

Supporting Information for:

**Total Synthesis of (-)-Curvulamine**

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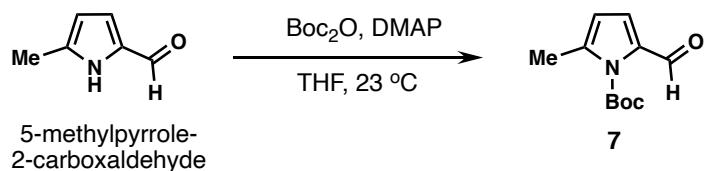
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**General Procedures:** All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air-and moisture-sensitive liquids were transferred via syringe. When indicated, solvents or reagents were degassed by sparging with argon for 10 minutes in an ultrasound bath at 25 °C. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, Merck TLC Silicagel 60 F<sub>254</sub>) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution or ceric ammonium molybdate solution, followed by brief heating on a hot plate. Flash column chromatography was performed with silica gel purchased from Silicycle (SiliaFlash®, 60 Å, 230-400 mesh, 40-63 µm). Ethyl vinyl ether and 2-bromopropanoic acid methyl ester were distilled over calcium hydride prior to use. NaHMDS solutions were purchased from Sigma. All other reagents were used as received from commercial sources, unless stated otherwise. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), methanol (MeOH), dimethylformamide (DMF), and toluene (PhMe) were obtained by passing these previously degassed solvents through activated alumina columns. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra and carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on Bruker AV-600 spectrometer at 23 °C. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual solvent (CDCl<sub>3</sub>: δ 7.26, C<sub>6</sub>D<sub>6</sub>: δ 7.16), unless stated otherwise. Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the solvent (CDCl<sub>3</sub>: δ 77.16, C<sub>6</sub>D<sub>6</sub>: δ 128.06), unless stated otherwise. Data is represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd, doublet of doublet of doublet, dt = triplet of doublets, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT- IR spectrometer as thin films and are reported in frequency of absorption (cm<sup>-1</sup>). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo Electron Corporation). X-ray diffraction data was collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Rigaku XtaLAB P200 equipped with a MicroMax

007HF rotating anode and Pilatus3 R 200K-A hybrid pixel array detector. Data were collected using CuK $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ).



**Aldehyde 7:** To a 1 L round bottom flask containing 5-methylpyrrole-2-carboxaldehyde (32.4 g, 296.9 mmol, 1.0 equiv.) was added THF (590 mL). The vigorously stirring solution was cooled to 0 °C, and DMAP (1.81 g, 14.8 mmol, 0.05 equiv.) and Di-*tert*-butyl dicarbonate (77.7 g, 356 mmol, 1.2 equiv.) were added in a single portion sequentially. The resulting suspension was removed from the cooling bath and warmed to room temp, at which point the septum was removed allowing for evolved gases to escape. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq.* NaHCO<sub>3</sub> (300 mL) and stirred for 30 minutes. The biphasic reaction mixture was poured into a separatory funnel and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The dark brown colored crude product was first filtered through a short silica gel plug (eluting with 50% EtOAc in hexanes), concentrated *in vacuo*, and purified by column chromatography (10% EtOAc in hexanes → 40% EtOAc) to afford aldehyde 7 (56.5 g, 270 mmol, 91% yield) as a yellow oil.

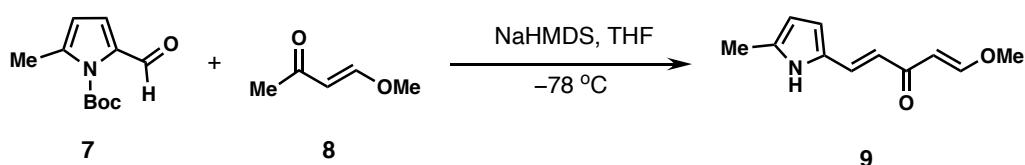
**TLC:** R<sub>f</sub> = 0.3 (40% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 9.33 (s, 1H), 6.86 (d, *J* = 3.6 Hz, 1H), 5.63 (d, *J* = 3.4 Hz, 1H), 2.13 (s, 3H), 1.28 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 178.3, 148.5, 138.2, 134.4, 120.7, 111.1, 83.9, 26.5, 14.1.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2979, 2932, 1745, 1663, 1485, 1300, 1124, 861, 798, 777.

**HRMS (m/z):** (ESI) calcd. for C<sub>11</sub>H<sub>16</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 210.1125, found 210.1126.



**Dienone 9:** To a flame-dried 1L round bottom flask was added (*E*)-4-methoxybut-3-en-2-one (**8**) (8.13

mL, 79.7 mmol, 1.0 equiv.) and THF (478 mL). The resulting solution was cooled to  $-78^{\circ}\text{C}$  and NaHMDS (1 M in THF, 104 mL, 104 mmol, 1.3 equiv.) was transferred via cannula to the reaction mixture. The resulting suspension was then stirred for 30 minutes at  $-78^{\circ}\text{C}$ . In a separate flask, aldehyde **7** (20.0 g, 95.7 mmol, 1.2 equiv.) was azeotropically dried with benzene (3x) and then dissolved in THF (20 mL) under an atmosphere of nitrogen. The aldehyde solution was then transferred via cannula to the reaction mixture, with an additional THF (5 mL) rinse ensuring quantitative transfer. The resulting reaction mixture was then stirred at  $-78^{\circ}\text{C}$  for 1 hour, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with saturated *aq.* NH<sub>4</sub>Cl (200 mL) at  $-78^{\circ}\text{C}$ . The mixture was warmed to room temperature and extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The dark brown colored crude material was purified by column chromatography (10% EtOAc in hexanes  $\rightarrow$  45% EtOAc in hexanes) to afford dienone **9** (10.8 g, 56.5 mmol, 71%) as an orange solid.

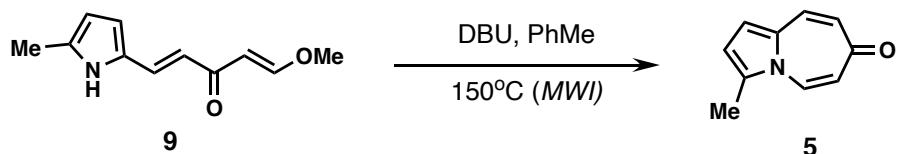
**TLC:** R<sub>f</sub> = 0.4 (40% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  9.08 (s, 1H), 7.70 (d, *J* = 12.3 Hz, 1H), 7.48 (d, *J* = 15.7 Hz, 1H), 6.50 (br s, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 5.98 (br s, 1H), 5.86 (d, *J* = 12.4 Hz, 1H), 3.75 (s, 3H), 2.34 (s, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  189.3, 162.6, 135.1, 132.8, 128.1, 118.0, 116.8, 109.8, 104.5, 57.6, 13.4.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3255, 1600, 1546, 1274, 1089, 1035, 778, 618.

**HRMS (m/z):** (ESI) calcd. for C<sub>11</sub>H<sub>14</sub>NO<sub>2</sub> [M+H]<sup>+</sup> m/z: 192.1019, found 192.1020.



**Pyrroloazepinone 5:** To a 20 mL Biotage microwave vial was added dienone **9** (2.0 g, 11.2 mmol, 1.0 equiv.), toluene (20 mL), and DBU (3.2 mL, 21.4 mmol, 2.0 equiv.). The resulting orange colored solution was sealed, placed in a Biotage microwave reactor, and heated at 150 °C for 2 hours. Upon cooling, the contents of five of these identical reactions were combined and concentrated *in vacuo*. The black-colored crude residue was filtered through a silica gel plug

(eluting with 60% EtOAc in hexanes), concentrated *in vacuo*, and then purified by column chromatography (15% EtOAc in hexanes → 50% EtOAc) to afford a yellow oil which slowly solidified. Slow overnight crystallization of **5** from benzene afforded a white solid (1.0 g, 6.2 mmol, 60% yield) of slightly higher purity.

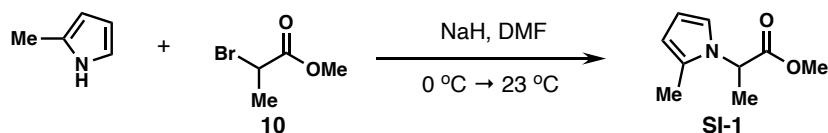
**TLC:**  $R_f = 0.4$  (50% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (d,  $J = 10.6$  Hz, 1H), 7.09 (d,  $J = 12.2$  Hz, 1H), 6.61 (d,  $J = 3.7$  Hz, 1H), 6.27 (d,  $J = 3.3$  Hz, 1H), 6.12 (dd,  $J = 12.2, 2.4$  Hz, 1H), 5.90 (dd,  $J = 10.6, 2.4$  Hz, 1H), 2.40 (s, 3H).

**$^{13}\text{C NMR}$**  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  187.6, 134.0, 132.7, 130.1, 130.0, 123.9, 117.8, 114.9, 112.7, 13.10.

**IR** (thin film)  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3108, 3031, 2980, 2923, 1640, 1610, 1495, 1396, 1347, 1261, 1139, 1027, 844, 763, 660.

**HRMS (m/z):** (ESI) calcd. for  $\text{C}_{10}\text{H}_{10}\text{ON} [\text{M}+\text{H}]^+$ : 160.0757, found 160.0756.



**Pyrrole Methyl Ester **SI-1**:** A dry 100 mL round bottom flask was charged NaH (964 mg (60% dispersion in mineral oil), 24.6 mmol, 2.0 equiv.) and evacuated and backfilled with nitrogen three times. Hexanes (10.0 mL) was added and the suspension was swirled. Upon settling of the suspension, the hexane was carefully removed via syringe under nitrogen. The flask containing the rinsed NaH was then charged with DMF (20.0 mL) and cooled to 0 °C, wherein 2-methyl pyrrole (1.06 mL, 12.3 mmol, 1.0 equiv.) was added and stirring continued for 30 minutes at 0 °C. Methyl 2-bromopropanoate (**10**) (2.47 mL, 24.6 mmol, 2.0 equiv.) was then added to the reaction mixture, and upon completion of the addition, the mixture was removed from the cooling bath and warmed to room temperature. Upon completion of the reaction, as indicated by TLC, the reaction was cooled back to 0 °C and quenched with saturated *aq.*  $\text{NH}_4\text{Cl}$  (100 mL). The mixture was warmed to room temperature and extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The brown colored crude material was purified by column chromatography (0% EtOAc in hexanes → 15% EtOAc in hexanes) to afford **SI-1** (1.47 g, 8.7 mmol, 71%) as a yellow oil.

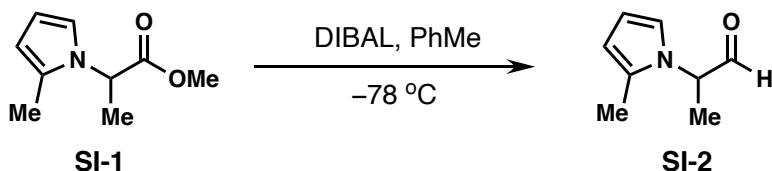
**TLC:**  $R_f = 0.4$  (10% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.68 (dd,  $J = 3.0, 1.8$  Hz, 1H), 6.28 (t,  $J = 3.2$  Hz, 1H), 6.03 (m, 1H), 4.34 (q,  $J = 7.2$  Hz, 1H), 3.16 (s, 3H), 2.01 (s, 3H), 1.31 (d,  $J = 7.2$  Hz, 3H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 171.4, 128.4, 117.4, 108.4, 107.9, 53.6, 51.8, 17.9, 12.1.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2989, 2950, 1742, 1420, 1296, 1204, 1086, 773, 700.

**HRMS (m/z):** (ESI) calcd. for C<sub>8</sub>H<sub>12</sub>ON [M+H]<sup>+</sup>: 168.1019, found 168.1013.



**Pyrrole Aldehyde SI-2:** To a 500 mL round bottom flask was added PhMe (250 mL) and pyrrole methyl ester **SI-1** (7.0 g, 41.9 mmol, 1.0 equiv.). The mixture was cooled to  $-78^\circ\text{C}$ , and DIBAL (1M in hexanes, 46 mL, 46.1 mmol, 1.1 equiv.) was added dropwise over 15 minutes. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq.* Rochelle's salt solution (50 mL) and warmed to room temperature by removing the vessel from the cooling bath. The resulting biphasic suspension was stirred until the cloudiness dissipated ( $\sim 2$  hours). The mixture was then poured into a separatory funnel and extracted with Et<sub>2</sub>O (3 x 300 mL), the combined organics were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (10% Et<sub>2</sub>O in hexanes  $\rightarrow$  50% Et<sub>2</sub>O in hexanes) to afford aldehyde **SI-2** (5.5 g, 40.1 mmol, 95%) as a colorless oil.

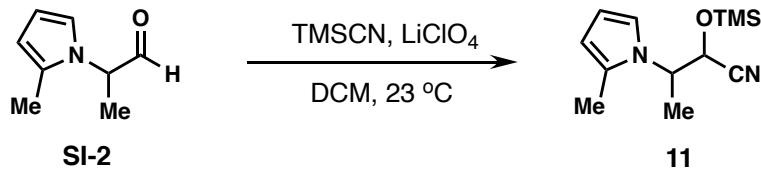
**TLC:**  $R_f = 0.4$  (40% Et<sub>2</sub>O in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 9.03 (d,  $J = 0.7$  Hz, 1H), 6.28 (dd,  $J = 11.3, 5.2$  Hz, 2H), 6.04 (m, 1H), 3.77 (q,  $J = 7.2$  Hz, 1H), 1.81 (s, 3H), 1.02 (d,  $J = 7.2$ , 3H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 197.9, 128.0, 117.4, 109.0, 108.6, 59.8, 14.9, 12.0.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2982, 2936, 2826, 1734, 1448, 1231, 703.

**HRMS (m/z):** (ESI) calcd. for C<sub>9</sub>H<sub>14</sub>O<sub>2</sub>N [M+H]<sup>+</sup>: 138.0913, found 138.0913.



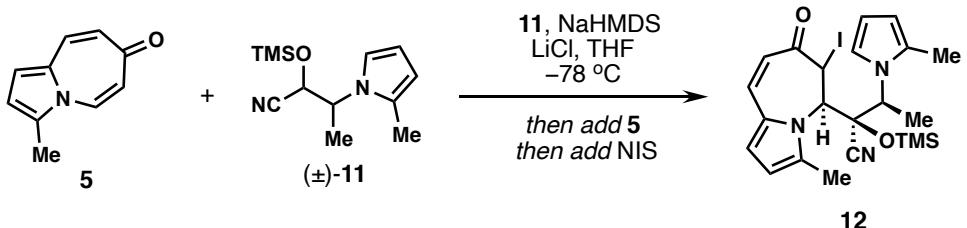
**Cyanohydrin 11:** [CAUTION: TMSCN AND LiClO<sub>4</sub> SHOULD BE HANDLED WITH CARE IN A WELL-VENTILATED FUMEHOOD]. A 1 L round bottom flask containing aldehyde **SI-2** (10.0 g, 73.0 mmol, 1.0 equiv.) was charged with CH<sub>2</sub>Cl<sub>2</sub> (500 mL) and vigorously stirred at room temperature. TMSCN (10.0 mL, 80.3 mmol, 1.1 equiv.) and LiClO<sub>4</sub> (8.2 g, 76.6 mmol, 1.1 equiv.) were added sequentially to the reaction mixture, at which time the reaction was sealed with a plastic cap. Upon consumption of aldehyde **SI-2** as indicated by TLC, the reaction mixture was quenched with saturated *aq.* NaHCO<sub>3</sub> (300 mL) and stirred for 5 minutes. The biphasic reaction mixture was poured into a separatory funnel containing *sat. aq.* NaHCO<sub>3</sub> (300 mL) and was extracted with Et<sub>2</sub>O (3 x 300 mL), the combined organic layers were washed with brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford **11** as a mixture of cyanohydrin diastereomers (~2.5:1 dr). The crude, colorless product (*ca.* 17.0 g) was used directly in the next step without further purification. An analytical sample could be prepared by distillation. [Note: this material decomposes on TLC].

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.57 (dd, *J* = 3.0, 1.7 Hz, 1H), 6.42 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.23 (t, *J* = 3.2, 1H), 6.21 (t, *J* = 3.2 Hz, 1H), 6.00 – 5.97 (m, 1H), 5.94 – 5.93 (m, 1H), 4.04 (d, *J* = 4.9 Hz, 1H), 3.95 (qd, *J* = 6.9, 4.9 Hz, 1H), 3.88 (q, *J* = 7.0 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H), 1.99 (s, 3H), 1.93 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 9H), -0.13 (s, 9H).

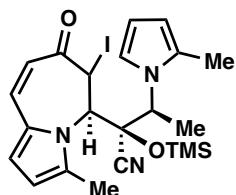
**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 129.2, 128.1, 118.5, 118.4, 117.2, 115.5, 108.9, 108.3, 107.9, 107.4, 67.0, 65.6, 54.3, 53.9, 16.2, 15.4, 12.3, 12.1, -0.91, -1.0.

**IR**  $\nu_{\max}$  (cm<sup>-1</sup>): 2957, 1418, 1290, 1254, 1134, 1101, 841, 753, 698.

**HRMS (m/z):** (ESI) calcd for C<sub>12</sub>H<sub>21</sub>ON<sub>2</sub>Si [M+H]<sup>+</sup>: 237.1418, found 237.1419.



**Iodide 12:** To a 500 mL round bottom flask was added LiCl (2.00 g, 47.1 mmol, 5.0 equiv.). The flask was flame-dried under high vacuum and then cooled to room temperature. In a separate 50 mL round bottom flask, cyanohydrin **11** (3.3 g, 14.1 mmol, 1.5 equiv.) was azeotropically dried with benzene (3x). The flask containing dry **11** was evacuated and backfilled with nitrogen (3x), charged with THF (100 mL), and added to the flask containing LiCl via cannula. Additional THF (10 mL) was used for quantitative transfer. The resulting solution was then cooled to -78 °C, wherein NaHMDS (1M in THF, 15.0 mL, 15.0 mmol, 1.6 equiv.) was added dropwise and stirred continued for 30 minutes. In a separate 25 mL round bottom flask, pyrroloazepinone **5** (1.50 g, 9.4 mmol, 1.0 equiv.) was azeotropically dried with benzene (3x), dissolved in THF (10 mL) under nitrogen, and added to the enolate solution. Additional THF (5mL) was used to ensure a quantitative transfer. The reaction mixture was then stirred until complete consumption of **5** was noted by TLC. At that point, a separate 25 mL round bottom flask was charged NIS (3.2 g, 14.1 mmol, 1.5 equiv.). The flask was evacuated and backfilled with nitrogen (3x), and charged with 15 mL of THF. The resulting THF solution of NIS was then transferred via cannula to the reaction mixture containing the *in-situ* generated enolate. The reaction was stirred for an additional five minutes at -78 °C and was quenched by the addition of saturated *aq.* NH<sub>4</sub>Cl (200 mL). The biphasic reaction mixture was transferred to a separatory funnel and the organic layer was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to afford a brown residue. The resulting crude residue was purified by column chromatography (10% EtOAc in hexanes → 40% EtOAc in hexanes) to afford iodides **12 (major isomer)** (2.7 g, 5.2 mmol, 55%) and **12 (minor isomer)** (0.44 g, 0.850 mmol, 9%) as yellow solids.



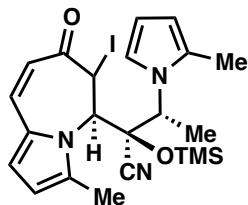
**TLC:**  $R_f = 0.5$  (25% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.87 (dd,  $J = 3.1, 1.7$  Hz, 1H), 6.23 (br s, 1H), 6.23 (br s, 1H), 6.23 (d,  $J = 11.9$  Hz, 1H), 5.93 (br s, 1H), 5.92 (br s, 1H), 5.64 (dd,  $J = 11.9, 1.8$  Hz, 1H), 5.02 (dd,  $J = 4.9, 1.8$  Hz, 1H), 4.43 (q,  $J = 7.1$  Hz, 1H), 4.40 (d,  $J = 4.9$  Hz, 1H), 2.27 (br s, 3H), 2.25 (br s, 3H), 1.01 (d,  $J = 7.0$  Hz, 3H), -0.21 (s, 9H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  191.6, 139.2, 133.5, 133.3, 130.8, 121.7, 117.9, 117.5, 117.0, 110.8, 109.7, 107.9, 80.0, 63.5, 55.7, 27.5, 17.3, 13.5, 12.8, 0.18.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2970, 1738, 1628, 1016, 1418, 1233, 901, 849, 773, 666.

**HRMS (m/z):** (ESI) calcd for C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>N<sub>3</sub>ISi [M+H]<sup>+</sup>: 522.1068, found 522.1071.



**12 (minor)**

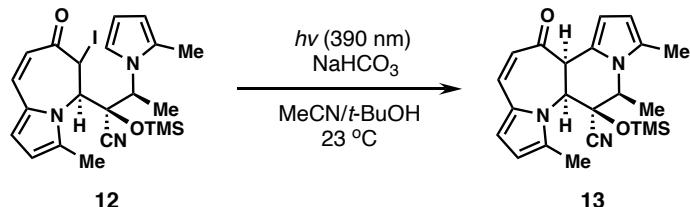
**TLC:**  $R_f = 0.4$  (25% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.99 (br s, 1H), 6.45 (d,  $J = 12.1$  Hz, 1H), 6.24 (br s, 1H), 6.23 (br s, 1H), 5.97 (br s, 1H), 5.96 (d,  $J = 12.1$  Hz, 1H), 5.78 (d,  $J = 3.8$  Hz, 1H), 5.18 (dd,  $J = 4.9, 1.9$  Hz, 1H), 4.39 (q,  $J = 6.7$  Hz, 1H), 4.30 (d,  $J = 4.9$  Hz, 1H), 2.18 (s, 3H), 1.98 (s, 3H), 1.19 (d,  $J = 6.7$  Hz, 3H), -0.05 (s, 9H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  191.3, 140.5, 133.6, 132.3, 128.6, 121.7, 118.6, 118.4, 117.8, 110.3, 109.8, 108.9, 75.4, 62.1, 56.1, 26.8, 18.9, 13.7, 12.0, 0.78.

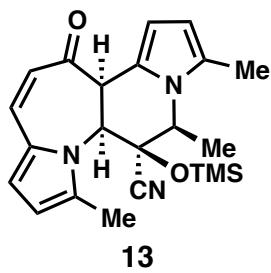
**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2954, 1684, 1625, 1559, 1233, 1216, 993, 826, 716.

**HRMS (m/z):** (ESI) calcd for C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>N<sub>3</sub>ISi [M+H]<sup>+</sup>: 522.1068, found 522.1074.



**Tetracycle 13:** Iodide 12 (1.00 g, 1.91 mmol, 1.0 equiv.) was transferred (in benzene) to a 250 mL cylindrical high-pressure screw cap tube and concentrated to dryness *in vacuo*. NaHCO<sub>3</sub> (806

mg, 9.60 mmol, 5.0 equiv.) was added to the reaction tube, which was then sealed, evacuated, and back filled with nitrogen (3x). To the mixture was added MeCN (100 mL) and *t*-BuOH (20.0 mL) and the tube was placed in a large vacuum dewar filled with water. The reaction mixture was irradiated with one 34W Kessil PR160-390 lamp placed 1cm away. A stream of air was continuously blown over the apparatus to maintain a temperature below 35 °C and the entire reaction apparatus was covered in aluminum foil. Upon completion of the reaction as indicated by TLC, the reaction mixture was poured into a separatory funnel containing saturated *aq.* NaHCO<sub>3</sub> (200 mL) and the solution was extracted with EtOAc (3 x 300 mL). The combined organics were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford tetracycle **13** (414 mg, 1.1 mmol, 55%) as a brown foam.



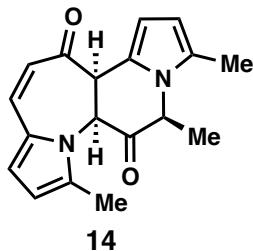
**TLC:** R<sub>f</sub> = 0.4 (25% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.34 (d, *J* = 12.1 Hz, 1H), 6.19 (d, *J* = 3.7 Hz, 1H), 6.06 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.92 (d, *J* = 3.4 Hz, 1H), 5.83 (dd, *J* = 3.8, 0.9 Hz, 1H), 5.73 (d, *J* = 12.1 Hz, 1H), 4.63 (q, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 3.8 Hz, 1H), 3.56 (d, *J* = 3.7 Hz, 1H), 1.96 (br s, 3H), 1.89 (br s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 194.3, 137.9, 132.5, 130.9, 126.8, 126.7, 120.9, 120.3, 120.2, 110.8, 108.6, 107.1, 73.3, 61.3, 60.6, 48.0, 18.7, 13.6, 12.7, 0.82.

**IR** (thin film)  $\nu_{\max}$  (cm<sup>-1</sup>): 2952, 1735, 1658, 1483, 1303, 848, 992, 848, 759, 680.

**HRMS (m/z):** (ESI) calcd for C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>N<sub>3</sub>Si [M+H]<sup>+</sup>: 394.1945, found 394.1948.



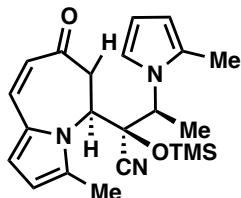
**TLC:**  $R_f = 0.4$  (40% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.41 (d,  $J = 12.3$  Hz, 1H), 6.27 (d,  $J = 3.7$  Hz, 1H), 6.14 – 6.06 (m, 2H), 5.88 (dd,  $J = 3.8, 0.9$  Hz, 1H), 5.75 (d,  $J = 12.3$  Hz, 1H), 4.91 (d,  $J = 5.1$  Hz, 1H), 4.18 (q,  $J = 7.2$  Hz, 1H), 3.76 (d,  $J = 5.1$  Hz, 1H), 1.85 (br s, 3H), 1.39 (br s, 3H), 1.26 (d,  $J = 7.2$  Hz, 3H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  201.5, 194.5, 137.4, 132.3, 130.9, 127.2, 126.3, 120.1, 118.3, 110.1, 108.2, 107.5, 63.2, 59.4, 49.3, 19.1, 12.2, 11.7.

**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2969, 2927, 1738, 1724, 1619, 1421, 1366, 1216, 666.

**HRMS (m/z):** (ESI) calcd for C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 295.1441, found 295.1441.



**15**

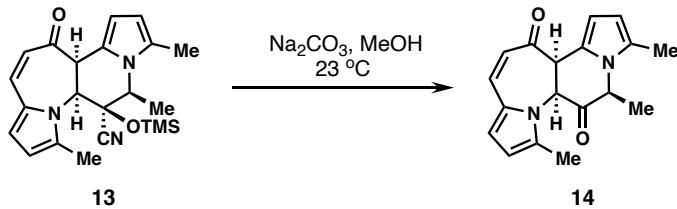
**TLC:**  $R_f = 0.3$  (25% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.96 (d,  $J = 1.4$  Hz, 1H), 6.38 (d,  $J = 11.8$  Hz, 1H), 6.25 (t,  $J = 3.3$  Hz, 1H), 6.21 (d,  $J = 3.8$  Hz, 1H), 5.94 (br s, 1H), 5.89 (d,  $J = 3.7$  Hz, 1H), 5.73 (dd,  $J = 11.8, 1.8$  Hz, 1H), 4.54 (q,  $J = 7.0$  Hz, 1H), 4.14 (dd,  $J = 5.6, 3.2$  Hz, 1H), 2.69 – 2.60 (m, 1H), 2.40 (dd,  $J = 15.3, 3.2$  Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.07 (d,  $J = 7.0$  Hz, 3H), -0.20 (s, 9H).

**$^{13}\text{C NMR}$**  (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  195.1, 137.5, 132.9, 132.9, 131.1, 121.1, 120.9, 118.5, 117.6, 110.5, 109.4, 107.6, 80.9, 57.1, 55.2, 42.4, 17.3, 14.0, 13.0, 0.13.

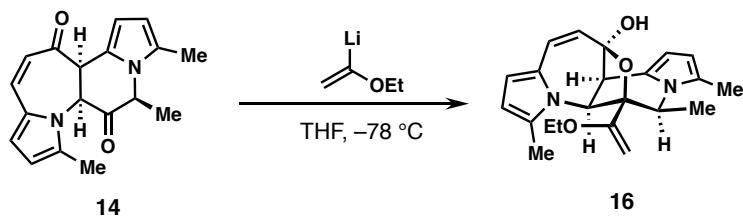
**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2973, 2901, 1649, 1612, 1539, 1482, 1285, 848.

**HRMS (m/z):** (ESI) calcd for C<sub>22</sub>H<sub>30</sub>O<sub>2</sub>N<sub>3</sub>Si [M+H]<sup>+</sup>: 396.2102, found 396.2103.



**Tetracyclic diketone 14:** To a 25 mL round bottom flask containing tetracycle **13** (400 mg, 1.02 mmol, 1.0 equiv) was added MeOH (10 mL). The resulting solution was vigorously stirred and Na<sub>2</sub>CO<sub>3</sub> (216 mg, 2.0 mmol, 2.0 equiv.) was added in one portion. Upon consumption of **13** as

indicated by TLC, the reaction mixture was quenched with saturated *aq.* NH<sub>4</sub>Cl (5 mL). The biphasic reaction mixture was poured into a separatory funnel and was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The combined organics were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (15% EtOAc in hexanes → 40% EtOAc in hexanes) to afford tetracyclic diketone **14** (285 mg, 0.97 mmol, 96%) as a white solid. Characterization data was listed previously (*vide supra*).



**Lactol 16:** To a reaction tube containing ethyl vinyl ether (0.15 mL, 1.6 mmol, 5.5 equiv.) was added THF (2.9 mL). The mixture was cooled to -78 °C and *t*-BuLi (0.9 mL, 1.5 mmol, 5.0 equiv) was added dropwise down the wall of the vessel. Upon completion of the addition, the reaction mixture was placed in a 0 °C ice bath, stirred for 30 minutes at 0 °C, and then re-cooled to -78 °C. In a separate 10 mL flask, **14** (85 mg, 0.29 mmol, 1.0 equiv) was azeotropically dried with benzene (3x), dissolved in THF (0.3 mL), and added to the solution at -78 °C. An additional THF (0.300 mL) rinse was used to ensure a quantitative transfer. The reaction mixture was stirred at -78 °C for one hour, and then quenched with saturated *aq.* NaHCO<sub>3</sub> (50 mL). The solution was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford lactol **16** (55 mg, 0.15 mmol, 52%) as a white solid.

**TLC:** R<sub>f</sub> = 0.6 (20% EtOAc in hexanes).

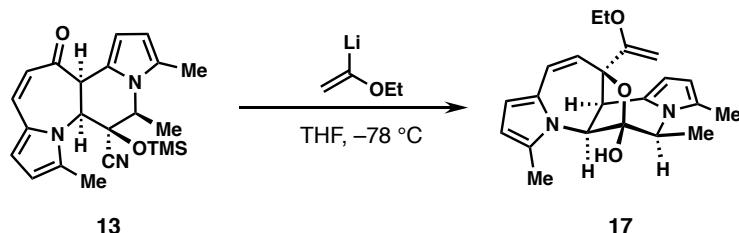
**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.19 (d, *J* = 11.7 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 6.03 (d, *J* = 11.7 Hz, 1H), 5.99 – 5.92 (m, 2H), 5.84 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.00 (d, *J* = 2.1 Hz, 1H), 4.74 (q, *J* = 6.3 Hz, 1H), 4.64 (d, *J* = 0.8 Hz, 1H), 3.85 (d, *J* = 2.1 Hz, 1H), 3.53 (d, *J* = 0.8 Hz, 1H), 3.27 – 3.19 (m, 1H), 3.18 (s, 1H), 3.11 (dq, *J* = 9.7, 7.0 Hz, 1H), 1.99 (br s, 3H), 1.77 (br s, 3H),

1.38 (d,  $J = 6.3$  Hz, 3H), 0.91 (t,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  156.8, 133.8, 130.5, 129.8, 125.7, 123.6, 122.1, 114.7, 108.8, 108.3, 108.2, 106.3, 92.1, 86.0, 64.5, 63.1, 57.7, 48.0, 16.0, 14.3, 13.9, 12.8.

**IR** (thin film)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2976, 2942, 1738, 1647, 1416, 1372, 1303, 1215, 1145, 979, 764.

**HRMS (m/z):** (ESI) calcd. for  $\text{C}_{22}\text{H}_{27}\text{O}_3\text{N}_2$  [ $\text{M}+\text{H}]^+$ : 367.2016, found 367.2019.



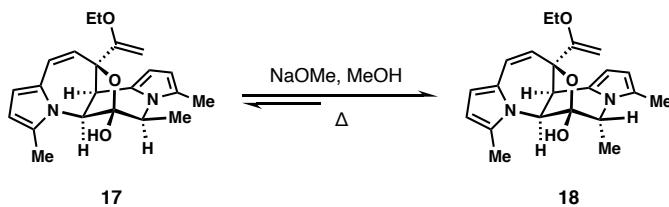
**Lactol 17:** To a reaction tube containing ethyl vinyl ether (2.30 mL, 23.8 mmol, 5.5 equiv.) was added THF (20.0 mL). The mixture was cooled to  $-78$  °C and *t*-BuLi (13.5 mL, 21.6 mmol, 5.0 equiv) was added dropwise down the wall of the vessel. Upon completion of the addition, the reaction mixture was placed in a 0 °C ice bath, stirred for 30 minutes at 0 °C, and then re-cooled to  $-78$  °C. In a separate 10 mL flask, **13** (1.7 g, 4.3 mmol, 1.0 equiv) was azeotropically dried with benzene (3x), dissolved in THF (10 mL), and added to the solution at  $-78$  °C. An additional THF (5 mL) rinse was used to ensure a quantitative transfer. The reaction mixture was stirred at  $-78$  °C for one hour, and then quenched with saturated *aq.*  $\text{NaHCO}_3$  (50 mL). The solution was extracted with EtOAc (3 x 100 mL) and the combined organics were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford lactol **17** (873 mg, 2.4 mmol, 55%) as a white solid.

**$^1\text{H}$  NMR** (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.26 (d,  $J = 11.5$  Hz, 1H), 6.13 (d,  $J = 3.5$  Hz, 1H), 5.96 (dd,  $J = 3.3, 1.0$  Hz, 1H), 5.90 (dd,  $J = 3.5, 0.9$  Hz, 1H), 5.86 (d,  $J = 3.3$  Hz, 1H), 5.79 (d,  $J = 11.5$  Hz, 1H), 4.69 (d,  $J = 1.7$  Hz, 1H), 4.33 (d,  $J = 0.8$  Hz, 1H), 4.20 (q,  $J = 6.3$  Hz, 1H), 3.88 (d,  $J = 0.8$  Hz, 1H), 3.82 (d,  $J = 1.8$  Hz, 1H), 3.40 (dq,  $J = 9.3, 7.0$  Hz, 1H), 3.29 (dq,  $J = 9.3, 7.0$  Hz, 1H), 2.79 (s, 1H), 2.02 (d,  $J = 0.8$  Hz, 3H), 1.72 (d,  $J = 0.7$  Hz, 3H), 1.68 (d,  $J = 6.3$  Hz, 3H), 1.09 (t,  $J = 7.0$  Hz, 3H).

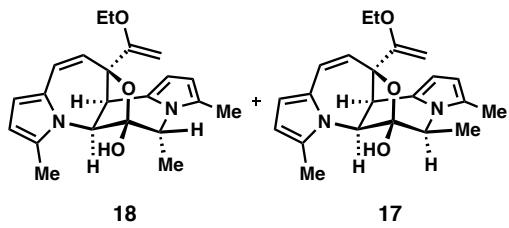
**$^{13}\text{C}$  NMR** (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  164.4, 135.1, 130.4, 130.2, 127.3, 125.7, 122.9, 114.4, 109.4, 109.0, 108.2, 104.9, 85.9, 80.7, 64.7, 63.0, 59.7, 45.9, 15.1, 14.6, 14.0, 12.9.

**IR (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>):** 2975, 2926, 1735, 1642, 1413, 1306, 1187, 1013, 818, 774, 679.

**HRMS (m/z):** (ESI) calcd. for C<sub>22</sub>H<sub>27</sub>O<sub>3</sub>N<sub>2</sub> [M+H]<sup>+</sup>. 367.2016, found 367.2020.



**Epimerization of 17:** In a nitrogen-filled glovebox, a reaction tube containing lactol **17** (1.0 g, 2.73 mmol, 1.0 equiv.) was charged with NaOMe (737 mg, 13.6 mmol, 5.0 equiv.). The reaction tube was sealed, removed from the glovebox, and placed under an atmosphere of nitrogen. Anhydrous MeOH (30 mL) was then added, the N<sub>2</sub> balloon was removed, and the sealed reaction vessel was heated at 90 °C for four hours. The reaction mixture was then cooled to room temperature and was poured into a separatory funnel containing saturated *aq.* NH<sub>4</sub>Cl solution (100 mL). The solution was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford an inseparable mixture of lactol epimers **18** and **17** (2.3:1 ratio) (850 mg, 2.3 mmol, 85%) as a brown foam.



**TLC:** R<sub>f</sub> = 0.5 (15% EtOAc in hexanes).

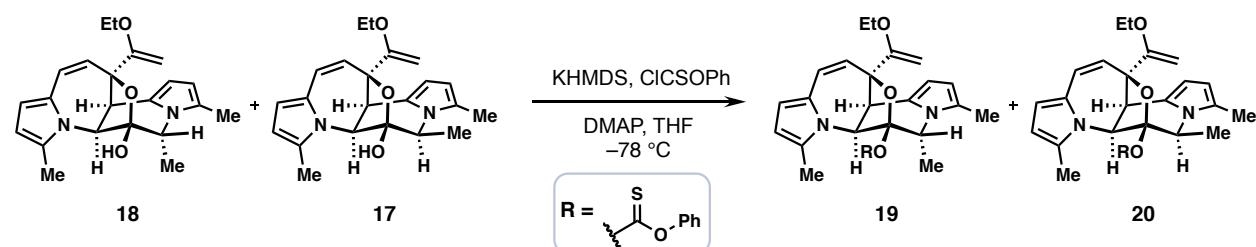
**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.28 (d, *J* = 11.7 Hz, 1H), 6.26 (d, *J* = 11.5 Hz, 1H), 6.16 (d, *J* = 3.6 Hz, 1H), 6.13 (d, *J* = 3.5 Hz, 1H), 5.96 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 5.90 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.86 (d, *J* = 3.3 Hz, 1H), 5.82 (d, *J* = 11.6 Hz, 1H), 5.79 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 1.7 Hz, 1H), 4.57 (s, 1H), 4.45 (d, *J* = 1.3 Hz, 1H), 4.19 (q, *J* = 6.2 Hz, 1H), 4.33 (d, *J* = 0.8 Hz, 1H), 4.20 (q, *J* = 6.3 Hz, 1H), 3.88 (d, *J* = 0.8 Hz, 1H), 3.87 (s, 1H), 3.82 (d, *J* = 1.8 Hz, 1H), 3.42 – 3.39 (m, 4H), 3.31 – 3.28 (m, 4H), 2.79 (s, 1H), 2.02 (d, *J* = 0.8 Hz, 3H), 1.97 (s, 3H), 1.87 (s, 3H), 1.72 (d, *J* = 0.7 Hz, 3H), 1.68 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J*

= 6.5 Hz, 3H), 1.11 (t,  $J$  = 7.0 Hz, 3H), 1.09 (t,  $J$  = 7.0 Hz, 3H).

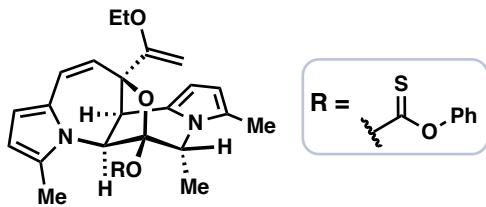
**$^{13}\text{C}$  NMR** (150.9 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  164.4, 163.8, 135.1, 135.1, 130.7, 130.4, 130.2, 129.0, 127.3, 127.1, 125.8, 125.1, 122.9, 122.8, 114.5, 114.4, 110.3, 109.5, 109.0, 109.0, 108.2, 107.9, 105.1, 104.9, 86.9, 85.9, 80.7, 79.2, 64.7, 63.1, 63.0, 60.4, 60.3, 59.7, 46.5, 45.9, 19.1, 15.1, 14.7, 14.6, 14.0, 13.3, 12.9, 12.7.

**IR** (thin film)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ). 2976, 2975, 2926, 1735, 1643, 1642, 1415, 1413, 1306, 1304, 1189, 1187, 1013, 1010, 818, 815, 774, 773, 671, 679.

**HRMS (m/z):** (ESI) calcd. for  $\text{C}_{22}\text{H}_{26}\text{O}_3\text{N}_2\text{Na} [\text{M}+\text{Na}]^+$ : 389.1836, found 389.1834.



**Thiocarbonates **19** and **20**:** Lactol epimers **17** and **18** (100 mg, 70% of the desired methyl lactol epimer **18**, 0.27 mmol, 1.0 equiv.) were azeotropically dried with benzene (3x) and then dissolved in THF (10 mL) under an inert atmosphere. The solution was cooled to  $-78^\circ\text{C}$  and KHMDS (1M in THF, 437  $\mu\text{L}$ , 0.44 mmol, 1.6 equiv.) was added dropwise down the side of the reaction vessel. The reaction was stirred for 30 minutes at which point the cap was quickly removed and DMAP (67 mg, 0.55 mmol, 2.0 equiv.) added followed by *O*-phenyl chlorothionoformate (75  $\mu\text{L}$ , 0.55 mmol, 2.0 equiv.). The vessel was re-sealed and stirring continued for 15 minutes at  $-78^\circ\text{C}$ , after which point the cooling bath was exchanged for a  $0^\circ\text{C}$  ice bath and the mixture was stirred for an additional 20 minutes. The reaction was quenched by the addition of saturated *aq.*  $\text{NaHCO}_3$  (2 mL), and the resulting mixture was poured into a separatory funnel containing 10 mL of EtOAc and 15 mL of saturated *aq.*  $\text{NaHCO}_3$ . The organic layer was extracted with EtOAc (10 mL x 3) and the combined organics were washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (15% EtOAc in hexanes) to afford a separable mixture of thiocarbonates **19** (68 mg, 0.14 mmol, 50%) and **20** (29 mg, 0.06 mmol, 21%), both as a yellow oils.



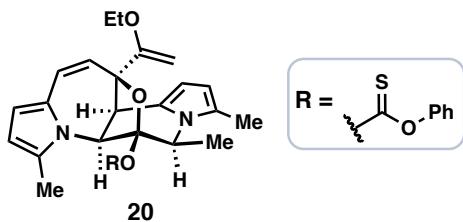
**TLC:**  $R_f = 0.5$  (10% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.87 (dd,  $J = 8.5, 7.3$  Hz, 2H), 6.81 – 6.76 (m, 1H), 6.60 (br d,  $J = 7.5$  Hz, 2H), 6.31 (d,  $J = 11.5$  Hz, 1H), 6.19 (d,  $J = 3.6$  Hz, 1H), 5.99 (q,  $J = 6.5$  Hz, 1H), 5.98 (br s, 1H), 5.97 (br s, 1H), 5.86 (d,  $J = 3.4$  Hz, 1H), 5.77 (d,  $J = 11.5$  Hz, 1H), 4.93 (br s, 1H), 4.73 (br s, 1H), 3.95 (br s, 1H), 3.65 (br s, 1H), 3.37 (dq,  $J = 9.30, 7.0$  Hz, 1H), 3.28 (dq,  $J = 9.3, 7.1$  Hz, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.40 (d,  $J = 6.5$  Hz, 3H), 1.10 (t,  $J = 7.70$  Hz, 3H).

**<sup>13</sup>C NMR** (150.9 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  190.4, 163.1, 153.6, 135.4, 130.7, 129.6, 128.8, 127.5, 126.5, 124.3, 122.6, 122.2, 115.5, 115.4, 109.0, 108.3, 105.3, 91.0, 80.0, 63.1, 61.6, 57.4, 45.5, 18.6, 14.7, 13.5, 12.7.

**IR** (thin film)  $\nu_{\max}$  (cm<sup>-1</sup>): 2976, 2927, 1641, 1555, 1514, 1377, 1301, 1195, 1110, 1009, 756.

**HRMS (m/z):** (ESI) calcd. for C<sub>29</sub>H<sub>31</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 503.1999, found 503.2003.



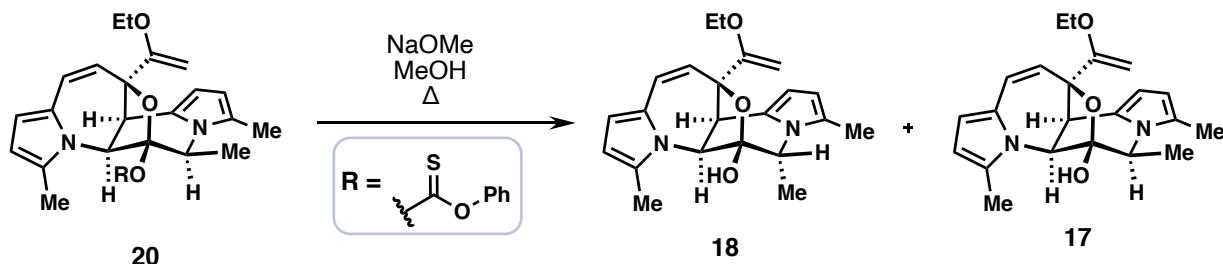
**TLC:**  $R_f = 0.5$  (10% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  7.00 (dd,  $J = 8.6, 7.3$  Hz, 2H), 6.97 – 6.92 (m, 2H), 6.88 – 6.81 (m, 1H), 6.10 (d,  $J = 11.6$  Hz, 1H), 6.04 (d,  $J = 3.5$  Hz, 1H), 5.94 (dd,  $J = 3.4, 1.1$  Hz, 1H), 5.89 (dd,  $J = 3.5, 1.0$  Hz, 1H), 5.82 (d,  $J = 3.4$  Hz, 1H), 5.60 (d,  $J = 11.5$  Hz, 1H), 4.98 (q,  $J = 6.2$  Hz, 1H), 4.70 (br s, 1H), 4.65 (br s, 1H), 3.85 (br s, 1H), 3.80 (br s, 1H), 3.35 (dq,  $J = 9.3, 7.0$  Hz, 1H), 3.27 (dq,  $J = 9.4, 7.0$  Hz, 1H), 2.01 (br s, 3H), 1.88 (br s, 3H), 1.72 (d,  $J = 6.2$  Hz, 3H), 1.05 (t,  $J = 7.0$  Hz, 3H).

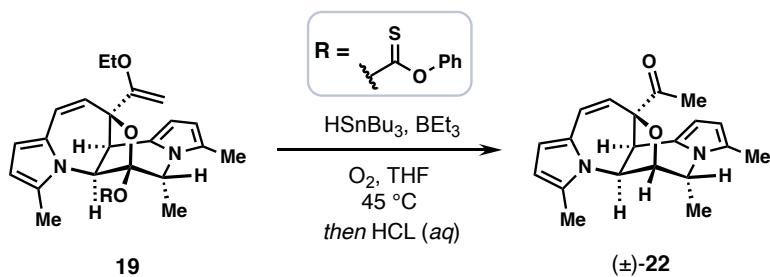
**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  190.4, 163.8, 154.2, 135.3, 131.3, 129.8, 129.4, 128.1, 126.4, 124.5, 122.6, 122.4, 117.7, 115.7, 109.2, 108.5, 105.1, 89.2, 80.7, 64.1, 63.1, 60.1, 45.9, 14.8, 14.6, 14.1, 13.2.

**IR (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>):** 2976, 2925, 1643, 1558, 1457, 1341, 1193, 1073, 757.

**HRMS (m/z):** (ESI) calcd. for C<sub>29</sub>H<sub>31</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 503.1999, found 503.2004.



**Recycling of 20:** In a N<sub>2</sub> filled glovebox, a reaction tube containing thiocarbonate **20** (18 mg, 0.036 mmol, 1.0 equiv.) was charged with NaOMe (10 mg, 0.18 mmol, 5.0 equiv.). The reaction tube was sealed, removed from the glovebox, and MeOH (0.5 mL) added under at atmosphere of nitrogen. The N<sub>2</sub> balloon was then removed and the sealed vessel heated at 90 °C for four hours. The reaction mixture was then cooled to room temperature, quenched with saturated *aq.* NH<sub>4</sub>Cl solution (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford an inseparable mixture of lactol epimers **18** and **17** (2.3:1) (10 mg, 0.027 mmol, 76%) as a brown foam.



**Ketone 22:** Thiocarbonate **19** (50 mg, 0.10 mmol, 1.0 equiv.) was dissolved in THF (2 mL) and the solution degassed by sparging with argon for five minutes. Tributyltin hydride (54 μL, 0.20 mmol, 2.0 equiv.) and 1M BEt<sub>3</sub> solution (100 μL, 0.10 mmol, 1.0 equiv.) were then added to the mixture. A syringe containing 3 mL of air was placed into the reaction solution, and air was bubbled into the mixture at a rate of approximately 1mL/hr. Upon completion of the reaction as indicated by TLC, the mixture was cooled to 0 °C and 1M *aq.* HCl was added dropwise. The resulting solution was vigorously stirred for 10 minutes, and was then poured into a separatory funnel containing 50 mL

of EtOAc and 50 mL of saturated *aq.* NH<sub>4</sub>Cl. The organic layer was extracted with EtOAc (3x) and the combined organics were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (20% EtOAc in hexanes) to afford ketone ( $\pm$ )-**22** (13 mg, 0.04 mmol, 40%) as a white solid.

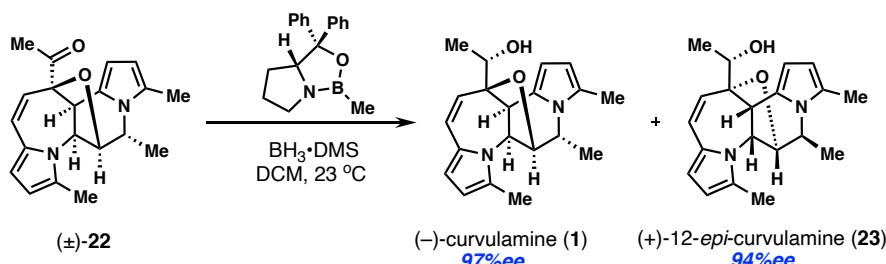
**TLC:** R<sub>f</sub> = 0.5 (40% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.28 (d, *J* = 11.5 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 5.94 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.87 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.77 (d, *J* = 3.4 Hz, 1H), 5.74 (d, *J* = 11.5 Hz, 1H), 4.46 (br s, 1H), 4.14 (br s, 1H), 3.72 (br s, 1H), 3.69 (dq, *J* = 6.7, 2.1 Hz, 1H), 1.83 (d, *J* = 0.9 Hz, 3H), 1.73 (s, 3H), 1.53 (s, 3H), 0.73 (d, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR** (150.9 MHz, C<sub>6</sub>D<sub>6</sub>) δ 209.7, 132.8, 130.6, 128.6, 127.4, 124.0, 121.6, 114.5, 109.0, 108.9, 106.3, 94.0, 90.5, 60.0, 56.7, 46.1, 25.2, 19.1, 13.4, 12.3.

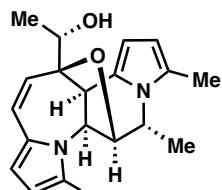
**IR** (thin film)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2972, 2932, 1741, 1682, 1640, 1456, 1378, 1214, 1071, 786, 734.

**HRMS (m/z):** (ESI) calcd. for C<sub>20</sub>H<sub>23</sub>O<sub>2</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 323.1754, found 323.1756.



**CBS reduction of 22:** In a N<sub>2</sub> filled glovebox, a reaction tube was charged with (*R*)-(+)-2-methyl-CBS-oxazaborolidine (8.6 mg, 0.031 mmol, 1.0 equiv.). The reaction tube was sealed and brought out of the glovebox under inert atmosphere. DCM (0.20 mL) was added followed by BH<sub>3</sub>•DMS (6 μL, 0.06 mmol, 2.0 equiv.) and the mixture stirred for 15 minutes. Methyl ketone ( $\pm$ )-**22** (10 mg, 0.031 mmol, 1.0 equiv.) was dissolved in DCM (0.150 mL) and added dropwise to the reaction mixture. Additional DCM (0.150 mL) was used to render the transfer quantitative. Upon completion of the reaction as indicated by TLC, saturated *aq.* NH<sub>4</sub>Cl solution (1 mL) was added and the mixture stirred for five minutes. The biphasic mixture was poured into a separatory funnel and the organic layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (50% Et<sub>2</sub>O in hexanes) to afford (−)-

curvulamine **1** (4.5 mg, 0.014 mmol, 45%, 97% ee) and (+)-12-*epi*-curvulamine **23** (4.5 mg, 0.014 mmol, 45%, 94% ee) both as white solids.



(*-*)-**1**

**TLC:**  $R_f = 0.4$  (40% EtOAc in hexanes).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 6.45 (d, *J*=11.6 Hz, 1H), 6.13 (d, *J*= 3.6 Hz, 1H), 5.94 (br d, *J*= 3.6 Hz, 1H), 5.93 (d, *J*= 3.4 Hz, 1H), 5.92 (d, *J*= 3.4 Hz, 1H), 5.72 (d, *J*= 11.6 Hz, 1H), 4.94 (br, s, 1H), 4.50 (br, s, 1H), 4.21 (qd, *J*= 6.7, 1.9 Hz, 1H), 3.95 (br, s, 1H), 2.67 (br s, 1H), 2.31 (br s, 3H), 2.29 (br s, 3H), 1.51 (d, *J*= 6.7 Hz, 3H), 1.24 (d, *J*= 6.4 Hz, 3H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 132.4, 130.4, 129.8, 128.5, 124.2, 119.7, 113.4, 108.5, 107.8, 103.5, 89.4, 89.0, 70.2, 60.3, 57.4, 44.9, 19.5, 17.3, 13.8, 12.8.

**IR**  $\nu_{\text{max}}$  (cm<sup>-1</sup>) 3466, 2972, 2925, 3852, 1643, 1425, 1393, 1322, 1301, 1044, 1011, 763.

**HRMS (m/z):** (ESI) calcd. for C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>N<sub>2</sub>Na [M+Na]<sup>+</sup>: 347.1730, found 347.1731.

$[\alpha]_D^{25} = -246^\circ$  (*c* = 0.03, MeOH).

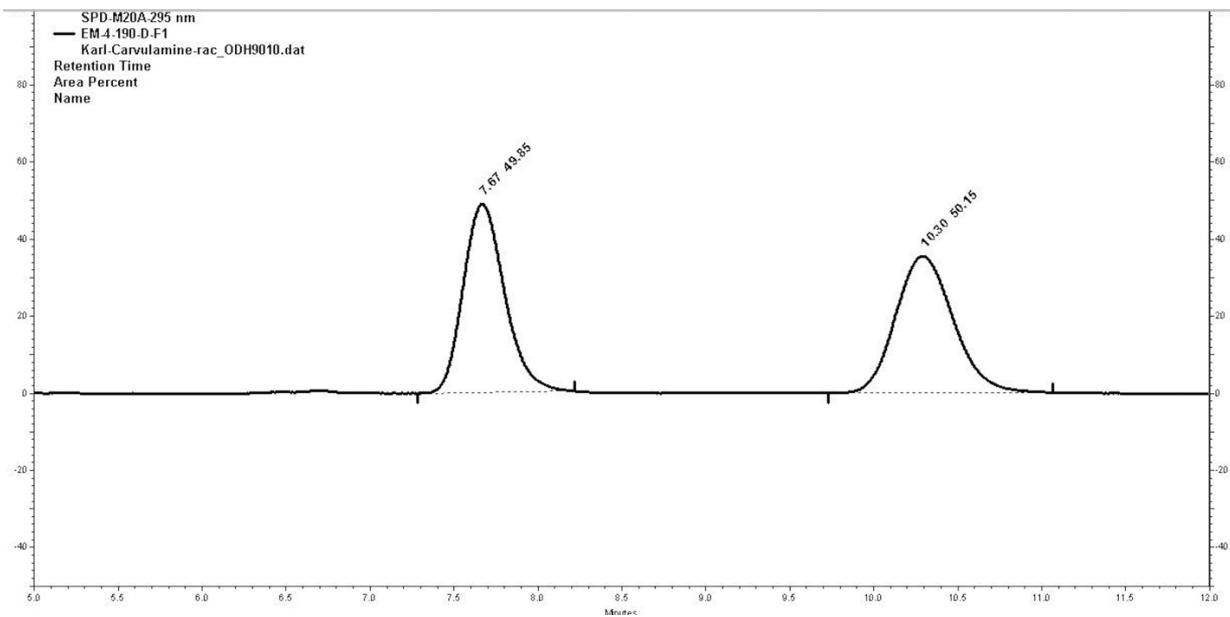
#### Enantiomeric excess determination of **1** by HPLC

Column: Chiralcel OD-H

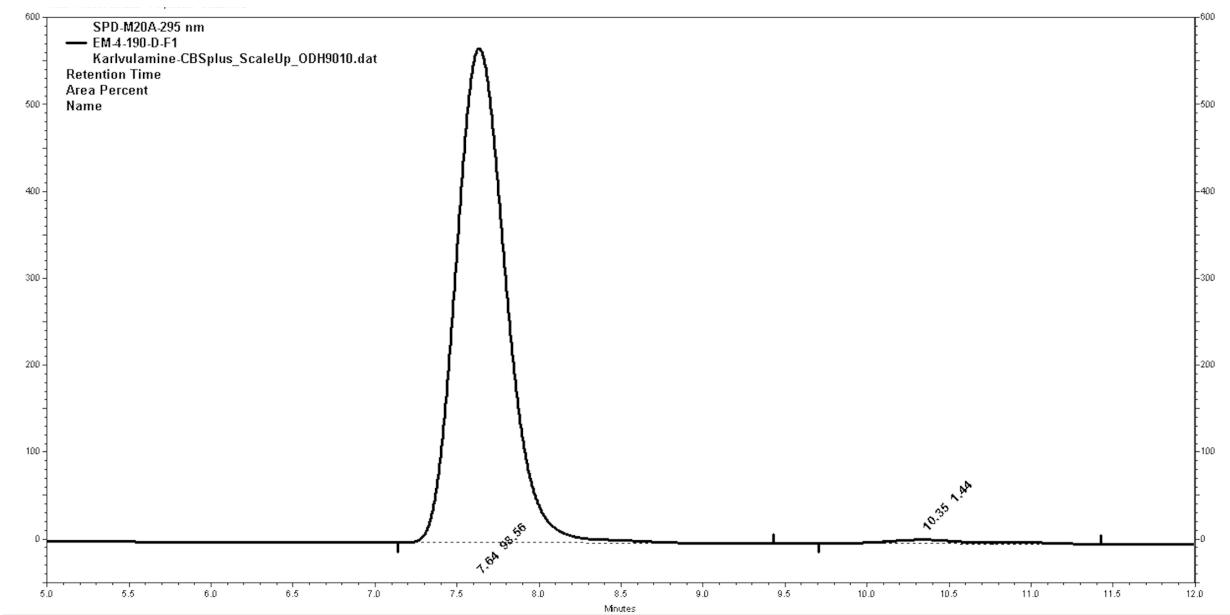
Dimensions: 4.6 mm x 250 mm

Eluent: hexanes : isopropyl alcohol 90:10

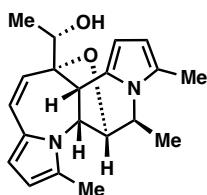
Flow rate: 1 mL/min



**Figure SI-1.** Chromatogram of racemic curvulamine.



**Figure SI-2.** (-)-curvulamine of 97% ee prepared by CBS reduction.



(+)-23

**TLC:**  $R_f = 0.2$  (40% EtOAc in hexanes).

**$^1\text{H NMR}$**  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.41 (d,  $J = 11.7$  Hz, 1H), 6.10 (d,  $J = 3.6$  Hz, 1H), 5.91 (dd,  $J = 3.6, 0.9$  Hz, 1H), 5.86 (dd,  $J = 3.4, 1.0$  Hz, 1H), 5.79 (d,  $J = 3.4$  Hz, 1H), 5.75 (d,  $J = 11.7$  Hz, 1H), 4.90 (br, s, 1H), 4.56 (br, s, 1H), 4.23 (qd,  $J = 6.7, 2.1$  Hz, 1H), 3.71 (br, s, 1H), 2.71 (q,  $J = 6.3$  Hz, 1H), 2.27 (br s, 3H), 2.26 (br s, 3H), 2.05 (d,  $J = 2.2$  Hz, 3H), 1.48 (d,  $J = 6.7$  Hz, 3H), 1.10 (d,  $J = 6.3$  Hz, 3H).

**$^{13}\text{C NMR}$**  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  132.6, 130.3, 128.4, 128.0, 124.1, 118.9, 113.5, 108.5, 107.2, 105.0, 90.6, 89.4, 89.1, 72.0, 61.0, 57.6, 43.7, 19.4, 16.9, 13.8, 12.8.

**IR**  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3468, 2925, 1644, 1415, 1299, 1077, 776, 670.

**HRMS (m/z):** (ESI) calcd. for  $\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2\text{Na}$  [ $\text{M}+\text{Na}]^+$ : 347.1730, found 347.1731.

$[\alpha]_D^{25} = +225^\circ$  ( $c = 0.3$ , MeOH).

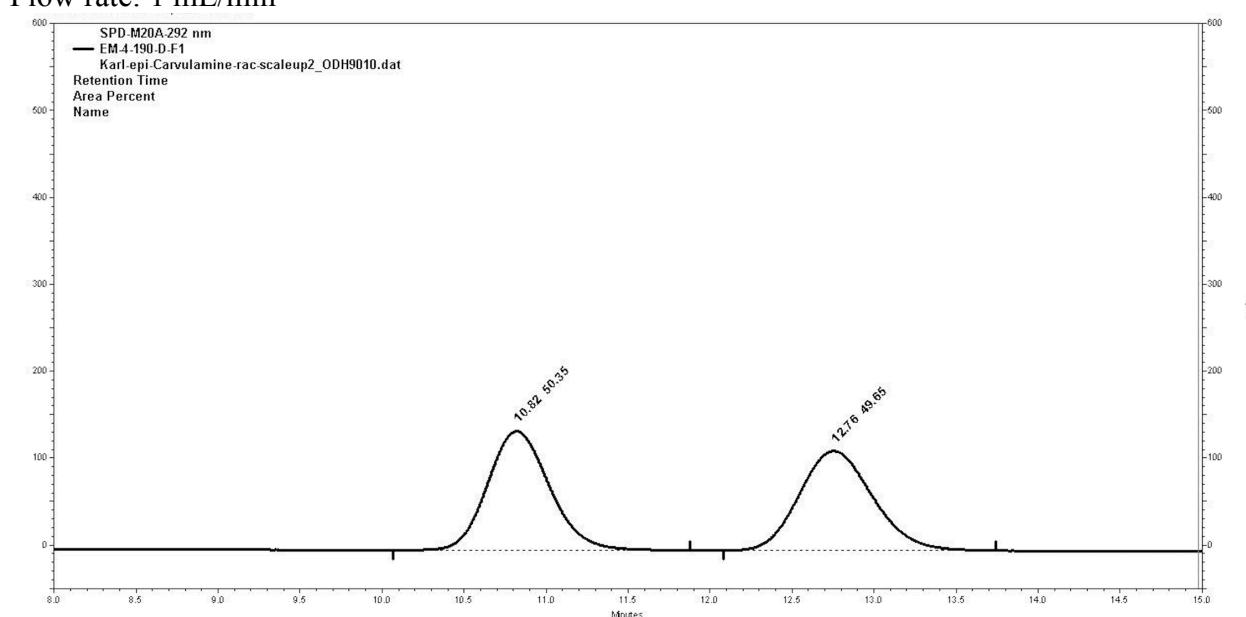
#### Enantiomeric excess determination of **23** by HPLC

Column: Chiralcel OD-H

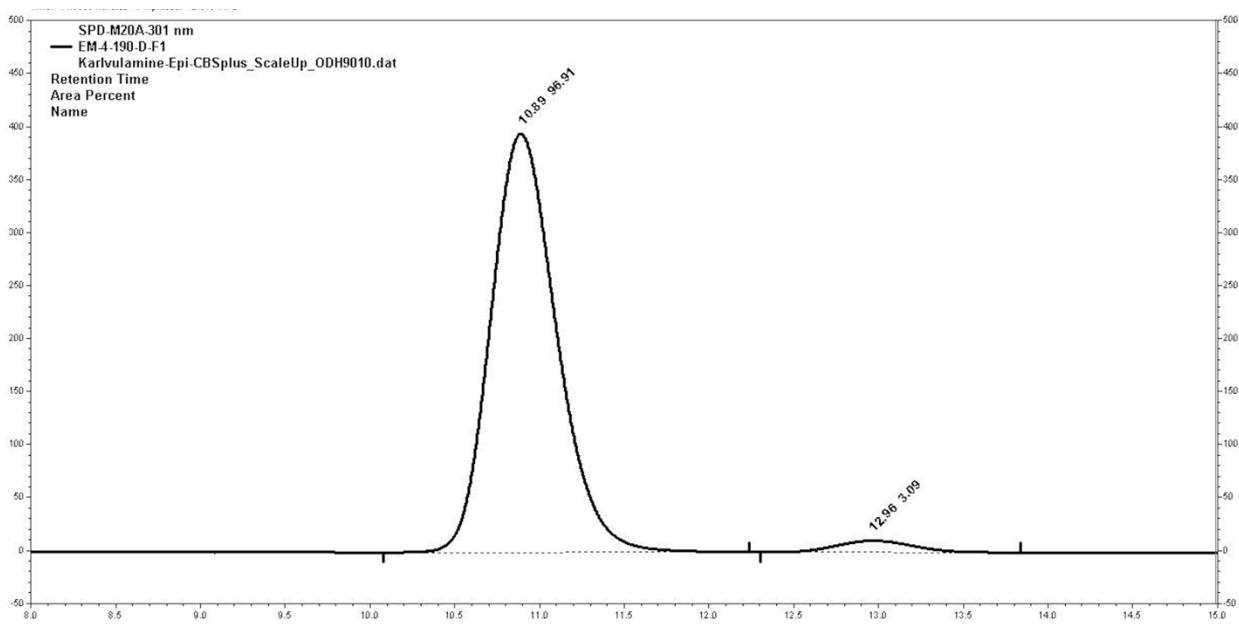
Dimensions: 4.6 mm x 250 mm

Eluent: hexanes : isopropyl alcohol 90:10

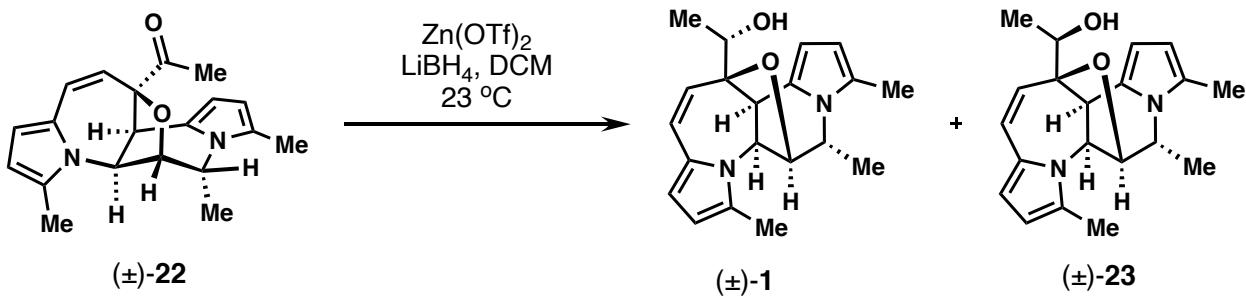
Flow rate: 1 mL/min



**Figure SI-3.** Chromatogram of racemic  $(\pm)$ -12-*epi*-curvulamine



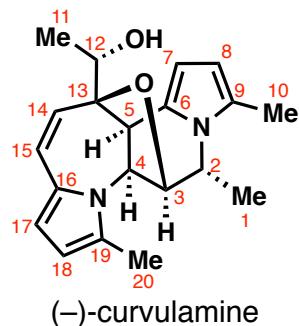
**Figure SI-4.** Chromatogram of (+)-12-*epi*-curvulamine of 94% ee prepared by CBS reduction.



**Preparation of racemic standards of 1 and 23:** In a  $N_2$  filled glovebox, a reaction tube containing methyl ketone ( $\pm$ )-22 (5.0 mg, 0.016 mmol, 1.0 equiv.) was charged with  $Zn(OTf)_2$  (8.7 mg, 0.024 mmol, 1.5 equiv.). A separate reaction tube was charged with  $LiBH_4$  (1.0 mg, 0.032 mmol, 2.0 equiv.). Both reaction tubes were sealed and brought out of the glovebox and kept inert with a  $N_2$  balloon. The reaction tube containing **22** mixture was dissolved in DCM (0.2 mL) and stirred for 10 minutes.  $LiBH_4$  was dissolved in DCM (0.10 mL) and transferred to the reaction mixture using an additional DCM (0.10 mL) rinse for quantitative transfer. Upon completion of the reaction as indicated by TLC, saturated *aq.*  $NH_4Cl$  solution (1 mL) was added and the reaction mixture stirred for five minutes. The biphasic mixture was poured into a

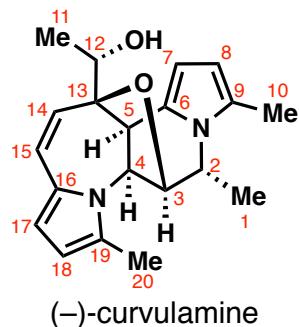
separatory funnel and the organic layer was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (50% Et<sub>2</sub>O in hexanes) to afford ( $\pm$ )-curvulamine ( **$\pm$ -1**) (2.8 mg, 0.01 mmol, 54%) and ( $\pm$ )-12-*epi*-curvulamine ( **$\pm$ -23**) (1.8 mg, 0.006 mmol, 36%) both as white solids.

(-)curvulamine  $^1\text{H}$  spectra comparison:



| Position | $^1\text{H}$ ( $\delta$ )                                  | $^1\text{H}$ ( $\delta$ )                       |
|----------|--|---|
|          | Natural Sample<br>(500 MHz, $\text{CDCl}_3$ ) <sup>1</sup> | Synthetic Sample<br>(600 MHz, $\text{CDCl}_3$ ) |
| 1        | 1.51 (d, $J = 7.0$ Hz, 3H)                                 | 1.51 (d, $J = 6.7$ Hz, 3H)                      |
| 2        | 4.21 (q, $J = 7.0$ Hz, 1H)                                 | 4.21 (qd, $J = 6.7, 1.9$ Hz, 1H)                |
| 3        | 4.50 (br, s, 1H)   | 4.50 (br, s, 1H)                                |
| 4        | 4.94 (br, s, 1H)   | 4.94 (br, s, 1H)                                |
| 5        | 3.95 (br, s, 1H)   | 3.95 (br, s, 1H)                                |
| 6        | -  | -   |
| 7        | 5.92 (d, $J = 3.0$ Hz, 1H)                                 | 5.92 (d, $J = 3.4$ Hz, 1H)                      |
| 8        | 5.93 (br d, $J = 3.0$ Hz, 1H)                              | 5.93 (d, $J = 3.4$ Hz, 1H)                      |
| 9        | -  | -   |
| 10       | 2.30 (br s, 3H)  | 2.31 (br s, 3H)                                 |
| 11       | 1.24 (d, $J = 6.0$ Hz, 3H)                                 | 1.24 (d, $J = 6.4$ Hz, 3H)                      |
| 12       | 2.67 (q, $J = 6.0$ Hz, 1H)                                 | 2.67 (br s, 1H)                                 |
| 13       | -  | -   |
| 14       | 5.72 (d, $J = 12.0$ Hz, 1H)                                | 5.72 (d, $J = 11.6$ Hz, 1H)                     |
| 15       | 6.45 (br d, $J = 12.0$ Hz, 1H)                             | 6.45 (br d, $J = 11.6$ Hz, 1H)                  |
| 16       | -  | -   |
| 17       | 6.13 (d, $J = 3.5$ Hz, 1H)                                 | 6.13 (d, $J = 3.6$ Hz, 1H)                      |
| 18       | 5.94 (br d, $J = 3.5$ Hz, 1H)                              | 5.94 (br d, $J = 3.6$ Hz, 1H)                   |
| 19       | -  | -   |
| 20       | 2.28 (br s, 3H)  | 2.29 (br s, 3H)                                 |

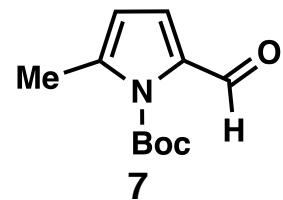
(-)curvulamine  $^{13}\text{C}$  spectra comparison:



| Position | $^{13}\text{C}$ ( $\delta$ )                               | $^{13}\text{C}$ ( $\delta$ )                    |
|----------|--|---|
|          | Natural Sample<br>(125 MHz, $\text{CDCl}_3$ ) <sup>1</sup> | Synthetic Sample<br>(151 MHz, $\text{CDCl}_3$ ) |
| 1        | 19.5   | 19.5  |
| 2        | 57.4   | 57.4  |
| 3        | 89.0   | 89.0  |
| 4        | 60.3   | 60.3  |
| 5        | 44.9   | 44.9  |
| 6        | 129.8  | 129.8   |
| 7        | 103.5  | 103.5   |
| 8        | 107.8  | 107.8   |
| 9        | 128.5  | 128.5   |
| 10       | 12.7   | 12.8  |
| 11       | 17.3   | 17.3  |
| 12       | 70.2   | 70.2  |
| 13       | 89.4   | 89.4  |
| 14       | 119.7  | 119.7   |
| 15       | 124.1  | 124.2   |
| 16       | 130.4  | 130.4   |
| 17       | 113.4  | 113.4   |
| 18       | 108.5  | 108.5   |
| 19       | 132.4  | 132.4   |
| 20       | 13.7   | 13.7  |

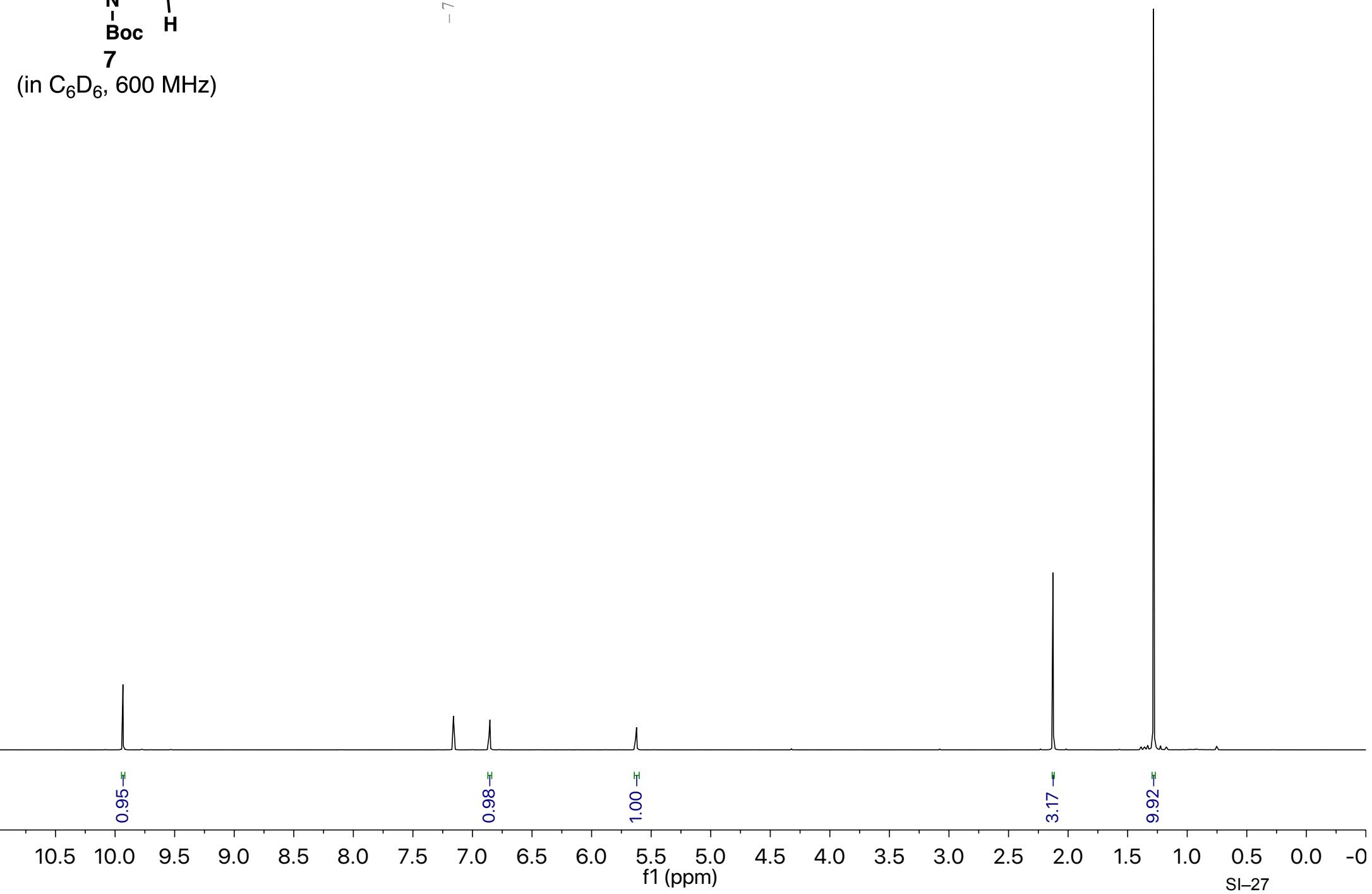
**References:**

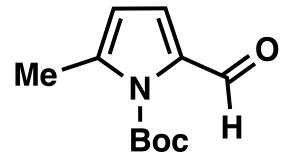
- 1) Han, W., B.; Lu, Y., H.; Zhang, G., F.; Mei, Y., N.; Jiang, N.; Lei, X.; Song, Y., C.; Ng, S., W.; Tan, R., X. *Org. Lett.* **2014**, 16, 5366-5396.



7  
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

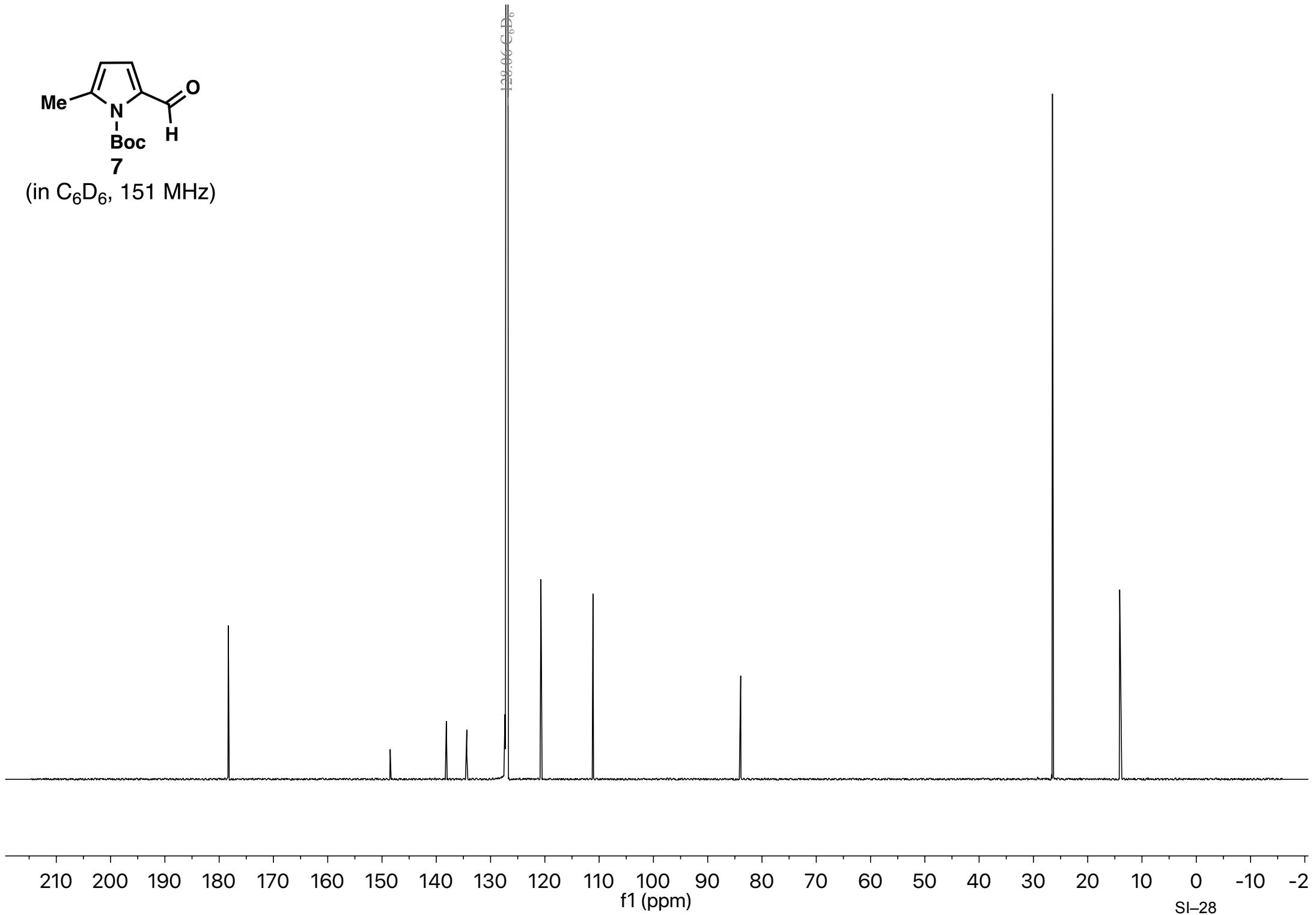
- 7.16 C<sub>6</sub>D<sub>6</sub>

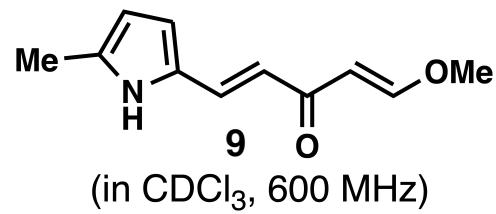




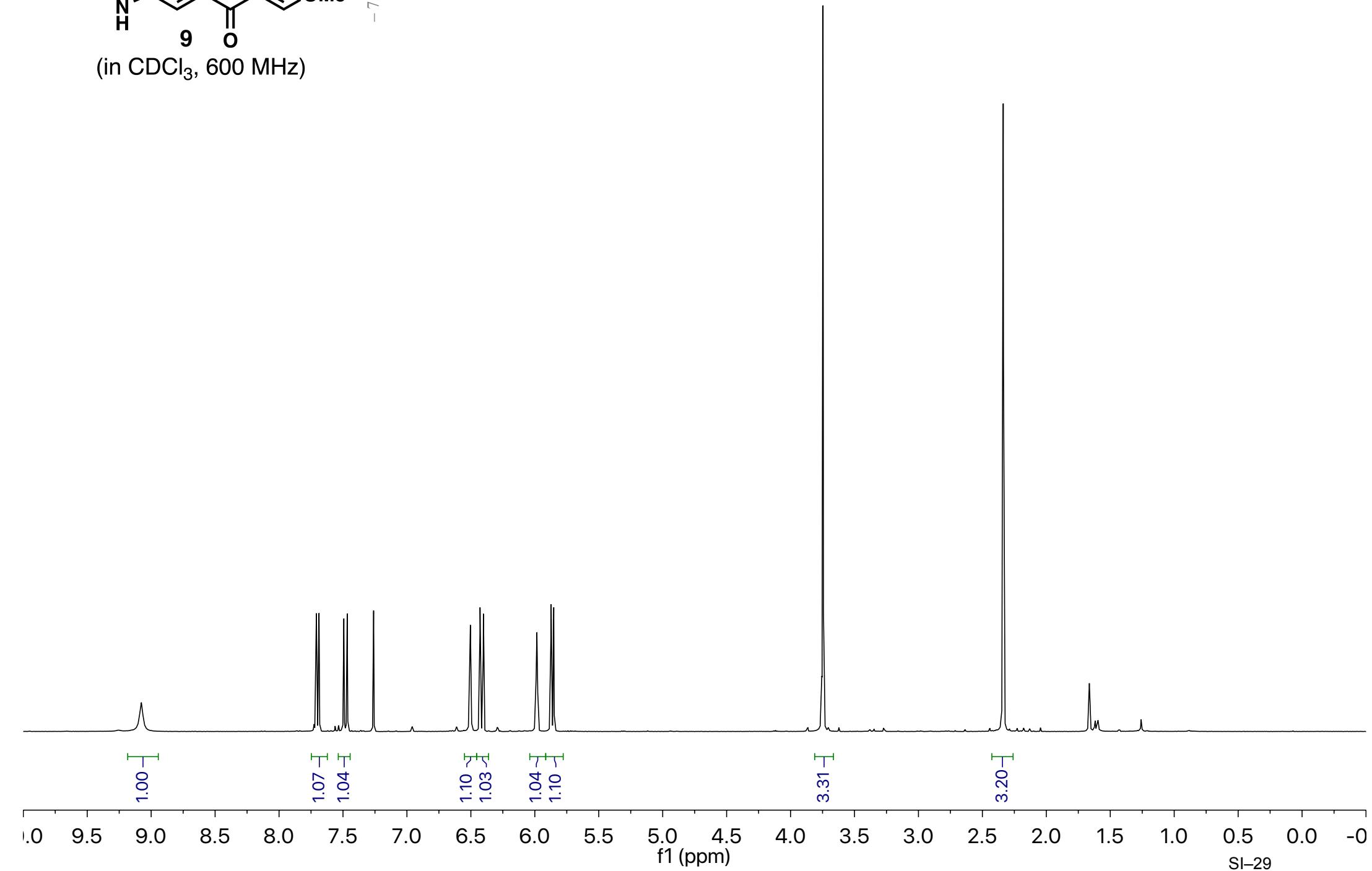
7

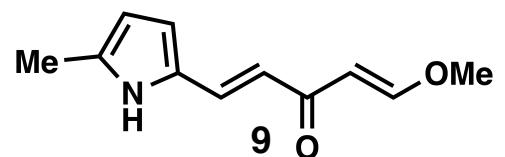
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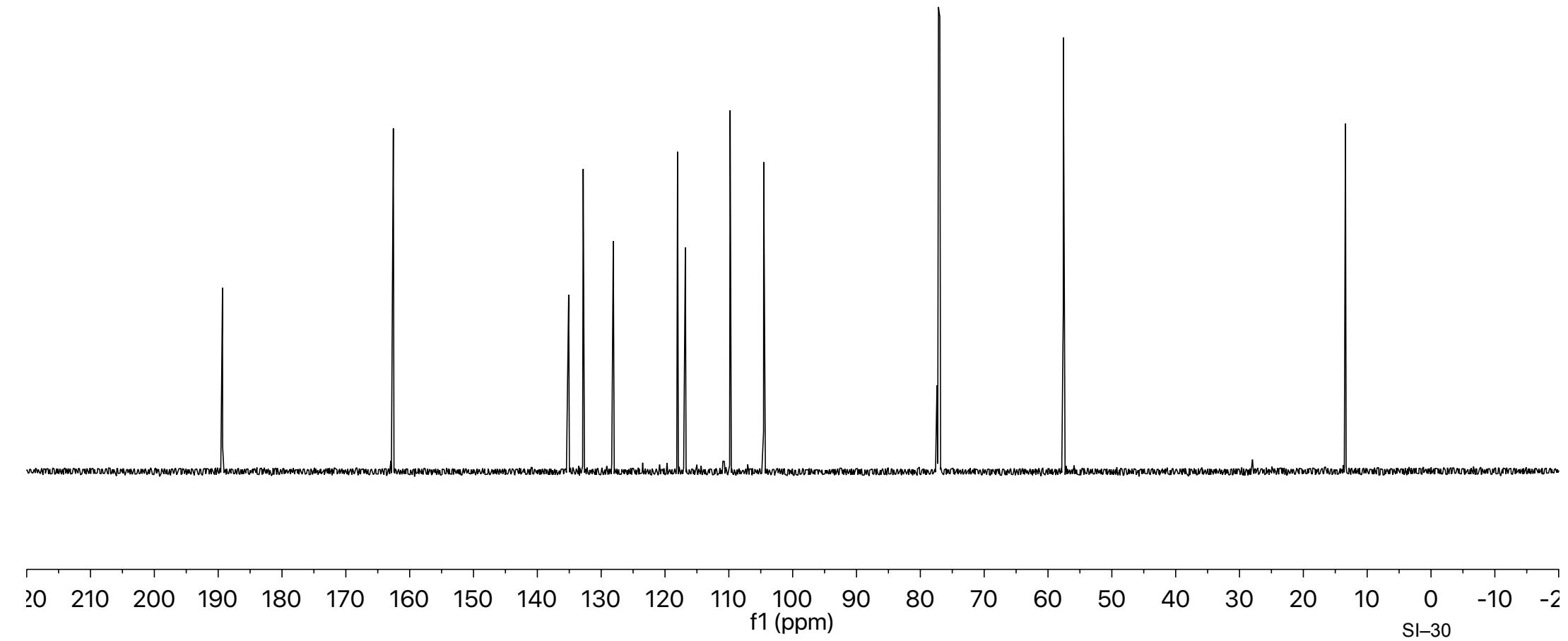
- 7.26  $\text{CDCl}_3$



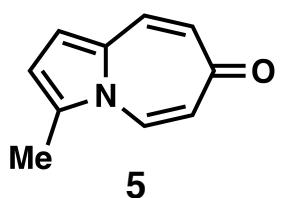


(in  $\text{CDCl}_3$ , 151 MHz)

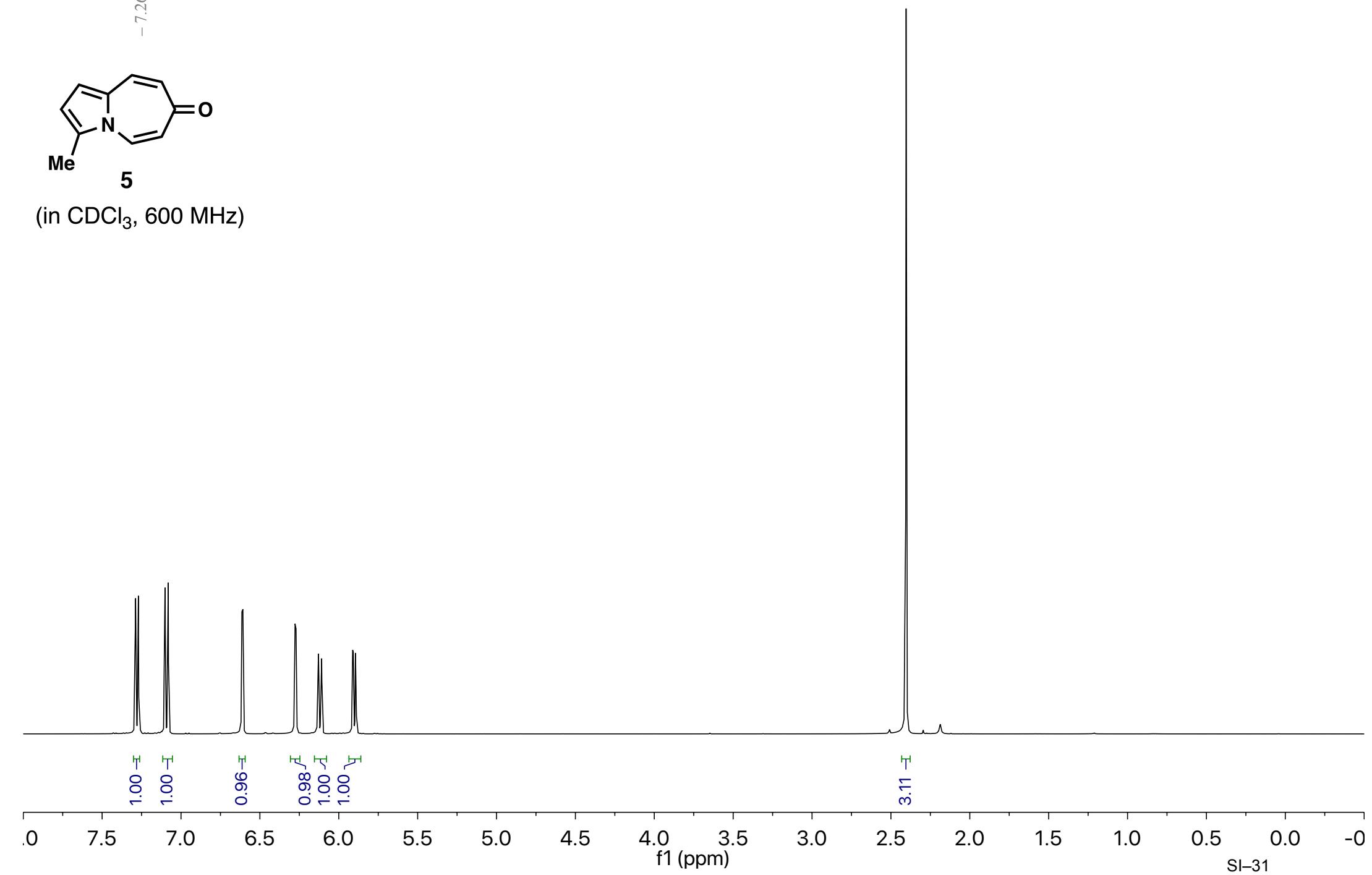
- 77.16  $\text{CDCl}_3$

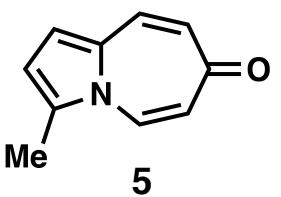


- 7.26 CDCl<sub>3</sub>



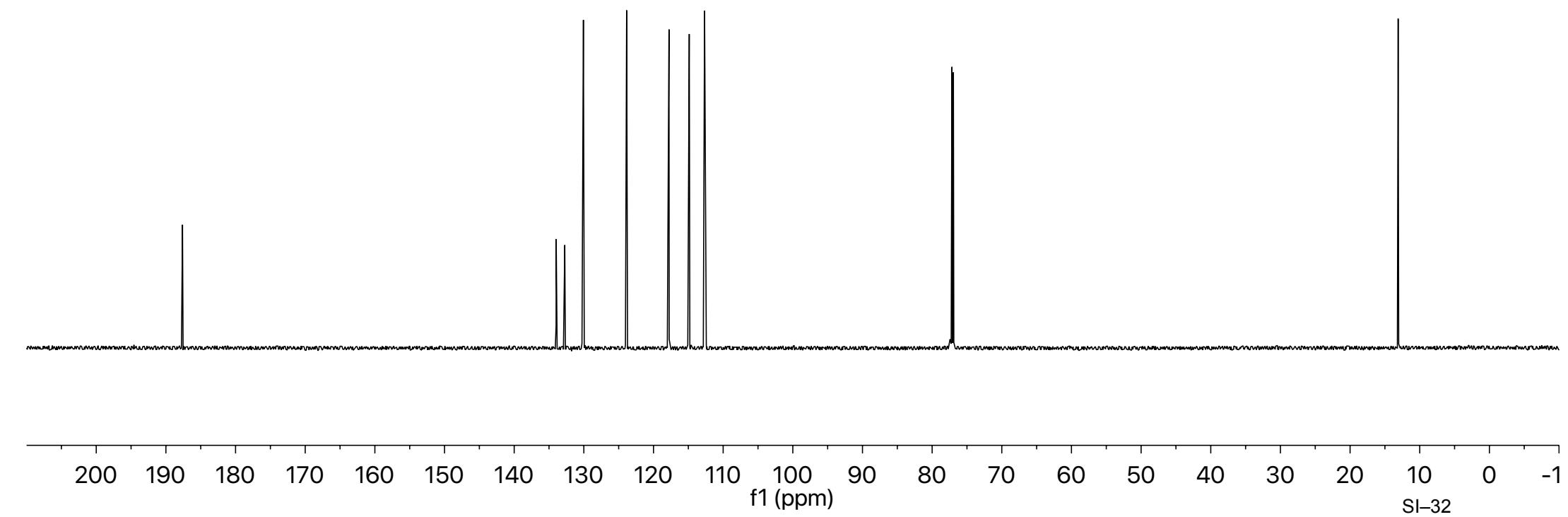
(in CDCl<sub>3</sub>, 600 MHz)

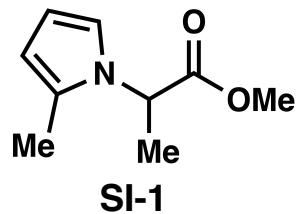




(in  $\text{CDCl}_3$ , 151 MHz)

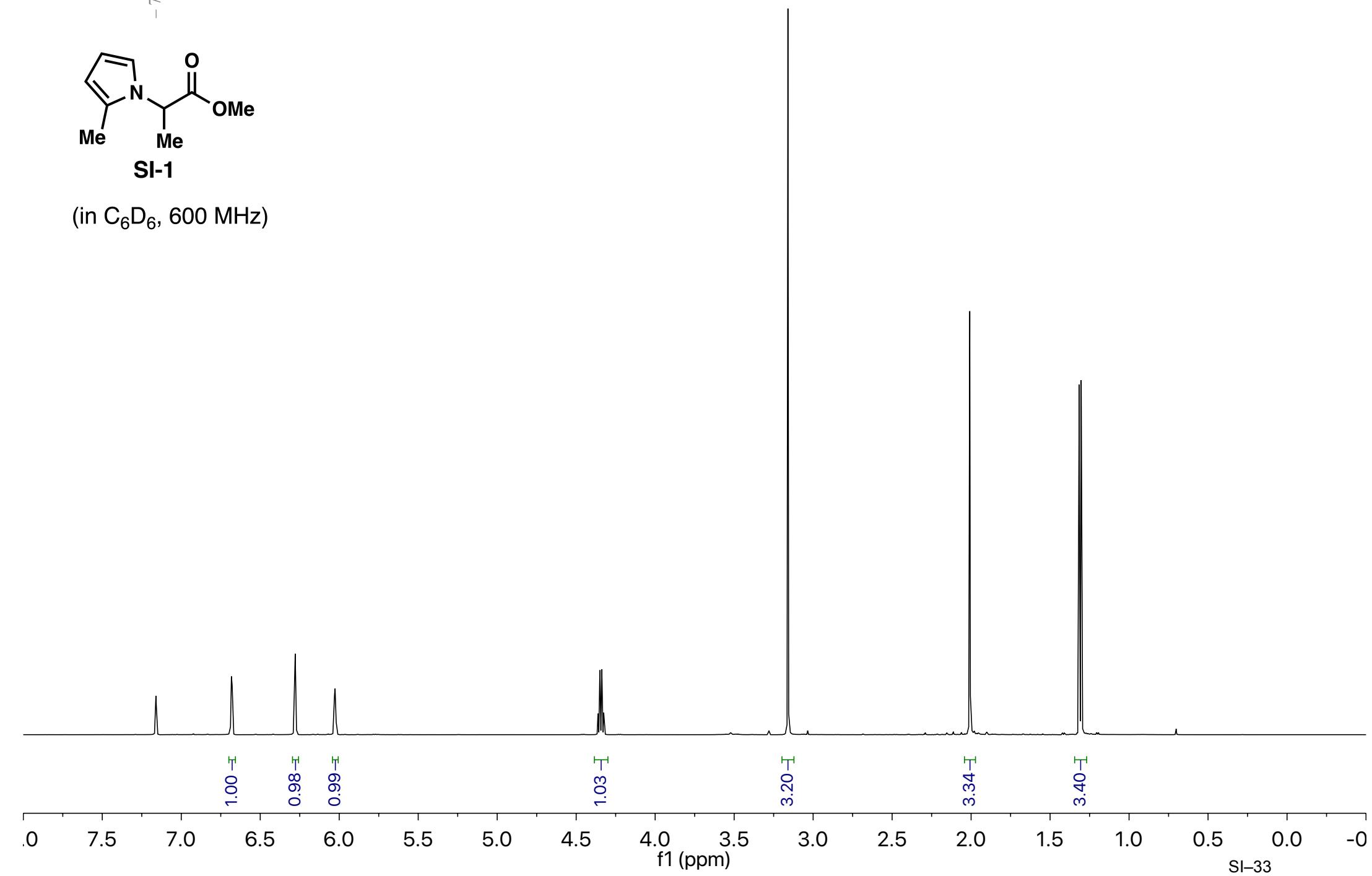
- 77.16  $\text{CDCl}_3$

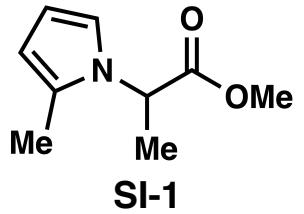




- 7.16 C<sub>6</sub>D<sub>6</sub>

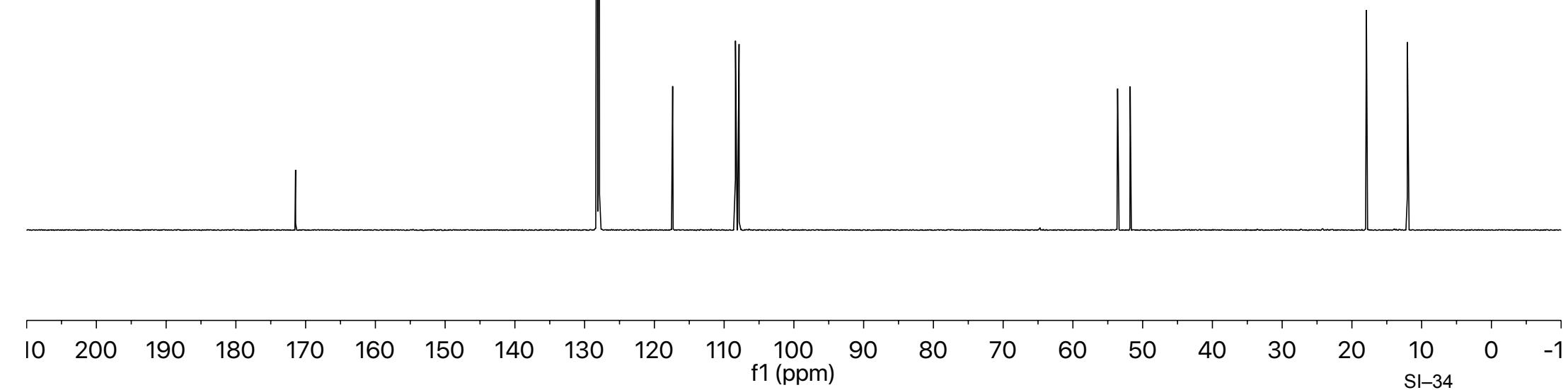
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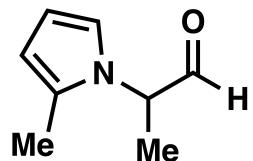


(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

128.06 C<sub>6</sub>D<sub>6</sub>

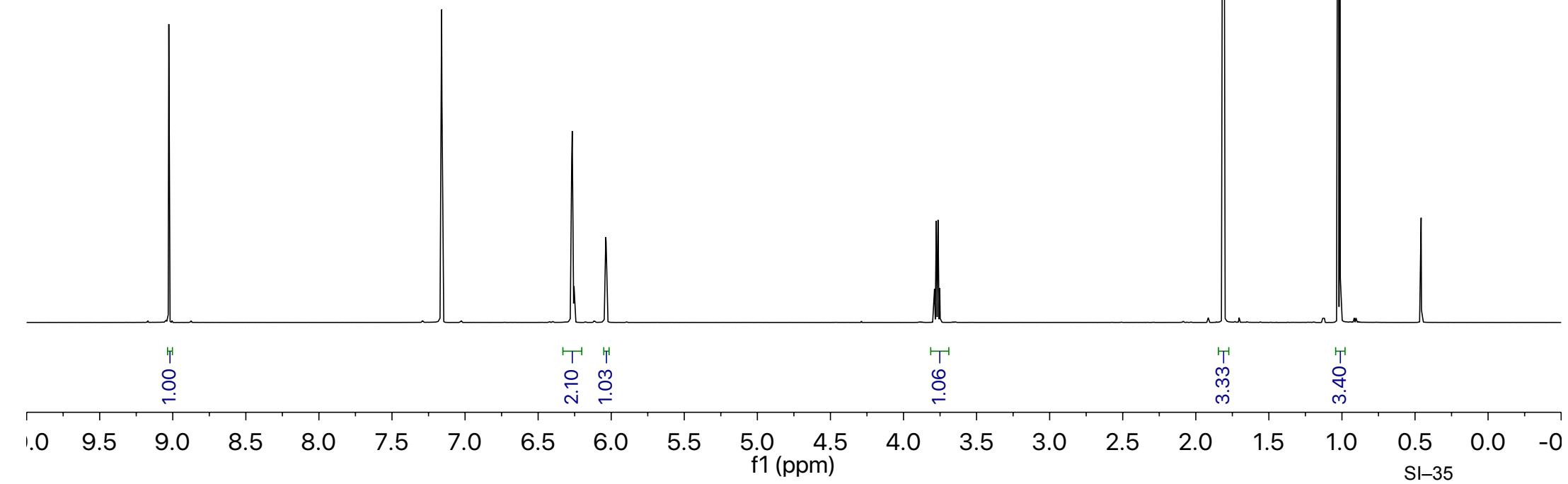


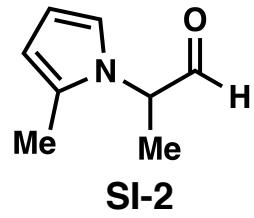
- 7.16 C<sub>6</sub>D<sub>6</sub>



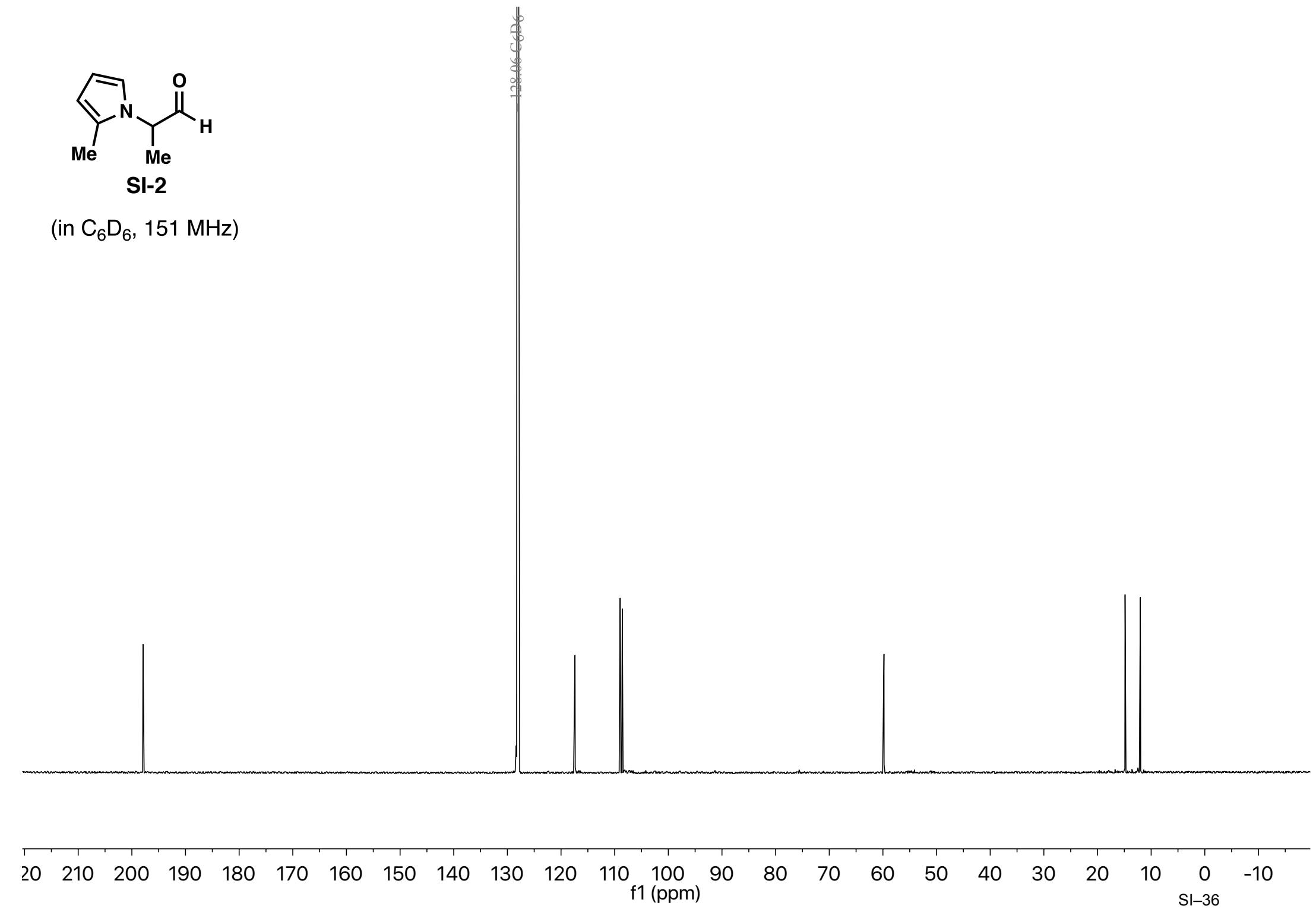
**SI-2**

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

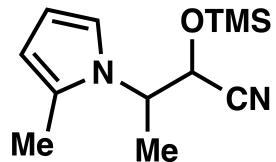




(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

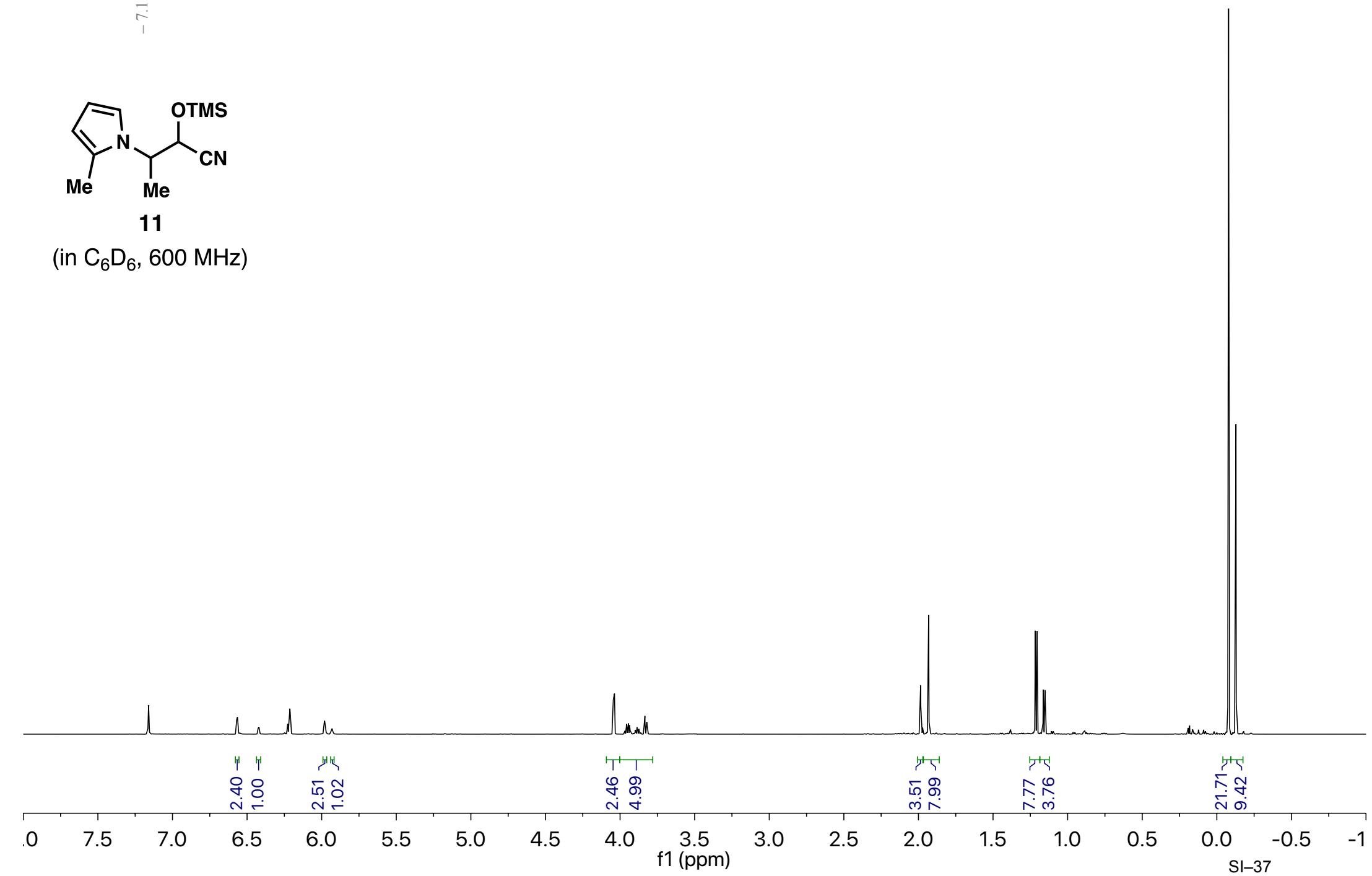


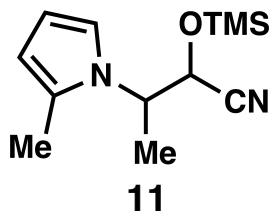
- 7.16 C<sub>6</sub>D<sub>6</sub>



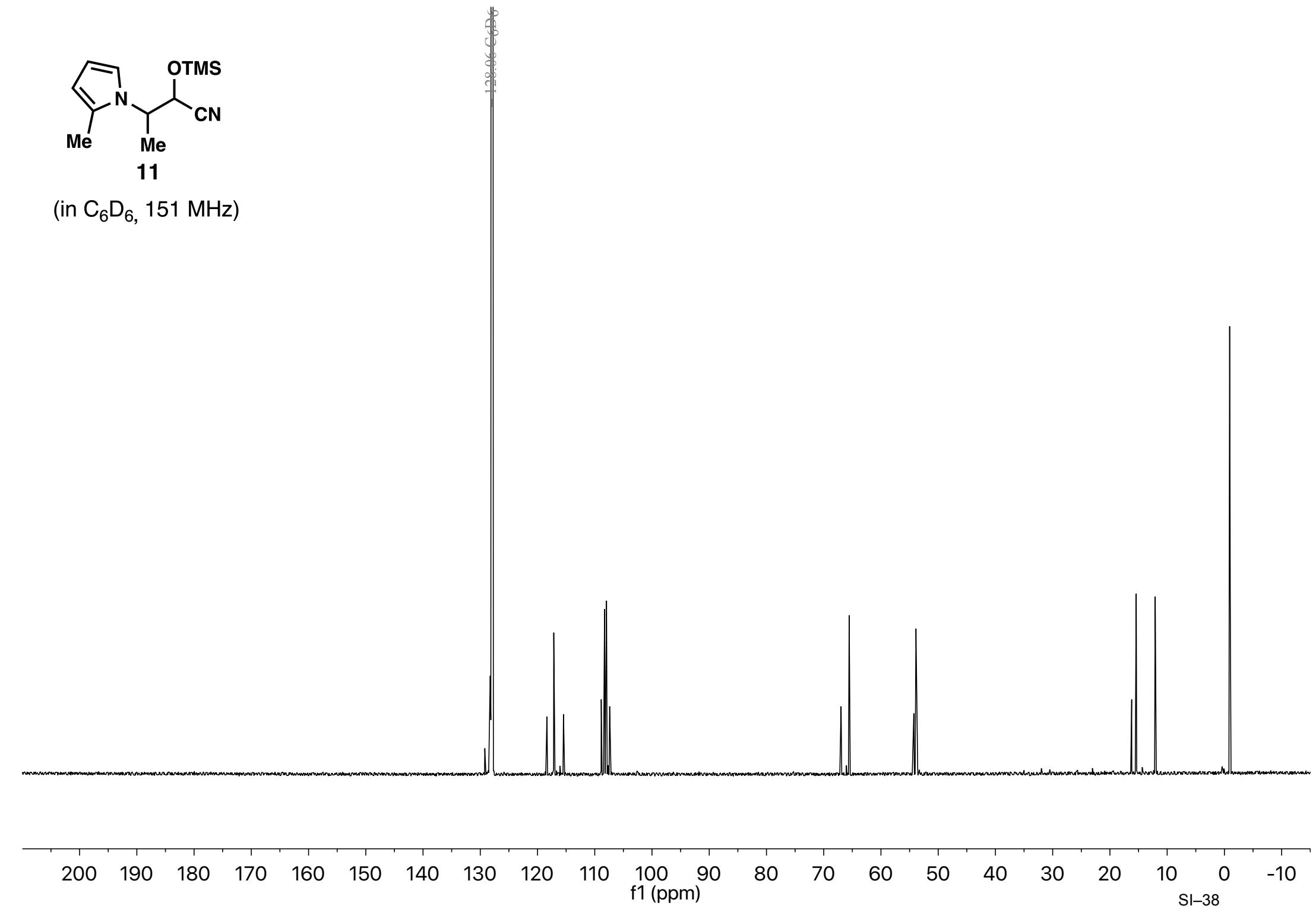
**11**

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

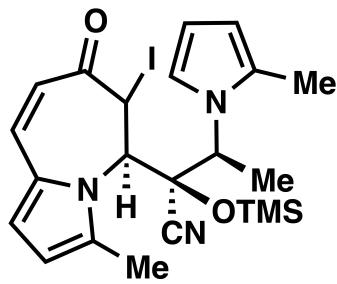




(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

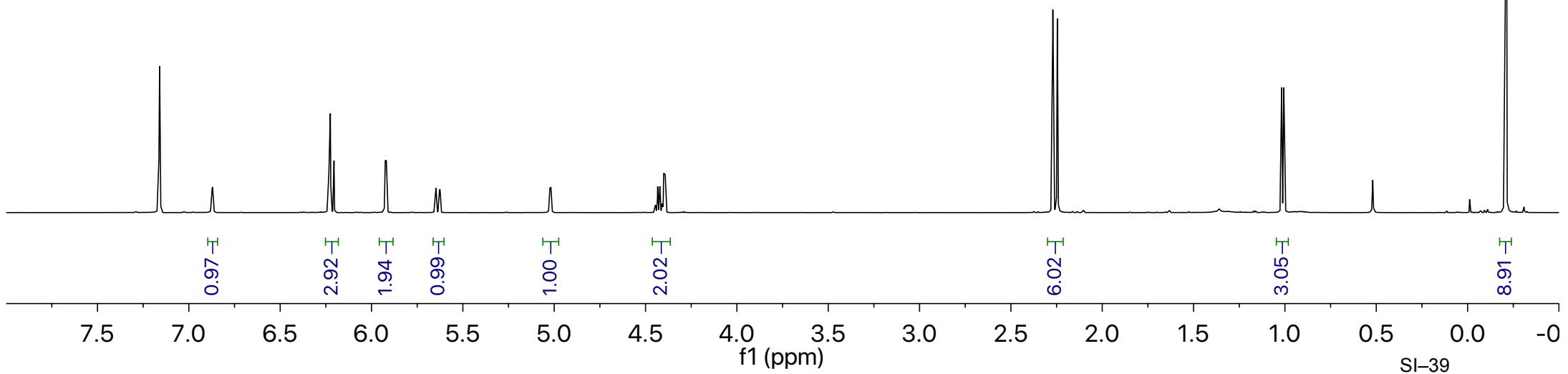


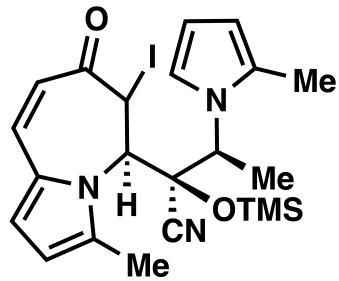
- 7.16 C<sub>6</sub>D<sub>6</sub>



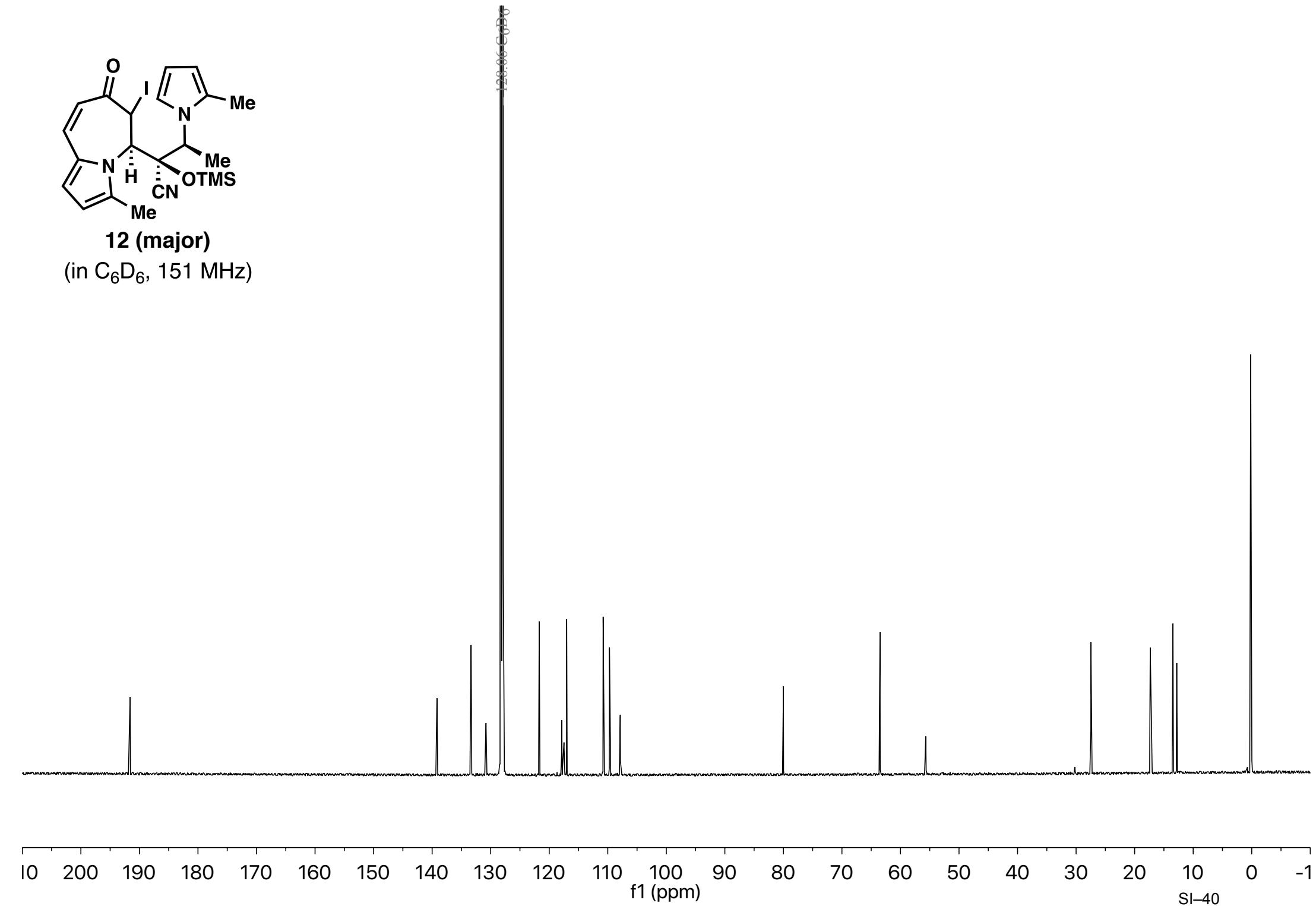
**12 (major)**

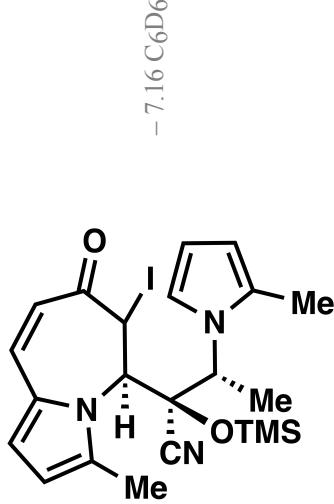
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)



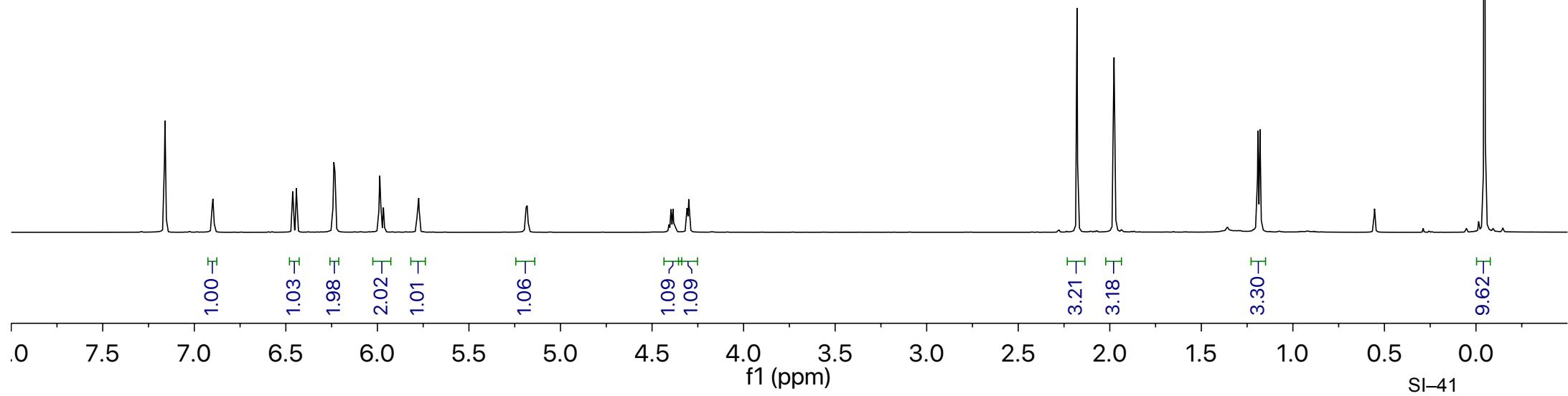


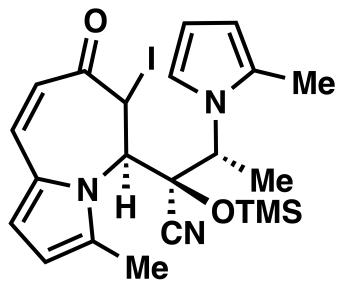
**12 (major)**  
(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)





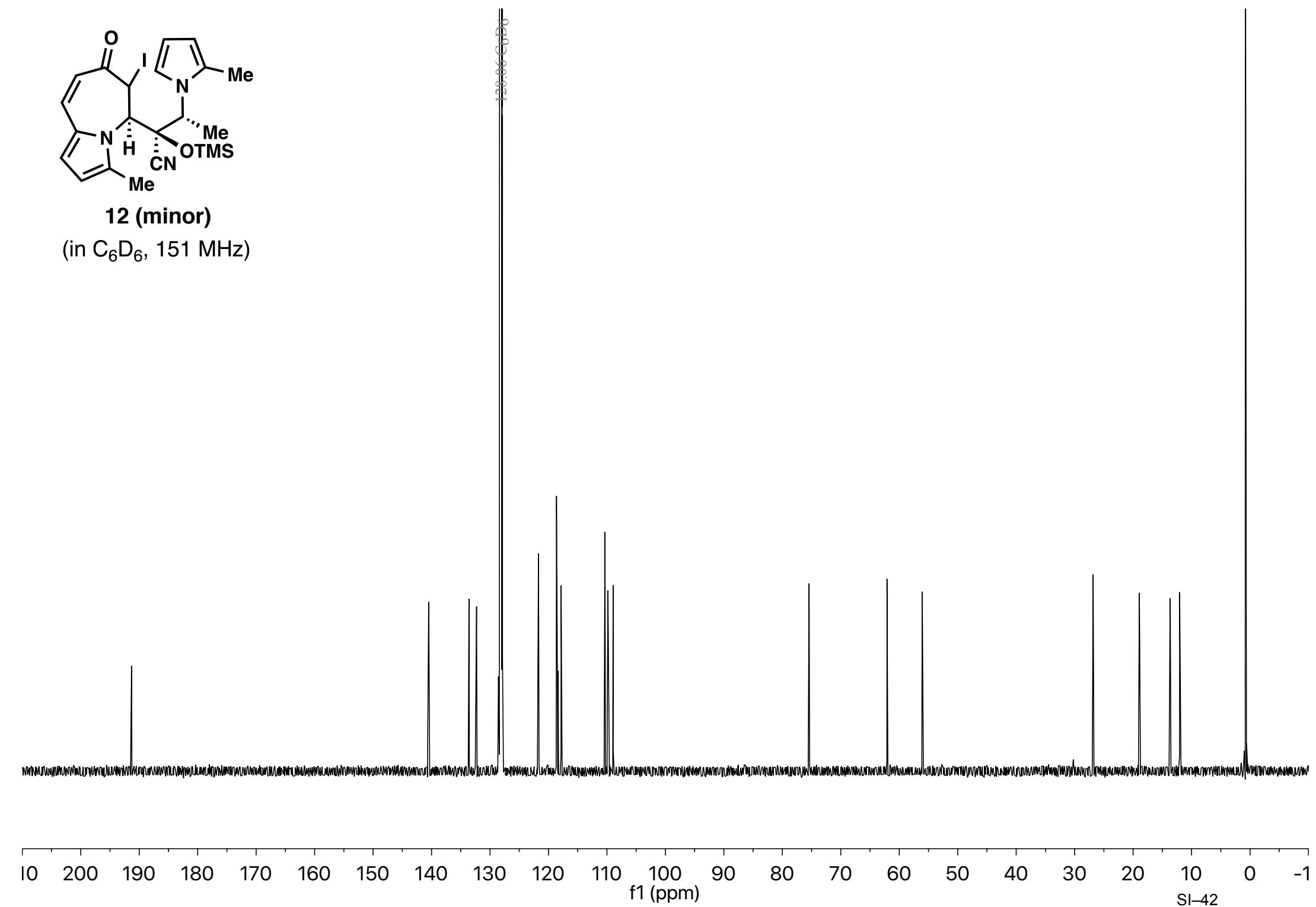
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)



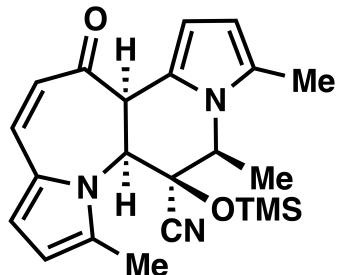


**12 (minor)**

(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

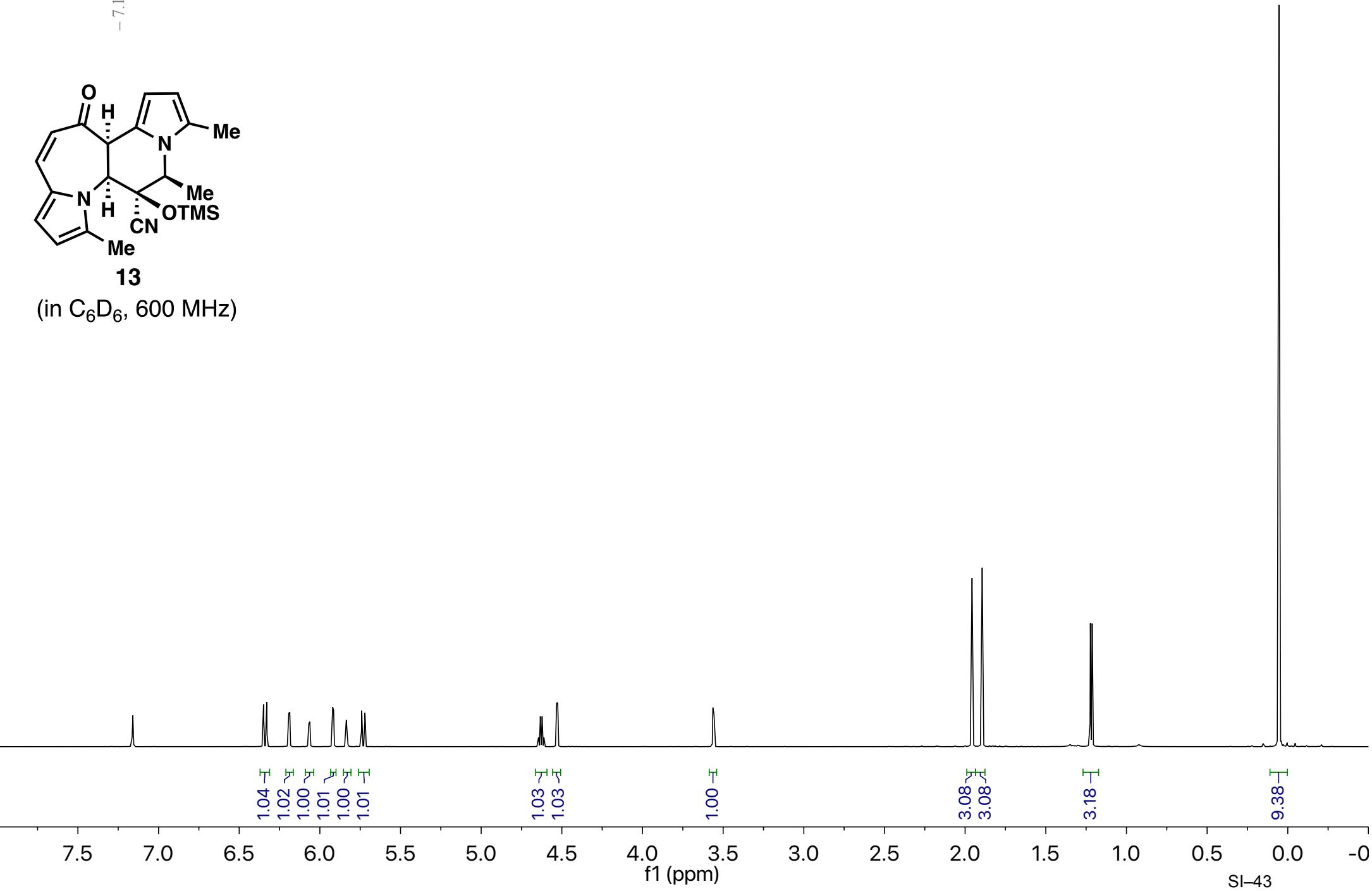


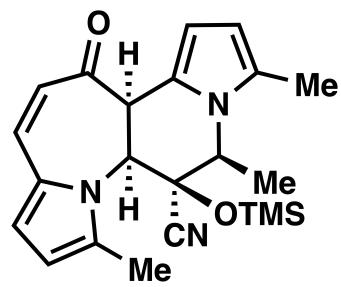
- 7.16 C<sub>6</sub>D<sub>6</sub>



**13**

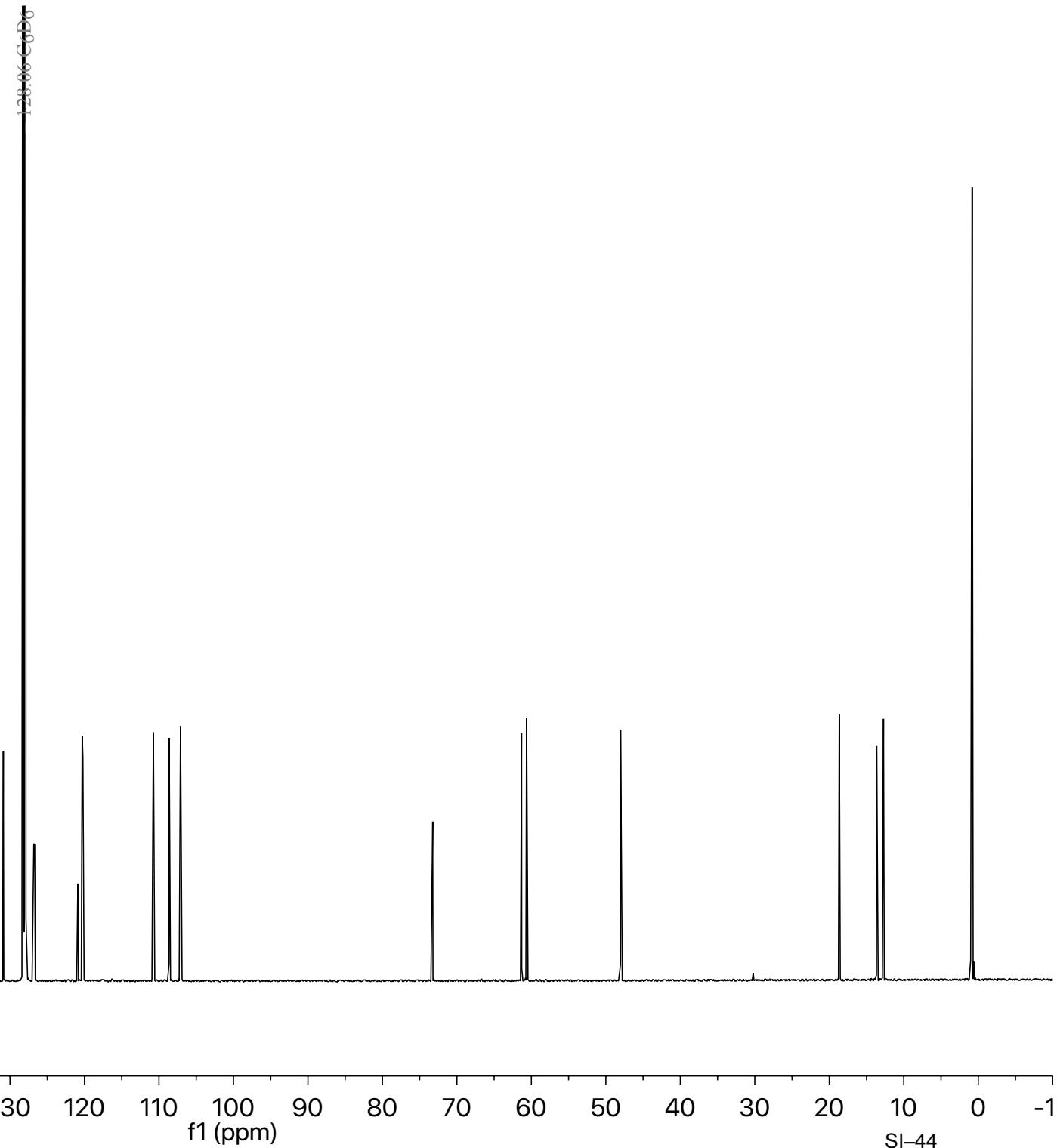
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)





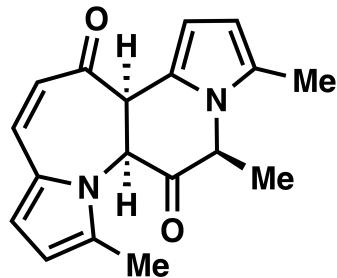
13

(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)



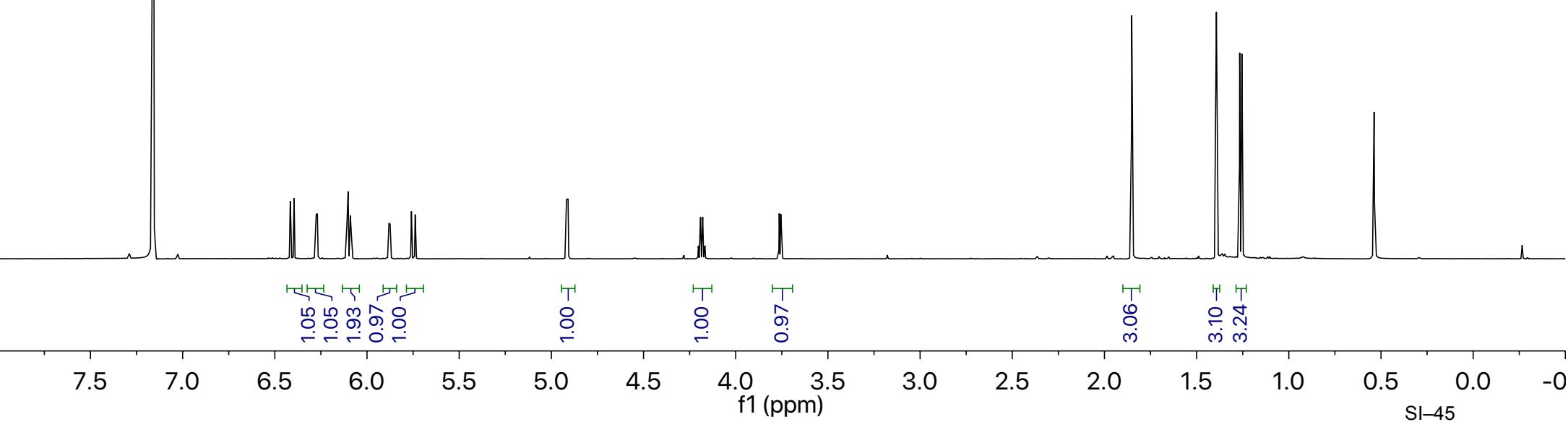
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1  
f1 (ppm)  
SI-44

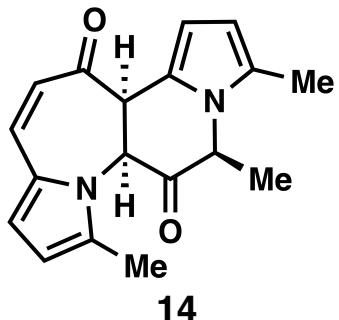
7.116 C<sub>6</sub>D<sub>6</sub>



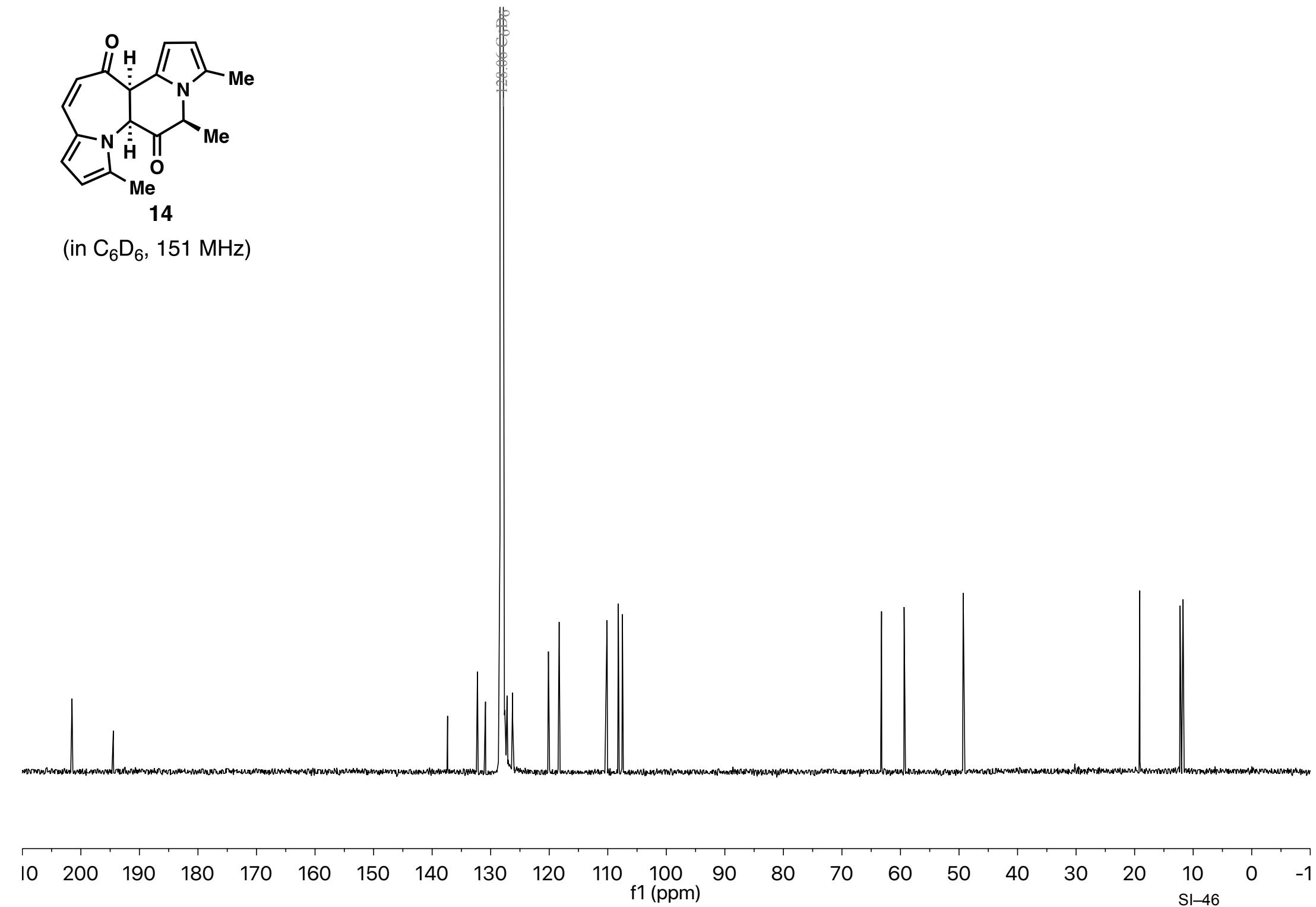
**14**

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

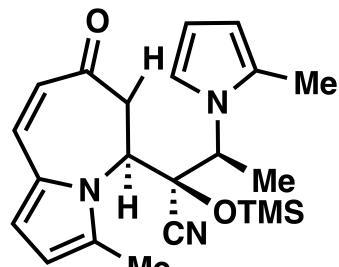




(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

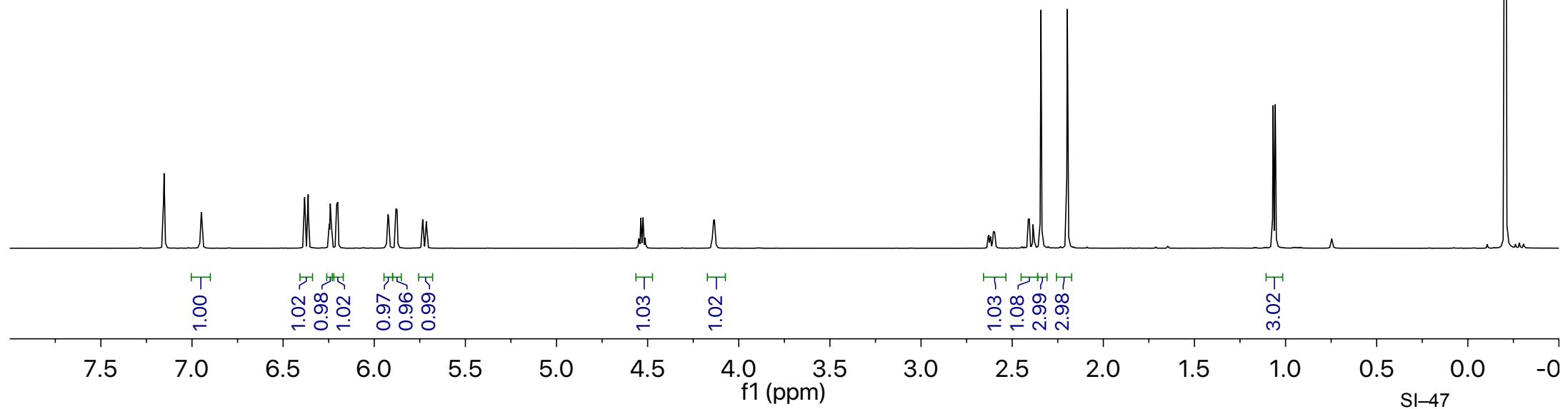


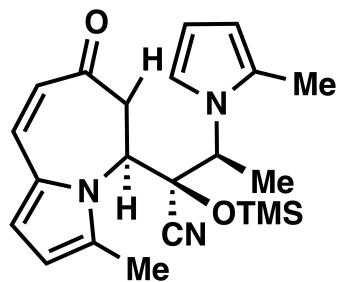
- 7.16 C<sub>6</sub>D<sub>6</sub>



**15**

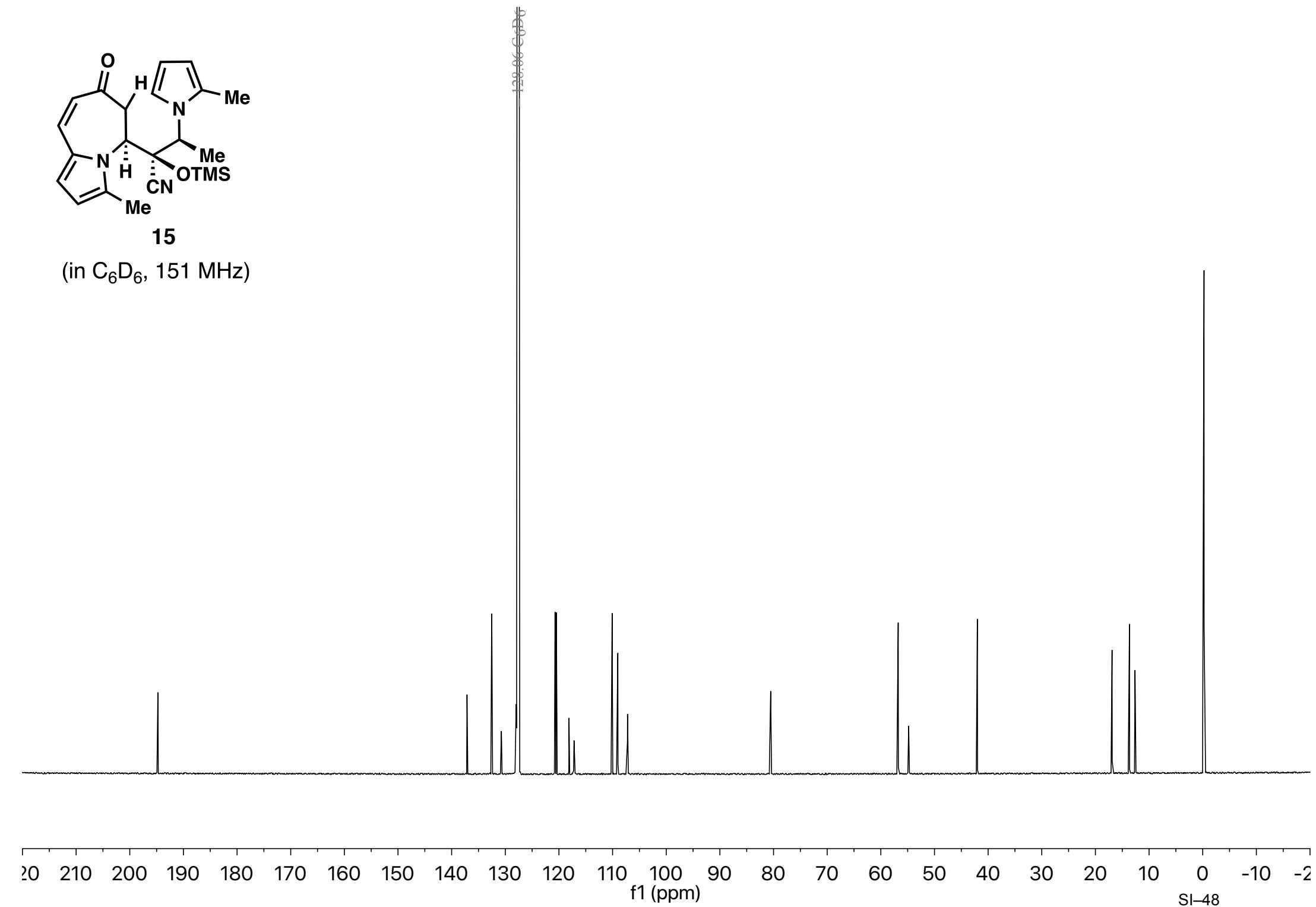
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)



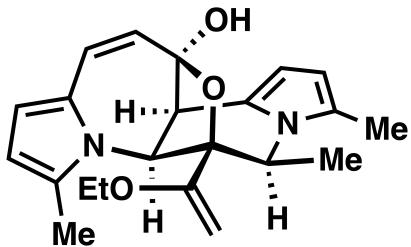


15

(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)



7.116 C<sub>6</sub>D<sub>6</sub>



**16**  
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

1.04  
1.04  
1.05  
1.96  
1.96

0.99  
1.00  
0.98  
0.98

1.03  
0.98  
2.04  
1.03

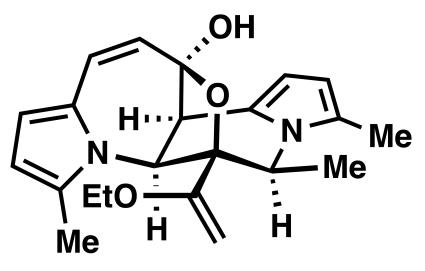
2.99  
2.98  
3.08

3.03

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

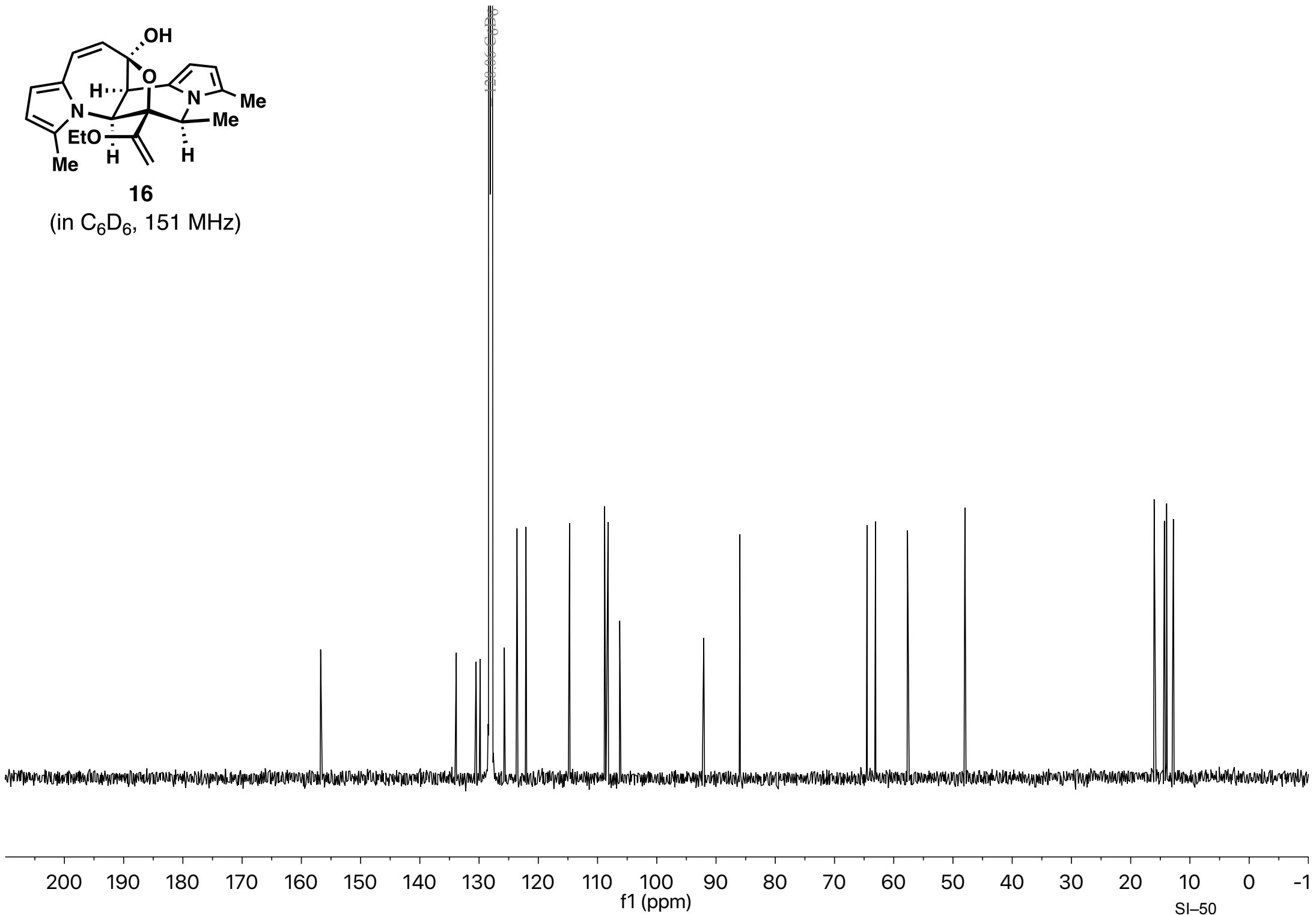
f1 (ppm)

SI-49

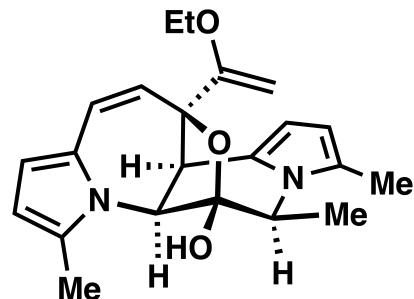


**16**

(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

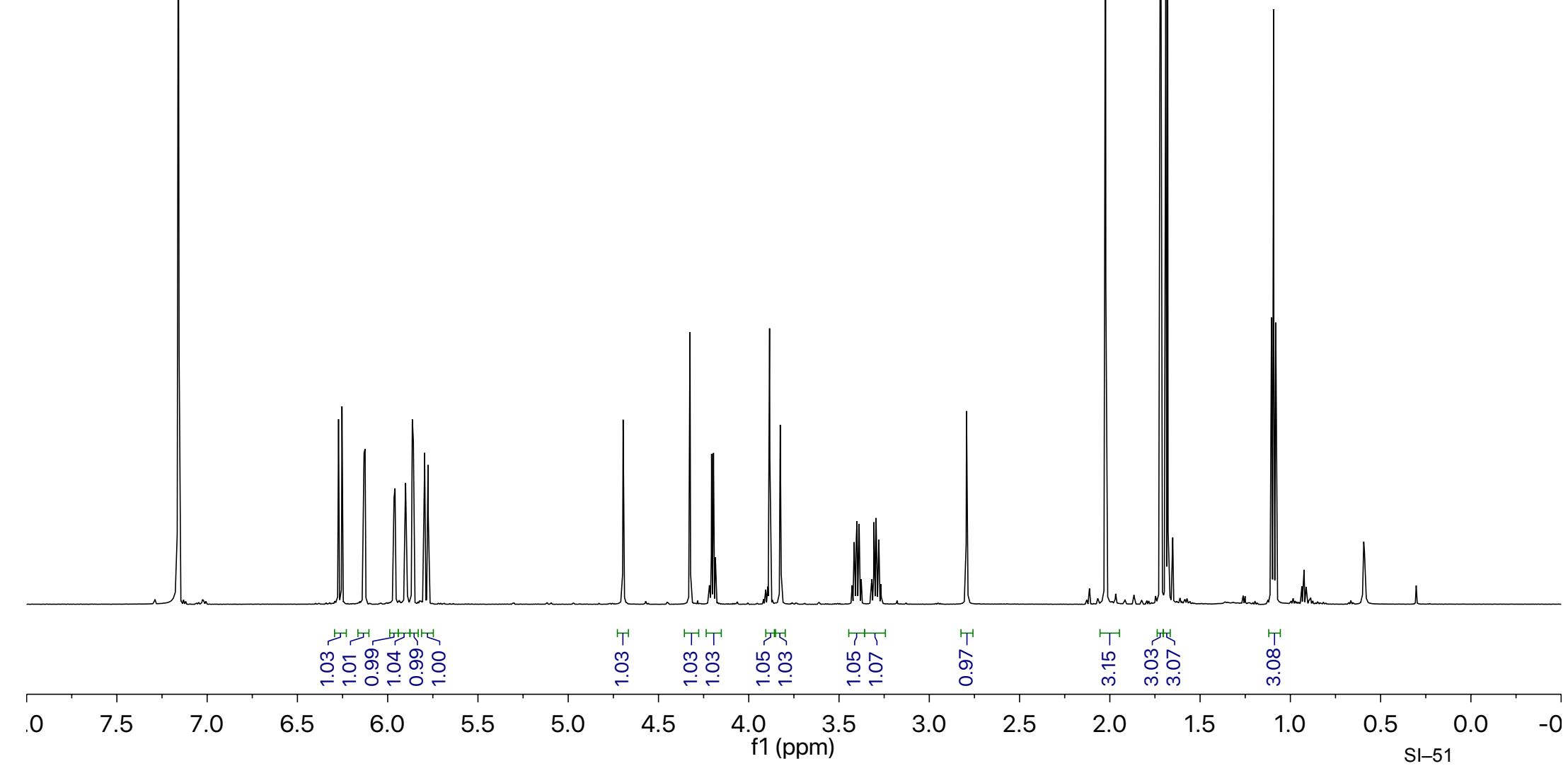


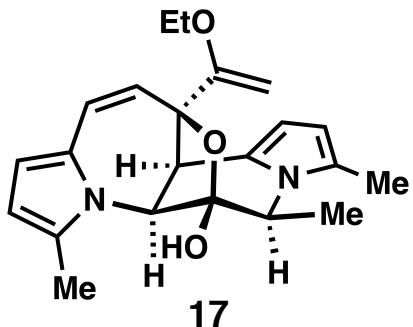
- 7.16 C<sub>6</sub>D<sub>6</sub>



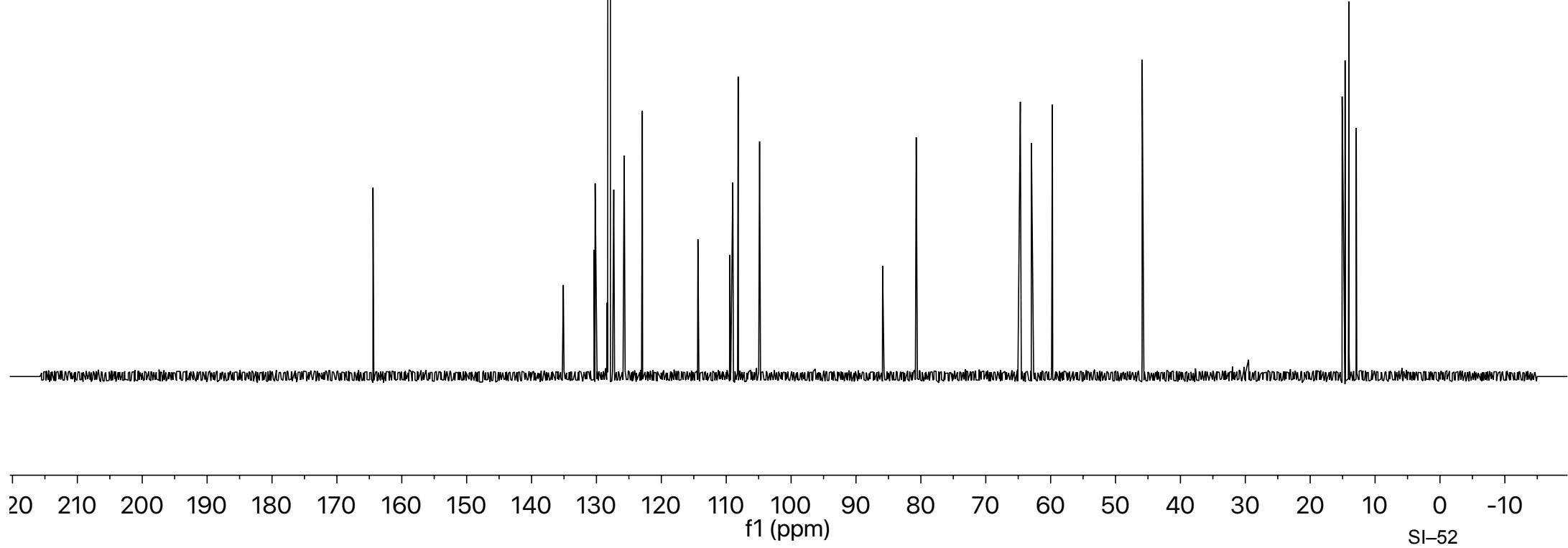
**17**

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

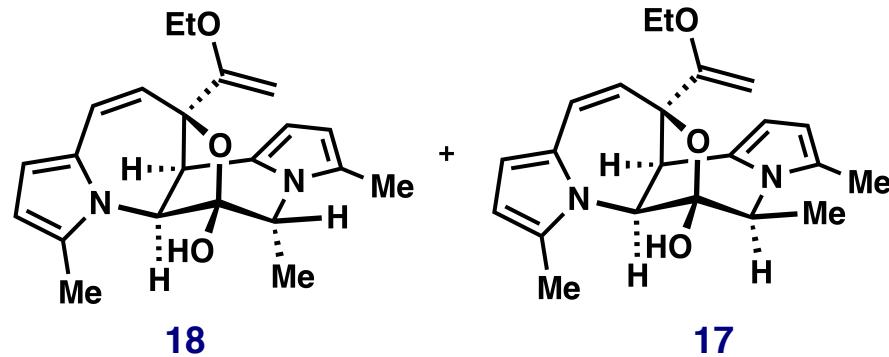




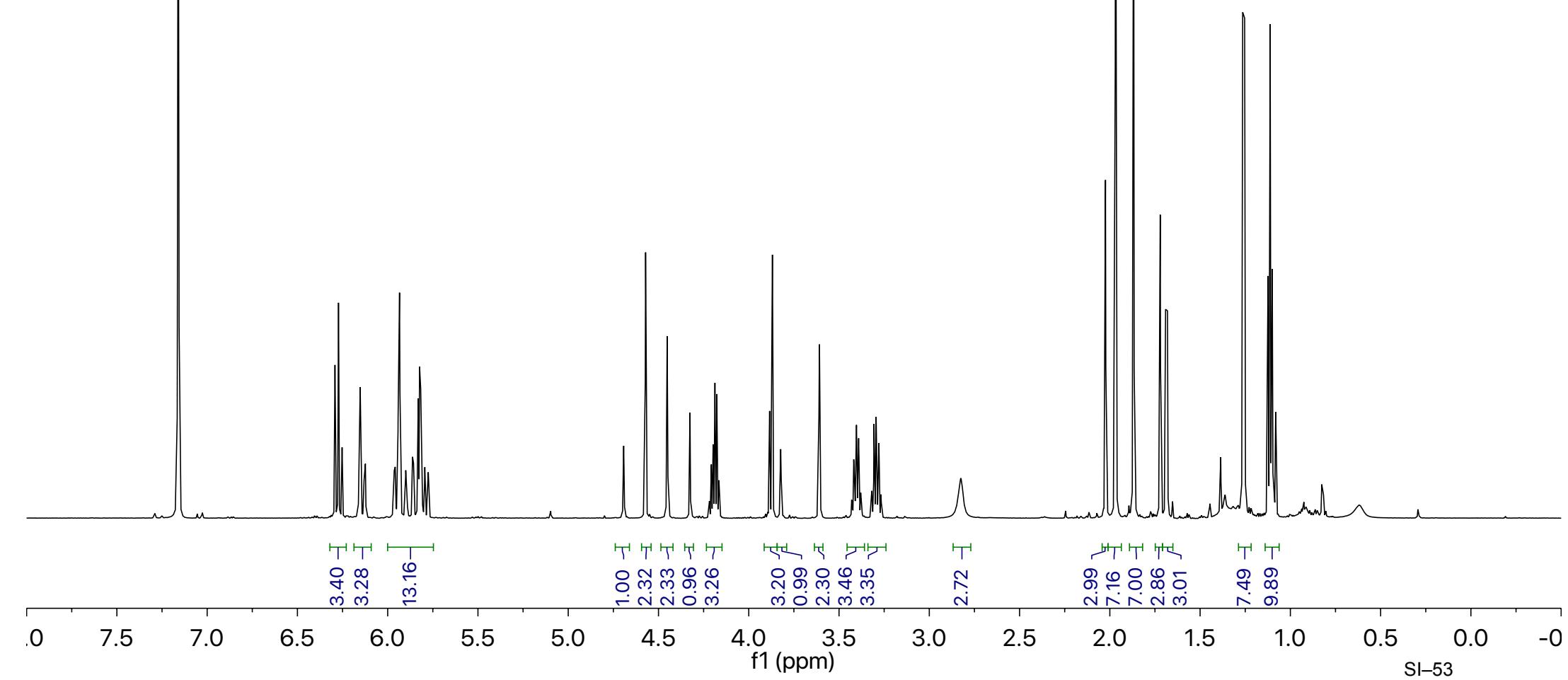
(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

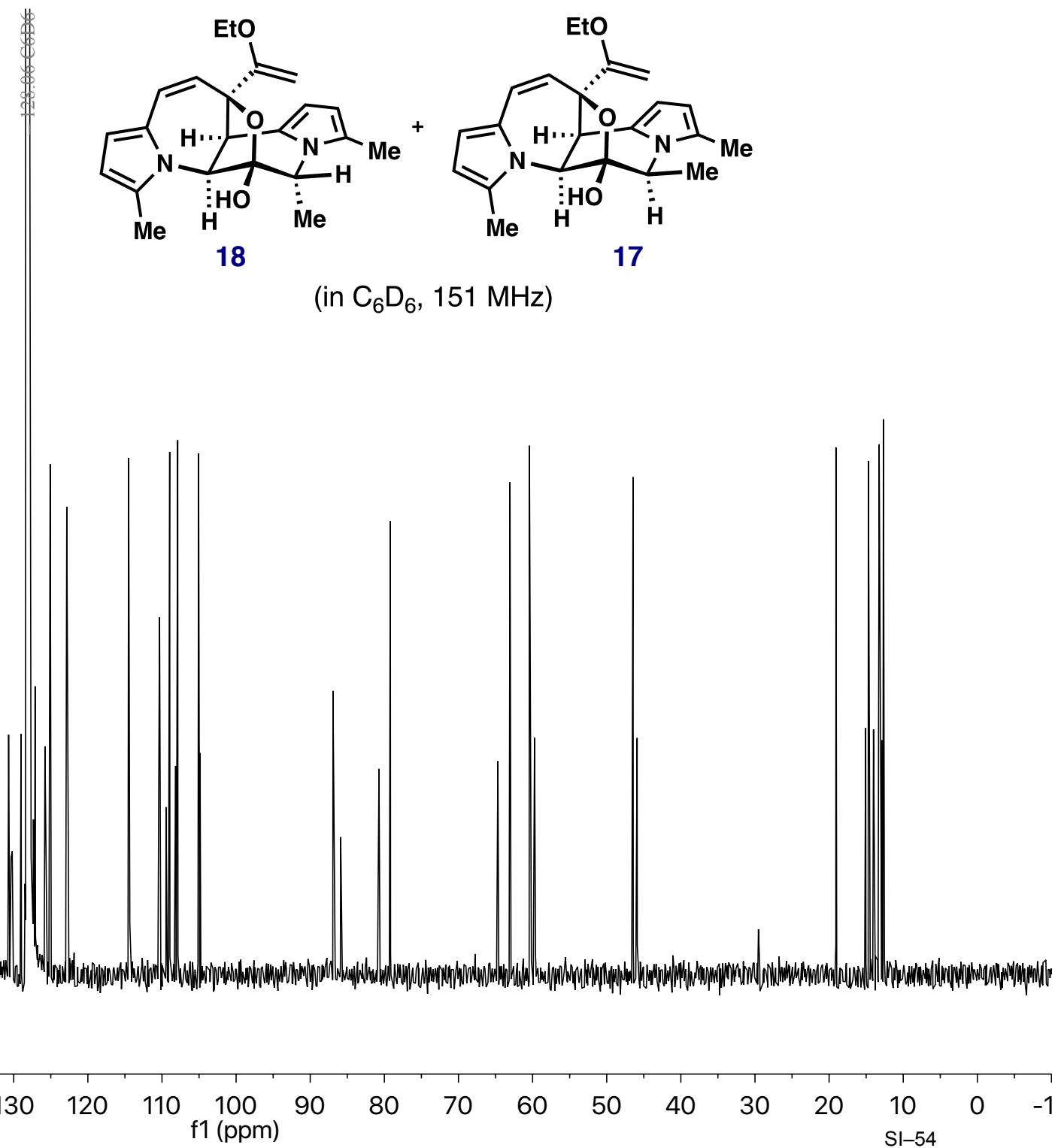


- 7.16 C<sub>6</sub>D<sub>6</sub>

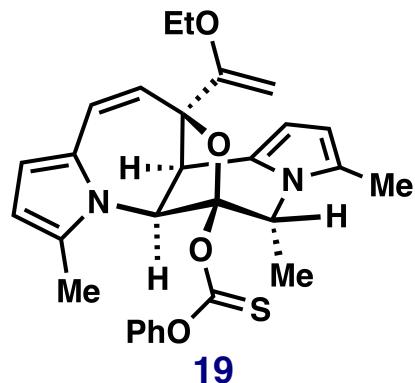


(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)



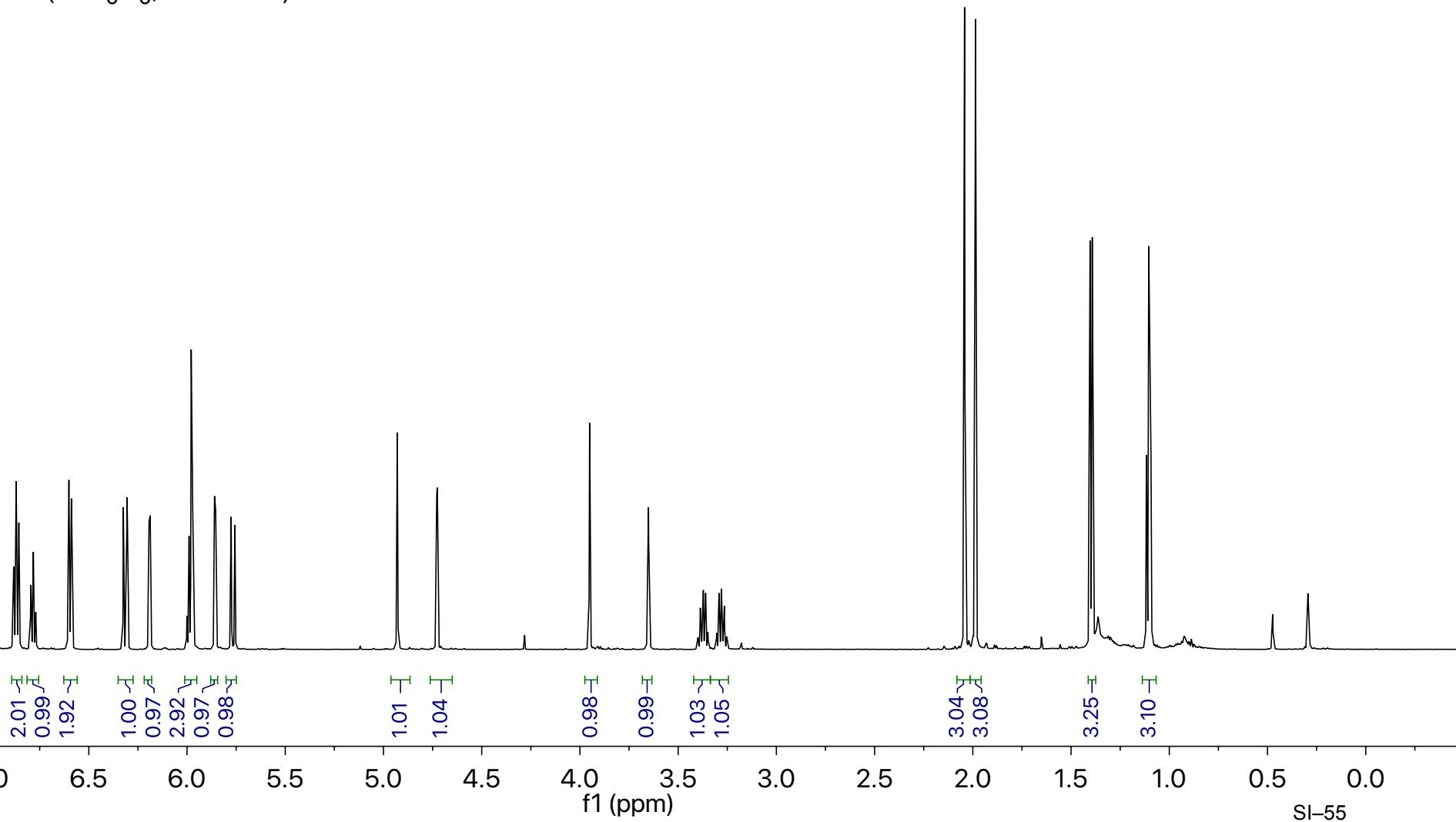


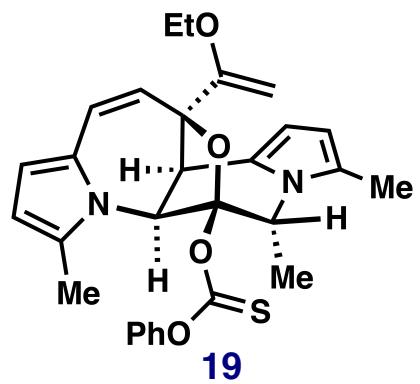
7.116 C<sub>6</sub>D<sub>6</sub>



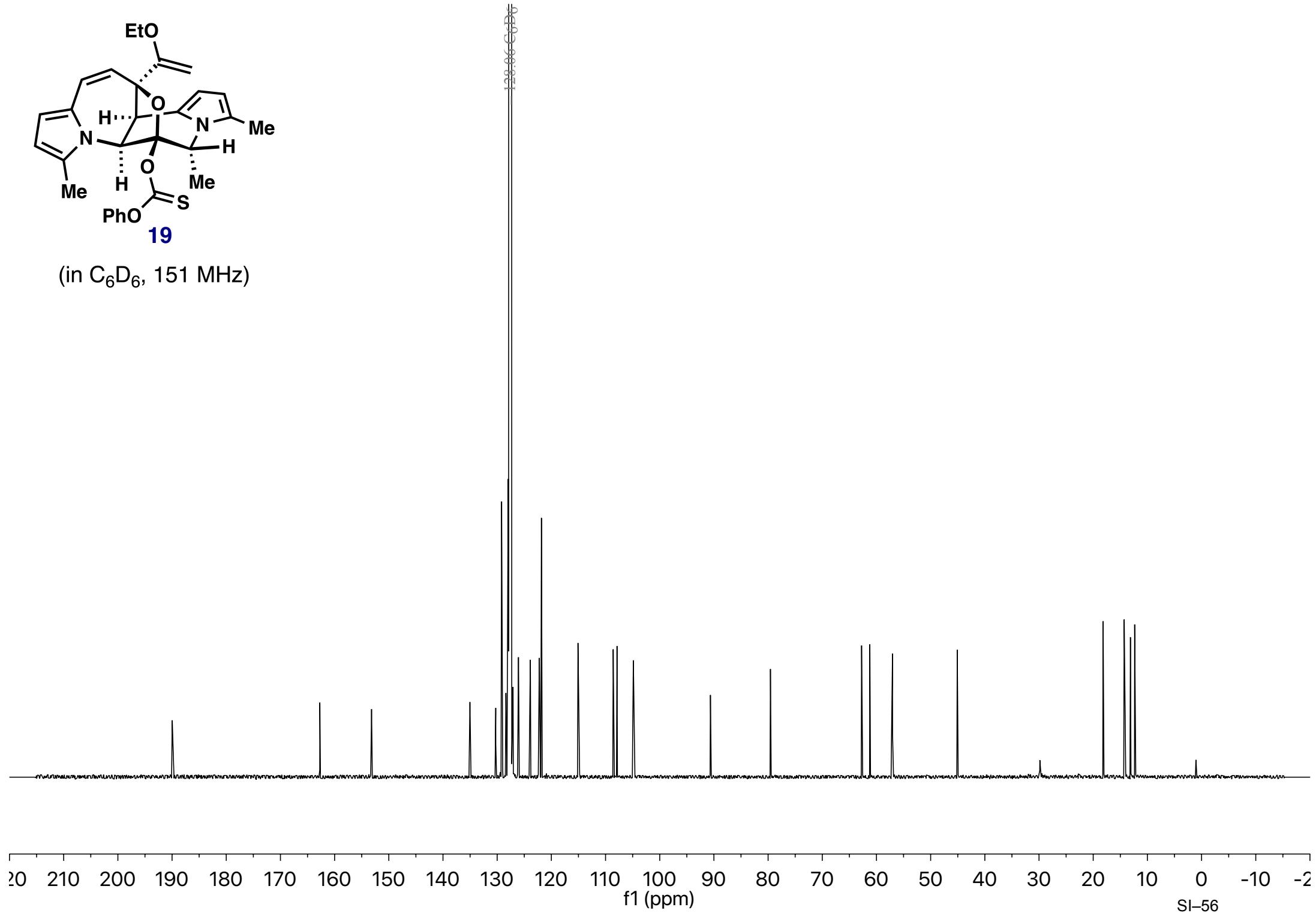
**19**

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

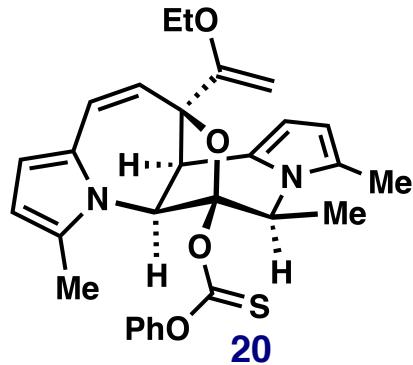




(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

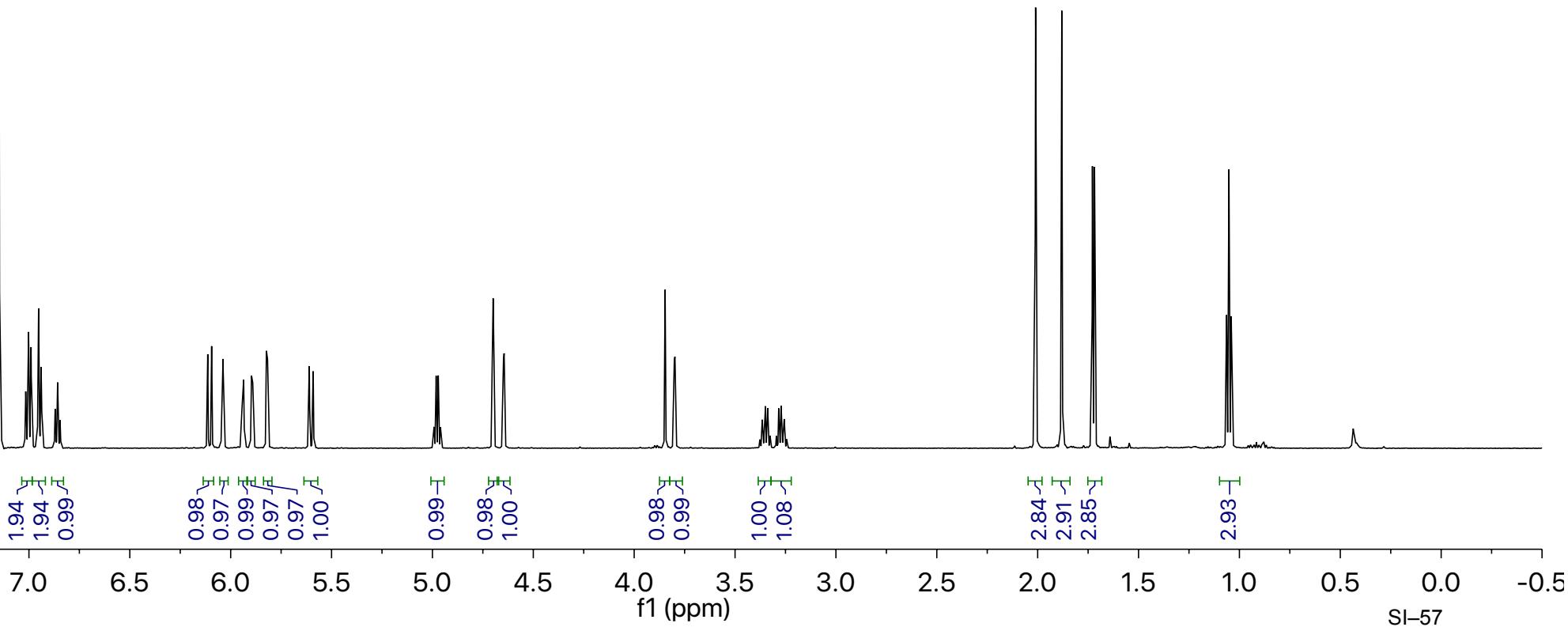


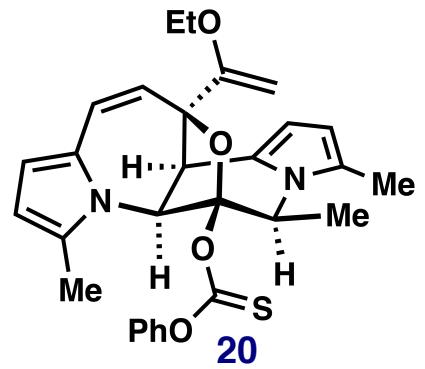
7.16 C<sub>6</sub>D<sub>6</sub>



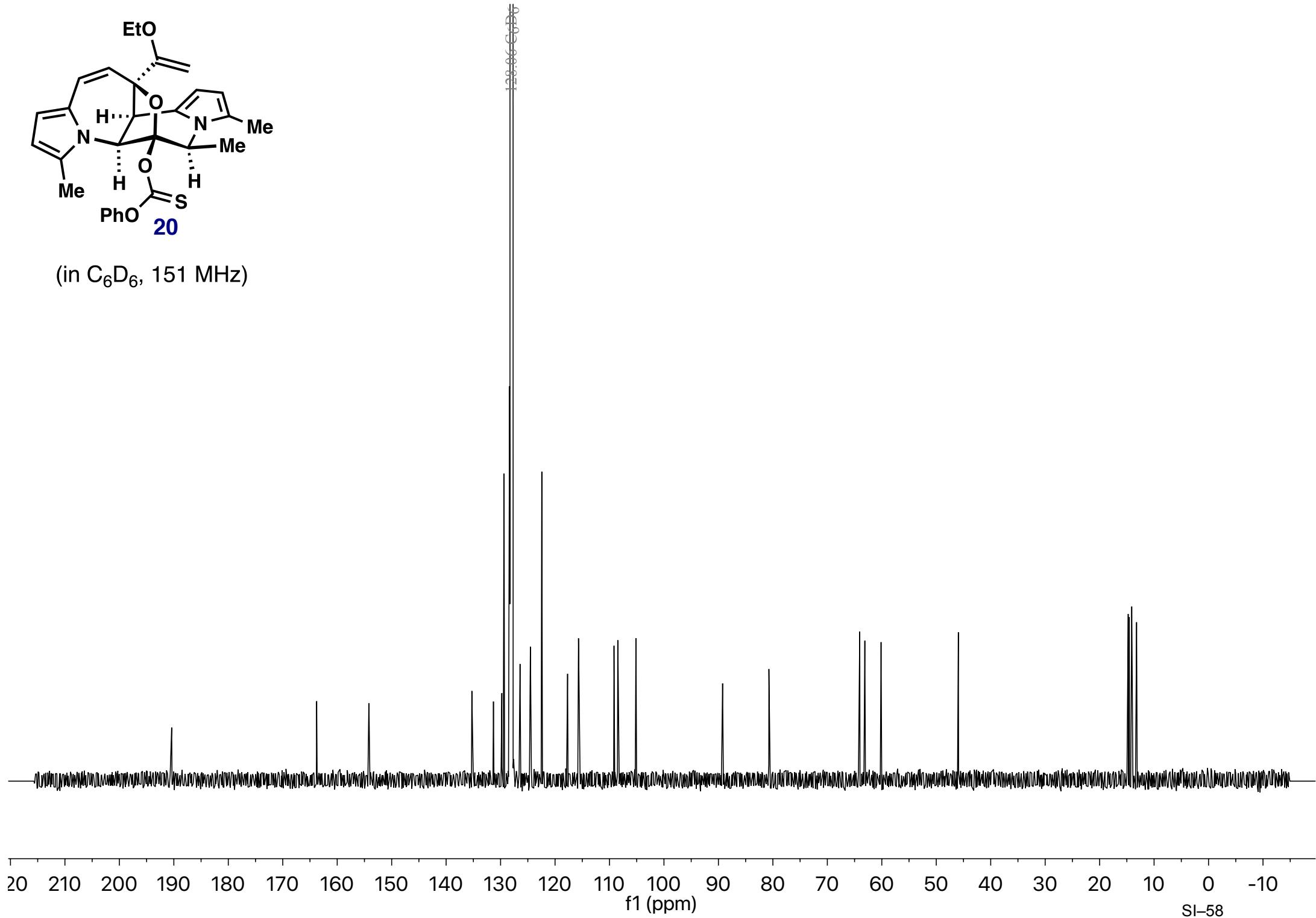
20

(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)

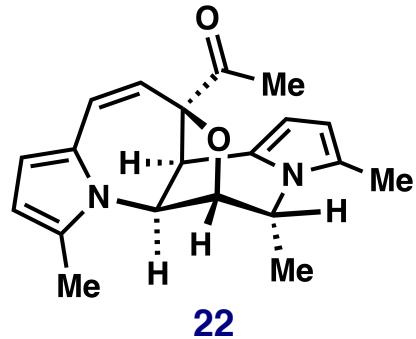




(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

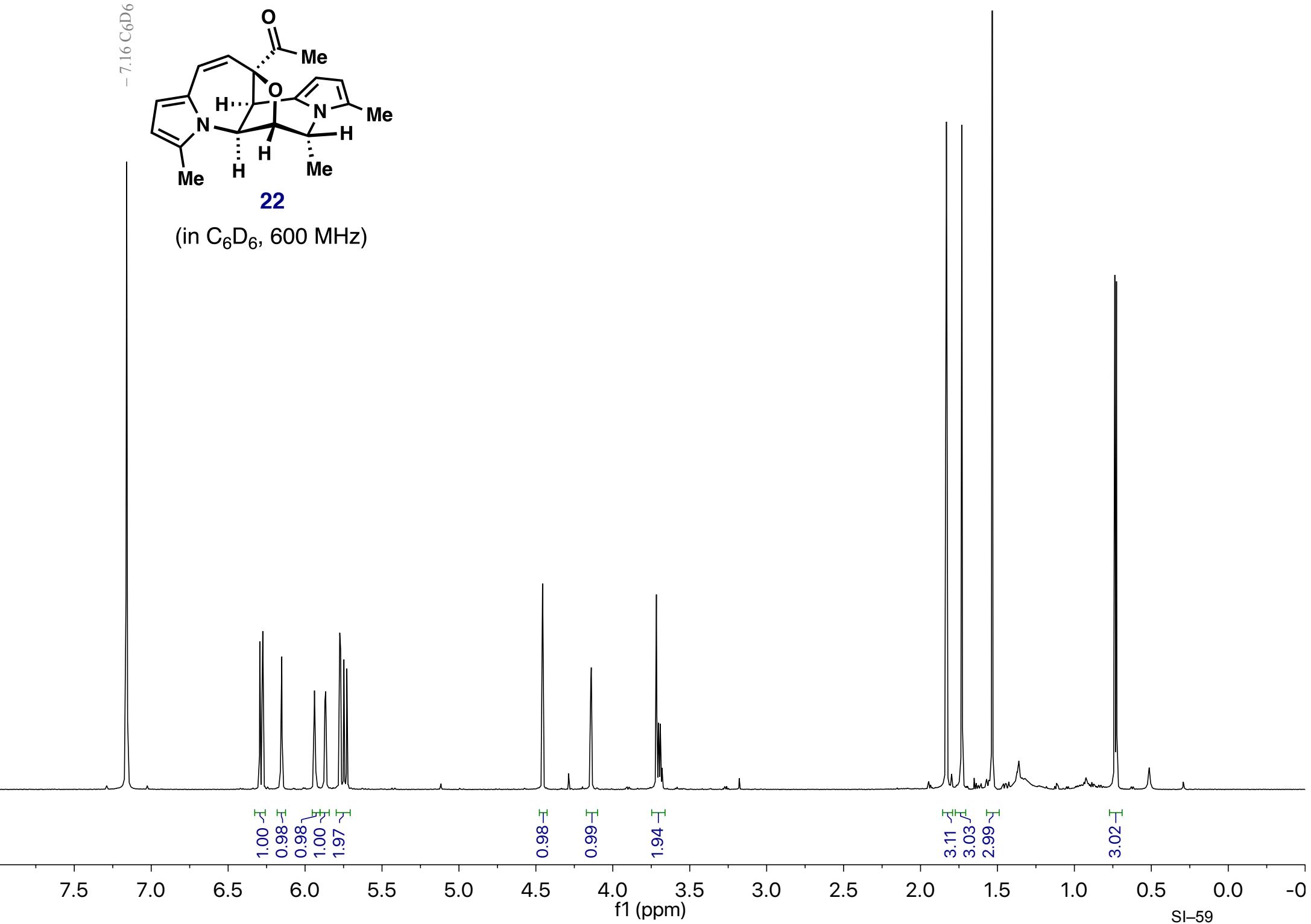


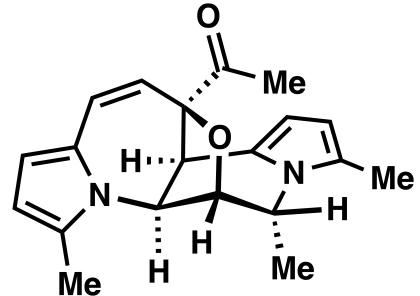
- 7.16 C<sub>6</sub>D<sub>6</sub>



**22**

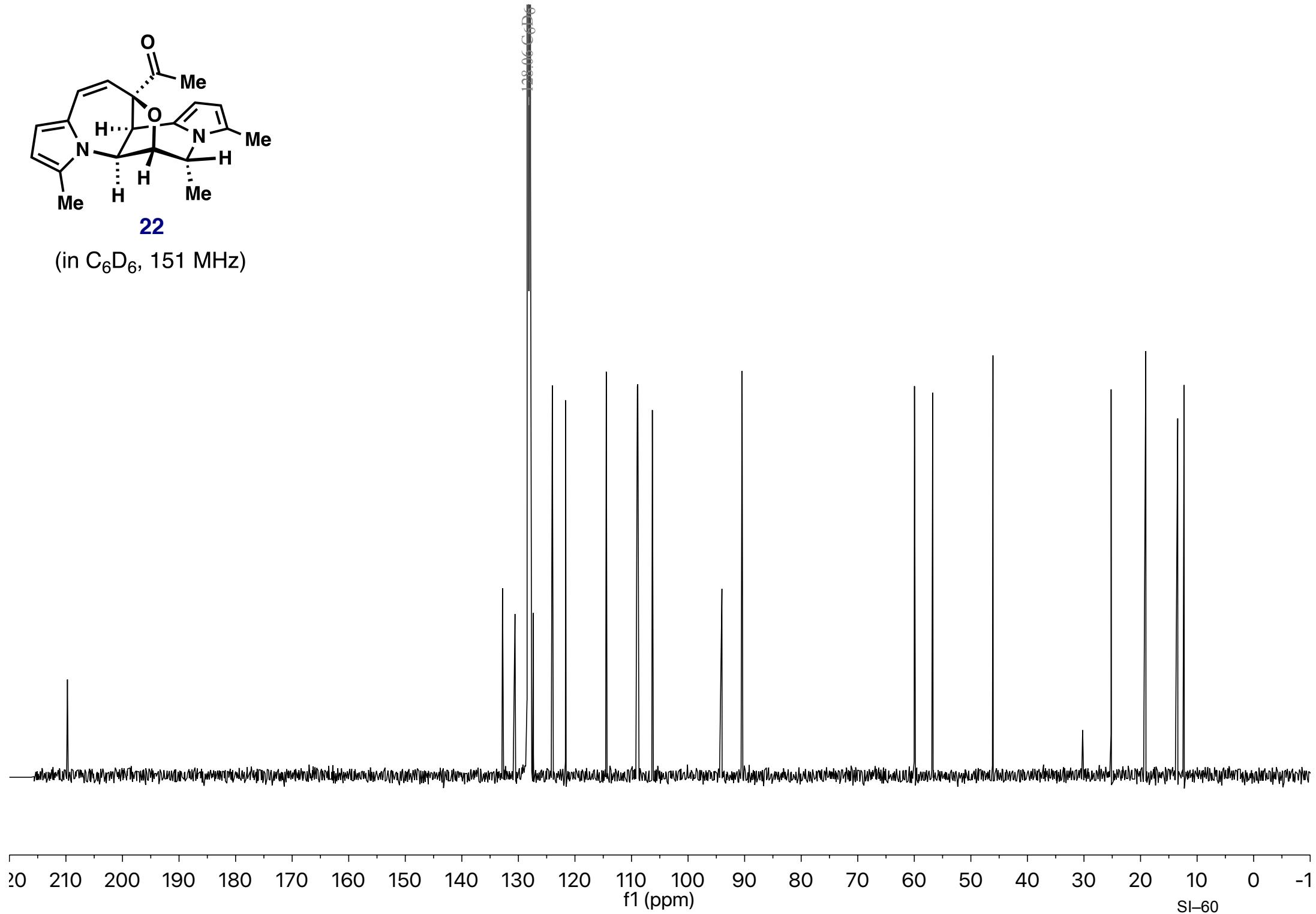
(in C<sub>6</sub>D<sub>6</sub>, 600 MHz)



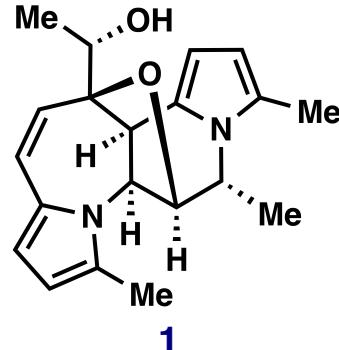


22

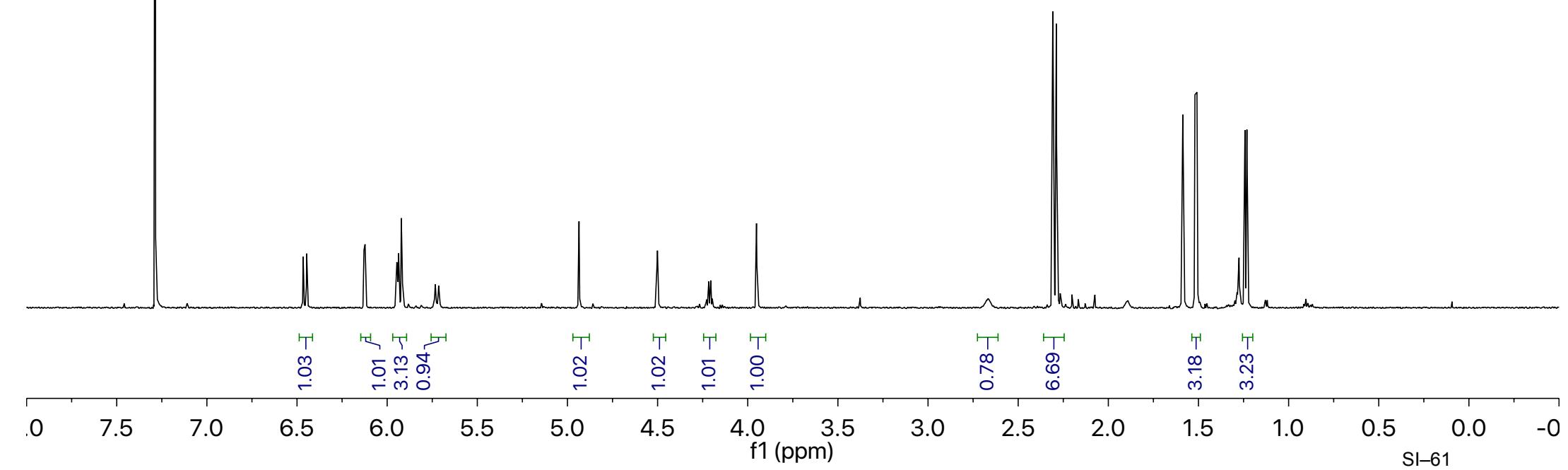
(in C<sub>6</sub>D<sub>6</sub>, 151 MHz)

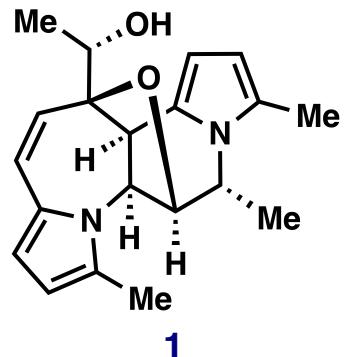


7.287 CDCl<sub>3</sub>

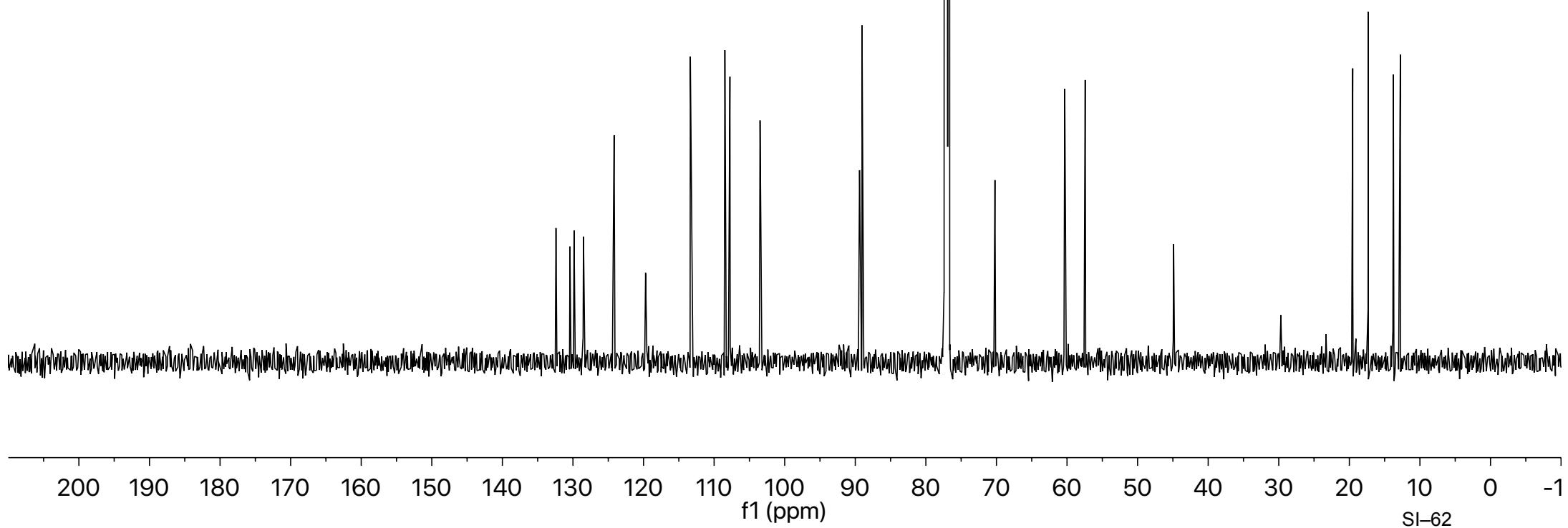


(in CDCl<sub>3</sub>, 600 MHz)

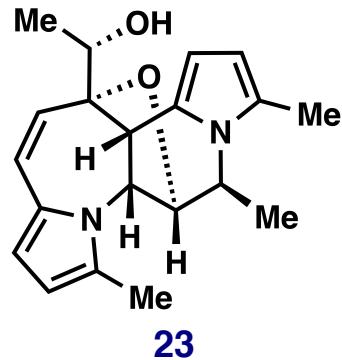




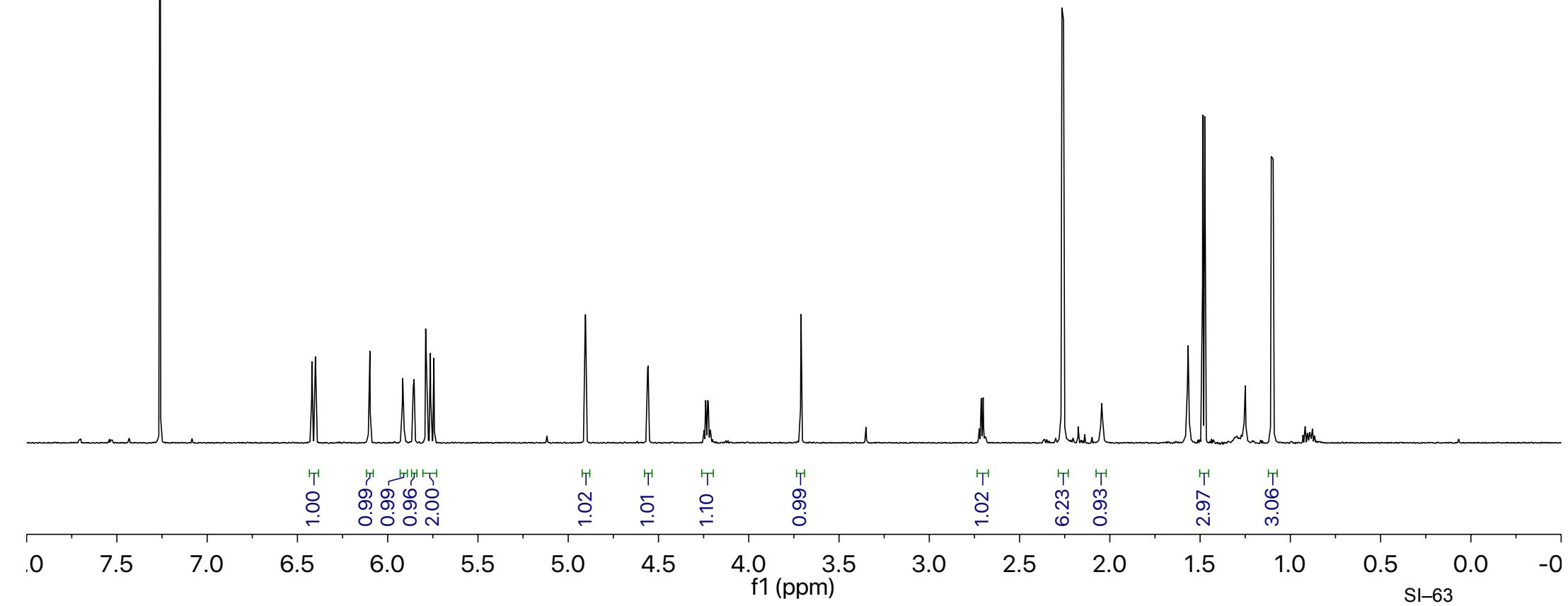
(in  $\text{CDCl}_3$ , 600 MHz)

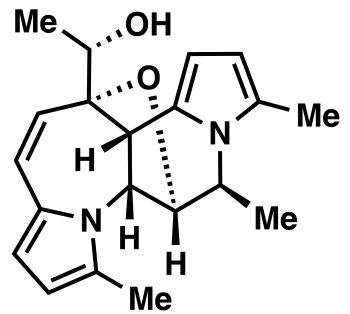


7.287 CDCl<sub>3</sub>



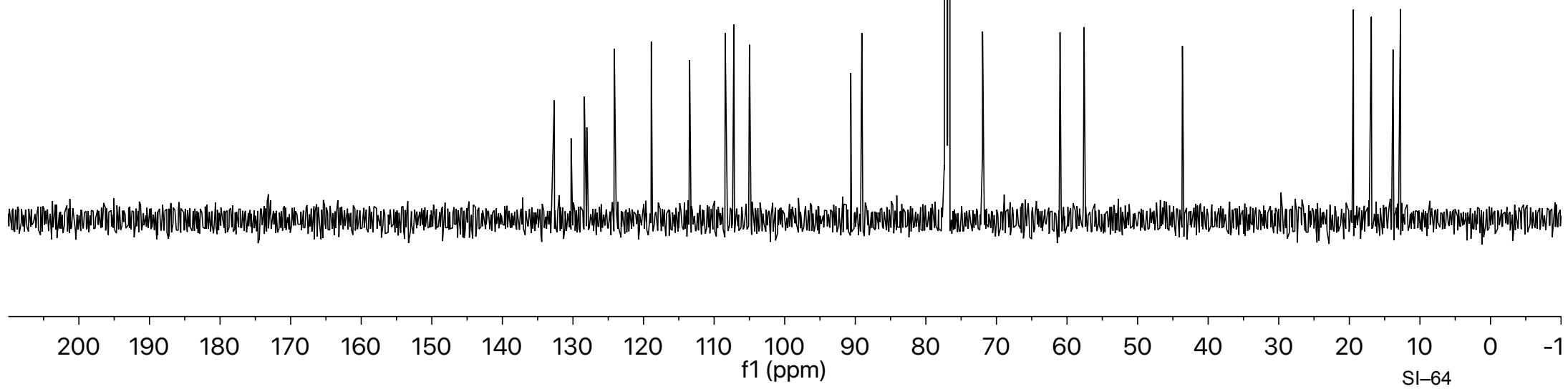
(in CDCl<sub>3</sub>, 600 MHz)



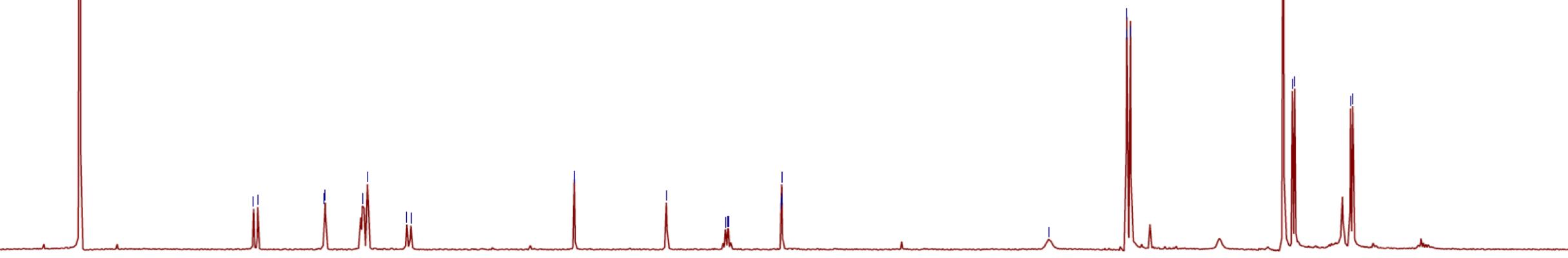


**23**

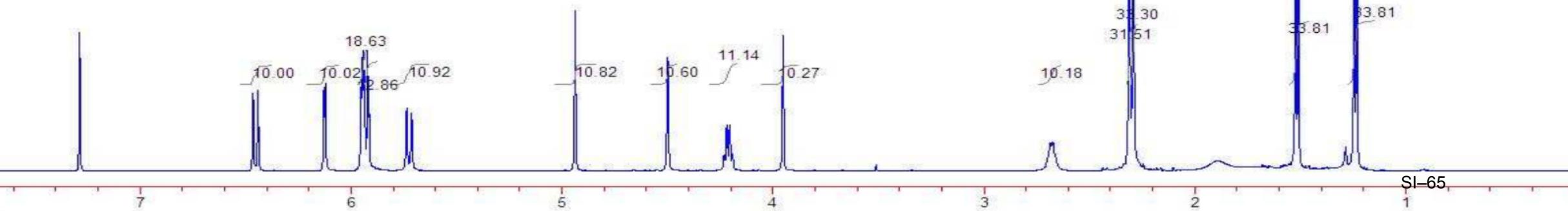
(in  $\text{CDCl}_3$ , 151 MHz)



**Synthetic Curvulamine  $^1\text{H}$  NMR (this work)**



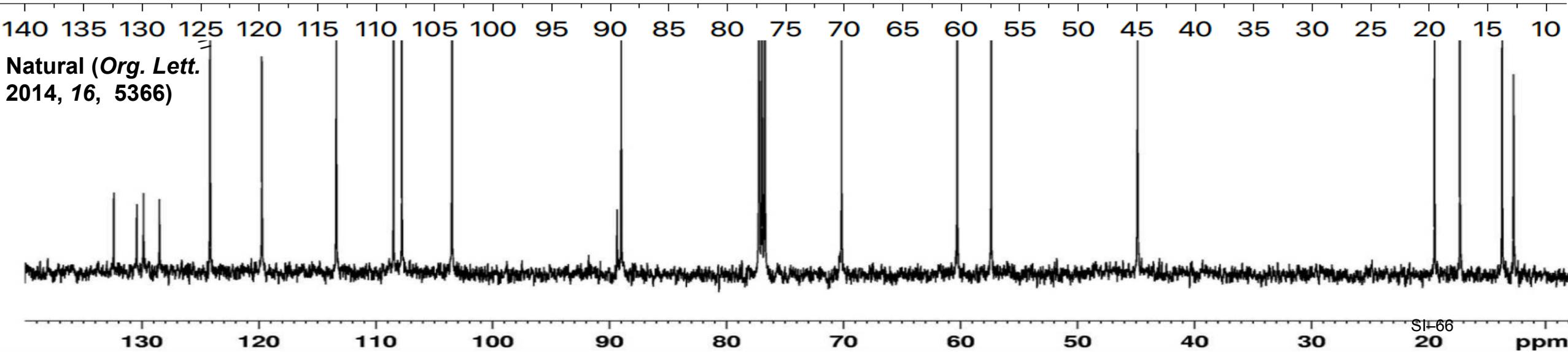
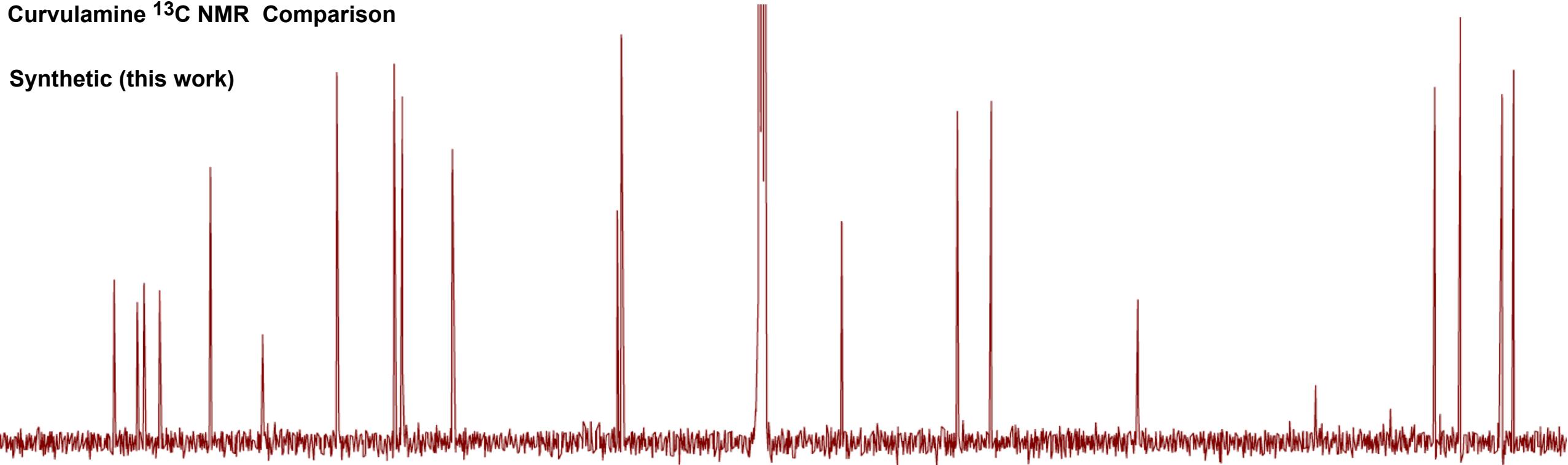
**Natural Curvulamine  $^1\text{H}$  NMR (from *Org. Lett.* 2014, 16, 5366-5369)**



SI-65

# Curvularamine $^{13}\text{C}$ NMR Comparison

Synthetic (this work)



SI-66

ppm