

Azomethine Ylide Annulations: Facile Access to Polycyclic Ring Systems

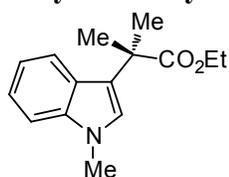
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Supporting Information

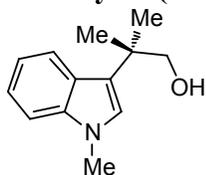
General Information: Reagents and solvents were purchased from commercial sources and were used as received. Toluene was freshly distilled from sodium under nitrogen prior to use. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F₂₅₄ plates. Visualization was accomplished with UV light and permanganate stain, followed by heating. A CEM Discover-S microwave was used for reactions conducted under microwave irradiation. If so mentioned, a silicon carbide passive heating element (diameter: 10 mm, length: 18 mm) was used for efficient microwave absorption. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (¹H-NMR) were recorded on a Varian VNMRS-500 MHz and VNMRS-400 instrument and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm, (CD₃)₂SO at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (¹³C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm, (CD₃)₂SO at 39.5 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Starting materials **3**,¹ **8**,² **10**,³ **16**⁴ and **33b**,⁵ were prepared according to literature methods.

Ethyl 2-methyl-2-(1-methyl-1H-indol-3-yl)propanoate (36): THF (28.8 mL) was added to a flame-dried 200-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to –78 °C, followed by addition of KHMDS (6.5 mL, 0.5 M in toluene, 2.4 mmol). A solution of ethyl 2-(1H-indol-3-yl)-2-methylpropanoate⁶ (0.5g, 2.16 mmol) in 5 mL THF was added via syringe. The resulting mixture was then warmed to 0 °C and stirred for 2 hours before re-cooling to –78 °C. Methyl iodide (0.41 mL, 6.5 mmol) was then added. The mixture was allowed to warm to 0 °C and stirred for 3 hours. The reaction mixture was then placed in a freezer (–20 °C) for 24 hours. Subsequently, the reaction was quenched by addition of water (10 mL) and then extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 75% yield. (R_f = 0.33 in 10% EtOAc/hexanes); mp: 74–75 °C; IR (KBr) 3415, 3121, 3059, 2989, 2975, 2933, 2873, 1718, 1485, 1476, 1458, 1444, 1426, 1394, 1382, 1373, 1361, 1339, 1330, 1300, 1261, 1231, 1178, 1154, 1131, 1108, 1097, 1058, 1023, 995, 826, 769, 744, 671 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.68 (app d, *J* = 8.1 Hz, 1H), 7.29 (app d, *J* = 8.2 Hz, 1H), 7.24–7.19 (m, 1H), 7.11–7.06 (m, 1H), 6.94 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.69 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ

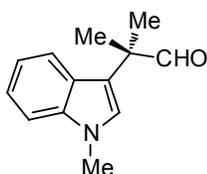


177.0, 137.5, 126.1, 125.3, 121.4, 120.5, 119.3, 118.8, 109.3, 60.7, 42.0, 32.7, 26.3, 14.2; m/z (ESIMS) 246.1 $[M + H]^+$.

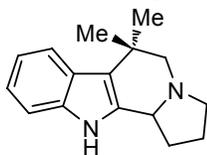
2-Methyl-2-(1-methyl-1H-indol-3-yl)propan-1-ol (37): Compound **36** (0.43 g, 1.75 mmol), dissolved in ether (10 mL), was added dropwise over 30 minutes to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in ether (10 mL). The resulting mixture was then heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature and excess of lithium aluminum hydride was carefully quenched with ice-water (100 mL). The organic layer was separated and the aqueous layer was extracted further with ether (5 x 50 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a colorless oil in 99% yield. (R_f = 0.30 in 30% EtOAc/hexanes); IR (film) 3386, 3047, 2961, 2871, 1613, 1543, 1484, 1464, 1423, 1374, 1360, 1327, 1241, 1151, 1107, 1040, 765, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.80 (app dd, J = 8.1, 0.8 Hz, 1H), 7.33 (app d, J = 8.2 Hz, 1H), 7.25 (ddd, J = 8.2, 5.4, 1.0 Hz, 1H), 7.15–7.09 (m, 1H), 6.91 (app d, J = 3.4 Hz, 1H), 3.80 (d, J = 2.4 Hz, 2H), 3.77 (s, 3H), 1.47 (s, 6H), 1.31 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.8, 127.0, 126.0, 121.4, 120.9, 119.4, 118.6, 109.5, 71.5, 37.6, 32.6, 25.4; m/z (ESIMS) 204.1 $[M + H]^+$.



2-Methyl-2-(1-methyl-1H-indol-3-yl)propanal (33a): Dichloromethane (4.3 mL) was added to a flame-dried 25-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to -78°C and oxalyl chloride (0.20 mL, 2.4 mmol) was added. DMSO (0.32 mL, 4.5 mmol) was then added dropwise and the mixture was allowed to stir at -78°C for 10 minutes. Subsequently, **37** (0.35 g, 1.7 mmol), dissolved in 4 mL of dichloromethane, was added dropwise at -78°C . After stirring for 15 minutes, triethylamine (1.25 mL, 9.0 mmol) was added dropwise and the mixture was allowed to stir for another 15 minutes at -78°C . The flask was then transferred into an ice bath and stirred for 10 minutes. The reaction mixture was poured into ice-cold 1 M HCl solution (15 mL), extracted with dichloromethane (3 x 10 mL), washed with pH 7.4 buffer (10 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a pink solid in 68% yield. (R_f = 0.30 in 10% EtOAc/hexanes); mp: $59\text{--}60^\circ\text{C}$; IR (KBr) 3409, 3120, 3051, 2986, 2966, 2925, 2807, 2708, 1713, 1676, 1537, 1485, 1463, 1419, 1389, 1379, 1359, 1329, 1253, 1232, 1135, 1108, 1015, 980, 908, 842, 828 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.50 (s, 1H), 7.56 (app d, J = 8.1 Hz, 1H), 7.32 (app d, J = 8.3 Hz, 1H), 7.26–7.21 (m, 1H), 7.13–7.06 (m, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.2, 137.6, 126.6, 126.2, 121.9, 120.2, 119.3, 115.1, 109.5, 46.5, 32.8, 21.9; m/z (ESIMS) 202.2 $[M + H]^+$.

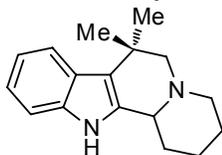


6,6-Dimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (4): Toluene (5 mL) was added to a round-bottom flask containing L-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130°C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **3** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The residue was purified by flash column



chromatography. The title compound was obtained as a yellow solid in 80% yield. ($R_f = 0.28$ in 25% MeOH/EtOAc); mp: 44–47 °C; IR (film) 3398, 3187, 3053, 2956, 2874, 1656, 1620, 1459, 1386, 1361, 1331, 1287, 1264, 1218, 1149, 1093, 1060, 738, 765, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (br s, 1H), 7.68 (app dd, $J = 13.0, 5.3$ Hz, 1H), 7.34–7.28 (m, 1H), 7.16–7.03 (comp, 2H), 3.62 (dd, $J = 9.5, 6.9$ Hz, 1H), 3.08 (ddd, $J = 10.1, 8.3, 3.2$ Hz, 1H), 2.87 (d, $J = 11.3$ Hz, 1H), 2.81 (app dd, $J = 18.2, 8.3$ Hz, 1H), 2.51 (d, $J = 11.3$ Hz, 1H), 2.20–2.08 (m, 1H), 2.01 (app qdd, $J = 14.6, 9.1, 6.4$ Hz, 1H), 1.86–1.67 (comp, 2H), 1.49 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.3, 133.9, 125.9, 120.9, 119.7, 119.1, 116.3, 111.1, 63.2, 59.3, 53.4, 33.7, 28.7, 28.3, 27.8, 22.8; m/z (ESIMS) 241.2 $[\text{M} + \text{H}]^+$.

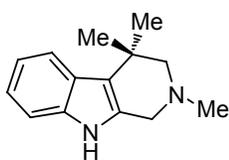
7,7-Dimethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (5): Toluene (5 mL) was added



to a round-bottom flask containing DL-pipecolic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **3** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent

to the addition, the reaction mixture was heated under reflux for an additional 24 hours. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 90% yield. ($R_f = 0.35$ in 30% EtOAc/hexanes); mp: 46–48 °C; IR (film) 3414, 3261, 3053, 2935, 2857, 2796, 2750, 1618, 1459, 1442, 1391, 1373, 1357, 1321, 1307, 1283, 1265, 1205, 1127, 1110, 1082, 1050, 764, 738 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.73–7.62 (comp, 2H), 7.31 (app d, $J = 7.9$ Hz, 1H), 7.19–7.08 (comp, 2H), 3.13 (dd, $J = 10.8, 2.5$ Hz, 1H), 2.96 (app d, $J = 11.1$ Hz, 1H), 2.59 (d, $J = 11.2$ Hz, 1H), 2.46 (d, $J = 11.2$ Hz, 1H), 2.40–2.30 (m, 1H), 2.03 (app dd, $J = 16.4, 13.5$ Hz, 1H), 1.93 (app d, $J = 12.3$ Hz, 1H), 1.82–1.67 (comp, 2H), 1.62–1.40 (comp, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.1, 134.5, 126.1, 120.7, 119.7, 119.0, 116.7, 110.9, 68.8, 60.4, 55.8, 32.8, 30.1, 28.4, 27.0, 25.8, 24.5; m/z (ESIMS) 255.2 $[\text{M} + \text{H}]^+$.

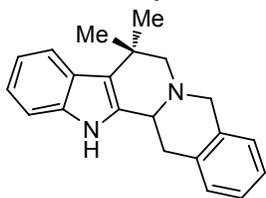
2,4,4-Trimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (6): Sarcosine (6.0 mmol) and **3** (0.5



mmol) along with 10 mL of xylenes were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 20 hours, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent, the residue was purified by flash column chromatography. The title compound was obtained as a white

solid in 61% yield. ($R_f = 0.31$ in 70% EtOAc/hexanes); mp: 174–176 °C; IR (KBr) 3140, 3103, 3060, 2925, 2851, 2796, 2752, 1453, 1397, 1384, 1360, 1330, 1299, 1263, 1238, 1179, 1103, 1031, 881, 742 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.94 (br s, 1H), 7.64 (app t, $J = 8.4$ Hz, 1H), 7.22 (app dd, $J = 11.7, 4.5$ Hz, 1H), 7.13–7.04 (comp, 2H), 3.38 (s, 2H), 2.45 (s, 2H), 2.44 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.3, 130.8, 125.8, 120.9, 119.6, 119.0, 116.6, 111.1, 68.9, 52.8, 46.1, 33.1, 27.8; m/z (ESIMS) 215.1 $[\text{M} + \text{H}]^+$.

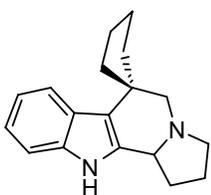
8,8-Dimethyl-5,7,8,13,13b,14-hexahydroindolo[2',3':3,4]pyrido[1,2-b]isoquinoline (7): (*S*)-(-)-



1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (1.0 mmol) and **3** (0.5 mmol) along with 10 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was sealed and irradiated for 20 minutes (250 °C, 160 psi). The reaction mixture was then allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was

obtained as a light orange-colored solid in 52% yield and **23** was obtained as a light yellow solid in 25% yield. ($R_f = 0.36$ in 15% EtOAc/hexanes); mp: 58–61 °C; IR (KBr) 3405, 3049, 2952, 2923, 2862, 2797, 2738, 1491, 1458, 1374, 1356, 1340, 1320, 1309, 1263, 1146, 1107, 1085, 742, 686 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.76 (br s, 1H), 7.71 (app d, $J = 7.8$ Hz, 1H), 7.36 (app dd, $J = 8.0, 0.6$ Hz, 1H), 7.24–7.07 (comp, 6H), 4.06 (d, $J = 14.9$ Hz, 1H), 3.74 (d, $J = 14.9$ Hz, 1H), 3.64 (dd, $J = 11.4, 3.6$ Hz, 1H), 3.19 (dd, $J = 15.5, 3.6$ Hz, 1H), 3.06–2.97 (m, 1H), 2.82 (d, $J = 11.2$ Hz, 1H), 2.58 (d, $J = 11.2$ Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.5, 134.9, 133.5, 133.3, 128.7, 126.5, 126.3, 126.1, 125.9, 121.2, 119.9, 119.3, 117.4, 111.0, 67.4, 57.7, 56.5, 34.9, 32.7, 28.4, 26.9; m/z (ESIMS) 303.2 $[\text{M} + \text{H}]^+$.

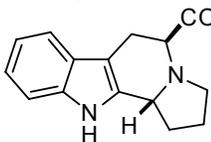
1',2',3',5',11',11b'-Hexahydrospiro[cyclopentane-1,6'-indolizino[8,7-b]indole] (9): Toluene (5 mL)



was added to a round-bottom flask containing L-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **8** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours.

The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a light brown solid in 79% yield. ($R_f = 0.20$ in 20% MeOH/EtOAc); mp: 60–62 °C; IR (film) 3396, 3142, 3053, 2952, 2869, 1453, 1332, 1263, 1181, 1061, 1013, 738, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.22 (br s, 1H), 7.61 (app t, $J = 10.1$ Hz, 1H), 7.28 (app t, $J = 7.6$ Hz, 1H), 7.15–7.03 (comp, 2H), 3.68 (dd, $J = 8.9, 7.5$ Hz, 1H), 3.12–3.01 (m, 1H), 2.94 (d, $J = 11.5$ Hz, 1H), 2.87–2.76 (m, 1H), 2.57 (d, $J = 11.5$ Hz, 1H), 2.30–2.06 (comp, 3H), 2.04–1.89 (comp, 3H), 1.87–1.71 (comp, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.5, 134.6, 125.4, 120.9, 119.2, 119.1, 115.4, 111.2, 61.1, 59.0, 53.2, 44.0, 38.0, 38.0, 28.6, 25.9, 25.8, 23.0; m/z (ESIMS) 267.2 $[\text{M} + \text{H}]^+$.

Methyl 2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-5-carboxylate (11): L-Proline (1.0

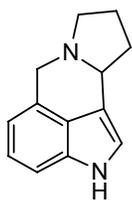


mmol) and **10** (0.5 mmol) along with 10 mL of xylenes were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 1.75 hours, the reaction mixture was allowed to cool to room temperature and concentrated under

reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a mixture of diastereomers in 52% yield, dr = 70:30 as determined by integration of one set of ^1H -NMR signals (δ_{major} 3.66 ppm, δ_{minor} 3.84 ppm). The relative configuration of the major diastereomer was determined by NOSY. ($R_f = 0.15$ in EtOAc); IR (film) 3395, 3055, 2951, 2874, 1735, 1621, 1451, 1360, 1328, 1305, 1267, 1206, 1177, 1141, 1107, 1010, 908, 736, 702, 644 cm^{-1} ; ^1H NMR of the major diastereomer (500 MHz, CDCl_3) δ 7.74 (br s, 1H), 7.53–7.46 (m, 1H), 7.34–7.28 (m, 1H), 7.19–7.07 (comp, 2H), 4.75–4.66 (m, 1H), 4.13 (app t, $J = 4.2$ Hz, 1H), 3.66 (s, 3H), 3.22–

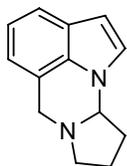
3.17 (comp, 2H), 3.01–2.93 (m, 1H), 2.85 (app dd, $J = 16.1, 8.1$ Hz, 1H), 2.44–2.30 (m, 1H), 2.04–1.70 (comp, 3H); ^{13}C NMR of diastereomers (125 MHz, CDCl_3) δ 173.2, 172.8, 136.2, 136.0, 135.1, 134.7, 127.2, 127.1, 121.8, 121.6, 119.7, 119.4, 118.1, 110.8, 110.7, 107.3, 105.2, 58.7, 58.1, 57.5, 52.8, 52.3, 52.1, 50.3, 44.3, 30.2, 28.8, 23.1(4), 23.1(3), 19.7, 19.0; m/z (ESIMS) 271.2 $[\text{M} + \text{H}]^+$.

2,6,8,9,10,10a-Hexahydrodipyrrolo[1,2-b:4',3',2'-de]isoquinoline (13): *n*-Butanol (5 mL) was added



to a round-bottom flask containing L-proline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **12** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a pale pink solid in 63% yield. ($R_f = 0.19$ in 50% MeOH/EtOAc); mp: 185–188 °C; IR (KBr) 3407, 3143, 3088, 3054, 3000, 2967, 2933, 2868, 2811, 2738, 1602, 1457, 1444, 1367, 1340, 1311, 1248, 1228, 1150, 1105, 1026, 977, 925, 871, 817, 757, 741 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 10.78 (br s, 1H), 7.17 (app d, $J = 8.1$ Hz, 1H), 7.09–6.97 (comp, 2H), 6.78 (app d, $J = 7.0$ Hz, 1H), 4.17 (d, $J = 15.2$ Hz, 1H), 4.11–3.93 (comp, 2H), 2.85 (app d, $J = 3.4$ Hz, 1H), 2.74 (app d, $J = 6.8$ Hz, 1H), 2.34–2.20 (m, 1H), 1.96–1.70 (comp, 3H); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ 134.2, 127.6, 125.5, 122.7, 118.56, 114.6, 113.0, 110.0, 59.8, 51.1, 51.0, 29.6, 22.4; m/z (ESIMS) 199.2 $[\text{M} + \text{H}]^+$.

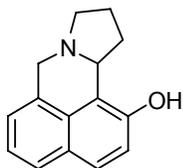
8,9,10,10a-Tetrahydro-6H-dipyrrolo[2,1-b:3',2',1'-ij]quinazoline (15): L-Proline (1.0 mmol) and



14 (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 30 minutes (200 °C, 110 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. ($R_f = 0.33$ in 30% EtOAc/hexanes); mp: 84–86 °C; IR (KBr) 3072, 2930, 2840, 1480, 1450, 1361, 1341, 1275, 1195, 1112, 1075, 775, 726 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (app t, $J = 10.3$ Hz, 1H), 7.12 (d, $J = 3.1$ Hz, 1H), 7.10–7.04 (m, 1H), 6.92 (app dd, $J = 17.8, 7.1$ Hz, 1H), 6.51 (d, $J = 3.1$ Hz, 1H), 5.39 (app dt, $J = 19.9, 10.0$ Hz, 1H), 4.53 (d, $J = 16.5$ Hz, 1H), 4.14 (d, $J = 16.5$ Hz, 1H), 3.10 (app td, $J = 9.0, 3.9$ Hz, 1H), 2.67 (app td, $J = 9.2, 7.3$ Hz, 1H), 2.52–2.31 (comp, 2H), 2.14–1.96 (m, 1H), 1.90–1.67 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.8, 126.0, 122.9, 119.8, 118.6, 118.4, 117.3, 101.1, 73.2, 49.4, 46.8, 30.4, 21.6; m/z (ESIMS) 199.1 $[\text{M} + \text{H}]^+$.

Alternate preparation of 15 (Chart 2): *n*-Butanol (5 mL) was added to a round-bottom flask containing pyrrolidine (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **14** (0.5 mmol) in *n*-butanol (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield.

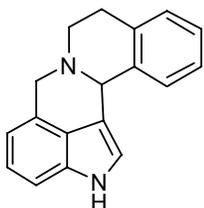
1-Benzyl-2-(4-phenylbut-1-yn-1-yl)pyrrolidine 9,10,11,11a-tetrahydro-7H-benzo- [de]pyrrolo[2,1-a]isoquinolin-1-ol (17):



L-Proline (0.75 mmol) and **16** (0.5 mmol) along with 10 mL of toluene were added to a round-bottom flask equipped with a reflux condenser. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent under vacuo, the residue was purified by flash column chromatography.

The title compound was obtained as a white solid in 91% yield. (R_f = 0.30 in 25% MeOH/EtOAc); mp: 176–177 °C; IR (KBr) 3048, 2955, 2877, 2807, 1625, 1587, 1508, 1434, 1381, 1358, 1320, 1308, 1267, 1128, 1112, 1103, 971, 963, 941, 911, 878, 823, 758, 629, 562 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.49 (br s, 1H), 7.71–7.48 (comp, 2H), 7.24–7.03 (comp, 3H), 4.06 (d, J = 14.3 Hz, 1H), 3.75–3.58 (comp, 2H), 3.13–2.97 (m, 1H), 2.63–2.51 (comp, 2H), 1.95–1.63 (comp, 3H); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ 150.3, 132.4, 129.4, 127.3, 126.8, 125.7, 122.0, 122.0, 118.3, 117.8, 60.8, 52.9, 52.7, 29.5, 21.6; m/z (ESIMS) 226.3 $[\text{M} + \text{H}]^+$.

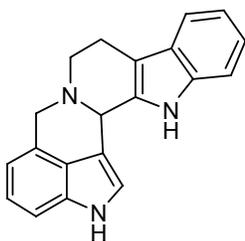
6,8,9,13b-Tetrahydro-2H-isoquinolino[2,1-b]pyrrolo[4,3,2-de]isoquinoline (20):



n-Butanol (5 mL) was added to a round-bottom flask containing tetrahydroisoquinoline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **12** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an

additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 78% yield. (R_f = 0.34 in 40% EtOAc/hexanes); mp: 194–197 °C; IR (KBr) 3416, 3136, 3082, 3032, 3000, 2924, 2852, 2791, 2735, 1737, 1614, 1494, 1442, 1381, 1371, 1354, 1298, 1383, 1237, 1153, 1124, 1098, 1064, 1047, 1028, 941, 925, 797, 766, 748, 739, 713, 703, 635, 597, 581, 521 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 10.64 (br s, 1H), 7.43 (app d, J = 7.5 Hz, 1H), 7.24 (app t, J = 7.3 Hz, 1H), 7.15 (app dt, J = 14.8, 7.1 Hz, 3H), 7.01 (app t, J = 7.5 Hz, 1H), 6.78–6.68 (comp, 2H), 5.32 (s, 1H), 4.33 (d, J = 15.8 Hz, 1H), 3.95 (d, J = 15.8 Hz, 1H), 2.99–2.86 (m, 1H), 2.76–2.59 (comp, 3H); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ 137.4, 133.6, 133.5, 128.9, 127.8, 126.8, 126.0, 125.5, 124.4, 122.0, 119.7, 113.4, 113.2, 109.0, 57.3, 54.9, 46.0, 29.1; m/z (ESIMS) 261.2 $[\text{M} + \text{H}]^+$.

4,6,7,12,12b,14-Hexahydroindolo[2',3':3,4]pyrido[1,2-b]pyrrolo[4,3,2-de]isoquinoline (22):

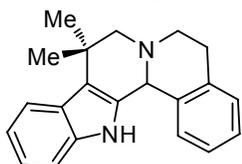


n-Butanol (5 mL) was added to a round-bottom flask containing **21** (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **12** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was

purified by flash column chromatography. The title compound was obtained as a yellow solid in 54% yield. (R_f = 0.30 in 60% EtOAc/hexanes); mp: 226–231 °C; IR (KBr) 3448, 3085, 3050, 2956, 2931, 2882, 2845, 2818, 1617, 1457, 1328, 1307, 1254, 1232, 1113 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 10.94 (br s, 1H), 10.75 (br s, 1H), 7.41–7.35 (comp, 2H), 7.25 (s, 1H), 7.15 (app d, J = 8.1 Hz, 1H),

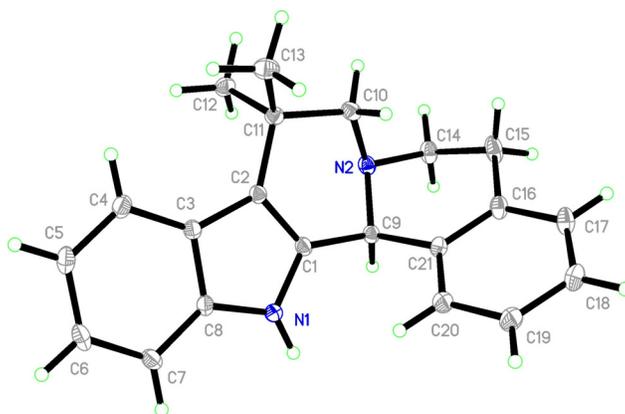
7.07–7.00 (comp, 2H), 6.96 (app t, $J = 7.4$ Hz, 1H), 6.76 (app d, $J = 7.0$ Hz, 1H), 5.27 (s, 1H), 4.18 (d, $J = 15.3$ Hz, 1H), 4.06 (d, $J = 15.3$ Hz, 1H), 3.02 (app dd, $J = 11.3, 5.6$ Hz, 1H), 2.92 (app dt, $J = 11.7, 5.9$ Hz, 1H), 2.80–2.70 (comp, 2H); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ 136.2, 134.8, 133.1, 128.6, 126.6, 124.8, 122.0, 120.4, 118.9, 118.3, 117.5, 113.2, 111.4, 111.2, 108.9, 105.9, 54.5, 54.1, 49.2, 21.3; m/z (ESIMS) 300.2 $[\text{M} + \text{H}]^+$.

9,9-Dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-a]isoquinoline (23):



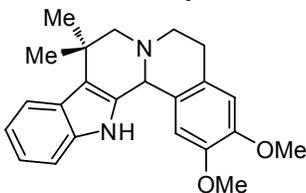
Tetrahydroisoquinoline (1.5 mmol) and **3** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a light yellow solid in 64% yield. ($R_f = 0.21$ in 30% EtOAc/hexanes); mp: 148–151 °C; IR (KBr) 3140, 3101, 3059, 2925, 2864, 2847, 1457, 1332, 1302, 1262, 1190, 1101, 1075, 970, 908, 880, 742, 662 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.79 (br s, 1H), 7.68 (app d, $J = 7.8$ Hz, 1H), 7.39 (app d, $J = 7.4$ Hz, 1H), 7.32–7.22 (comp, 3H), 7.19 (app d, $J = 7.3$ Hz, 1H), 7.15–7.06 (comp, 2H), 5.22 (s, 1H), 3.27–3.14 (comp, 2H), 3.10–3.03 (comp, 2H), 2.97–2.83 (comp, 2H), 1.53 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.9, 134.9, 134.8, 132.2, 129.8, 127.0, 126.6, 126.4, 126.2, 121.1, 120.0, 119.2, 115.7, 111.1, 64.7, 57.2, 48.0, 32.2, 29.3, 28.7, 28.2; m/z (ESIMS) 303.2 $[\text{M} + \text{H}]^+$.

The title compound was further characterized by X-ray crystallography:



The requisite CIF file has been submitted to the journal.

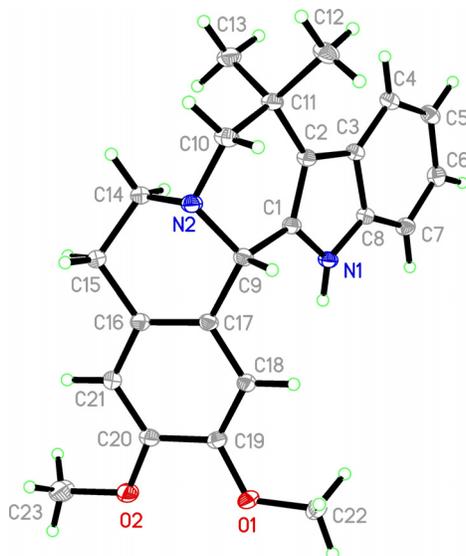
2,3-Dimethoxy-9,9-dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-a]isoquinoline (25):



24 (1.5 mmol) and **3** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. ($R_f = 0.31$ in 50% EtOAc/hexanes); mp: 188–190 °C; IR (KBr) 3379, 2998, 2969, 2954, 2920, 2903, 2861, 2831, 1612, 1519, 1455, 1444, 1374, 1355, 1339, 1327, 1296, 1279, 1259,

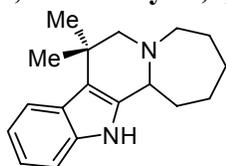
1238, 1226, 1212, 1197, 1141, 1102, 1064, 1036, 1012, 871, 845, 180, 744 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.92 (br s, 1H), 7.69 (app d, $J = 7.6$ Hz, 1H), 7.32 (app d, $J = 7.7$ Hz, 1H), 7.18–7.05 (comp, 2H), 6.88 (s, 1H), 6.67 (s, 1H), 5.11 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.23 (ddd, $J = 12.6, 7.8, 5.1$ Hz, 1H), 3.19–3.12 (m, 1H), 3.11–3.01 (comp, 2H), 2.89–2.73 (comp, 2H), 1.53 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.2, 147.5, 136.0, 132.5, 126.9, 126.5, 126.4, 121.0, 120.0, 119.12, 115.6, 112.3, 111.2, 110.1, 64.3, 56.7, 56.3, 55.8, 47.9, 32.1, 29.4, 28.6, 27.5; m/z (ESIMS) 363.2 $[\text{M} + \text{H}]^+$.

The title compound was further characterized by X-ray crystallography:

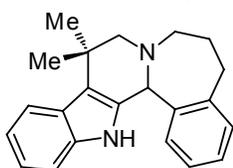


The requisite CIF file has been submitted to the journal.

8,8-Dimethyl-2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole (27): Azepane (5.0 mmol) and **3** (0.5 mmol) along with 2 mL of *n*-butanol were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 5 hours (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a yellow oil in 43% yield. ($R_f = 0.33$ in EtOAc); IR (film) 3404, 3247, 3053, 2926, 2857, 1459, 1376, 1356, 1325, 1274, 1129, 1114, 1082, 1015, 762, 740 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.70–7.59 (comp, 2H), 7.32–7.24 (m, 1H), 7.15–7.03 (comp, 2H), 3.74 (dd, $J = 8.6, 3.4$ Hz, 1H), 2.94–2.83 (comp, 2H), 2.70 (d, $J = 11.5$ Hz, 1H), 2.60 (d, $J = 11.5$ Hz, 1H), 2.05–1.95 (m, 1H), 1.92–1.54 (comp, 7H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.2, 135.9, 126.0, 120.8, 119.8, 118.9, 117.0, 110.8, 66.8, 60.3, 56.8, 33.8, 33.0, 27.7, 27.41, 27.37, 27.0, 25.6; m/z (ESIMS) 269.2 $[\text{M} + \text{H}]^+$.

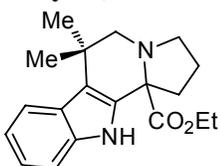


10,10-Dimethyl-6,7,9,10,15,15b-hexahydro-5H-benzo[3',4']azepino [1',2':1,2]pyrido[3,4-b]indole



(29): **28** (2.5 mmol) and **3** (0.5 mmol) along with 2 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 1 hour (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a thick yellow oil in 54% yield. ($R_f = 0.20$ in 10% EtOAc/hexanes); IR (film) 3400, 3174, 3056, 2927, 2859, 1458, 1376, 1355, 1327, 1266, 1113, 1079, 740, 635 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.74 (app d, $J = 7.7$ Hz, 1H), 7.61 (br s, 1H), 7.28 (app d, $J = 7.8$ Hz, 1H), 7.20–7.09 (comp, 4H), 7.08–7.03 (m, 1H), 6.52 (app d, $J = 7.5$ Hz, 1H), 5.30 (s, 1H), 3.33–3.22 (m, 1H), 3.04–2.94 (m, 1H), 2.92–2.82 (m, 1H), 2.66–2.57 (m, 1H), 2.50 (d, $J = 11.6$ Hz, 1H), 2.36 (d, $J = 11.6$ Hz, 1H), 2.09–2.01 (m, 1H), 1.96–1.81 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.5, 136.4, 132.3, 128.9, 128.4, 127.5, 126.1, 125.7, 121.2, 120.0, 119.5, 119.1, 111.0, 63.8, 58.7, 33.1, 32.7, 29.7, 27.5(1), 27.4(8), 25.7; m/z (ESIMS) 317.3 $[\text{M} + \text{H}]^+$.

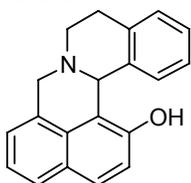
Ethyl 6,6-dimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-11b-carboxylate (31): **24**



(1.5 mmol) and **3** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 114 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The

title compound was obtained as a thick yellow oil in 74% yield. ($R_f = 0.40$ in 10% MeOH/EtOAc); IR (film) 3388, 3055, 2956, 1715, 1617, 1457, 1385, 1364, 1320, 1297, 1262, 1101, 1023, 857, 765, 738, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.19 (br s, 1H), 7.71 (app t, $J = 10.3$ Hz, 1H), 7.36 (app d, $J = 8.1$ Hz, 1H), 7.21–7.14 (m, 1H), 7.10 (app t, $J = 7.3$ Hz, 1H), 4.31–4.12 (comp, 2H), 3.33 (ddd, $J = 9.5, 7.3, 5.3$ Hz, 1H), 3.21 (app dt, $J = 9.5, 7.1$ Hz, 1H), 3.13 (d, $J = 13.2$ Hz, 1H), 3.00 (d, $J = 13.2$ Hz, 1H), 2.64 (ddd, $J = 12.5, 7.9, 4.5$ Hz, 1H), 2.30–2.15 (m, 1H), 1.94–1.79 (comp, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.1, 136.5, 131.7, 125.5, 121.6, 120.3, 119.1, 118.0, 111.1, 67.3, 61.6, 59.9, 53.1, 37.4, 32.6, 28.5, 28.4, 23.8, 14.2; m/z (ESIMS) 313.2 $[\text{M} + \text{H}]^+$.

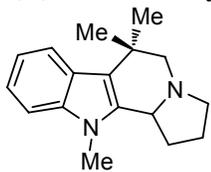
5,6,8,14b-Tetrahydrobenzo[de]isoquinolino[1,2-a]isoquinolin-14-ol (32): Tetrahydroisoquinoline



(1.5 mmol), **16** (0.5 mmol) and 10 mL of toluene were added to a round-bottom flask equipped with a condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield. ($R_f = 0.27$ in 60% EtOAc/hexanes); mp: 224–227 °C;

IR (KBr) 3056, 2939, 2821, 1629, 1589, 1514, 1484, 1452, 1436, 1374, 1316, 1277, 1121, 1040, 954, 881, 820, 763, 744 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.81 (br s, 1H), 7.71 (app d, $J = 8.9$ Hz, 1H), 7.60 (app d, $J = 8.1$ Hz, 1H), 7.26 (app d, $J = 8.9$ Hz, 1H), 7.18–7.13 (m, 1H), 7.12–7.05 (comp, 3H), 6.96 (app t, $J = 7.0$ Hz, 1H), 6.74 (app d, $J = 7.7$ Hz, 1H), 5.51 (s, 1H), 4.00 (d, $J = 14.7$ Hz, 1H), 3.79 (d, $J = 14.7$ Hz, 1H), 3.65–3.53 (m, 1H), 3.40–3.34 (m, 1H), 3.24–3.13 (m, 1H), 2.69 (app dd, $J = 17.7, 6.2$ Hz, 1H); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$) δ 150.3, 135.1, 133.9, 132.3, 128.8, 128.4, 128.4, 127.6, 127.5, 126.2, 125.8, 125.5, 122.2, 121.9, 117.9, 117.6, 55.5, 49.6, 47.8, 22.2; m/z (ESIMS) 288.3 $[\text{M} + \text{H}]^+$.

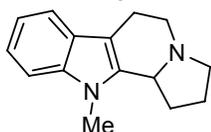
6,6,11-Trimethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (34a): Toluene (5 mL) was



added to a round-bottom flask containing L-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **33a** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump

over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 85% yield. ($R_f = 0.28$ in 5% MeOH/EtOAc); IR (film) 3416, 3045, 2953, 2870, 2789, 1667, 1468, 1417, 1383, 1359, 1328, 1316, 1291, 1265, 1224, 1196, 1161, 1101, 1083, 1061, 1018, 762, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.73 (app d, $J = 7.9$ Hz, 1H), 7.30 (app d, $J = 8.2$ Hz, 1H), 7.19 (app dd, $J = 11.2, 4.0$ Hz, 1H), 7.11 (app td, $J = 7.5, 0.9$ Hz, 1H), 3.87–3.77 (m, 1H), 3.66 (s, 3H), 3.11 (ddd, $J = 11.0, 8.3, 2.7$ Hz, 1H), 3.02–2.94 (m, 1H), 2.79 (d, $J = 11.0$ Hz, 1H), 2.48 (d, $J = 11.0$ Hz, 1H), 2.34–2.24 (m, 1H), 2.18–2.06 (m, 1H), 1.99–1.77 (comp, 2H), 1.51 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.3, 136.1, 125.3, 120.4, 119.8, 118.6, 115.5, 108.9, 62.7, 58.5, 54.1, 33.6, 30.0, 29.2, 27.9, 27.7, 23.2; m/z (ESIMS) 255.2 $[\text{M} + \text{H}]^+$.

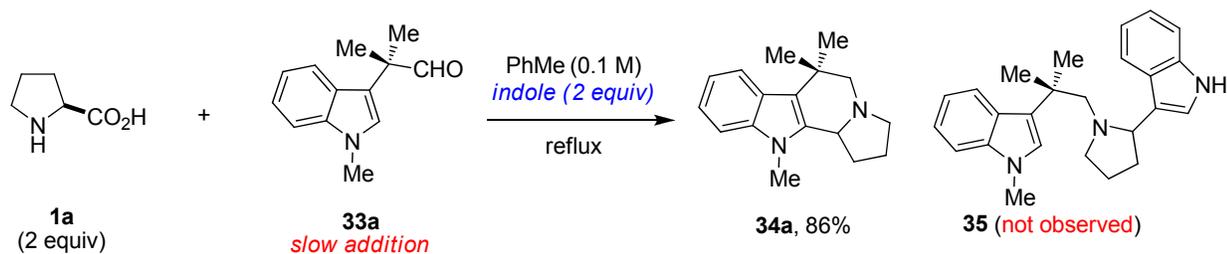
11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (34b): Toluene (5 mL) was added



to a round-bottom flask containing L-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of

33b (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the reaction mixture was cooled to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 60% yield. ($R_f = 0.25$ in 30% MeOH/EtOAc); IR (film) 3397, 3049, 2934, 2842, 1660, 1614, 1470, 1376, 1352, 1321, 1283, 1244, 1188, 1157, 1129, 1086, 1011 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.52 (app dd, $J = 7.8, 0.7$ Hz, 1H), 7.29 (app dd, $J = 8.2, 0.7$ Hz, 1H), 7.23–7.18 (m, 1H), 7.14–7.09 (m, 1H), 4.30–4.22 (m, 1H), 3.66 (s, 3H), 3.29–3.20 (m, 1H), 3.06–2.89 (comp, 4H), 2.78–2.68 (m, 1H), 2.50–2.39 (m, 1H), 2.01–1.90 (comp, 2H), 1.90–1.81 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.3, 137.0, 126.6, 120.8, 118.8, 118.0, 108.6, 106.6, 56.2, 50.9, 46.4, 30.3, 30.1, 23.7, 18.7; m/z (ESIMS) 227.2 $[\text{M} + \text{H}]^+$.

Reaction between indole, 33 and L-proline:

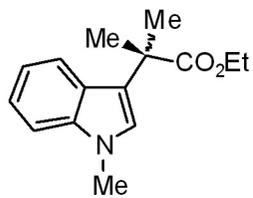


Toluene (5 mL) was added to a round-bottom flask containing L-proline (1.0 mmol) and indole (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **33a** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the reaction mixture was allowed to cool to room temperature and the residue was purified by flash column chromatography. Compound **34a** was obtained as yellow oil in 86% yield.

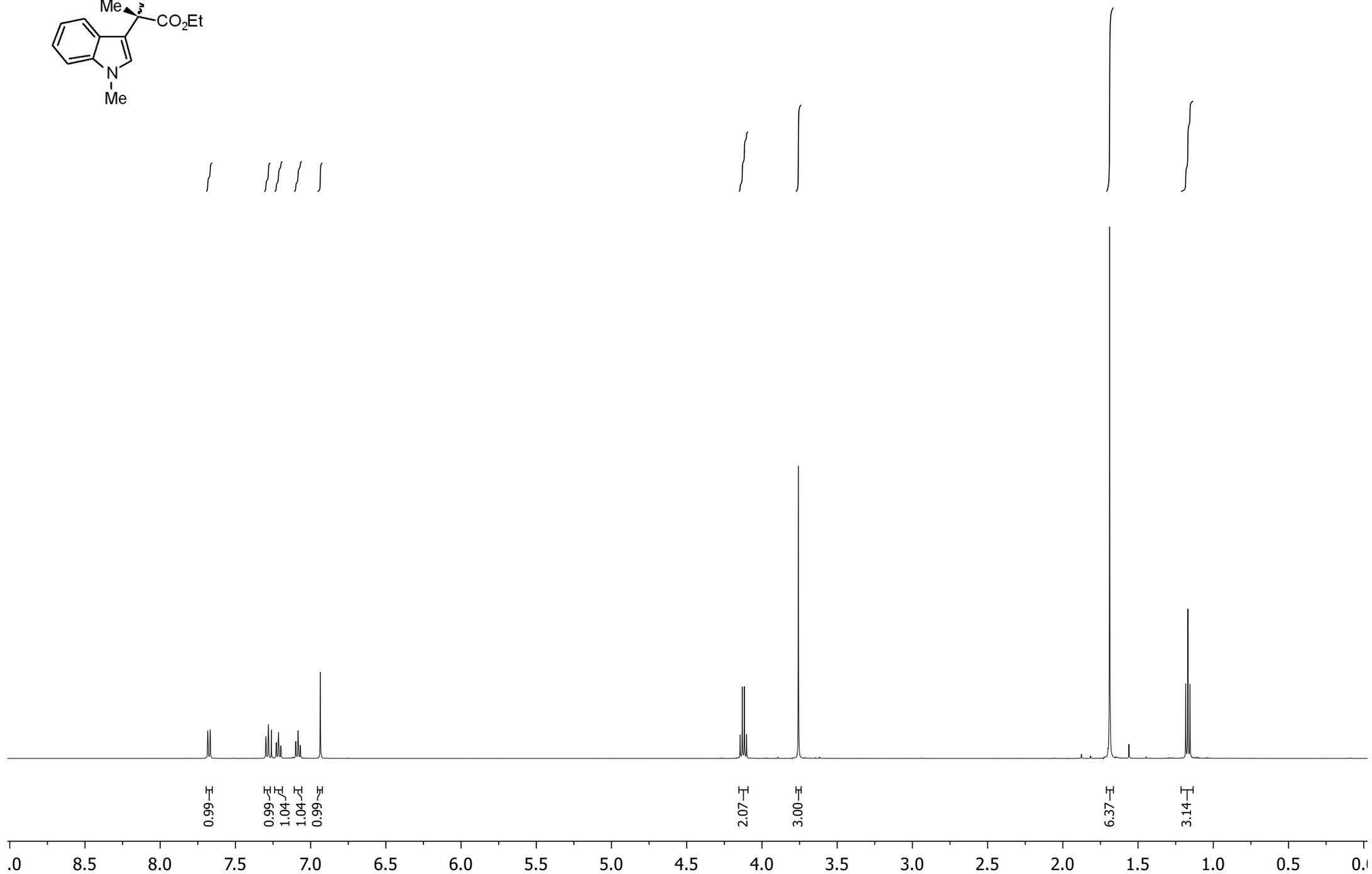
References:

- (1) Houghton, E.; Saxton, John E. *J. Chem. Soc. C* **1969**, 4, 595.
- (2) Horwell, David C.; McKiernan, Mary J.; Osborne, Simon. *Tetrahedron Lett.* **1998**, 39, 8729.
- (3) Nishizawa, T.; Grueschow, S.; Jayamaha, D.-H. E.; Nishizawa-Harada, C.; Sherman, D. H. *J. Am. Chem. Soc.* **2006**, 128, 724.
- (4) Chamontin, K.; Lokshin, V.; Rossollin, V.; Samat, A.; Guglielmetti, R. *Tetrahedron* **1999**, 55, 5821.
- (5) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, 130, 2746.
- (6) Erdtman, H.; Jönsson, Å. *Acta Chem. Scand.*, **1954**, 8, 119.

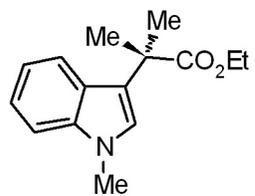
^1H NMR of **36** in CDCl_3



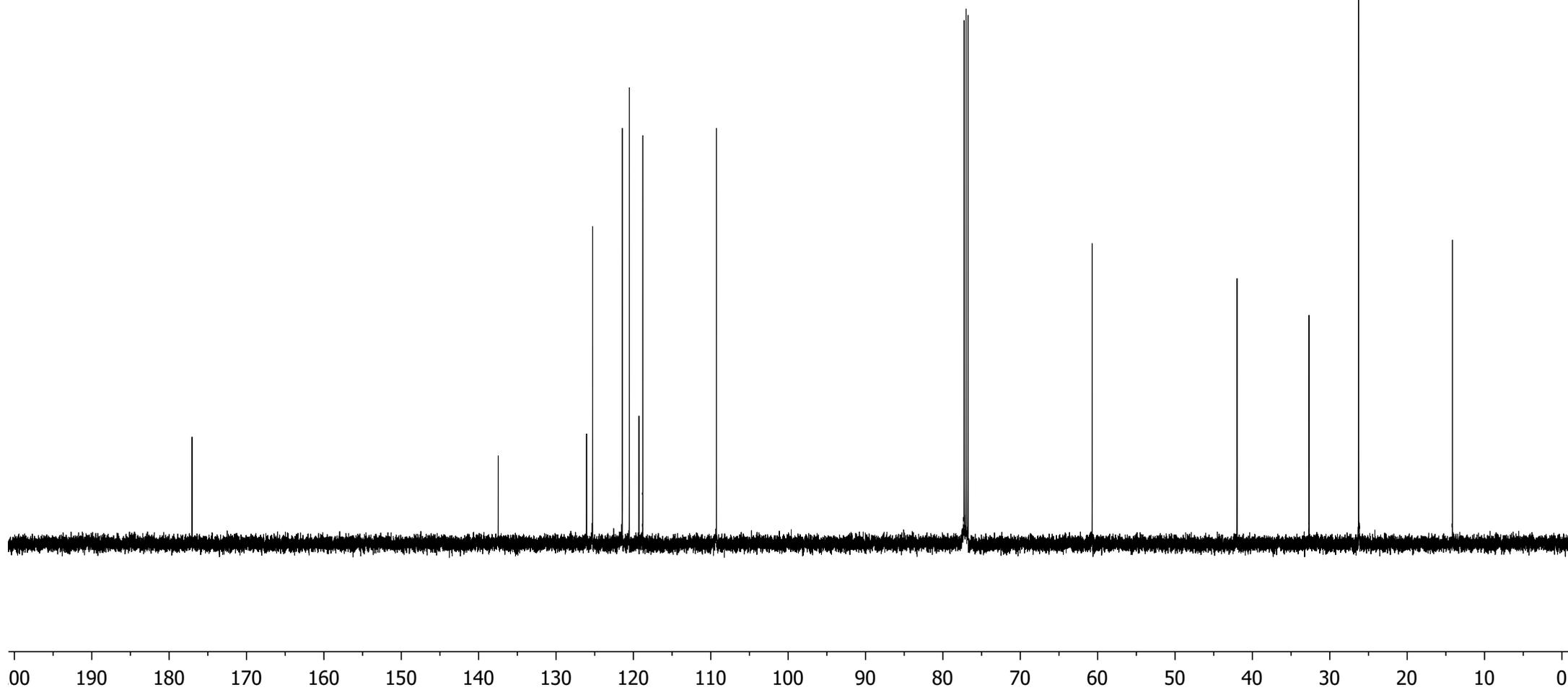
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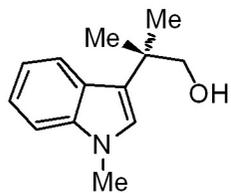
^{13}C NMR of **36** in CDCl_3



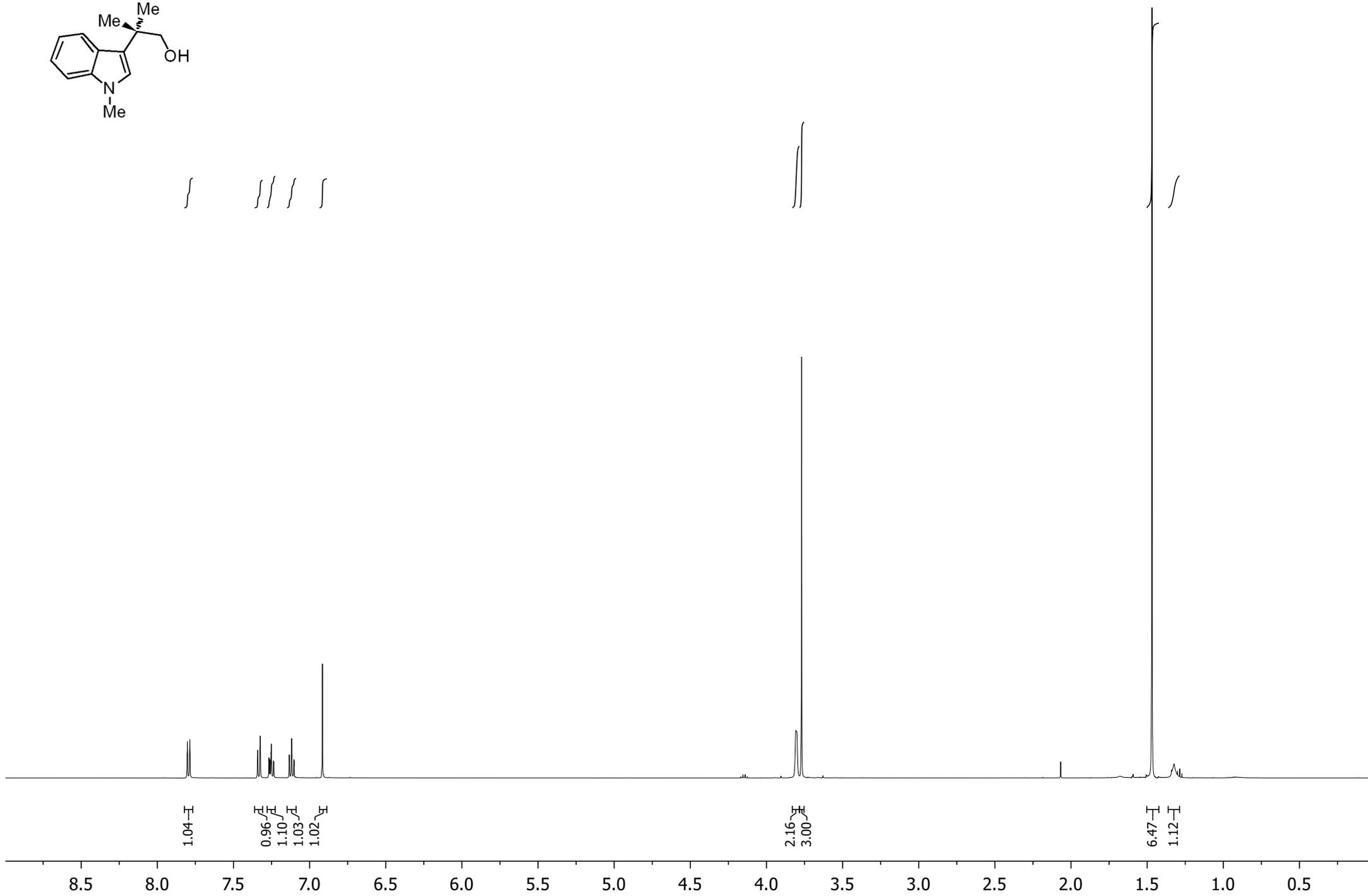
Supplementary Material (ESI) for Chemical Science
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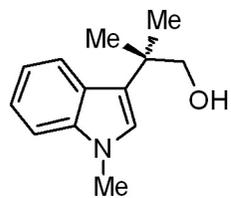
^1H NMR of **37** in CDCl_3



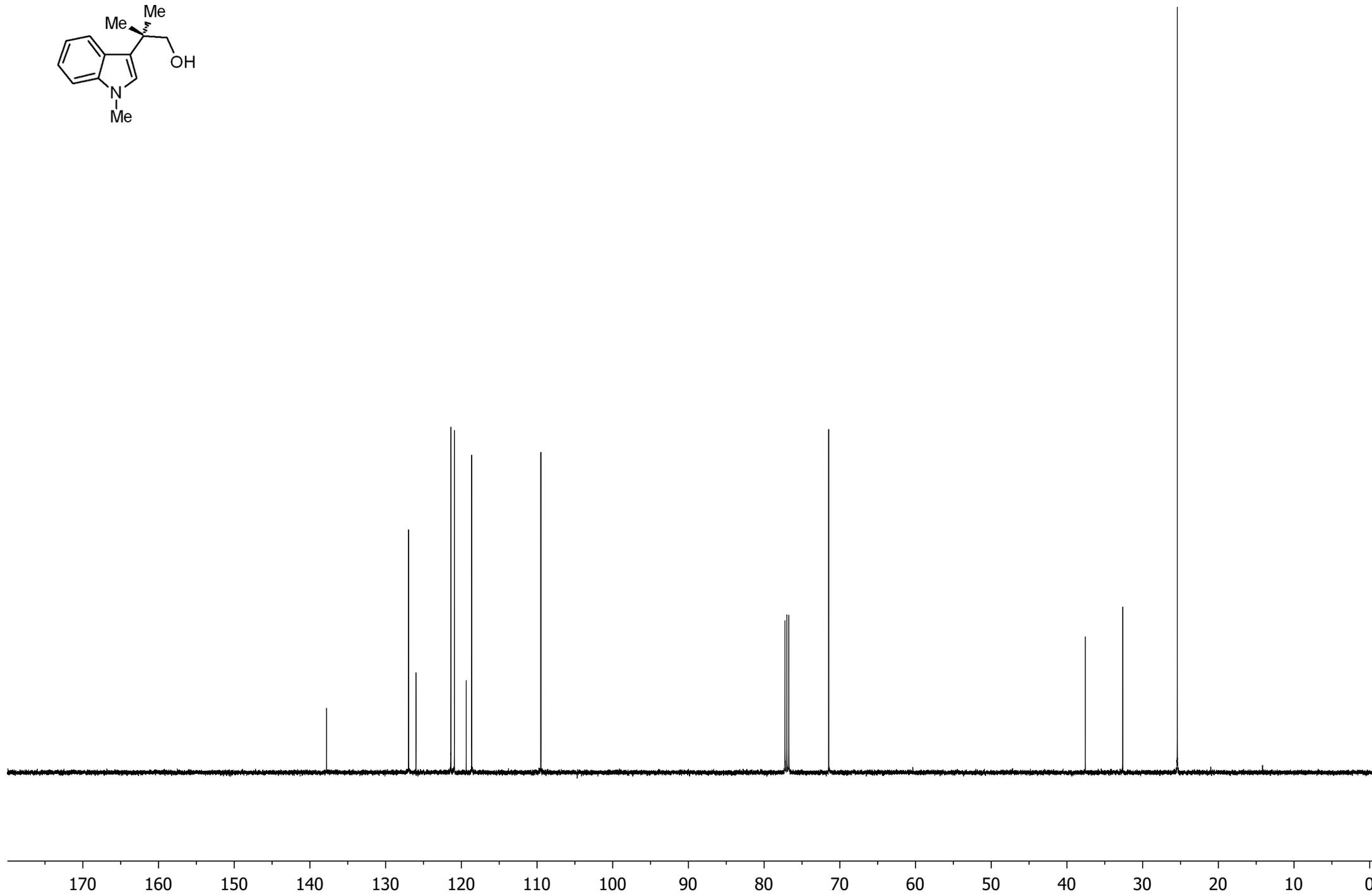
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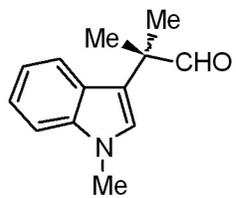
^{13}C NMR of **37** in CDCl_3



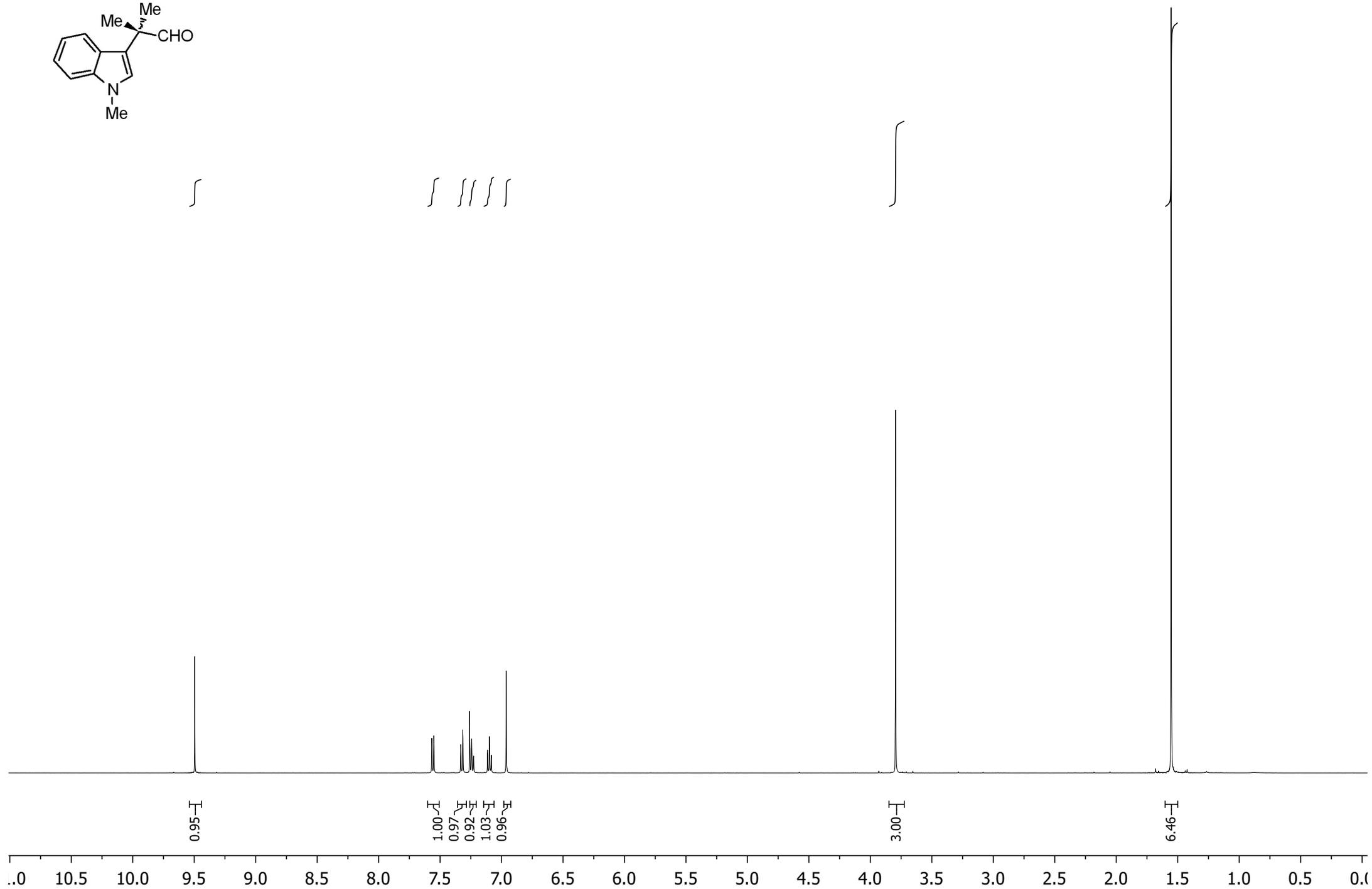
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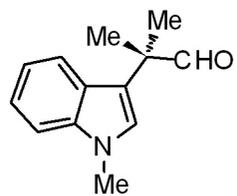
¹H NMR of **33a** in CDCl₃



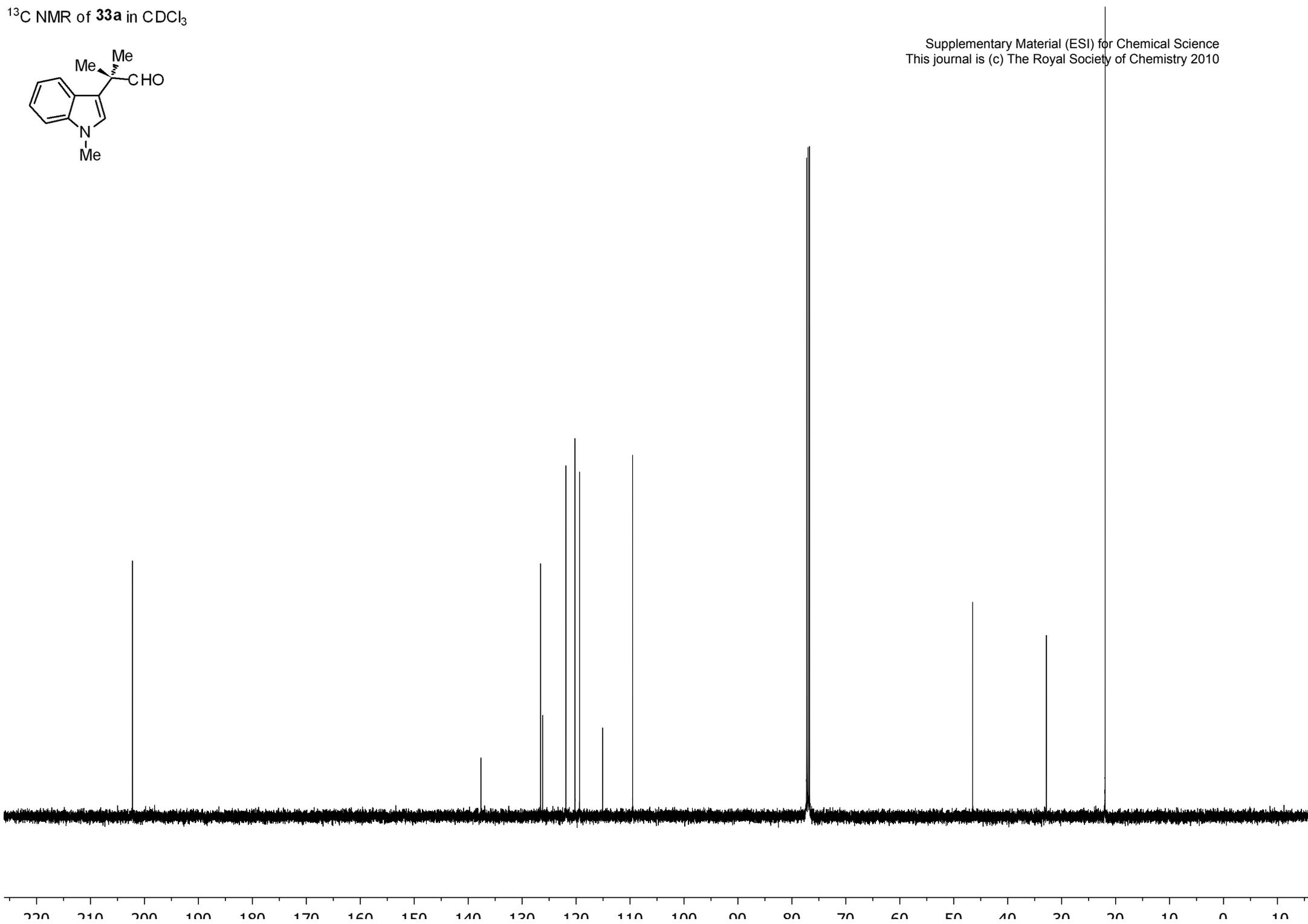
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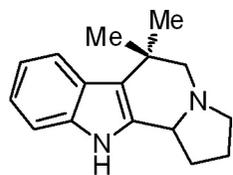
^{13}C NMR of **33a** in CDCl_3



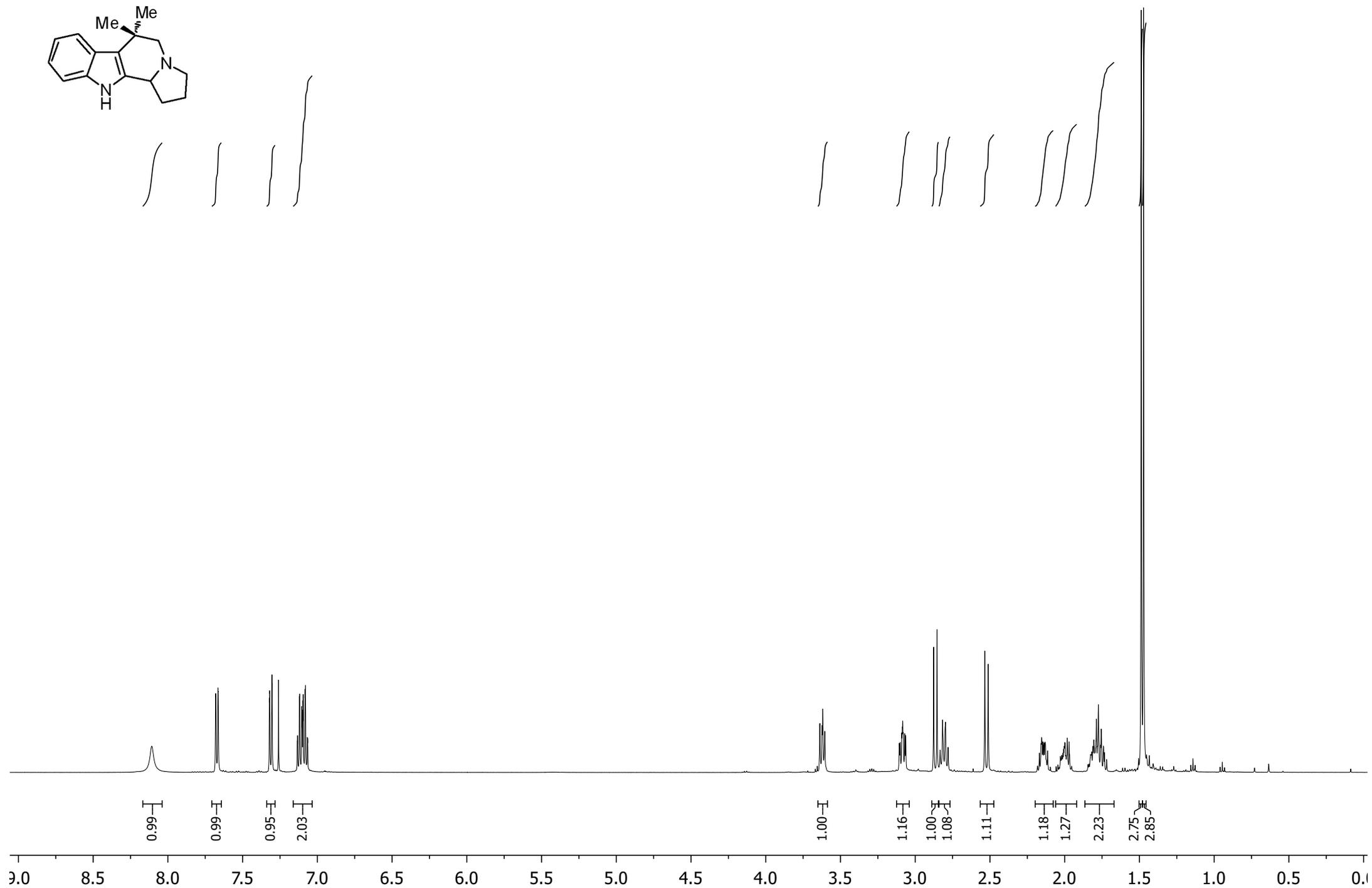
Supplementary Material (ESI) for Chemical Science
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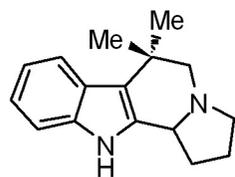
^1H NMR of **4** in CDCl_3



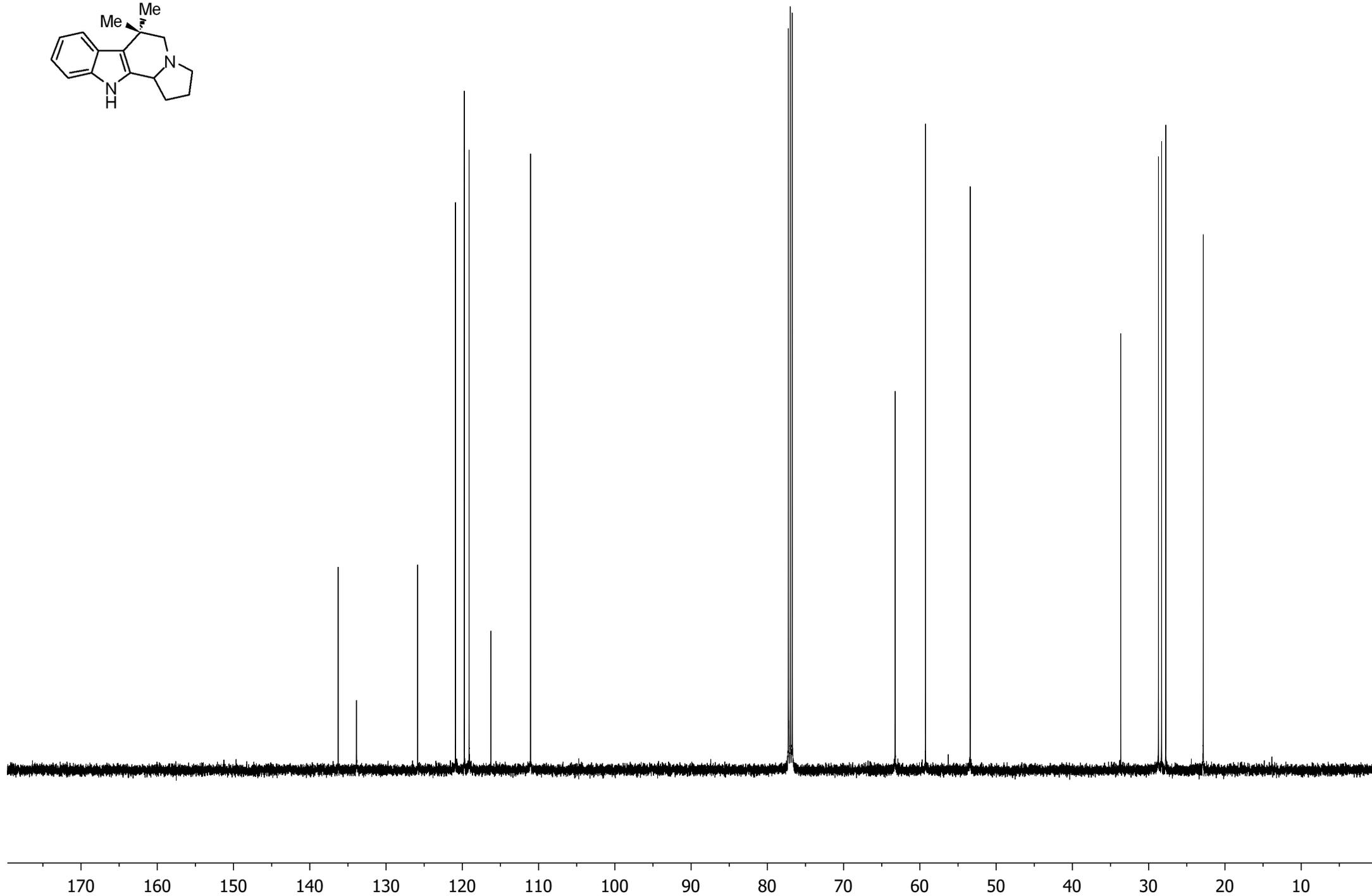
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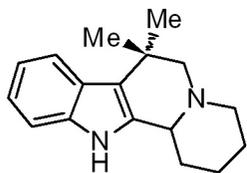
^{13}C NMR of **4** in CDCl_3



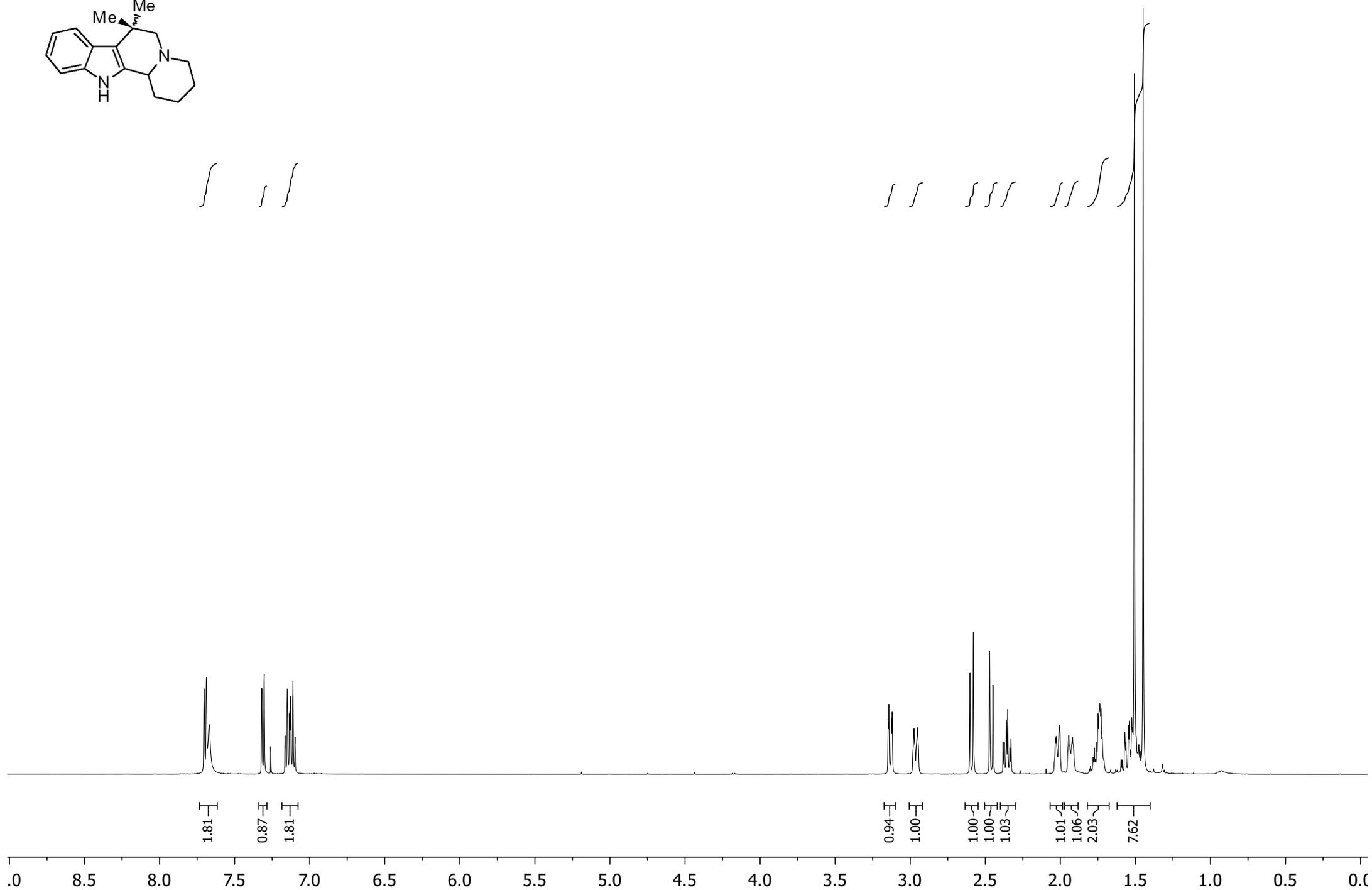
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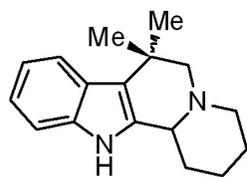
^1H NMR of **5** in CDCl_3



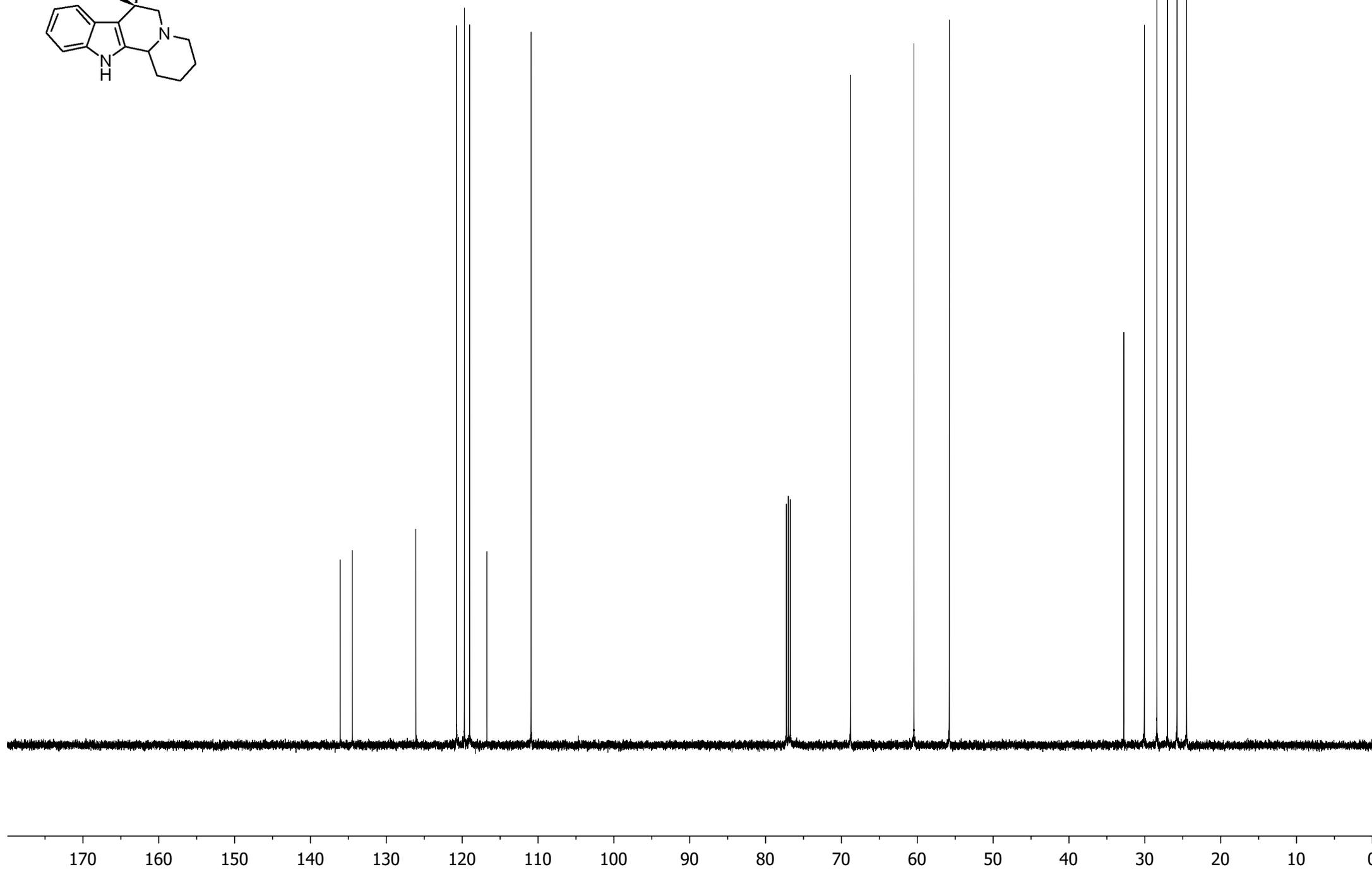
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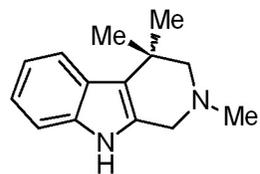
^{13}C NMR of **5** in CDCl_3



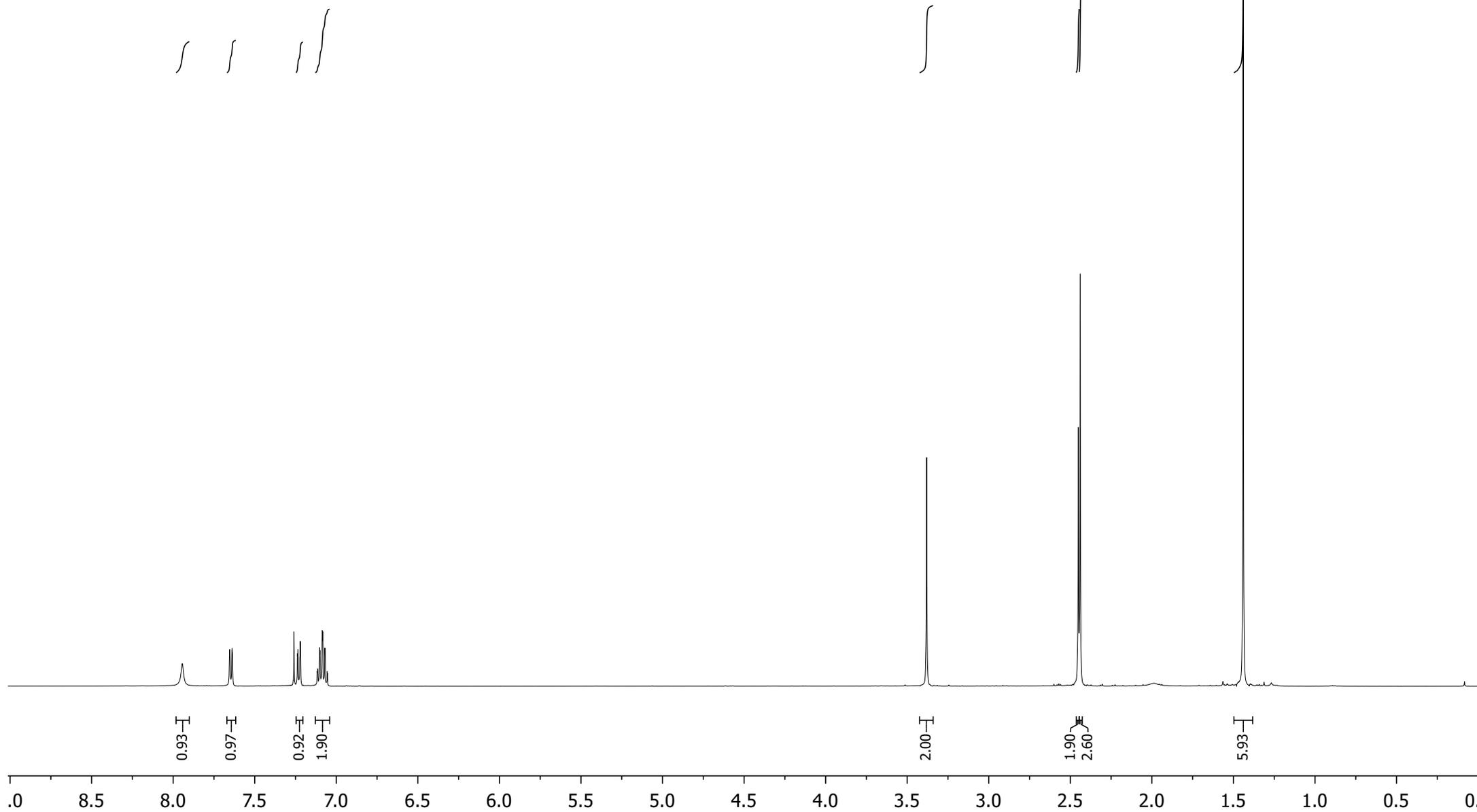
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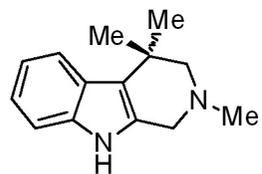
^1H NMR of **6** in CDCl_3



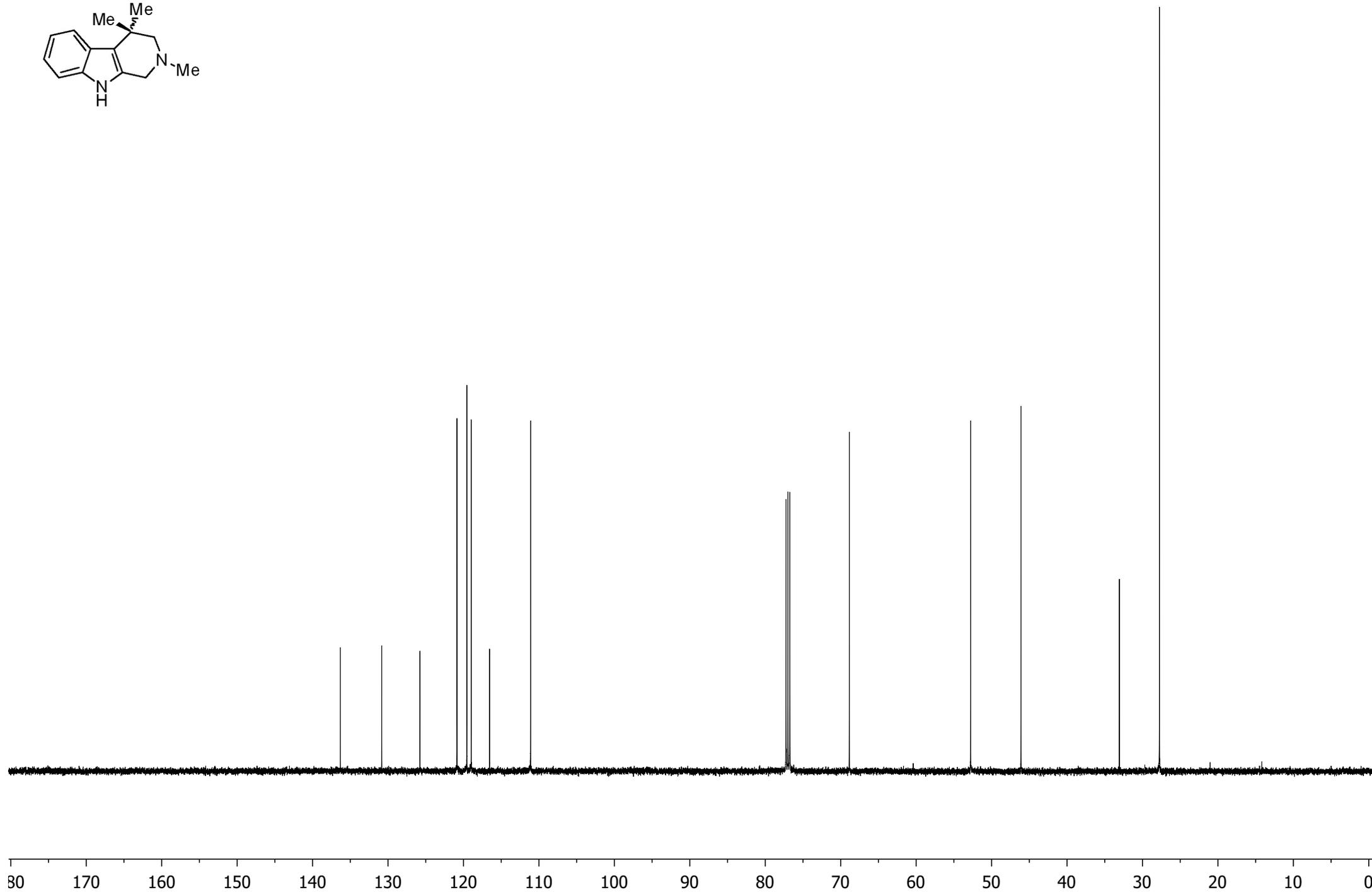
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^{13}C NMR of **6** in CDCl_3

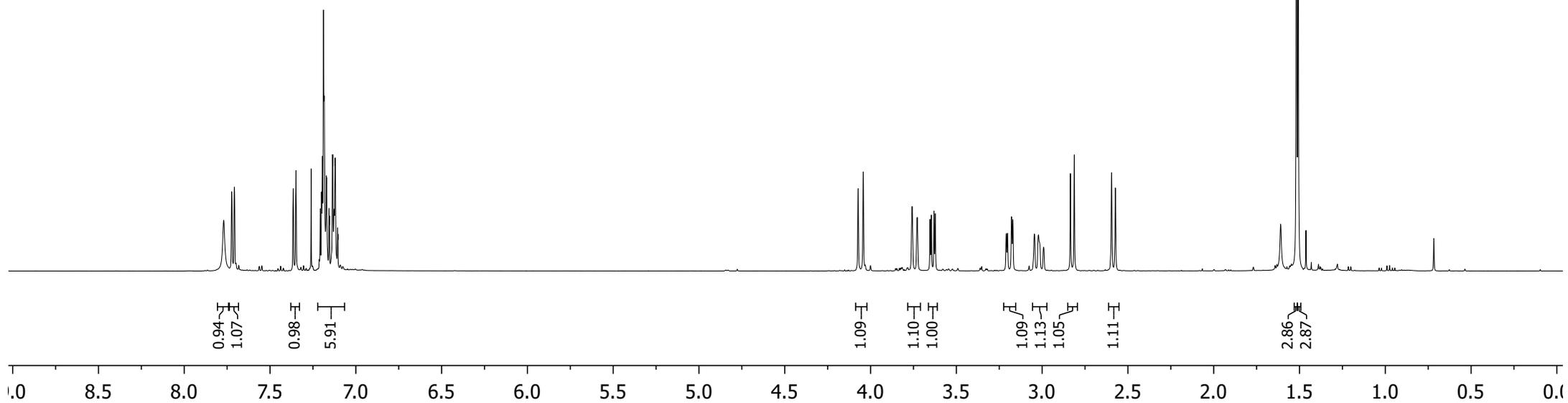
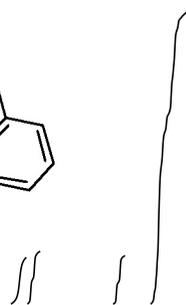
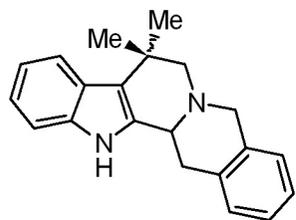


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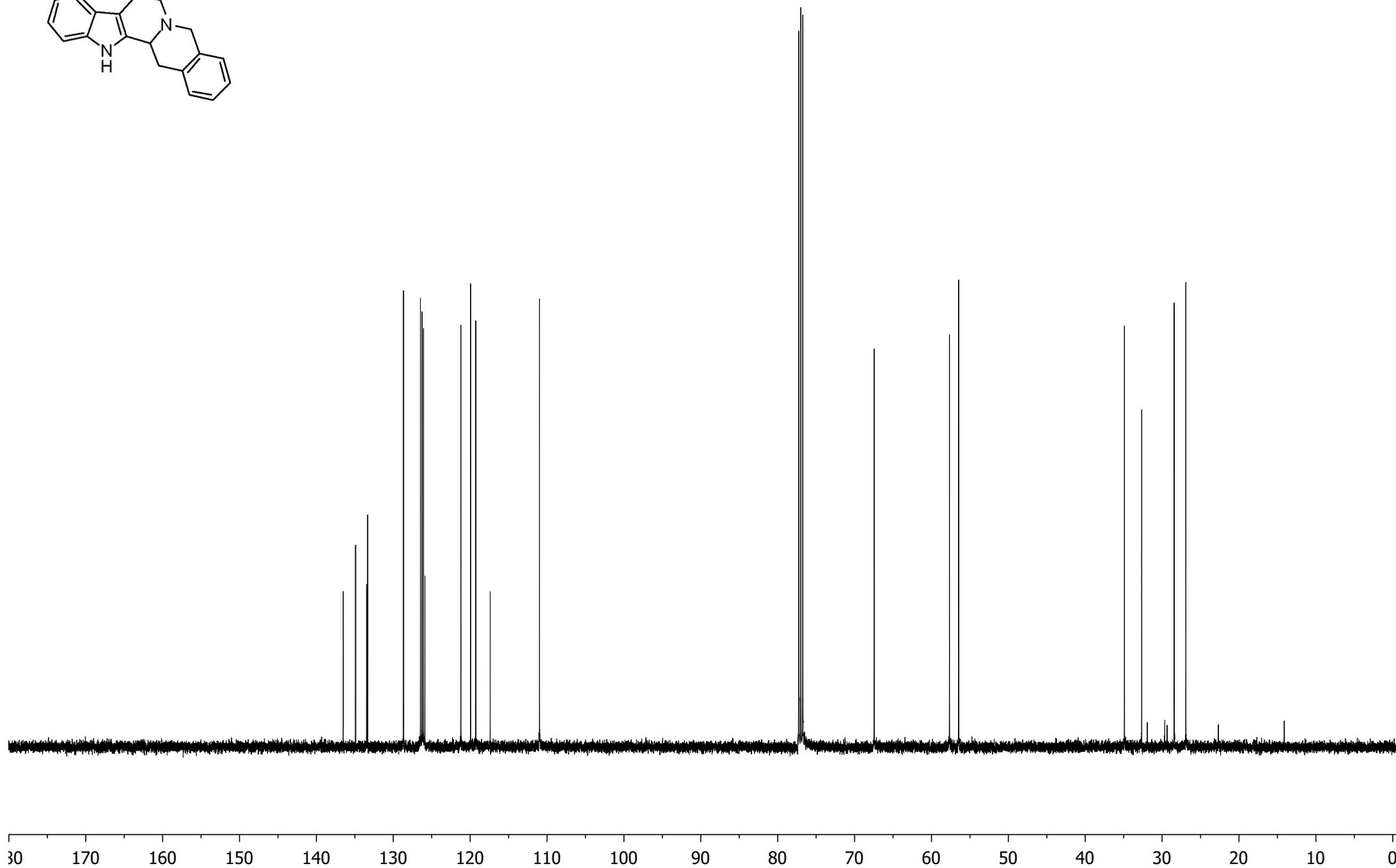
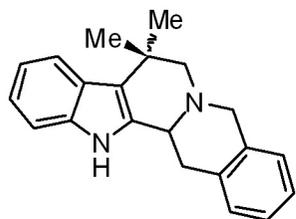
^1H NMR of **7** in CDCl_3

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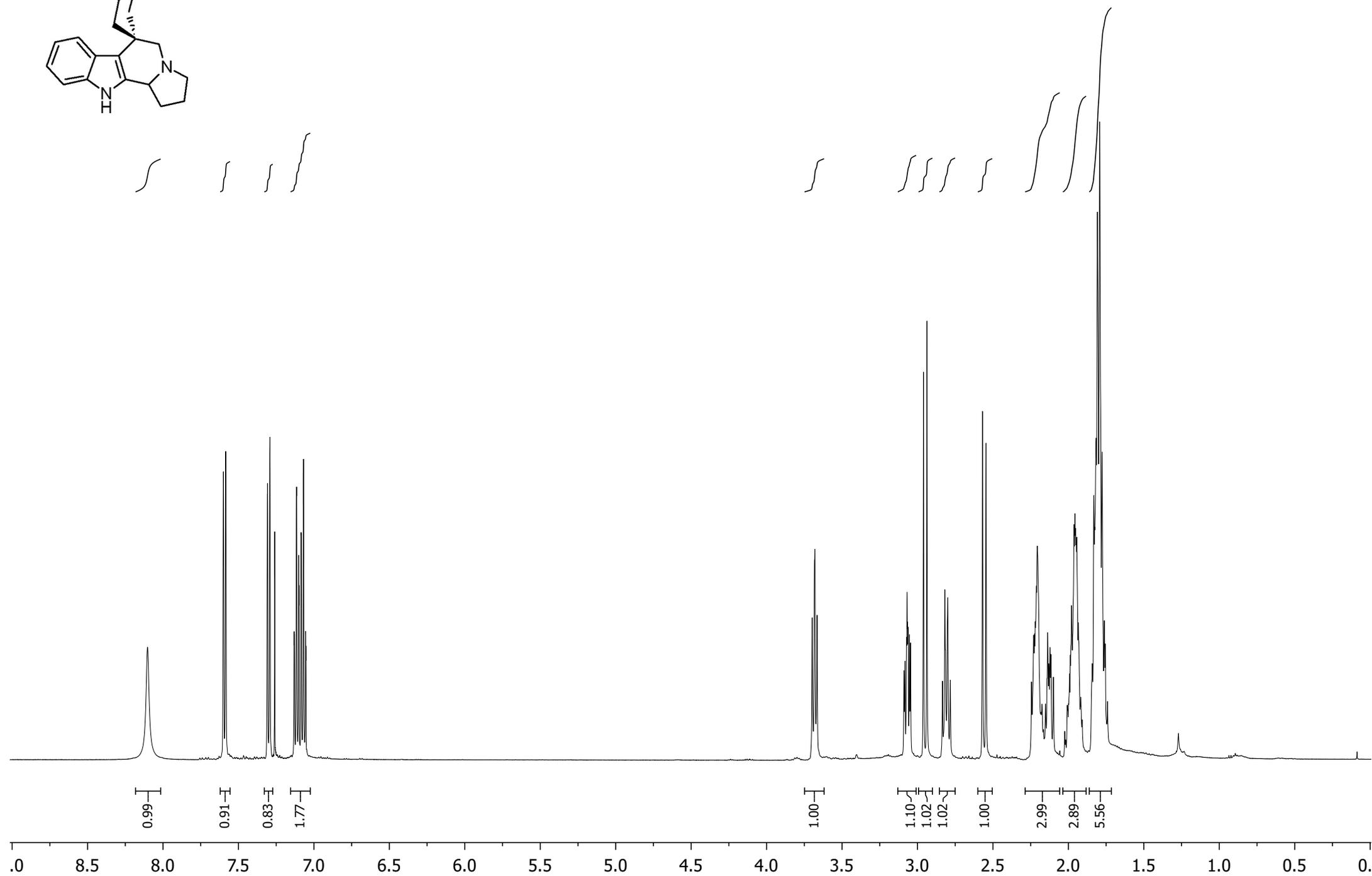
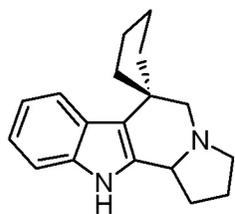
^{13}C NMR of **7** in CDCl_3

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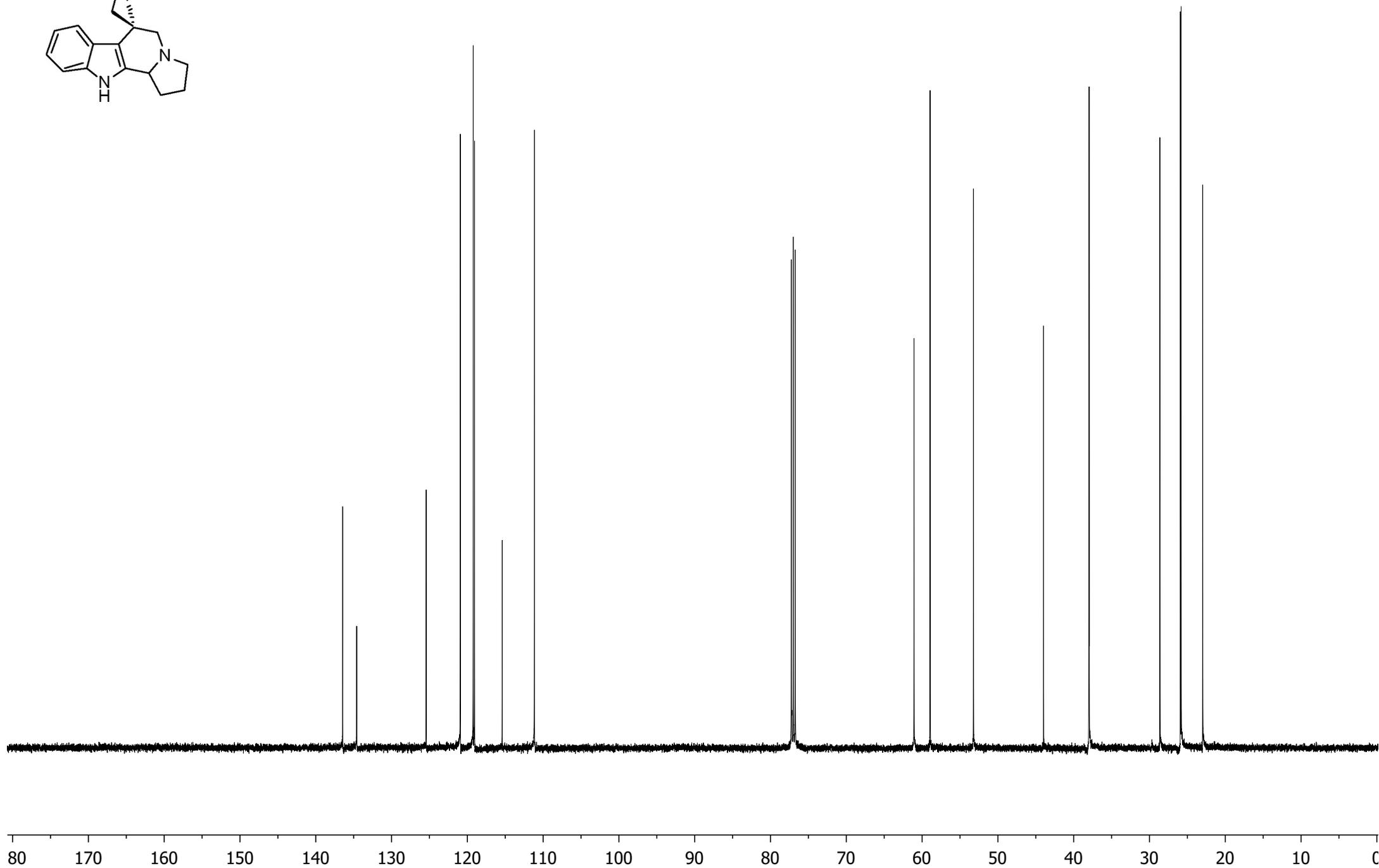
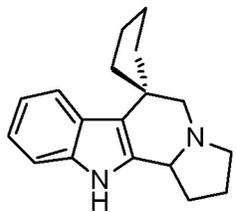
^1H NMR of **9** in CDCl_3

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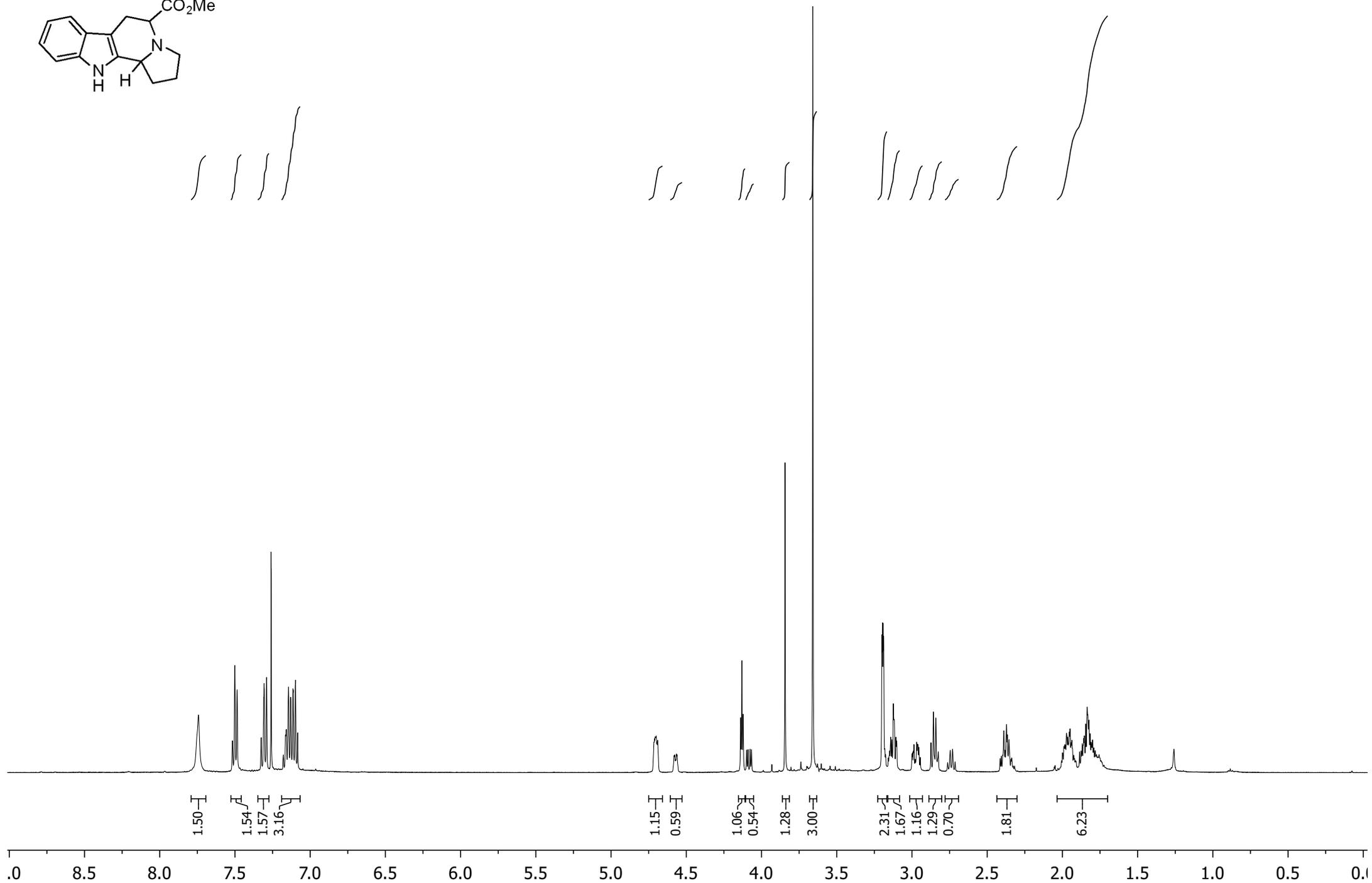
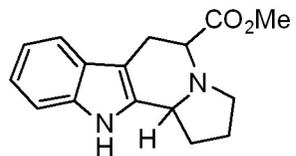
^{13}C NMR of **9** in CDCl_3

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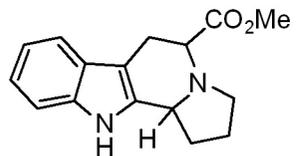


¹H NMR of **11** in CDCl₃

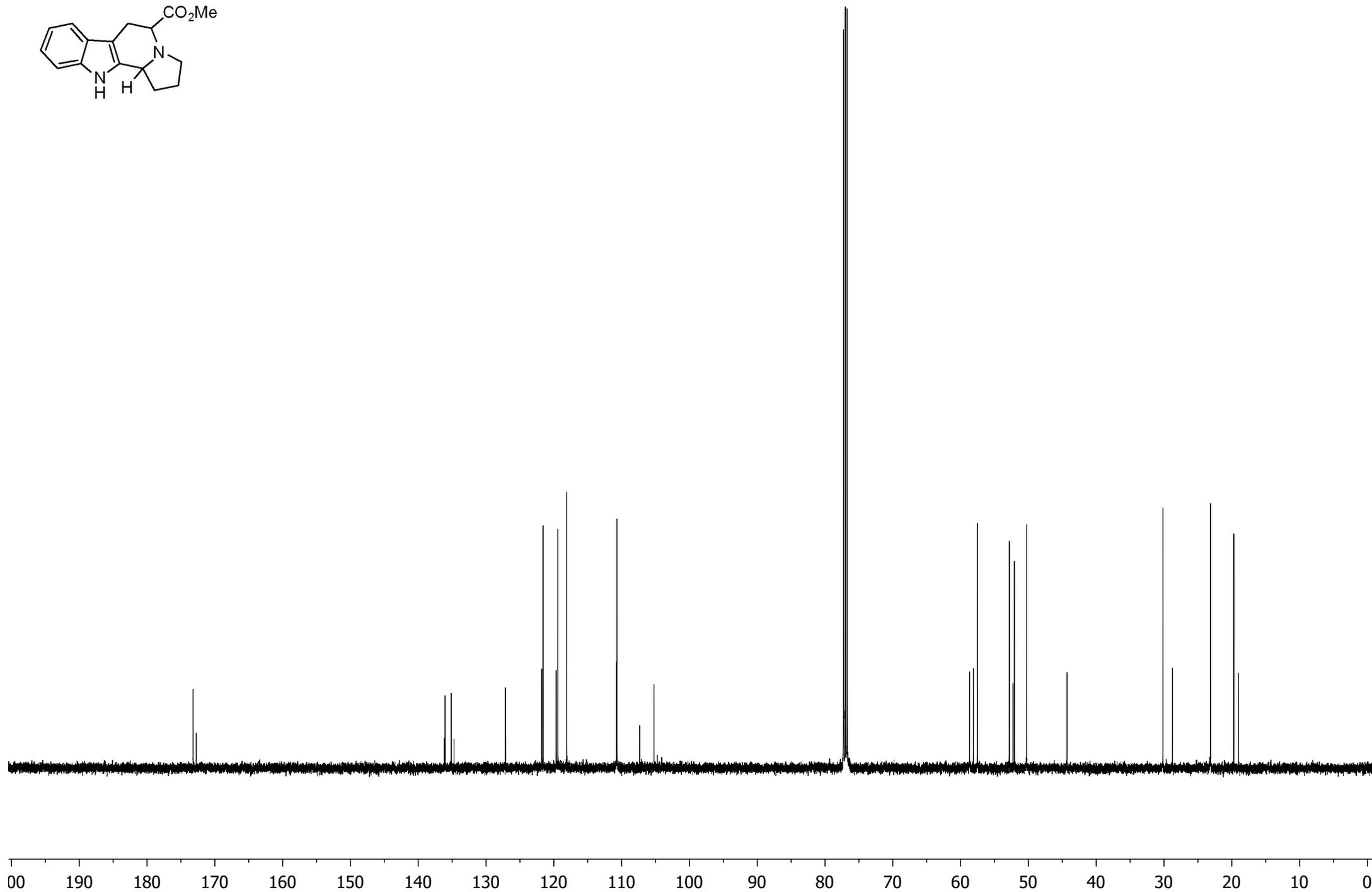
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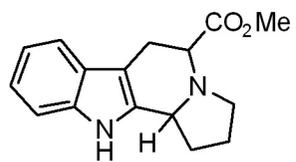
^{13}C NMR of **11** in CDCl_3



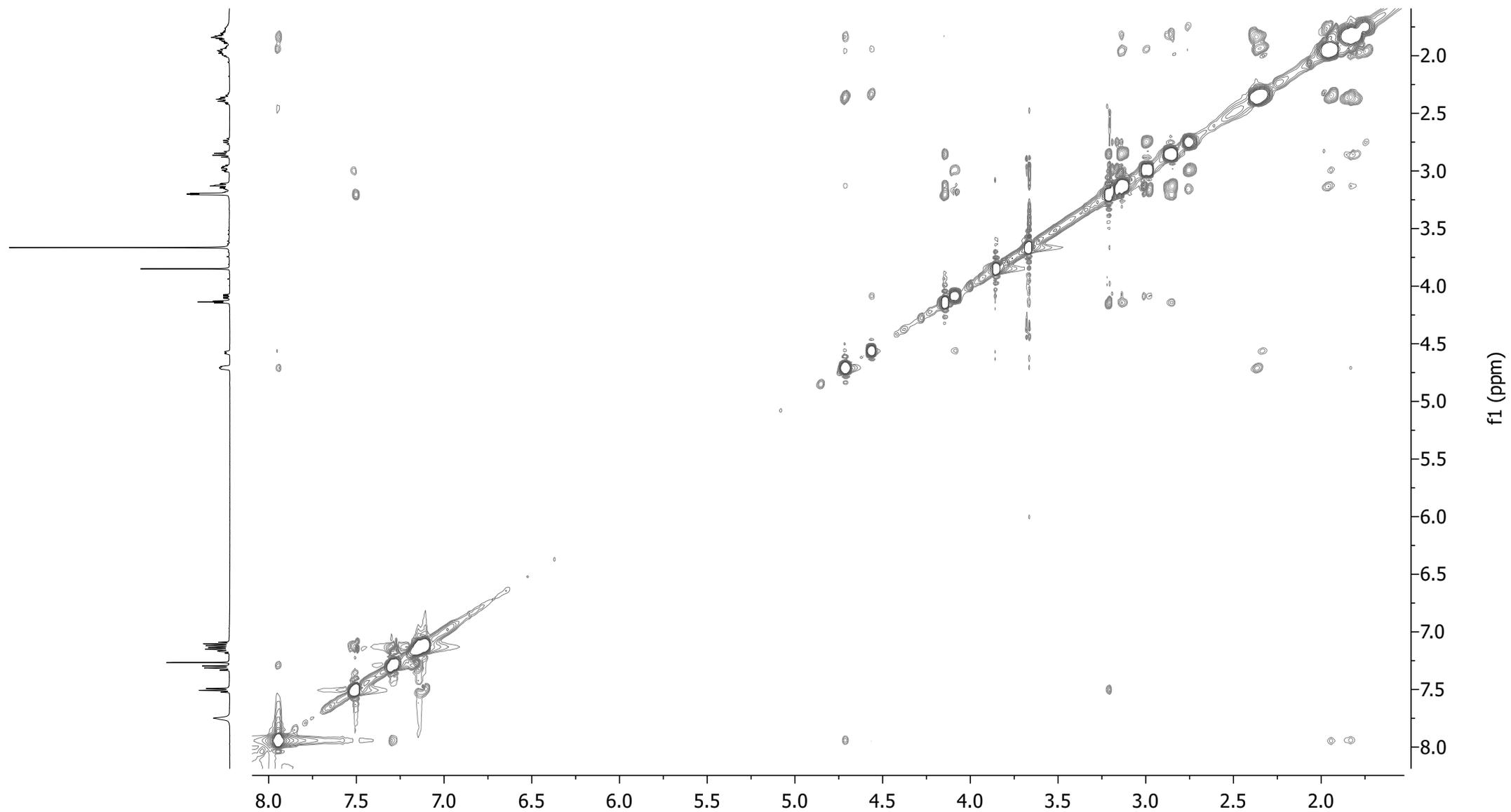
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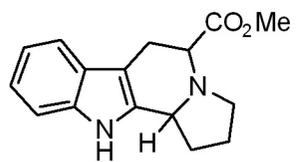
Nosy of **11** in CDCl₃



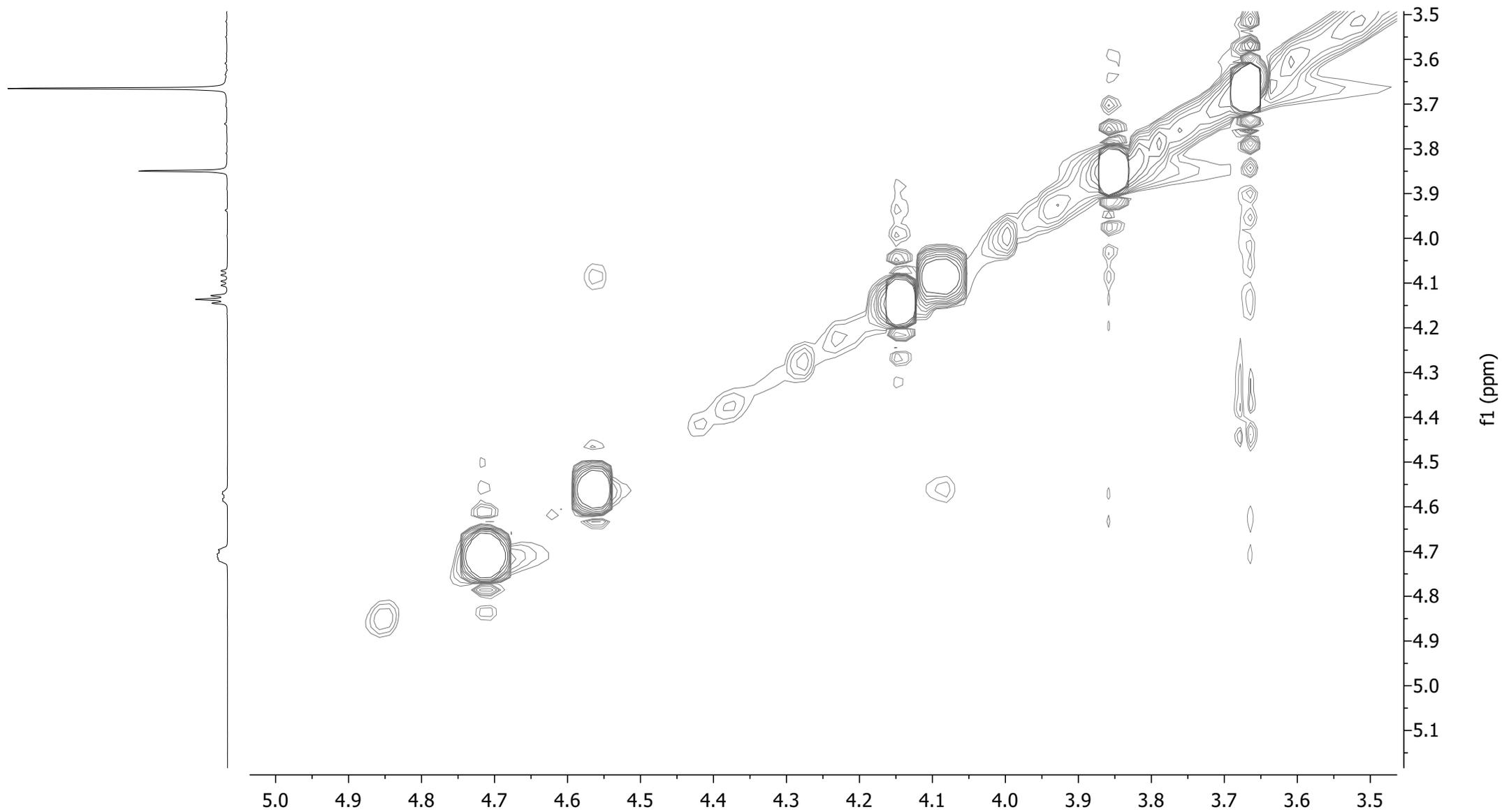
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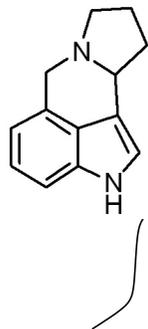
Nosy of **11** in CDCl₃



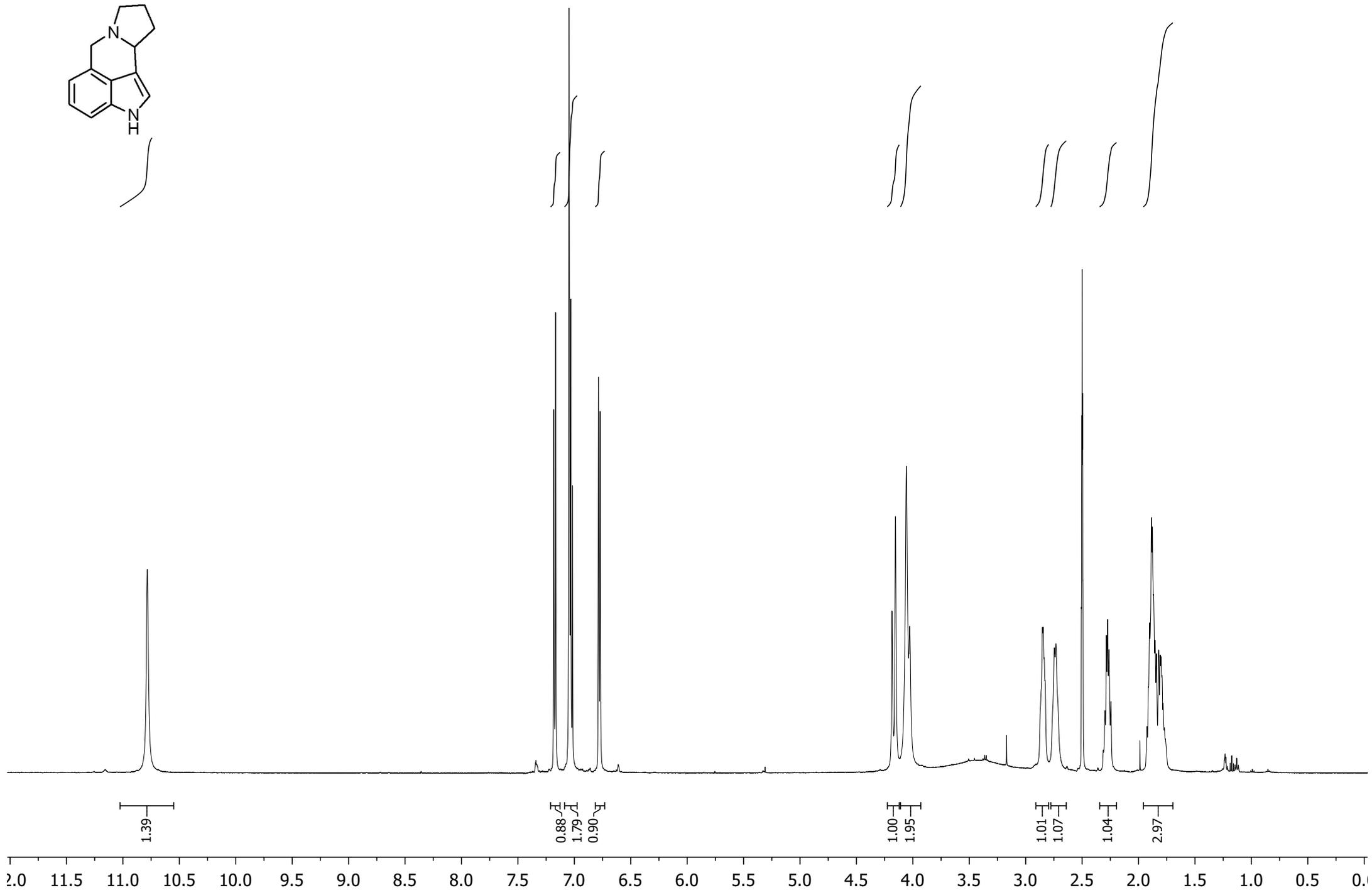
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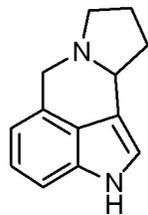
^1H NMR of **13** in $\text{DMSO-}d_6$



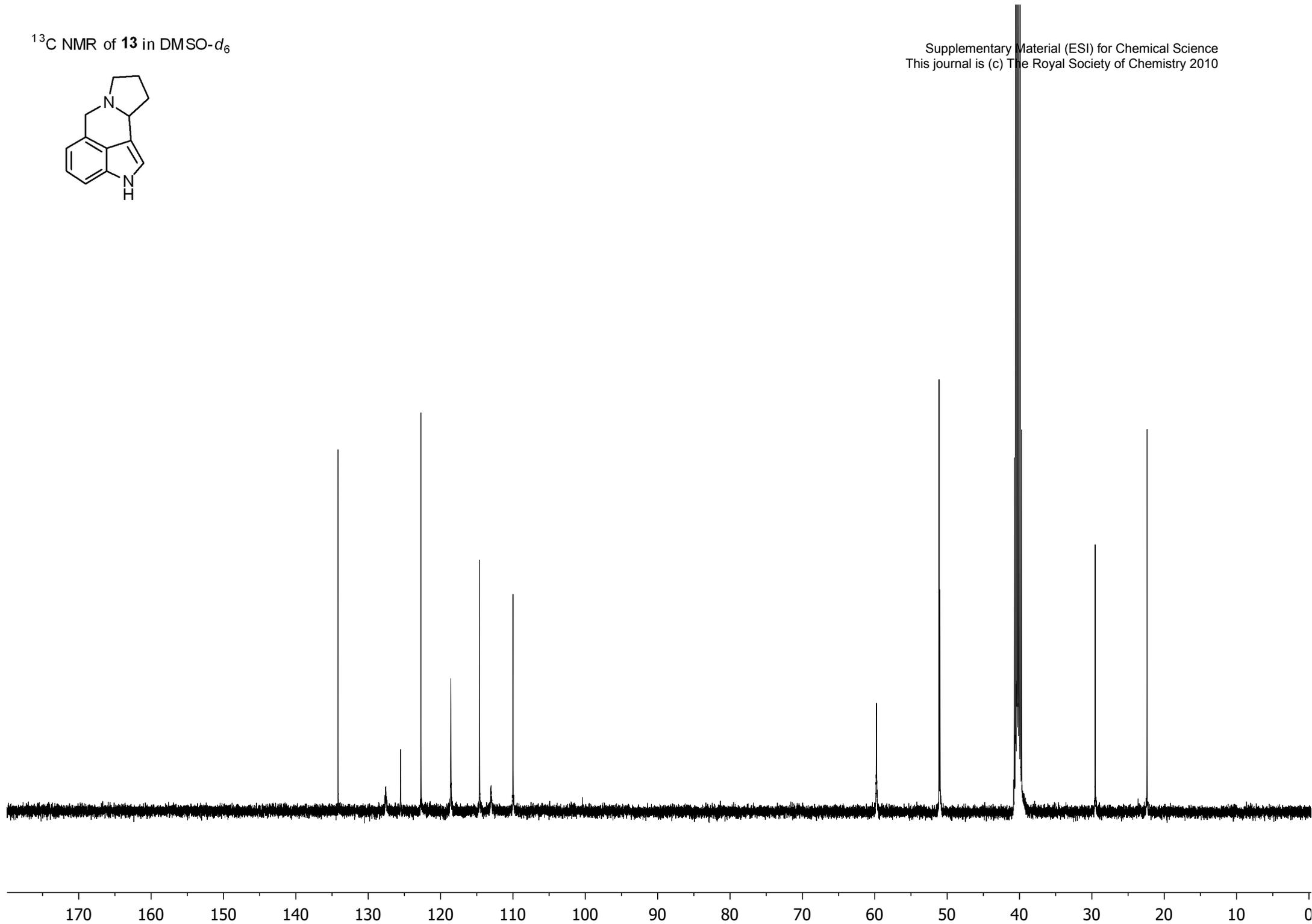
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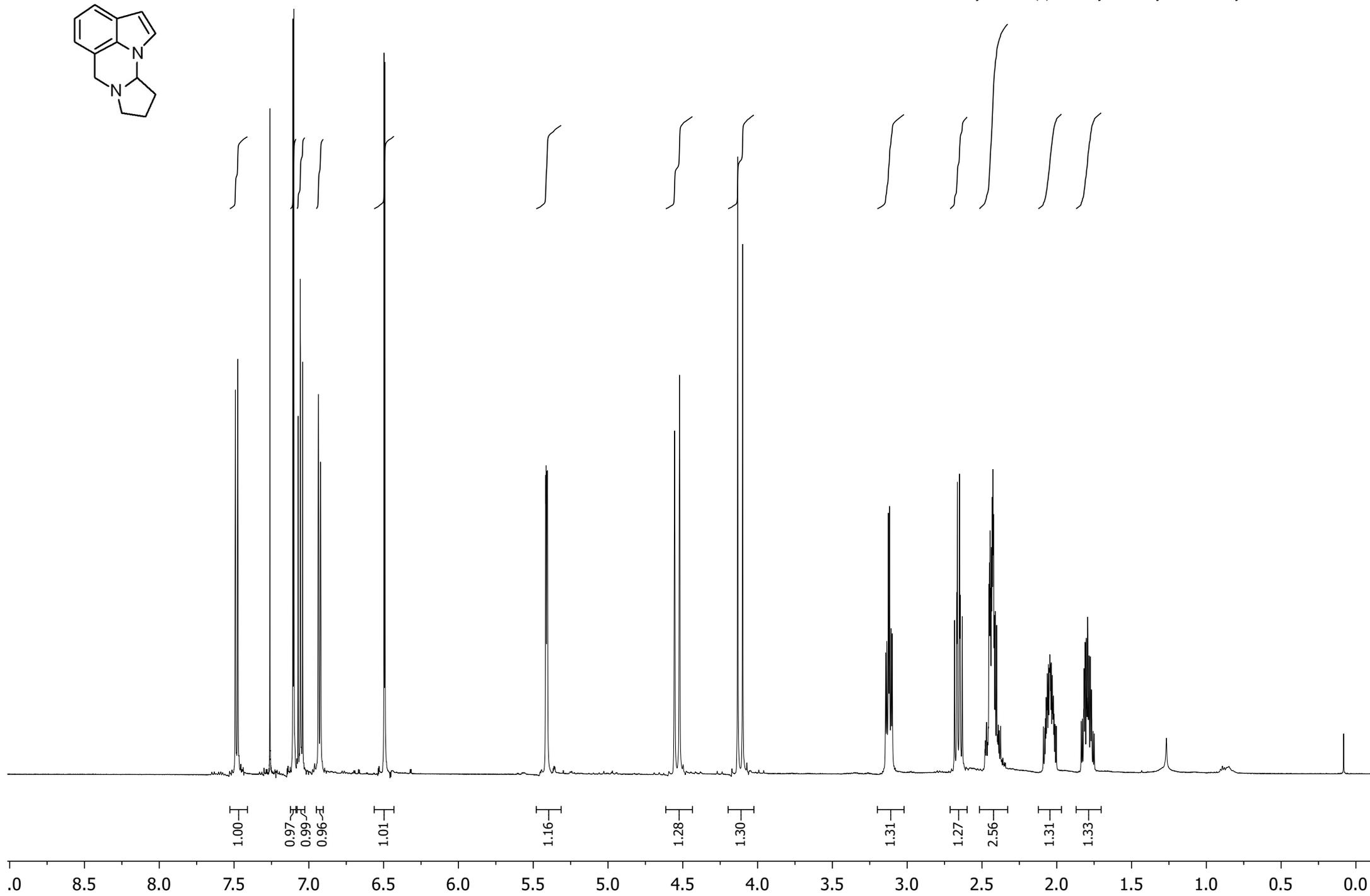
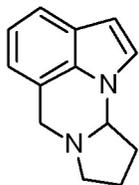


^{13}C NMR of **13** in $\text{DMSO-}d_6$



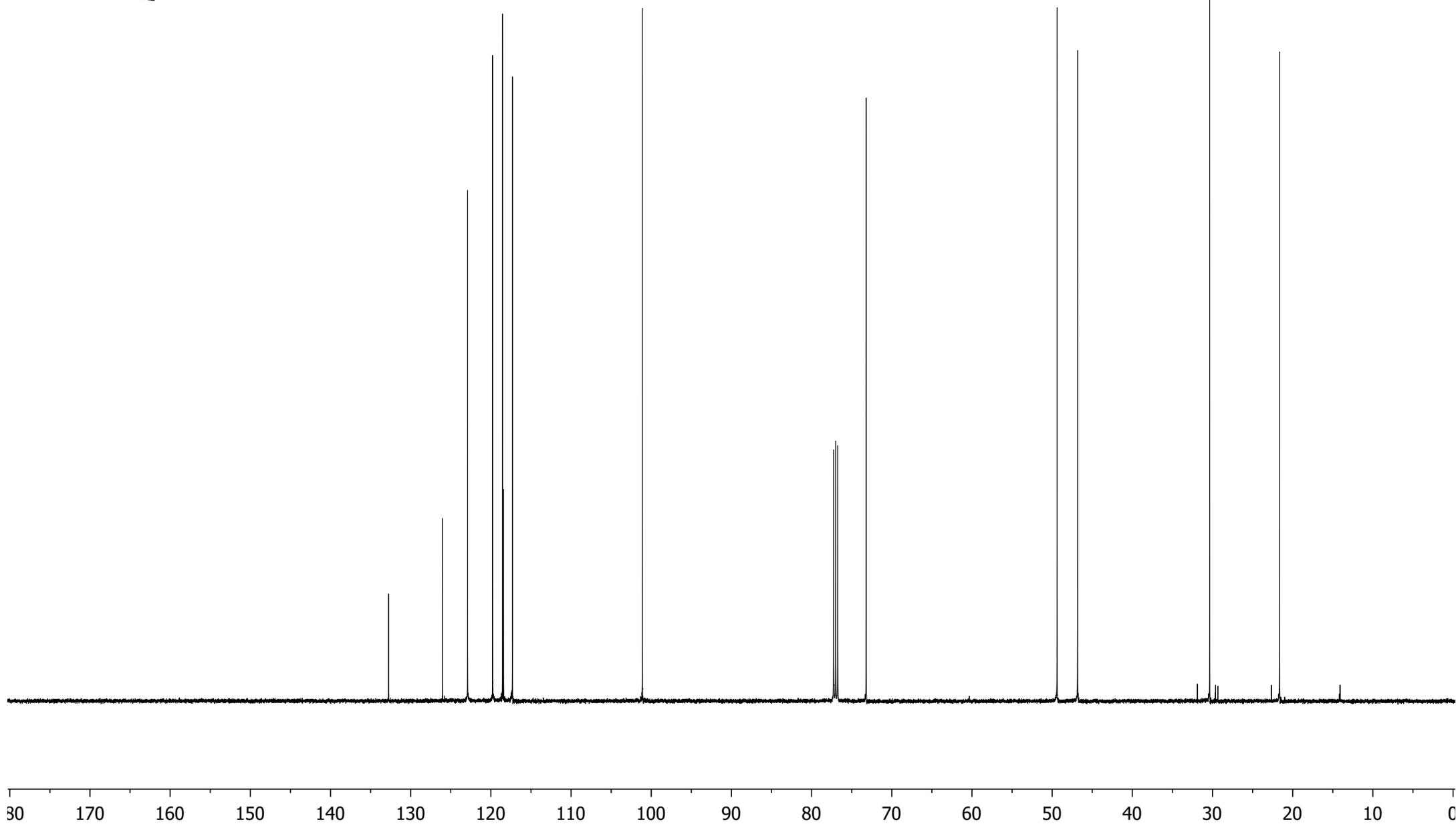
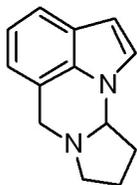
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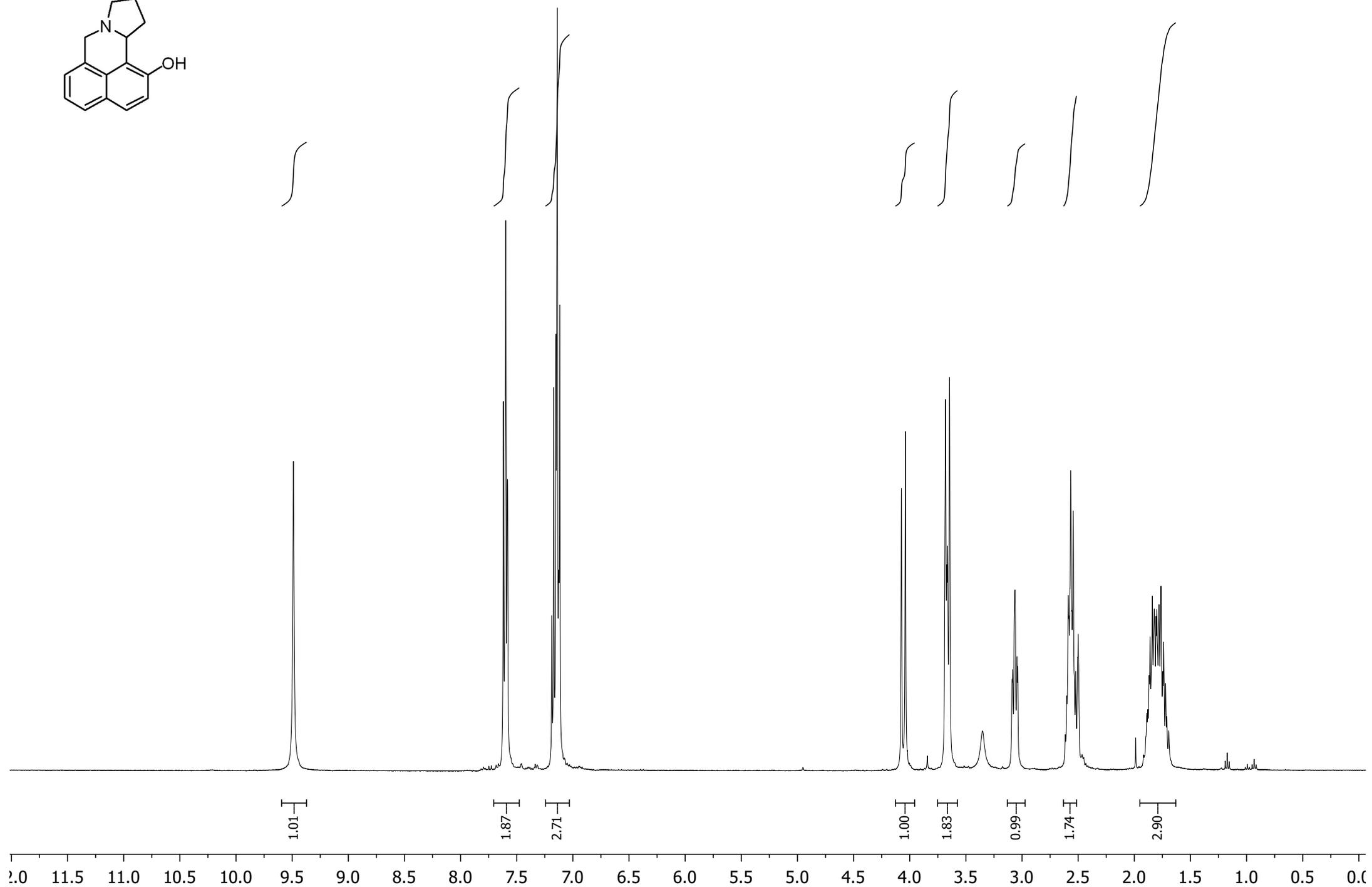
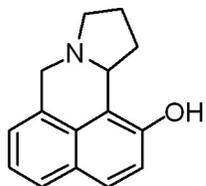




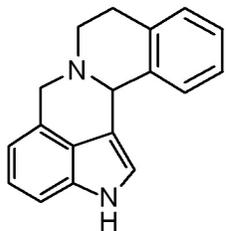
^{13}C NMR of **15** in CDCl_3

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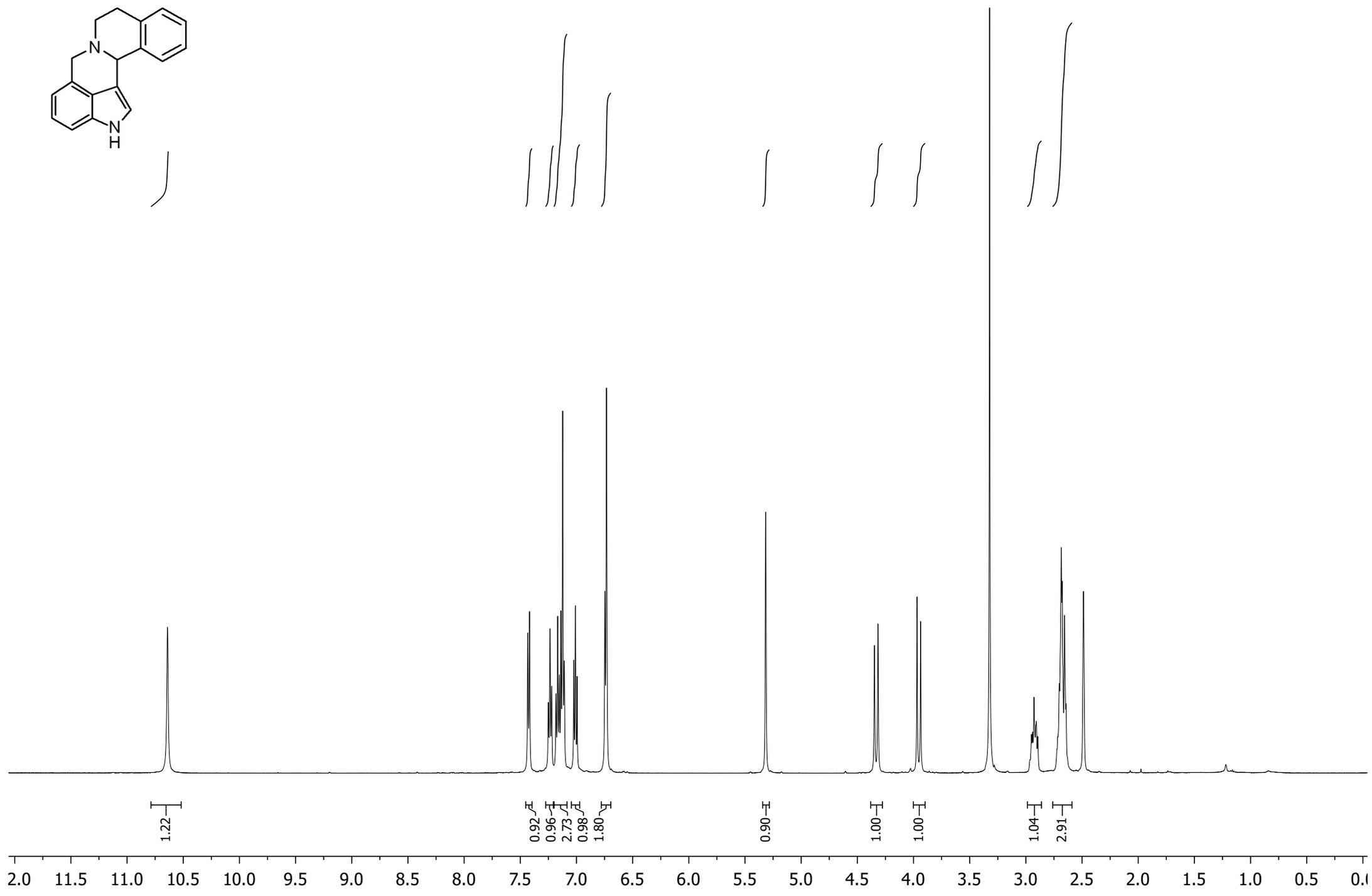




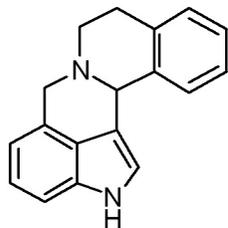
^1H NMR of **20** in $\text{DMSO}-d_6$



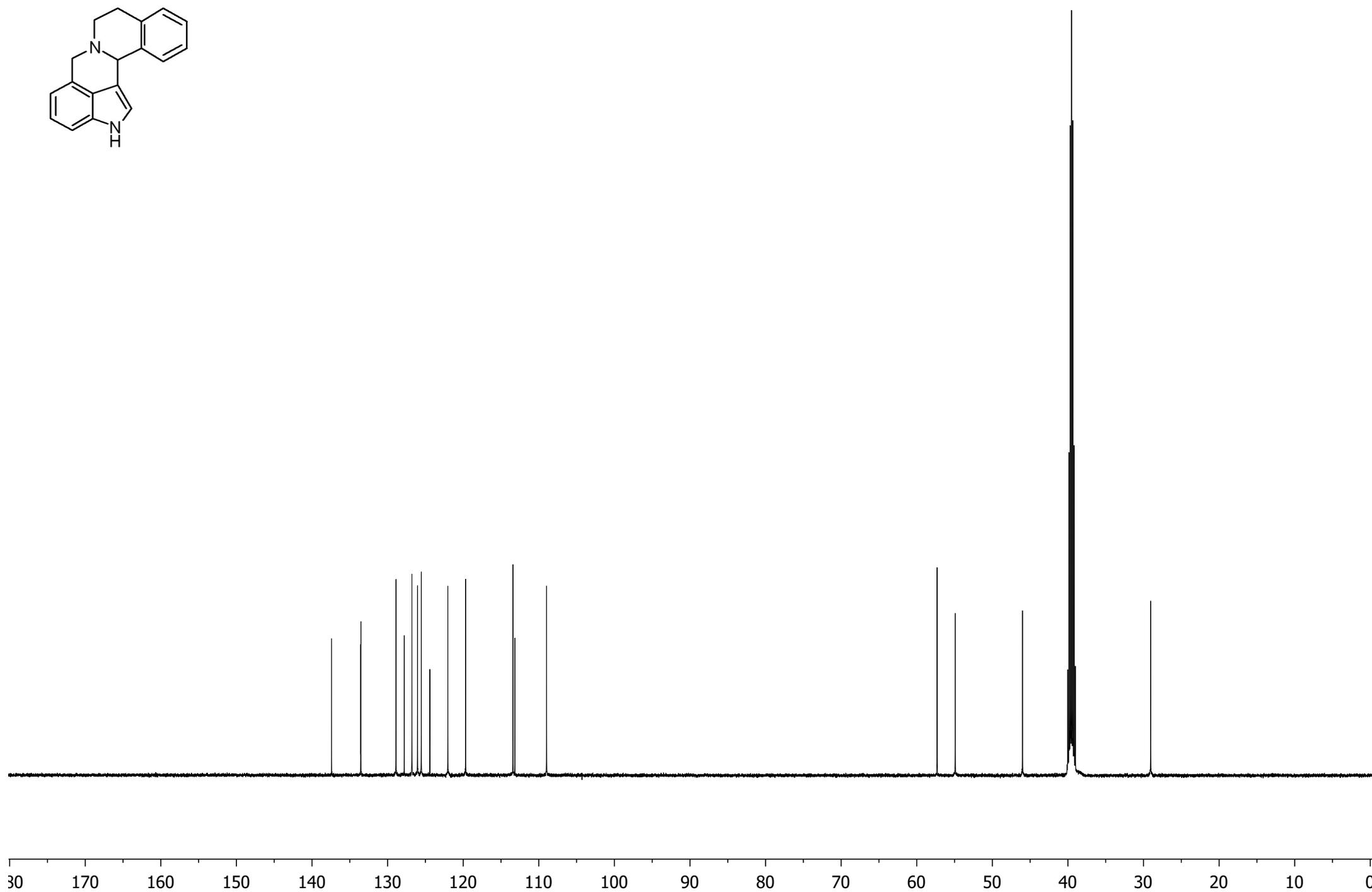
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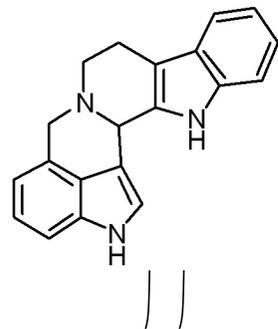
^{13}C NMR of **20** in $\text{DMSO-}d_6$



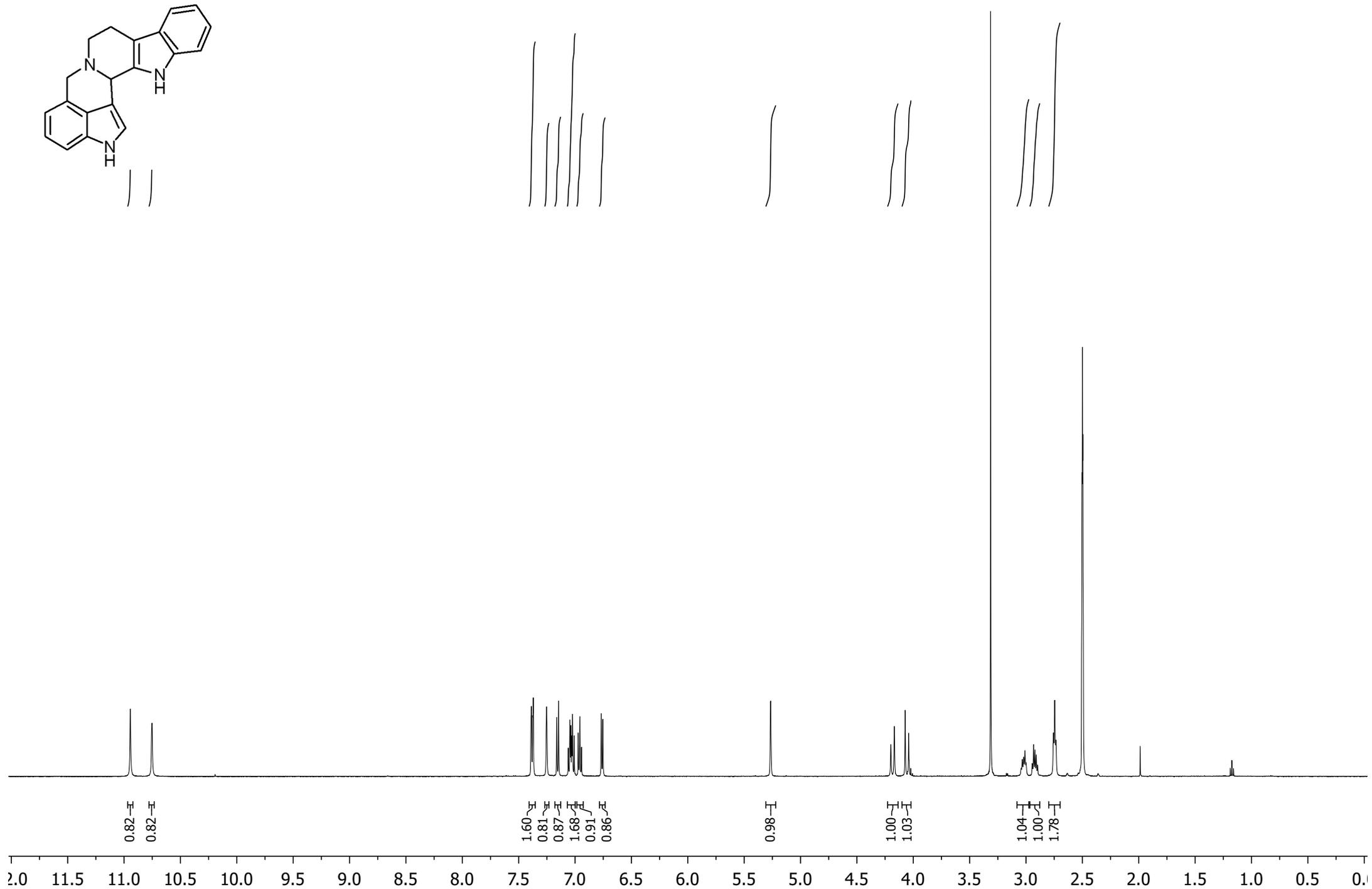
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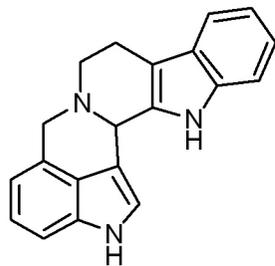
^1H NMR of **22** in $\text{DMSO-}d_6$



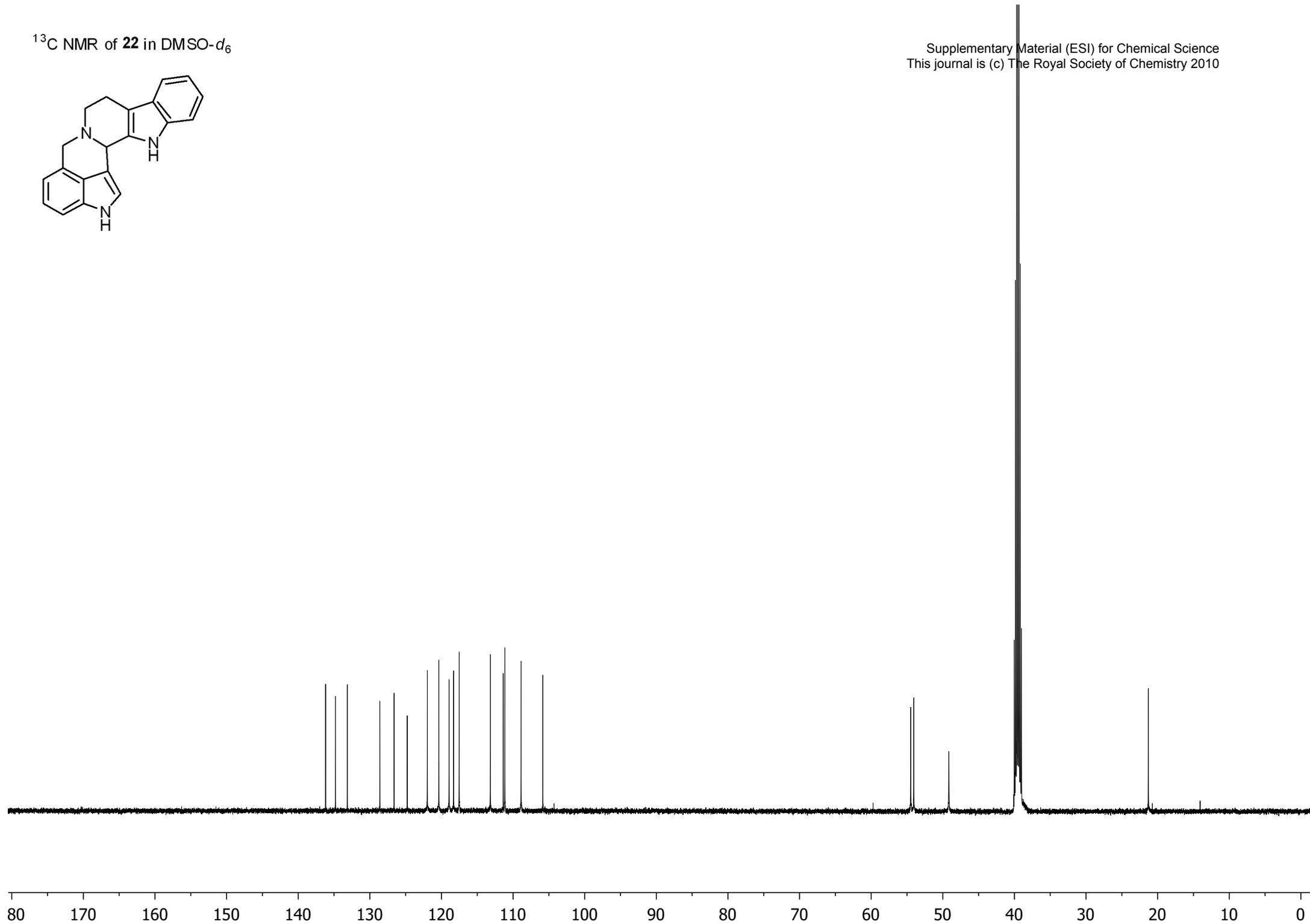
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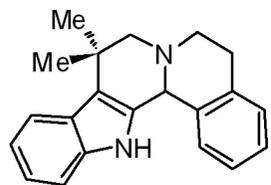
^{13}C NMR of **22** in $\text{DMSO-}d_6$



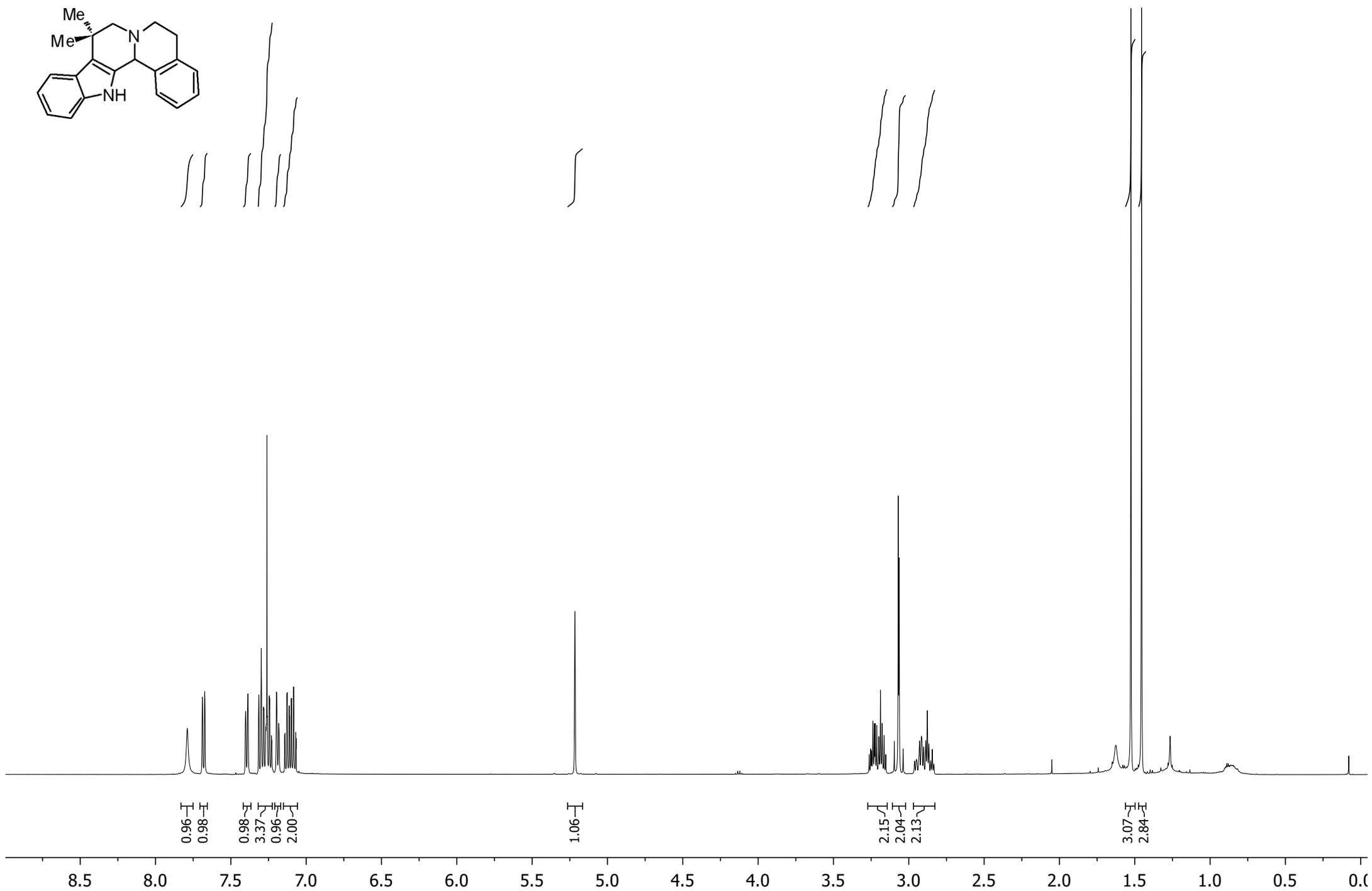
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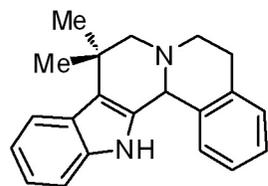
^1H NMR of **23** in CDCl_3



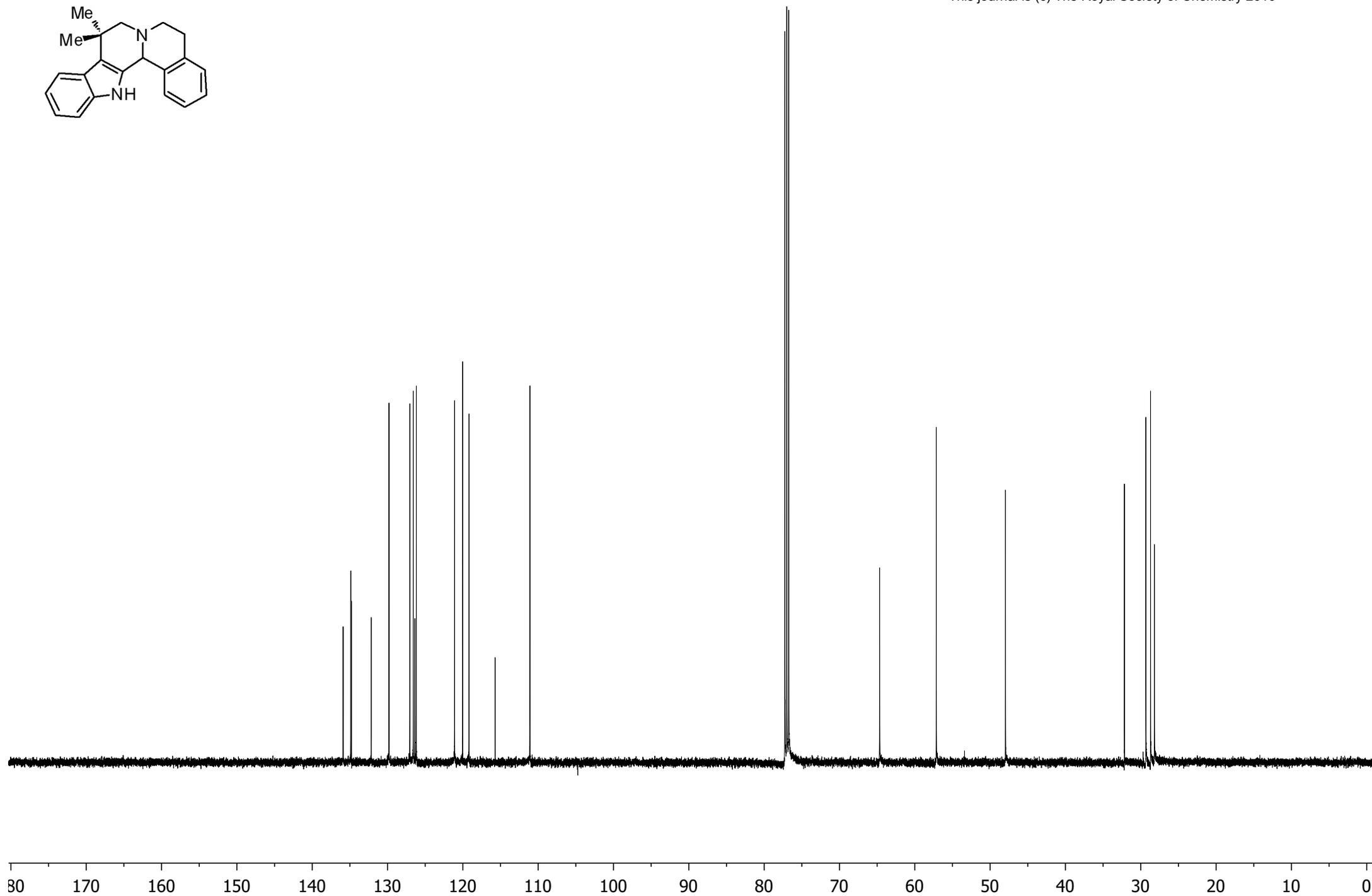
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^{13}C NMR of **23** in CDCl_3

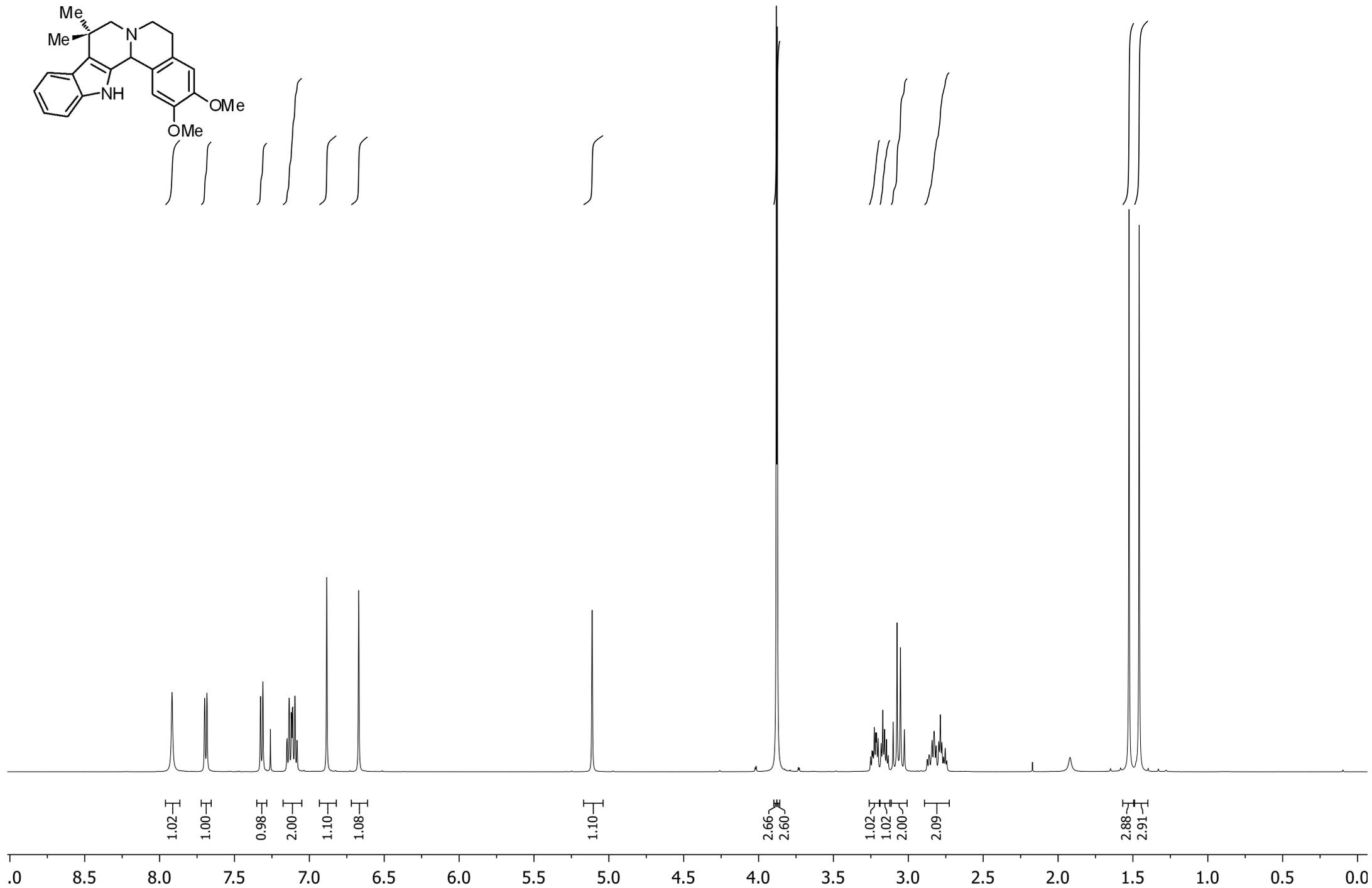
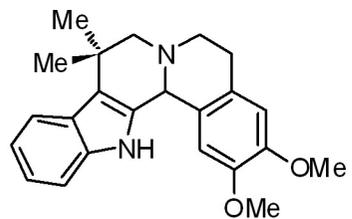


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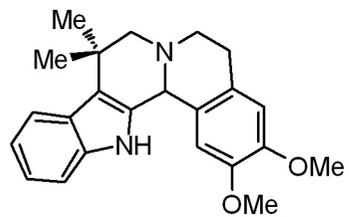


^1H NMR of **25** in CDCl_3

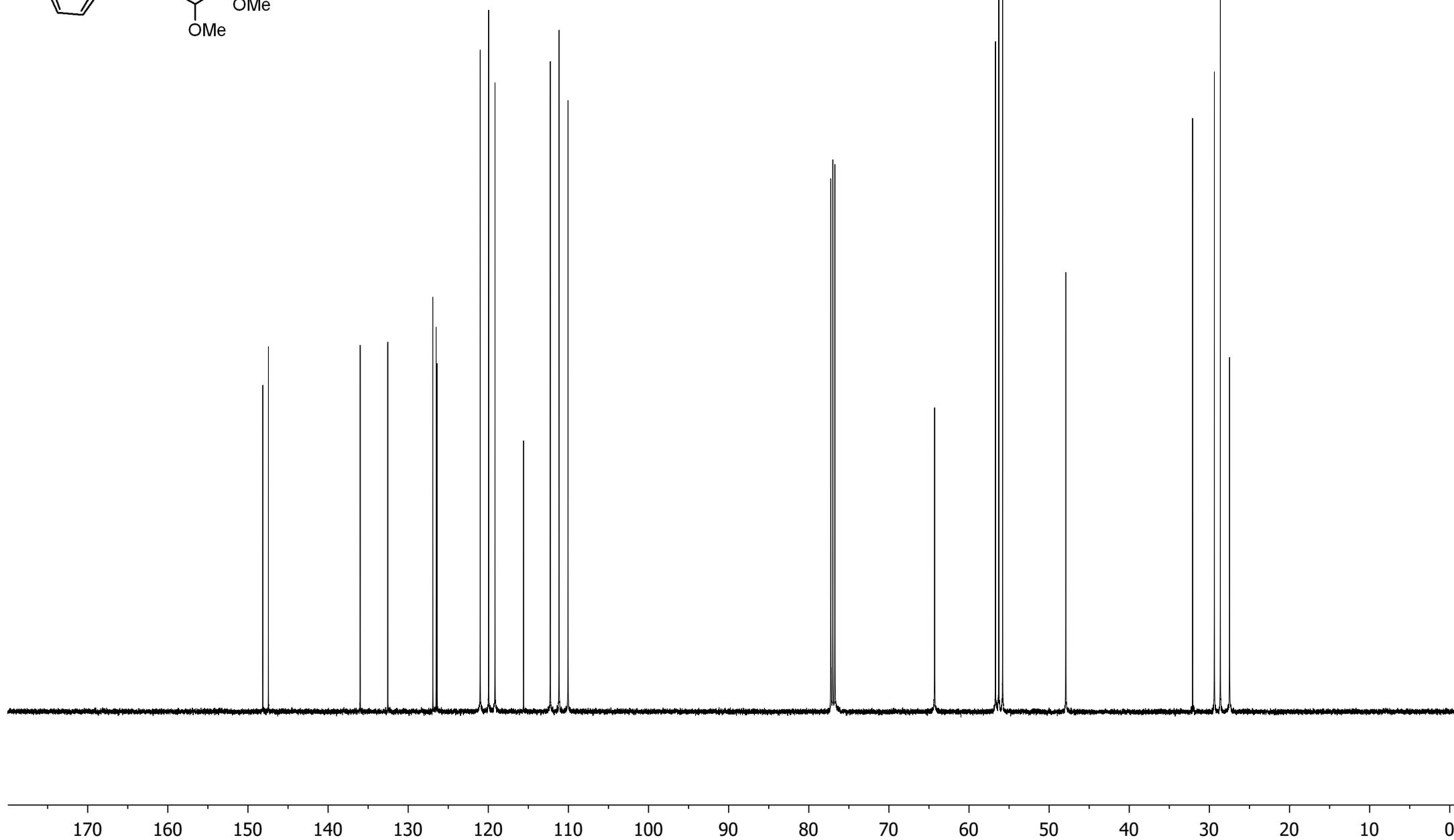
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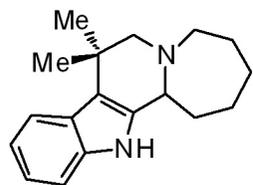
^{13}C NMR of **25** in CDCl_3



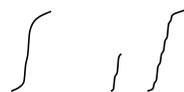
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^1H NMR of **27** in CDCl_3



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1.95

0.91

1.98

1.00

2.02

1.07

1.02

1.04

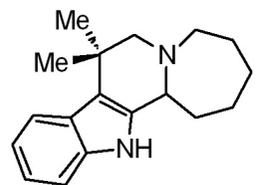
7.15

2.74

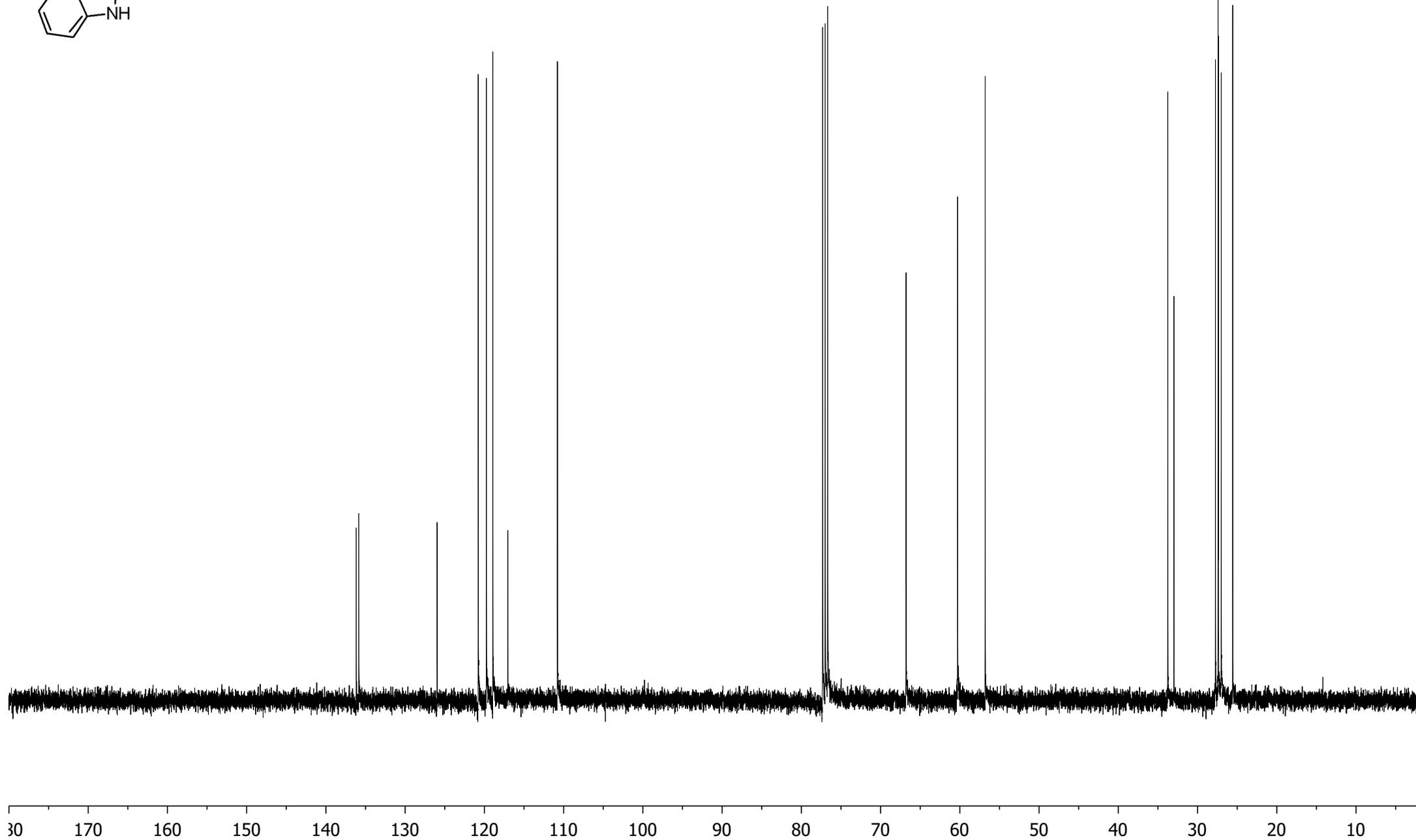
2.82

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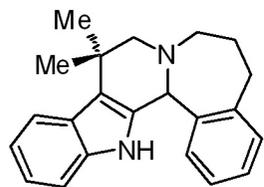
^{13}C NMR of **27** in CDCl_3



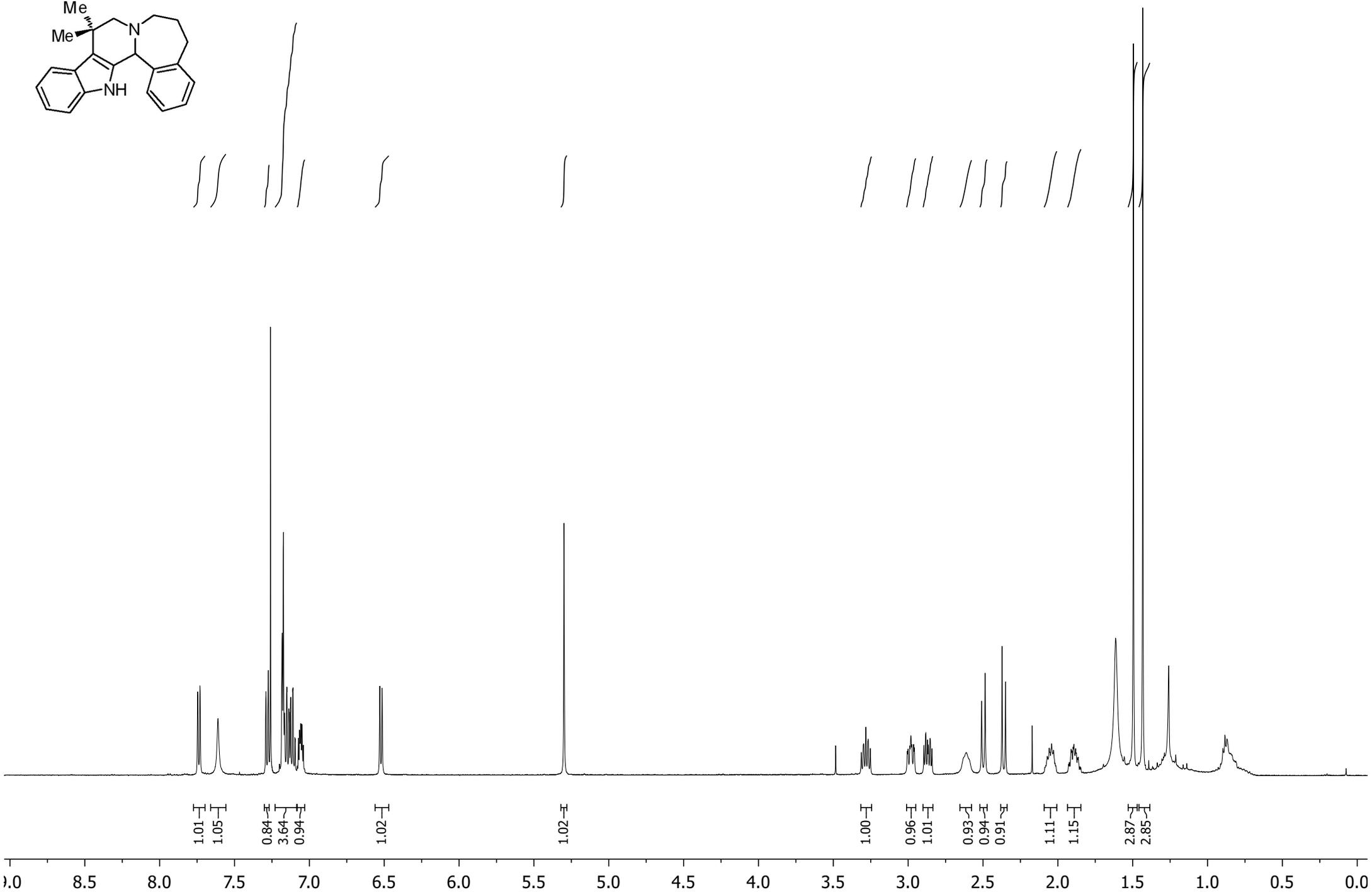
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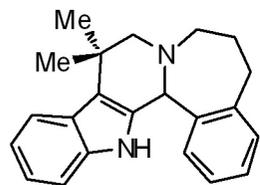
^1H NMR of **29** in CDCl_3



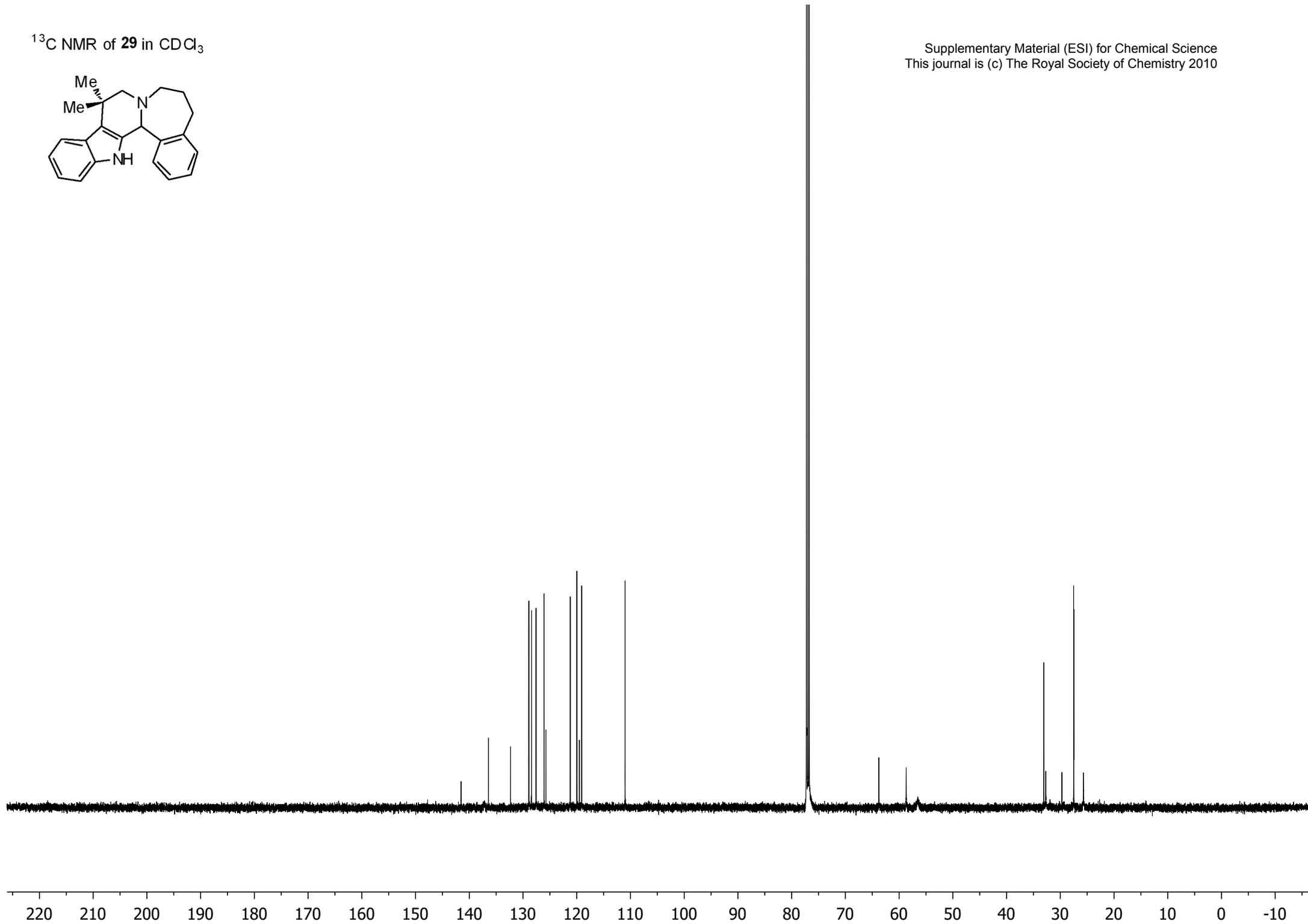
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^{13}C NMR of **29** in CDCl_3

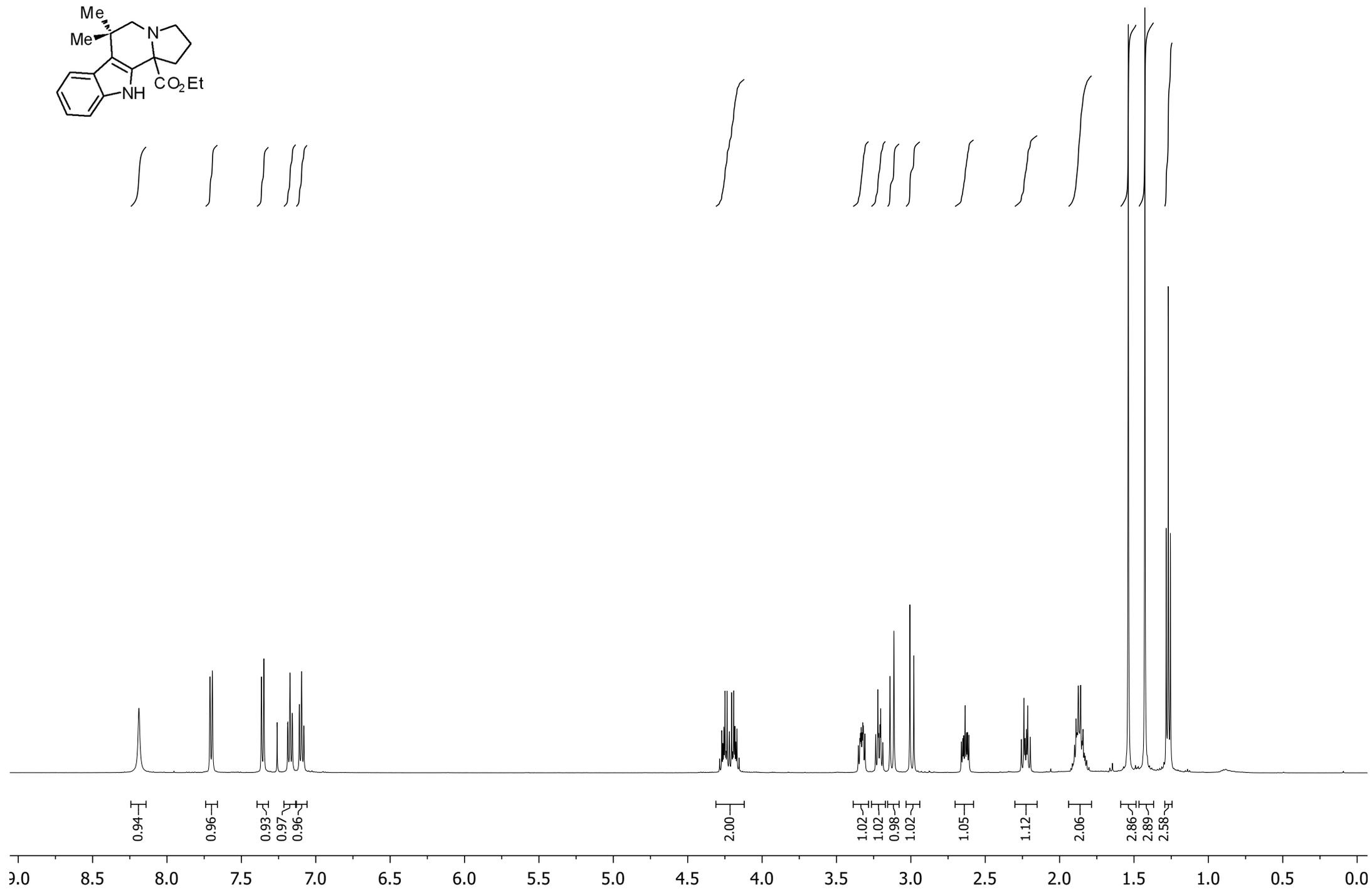
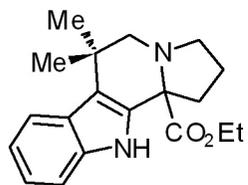


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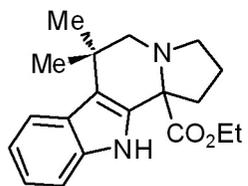


^1H NMR of **31** in CDCl_3

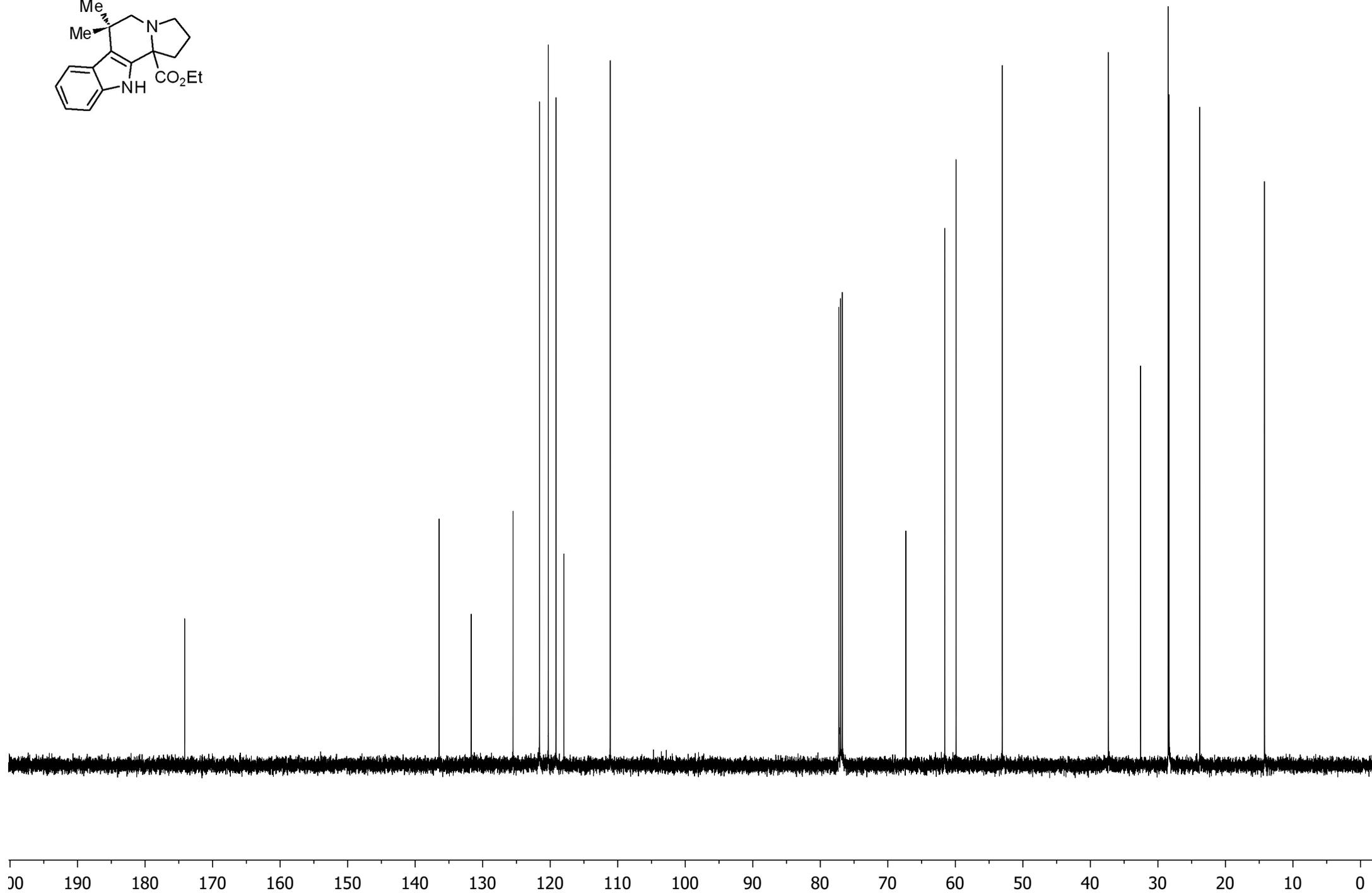
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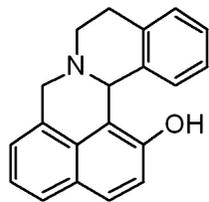
^{13}C NMR of **31** in CDCl_3



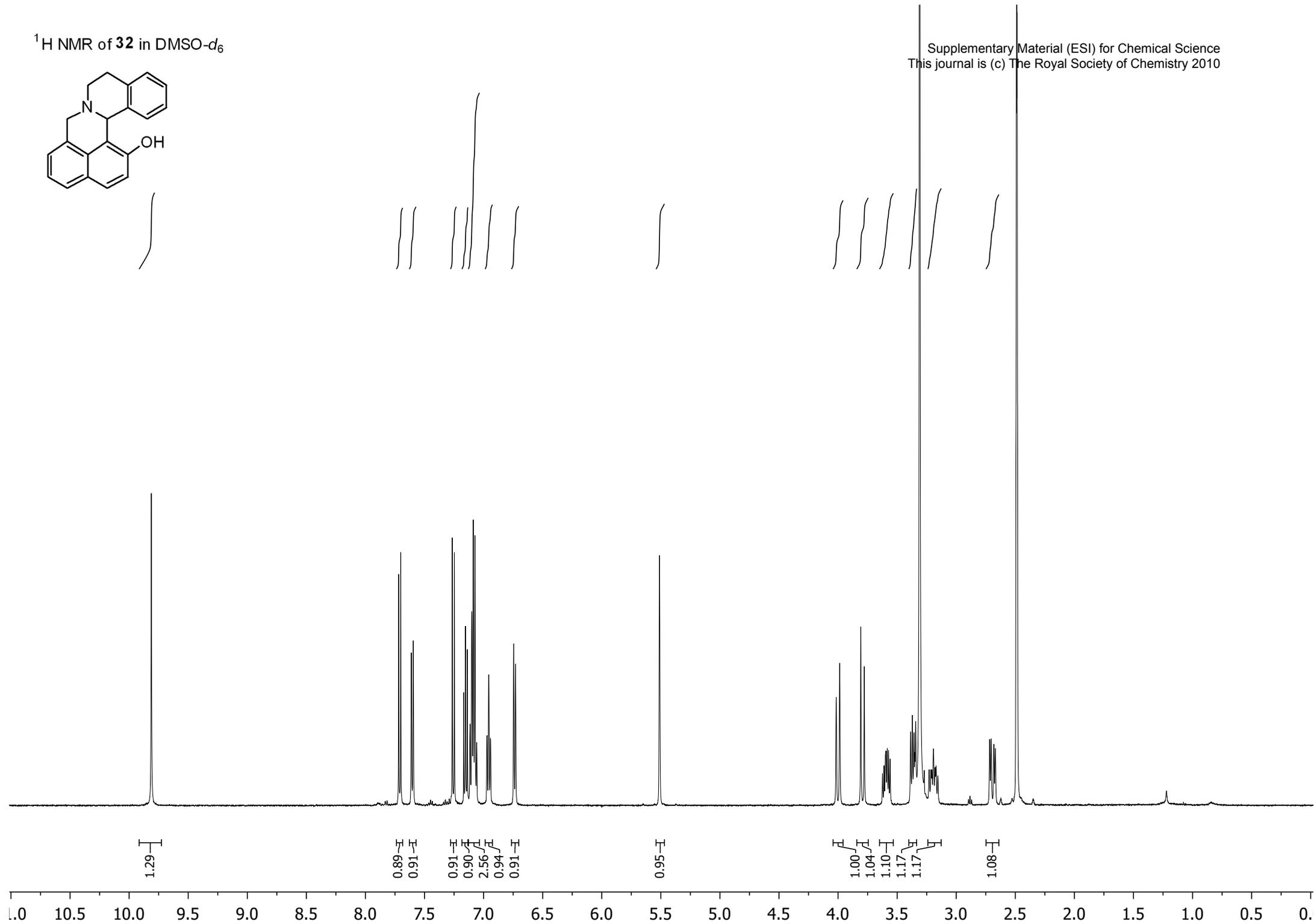
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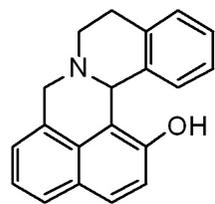
¹H NMR of **32** in DMSO-*d*₆



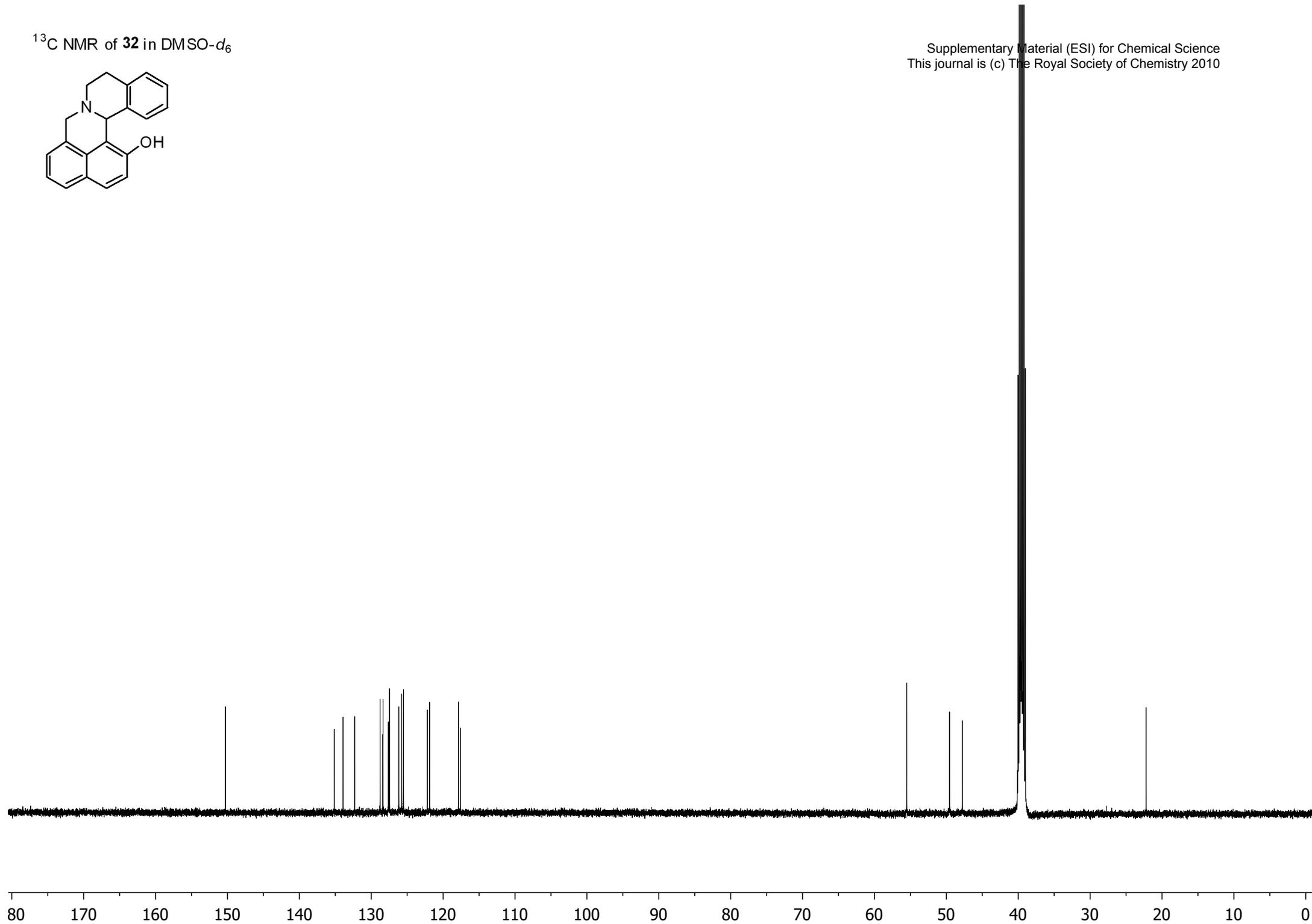
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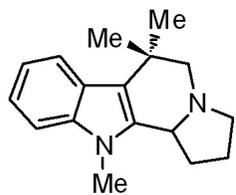
^{13}C NMR of **32** in $\text{DMSO}-d_6$



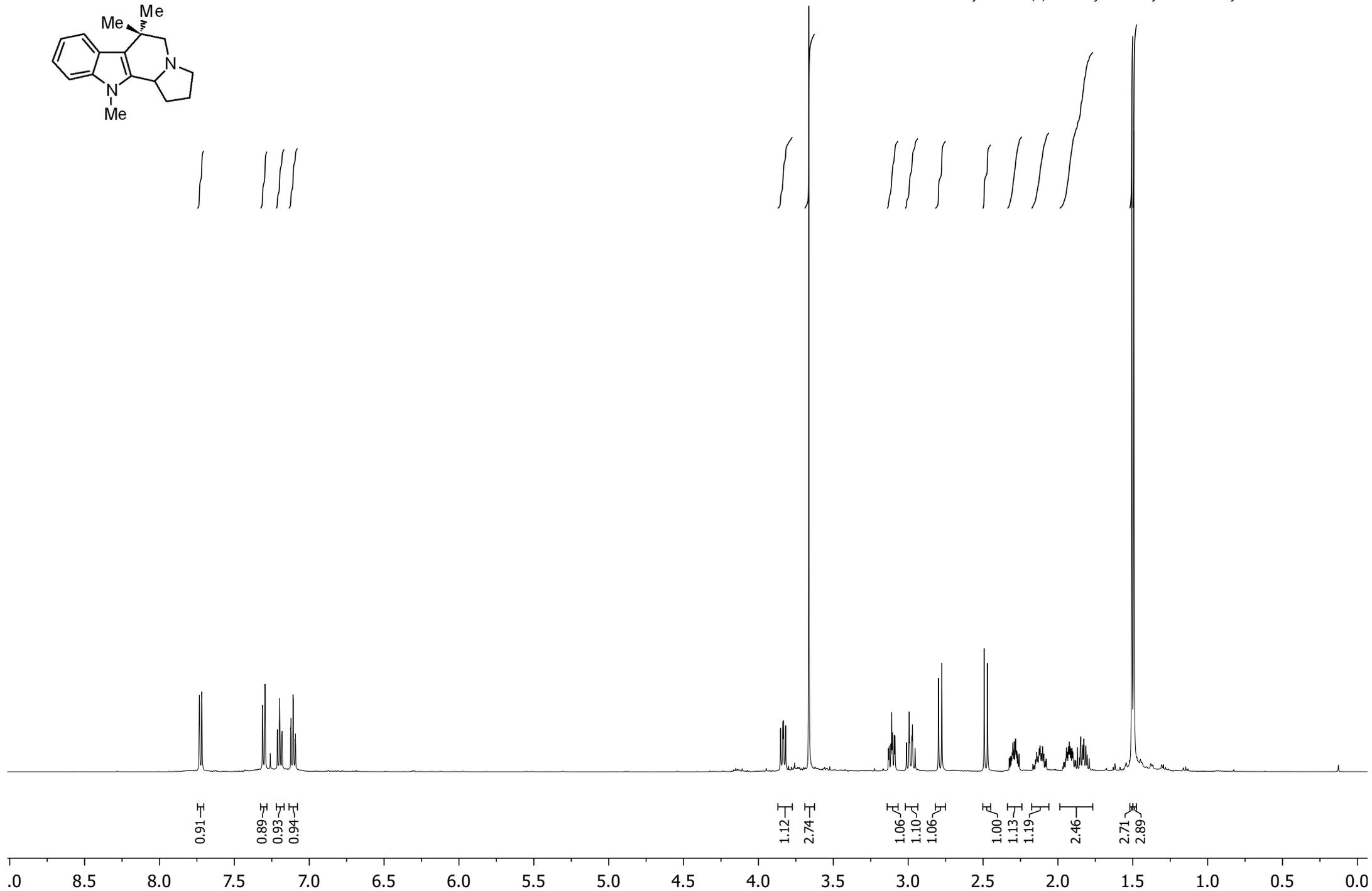
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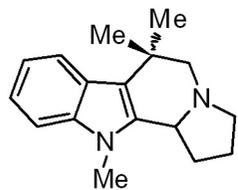
^1H NMR of **34a** in CDCl_3



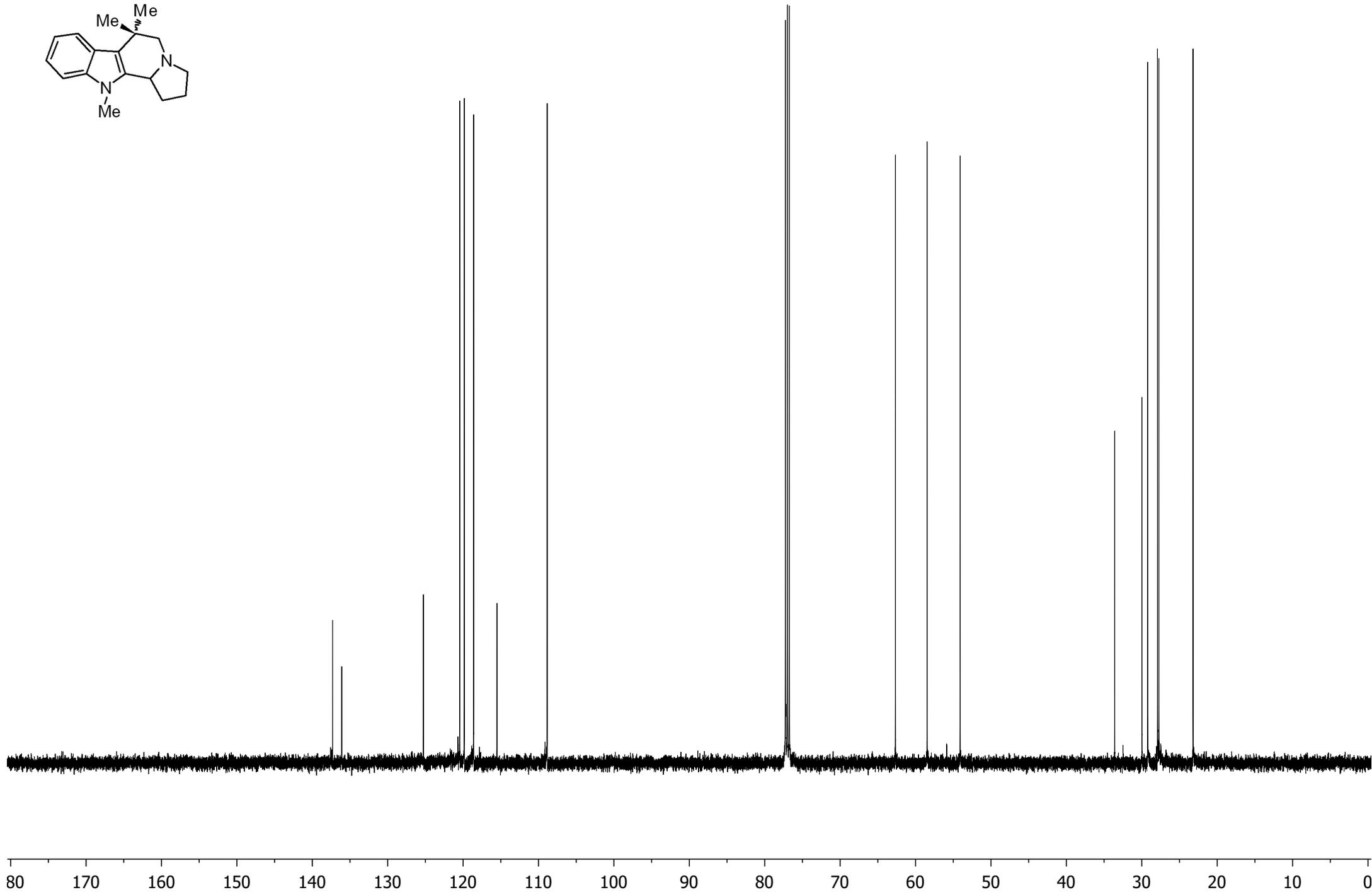
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^{13}C NMR of **34a** in CDCl_3

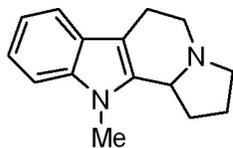


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¹H NMR of **34b** in CDCl₃

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0.74
0.81
0.85
0.88

0.85

2.50

1.02

3.80

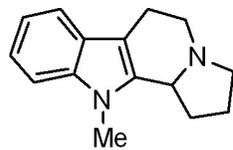
1.06

1.00

1.90
0.99

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 1.0 0.5 0.0

^{13}C NMR of **34b** in CDCl_3



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