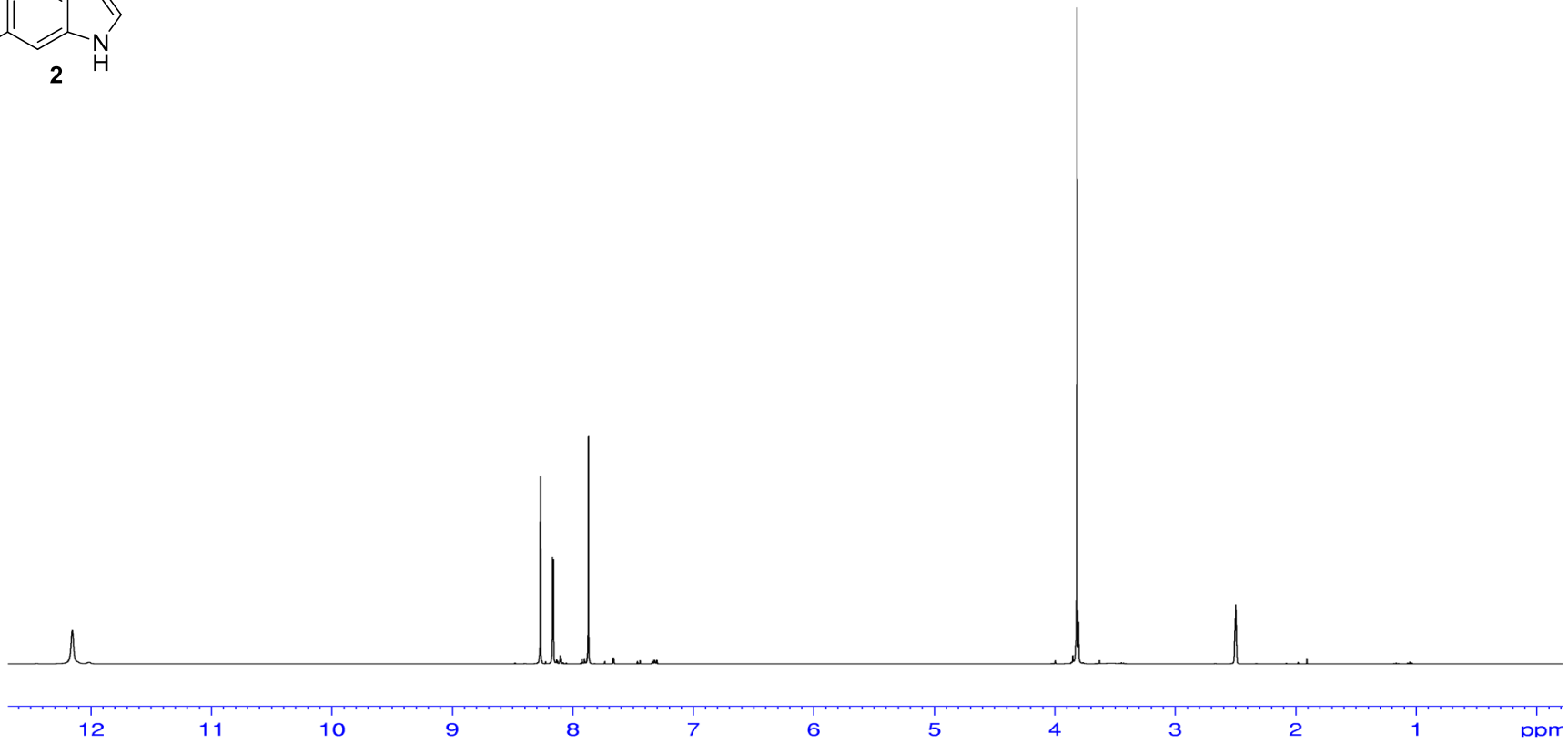
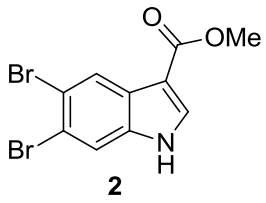


Methyl 5,6-dibromo-1*H*-indole-3-carboxylate **2**; DMSO-D_6, 100 MHz



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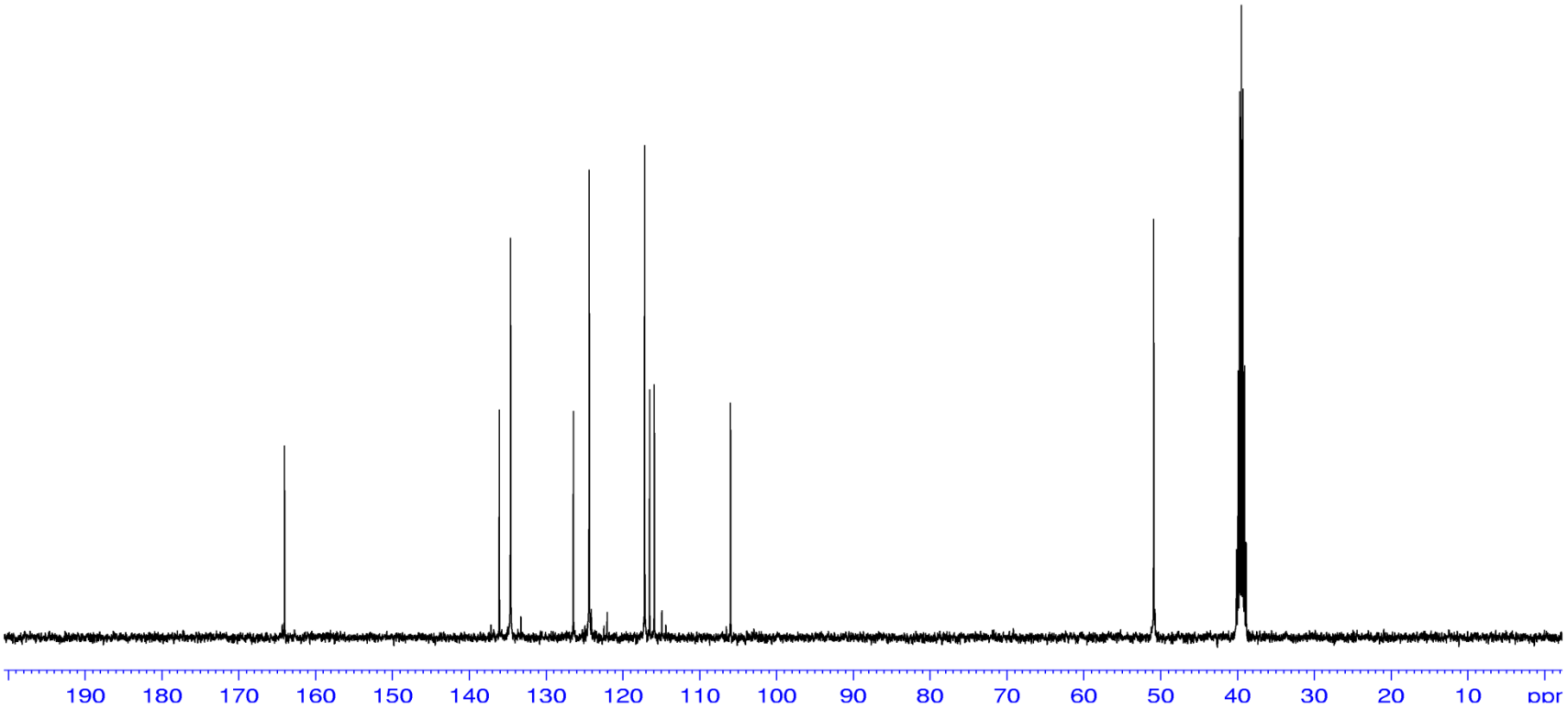
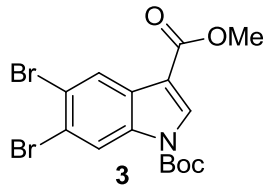


1-*tert*-Butyl-3-methyl 5,6-dibromo-1*H*-indole-1,3-dicarboxylate **3**; $CDCl_3$, 400 MHz



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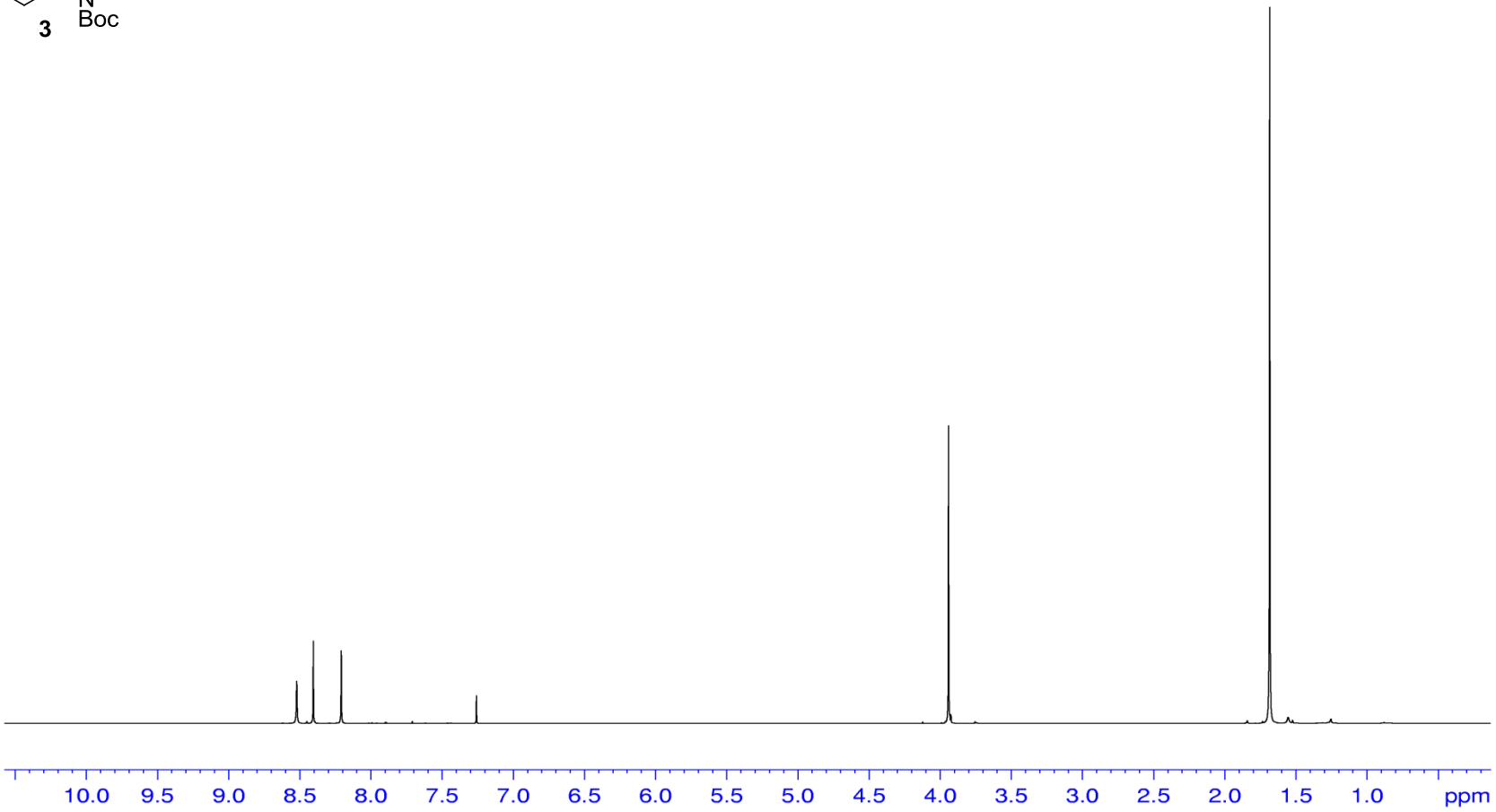

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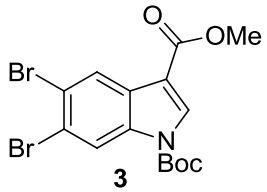

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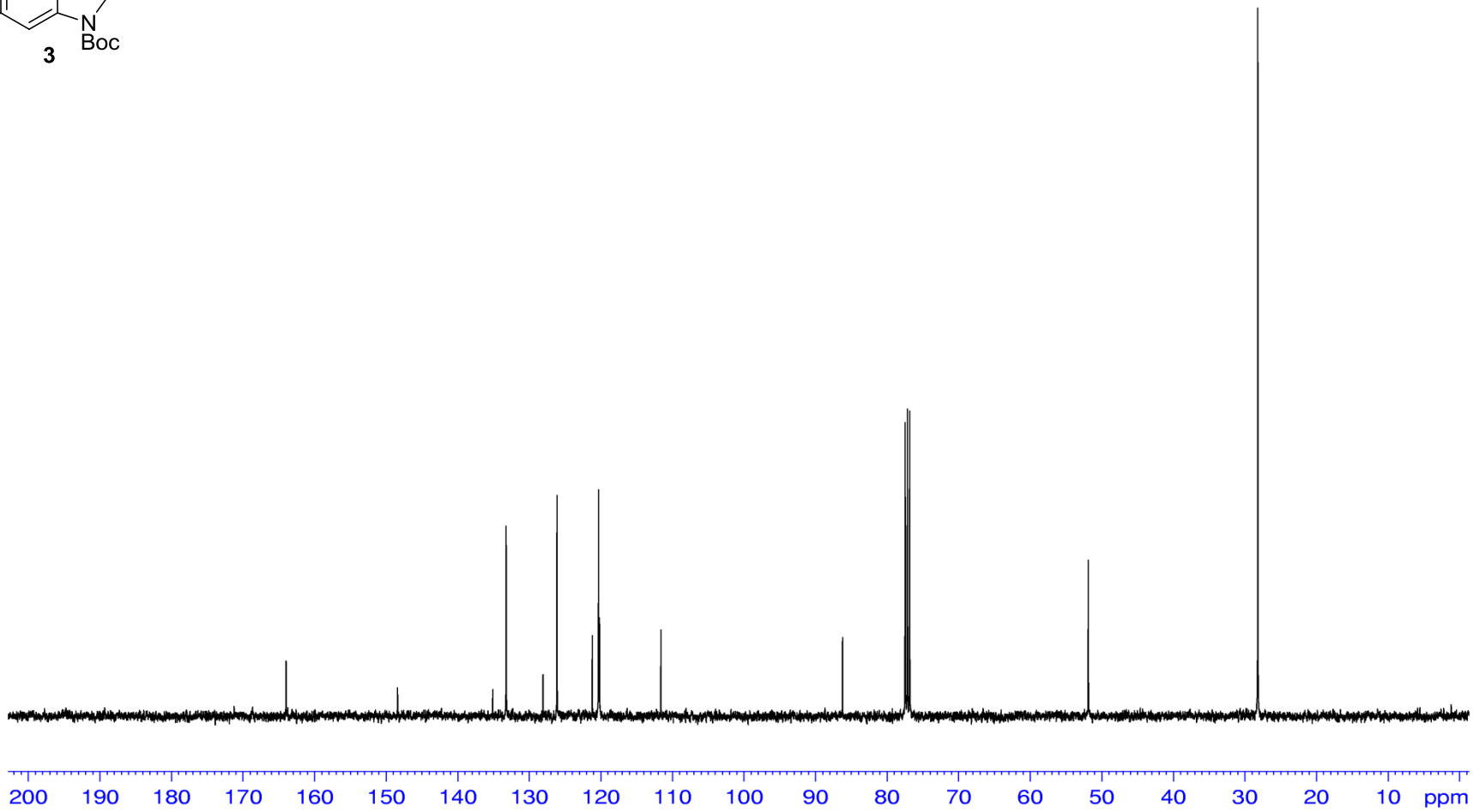
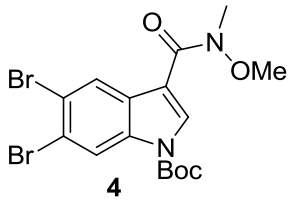


tert-Butyl 5,6-dibromo-3-(methoxy(methyl)carbamoyl)-1*H*-indole-1-carboxylate **4**; $CDCl_3$, 300 MHz



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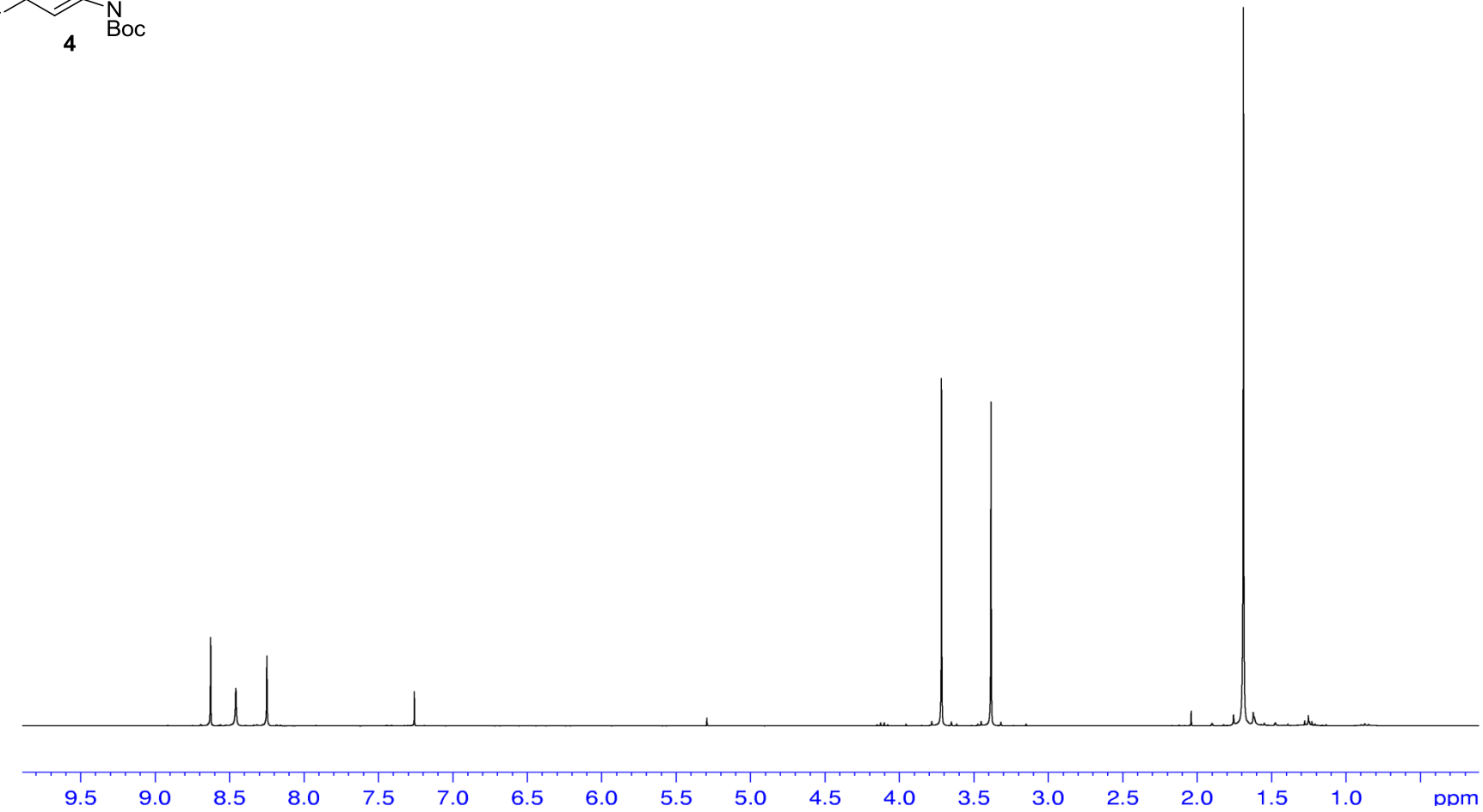

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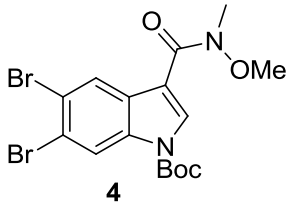

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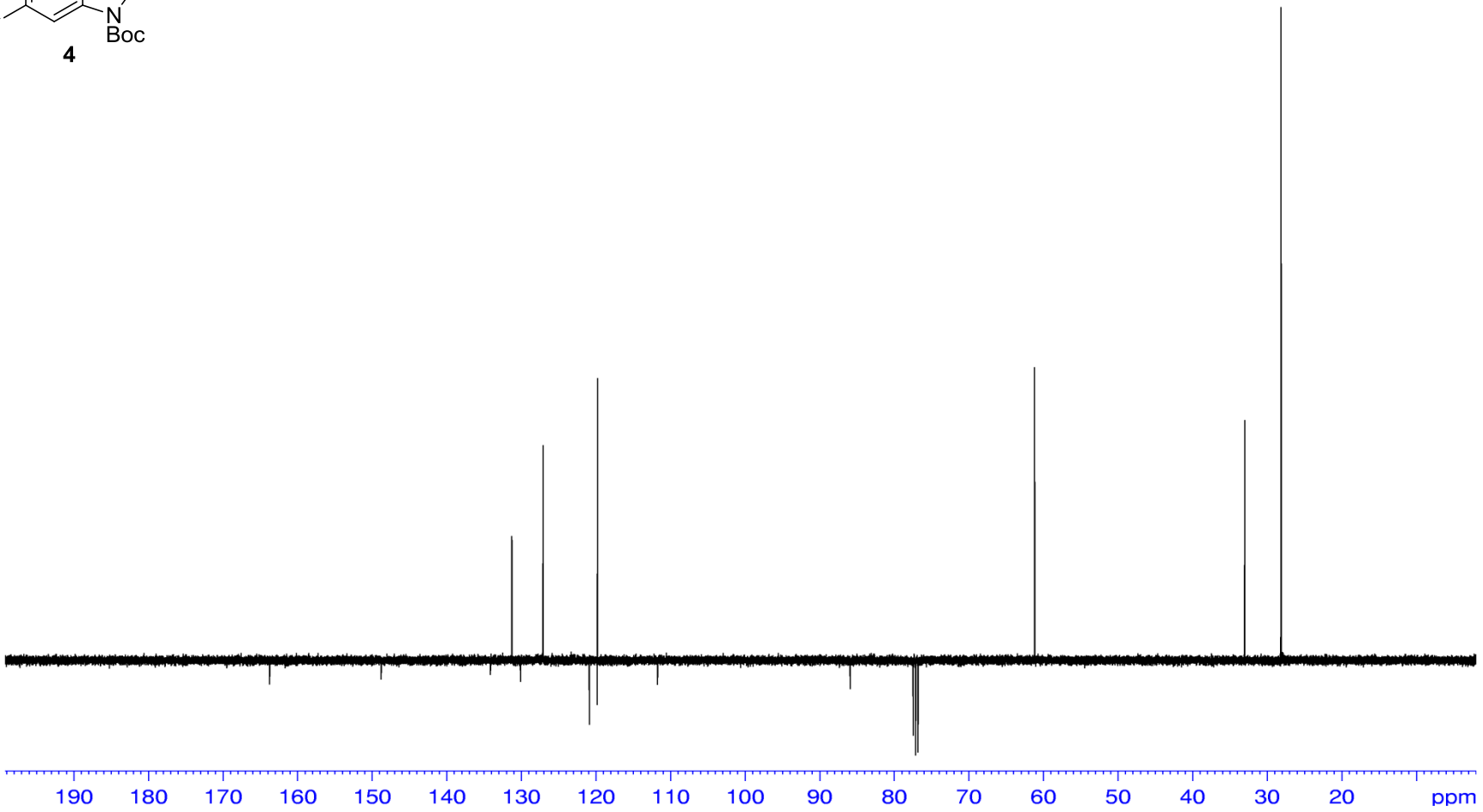

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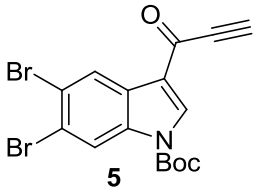

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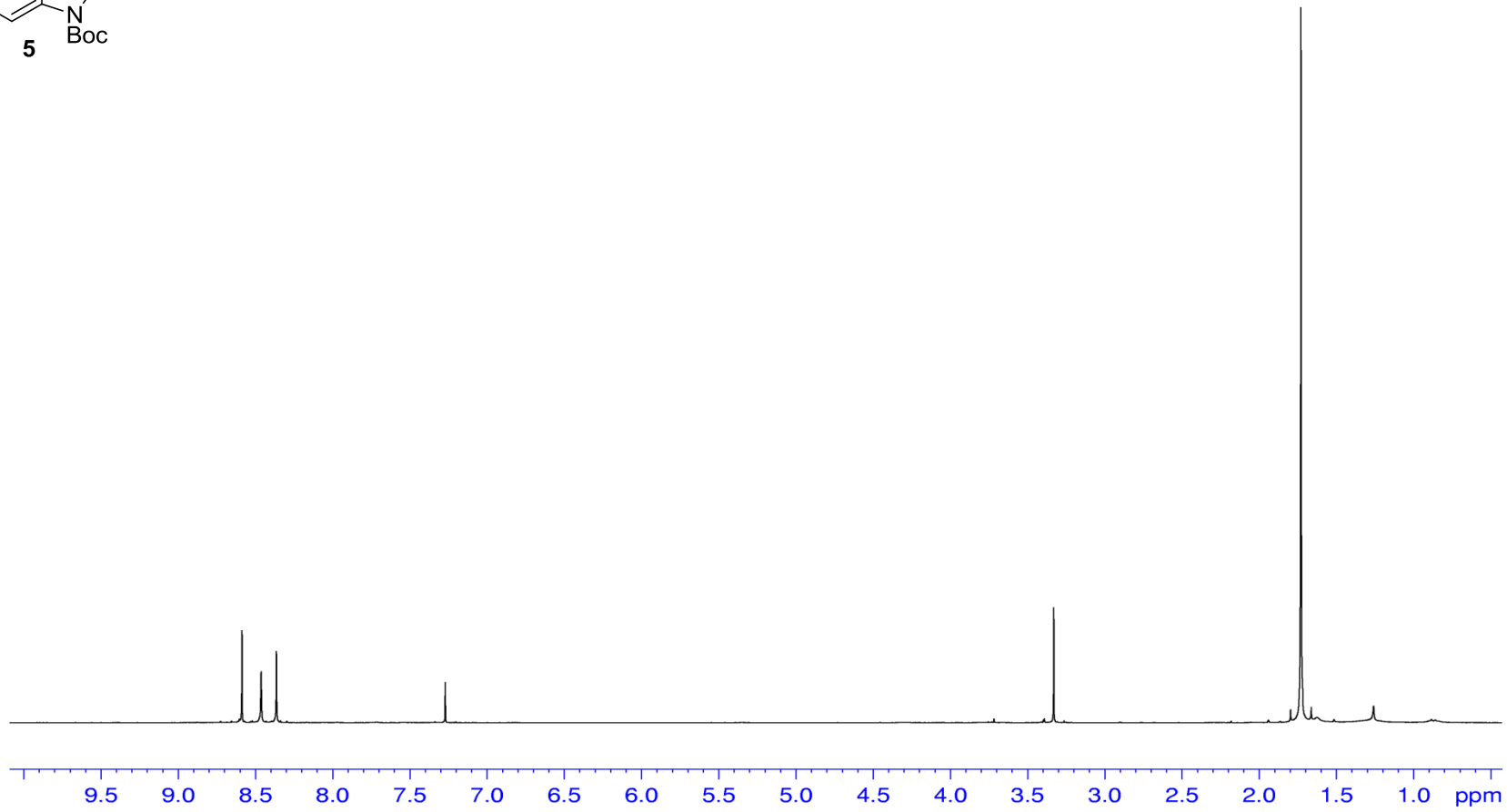
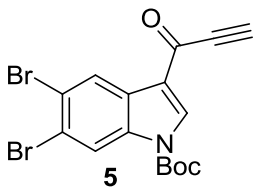
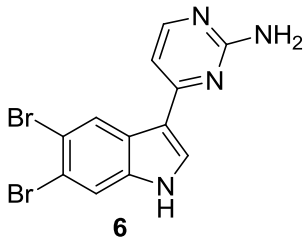


tert-Butyl 5,6-dibromo-3-propioloyl-1*H*-indole-1-carboxylate **5**; $CDCl_3$, 100 MHz



5

Meridianin F [4-(5,6-dibromo-1*H*-indol-3-y1) pyrimidin-2-amine] **6**; DMSO-D_6, 300 MHz



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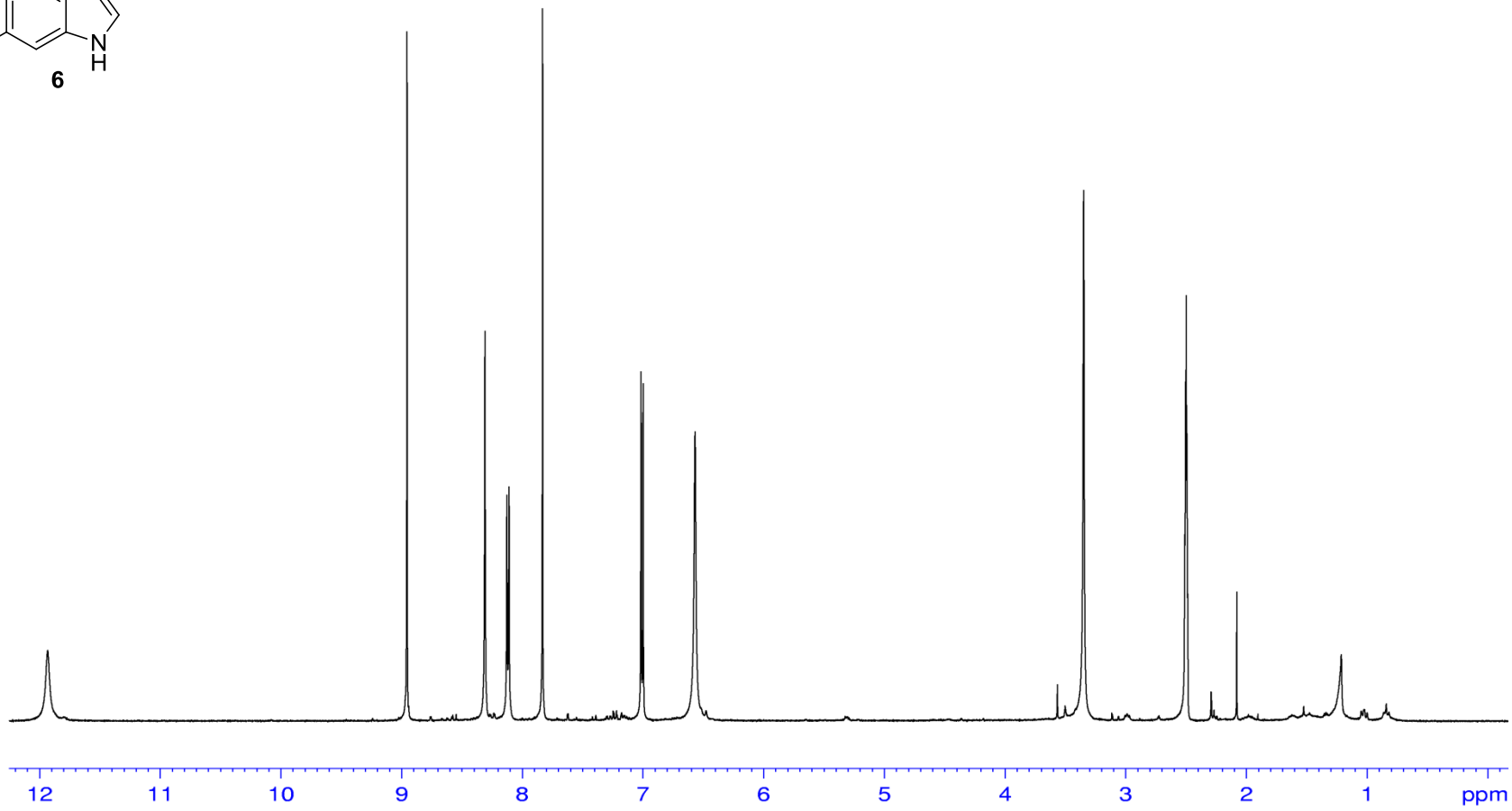
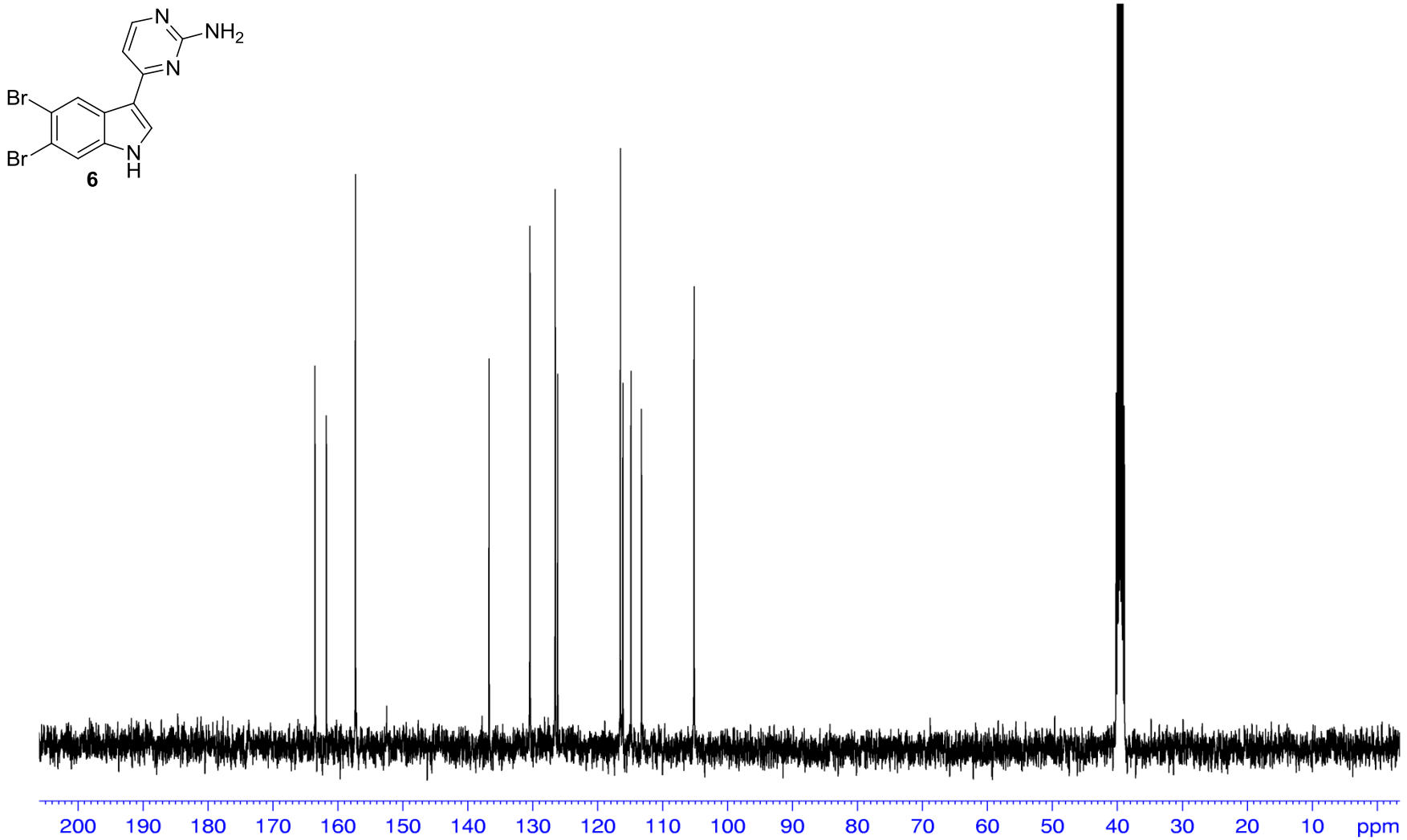
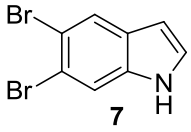


Meridianin F [4-(5,6-dibromo-1*H*-indol-3-y1) pyrimidin-2-amine] **6**; DMSO-D_6, 100 MHz



5,6-Dibromo-1*H*-indole **7**; $CDCl_3$, 300 MHz



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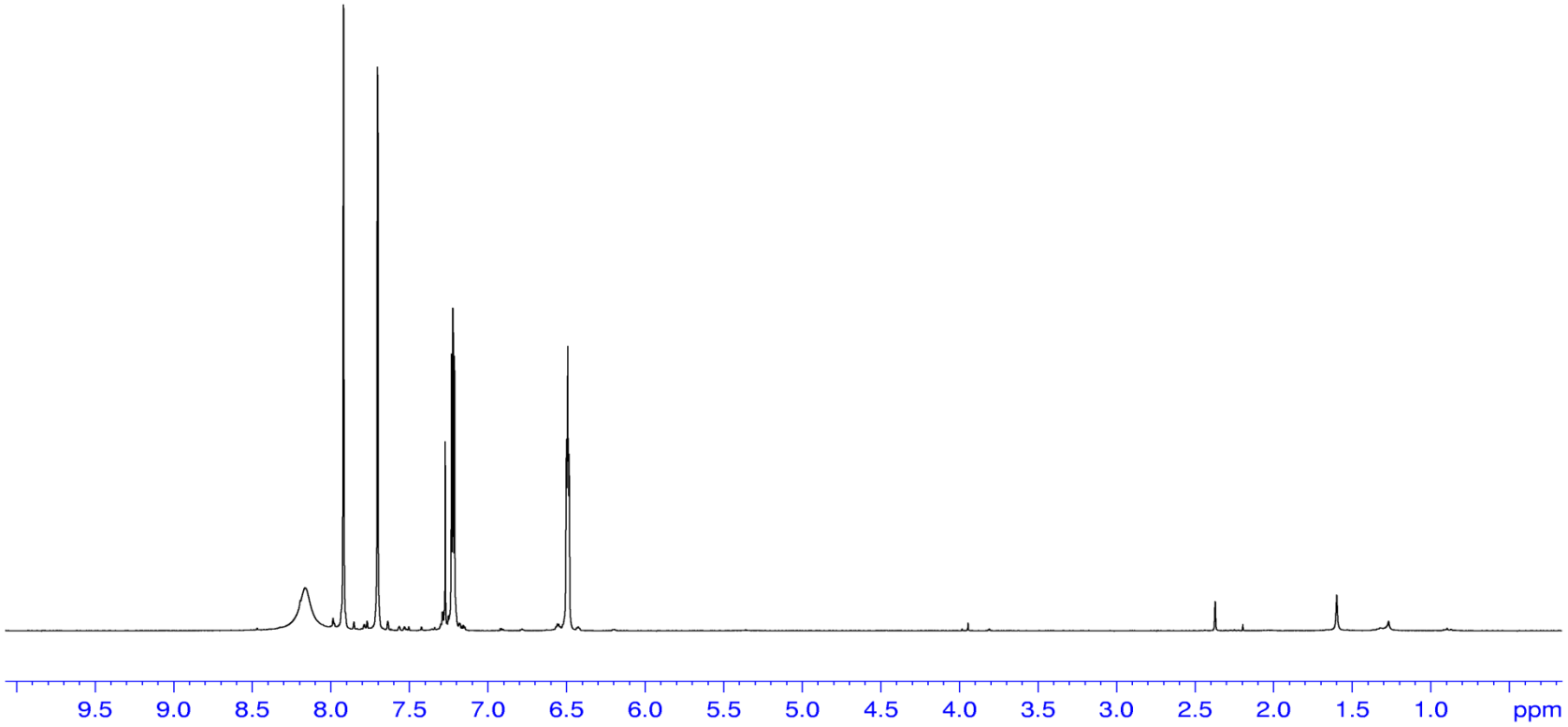
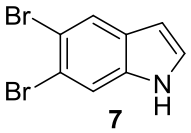


5,6-Dibromo-1H-indole **7**; $CDCl_3$, 100 MHz



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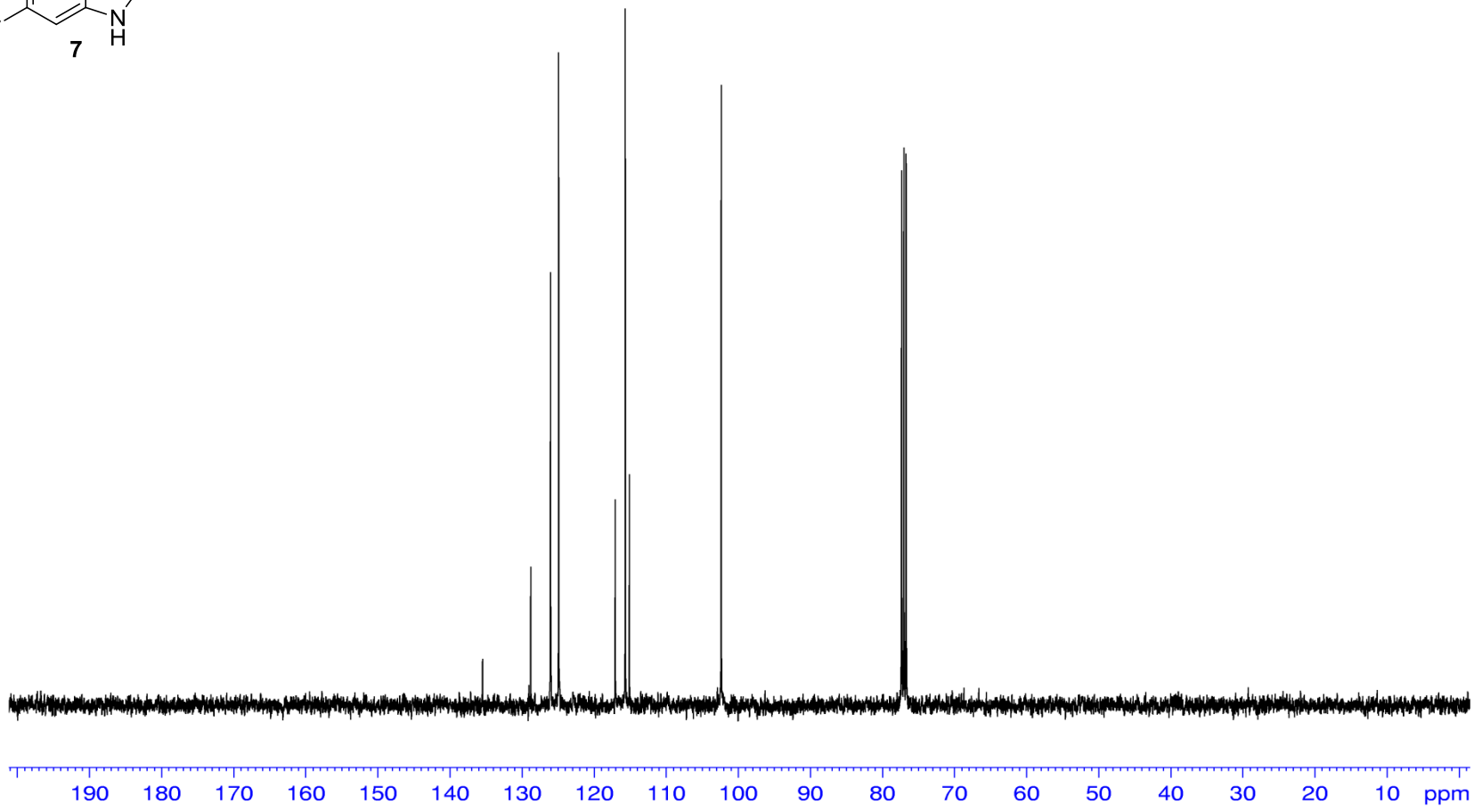
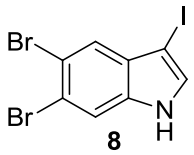


5,6-Dibromo-3-iodo-1*H*-indole **8**; $CDCl_3$, 400 MHz



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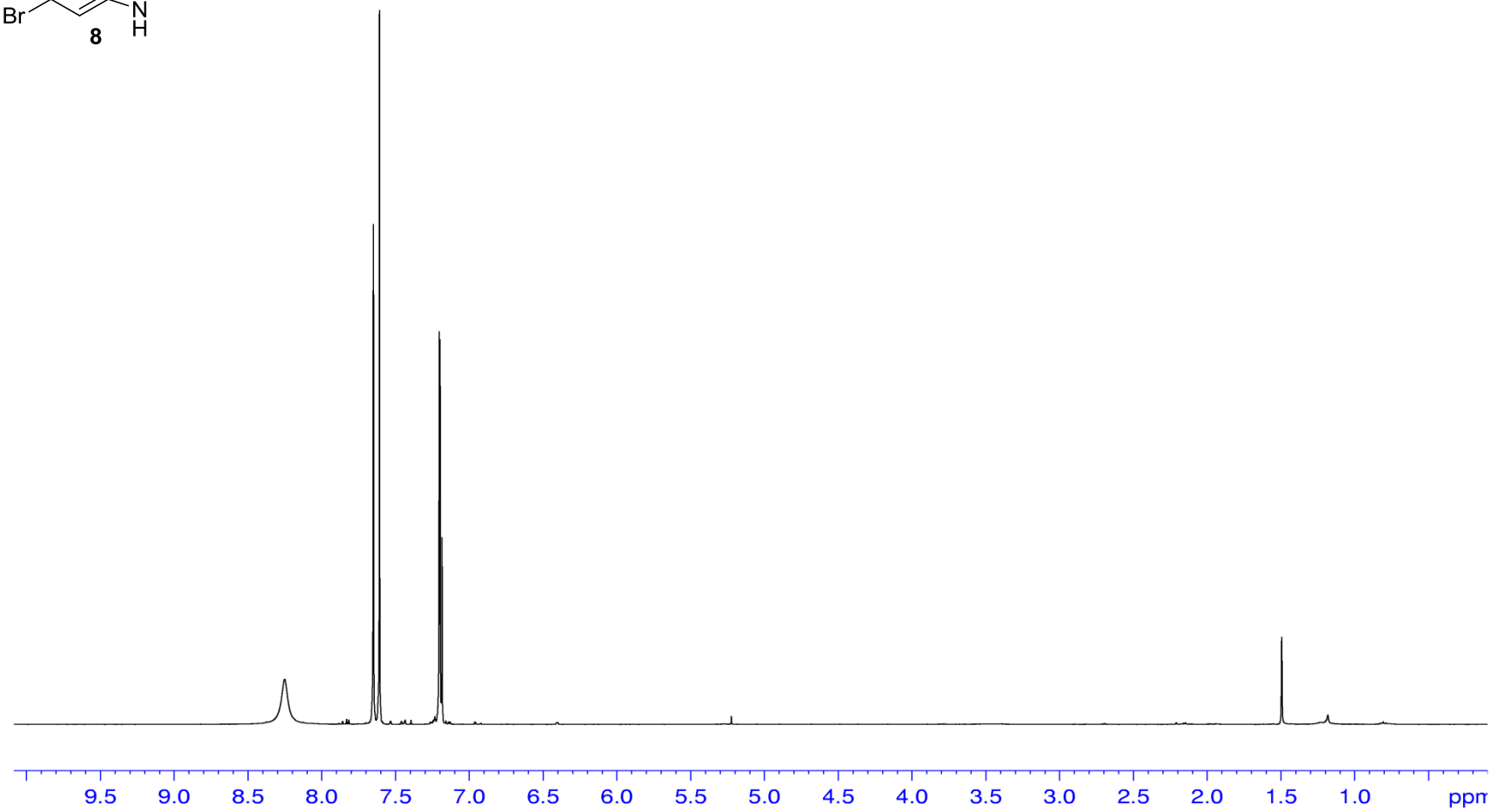
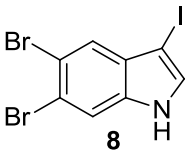


5,6-Dibromo-3-iodo-1*H*-indole **8**; $CDCl_3$, 100 MHz



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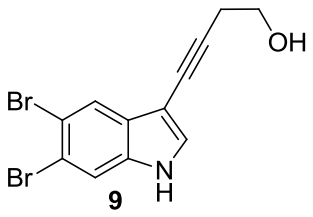
4-(5,6-Dibromo-1*H*-indol-3-yl)but-3-yn-1-ol **9**; $CDCl_3$, 400 MHz



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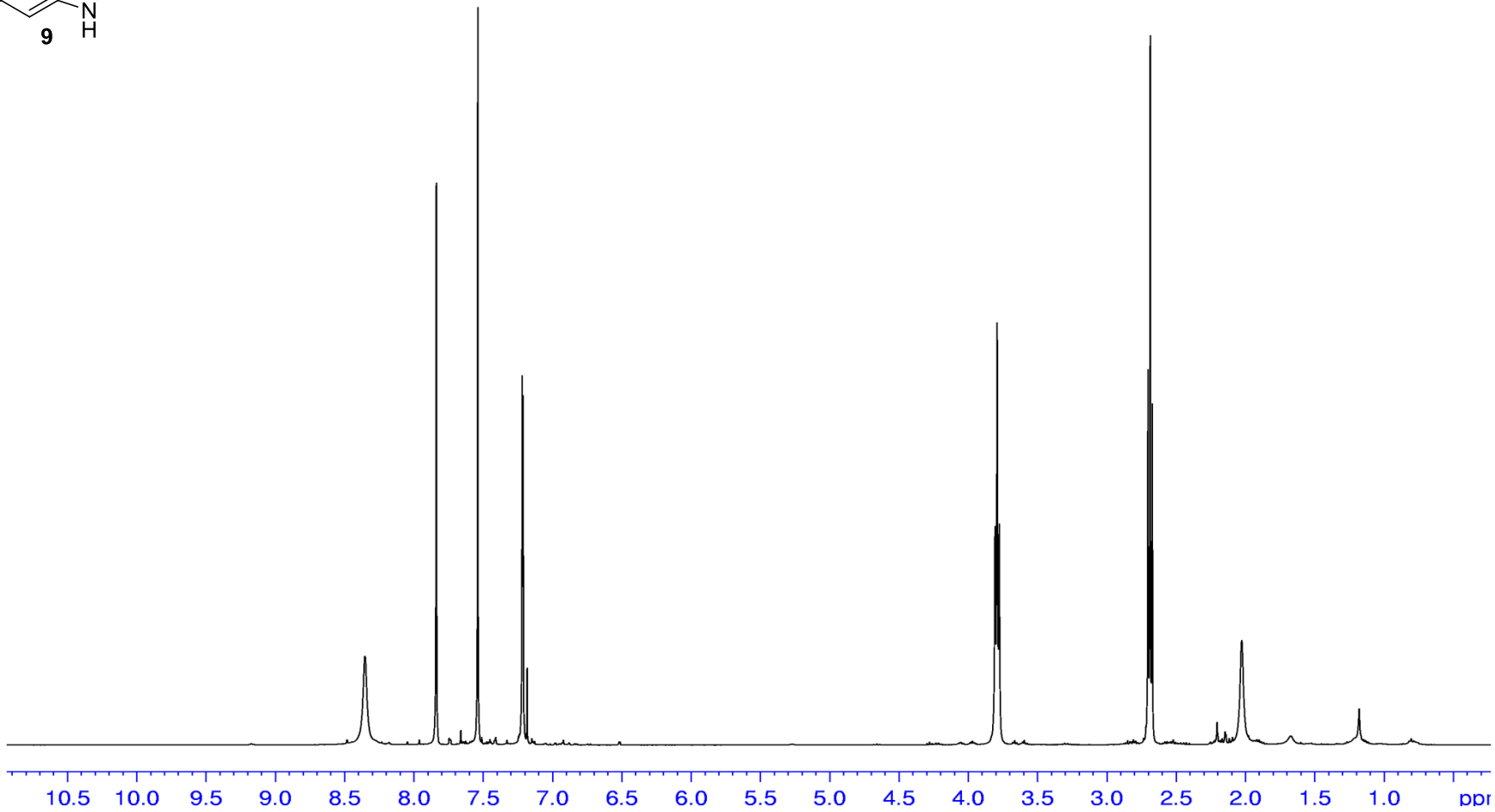
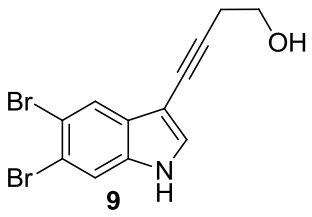


4-(5,6-Dibromo-1*H*-indol-3-yl)but-3-yn-1-ol **9**; $CDCl_3$, 100 MHz



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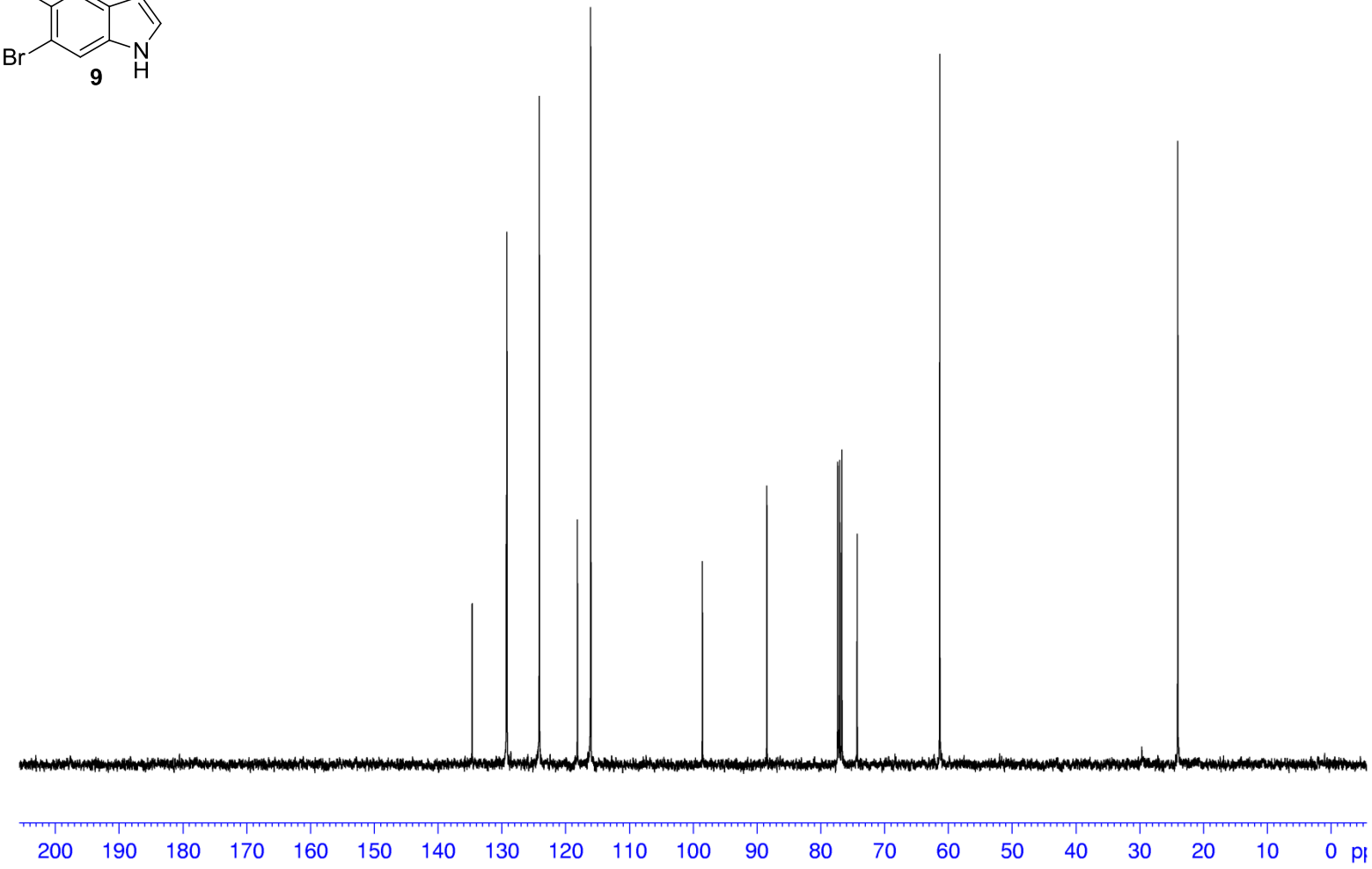
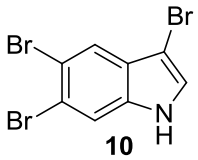


3,5,6-Tribromo-1*H*-indole **10**; $CDCl_3$, 300 MHz



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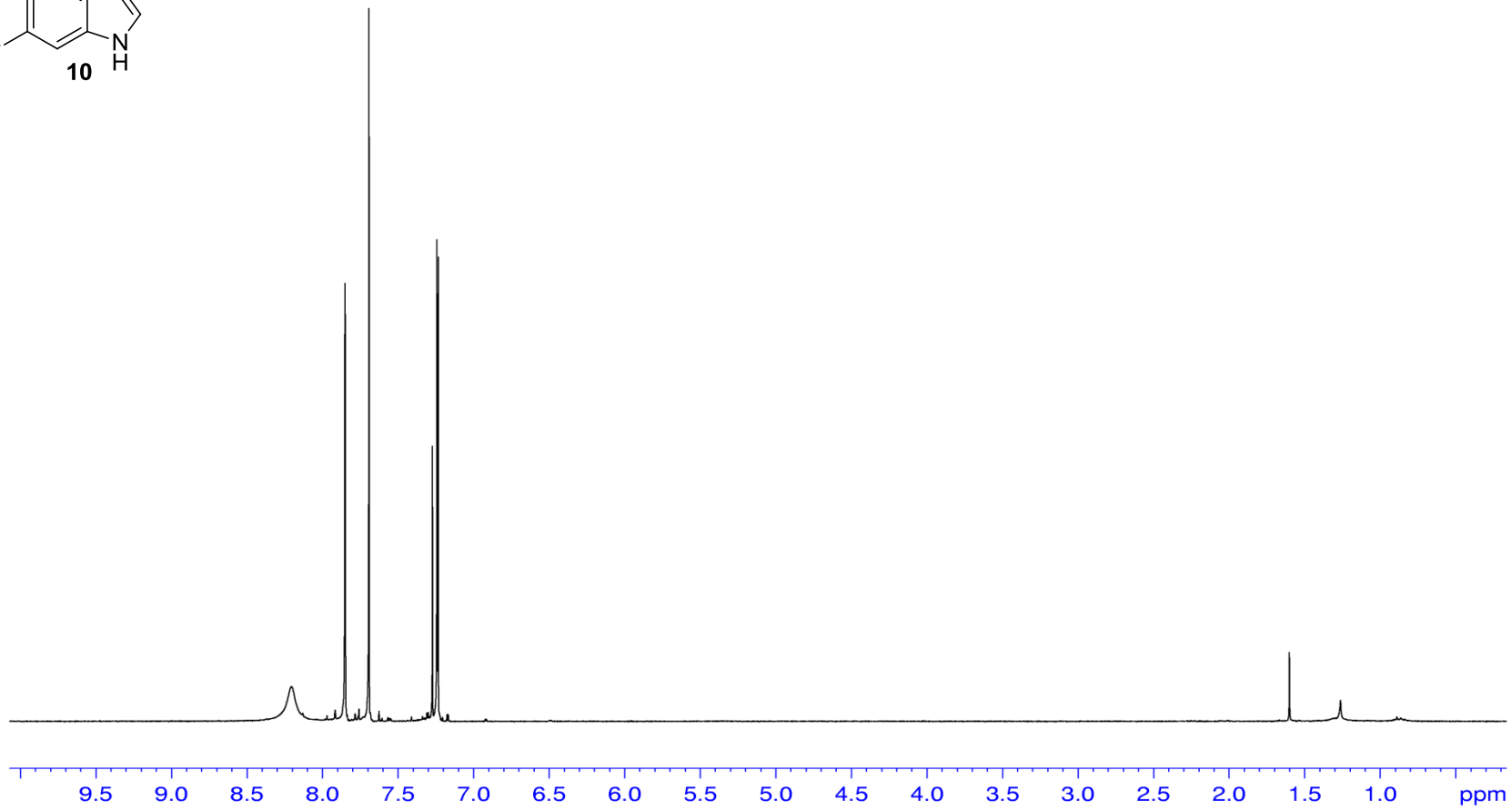
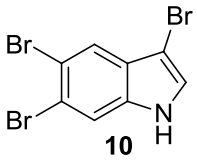


3,5,6-Tribromo-1*H*-indole **10**; $CDCl_3$, 100 MHz



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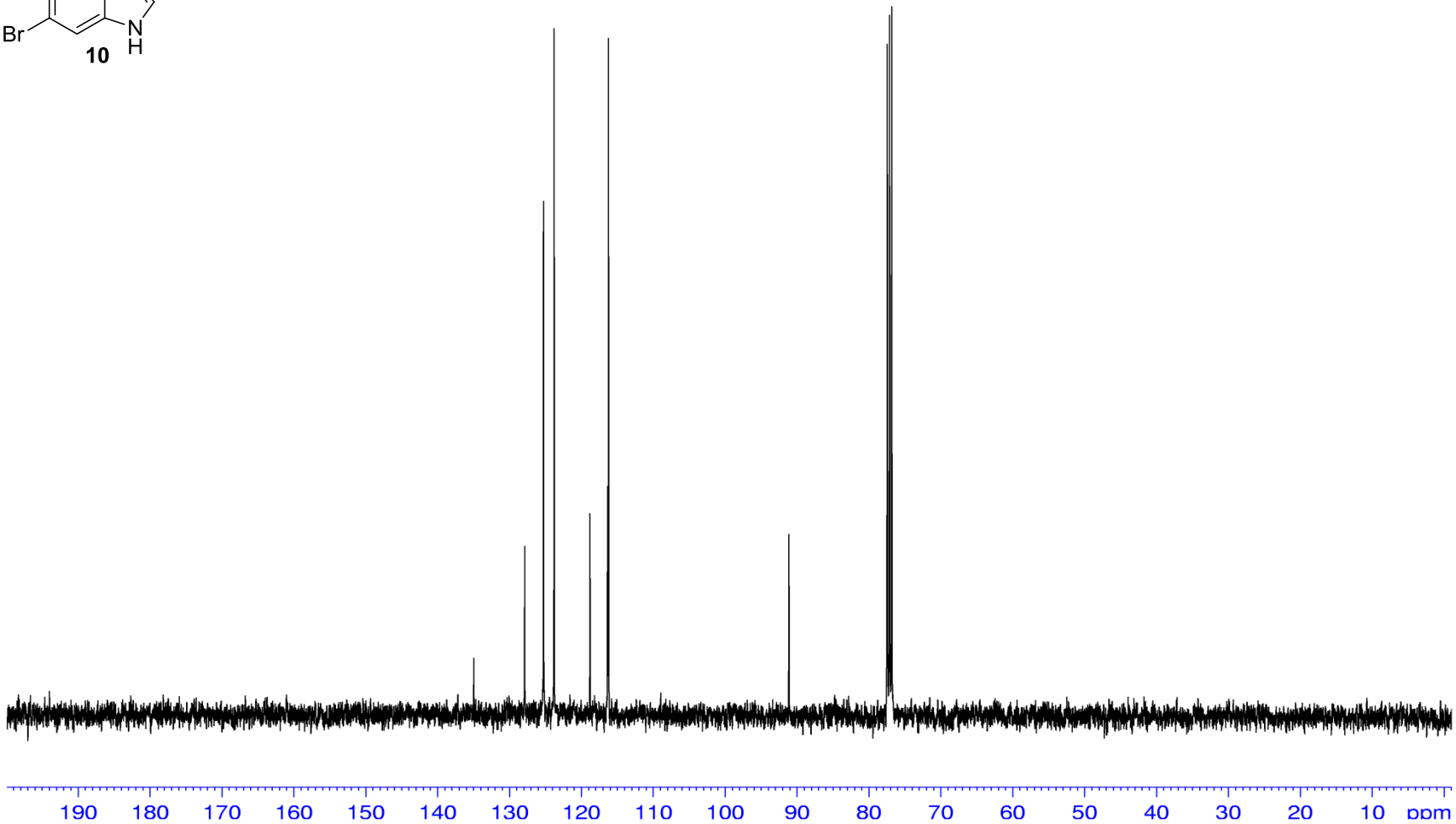
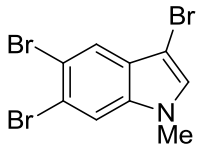
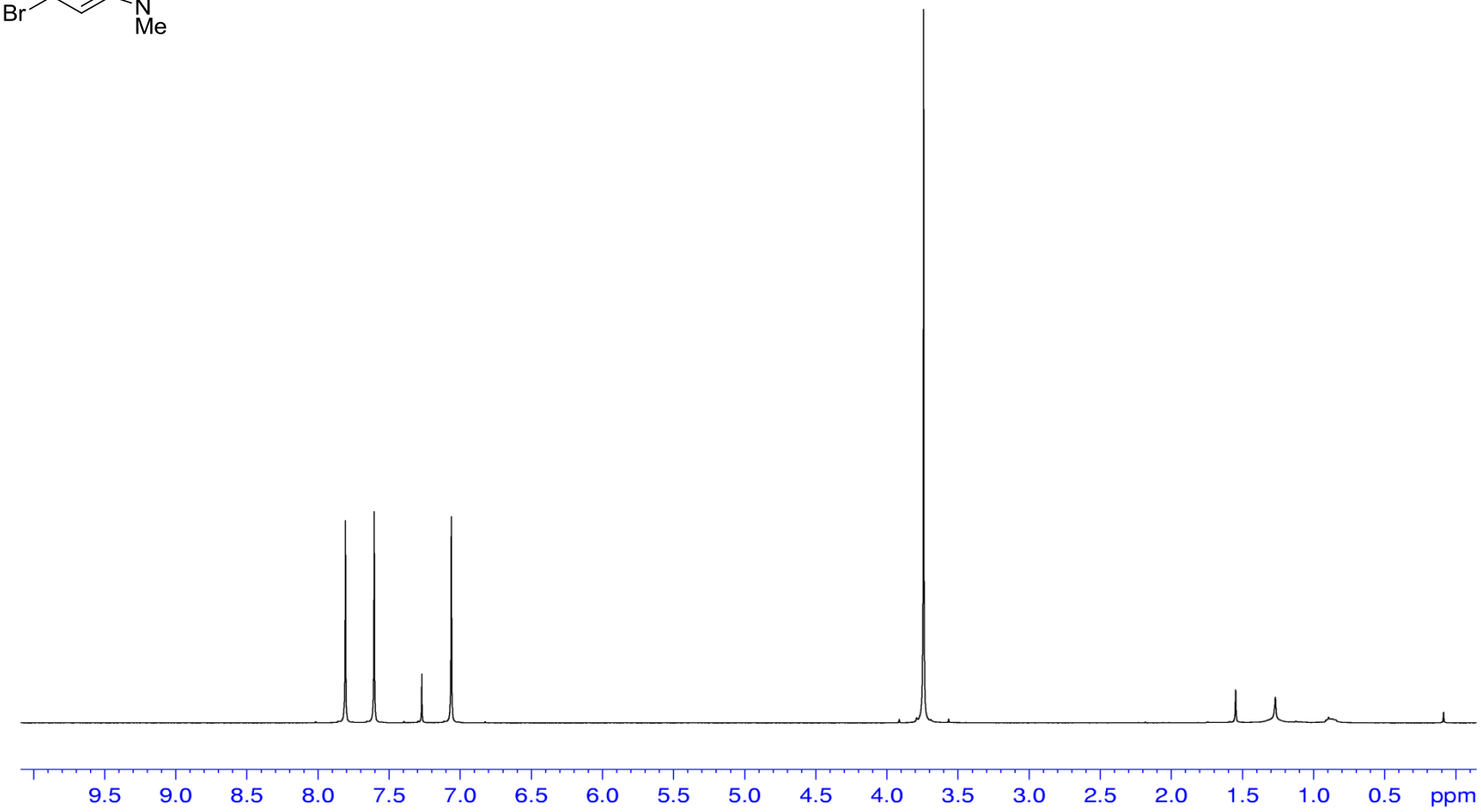
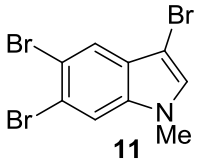


3,5,6-Tribromo-1-methyl-1*H*-indole **11**; $CDCl_3$, 400 MHz





3,5,6-Tribromo-1-methyl-1*H*-indole **11**; $CDCl_3$, 100 MHz



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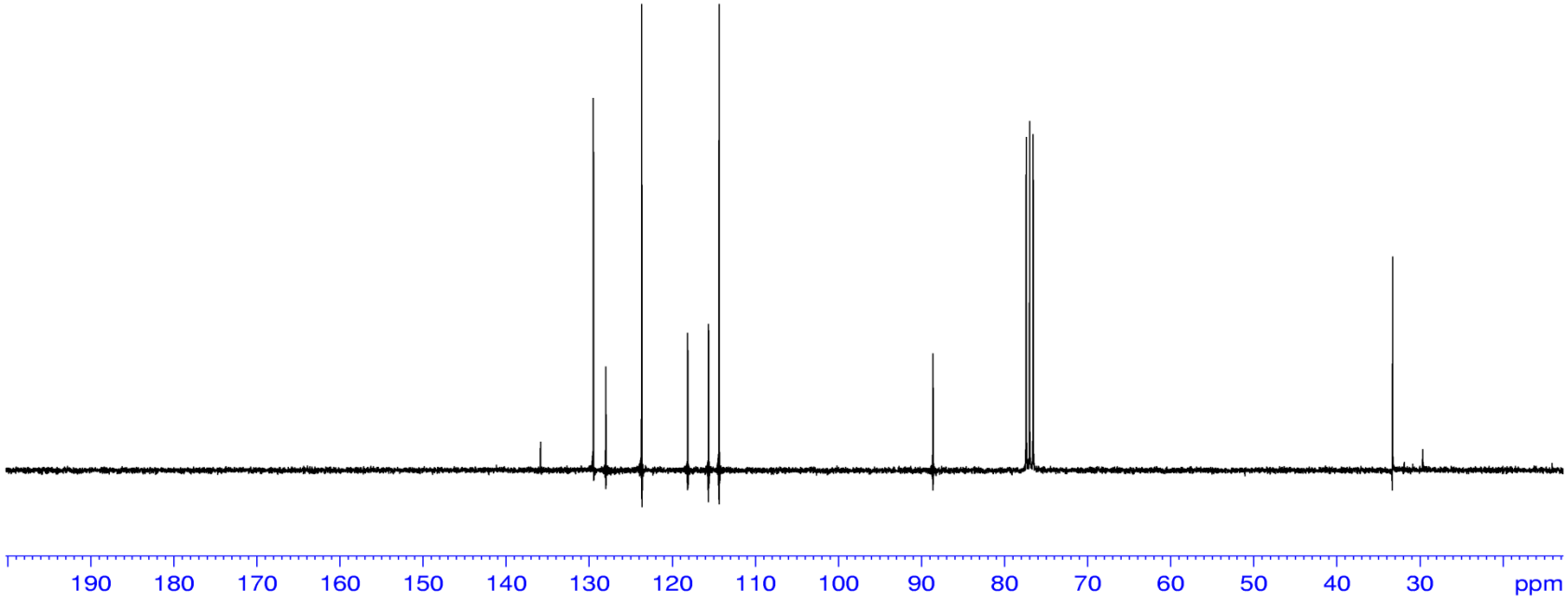
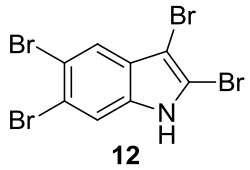


2,3,5,6-Tetrabromo-1*H*-indole **12**; Acetone-D_6, 300 MHz



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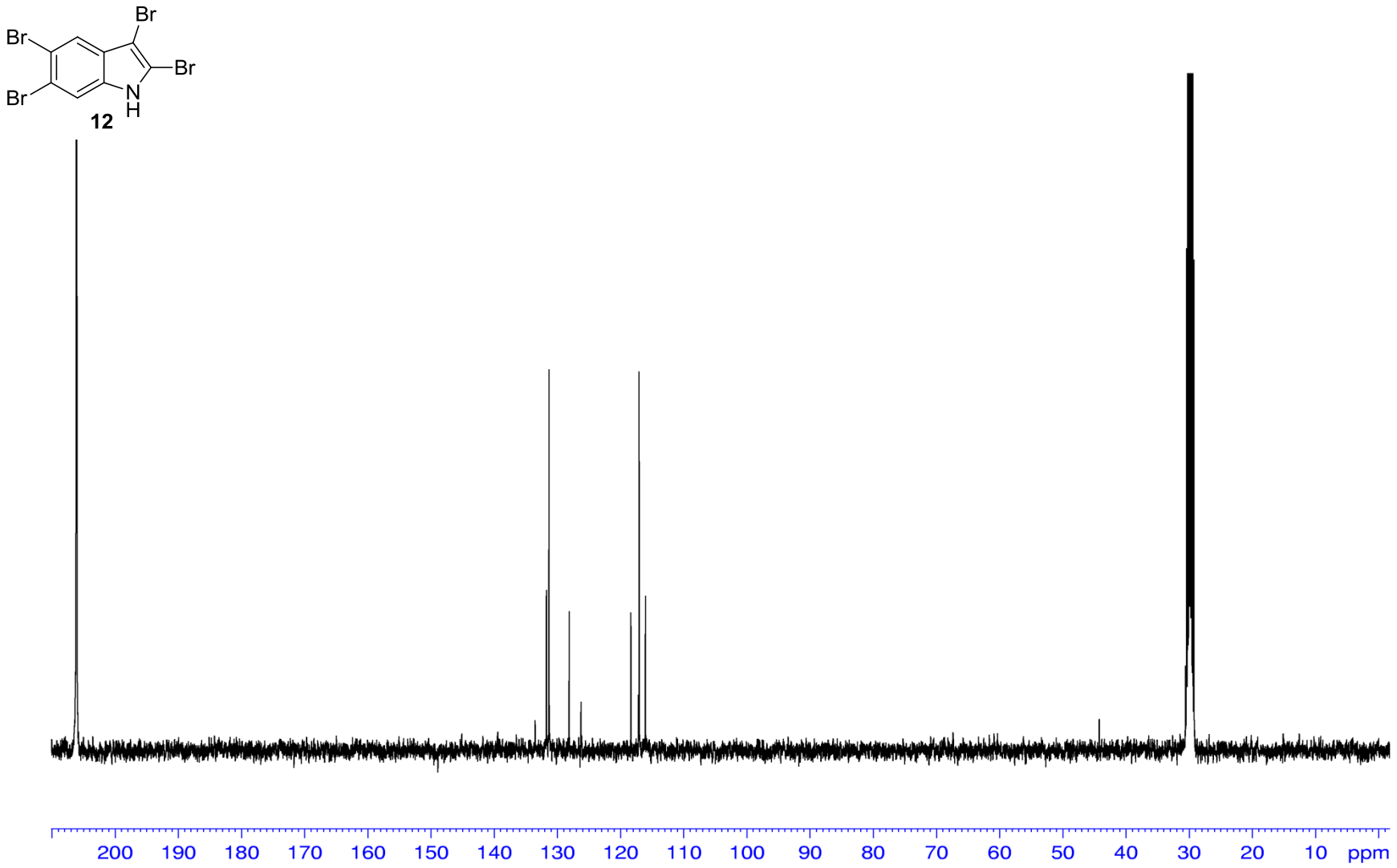
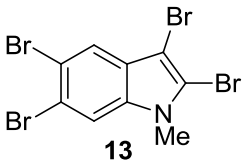
2,3,5,6-Tetrabromo-1*H*-indole **12**; Acetone-D6, 100 MHz



2,3,5,6-Tetrabromo-1-methyl-1*H*-indole **13**; $CDCl_3$, 300 MHz



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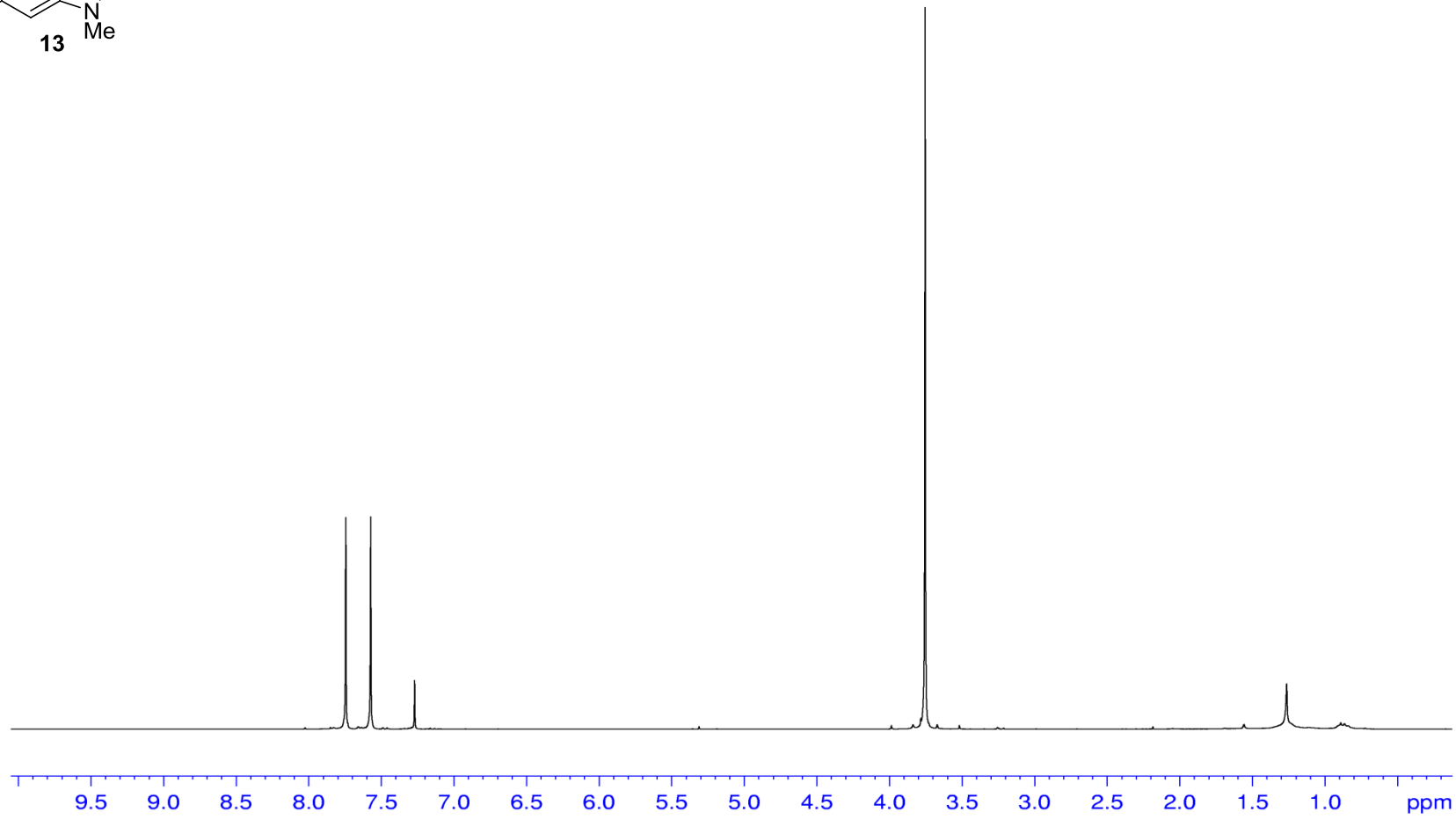
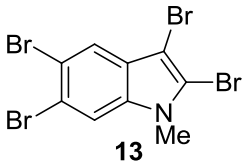


2,3,5,6-Tetrabromo-1-methyl-1*H*-indole **13**; $CDCl_3$, 100 MHz



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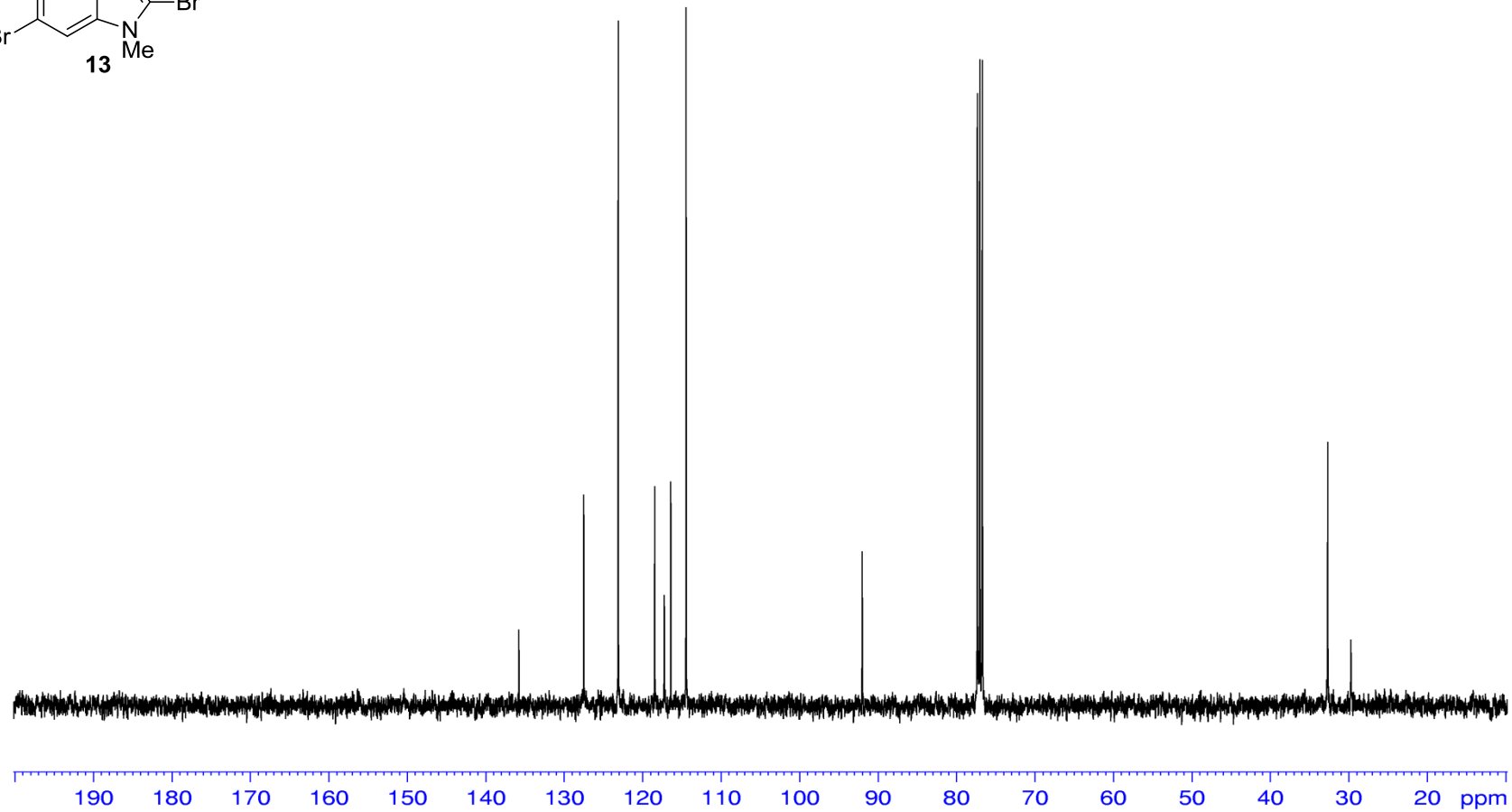
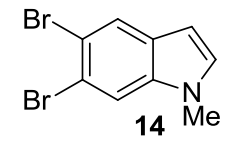


5,6-Dibromo-1-methyl-1*H*-indole **14**; $CDCl_3$, 300 MHz



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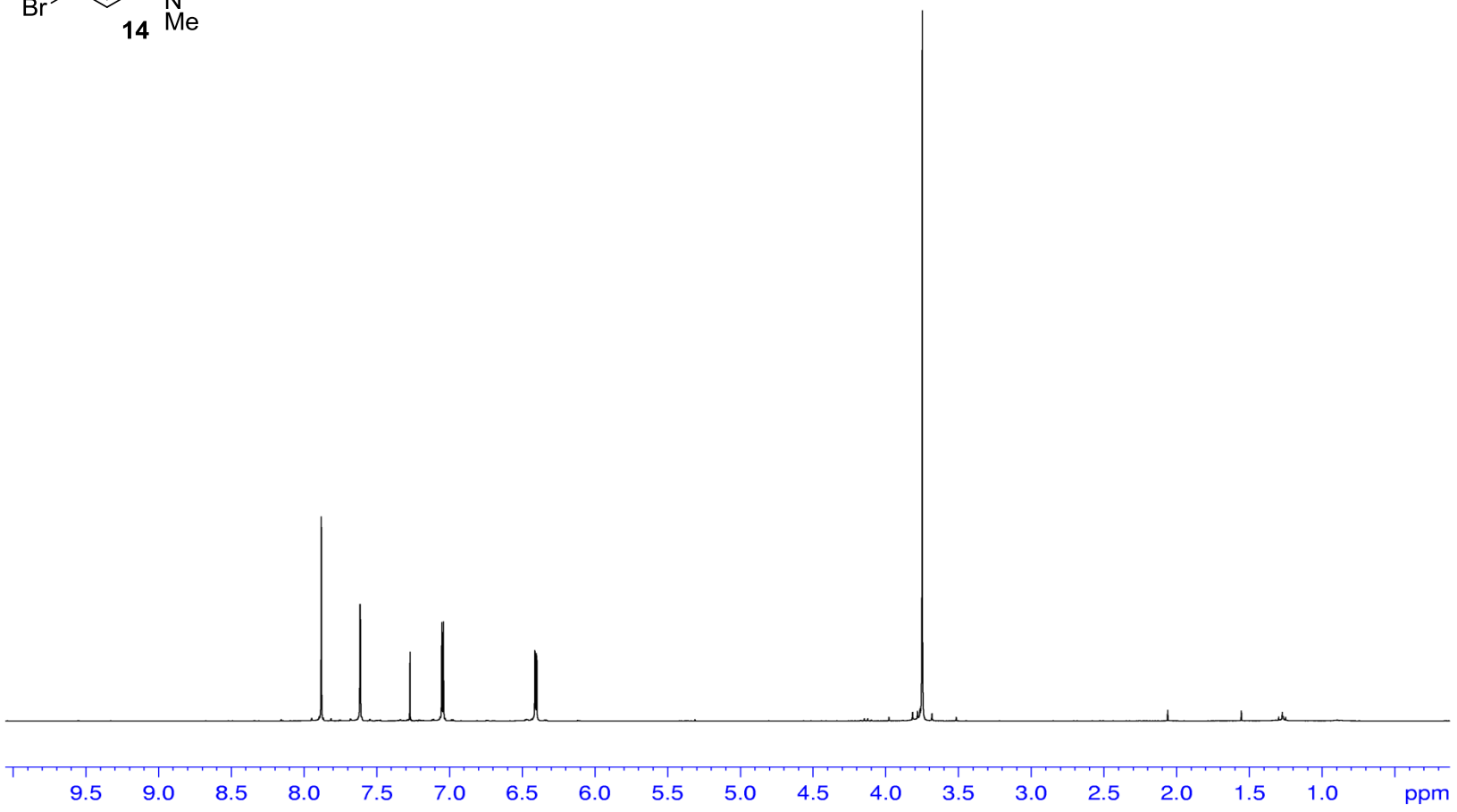
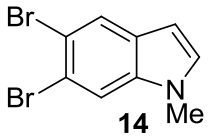


5,6-Dibromo-1-methyl-1*H*-indole **14**; $CDCl_3$, 100 MHz



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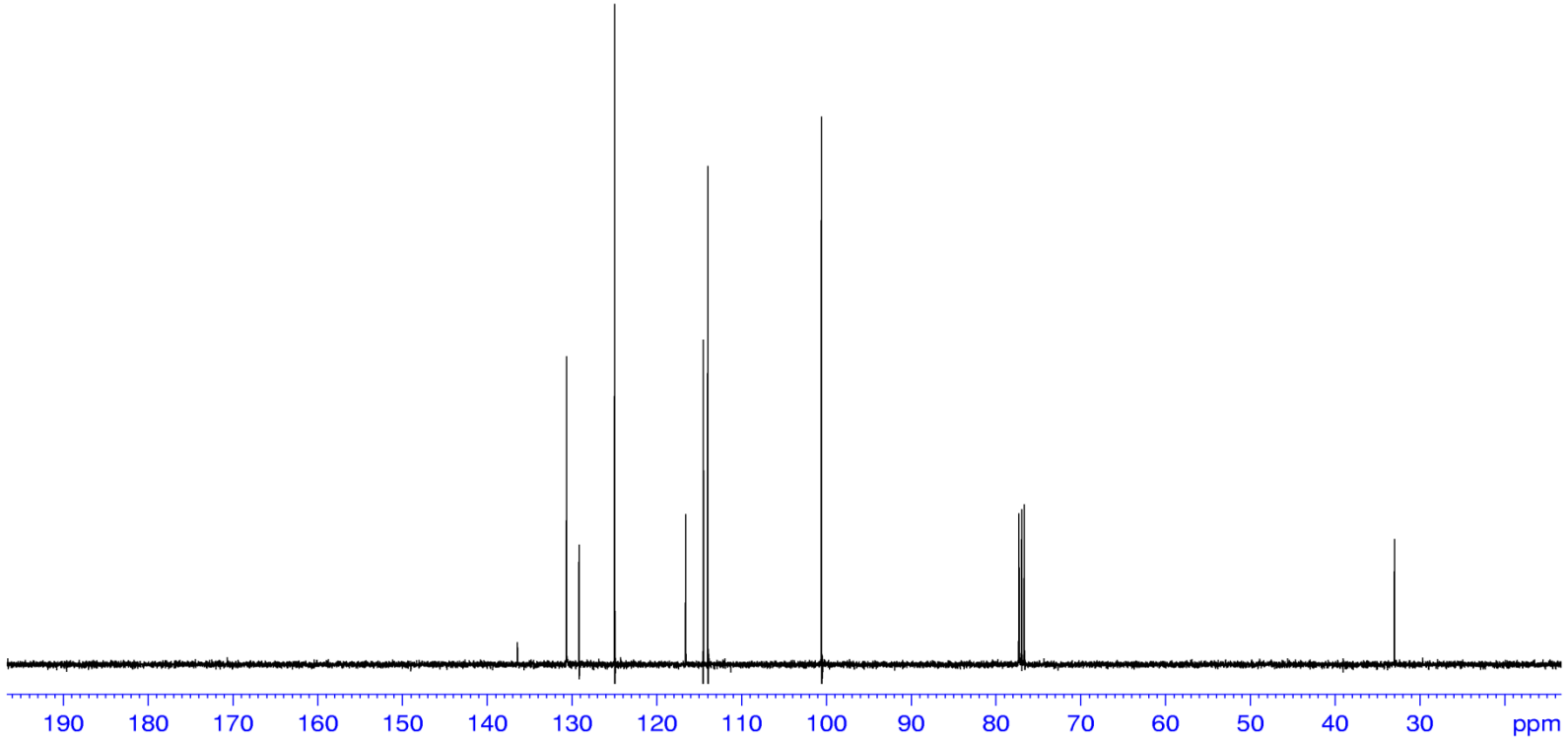
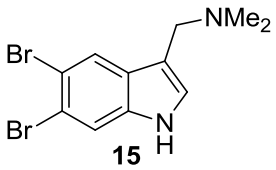
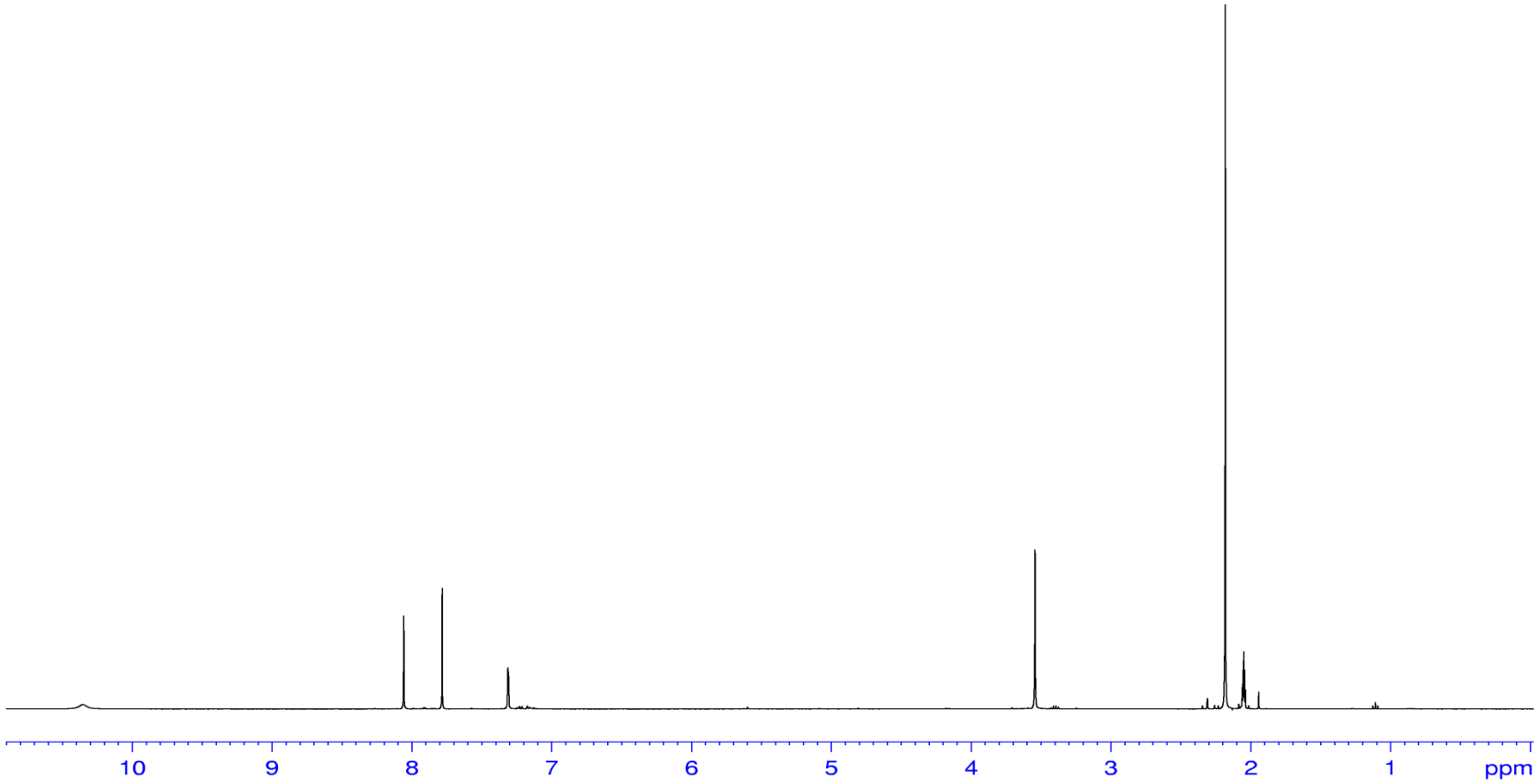


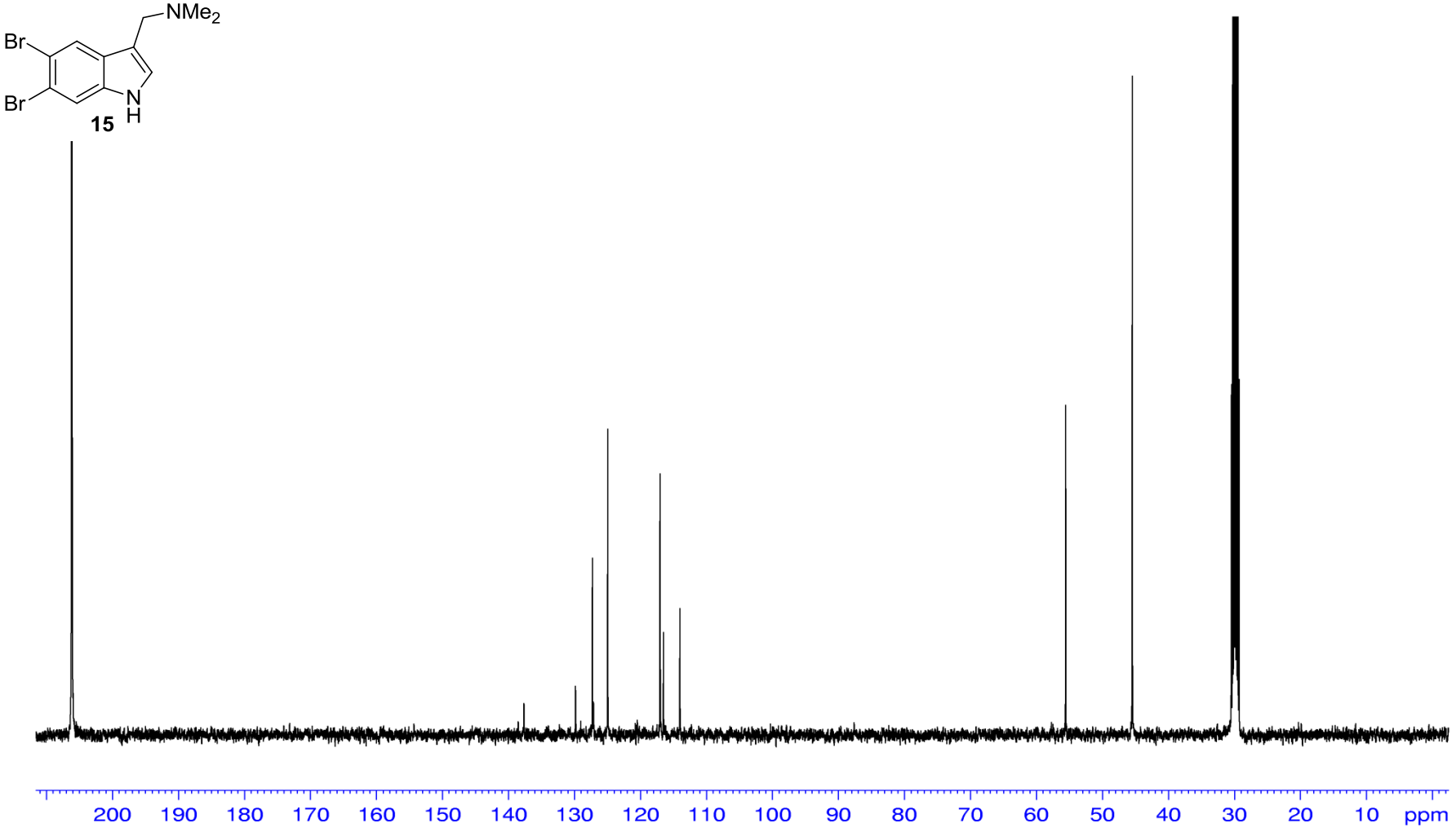
5,6-Dibromogramine [1-(5,6-dibromo-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine] **15**; $CDCl_3$, 400 MHz



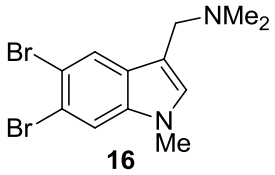
15



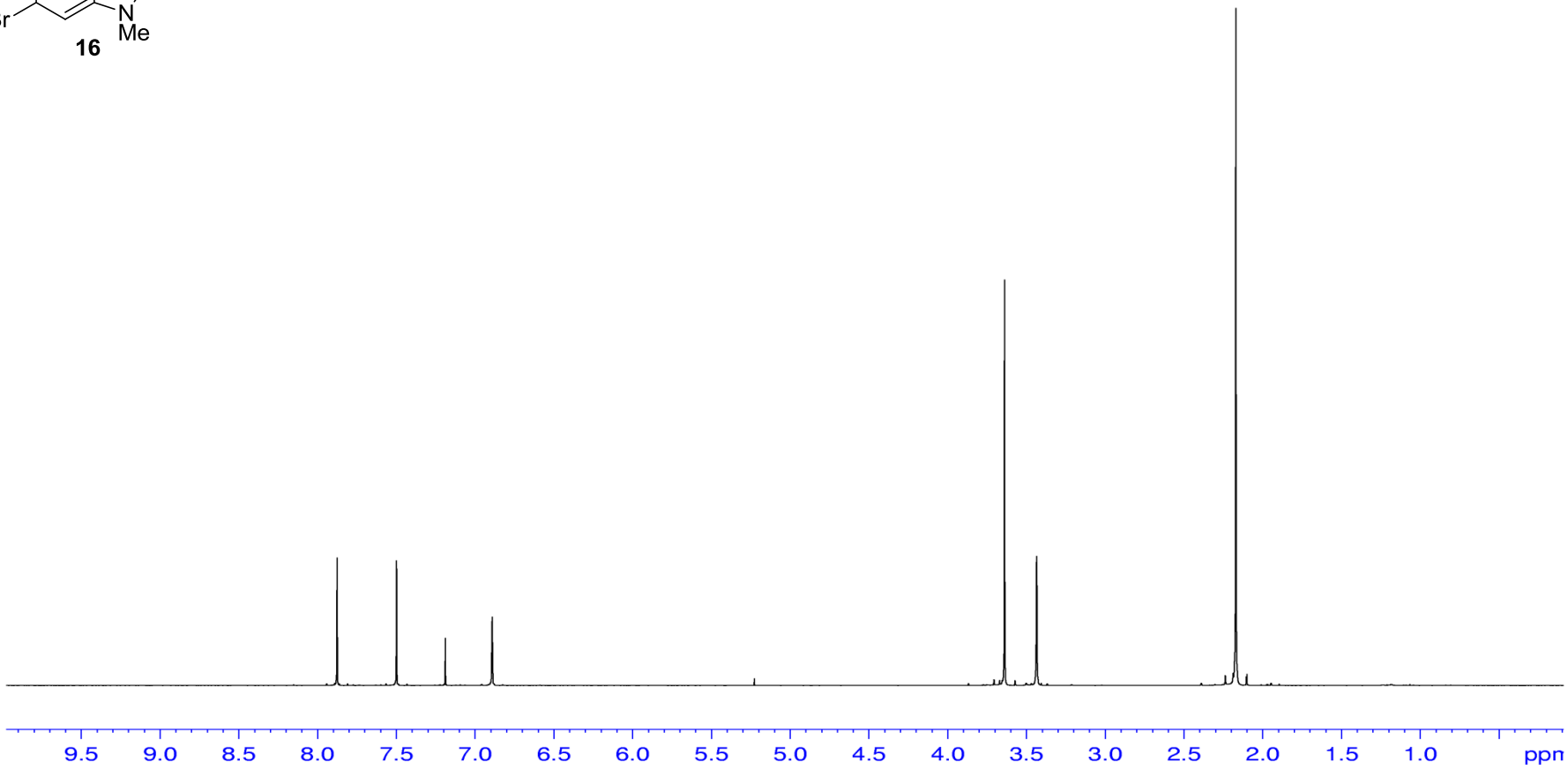
5,6-Dibromogramine [1-(5,6-dibromo-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine] **15**; $CDCl_3$, 100 MHz



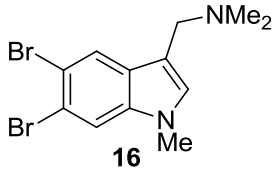
5,6-Dibromo-1-methylgramine [1-(5,6-dibromo-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine] **16**; $CDCl_3$, 300 MHz



16

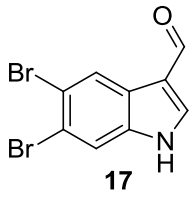


5,6-Dibromo-1-methylgramine [1-(5,6-dibromo-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine] **16**; $CDCl_3$, 100 MHz

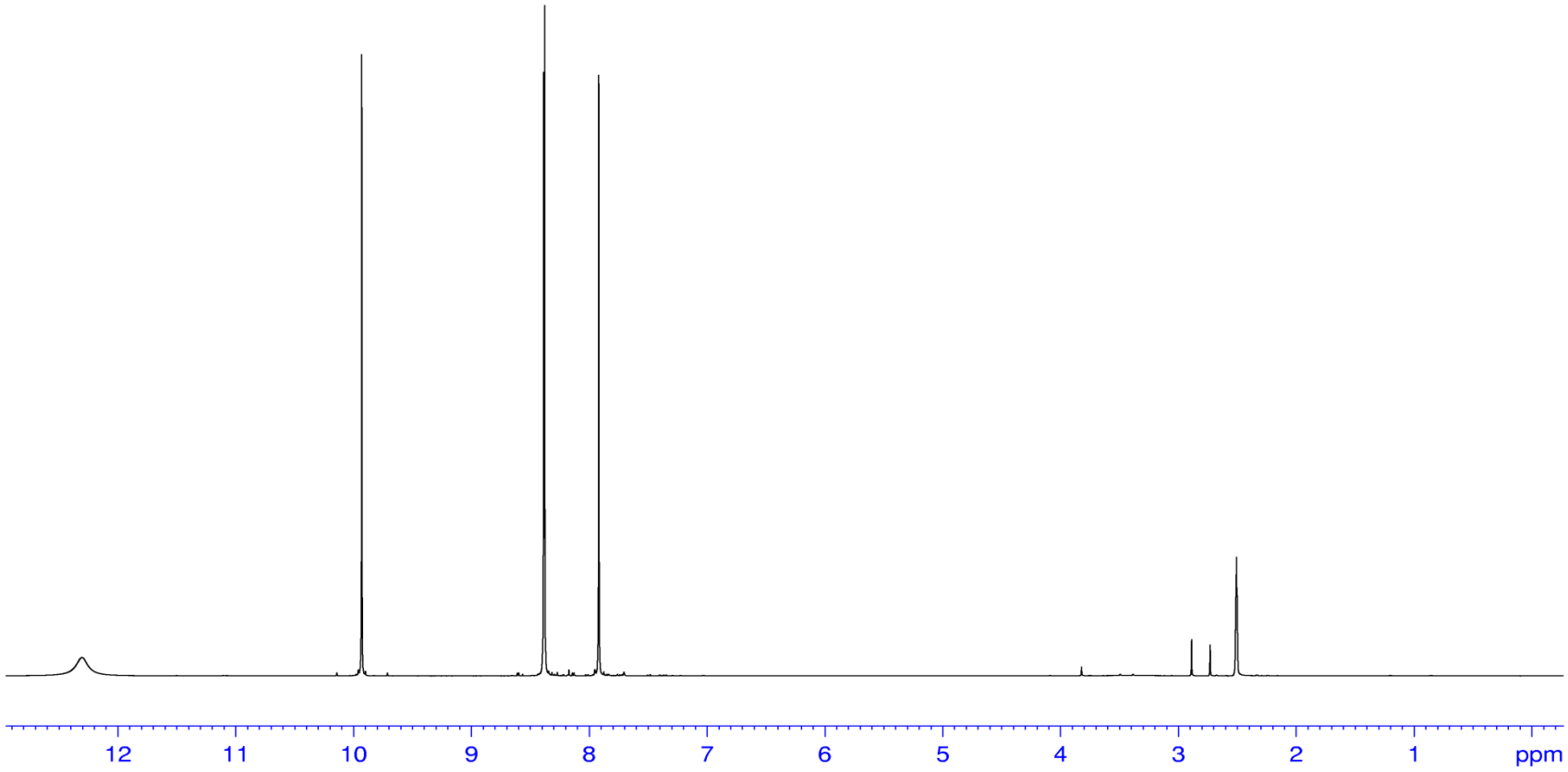


16

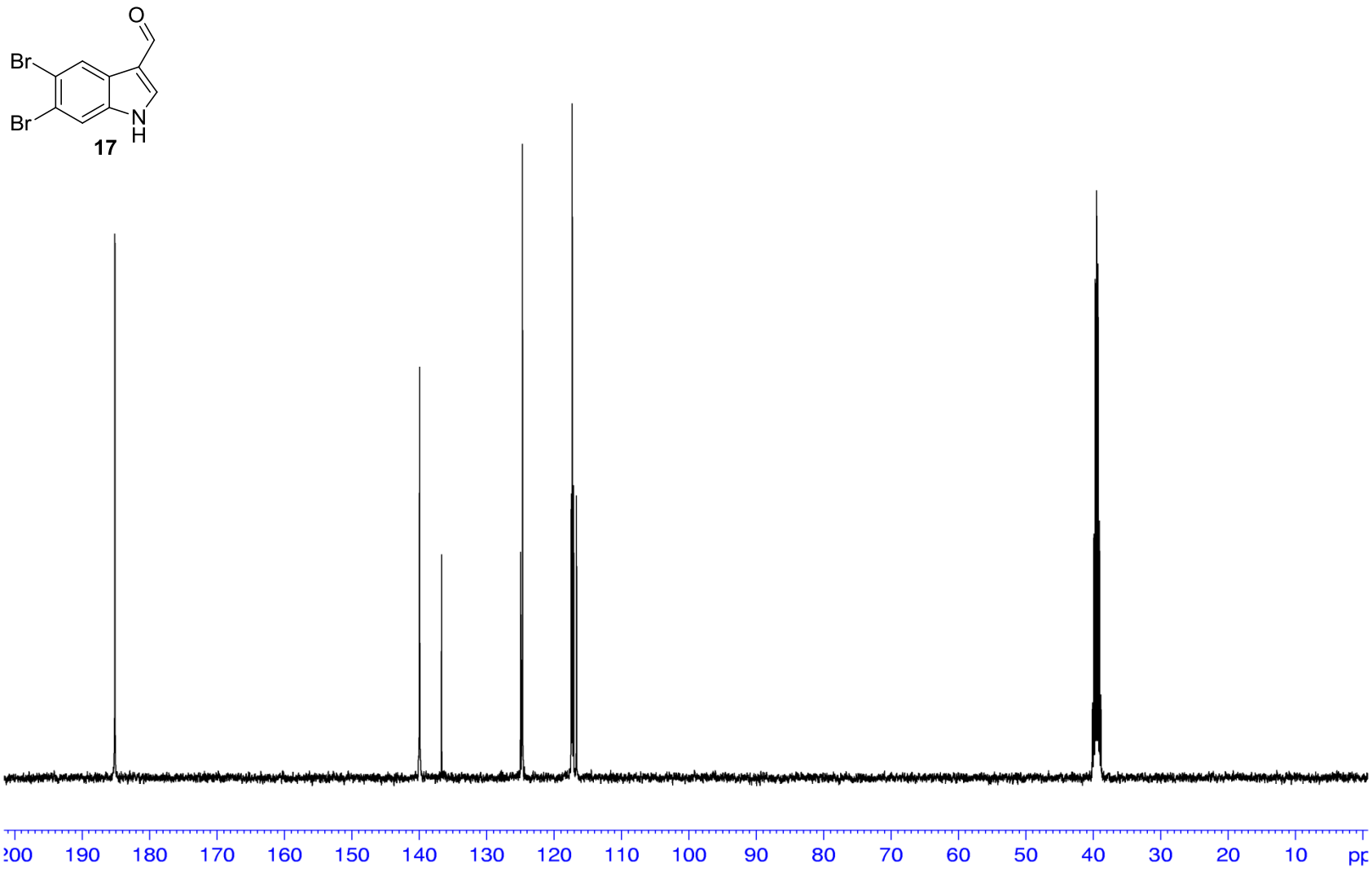
5,6-Dibromo-1-*H*-indole-3-carbaldehyde **17**; DMSO-D_6, 400 MHz



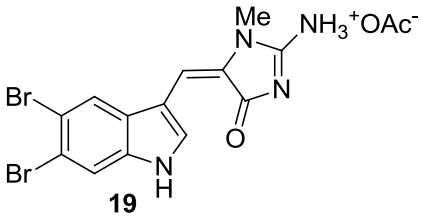
17



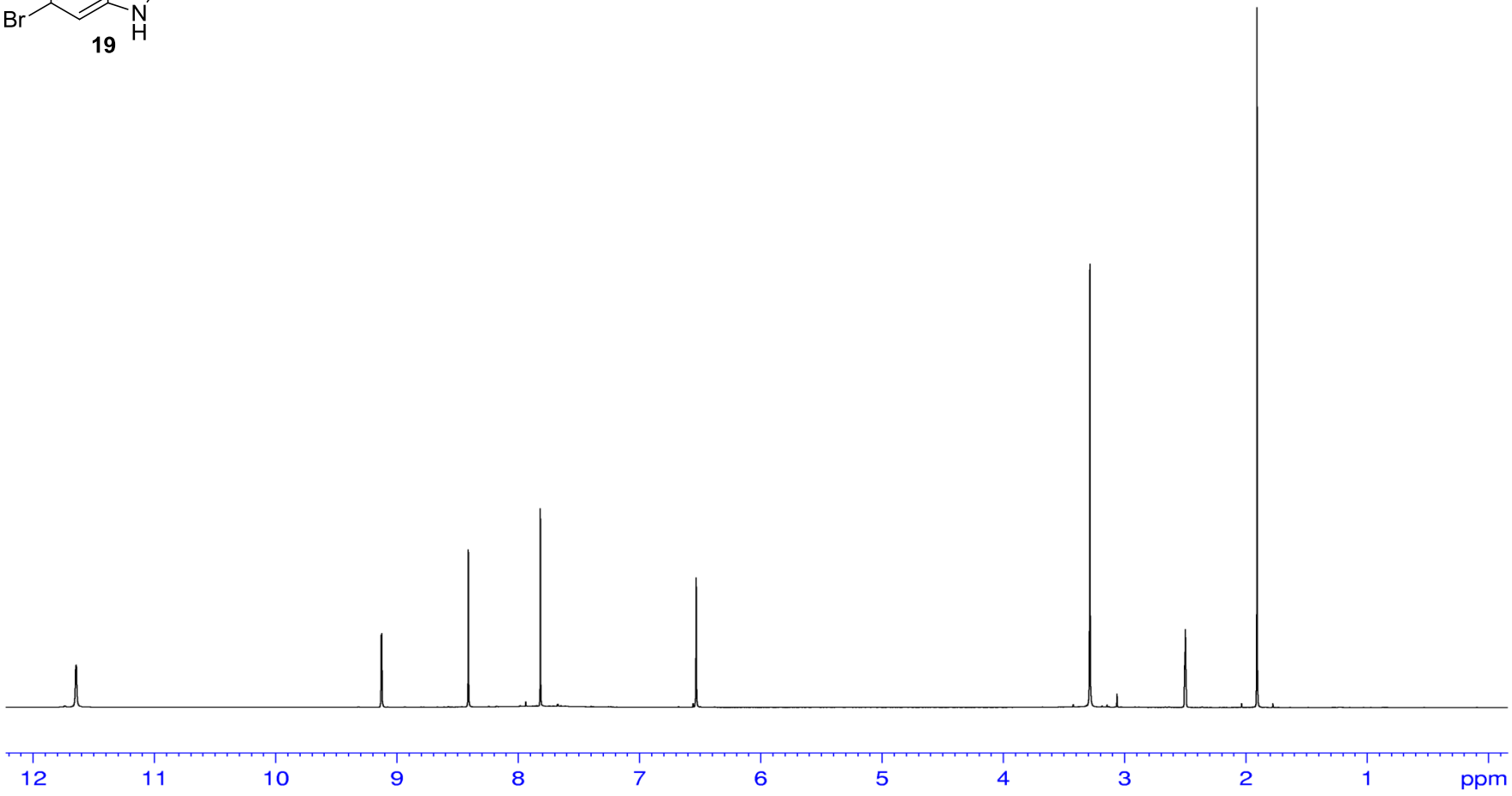
5,6-Dibromo-1-*H*-indole-3-carbaldehyde **17**; DMSO-D_6, 100 MHz



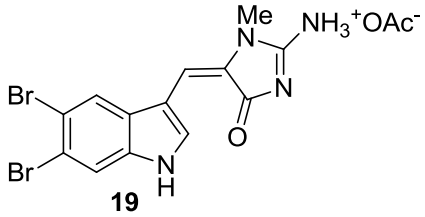
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19** (from method 2); DMSO-D_6, 500 MHz



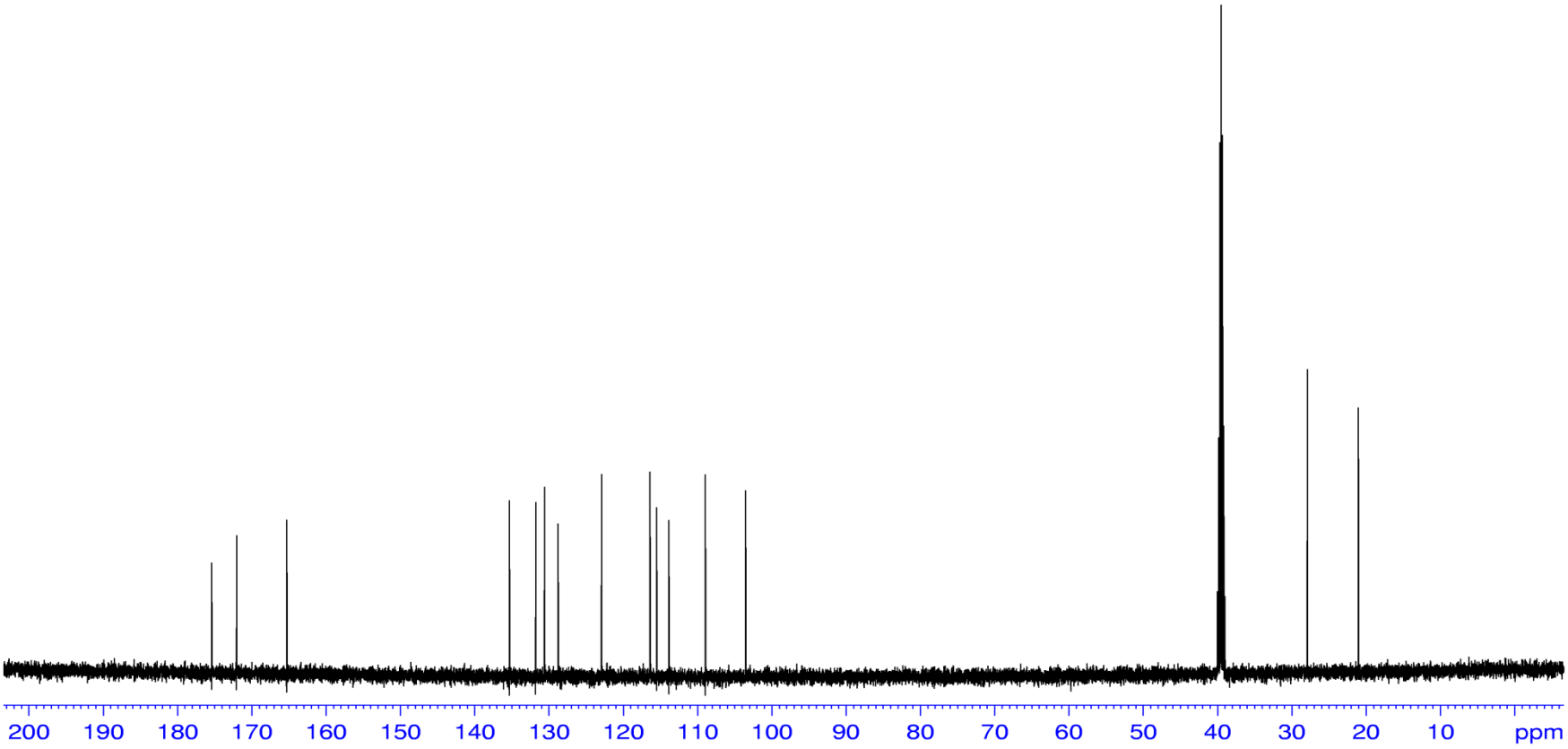
19



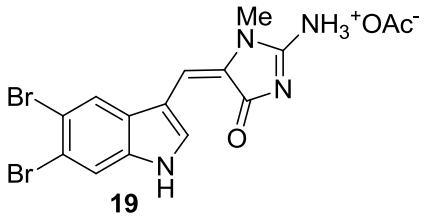
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19** (from method 2); DMSO-D_6, 125 MHz



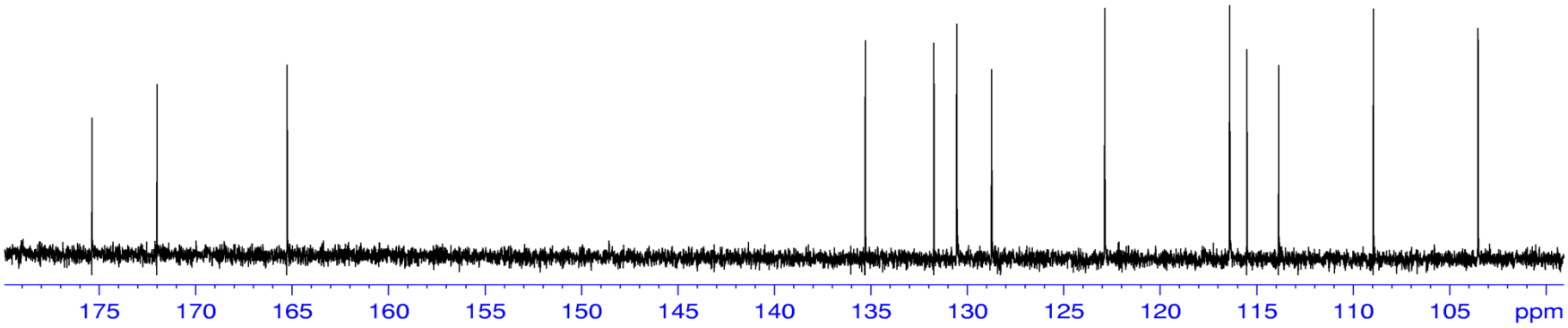
19



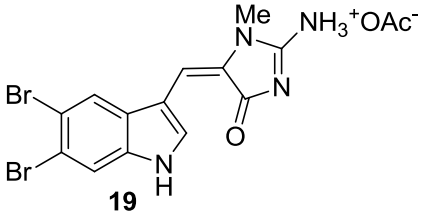
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19** (from method 2); DMSO-D_6, 125 MHz



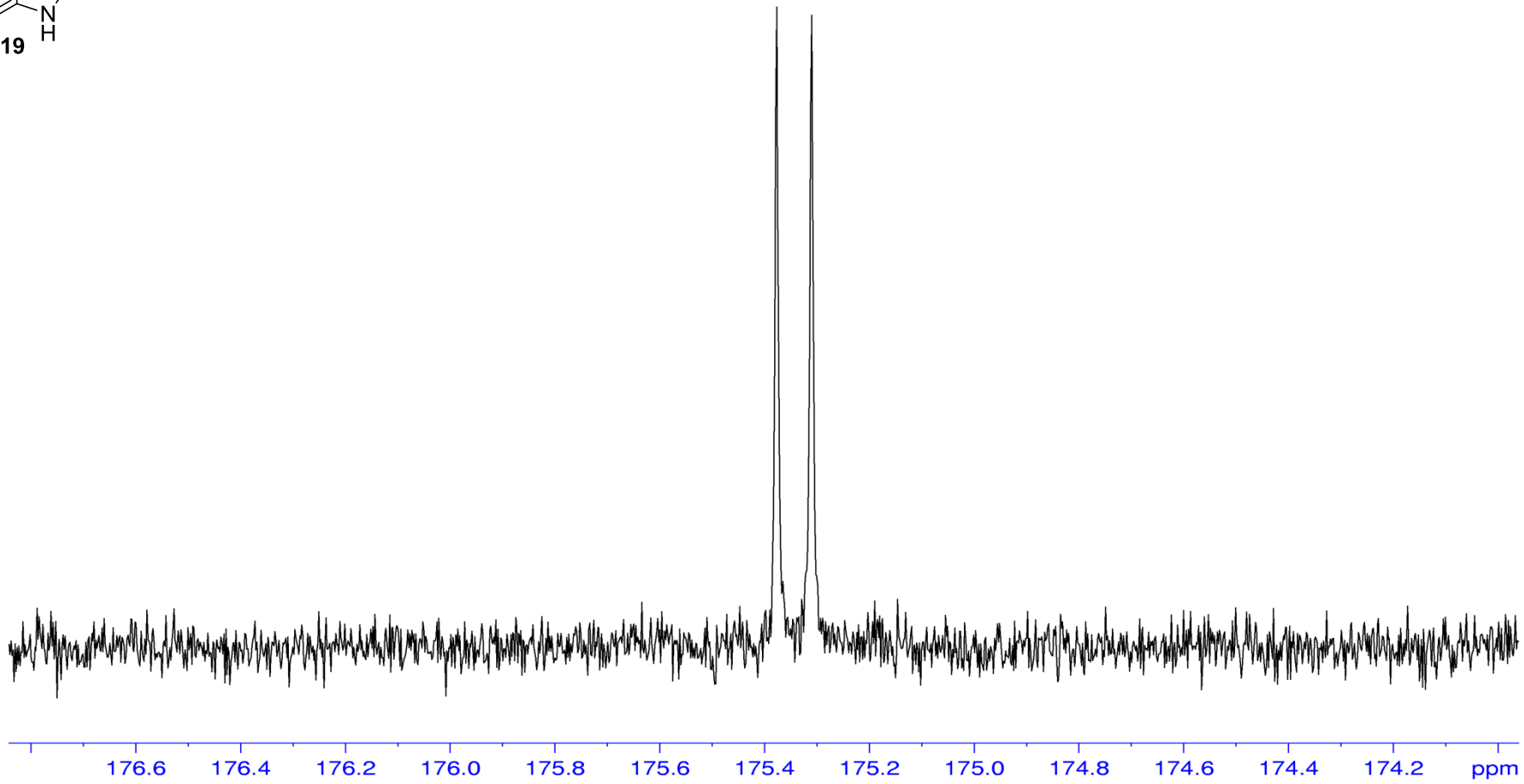
19



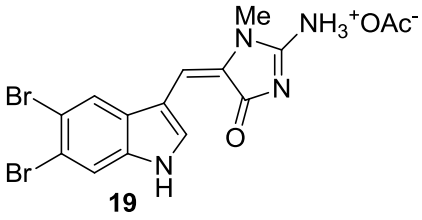
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19**; DMSO-D_6, 125 MHz, carbon-coupled HMBC.



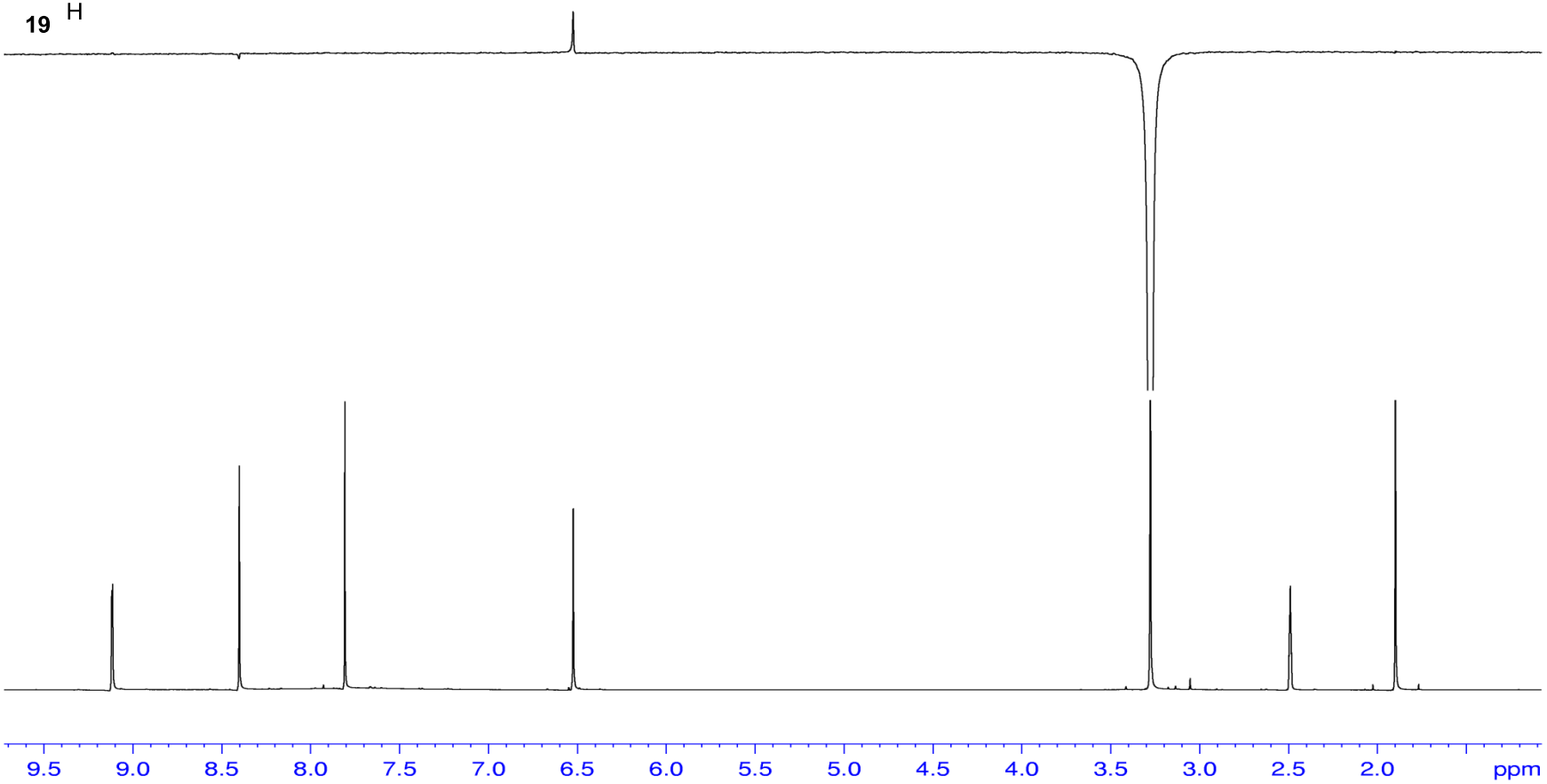
19



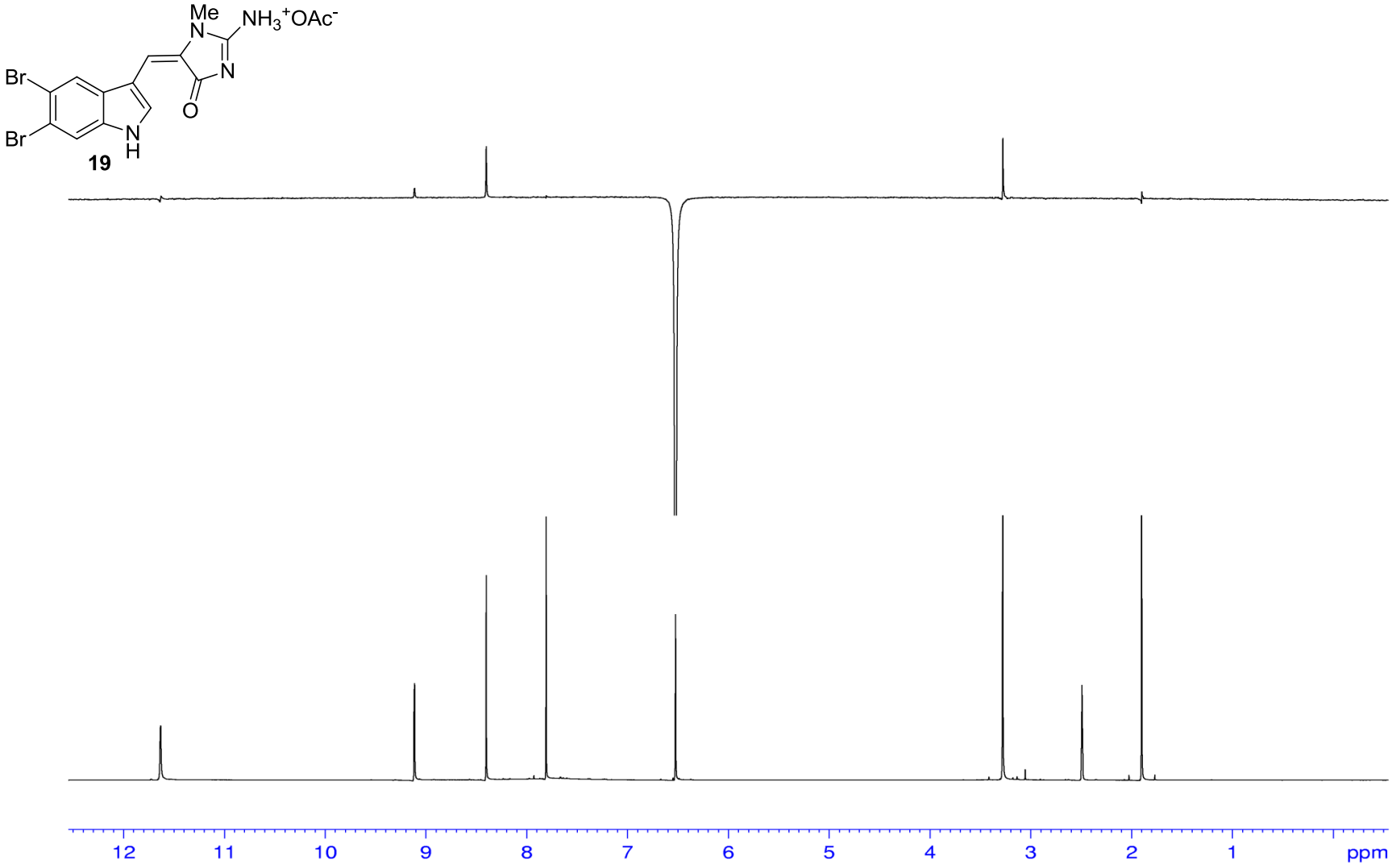
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19**; DMSO-D_6, 500 MHz, nOe irradiation of NMe



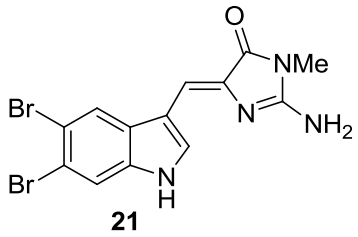
19



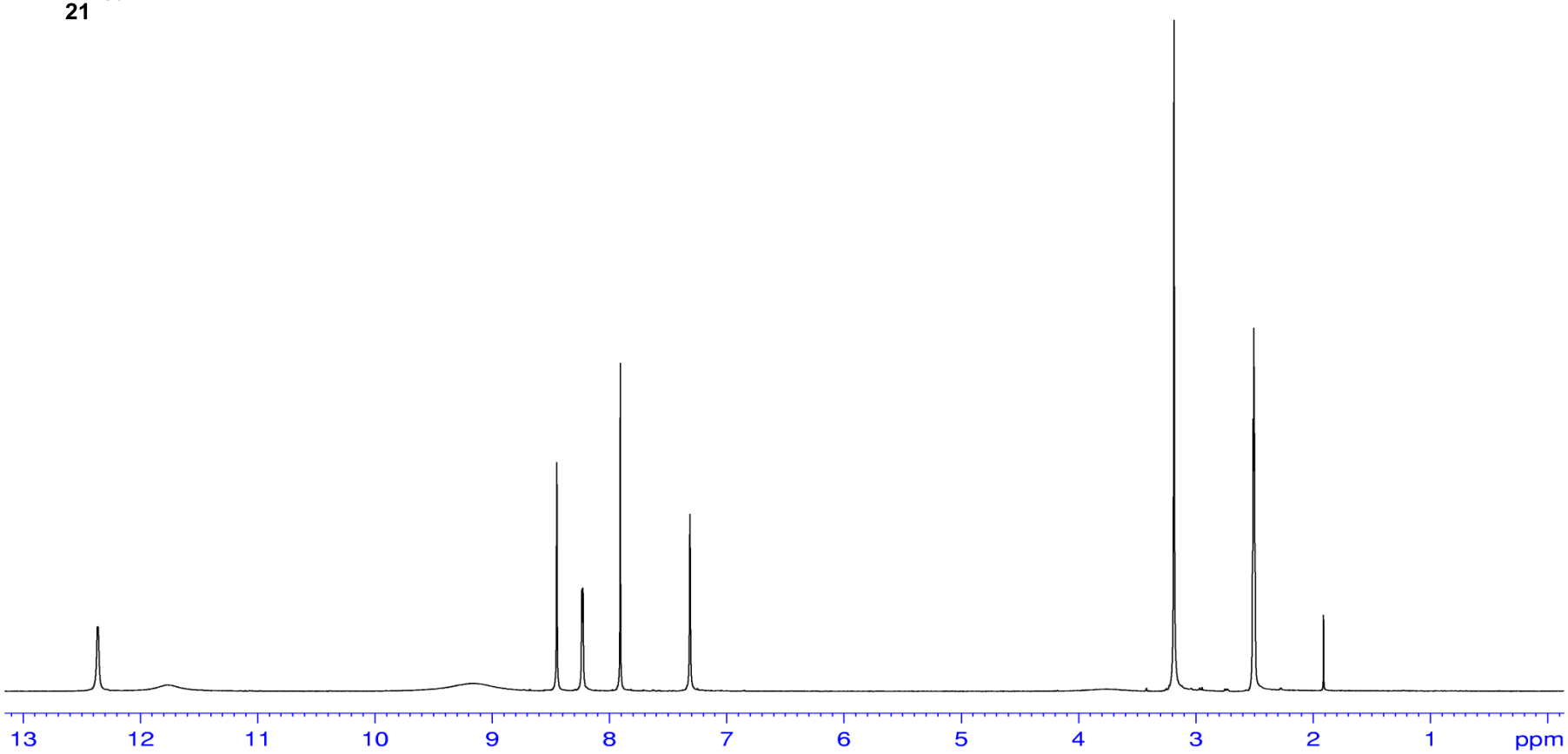
(*E*) 5,6-Dibromo-4'-demethylaplysinopsin acetate salt **19**; DMSO-D_6, 500 MHz, nOe irradiation of H-8



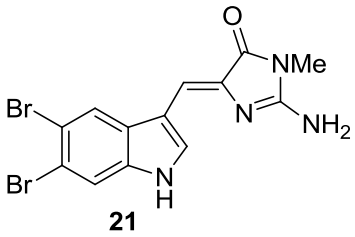
(*Z*) 5,6-Dibromo-2'-demethylaplysinopsin **21** (from method 2); DMSO-D_6, 400 MHz



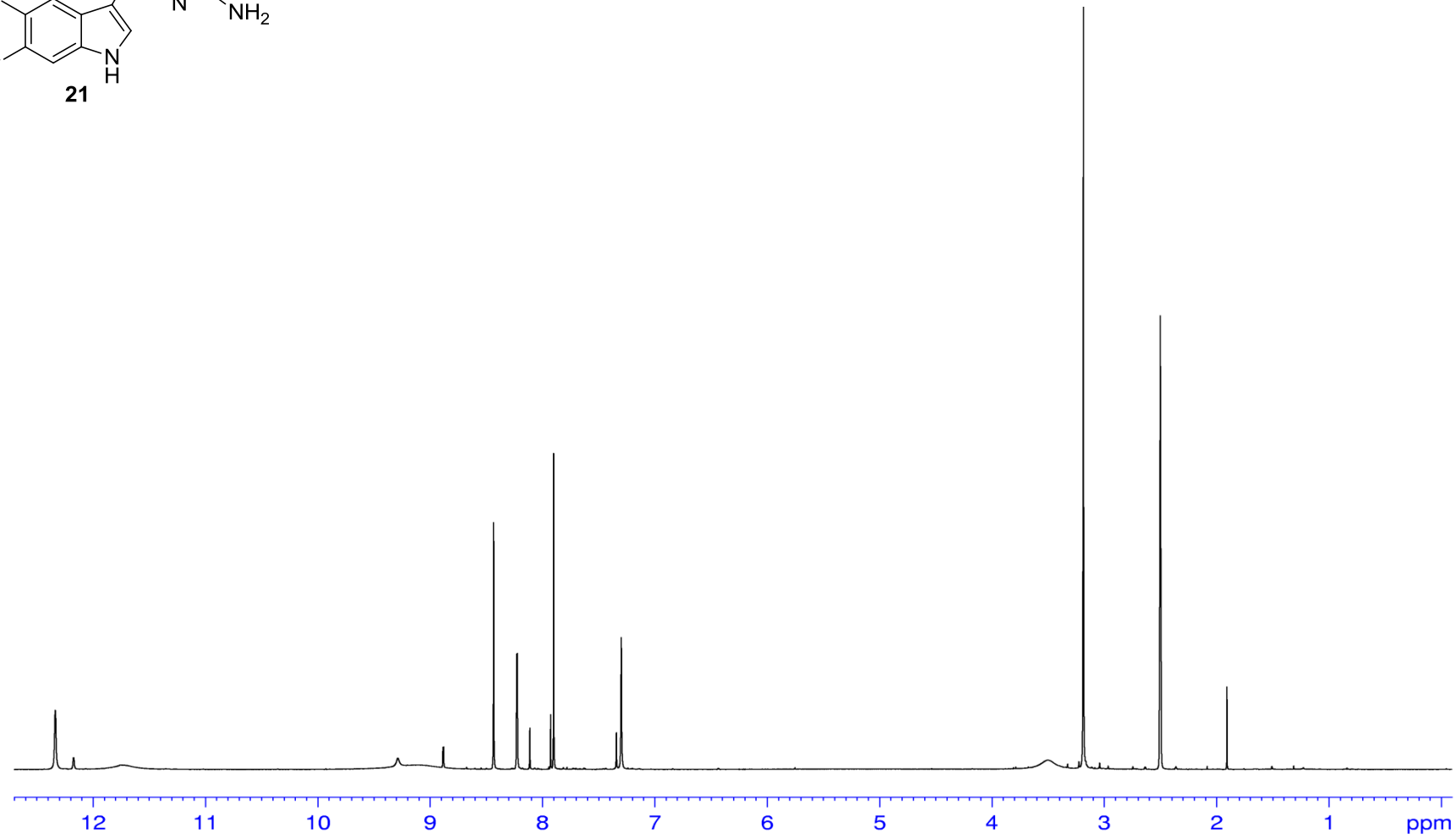
21



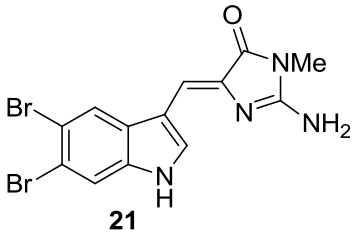
(*Z*) 5,6-Dibromo-2'-demethylaplysinopsin **21** (from method 2) after 1 week in DMSO exposed to sunlight; DMSO-D_6, 500 MHz



21

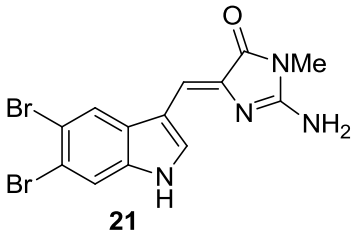


(*Z*) 5,6-Dibromo-2'-demethylaplysinopsin **21** (from method 2) after 1 week in DMSO exposed to sunlight; DMSO-D_6, 125 MHz



21

(*Z*) 5,6-Dibromo-2'-demethylaplysinopsin **21** (from method 2) after 1 week in DMSO exposed to sunlight; DMSO-D_6, 125 MHz



21