

*Supporting Information for:*

**Total Synthesis of ( $\pm$ )-Cephalolides B and C via a Palladium-Catalyzed Cascade  
Cyclization and Late-stage  $sp^3$  C–H Bond Oxidation**

Lun Xu,<sup>‡</sup> Chao Wang,<sup>‡</sup> Ziwei Gao, Yu-Ming Zhao\*

Key Laboratory of Applied Surface and Colloid Chemistry of MOE & School of Chemistry and Chemical Engineering  
Shaanxi Normal University, 620 West Chang'an Ave, Xi'an, 710119, China  
ymzhao@snnu.edu.cn

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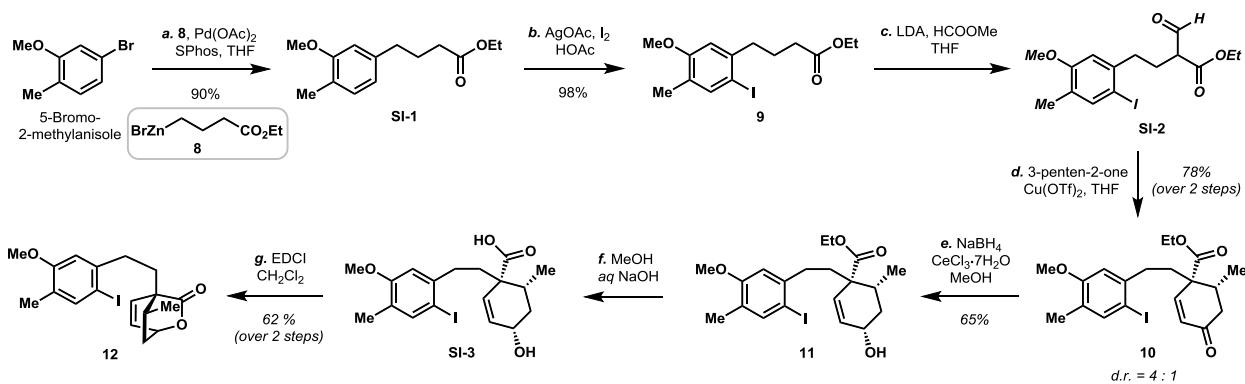
## 1. General Information

Unless otherwise stated, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry nitrogen. Anhydrous dichloromethane was purified by distillation over calcium hydride. Anhydrous tetrahydrofuran and toluene were freshly distilled from sodium-benzophenone. Dry methanol, benzene and N,N-dimethyl formamide (DMF) were purchased from Energy Chemical (water  $\leq 50$  ppm by K.F.) and stored in glove box with 4 Å molecular sieves. Alkyl zinc bromide **8** was prepared according to the literature protocol.<sup>1,2</sup> All other solvents and reagents were purchased at the highest commercial grade and were used as received, without further purification.

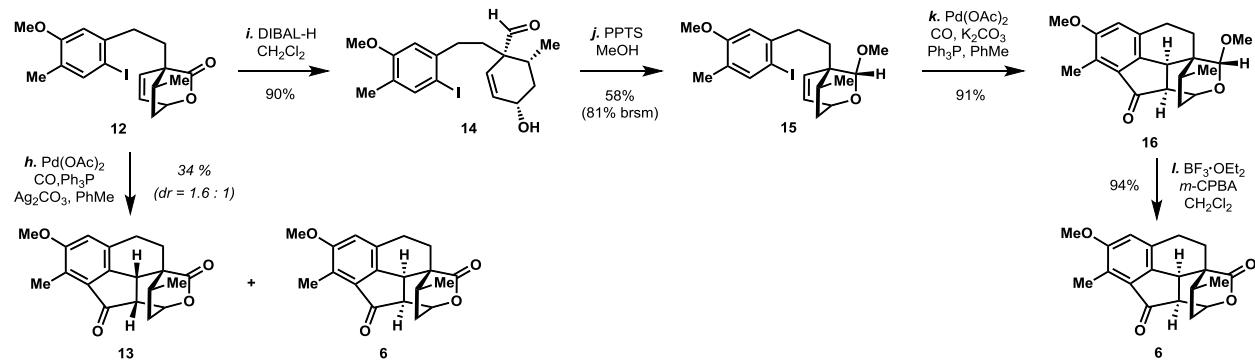
Reactions were monitored by thin layer chromatography (TLC) (250  $\mu\text{m}$  thickness, F-254 indicator) and visualized by UV irradiation and staining with *p*-anisaldehyde, phosphomolybdic acid, or potassium permanganate developing agents. Volatile solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed over silica gel (230-400 mesh) purchased from Yantai Xinnuo Co., China.

Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) and carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded on a Bruker AV 600 MHz spectrometer using residue solvent peaks as an internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3 = 7.26$ , Methanol- $d_4 = 3.31$ ;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3 = 77.16$ , Methanol- $d_4 = 49.00$ ). Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent signal. Peak multiplicities are reported as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet. Melting points were determined using MEI-TEMP™ apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor27 FT-IR spectrometer. High-resolution mass spectra (HRMS) were collected on a Bruker Maxis System. X-ray crystallographic analyses were performed on Bruker D8 Quest or Bruker D8 Venture.

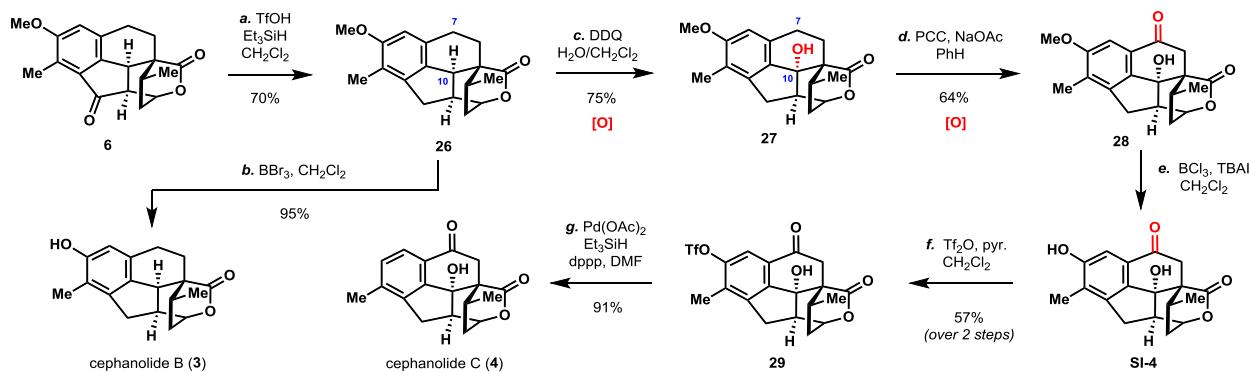
## 2. Supplementary Schemes



**Scheme SI-1:** Synthesis of precursor lactone **12**.



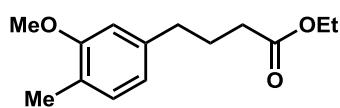
**Scheme SI-2:** Synthesis of common pentacyclic core intermediate **6**.



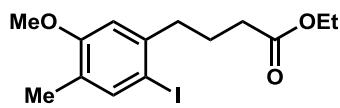
**Scheme SI-3:** Completion of the syntheses of Cephalolides B and C from common pentacycle **6**.

### 3. Experimental Procedures

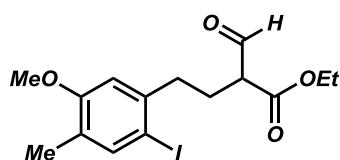
#### 3.1 Total Syntheses of Cephalolides B and C



**Ester SI-1.** A 1000 mL flame-dried flask was charged with 5-bromo-2-methylanisole (24.1 g, 120 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub> (539 mg, 2.4 mmol, 0.02 equiv) and S-Phos (2.0 g, 4.8 mmol, 0.04 equiv). The reaction flask was evacuated and backfilled with nitrogen and this process repeated for a total of three times. Degassed THF (250 mL) was added and the mixture was stirred for 5 min at room temperature, 4-ethoxy-4-oxobutylzinc bromide **8** (300 mL, 1.5 equiv, 0.6 M in THF) was added (mildly exothermic) dropwise via syringe, affording a light-yellow solution. The reaction mixture was heated to 50 °C and kept this temperature for 8 hours, during which time the color had progressed to dark brown/black. Then, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous NH<sub>4</sub>Cl solution (100 mL), and extracted with ethyl acetate (500 mL). The organic phase was washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford **SI-1** (25.5 g, 90% yield) as a colorless oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.07 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.69 (s, 1H), 4.16 (q, *J* = 7.6 Hz, 2H), 3.85 (s, 3H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.23 (s, 3H), 2.02 - 1.97 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 173.4, 157.7, 140.3, 130.4, 124.0, 120.2, 110.2, 60.2, 55.1, 35.1, 33.6, 26.7, 15.8, 14.2; IR (KBr, cm<sup>-1</sup>) 3419, 2938, 1734, 1510, 1461, 1413, 1258, 1139, 1040; HRMS (ESI) calcd. for [C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 259.1310, found 259.1310.

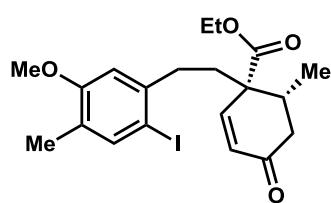


**Ester 9.** To a solution of **SI-1** (18.5 g, 78.3 mmol, 1.0 equiv) in AcOH (200 mL) was added AgOAc (13.1 g, 78.3 mmol, 1.0 equiv) and I<sub>2</sub> (19.9 g, 78.3 mmol, 1.0 equiv) sequentially at room temperature. The reaction mixture was stirred for 12 h at same temperature. The resulting suspension was filtered through a pad of silica and eluted with ether (300 mL). The eluent solution was placed into a separatory funnel and washed with a mixture of saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and NaHCO<sub>3</sub> solution (1:1 v:v, 3 x 60 mL). The organic phase was separated and washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was enough pure and used directly in the next step without further purification. This afforded ester **9** (27.8 g, 98% yield) as a yellowish oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.50 (s, 1H), 6.67 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.74 - 2.66 (m, 2H), 2.36 (d, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.94 - 1.89 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 173.4, 158.1, 142.4, 140.5, 127.0, 111.4, 88.5, 60.4, 55.4, 39.9, 33.6, 25.6, 15.4, 14.3; IR (KBr, cm<sup>-1</sup>) 3416, 1732, 1620, 1400, 1156, 616; HRMS (ESI) calcd. for [C<sub>14</sub>H<sub>19</sub>IO<sub>3</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 385.0277, found 385.0267.



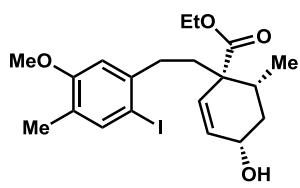
**SI-2.** A 500 mL flame-dried flask was charged with ester **9** (26.4 g, 72.9 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of THF (200 mL). After cooling the reaction flask to -78 °C, a freshly prepared solution of lithium diisopropylamide (109 mL, 109.4 mmol, 1.5 equiv, 1.0 M in THF) was added dropwise via syringe. The reaction mixture was stirred for 45 min at -78 °C and then HCO<sub>2</sub>Me

(13.5 mL, 218.7 mmol, 3.0 equiv) was added dropwise via syringe. The resulting reaction mixture was stirred for 30 min at -78 °C and warmed to room temperature over the course of 4 h, and then quenched with water (60 mL) at 0 °C. The reaction mixture was diluted with ether (150 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The crude **SI-2** (*ca.* 27 g) was used directly in the next step without further purification.

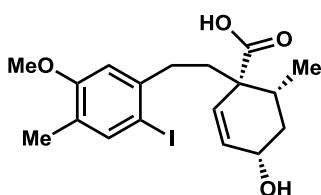


**Enone 10.** A 500 mL flame-dried flask was charged with freshly prepared **SI-2** (27.0 g, 69.2 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of 3-penten-2-one (10 mL, 103.8 mmol, 1.5 equiv) and THF (250 mL). After stirring for 5 min, Cu(OTf)<sub>2</sub> (5.0 g, 13.8 mmol, 0.2 equiv) was added and the reaction mixture was heated to 50 °C and kept this temperature

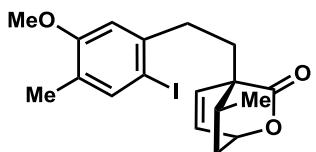
for 7 days. After cooling the reaction flask to room temperature, the resulting dark brown mixture was directly concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford an inseparable 4:1 mixture of **10** and its diastereomer (26 g, 78% yield over two steps); Major diastereomer, a yellowish oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.50 (s, 1H), 7.20 (d, *J* = 9.8 Hz, 1H), 6.61 (s, 1H), 6.13 (d, *J* = 10.2 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.69 (t, *J* = 4.3 Hz, 1H), 2.67 (d, *J* = 4.8 Hz, 1H), 2.59 (dd, *J* = 12.8, 4.7 Hz, 1H), 2.56 - 2.51 (m, 1H), 2.39 (dd, *J* = 17.1, 6.4 Hz, 1H), 2.18 - 2.14 (m, 1H), 2.12 (d, *J* = 2.7 Hz, 3H), 2.08 (dd, *J* = 13.3, 4.9 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 198.4, 172.6, 158.5, 149.7, 142.1, 140.7, 129.4, 127.6, 111.3, 88.1, 61.5, 55.5, 51.8, 41.9, 38.8, 36.6, 36.3, 17.0, 15.5, 14.5; IR (KBr, cm<sup>-1</sup>) 3475, 3415, 1621, 1400, 621; HRMS (ESI) calcd. for [C<sub>20</sub>H<sub>25</sub>IO<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 479.0695, found 479.0674.



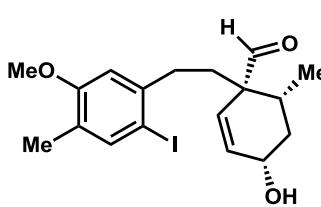
**Allylic alcohol 11.** To a solution of enone **10** (19.5 g, 42.7 mmol, 1.0 equiv) in MeOH (200 mL) at 0 °C was added CeCl<sub>3</sub>·7H<sub>2</sub>O (19.1 g, 51.2 mmol, 1.2 equiv), followed by the addition of NaBH<sub>4</sub> (1.3 g, 34.2 mmol, 0.8 equiv) in four portions over 30 min. The reaction mixture was stirred for 2 h at this temperature and quenched with saturated aqueous NH<sub>4</sub>Cl solution (50 mL). The reaction mixture was extracted with EtOAc (2 x 150 mL) and the combined organic layers were washed with brine (80 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford allylic alcohol **11** (12.7 g, 65% yield) as a colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.48 (s, 1H), 6.64 (s, 1H), 5.97 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.77 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.30 - 4.27 (m, 1H), 4.23 - 4.07 (m, 2H), 3.78 (s, 3H), 2.62 (td, *J* = 12.8, 5.2 Hz, 1H), 2.52 (td, *J* = 12.7, 4.6 Hz, 1H), 2.10 (s, 3H), 2.00 - 1.85 (m, 4H), 1.74 (td, *J* = 12.5, 9.0 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 173.9, 158.2, 143.1, 140.4, 133.6, 130.1, 127.0, 111.2, 88.3, 66.9, 60.8, 55.4, 50.9, 37.2, 36.7, 36.0, 33.6, 17.3, 15.4, 14.4; IR (KBr, cm<sup>-1</sup>) 3421, 2962, 1721, 1458, 1377, 1243, 1157, 1027; HRMS (ESI) calcd. for [C<sub>20</sub>H<sub>27</sub>IO<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 481.0852, found 481.0830.



**Acid SI-3.** To a solution of allylic alcohol **11** (12.7 g, 27.7 mmol, 1.0 equiv) in deionized water (60 mL) and MeOH (60 mL) was added sodium hydroxide (11.1 g, 277 mmol, 10.0 equiv) at room temperature. The reaction mixture was heated to 70 °C and kept this temperature for 12 h. The reaction mixture was then cooled to room temperature, acidified with 1 M HCl (pH 2-3), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The crude acid **SI-3** (*ca.* 12.0 g) was used directly in the next step without further purification. An analytical sample was isolated by preparative TLC. White solid: m.p.=146-148 °C; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD) δ 7.45 (s, 1H), 6.74 (s, 1H), 5.91 (d, *J* = 10.2 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 4.25 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 2.60 (m, 1H), 2.55 - 2.44 (m, 1H), 2.08 (s, 3H), 1.98 - 1.95 (m, 1H), 1.90 - 1.85 (m, 4H), 1.07 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD) δ 177.3, 159.6, 144.6, 141.3, 134.5, 131.5, 127.8, 112.3, 88.6, 67.8, 55.8, 52.0, 37.8, 37.8, 36.9, 34.1, 17.8, 15.6; IR (KBr, cm<sup>-1</sup>) 3417, 1640, 1392, 1248, 1159, 620; HRMS (ESI) calcd. for [C<sub>18</sub>H<sub>23</sub>IO<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 453.0539, found 435.0529.

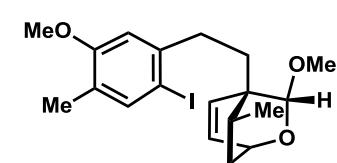


**Lactone 12.** To a solution of crude acid **SI-3** (12.0 g, 27.9 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added EDCI (6.4 g, 33.5 mmol, 1.2 equiv) and DMAP (684 mg, 5.6 mmol, 0.2 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with bine (50 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford lactone **12** (7.1 g, 62 % yield over two steps) as a white solid: m.p.=112-113 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.52 (s, 1H), 6.81 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.53 (dd, *J* = 7.8, 4.9 Hz, 1H), 5.13 (s, 1H), 3.82 (s, 3H), 2.89 (td, *J* = 13.0, 4.3 Hz, 1H), 2.73 (td, *J* = 12.9, 4.8 Hz, 1H), 2.14 (s, 3H), 2.12 - 2.02 (m, 2H), 1.95 - 1.84 (m, 2H), 1.69 (dt, *J* = 13.3, 4.4 Hz, 1H), 1.06 (d, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.7, 158.4, 143.0, 140.4, 135.6, 131.8, 127.2, 111.5, 88.3, 74.0, 55.6, 51.4, 36.3, 36.1, 31.5, 30.4, 17.9, 15.5; IR (KBr, cm<sup>-1</sup>) 3475, 3416, 1621, 1401, 1117, 620; HRMS (ESI) calcd. for [C<sub>18</sub>H<sub>21</sub>IO<sub>3</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 435.0433, found 435.0424.

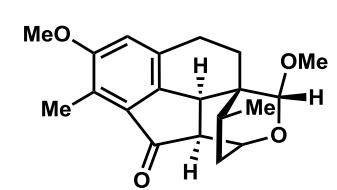


**Aldehyde 14.** A 250 mL flame-dried flask was charged with lactone **12** (5.0 g, 12.1 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of CH<sub>2</sub>Cl<sub>2</sub> (100 mL). After cooling the reaction flask to -78 °C, DIBAL-H (16.1 mL, 1.5 M in toluene, 2.0 equiv) was added dropwise via syringe over the course of 20 min. The reaction mixture was stirred for 12 h at this temperature and then quenched with saturated aqueous Na<sub>2</sub>SO<sub>4</sub> (30 mL). The resulting reaction mixture was warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford aldehyde **14** (4.5 g, 90%

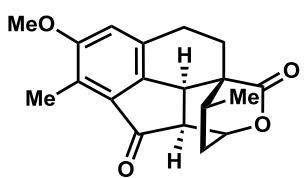
yield) as a colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  9.71 (d,  $J = 1.2$  Hz, 1H), 7.49 (s, 1H), 6.65 (s, 1H), 6.14 (d,  $J = 10.0$  Hz, 1H), 5.47 (d,  $J = 10.1$  Hz, 1H), 4.39 (s, 1H), 3.79 (s, 3H), 2.59 (td,  $J = 12.8, 6.0$  Hz, 1H), 2.53 (s, 1H), 2.50 - 2.44 (m, 1H), 2.11 (s, 3H), 2.10 - 2.02 (m, 2H), 1.94 - 1.82 (m, 2H), 1.68 (td,  $J = 12.9, 9.6$  Hz, 1H), 1.10 (d,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  203.4, 158.3, 142.7, 140.5, 137.2, 128.3, 127.2, 111.2, 88.3, 67.1, 55.5, 54.4, 37.6, 35.4, 32.8, 32.7, 16.3, 15.4; IR (KBr,  $\text{cm}^{-1}$ ) 3423, 2931, 1715, 1488, 1457, 1245, 1155; HRMS (ESI) calcd. for  $[\text{C}_{18}\text{H}_{23}\text{IO}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  437.0590, found 437.0581.



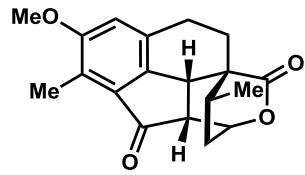
**Acetal 15.** To a solution of aldehyde **14** (2.0 g, 4.8 mmol, 1.0 equiv) in MeOH (40 mL) was added PPTS (121 mg, 0.48 mmol, 0.1 equiv) at room temperature. The reaction mixture was heated to 50 °C and kept this temperature for 7 h. After cooling the reaction flask to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 60 mL). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  (50 mL), brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in *vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford acetal **15** (1.2 g, 58% yield, 81% brsm) as a white solid: m.p.=111-113 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 (s, 1H), 6.70 (s, 1H), 6.55 (dd,  $J = 8.2, 5.3$  Hz, 1H), 6.45 (d,  $J = 8.2$  Hz, 1H), 4.69 (s, 1H), 4.49 (d,  $J = 1.5$  Hz, 1H), 3.81 (s, 3H), 3.30 (s, 3H), 2.80 - 2.70 (m, 2H), 2.14 (s, 3H), 1.98 (td,  $J = 13.4, 4.2$  Hz, 1H), 1.83 - 1.70 (m, 3H), 1.51 (dd,  $J = 7.8, 3.5$  Hz, 1H), 1.20 (d,  $J = 6.3$  Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 143.7, 140.6, 136.0, 132.7, 127.1, 111.2, 101.5, 88.3, 67.6, 55.5, 55.5, 44.1, 36.9, 35.8, 31.7, 26.9, 16.0, 15.5; IR (KBr,  $\text{cm}^{-1}$ ) 3415, 1621, 1457, 1391, 1246, 1158, 1105, 621; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{25}\text{IO}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  451.0746, found 451.0739.



**Ketone 16.** A 100 mL flame-dried flask was charged with acetal **15** (2.0 g, 4.7 mmol, 1.0 equiv),  $\text{Pd}(\text{OAc})_2$  (21 mg, 0.094 mmol, 0.02 equiv),  $\text{Ph}_3\text{P}$  (49 mg, 0.188 mmol, 0.04 equiv), and potassium carbonate (1.3 g, 9.4 mmol, 2.0 equiv). The reaction flask was evacuated and backfilled with carbon monoxide (a total of three times) followed by addition of degassed toluene (85 mL). The reaction mixture was heated to 90 °C and kept this temperature for 18 h. After cooling the reaction flask to room temperature, the reaction mixture was filtered through a pad of silica and eluted with ethyl acetate (100 mL). The eluent solution was directly concentrated in *a* and the residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford ketone **16** (1.4 g, 91% yield) as a white solid: m.p.=182-183 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.86 (s, 1H), 4.90 (s, 1H), 4.29 (t,  $J = 4.9$  Hz, 1H), 3.84 (s, 3H), 3.49 (s, 3H), 3.30 (d,  $J = 8.3$  Hz, 1H), 3.24 - 3.20 (m, 1H), 3.08 (dd,  $J = 17.8, 9.8$  Hz, 1H), 2.65 (dt,  $J = 17.4, 8.5$  Hz, 1H), 2.46 (s, 3H), 2.05 (td,  $J = 13.8, 9.8, 8.2$  Hz, 1H), 1.82 (td,  $J = 13.9, 8.8, 1.9$  Hz, 1H), 1.30 - 1.22 (m, 1H), 1.15 - 1.07 (m, 1H), 1.03 - 0.93 (m, 1H), 0.85 (d,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  207.0, 157.8, 148.5, 135.1, 133.1, 124.3, 115.7, 101.0, 69.7, 56.6, 55.7, 52.0, 37.8, 35.2, 32.2, 24.4, 24.3, 23.4, 17.4, 10.1; IR (KBr,  $\text{cm}^{-1}$ ) 3416, 1620, 1400, 1107, 994, 620; HRMS (ESI) calcd. for  $[\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  351.1572, found 351.1568.

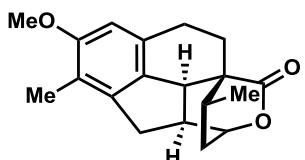


**Ketone 6.** To a solution of ketone **16** (2.0 g, 6.1 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (60 mL) at 0 °C was added *m*-CPBA (1.9 g, 9.2 mmol, 1.5 equiv, 85% w/w) and  $\text{BF}_3\cdot\text{OEt}_2$  (0.9 mL, 7.3 mmol, 1.2 equiv) sequentially. The reaction mixture was stirred for 1 hour at this temperature and  $\text{Et}_3\text{N}$  (2.5 mL, 18.3 mmol, 3.0 equiv) was added dropwise via syringe. The reaction mixture was warmed to room temperature and quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in *vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford ketone **6** (1.8 g, 94% yield) as a white solid: m.p.=212-214 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.91 (s, 1H), 4.96 (t,  $J$  = 5.2 Hz, 1H), 3.86 (s, 3H), 3.35 (t,  $J$  = 6.9 Hz, 1H), 3.23 (d,  $J$  = 8.4 Hz, 1H), 3.15 (dd,  $J$  = 18.0, 9.7 Hz, 1H), 2.71 (dt,  $J$  = 17.3, 8.4 Hz, 1H), 2.45 (s, 3H), 2.30 - 2.14 (m, 2H), 1.55 (dd,  $J$  = 14.8, 10.3 Hz, 1H), 1.33 - 1.29 (m, 1H), 1.19 - 1.15 (m, 1H), 0.82 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  203.3, 176.2, 158.7, 144.8, 135.0, 133.0, 125.0, 115.9, 76.7, 56.5, 51.2, 45.1, 41.1, 31.1, 26.1, 24.0, 22.4, 19.4, 10.1; IR (KBr,  $\text{cm}^{-1}$ ) 3416, 1622, 1401, 1270, 1095; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}]^+(\text{M}+\text{Na})^+$ :  $m/z$  335.1259, found 335.1256.



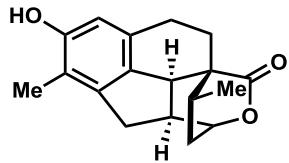
**Ketone 13.** A 20 mL flame-dried reaction tube was charged with lactone **12** (50 mg, 0.12 mmol, 1.0 equiv),  $\text{Pd}(\text{OAc})_2$  (1.3 mg, 0.006 mmol, 0.05 equiv),  $\text{Ph}_3\text{P}$  (3.1 mg, 0.012 mmol, 0.1 equiv),  $\text{Ag}_2\text{CO}_3$  (35 mg, 0.126 mmol, 1.05 equiv) and potassium carbonate (33 mg, 0.24 mmol, 2.0 equiv). The reaction tube was evacuated and backfilled with carbon monoxide (a total of three times) followed by addition of degassed toluene (2.5 mL). The reaction mixture was heated to 90 °C and kept this temperature for 18 h. After cooling the reaction tube to room temperature, the reaction mixture was filtered through a pad of silica and eluted with ethyl acetate (20 mL). The eluent solution was concentrated in *vacuo* and the residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford ketone **13** (8 mg, 21% yield,) along with ketone **6** (5 mg, 13% yield).

**13:** white solid, m.p.=186-188 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.87 (s, 1H), 4.96 (d,  $J$  = 1.9 Hz, 1H), 3.80 (s, 3H), 3.08 (d,  $J$  = 7.8 Hz, 1H), 3.00 (t,  $J$  = 7.4 Hz, 2H), 2.95 - 2.91 (m, 1H), 2.60 (dt,  $J$  = 13.7, 6.5 Hz, 1H), 2.42 (s, 3H), 2.25 - 2.17 (m, 2H), 1.73 - 1.61 (m, 2H), 1.01 (d,  $J$  = 6.1 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  204.3, 173.9, 158.4, 145.2, 134.3, 133.7, 124.4, 115.9, 77.0, 56.2, 51.8, 48.4, 40.6, 36.0, 35.5, 24.5, 24.4, 18.7, 10.2; IR (KBr,  $\text{cm}^{-1}$ ) 3416, 1620, 1401, 1091, 620; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}]^+(\text{M}+\text{Na})^+$ :  $m/z$  335.1259, found 335.1257.

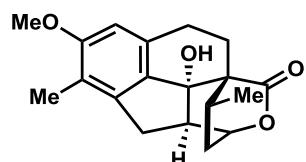


**Lactone 26.** To a solution of ketone **6** (500 mg, 1.6 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added  $\text{TfOH}$  (0.7 mL, 8.0 mmol, 5.0 equiv) and  $\text{Et}_3\text{SiH}$  (1.3 mL, 8.0 mmol, 5.0 equiv) at room temperature. After stirring for 20 h at this temperature, additional  $\text{TfOH}$  (0.7 mL, 8.0 mmol, 5.0 equiv) and  $\text{Et}_3\text{SiH}$  (1.3 mL, 8.0 mmol, 5.0 equiv) was added again. The reaction mixture was stirred for another 20 h and poured into a pre-cooled saturated aqueous  $\text{NaHCO}_3$  solution (20 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 50

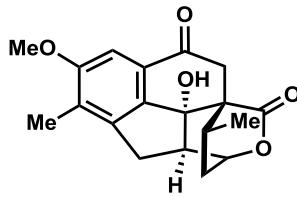
mL). The combined organic layers were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in *vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford lactone **26** (334 mg, 70% yield) as a white solid: m.p.=177-179 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.51 (s, 1H), 4.65 (t,  $J$  = 4.7 Hz, 1H), 3.80 (s, 3H), 3.26 - 3.20 (m, 2H), 3.15 - 3.11 (m, 1H), 3.01 (dd,  $J$  = 17.8, 9.7 Hz, 1H), 2.64 - 2.56 (m, 1H), 2.55 (d,  $J$  = 17.7 Hz, 1H), 2.10 (s, 3H), 2.09 - 2.03 (m, 1H), 1.69 (dd,  $J$  = 14.0, 10.0 Hz, 1H), 1.29 - 1.24 (m, 2H), 1.19 - 1.13 (m, 1H), 0.81 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 158.4, 141.6, 132.1, 131.9, 120.23, 108.2, 79.3, 56.1, 47.4, 45.8, 39.6, 32.9, 28.8, 26.4, 24.5, 23.2, 19.5, 12.6; IR (KBr,  $\text{cm}^{-1}$ ) 3419, 1748, 1625, 1401, 1119, 613; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{22}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  321.1467, found 321.1459.



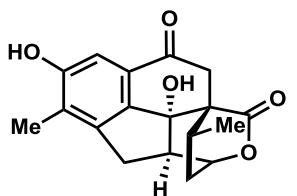
**Cephanolide B (3).** To a solution of lactone **26** (50 mg, 0.17 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added  $\text{BBr}_3$  (1.4 mL, 1.0 M in  $\text{CH}_2\text{Cl}_2$ , 8.0 equiv) at -78 °C. The reaction mixture was slowly warmed to room temperature over the course of 6 h and quenched with water (2 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in *vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford cephanolide B (**3**) (46 mg, 95% yield) as a white solid: m.p. = 208-210 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.48 (s, 1H), 4.83 (s, 1H), 4.67 - 4.64 (m, 1H), 3.24 (dd,  $J$  = 17.5, 9.7 Hz, 2H), 3.18 - 3.09 (m, 1H), 2.96 (dd,  $J$  = 17.4, 9.6; 1H), 2.59 - 2.47 (m, 2H), 2.13 (s, 3H), 2.11 - 1.98 (m, 2H), 1.70 (dd,  $J$  = 14.5, 10.3 Hz, 1H), 1.31 - 1.24 (m, 1H), 1.20 - 1.17 (m, 1H), 0.81 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.3, 154.4, 141.8, 132.7, 132.3, 117.8, 112.8, 79.3, 47.5, 45.9, 39.7, 33.0, 28.9, 26.5, 24.1, 23.1, 19.5, 12.3; IR (KBr,  $\text{cm}^{-1}$ ) 3475, 3414, 2908, 1716, 1617, 1375, 1085, 636; HRMS (ESI) calcd. for  $[\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  307.1310, found 307.1304.



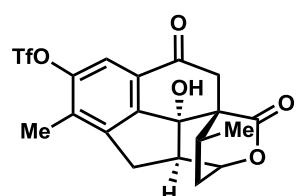
**Alcohol 27.** Lactone **26** (310 mg, 1.04 mmol, 1.0 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (15 mL). Deionized water (15 mL) was added followed by the addition of DDQ (472 mg, 2.08 mmol, 2.0 equiv) at room temperature. The resulting biphasic reaction mixture was stirred for 8 h at this temperature. The reaction mixture was quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution (15 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 50 mL). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  (20 mL), brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in *vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate/hexane) to afford alcohol **27** (245 mg, 75% yield) as a white solid: m.p. = 230-232 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.55 (s, 1H), 4.74 (t,  $J$  = 4.8 Hz, 1H), 3.81 (s, 3H), 3.37 (dd,  $J$  = 17.4, 9.3 Hz, 1H), 3.08 (dd,  $J$  = 17.5, 9.9 Hz, 1H), 2.99 - 2.95 (m, 1H), 2.67 - 2.54 (m, 2H), 2.42 (dd,  $J$  = 17.4, 2.9 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 1H), 2.03 - 1.95 (m, 1H), 1.68 - 1.59 (m, 1H), 1.33 - 1.29 (m, 1H), 1.01 - 0.95 (m, 1H), 0.85 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.9, 160.0, 142.1, 132.9, 132.3, 120.5, 109.0, 82.5, 78.7, 56.1, 51.2, 49.4, 30.9, 29.6, 28.8, 23.2, 19.6, 17.2, 12.3; IR (KBr,  $\text{cm}^{-1}$ ) 3421, 1626, 1400, 1119, 614; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{22}\text{O}_4\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  337.1416, found 337.1410.



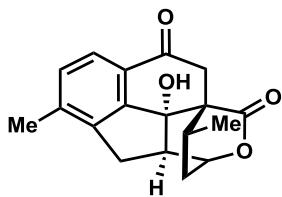
**Ketone 28.** To a solution alcohol **27** (220 mg, 0.67 mmol, 1.0 equiv) in dry benzene (40 mL) was added a pre-mixed mixture of PCC (578 mg, 2.68 mmol, 4.0 equiv), NaOAc (275 mg, 3.35 mmol, 5.0 equiv), and silicon gel (2.2 g) in a single portion at room temperature. The reaction mixture was then heated to 70 °C and kept this temperature for 12 h. After cooling the reaction to room temperature, the reaction mixture was filtered through a pad of silica and eluted with acetone (80 mL). The eluent solution was directly concentrated in *vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, acetone/hexane) to afford ketone **28** (141 mg, 64% yield) as a white solid (m.p.: 180 °C with decomposition); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.16 (s, 1H), 4.86 (t, *J* = 4.9 Hz, 1H), 3.88 (s, 3H), 3.55 (d, *J* = 18.6 Hz, 1H), 3.50 (dd, *J* = 17.5, 9.4 Hz, 1H), 3.09 (t, *J* = 6.4 Hz, 1H), 2.73 (d, *J* = 18.6 Hz, 1H), 2.58 (dd, *J* = 17.6, 3.2 Hz, 2H), 2.20 (s, 3H), 1.77 (dd, *J* = 14.7, 10.2 Hz, 1H), 1.46 - 1.42 (m, 1H), 0.89 (d, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 196.4, 172.9, 160.6, 142.0, 137.6, 130.6, 128.0, 106.1, 82.2, 78.8, 56.3, 54.1, 49.2, 36.5, 31.5, 30.6, 29.0, 19.5, 13.4; IR (KBr, cm<sup>-1</sup>) 3417, 1736, 1620, 1454, 1401, 1099, 621; HRMS (ESI) calcd. for [C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>Na]<sup>+</sup>(M+Na)<sup>+</sup>: *m/z* 351.1208, found 351.1200.



**Phenol SI-4.** A 50 mL flame-dried flask was charged with ketone **28** (78 mg, 0.24 mmol, 1.0 equiv) and <sup>7</sup>Bu<sub>4</sub>NI (355 mg, 0.96 mmol, 4.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of degassed CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The reaction mixture was cooled to -78 °C and BCl<sub>3</sub> (1.2 mL, 1.0 M in toluene, 5.0 equiv) was added dropwise via syringe. The reaction mixture was slowly warmed to -40 °C over the course of 4 h and quenched with water (10 mL). After warming the reaction flask to room temperature, the organic layer was separated and the aqueous layer was extracted with CHCl<sub>3</sub> (3 x 20 mL). The combined organic layers were washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The crude phenol **SI-4** (ca. 50 mg) was used directly in the next step without further purification.



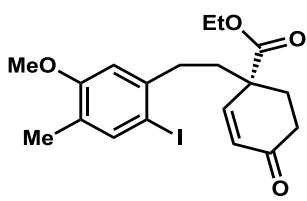
**Triflate 29.** To a stirred solution of crude phenol **SI-4** (50 mg, 0.16 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added pyridine (19  $\mu$ L, 0.24 mmol, 1.5 equiv) and Tf<sub>2</sub>O (32  $\mu$ L, 0.19 mmol, 1.2 equiv) sequentially at 0 °C. The reaction mixture was stirred for 1 h at this temperature and quenched with saturated aqueous NaHCO<sub>3</sub> solution (2 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford triflate **29** (61 mg, 57% yield over two steps) as a colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.57 (s, 1H), 4.90 - 4.87 (m, 1H), 3.56 (d, *J* = 19.2 Hz, 1H), 3.63 - 3.56 (m, 1H), 3.17 - 3.10 (m, 1H), 2.84 - 2.77 (m, 1H), 2.78 (d, *J* = 18.6 Hz, 1H), 2.69 - 2.59 (m, 1H), 2.39 (s, 3H), 2.17 (s, 1H), 1.79 (dd, *J* = 14.9, 10.2 Hz, 1H), 1.54 - 1.45 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 194.3, 172.2, 150.4, 144.2, 143.6, 135.1, 128.8, 118.8, 81.9, 78.3, 53.5, 49.0, 36.2, 31.9, 30.6, 28.9, 19.5, 14.3; IR (KBr, cm<sup>-1</sup>) 3418, 1637, 1400, 1119, 615; HRMS (ESI) calcd. for [C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>O<sub>7</sub>NaS]<sup>+</sup>(M+Na)<sup>+</sup>: *m/z* 469.0545, found 469.0526.



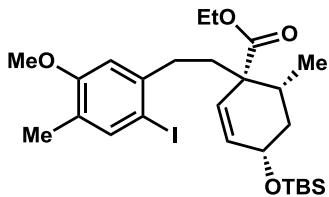
**Cephanolide C (4).** A 10 mL flame-dried reaction tube was charged with triflate **29** (48 mg, 0.11 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub> (2.5 mg, 0.011 mmol, 0.1 equiv), dppp (4.5 mg, 0.011 mmol, 0.1 equiv). The reaction tube was evacuated and backfilled with nitrogen, followed by addition of degassed DMF (1.5 mL). The reaction mixture was heated to 60 °C and triethylsilane (45 ul, 0.28 mmol, 2.5 equiv) was added in a single portion. The resulting mixture was stirred for 8 h at same temperature. After cooling the reaction tube to room temperature, the reaction mixture was extracted with ethyl acetate (50 mL) and the organic layer was washed with brine (3 x 5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford cephanolide C (**4**) (30 mg, 91%) as a white solid: m.p. = 263-265 °C; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 4.90 - 4.87 (m, 1H), 3.47 (dd, *J* = 17.6, 9.3 Hz, 1H), 3.43 (dd, *J* = 18.4, 1.7 Hz, 1H), 3.05 - 2.97 (m, 1H), 2.72 (dt, *J* = 17.6, 2.2 Hz, 1H), 2.61 (dd, *J* = 18.5, 1.7 Hz, 1H), 2.38 (s, 3H), 1.86 (dd, *J* = 14.8, 10.2 Hz, 1H), 1.41 - 1.34 (m, 1H), 1.24 - 1.16 (m, 1H), 0.83 (dd, *J* = 7.1, 1.7 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>OD) δ 198.2, 175.8, 147.2, 143.5, 142.3, 132.6, 129.2, 125.7, 82.7, 80.7, 54.8, 49.7, 37.4, 32.0, 31.4, 29.7, 19.5, 19.2; IR (KBr, cm<sup>-1</sup>) 3453, 1637, 1400, 1118, 614; HRMS (ESI) calcd. for [C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 321.1103, found 321.1095.

### 3.2 Preliminary Substrate Extension of Pd-catalyzed Cascade Reaction

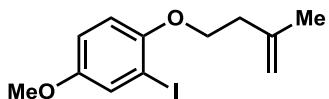
#### 3.2.1 Procedure for the syntheses of extended substrates:



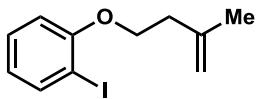
**17a.** A 100 mL flame-dried flask was charged with freshly prepared **SI-2** (2.0 g, 5.1 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of methyl vinyl ketone (0.62 mL, 7.7 mmol, 1.5 equiv) and THF (25 mL). After stirring for 5 min, Cu(OTf)<sub>2</sub> (369 mg, 1.0 mmol, 0.2 equiv) was added and the reaction mixture was heated to 50 °C and kept this temperature for 4 days. After cooling the reaction flask to room temperature, the resulting dark brown mixture was concentrated in *vacuo*. The residue was filtered through a pad of silica and eluted with ethyl acetate (100 mL). The eluent solution was concentrated in *vacuo* and the residue was diluted with toluene (50 mL). *p*-TsOH (194 mg, 1.0 mmol, 0.2 equiv) was added and the resulting mixture was heated to reflux and kept this temperature for 12 h. After cooling the reaction flask to room temperature, the reaction mixture was directly concentrated in *vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford enone **17a** (1.7 g, 76% yield) as a yellowish oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.51 (s, 1H), 7.04 (d, *J* = 10.2 Hz, 1H), 6.63 (s, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 4.32 - 4.18 (m, 2H), 3.80 (s, 3H), 2.73 - 2.60 (m, 2H), 2.57 - 2.52 (m, 3H), 2.20 - 2.09 (m, 1H), 2.12 (s, 3H), 2.04 (td, *J* = 13.5, 12.2, 5.3 Hz, 1H), 1.95 (td, *J* = 13.5, 12.2, 5.4 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 198.6, 173.2, 158.5, 150.9, 141.8, 140.8, 129.4, 127.6, 111.3, 88.2, 61.7, 55.6, 47.6, 39.4, 36.3, 34.8, 30.3, 15.5, 14.5; IR (KBr, cm<sup>-1</sup>) 3657, 2958, 1727, 1685, 1489, 1247, 1158; HRMS (ESI) calcd. for [C<sub>19</sub>H<sub>23</sub>IO<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 465.0533, found 465.0519.



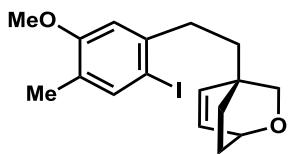
**17c.** To a stirred solution of allylic alcohol **11** (100 mg, 0.22 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added Et<sub>3</sub>N (61  $\mu$ L, 0.44 mmol, 2.0 equiv) and TBSOTf (61  $\mu$ L, 0.26 mmol, 1.2 equiv) sequentially at 0 °C. The reaction mixture was stirred for 1 h at this temperature and quenched with saturated aqueous NaHCO<sub>3</sub> solution (2 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1  $\times$  10 mL). The combined organic layers were washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford **17c** (120 mg, 95%) as a colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (s, 1H), 6.65 (s, 1H), 5.86 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.31 - 4.28 (m, 1H), 4.26 - 4.12 (m, 2H), 3.80 (s, 3H), 2.64 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.54 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.12 (s, 3H), 2.00 - 1.91 (m, 2H), 1.91 - 1.77 (m, 3H), 1.32 - 1.24 (m, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 158.4, 143.4, 140.6, 134.3, 129.2, 127.1, 111.4, 88.4, 67.6, 60.7, 55.5, 50.9, 37.40, 37.36, 36.2, 33.6, 26.1 (three carbons, overlapped), 18.3, 17.4, 15.5, 14.5, -4.29, -4.33; IR (KBr, cm<sup>-1</sup>) 2931, 1724, 1636, 1461, 1382, 1247, 1159, 1098, 838, 776; HRMS (ESI) calcd. for [C<sub>26</sub>H<sub>41</sub>IO<sub>4</sub>SiNa]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 595.1711, found 595.1705.



**17d** was prepared according to the known literature.<sup>3</sup> Colorless oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 (d, *J* = 3.0 Hz, 1H), 6.84 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 4.86 (s, 1H), 4.84 (s, 1H), 4.05 (t, *J* = 6.9 Hz, 2H), 3.74 (s, 3H), 2.55 (t, *J* = 6.9 Hz, 2H), 1.84 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  154.3, 152.1, 142.2, 124.7, 114.7, 113.3, 112.4, 87.1, 68.9, 55.9, 37.3, 23.1; IR (KBr, cm<sup>-1</sup>) 2936, 1488, 1271, 1216, 1042; HRMS (ESI) calcd. for [C<sub>12</sub>H<sub>15</sub>IO<sub>2</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 341.0009, found 341.0002.

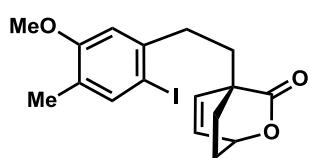


**17e** was prepared according to the known literature.<sup>3</sup> Colorless oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 4.98 - 4.77 (m, 2H), 4.13 (t, *J* = 6.9 Hz, 2H), 2.59 (t, *J* = 7.0 Hz, 2H), 1.87 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  157.6, 142.2, 139.6, 129.5, 122.6, 112.5, 112.2, 86.8, 68.1, 37.2, 23.1; IR (KBr, cm<sup>-1</sup>) 2932, 1578, 1467, 1279, 1244, 1047, 1016, 891, 746; HRMS (ESI) calcd. for [C<sub>11</sub>H<sub>13</sub>IONa]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 310.9903, found 310.9899.

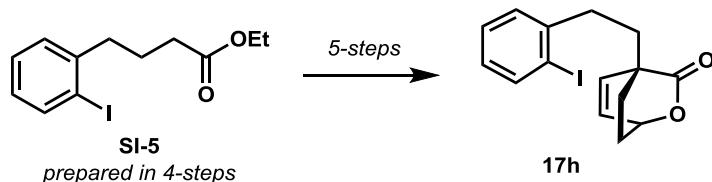


**17f.** A 50 mL flame-dried flask was charged with lactone **17g** (200 mg, 0.5 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen followed by the addition of CH<sub>2</sub>Cl<sub>2</sub> (20 mL). After cooling the reaction flask to 0 °C, DIBAL-H (1.0 mL, 1.5 M in toluene, 3.0 equiv) was added dropwise via syringe over the course of 2 min. The reaction mixture was slowly warmed to room temperature and stirred for 6 h at this temperature. The resulting mixture was quenched with saturated aqueous Na<sub>2</sub>SO<sub>4</sub> (15 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  20 mL). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The crude diol was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and *p*-TsOH (19 mg, 0.1

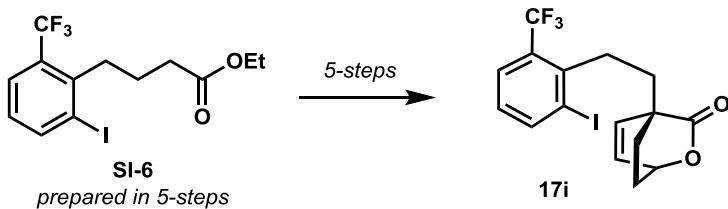
mmol, 0.2 equiv) was added. After stirring for 2 h at room temperature, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution (5 mL). The reaction mixture was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in *vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford ether **17f** (135 mg, 70% yield) as a colorless solid: m.p. = 84–86 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.52 (s, 1H), 6.69 (s, 1H), 6.55 – 6.45 (m, 2H), 4.42 – 4.40 (m, 1H), 3.82 (s, 3H), 3.62 (d, *J* = 7.0 Hz, 1H), 3.16 (dd, *J* = 7.1, 2.9 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.14 (s, 3H), 2.15 – 2.10 (m, 1H), 1.70 – 1.61 (m, 2H), 1.58 – 1.52 (m, 1H, overlapped with H<sub>2</sub>O), 1.44 – 1.38 (m, 2H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 158.5, 143.3, 140.7, 136.7, 132.8, 127.2, 111.2, 88.4, 71.2, 66.1, 55.6, 37.6, 36.2, 36.1, 27.3, 26.9, 15.5; IR (KBr, cm<sup>-1</sup>) 2924, 1638, 1488, 1456, 1376, 1244, 1155, 1045; HRMS (ESI) calcd. for [C<sub>17</sub>H<sub>21</sub>IO<sub>2</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 407.0478, found 407.0465.



**17g** was prepared from **17a** following the similar procedure that was used for preparation of lactone **12**. Colorless solid: m.p. = 99–101 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.52 (s, 1H), 6.83 (s, 1H), 6.56 – 6.51 (m, 2H), 5.24 – 5.21 (m, 1H), 3.82 (s, 3H), 2.99 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.86 (dd, *J* = 12.7, 4.8 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.14 (s, 3H), 2.09 (td, *J* = 13.8, 12.4, 4.8 Hz, 1H), 2.01 (td, *J* = 13.8, 12.5, 4.8 Hz, 1H), 1.77 (td, *J* = 12.2, 9.2, 3.1 Hz, 1H), 1.73 – 1.68 (m, 1H), 1.60 – 1.53 (m, 1H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 175.8, 158.5, 143.1, 140.5, 135.7, 131.7, 127.3, 111.7, 88.4, 73.9, 55.6, 47.2, 36.3, 33.5, 26.6, 25.6, 15.5; IR (KBr, cm<sup>-1</sup>) 1744, 1367, 1246, 1155; HRMS (ESI) calcd. for [C<sub>17</sub>H<sub>19</sub>IO<sub>3</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 421.0271, found 421.0266.



**17h** was prepared from the known ester **SI-5**<sup>4</sup> following the similar procedure that was used for preparation of lactone **12**. Colorless oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.80 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.36 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.29 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.89 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 2H), 5.22 – 5.20 (m, 1H), 3.02 (dd, *J* = 12.9, 4.8 Hz, 1H), 2.90 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.22 (dd, *J* = 13.2, 9.3, 5.0 Hz, 1H), 2.11 (td, *J* = 13.9, 12.5, 4.8 Hz, 1H), 2.02 (td, *J* = 13.9, 12.6, 4.8 Hz, 1H), 1.80 – 1.64 (m, 2H), 1.56 (td, *J* = 12.0, 10.8, 5.1 Hz, 1H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 175.5, 144.7, 139.5, 135.4, 131.8, 129.8, 128.7, 128.1, 100.4, 73.8, 47.0, 36.1, 33.1, 26.5, 25.4; IR (KBr, cm<sup>-1</sup>) 1742, 1460, 1362, 1126, 1007, 971; HRMS (ESI) calcd. for [C<sub>15</sub>H<sub>15</sub>IO<sub>2</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 377.0009, found 377.0005.

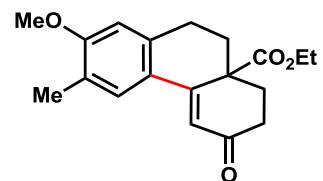


**17i** was prepared from ester **SI-6**<sup>4,5</sup> following the similar procedure that was used for preparation of lactone **12**. Yellowish oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.04 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.54 (dd, *J* = 7.9, 5.0 Hz, 1H), 5.22 - 5.20 (m, 1H), 3.17 (dd, *J* = 13.4, 4.6 Hz, 1H), 3.06 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.34 - 2.10 (m, 2H), 2.02 (dd, *J* = 13.7, 4.4 Hz, 1H), 1.82 - 1.62 (m, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 175.3, 144.0, 142.6, 135.1, 132.0, 129.70 (q, *J* = 30.2 Hz), 128.0, 126.72 (q, *J* = 6.0 Hz), 123.95 (q, *J* = 274.8 Hz), 103.7, 73.6, 46.9, 32.8, 31.5, 26.4, 24.6; IR (KBr, cm<sup>-1</sup>) 1746, 1307, 1121, 1082, 794; HRMS (ESI) calcd. for [C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>IO<sub>2</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 444.9883, found 444.9873.

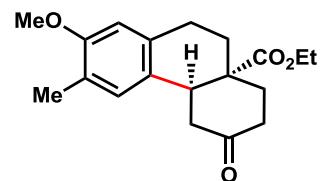
### 3.2.2 General procedure for the Pd-catalyzed cascade annulation:

A 10 mL flame-dried flask was charged with substrate (0.1 mmol, 1.0 equiv), Pd(OAc)<sub>2</sub> (2.2 mg, 0.01 mmol, 0.1 equiv), Ph<sub>3</sub>P (5.2 mg, 0.02 mmol, 0.2 equiv), and potassium carbonate (28 mg, 0.2 mmol, 2.0 equiv). The reaction flask was evacuated and backfilled with carbon monoxide (a total of three times) followed by addition of degassed toluene (1.5 mL). The reaction mixture was heated to 90 °C and kept this temperature for 18 h. After cooling the reaction flask to room temperature, the reaction mixture was filtered through a pad of silica and eluted with ethyl acetate (15 mL). The eluent solution was directly concentrated in *vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane) to afford annulated product.

### 3.2.3 Spectral Characterization of the Annulated Products:

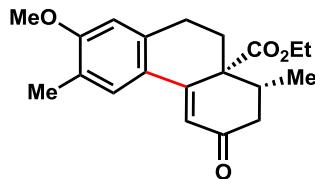


**19.** White solid: m.p. = 121-123 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.53 (s, 1H), 6.56 (s, 1H), 6.53 (s, 1H), 4.20 - 4.03 (m, 2H), 3.82 (s, 3H), 2.93 - 2.74 (m, 2H), 2.52 - 2.34 (m, 4H), 2.18 (s, 3H), 2.10 - 1.98 (m, 1H), 1.81 (dt, *J* = 13.2, 6.8 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 199.1, 173.3, 160.0, 155.2, 138.0, 128.0, 125.7, 123.5, 120.2, 109.9, 61.6, 55.4, 47.8, 34.9, 34.7 (two carbons, overlapped), 27.3, 16.3, 14.3; IR (KBr, cm<sup>-1</sup>) 3699, 3081, 1724, 1583, 1505, 1247; HRMS (ESI) calcd. for [C<sub>19</sub>H<sub>22</sub>O<sub>4</sub>Na]<sup>+</sup> (M+Na)<sup>+</sup>: *m/z* 337.1410, found 337.1411.

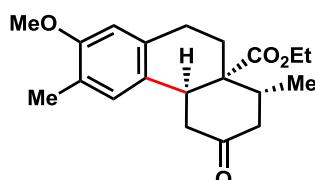


**20.** White solid: m.p. = 67-68 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.87 (s, 1H), 6.50 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.65 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.95 - 2.80 (m, 2H), 2.61 (dd, *J* = 15.4, 5.3 Hz, 1H), 2.53 (dd, *J* = 15.4, 10.8 Hz, 1H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.24 - 2.12 (m, 3H), 2.15 (s, 3H), 2.08 - 2.01 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 210.3, 175.9, 156.4, 132.5, 130.3, 129.4, 125.0, 110.1, 61.0, 55.4, 46.3, 45.2,

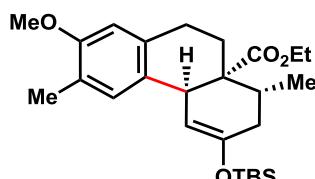
40.8, 37.1, 33.0, 26.54, 26.46, 16.1, 14.3; IR (KBr,  $\text{cm}^{-1}$ ) 3694, 2961, 1720, 1508, 1237; HRMS (ESI) calcd. for  $[\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}]^+ (\text{M}+\text{Na})^+$ :  $m/z$  339.1567, found 339.1562.



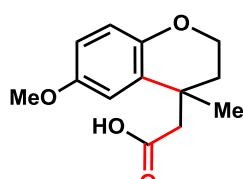
**21.** White solid: m.p. = 137-139 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (s, 1H), 6.57 (s, 1H), 6.54 (s, 1H), 4.17 - 4.12 (m, 1H), 4.03 - 3.99 (m, 1H), 3.83 (s, 3H), 3.15 - 3.09 (m, 1H), 2.85 - 2.77 (m, 2H), 2.47 (dd,  $J$  = 17.0, 14.0 Hz, 1H), 2.37 (dd,  $J$  = 16.9, 4.2 Hz, 1H), 2.29 - 2.21 (m, 1H), 2.18 (s, 3H), 1.64 - 1.59 (m, 1H), 1.15 - 1.08 (m, 6H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  199.4, 170.6, 160.2, 156.1, 138.1, 128.7, 125.7, 123.7, 121.2, 109.8, 61.3, 55.5, 50.8, 42.4, 38.7, 31.5, 26.8, 16.6, 16.3, 14.4; IR (KBr,  $\text{cm}^{-1}$ ) 3452, 1653, 1384, 1183, 1132; HRMS (ESI) calcd. for  $[\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}]^+ (\text{M}+\text{Na})^+$ :  $m/z$  351.1567, found 351.1566.



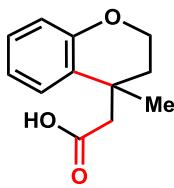
**22.** White solid: m.p. = 122-124 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.84 (s, 1H), 6.48 (s, 1H), 4.11 (q,  $J$  = 7.1 Hz, 2H), 3.76 (s, 3H), 3.64 (dd,  $J$  = 12.5, 5.4 Hz, 1H), 2.91 - 2.77 (m, 2H), 2.68 (dd,  $J$  = 14.6, 5.2 Hz, 1H), 2.57 (td,  $J$  = 15.5, 5.4, 1.9 Hz, 1H), 2.45 - 2.36 (m, 2H), 2.33 - 2.19 (m, 3H), 2.14 (s, 3H), 1.19 (t,  $J$  = 7.1 Hz, 3H), 0.97 (d,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  210.2, 174.6, 156.2, 131.9, 130.6, 130.4, 125.0, 110.0, 60.7, 55.3, 48.8, 47.3, 44.1, 38.5, 38.0, 27.0, 26.8, 17.0, 16.0, 14.3; IR (KBr,  $\text{cm}^{-1}$ ) 3450, 1718, 1638, 1508, 1385, 1235, 1172, 1111; HRMS (ESI) calcd. for  $[\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}]^+ (\text{M}+\text{Na})^+$ :  $m/z$  353.1723, found 353.1724.



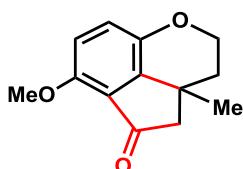
**23.** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.94 (s, 1H), 6.43 (s, 1H), 4.82 (t,  $J$  = 2.3 Hz, 1H), 4.10 (q,  $J$  = 7.5 Hz, 2H), 3.85 (s, 1H), 3.76 (s, 3H), 2.70 (td,  $J$  = 17.1, 5.6, 2.6 Hz, 1H), 2.60 (td,  $J$  = 17.2, 12.2, 5.5 Hz, 1H), 2.50 - 2.40 (m, 1H), 2.26 - 2.14 (m, 1H), 2.18 (s, 3H), 2.00 (td,  $J$  = 12.5, 5.5 Hz, 1H), 1.95 - 1.88 (m, 1H), 1.74 (dt,  $J$  = 17.5, 2.1 Hz, 1H), 1.19 (t,  $J$  = 7.1 Hz, 3H), 1.00 (d,  $J$  = 7.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  175.9, 155.7, 145.8, 133.0, 131.4, 131.0, 124.8, 109.7, 109.2, 60.4, 55.3, 48.4, 36.2, 35.1, 33.9, 27.5, 27.2, 25.8 (three carbons, overlapped), 18.1, 16.9, 16.2, 14.4, -4.1, -4.2; IR (KBr,  $\text{cm}^{-1}$ ) 3051, 1728, 1508, 1461, 1170, 952, 843; HRMS (ESI) calcd. for  $[\text{C}_{26}\text{H}_{40}\text{O}_4\text{SiNa}]^+ (\text{M}+\text{Na})^+$ :  $m/z$  467.2588, found 467.2578.



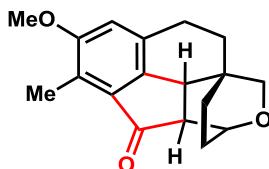
**24.** White solid: m.p. = 70-72 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.78 - 6.72 (m, 2H), 6.69 (dd,  $J$  = 8.9, 2.9 Hz, 1H), 4.19 (td,  $J$  = 11.0, 7.6, 3.2 Hz, 1H), 4.13 (td,  $J$  = 11.1, 7.6, 3.2 Hz, 1H), 3.76 (s, 3H), 2.70 (s, 2H), 2.29 (td,  $J$  = 14.1, 7.6, 3.3 Hz, 1H), 1.89 (td,  $J$  = 14.1, 7.6, 3.2 Hz, 1H), 1.47 (s, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  176.8, 153.6, 148.0, 130.2, 118.0, 113.7, 112.1, 62.8, 55.9, 46.3, 34.3, 33.4, 28.7; IR (KBr,  $\text{cm}^{-1}$ ) 3475, 1705, 1496, 1271, 1208, 811, 736; HRMS (ESI) calcd. for  $[\text{C}_{13}\text{H}_{16}\text{O}_4\text{Na}]^+ (\text{M}+\text{Na})^+$ :  $m/z$  259.0941, found 259.0932.



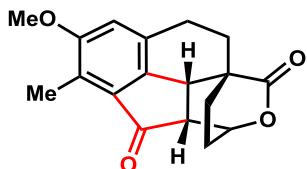
**25.** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.11 (td,  $J = 8.5, 7.2, 1.6$  Hz, 1H), 6.89 (td,  $J = 7.5, 1.3$  Hz, 1H), 6.81 (dd,  $J = 8.1, 1.3$  Hz, 1H), 4.22 (td,  $J = 32.8, 11.2, 7.6$  Hz, 2H), 2.72 (s, 2H), 2.31 (td,  $J = 14.1, 7.5, 3.3$  Hz, 1H), 1.92 (td,  $J = 14.1, 7.7, 3.3$  Hz, 1H), 1.48 (s, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.4, 153.9, 129.5, 127.9, 126.8, 120.7, 117.4, 62.8, 46.4, 34.2, 33.1, 28.6; IR (KBr,  $\text{cm}^{-1}$ ) 3444, 2924, 1706, 1487, 1449, 1300, 1222, 755; HRMS (ESI) calcd. for  $[\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  229.0835, found 229.0843.



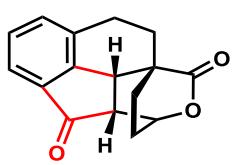
**18d.** Colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.90 (d,  $J = 8.7$  Hz, 1H), 6.68 (d,  $J = 8.7$  Hz, 1H), 4.51 - 4.37 (m, 2H), 3.87 (s, 3H), 2.67 (d,  $J = 16.4$  Hz, 1H), 2.59 - 2.47 (m, 1H), 2.06 - 1.98 (m, 1H), 1.93 (td,  $J = 13.3, 11.3, 7.3$  Hz, 1H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  201.6, 150.8, 145.7, 145.6, 122.4, 121.7, 111.6, 64.3, 56.3, 55.6, 34.1, 33.7, 28.7; IR (KBr,  $\text{cm}^{-1}$ ) 1711, 1494, 1299, 1262, 1051; HRMS (ESI) calcd. for  $[\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  241.0835, found 241.0828.



Mixture of two diastereomers (**18f : 18f'** = 2:1), colorless oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.90 (s, 2H), 6.88 (s, 1H), 4.21 (dt,  $J = 3.7, 1.9$  Hz, 1H), 4.16 (td,  $J = 5.7, 4.3, 1.4$  Hz, 2H), 3.95 (d,  $J = 7.7$  Hz, 2H), 3.85 (d,  $J = 8.1$  Hz, 9H), 3.75 (dd,  $J = 7.7, 3.6$  Hz, 2H), 3.31 (td,  $J = 7.8, 5.6, 1.8$  Hz, 2H), 3.15 (dd,  $J = 8.9, 1.6$  Hz, 1H), 3.00 (td,  $J = 28.6, 16.3, 10.7$  Hz, 3H), 2.92 - 2.84 (m, 3H), 2.81 - 2.64 (m, 5H), 2.49 (d,  $J = 13.3$  Hz, 8H), 2.26 - 2.15 (m, 1H), 1.86 - 1.83 (m, 2H), 1.78 - 1.63 (m, 6H), 1.45 (td,  $J = 13.4, 9.4, 3.9$  Hz, 2H), 1.35 (td,  $J = 14.3, 9.3, 5.1$  Hz, 1H), 1.16 - 1.06 (m, 2H), 1.00 (td,  $J = 13.9, 4.5, 1.8$  Hz, 2H), 0.63 (tq,  $J = 12.1, 4.0$  Hz, 2H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  208.2, 206.8, 158.1, 158.0, 148.7, 148.3, 135.04, 135.00, 133.6, 133.4, 124.3, 124.1, 115.8, 115.5, 75.1, 69.5, 68.5, 67.5, 56.68, 56.66, 53.2, 52.7, 40.0, 39.9, 32.4, 32.0, 31.8, 28.7, 28.2, 27.2, 25.5, 24.6, 24.3, 23.1, 10.2, 10.1; IR (KBr,  $\text{cm}^{-1}$ ) 2858, 1695, 1642, 1278, 1026, 755; HRMS (ESI) calcd. for  $[\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  307.1305, found 307.1295.

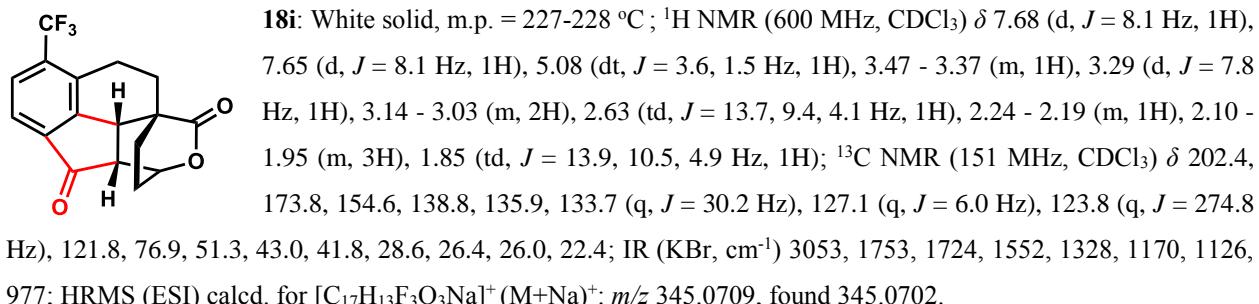


**18g.** White solid, m.p. = 197-199 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.89 (s, 1H), 5.08 - 4.97 (m, 1H), 3.82 (s, 3H), 3.10 (d,  $J = 7.8$  Hz, 1H), 3.03 (t,  $J = 7.4$  Hz, 2H), 2.97 (dd,  $J = 7.8, 1.8$  Hz, 1H), 2.55 (dt,  $J = 13.7, 7.0$  Hz, 1H), 2.45 (s, 3H), 2.22 - 2.12 (m, 1H), 2.02 - 1.89 (m, 3H), 1.76 (dt,  $J = 14.0, 7.7$  Hz, 1H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  204.2, 175.0, 158.6, 145.5, 134.5, 133.7, 124.8, 116.1, 77.20 (overlapped with  $\text{CDCl}_3$ ), 56.3, 51.9, 43.7, 40.4, 28.5, 26.5, 26.4, 24.6, 10.3; IR (KBr,  $\text{cm}^{-1}$ ) 1750, 1701, 1640, 1484, 1374, 1280, 1085; HRMS (ESI) calcd. for  $[\text{C}_{18}\text{H}_{18}\text{O}_4\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  321.1097, found 321.1093.



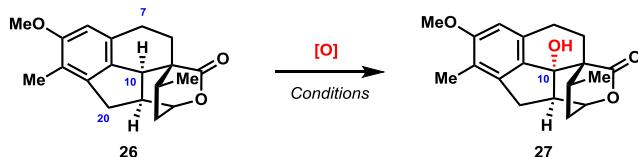
**18h:** White solid, m.p. = 234-236 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (d,  $J = 7.5$  Hz, 1H), 7.40 (d,  $J = 7.3$  Hz, 1H), 7.35 (t,  $J = 7.4$  Hz, 1H), 5.10 - 4.99 (m, 1H), 3.25 (d,  $J = 7.7$  Hz, 1H), 3.12 - 2.98 (m, 3H), 2.59 (td,  $J = 13.9, 8.6, 5.2$  Hz, 1H), 2.23 - 2.12 (m, 1H), 2.06 - 1.92 (m, 3H), 1.80 (td,  $J = 13.9, 9.5, 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  203.2, 174.5, 153.9,

136.8, 136.3, 134.0, 129.6, 121.7, 77.0, 51.3, 43.6, 41.7, 28.7, 26.5, 26.2, 24.4; IR (KBr,  $\text{cm}^{-1}$ ) 2930, 1746, 1697, 1639, 1379, 1099; HRMS (ESI) calcd. for  $[\text{C}_{16}\text{H}_{14}\text{O}_3\text{Na}]^+$  ( $\text{M}+\text{Na}$ ) $^+$ :  $m/z$  277.0835, found 277.0830.



### 3.3 Optimization of Late-stage $sp^3$ C-H Bond Oxidation

**Table S1:** Reaction optimization of late-stage regioselective oxidation of **26**.<sup>a</sup>

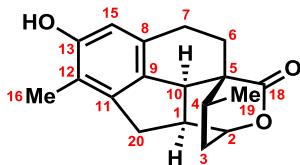


Entry	Reaction conditions	Yield <sup>b</sup>
<b>1<sup>c</sup></b>	CuCl (20 mol %), PhCOOO'Bu (5.0 equiv), PhH, 50 °C, 5 h	--
<b>2</b>	CuBr (20 mol %), PhCOOO'Bu (5.0 equiv), PhH, 50 °C, 5 h	--
<b>3</b>	NHPI (20 mol %), AIBN (20 mol %), O <sub>2</sub> (1 atm), CH <sub>3</sub> CN, 75 °C, 5 h; then Ph <sub>3</sub> P (1.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h	18%
<b>4</b>	NHPI (20 mol %), CH <sub>3</sub> CHO (20 mol %), O <sub>2</sub> (1 atm), CH <sub>3</sub> CN, 50 °C, 5 h; then Ph <sub>3</sub> P (1.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , rt, 5 h	26%
<b>5</b>	NHPI (20 mol %), 2-ethylbutyraldehyde (20 mol %), O <sub>2</sub> (1 atm), CH <sub>3</sub> CN, 50 °C, 5 h; then Ph <sub>3</sub> P (1.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , rt, 5 h	24%
<b>6</b>	NHPI (20 mol %), trimethylacetaldehyde (20 mol %), O <sub>2</sub> (1 atm), CH <sub>3</sub> CN, 50 °C, 5 h; then Ph <sub>3</sub> P (1.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , rt, 5 h	20%
<b>7<sup>d</sup></b>	DDQ (2.0 equiv), CH <sub>3</sub> CN/H <sub>2</sub> O (1:1), rt, 10 h	30%
<b>8<sup>e</sup></b>	DDQ (2.0 equiv), THF/H <sub>2</sub> O (1:1), rt, 10 h	--
<b>9<sup>d</sup></b>	DDQ (2.0 equiv), dioxone/H <sub>2</sub> O (1:1), rt, 10 h	28%
<b>10</b>	DDQ (2.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> /H <sub>2</sub> O (1:1), rt, 10 h	75%

<sup>a</sup>Reactions were performed on a 0.06 mmol scale. <sup>b</sup>Isolated yield. <sup>c</sup>Decomposed. <sup>d</sup>Yield > 85% (brsm). <sup>e</sup>No reaction. AIBN = 2,2'-azobis(2-methylpropionitrile), NHPI = N-hydroxyphthalimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

#### 4. Natural Product Spectral Comparisons

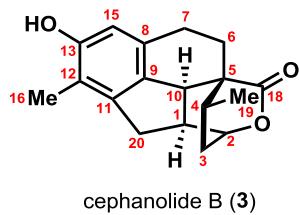
##### 4.1 Cephalolide B $^1\text{H}$ NMR spectra comparison:



cephalolide B (3)

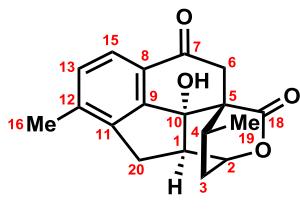
Position	Natural sample	Synthetic sample
	H NMR (400 MHz, $\text{CDCl}_3$ ) $\delta_{\text{H}}$ ( $J$ in Hz)	H NMR (600 MHz, $\text{CDCl}_3$ ) $\delta_{\text{H}}$ ( $J$ in Hz)
1	3.15 (m, 1H)	3.15 (m, 1H)
2	4.65 (m, 1H)	4.66 (m, 1H)
3 $\alpha$	1.70 (dd, $J = 14.4, 10.4$ ; 1H)	1.70 (dd, $J = 14.5, 10.3$ ; 1H)
3 $\beta$	1.28 (ddd, $J = 14.4, 4.6, 1.8$ ; 1H)	1.24 - 1.31 (m, 1H)
4	1.18 (m, 1H)	1.19 (m, 1H)
6	2.05 - 2.12, (m, 2H)	1.98 - 2.11 (m, 2H)
7 $\alpha$	2.96 (dd, $J = 17.5, 9.0$ ; 1H)	2.96 (dd, $J = 17.4, 9.6$ ; 1H)
7 $\beta$	2.56 (overlap, 1H)	2.47 - 2.59 (overlap, 1H)
10	3.23 (d, $J = 9.3$ , 1H)	3.23 (d, $J = 9.6$ , 1H)
15	6.46 (s, 1H)	6.48 (s, 1H)
16	2.13 (s, 3H)	2.13 (s, 3H)
19	0.81 (d, $J = 7.1$ , 3H)	0.81 (d, $J = 7.1$ , 3H)
20 $\alpha$	3.24 (dd, $J = 15.0, 9.6$ ; 1H)	3.24 (dd, $J = 17.5, 9.7$ ; 2H)
20 $\beta$	2.56 (overlap, 1H)	2.47 - 2.59 (overlap, 1H)
-OH	--	4.83 (bs, 1H)

**4.2 Cephalolide B  $^{13}\text{C}$ -NMR spectra comparison:**



Position	<b>Natural sample</b>		<b>Synthetic sample</b>	
	$^{13}\text{C}$ NMR (125 MHz, $\text{CDCl}_3$ )	$\delta_{\text{C}}$	$^{13}\text{C}$ NMR (151 MHz, $\text{CDCl}_3$ )	$\delta_{\text{C}}$
1		39.6		39.7
2		79.2		79.3
3		28.8		28.9
4		26.5		26.5
5		45.9		45.9
6		23.1		23.1
7		24.1		24.1
8		132.7		132.7
9		132.3		132.3
10		47.5		47.5
11		141.9		141.8
12		117.7		117.8
13		154.2		154.4
15		112.8		112.8
16		12.3		12.3
18		177.2		177.3
19		19.5		19.5
20		33.0		33.0

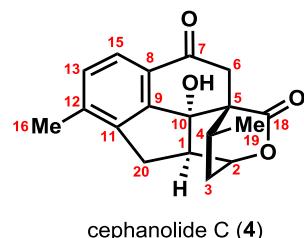
**4.3 Cephalolide C  $^1\text{H}$ -NMR spectra comparison:**



cephalolide C (4)

Position	Natural sample	Synthetic sample
	H NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta_{\text{H}}$ ( $J$ in Hz)	H NMR (600 MHz, $\text{CD}_3\text{OD}$ ) $\delta_{\text{H}}$ ( $J$ in Hz)
1	3.01 (m, 1H)	3.01 (m, 1H)
2	4.89 (m, 1H)	4.89 (overlap, 1H)
3 $\alpha$	1.85 (dd, $J = 14.8, 10.2$ ; 1H)	1.86 (dd, $J = 14.8, 10.2$ Hz, 1H)
3 $\beta$	1.37 (ddd, $J = 14.8, 4.7, 1.8$ ; 1H)	1.37 (m, 1H)
4	1.20 (m, 1H)	1.21 (m, 1H)
6 $\alpha$	3.43 (d, $J = 18.4$ , 1H)	3.43 (dd, $J = 18.4, 1.7$ Hz, 1H)
6 $\beta$	2.61 (d, $J = 18.4$ , 1H)	2.61 (dd, $J = 18.5, 1.7$ Hz, 1H)
13	7.33 (d, $J = 7.7$ , 1H)	7.33 (d, $J = 7.7$ , 1H)
15	7.55 (d, $J = 7.7$ , 1H)	7.55 (d, $J = 7.7$ , 1H)
16	2.38 (s, 3H)	2.38 (s, 3H)
19	0.83 (d, $J = 7.1$ , 3H)	0.83 (dd, $J = 7.1, 1.7$ Hz, 3H)
20 $\alpha$	3.48 (dd, $J = 17.7, 9.6$ ; 1H)	3.47 (dd, $J = 17.6, 9.3$ Hz, 1H)
20 $\beta$	2.71 ( $J = 17.7, 2.9$ ; 1H)	2.72 (dt, $J = 17.6, 2.2$ Hz, 1H)

**4.4 Cephalolide C  $^{13}\text{C}$ -NMR spectra comparison:**

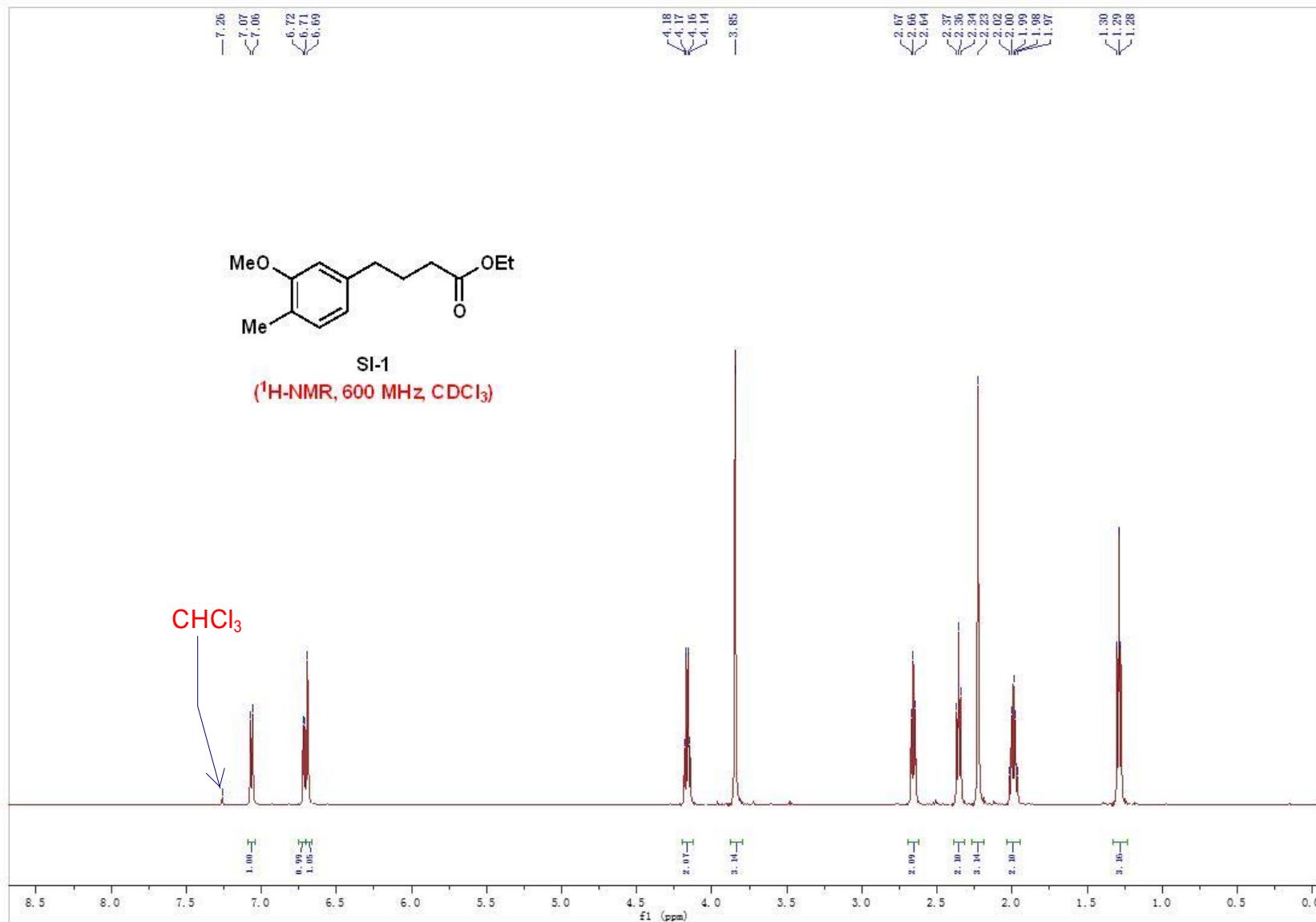


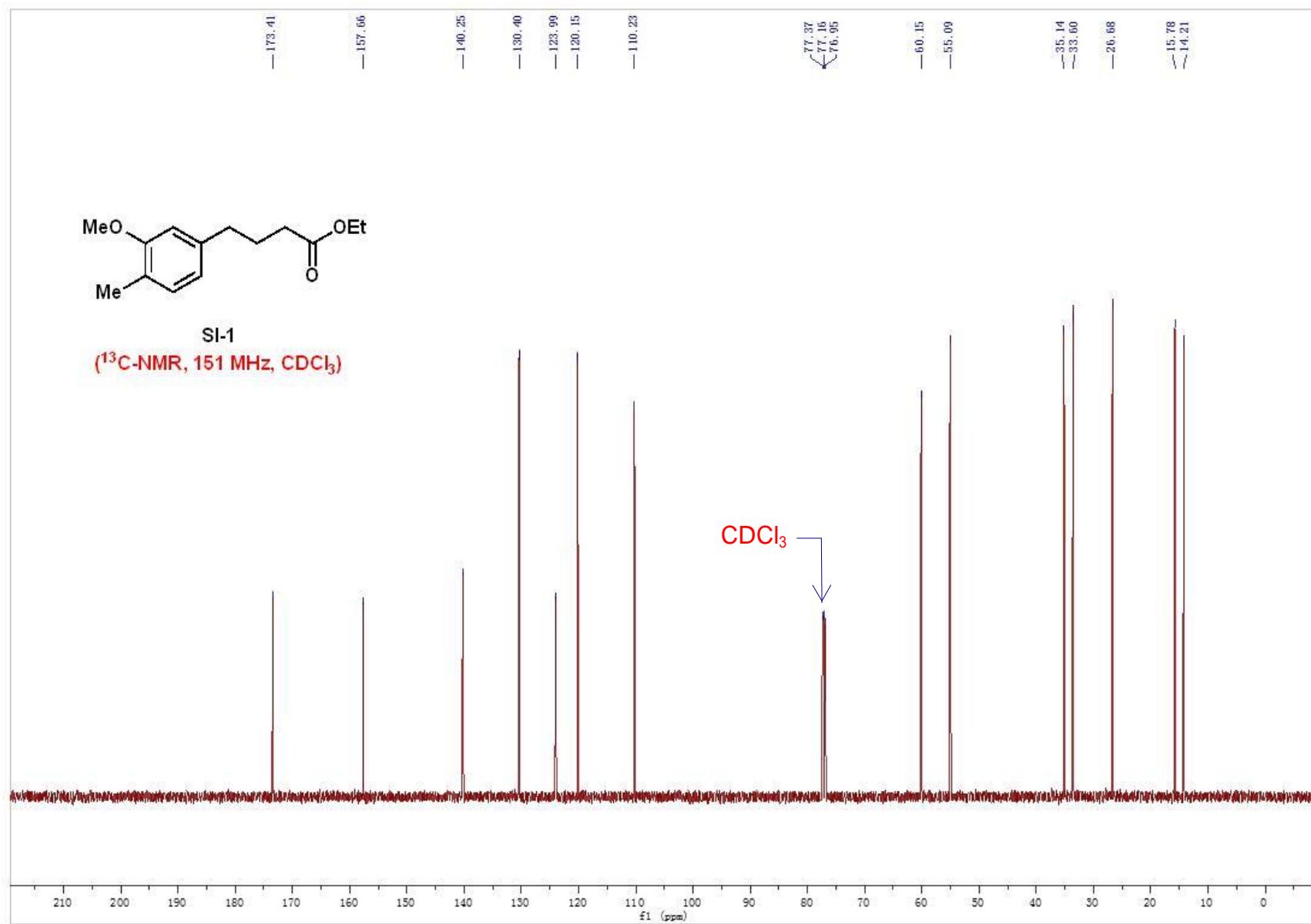
Position	<b>Natural sample</b>		<b>Synthetic sample</b>	
	$^{13}\text{C}$ NMR (125 MHz, CD <sub>3</sub> OD)	$\delta_{\text{C}}$	$^{13}\text{C}$ NMR (151 MHz, CD <sub>3</sub> OD)	$\delta_{\text{C}}$
1		49.9		49.7
2		80.7		80.7
3		29.7		29.7
4		31.4		31.4
5		54.8		54.8
6		37.3		37.4
7		198.3		198.2
8		129.2		129.2
9		147.2		147.2
10		82.7		82.7
11		142.3		142.3
12		143.5		143.5
13		132.6		132.6
15		125.7		125.7
16		19.2		19.2
18		175.9		175.8
19		19.5		19.5
20		32.0		32.0

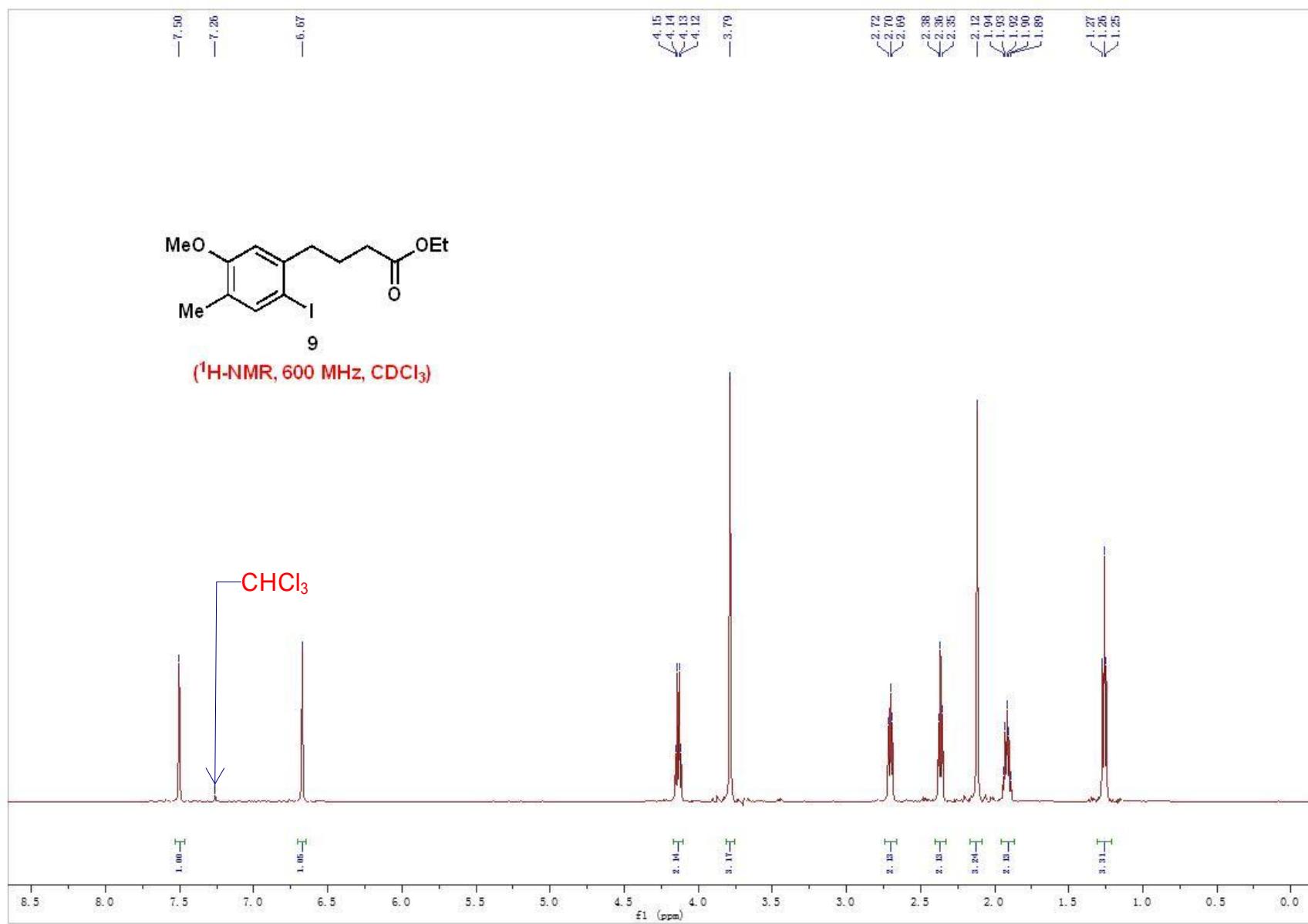
## 5. References

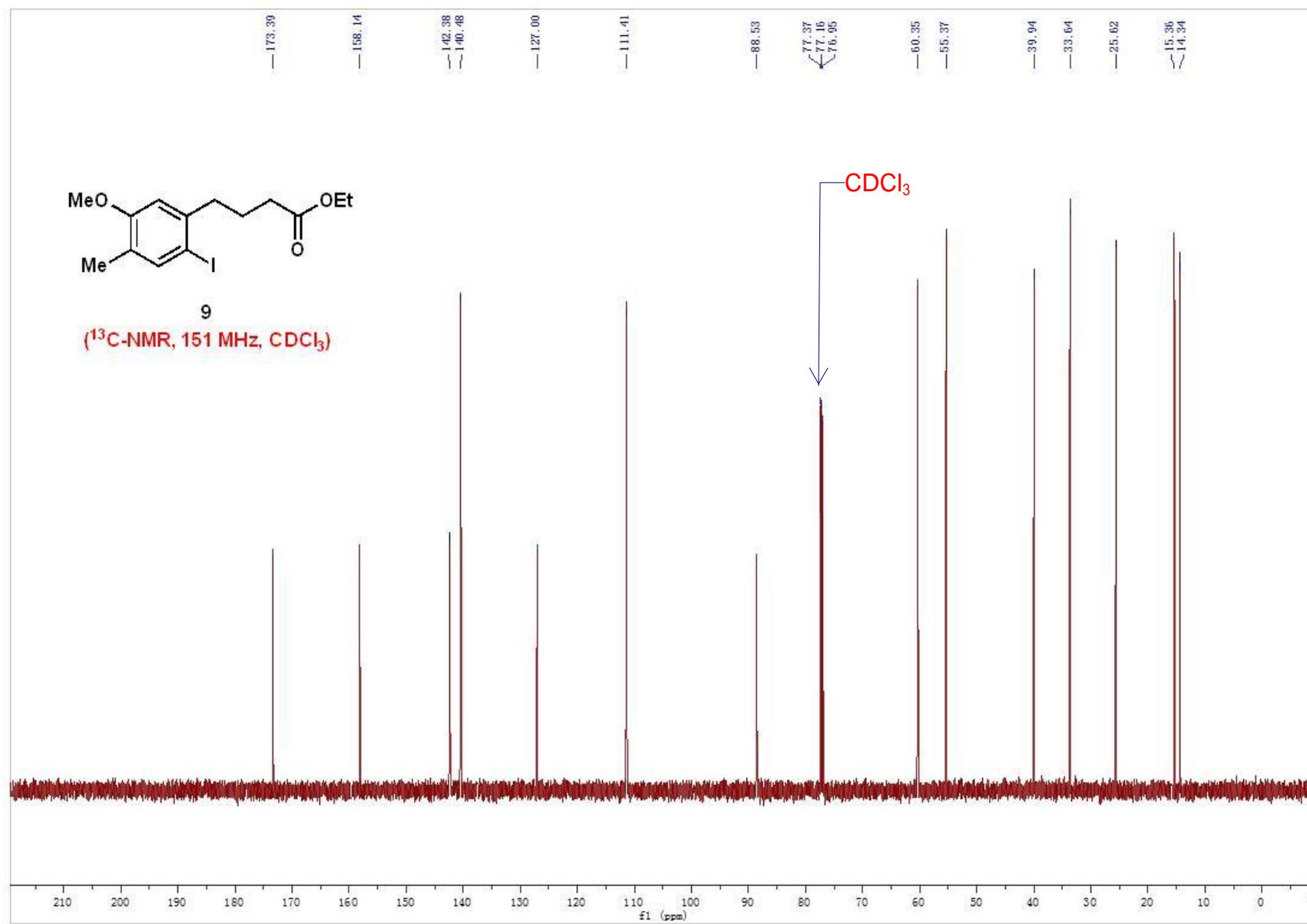
- [1]. (a) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422. (b) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
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- [4]. Tummatorn, G.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 1572.
- [5]. Mei, T. S.; Wang, D. H.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 3140.

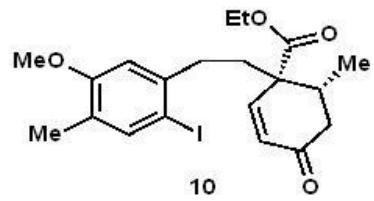
## 6. $^1\text{H}$ and $^{13}\text{C}$ -NMR Spectra





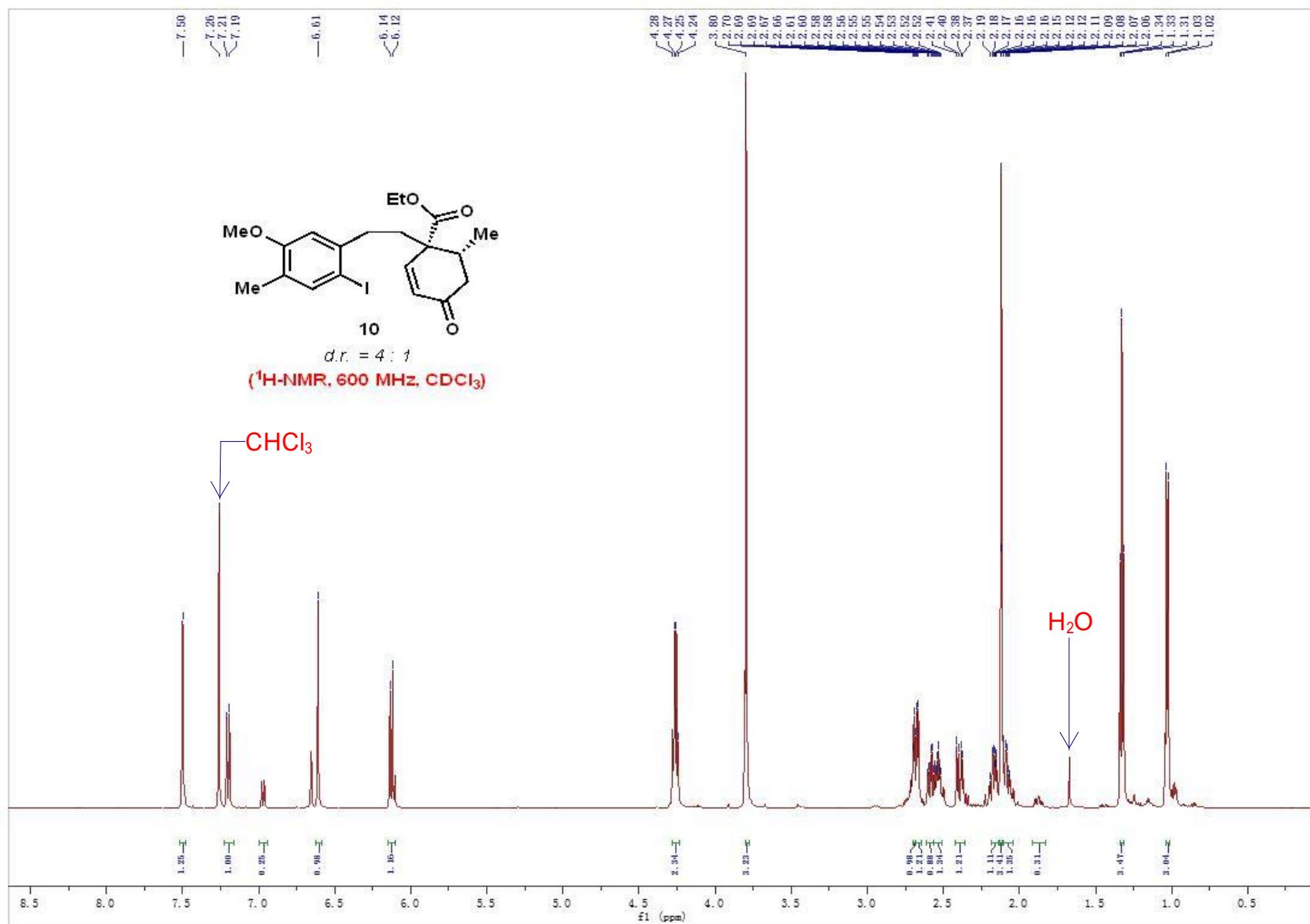


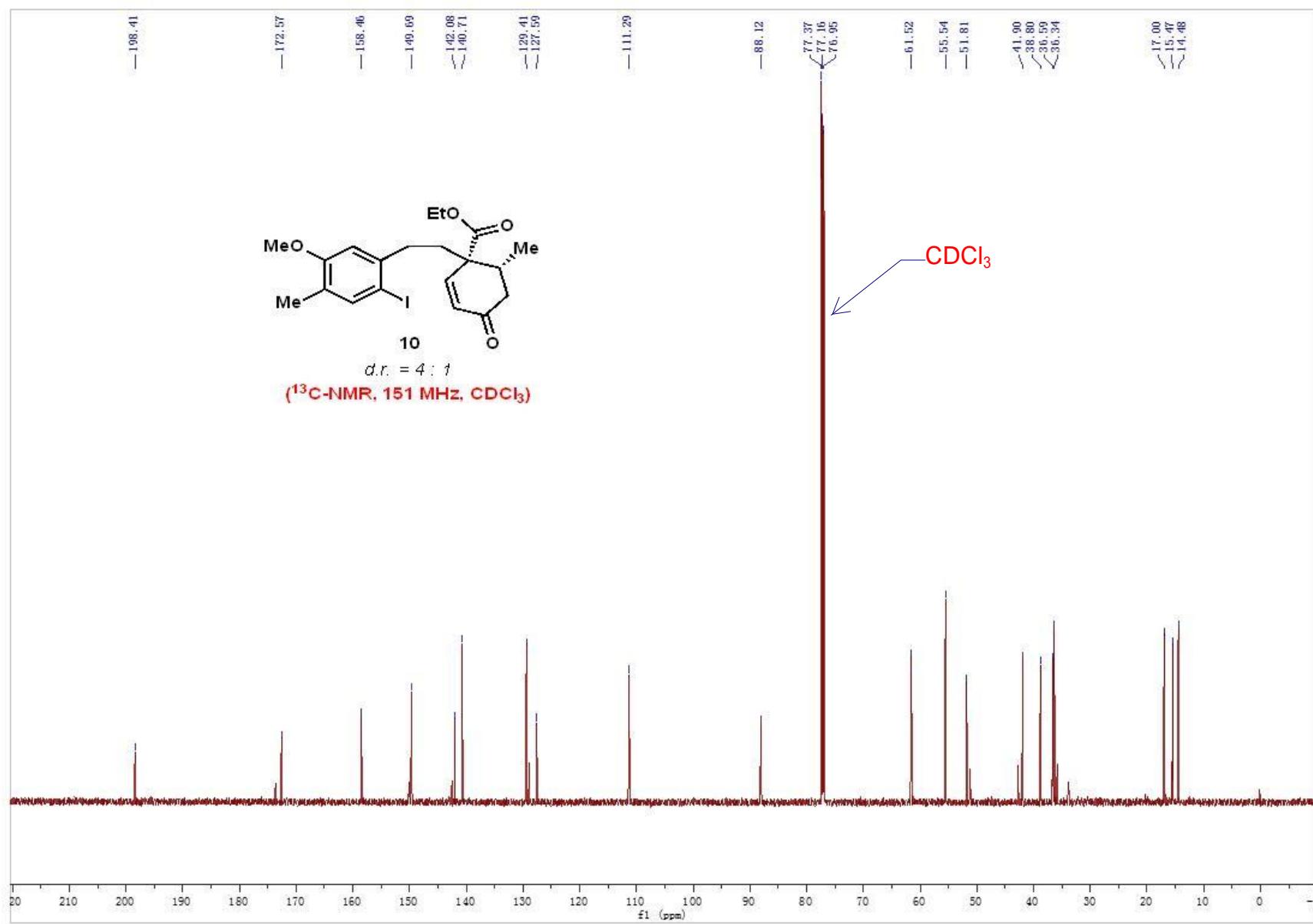


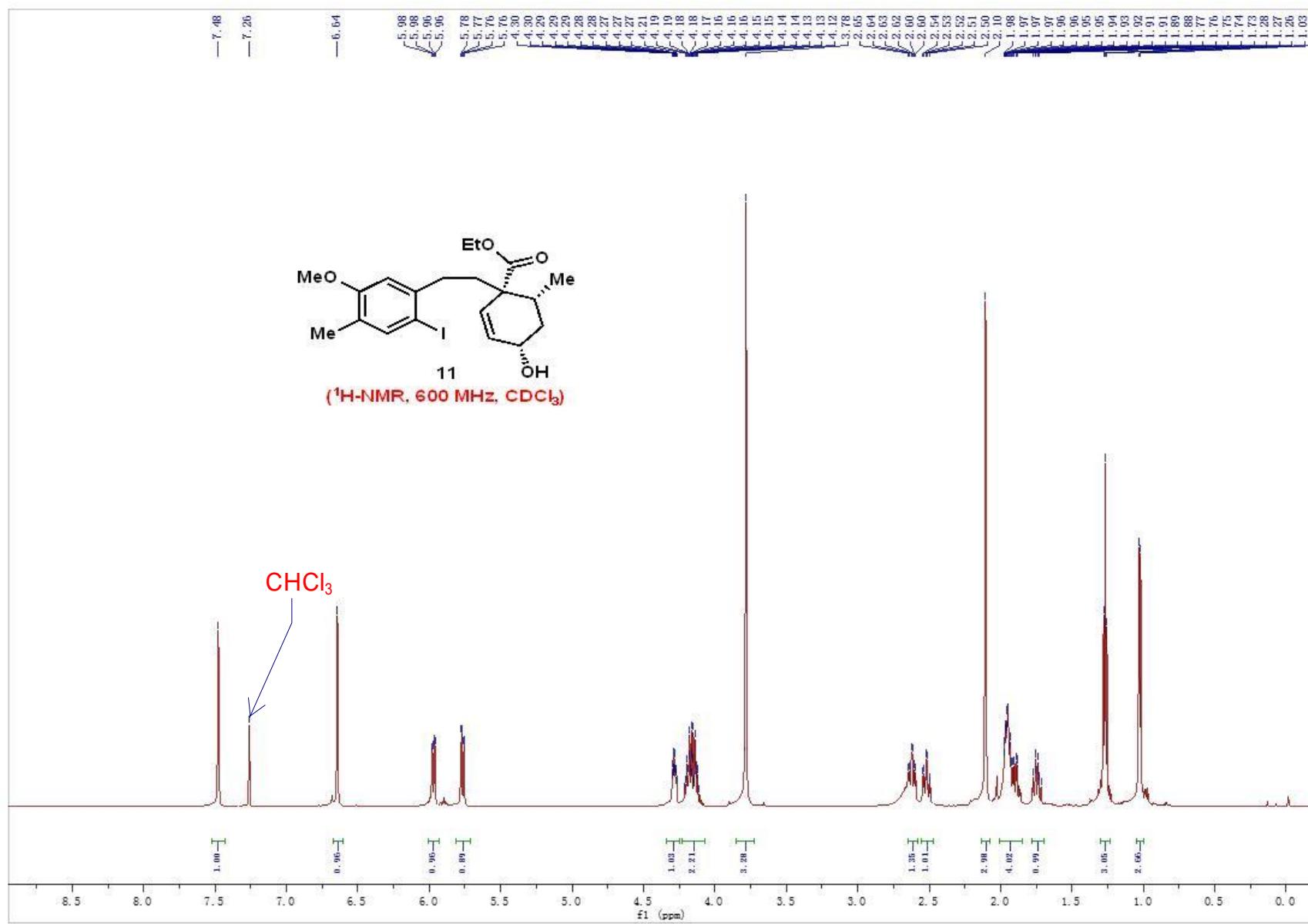


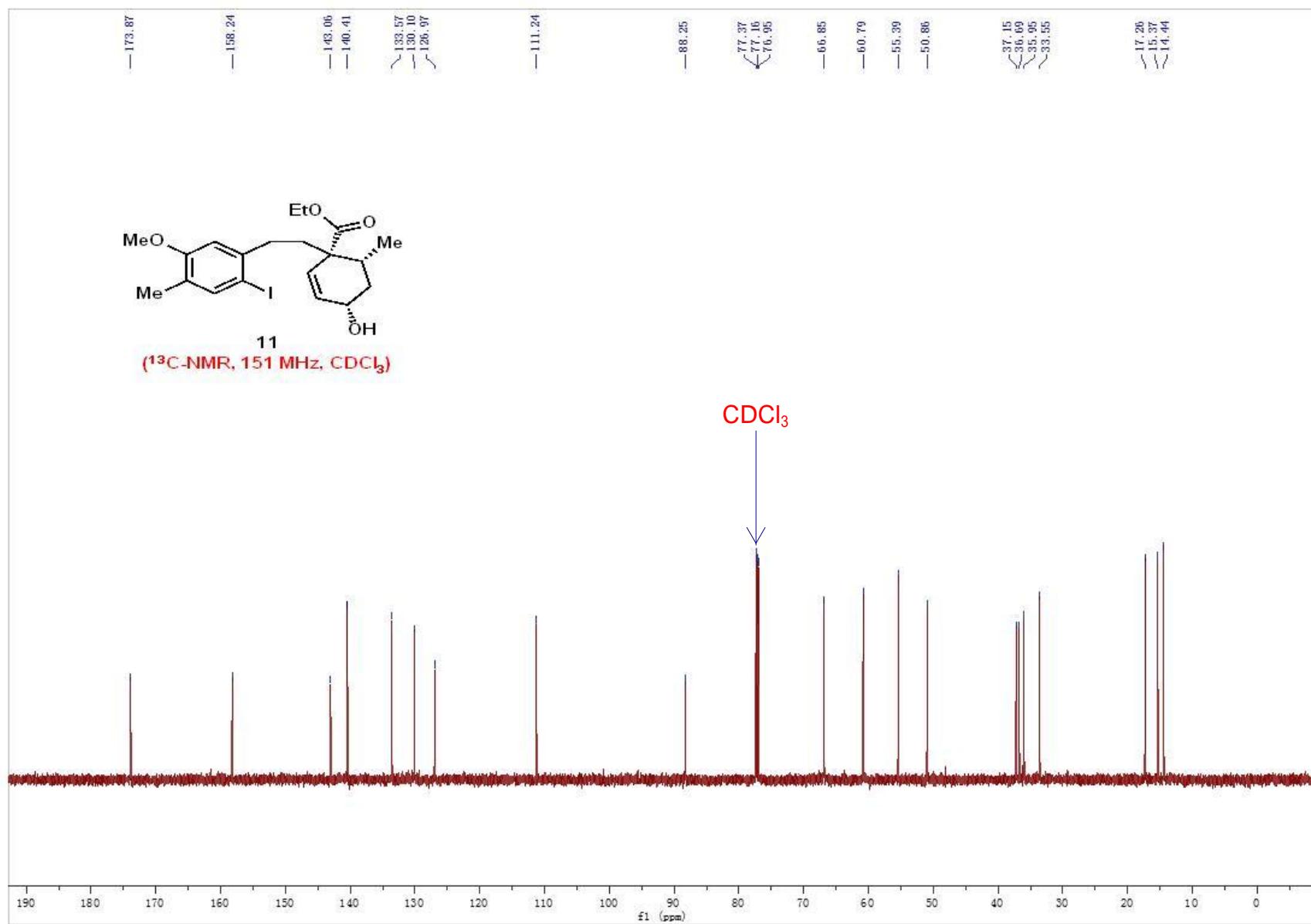
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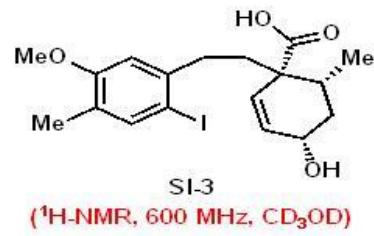
(<sup>1</sup>H-NMR, 600 MHz, CDCl<sub>3</sub>)



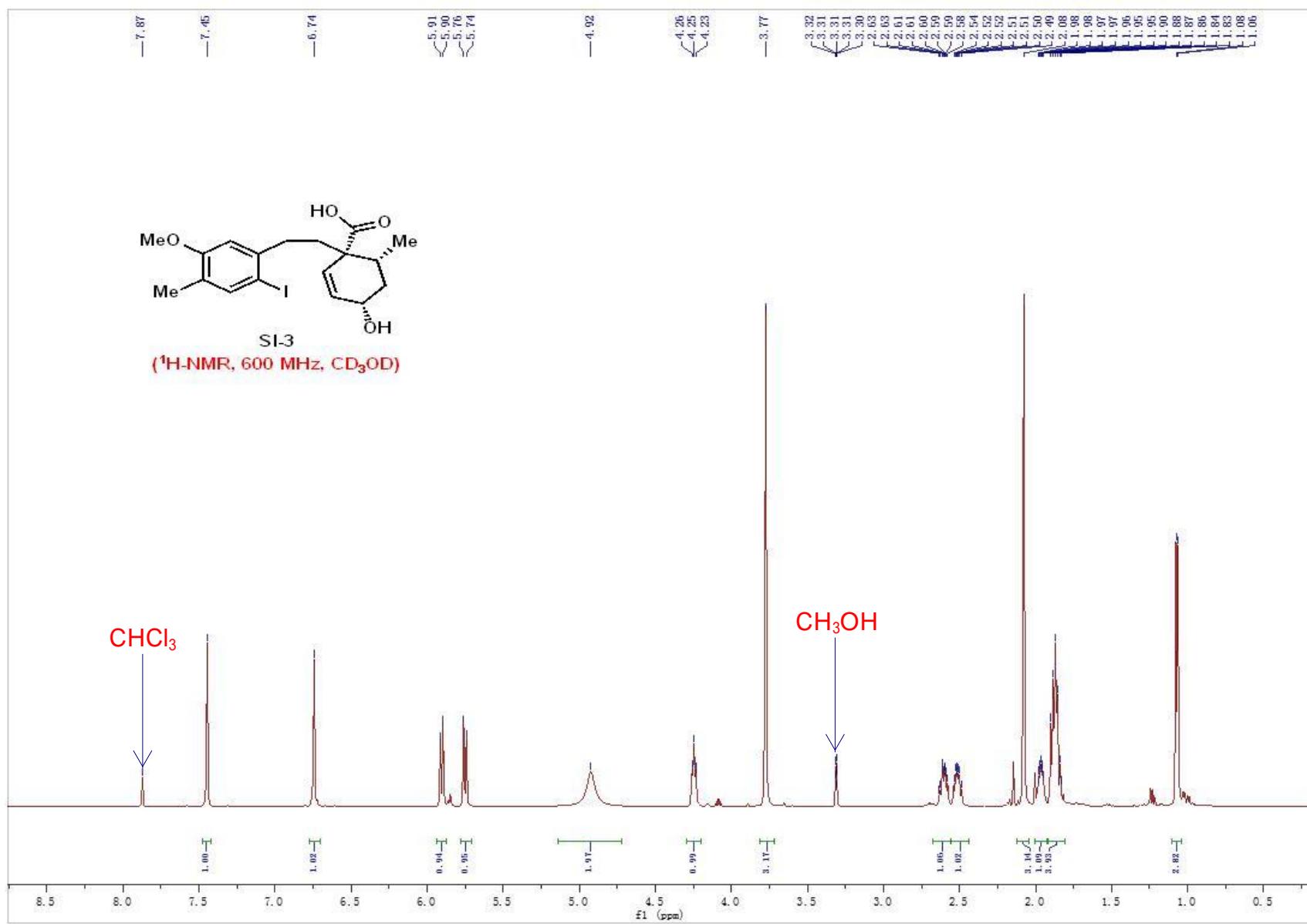


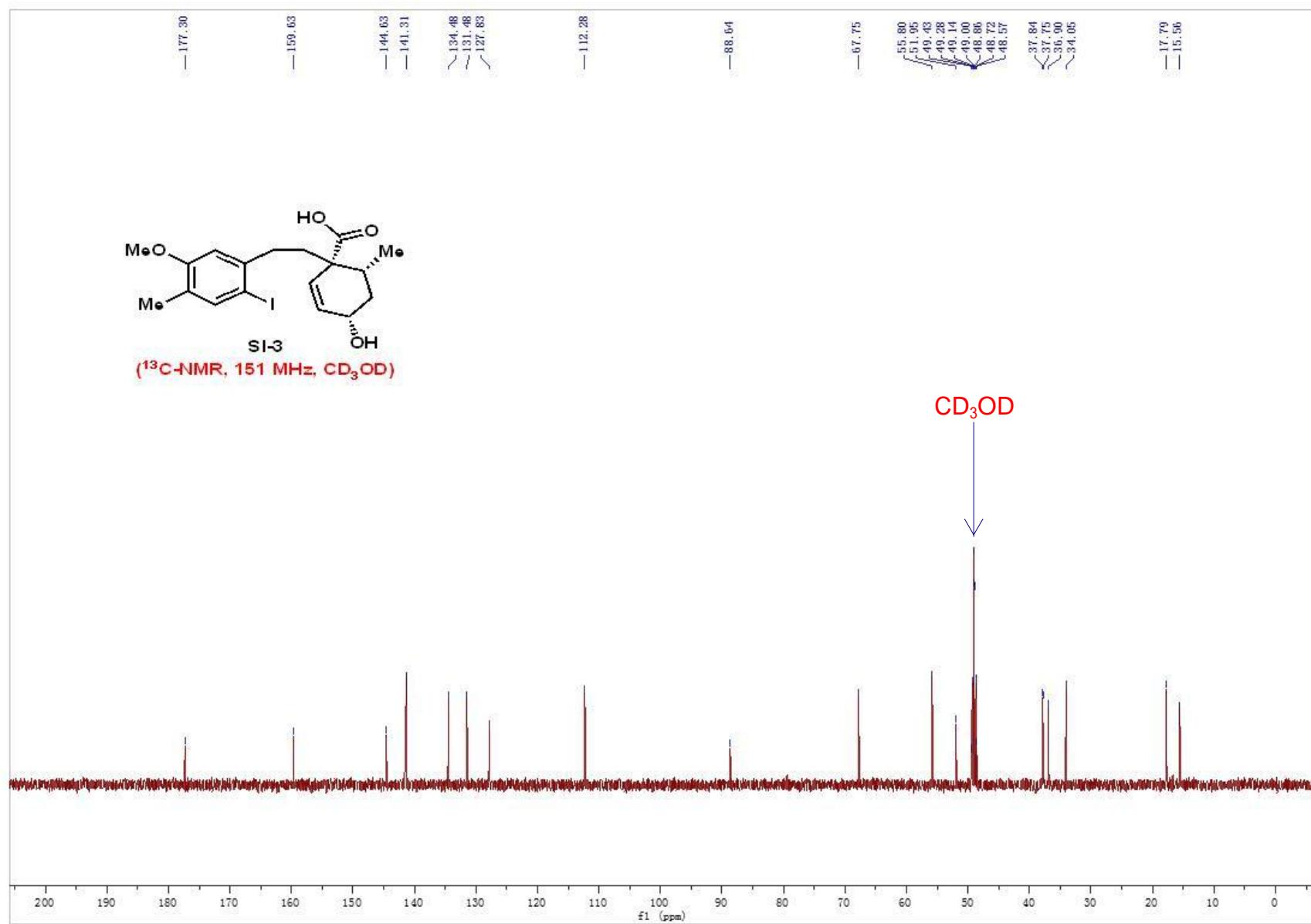


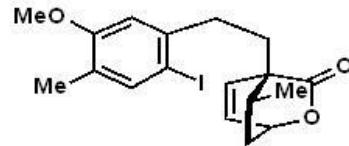




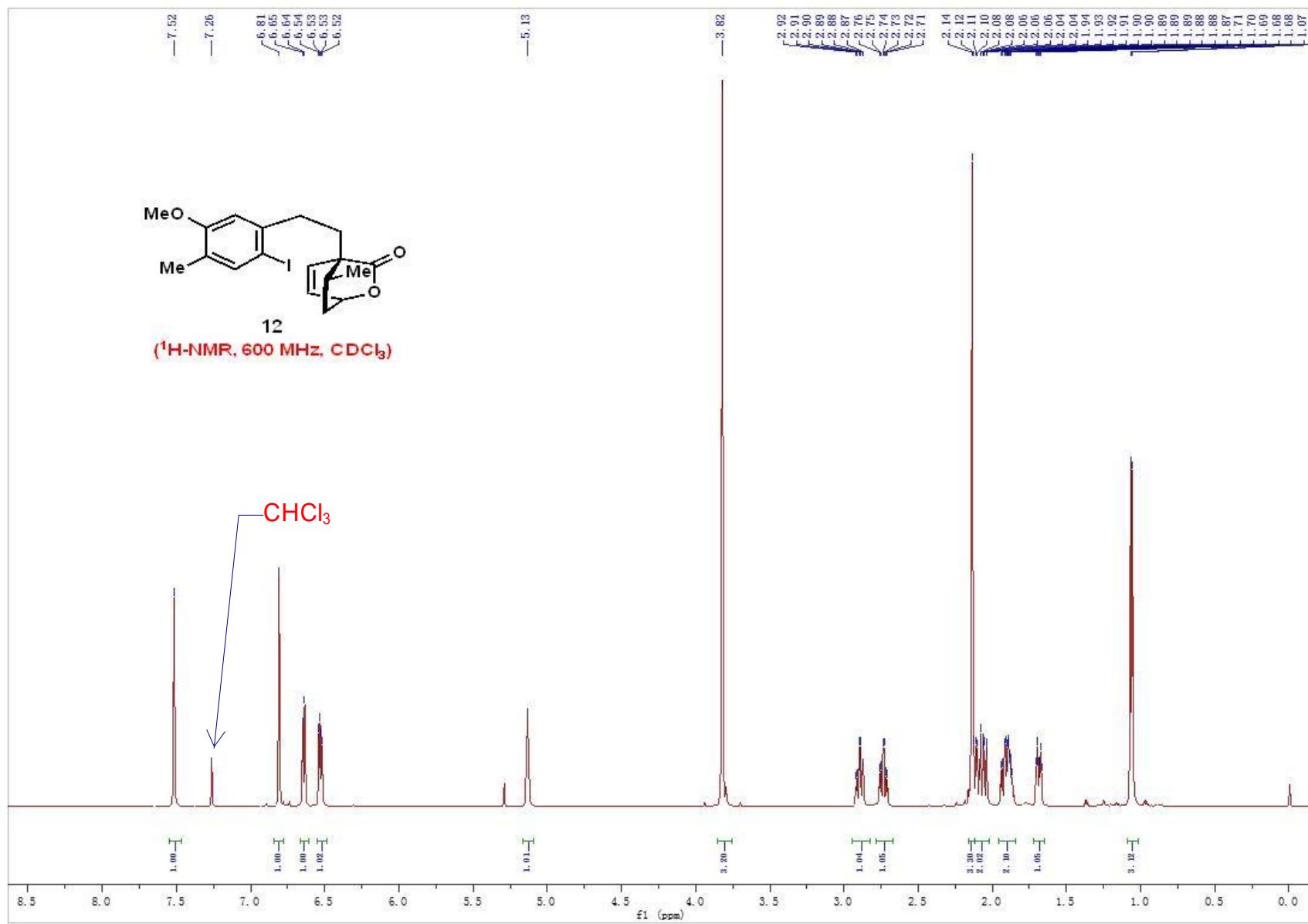
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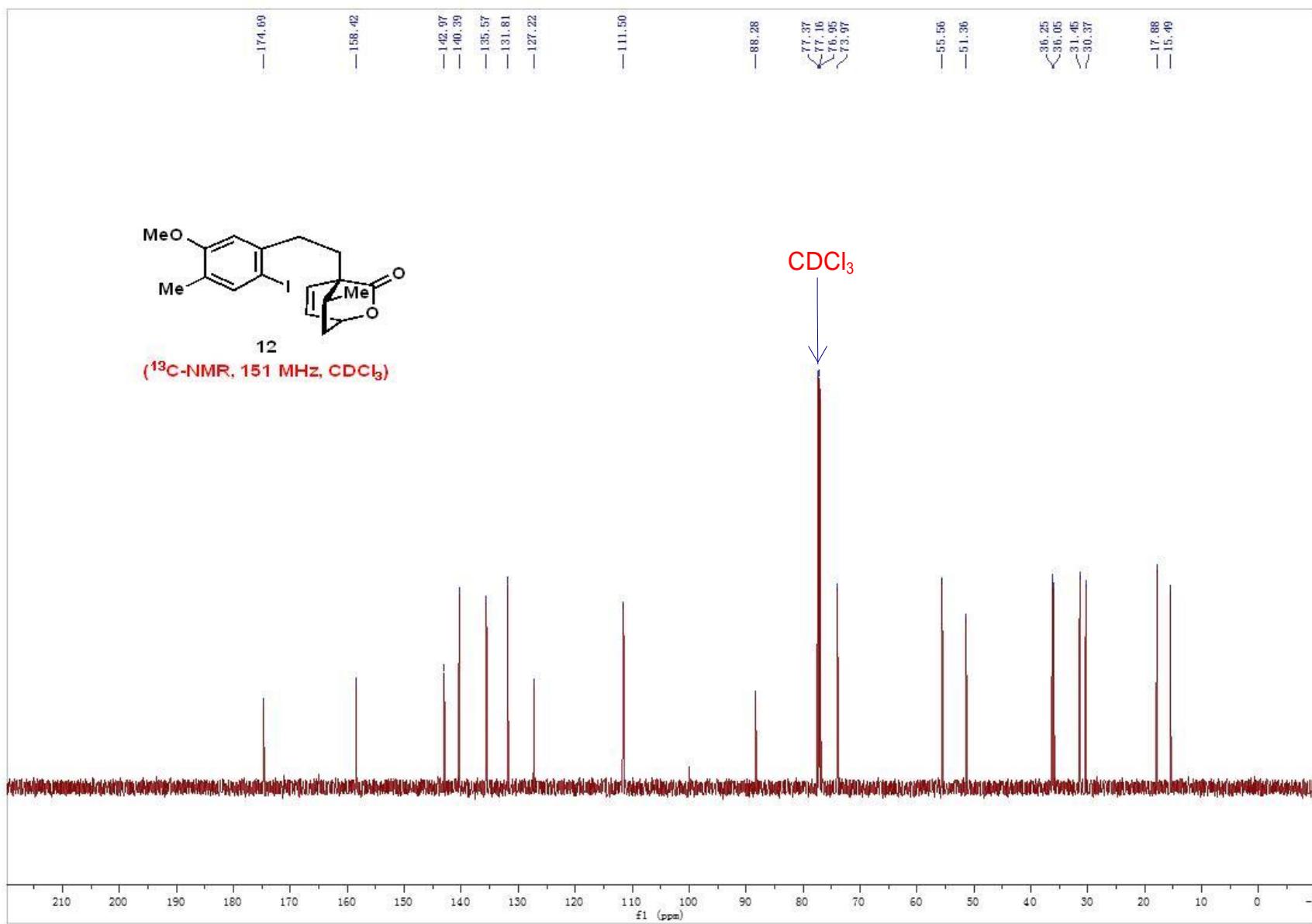


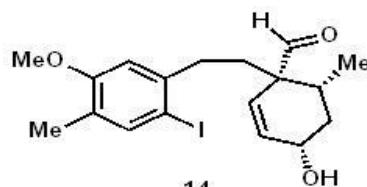




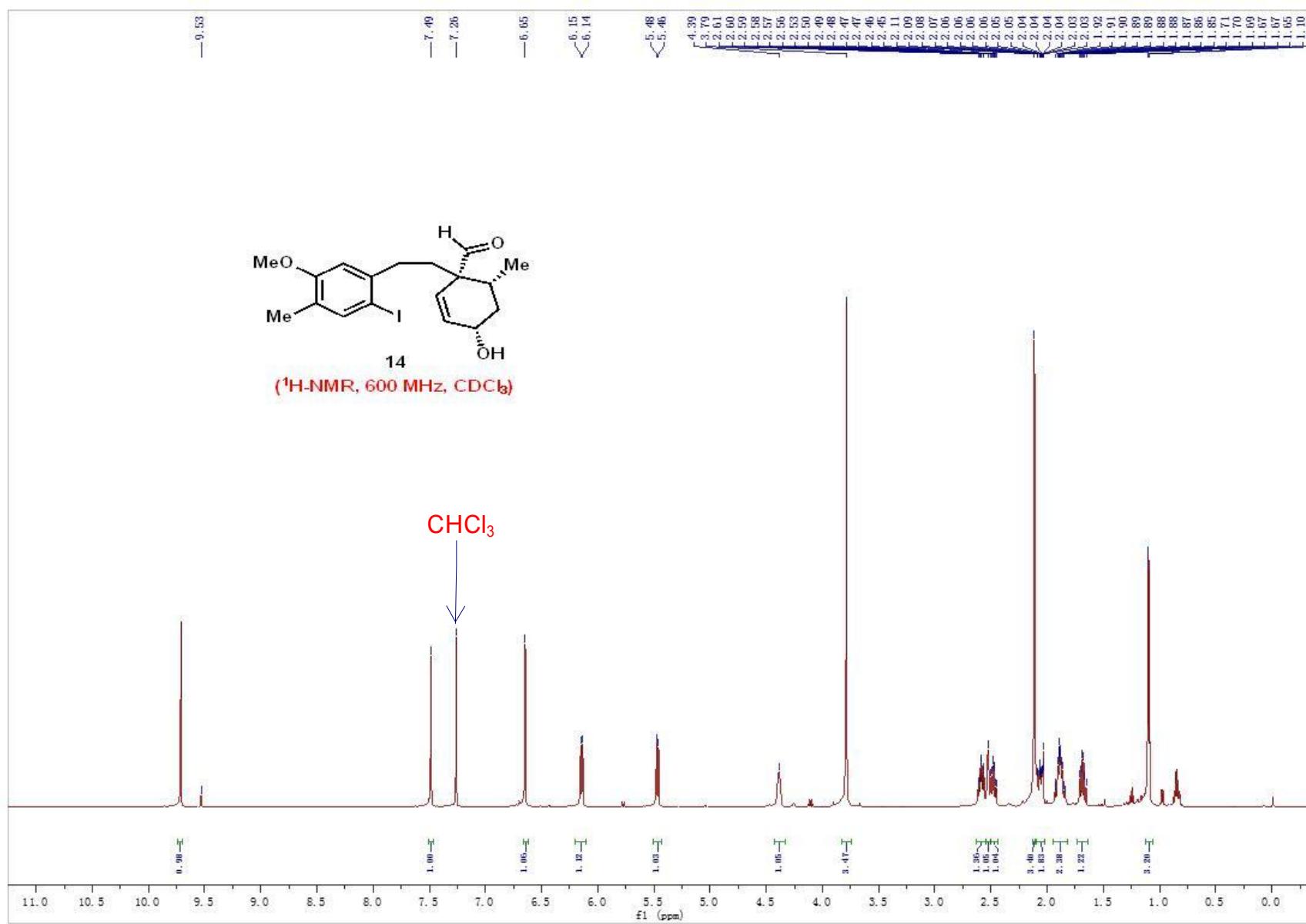
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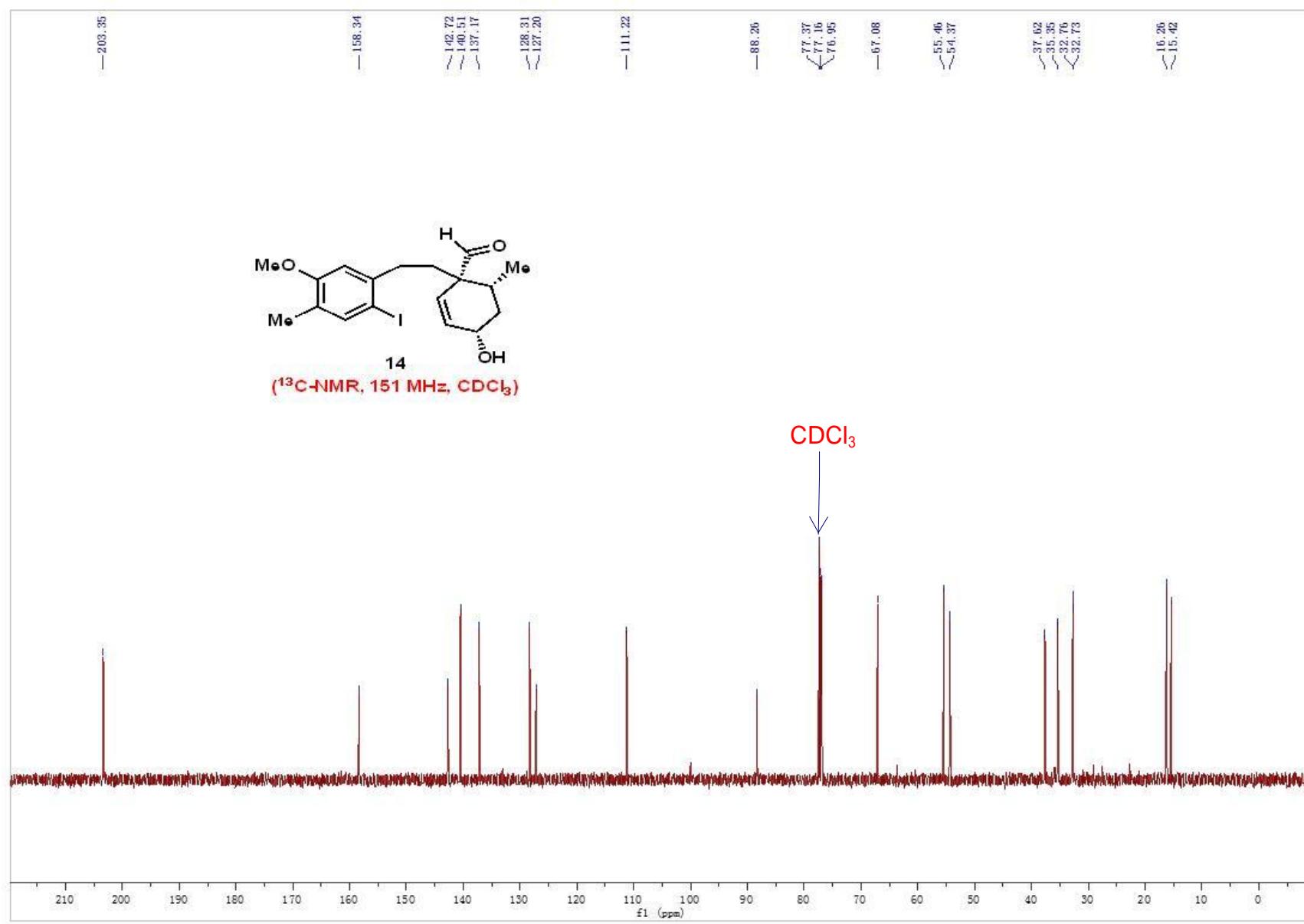


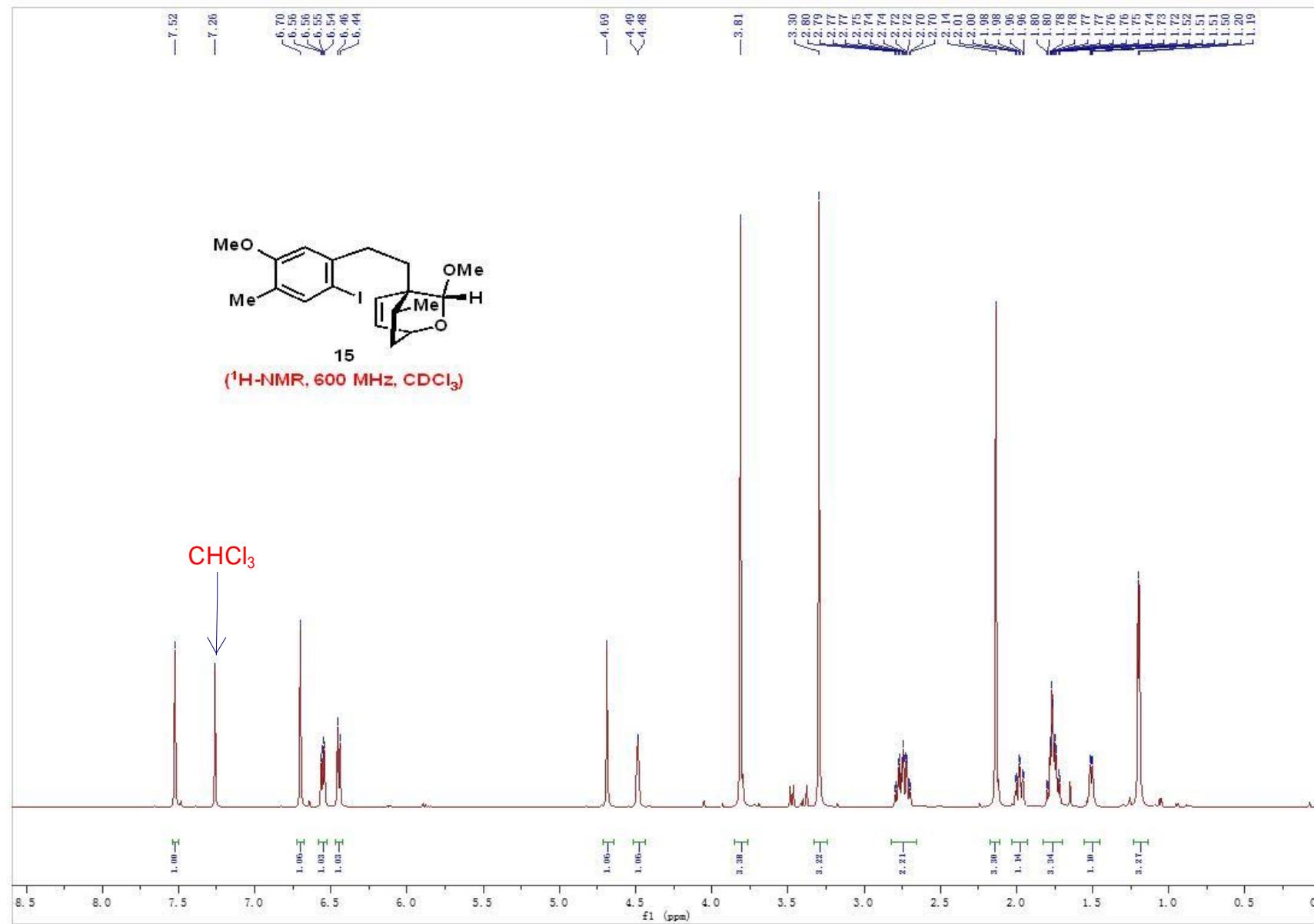


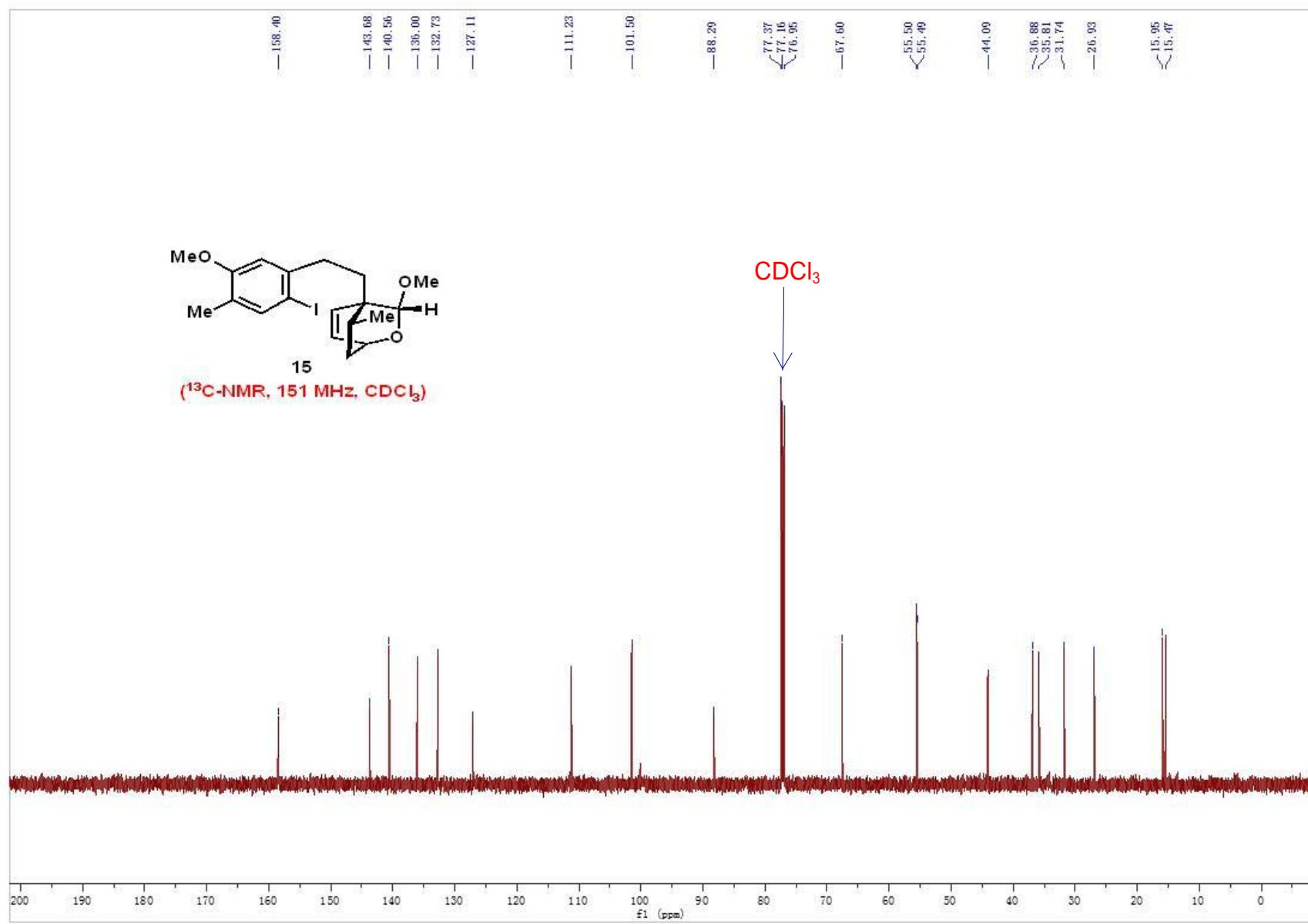


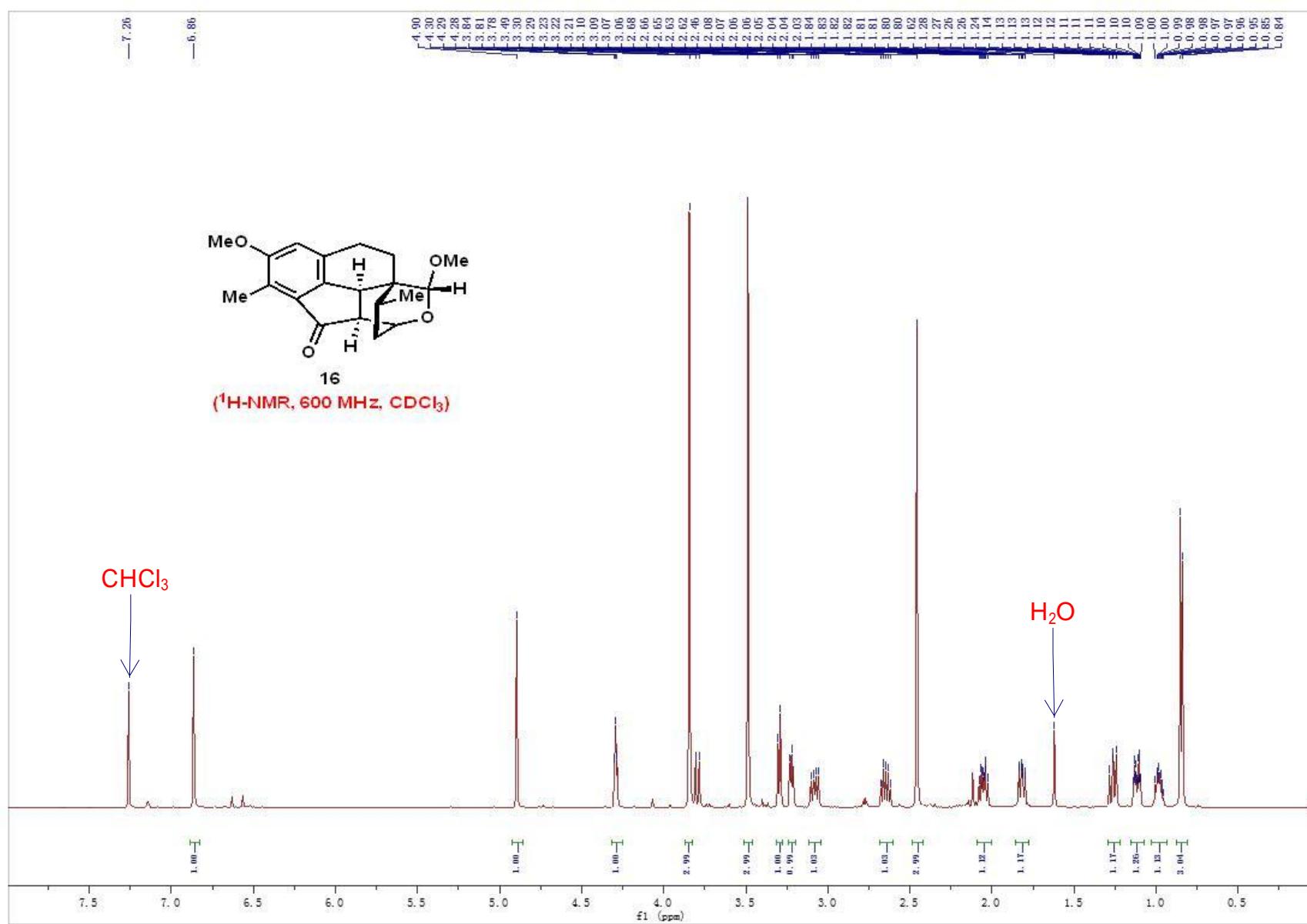
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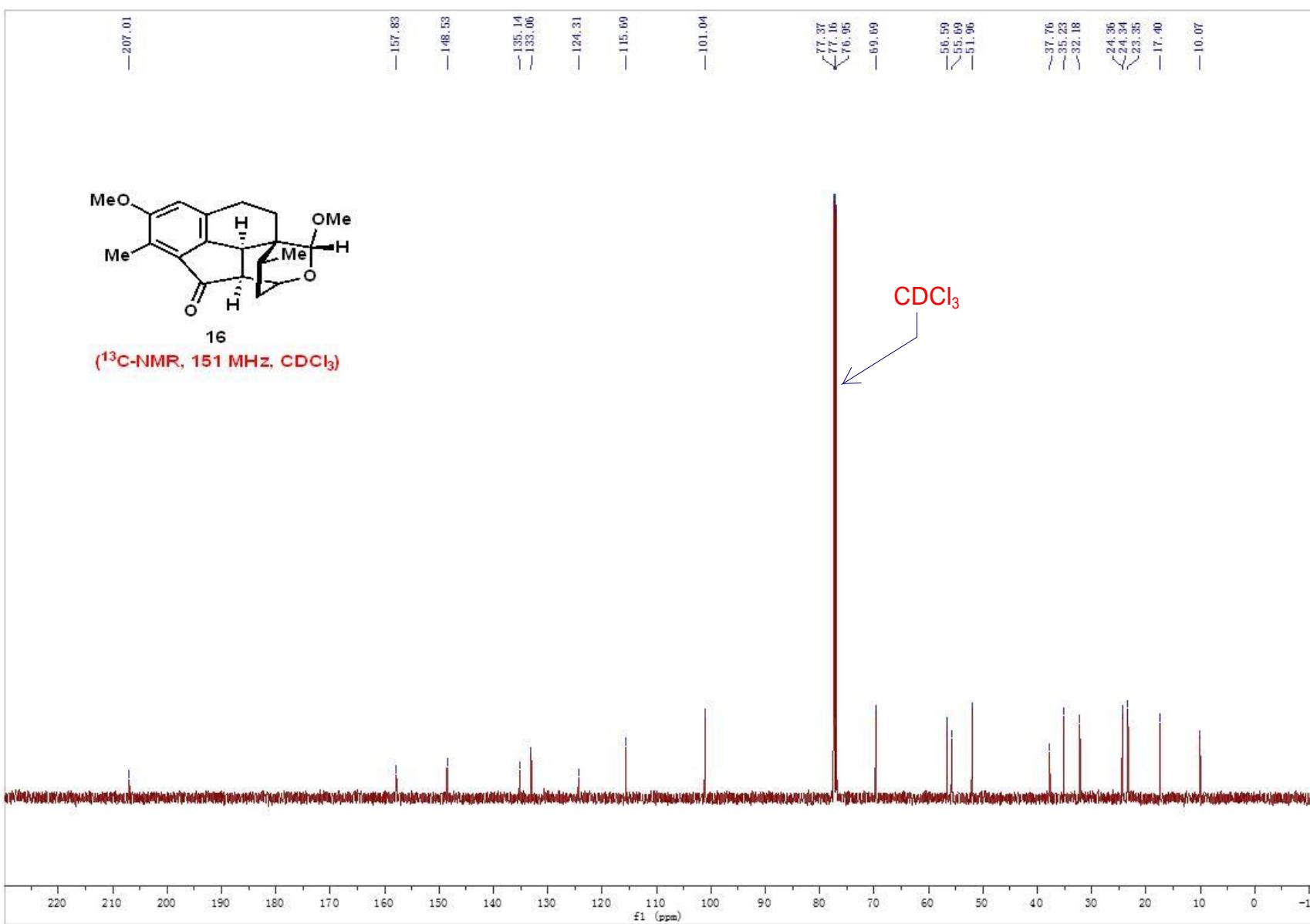


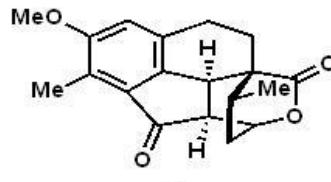




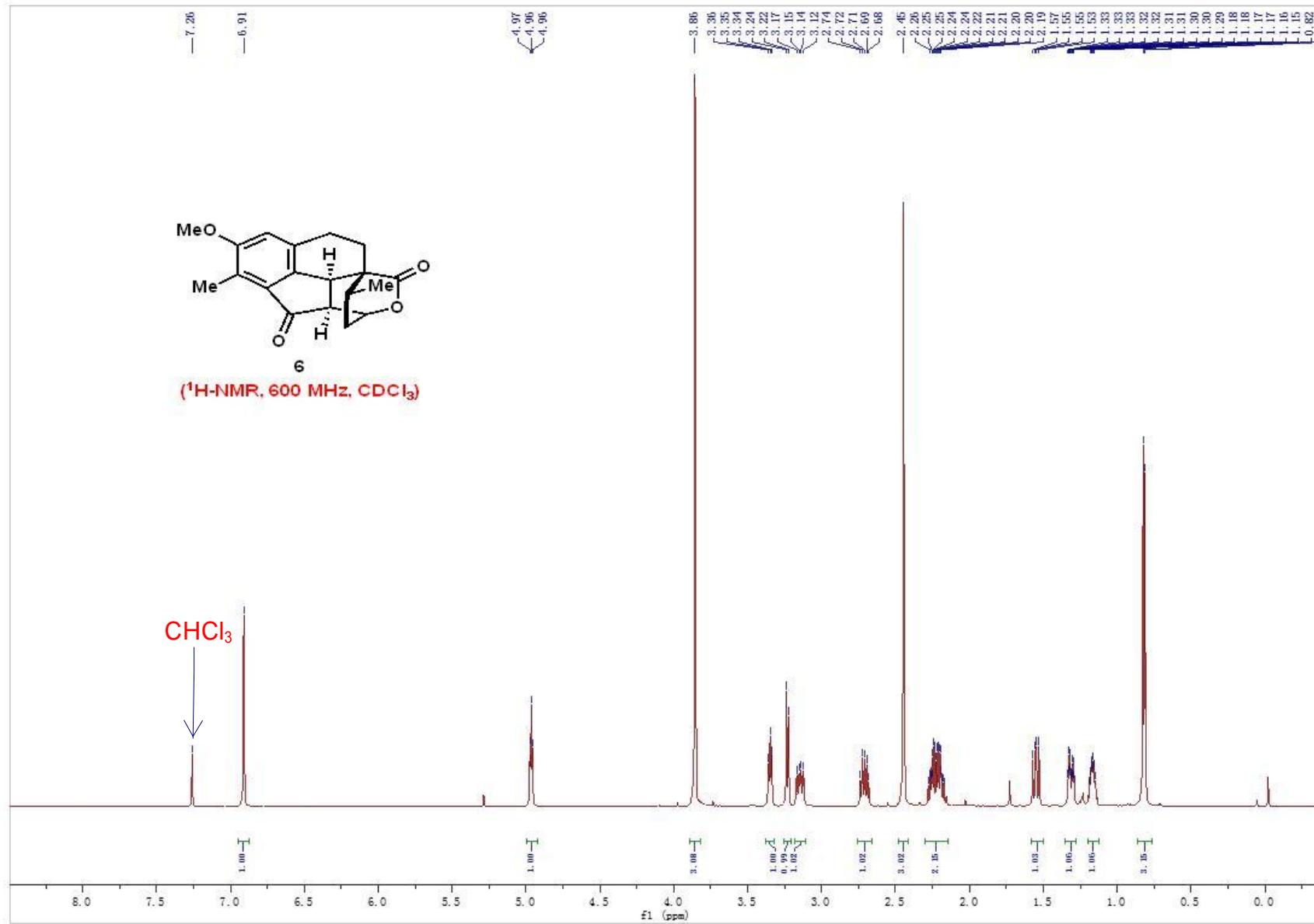


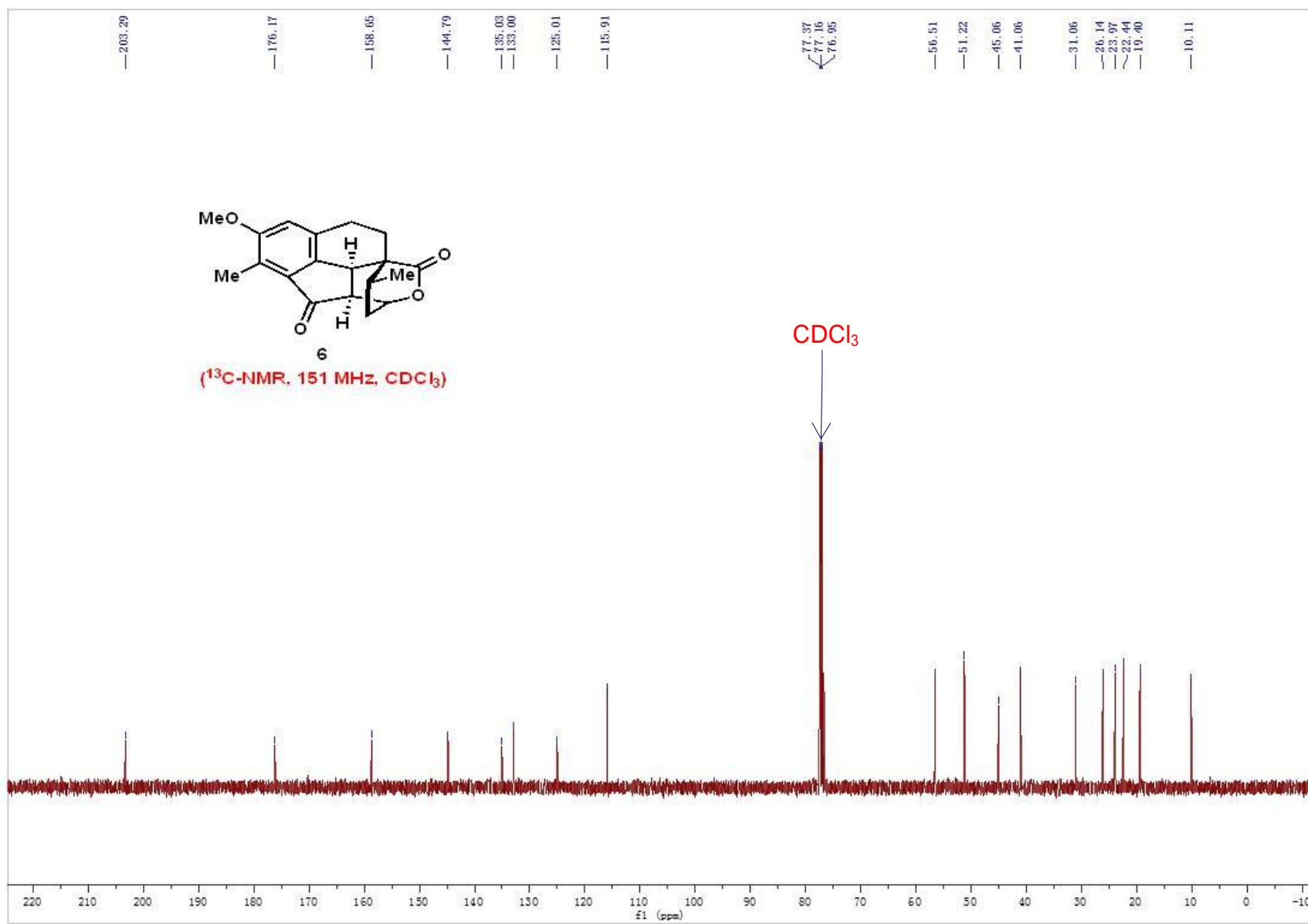


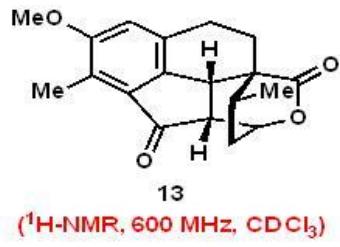




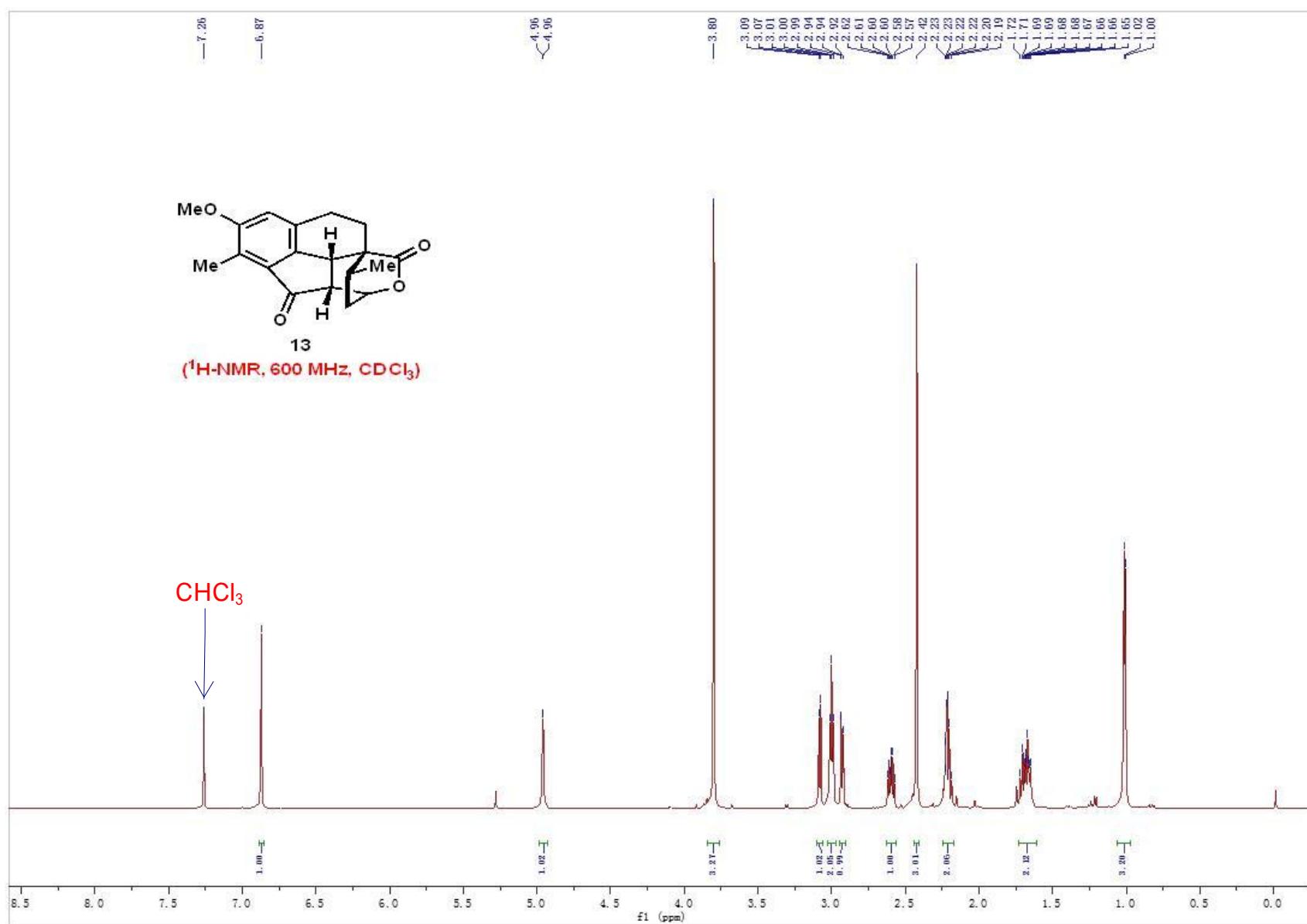
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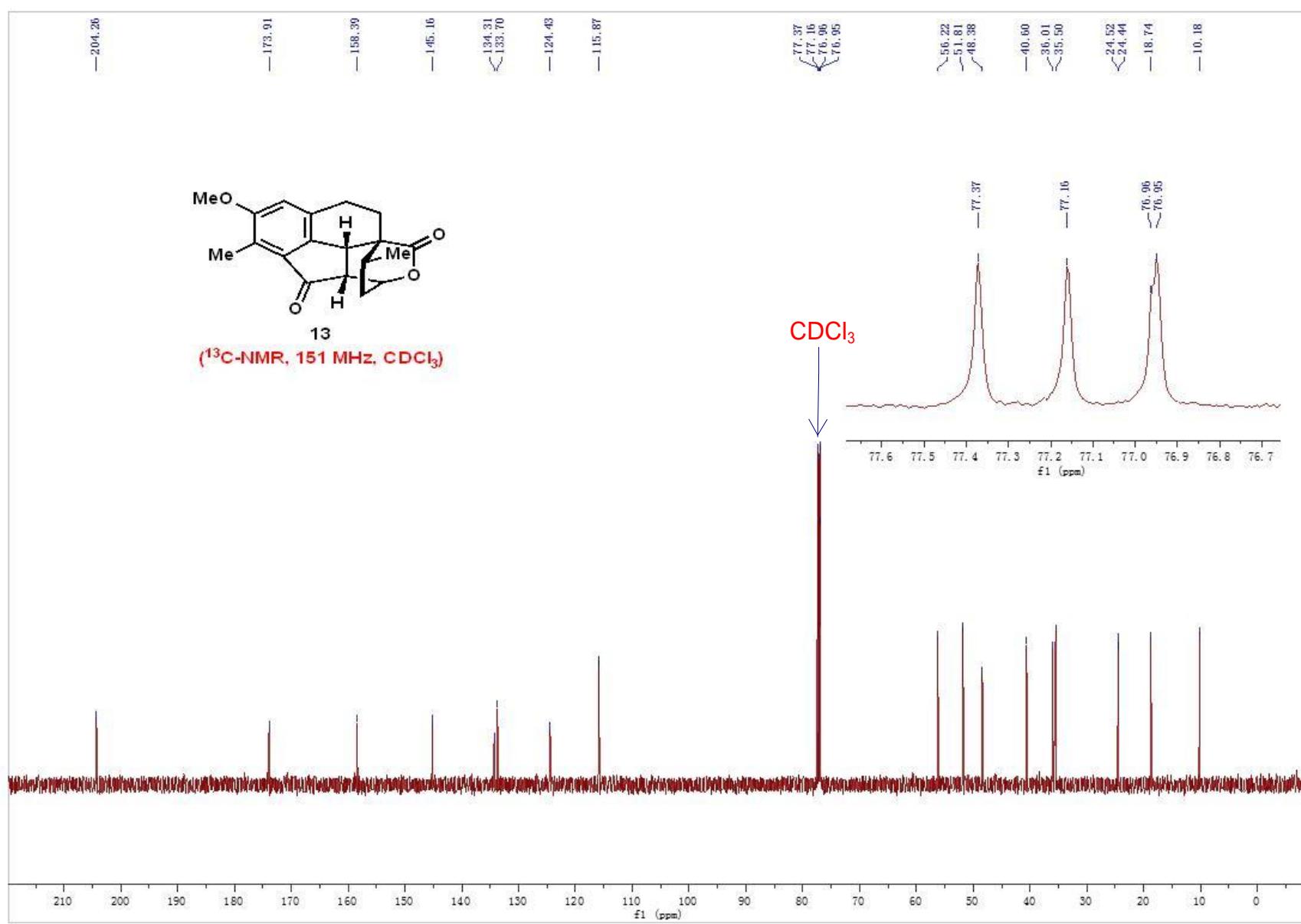


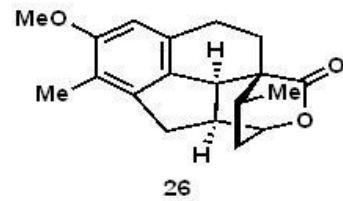




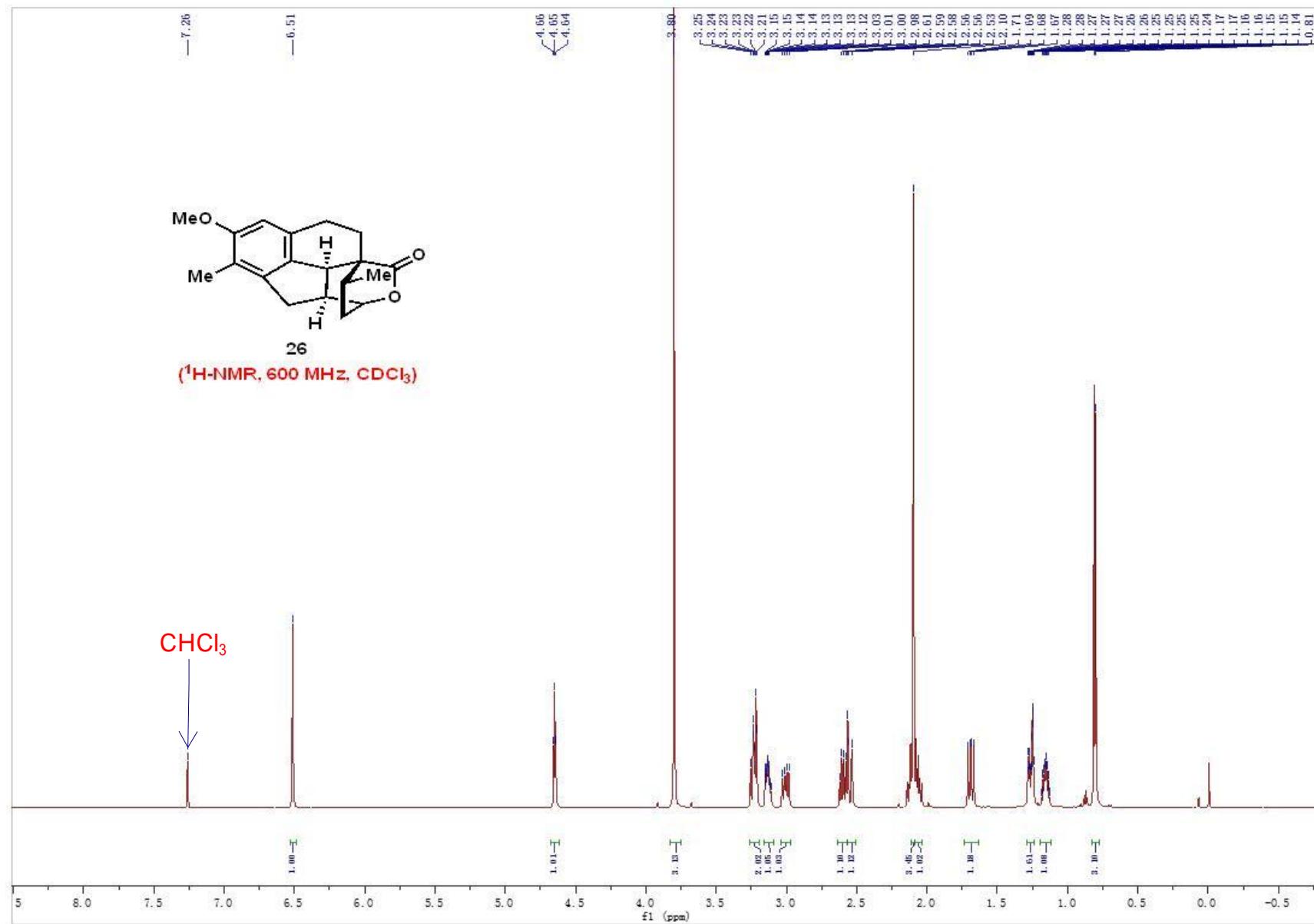
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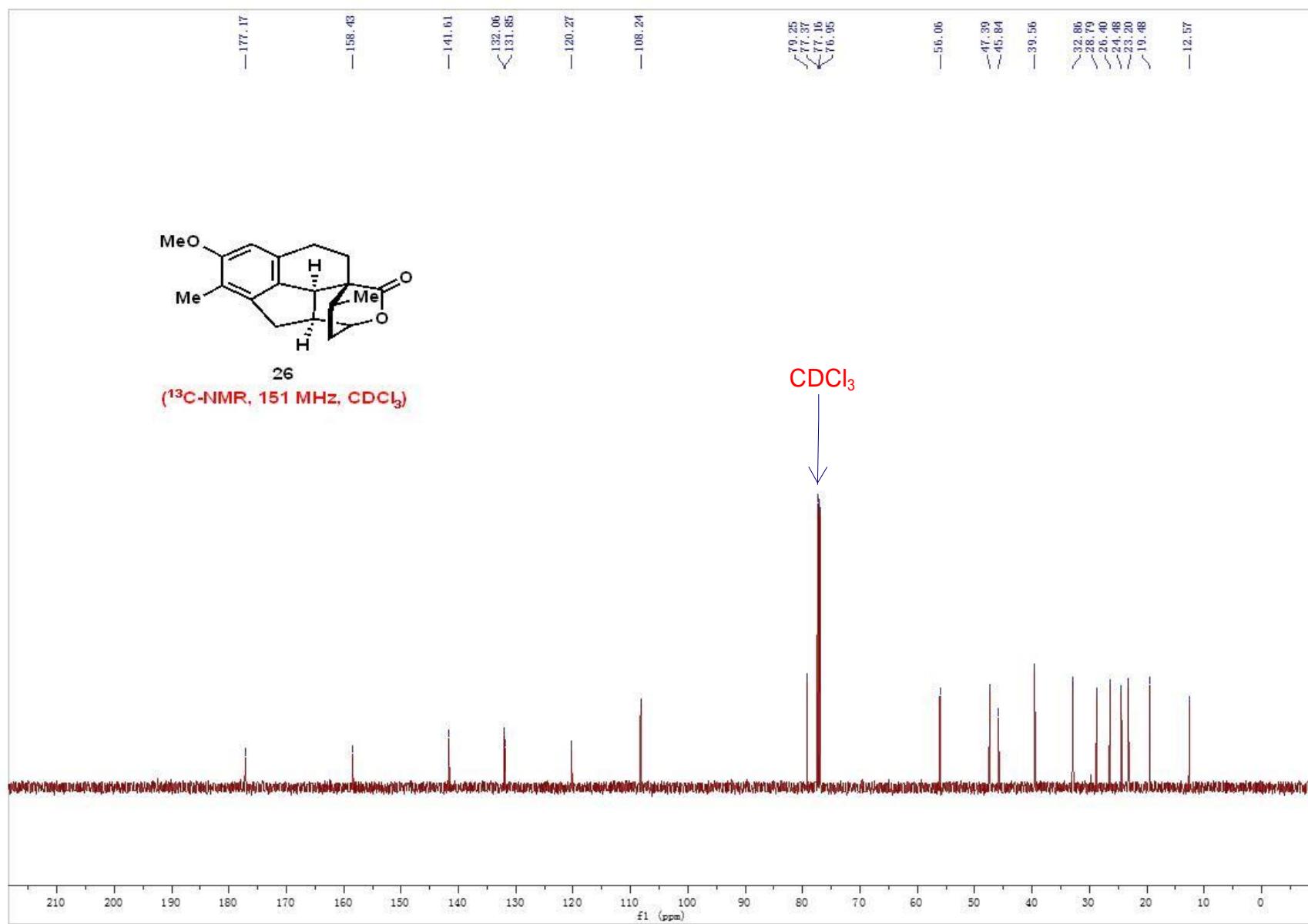


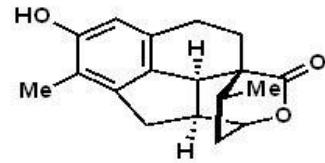




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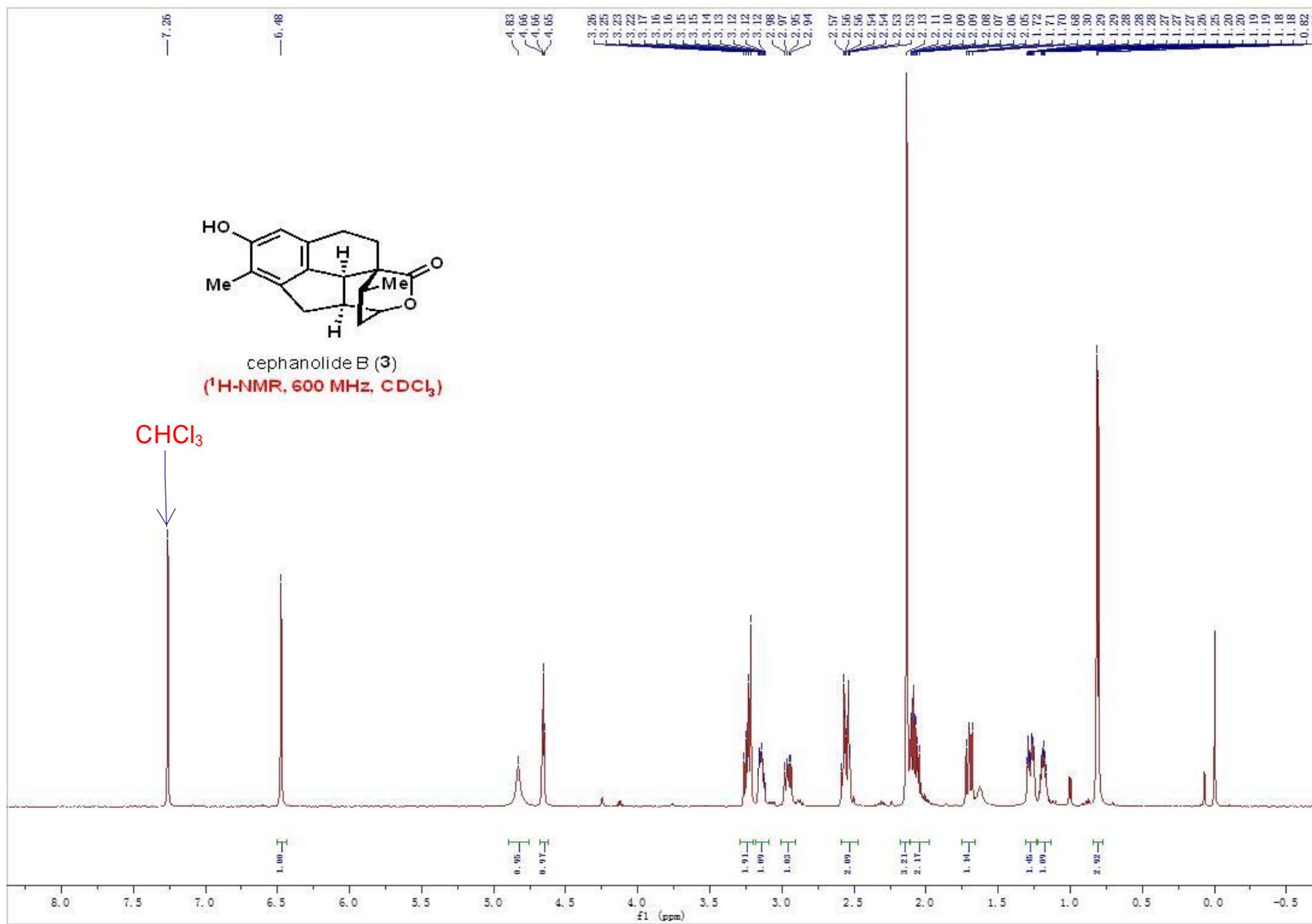


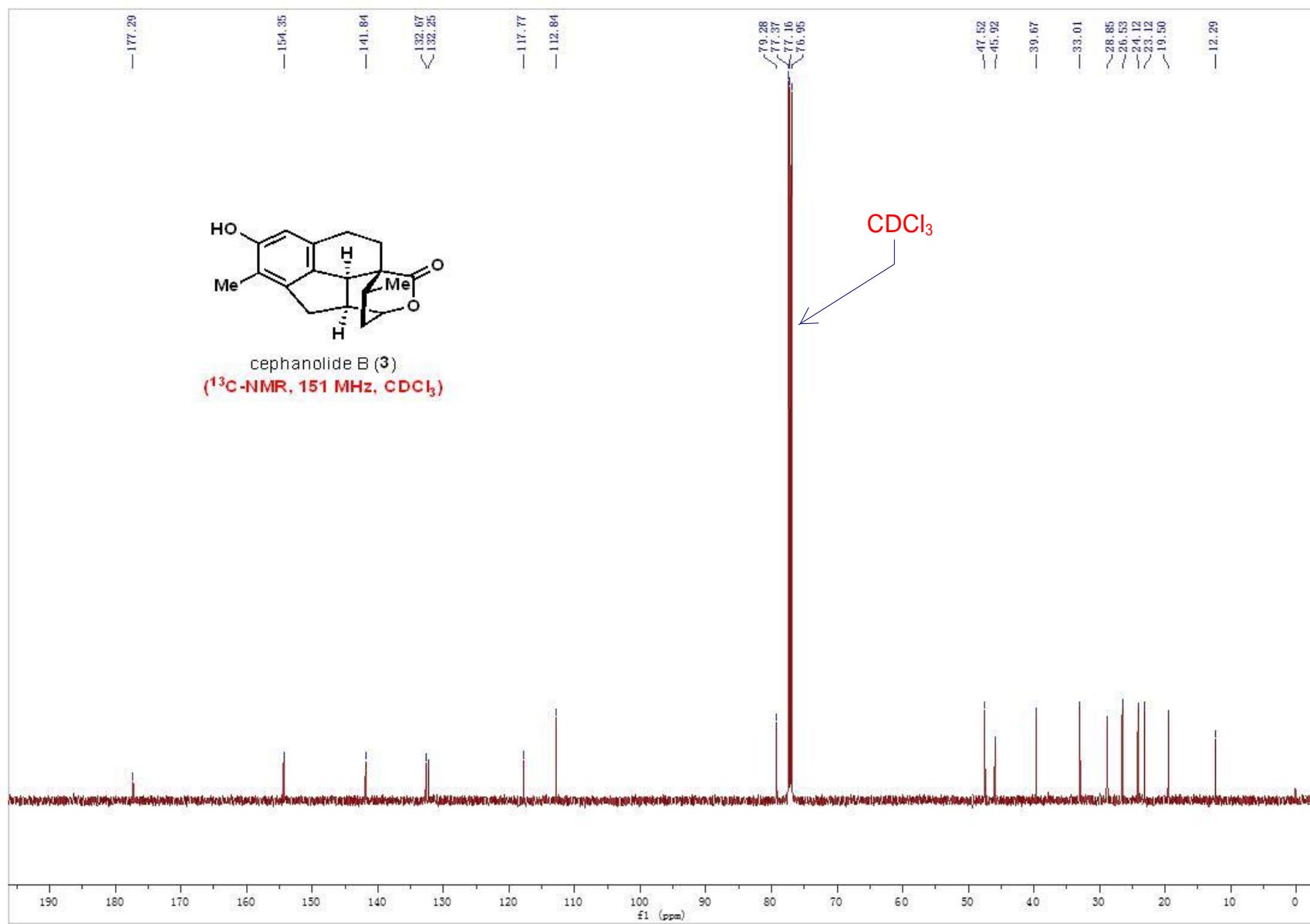


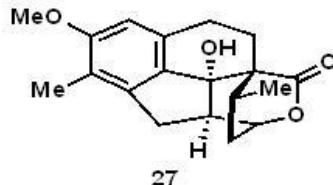


cephanolide B (**3**)  
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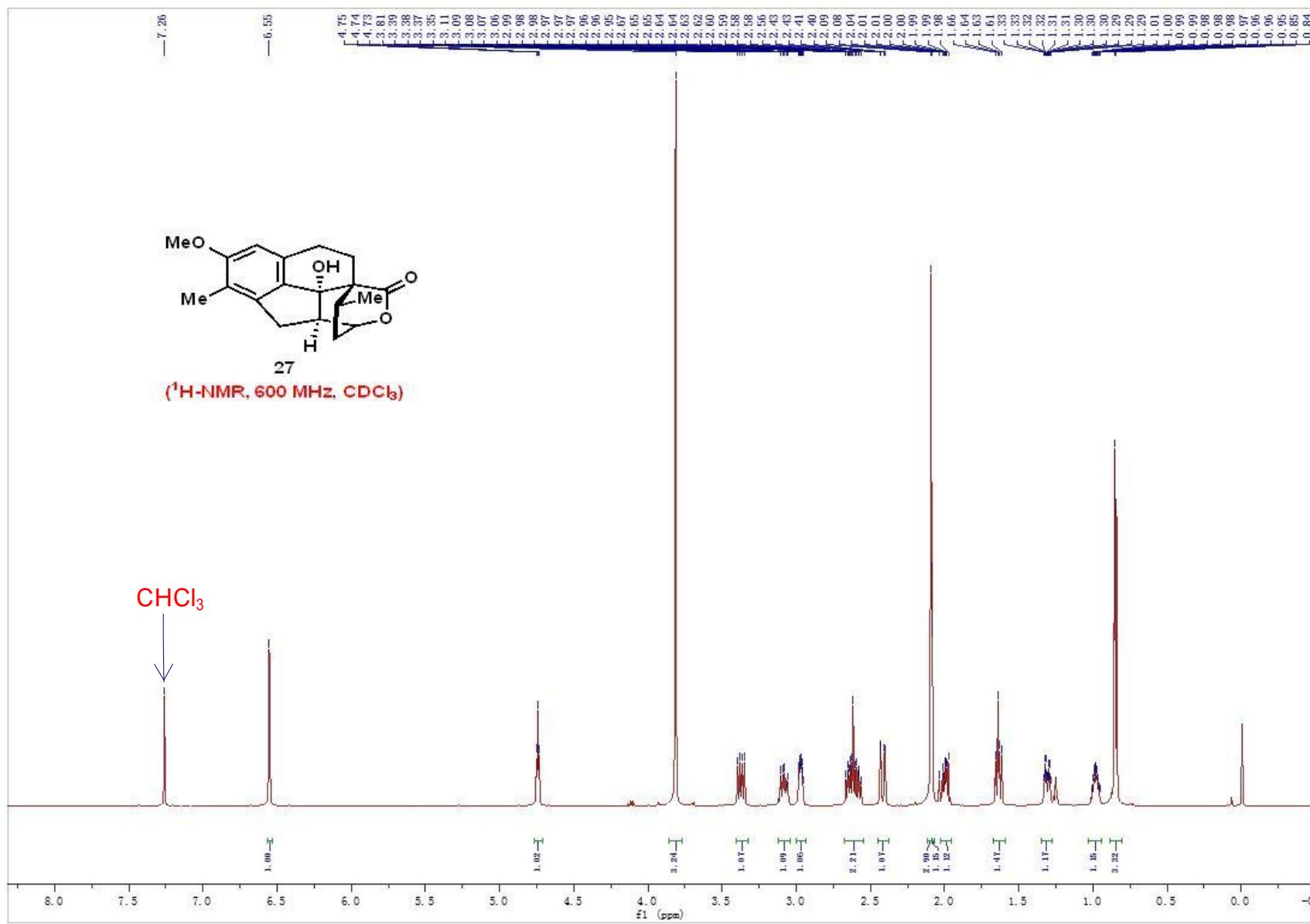
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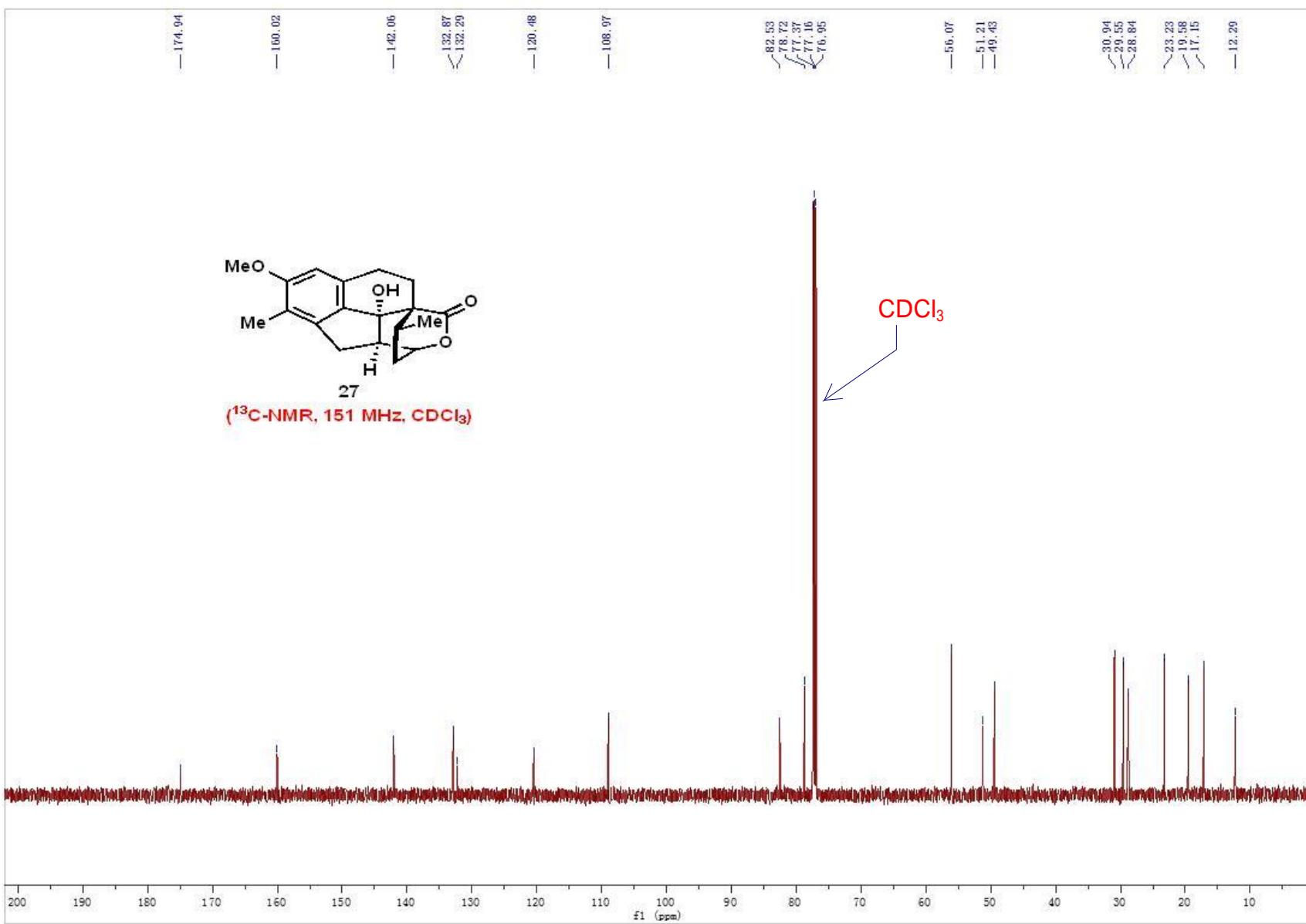


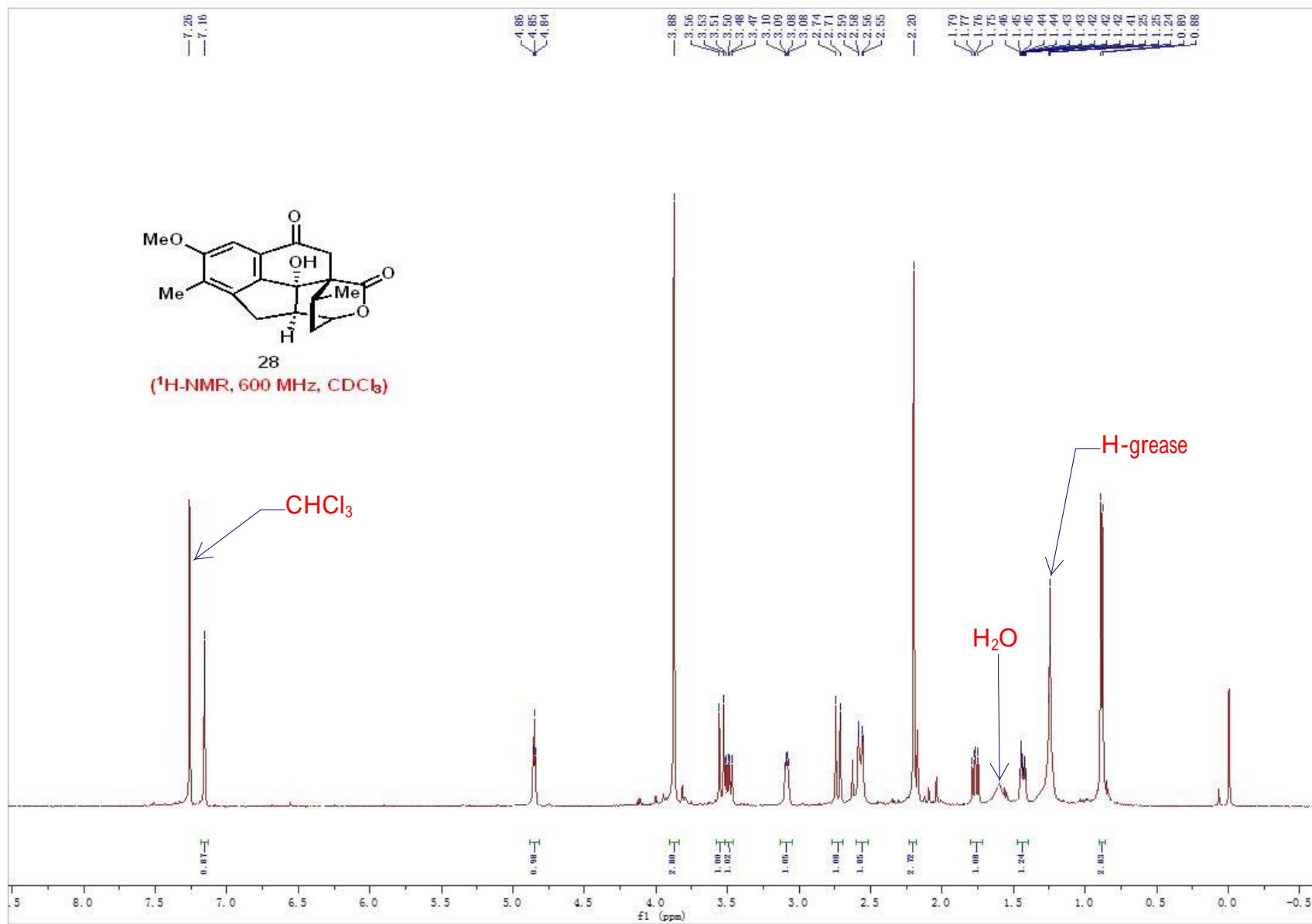


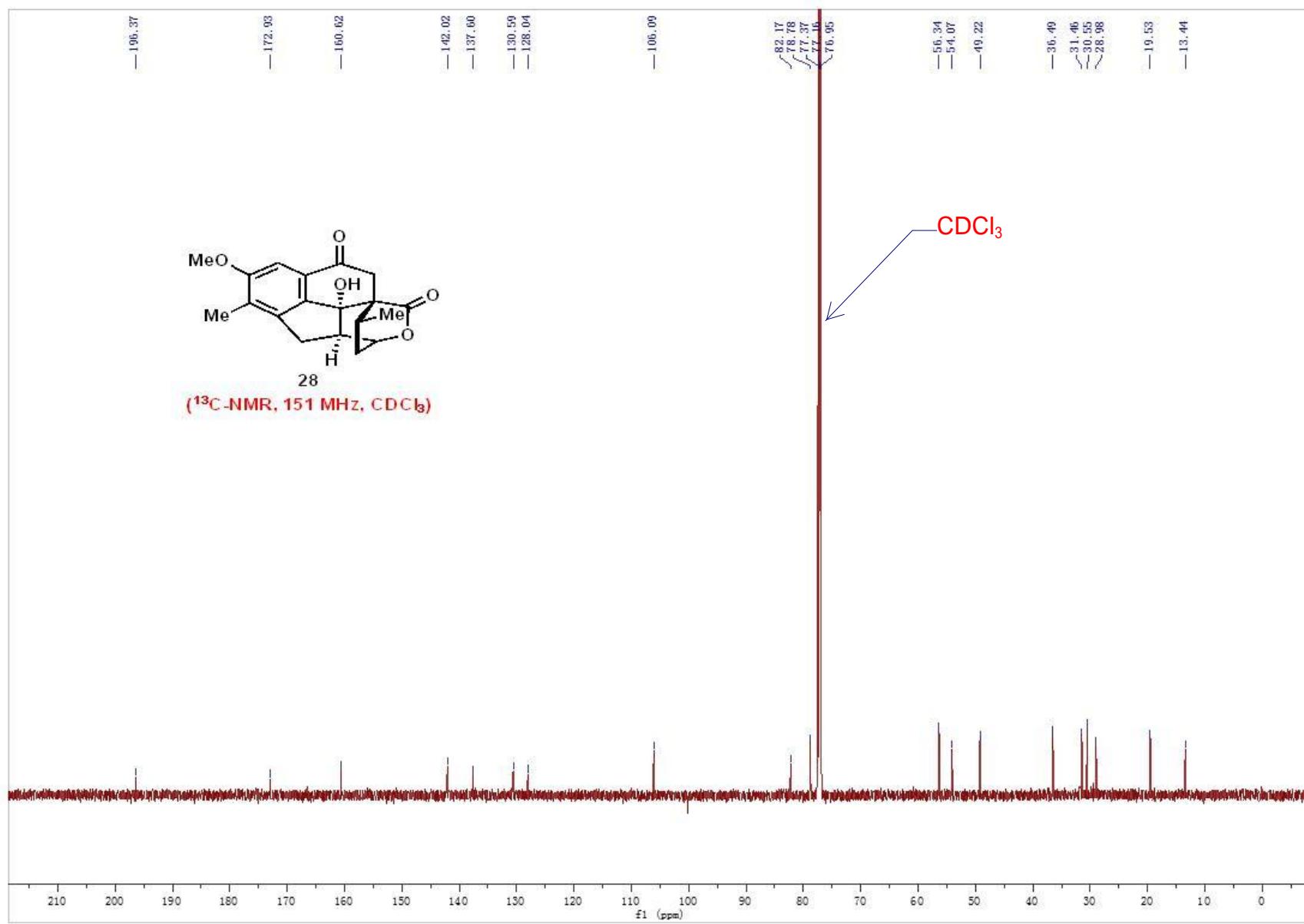


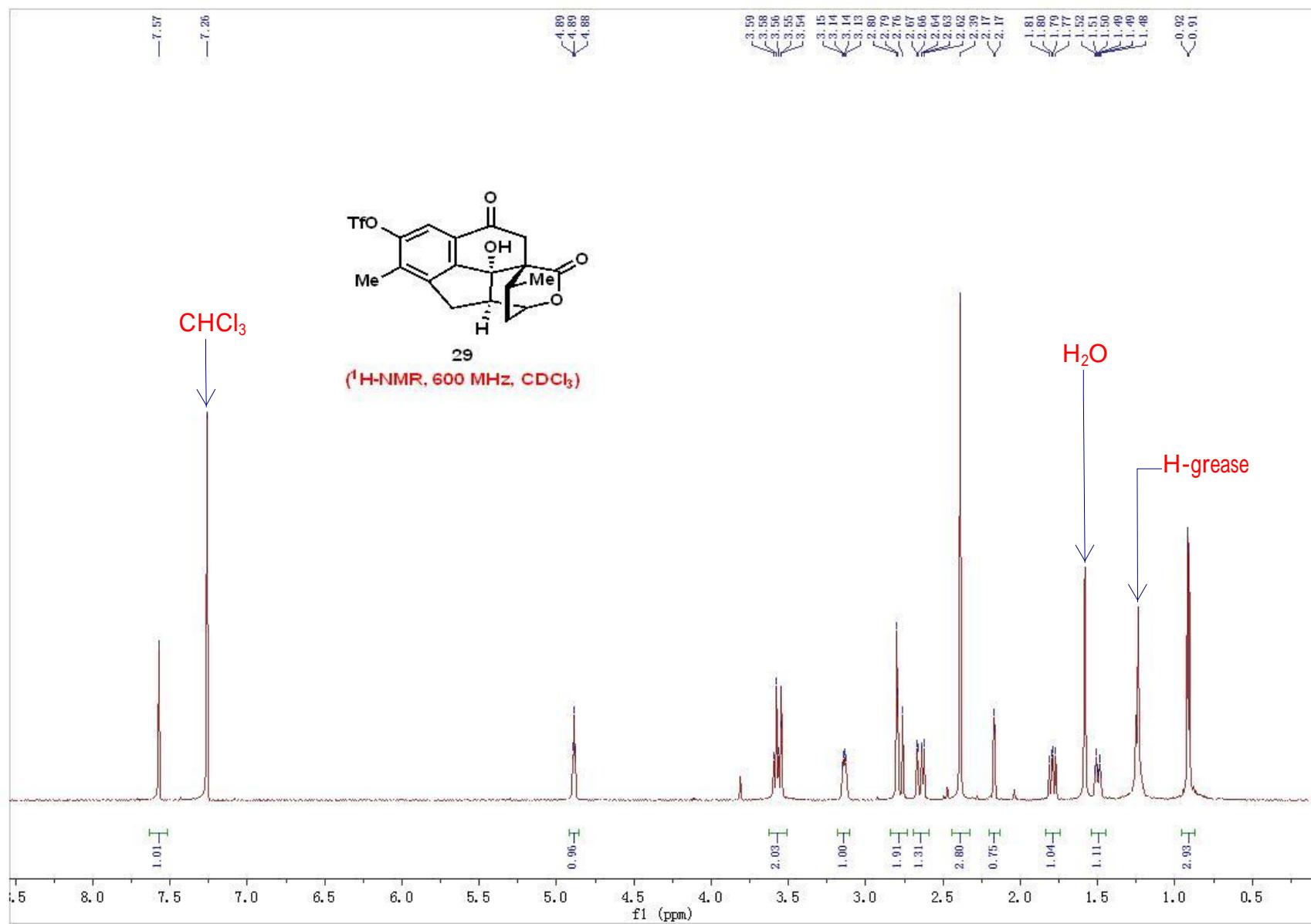
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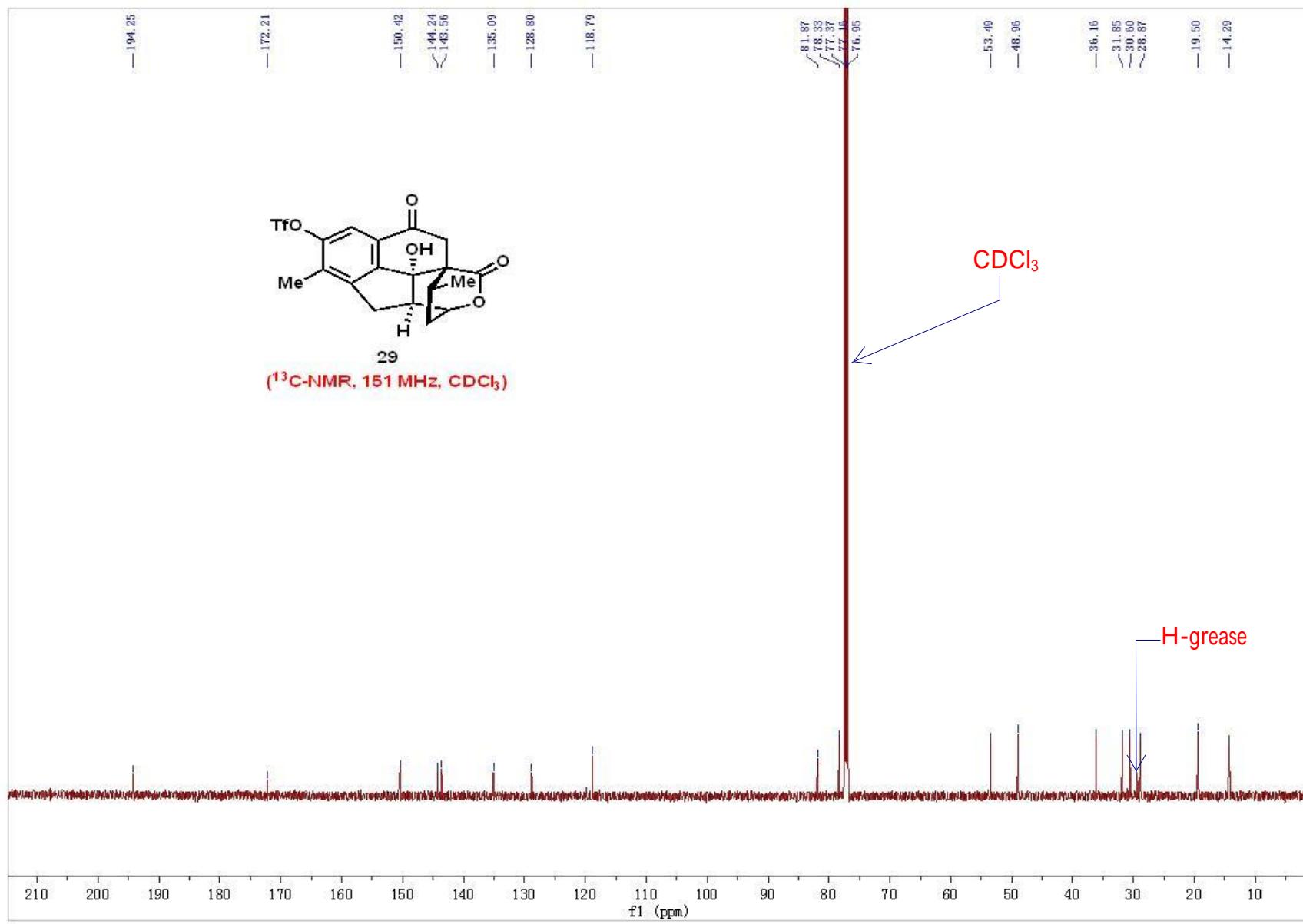


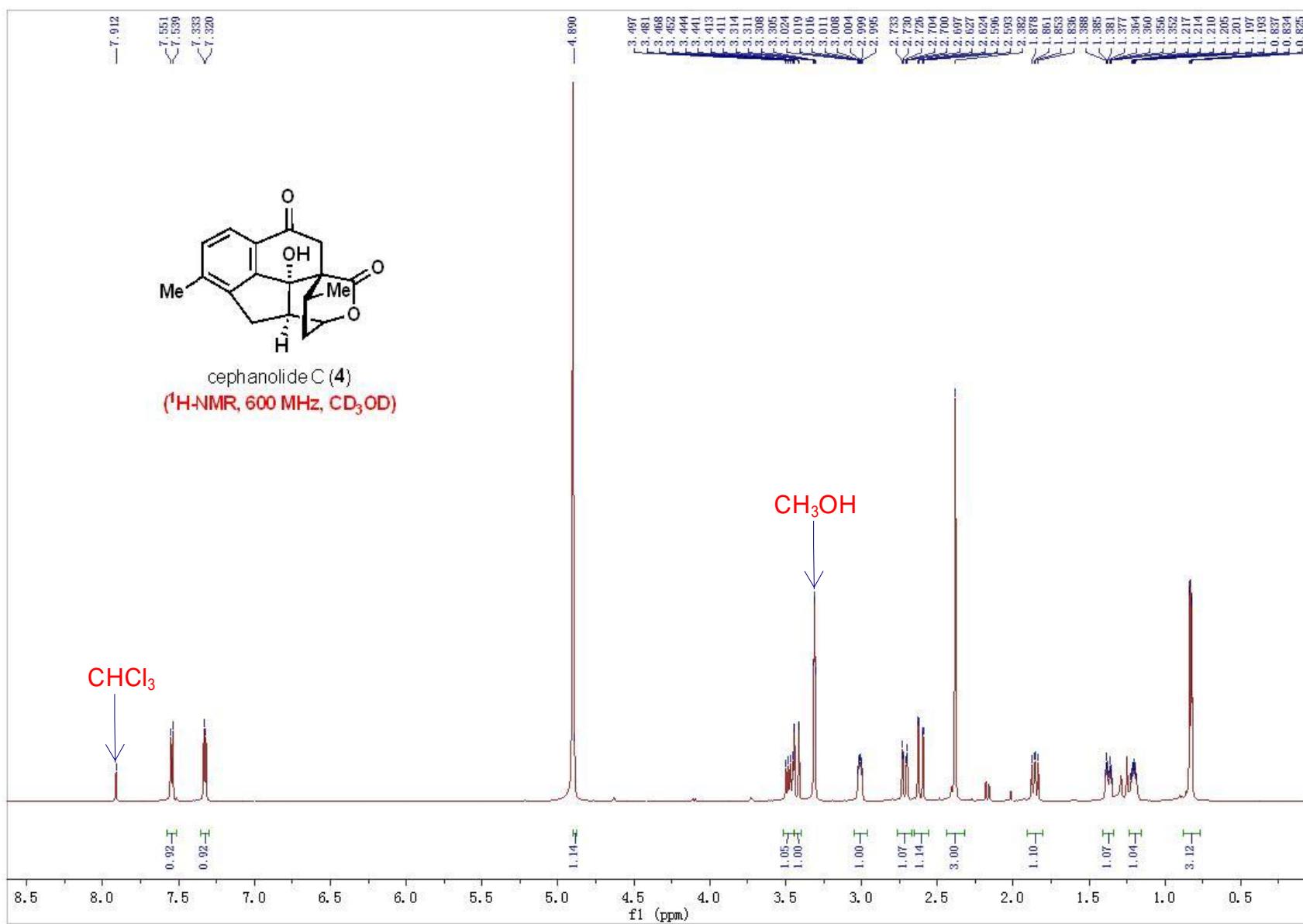


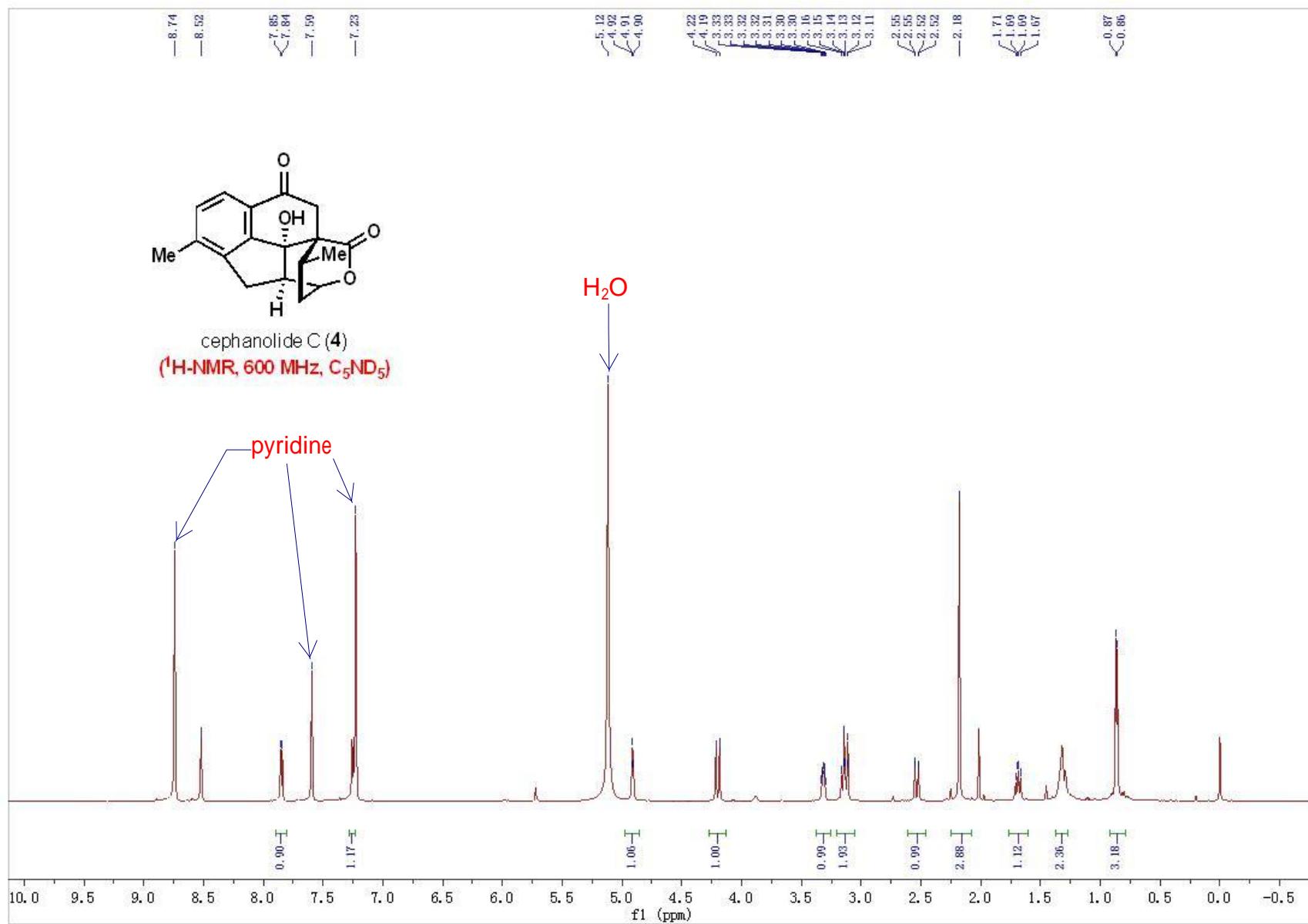


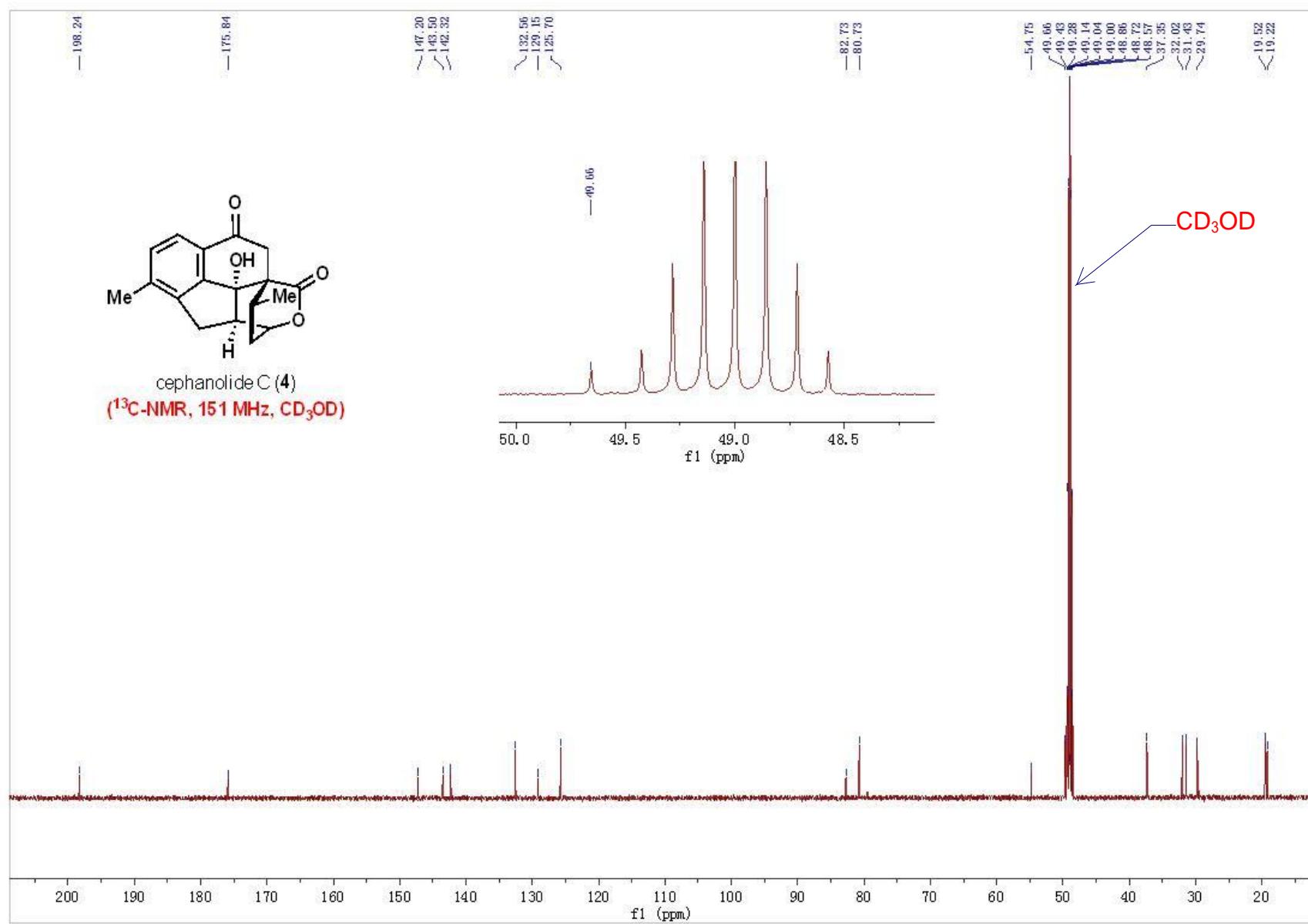


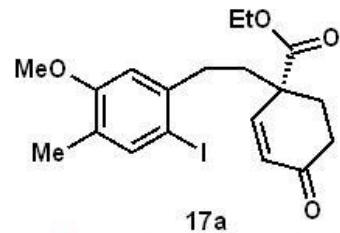




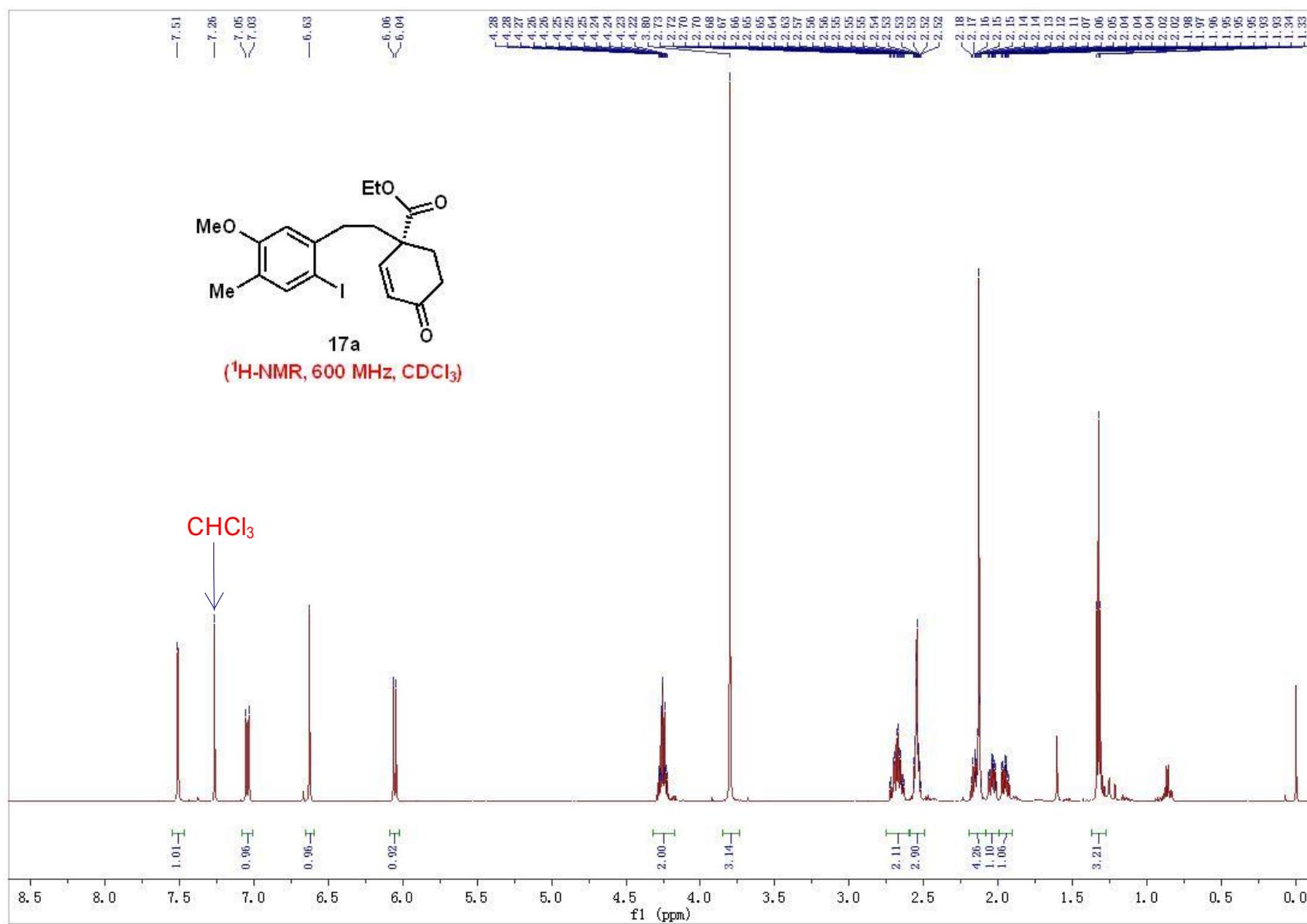


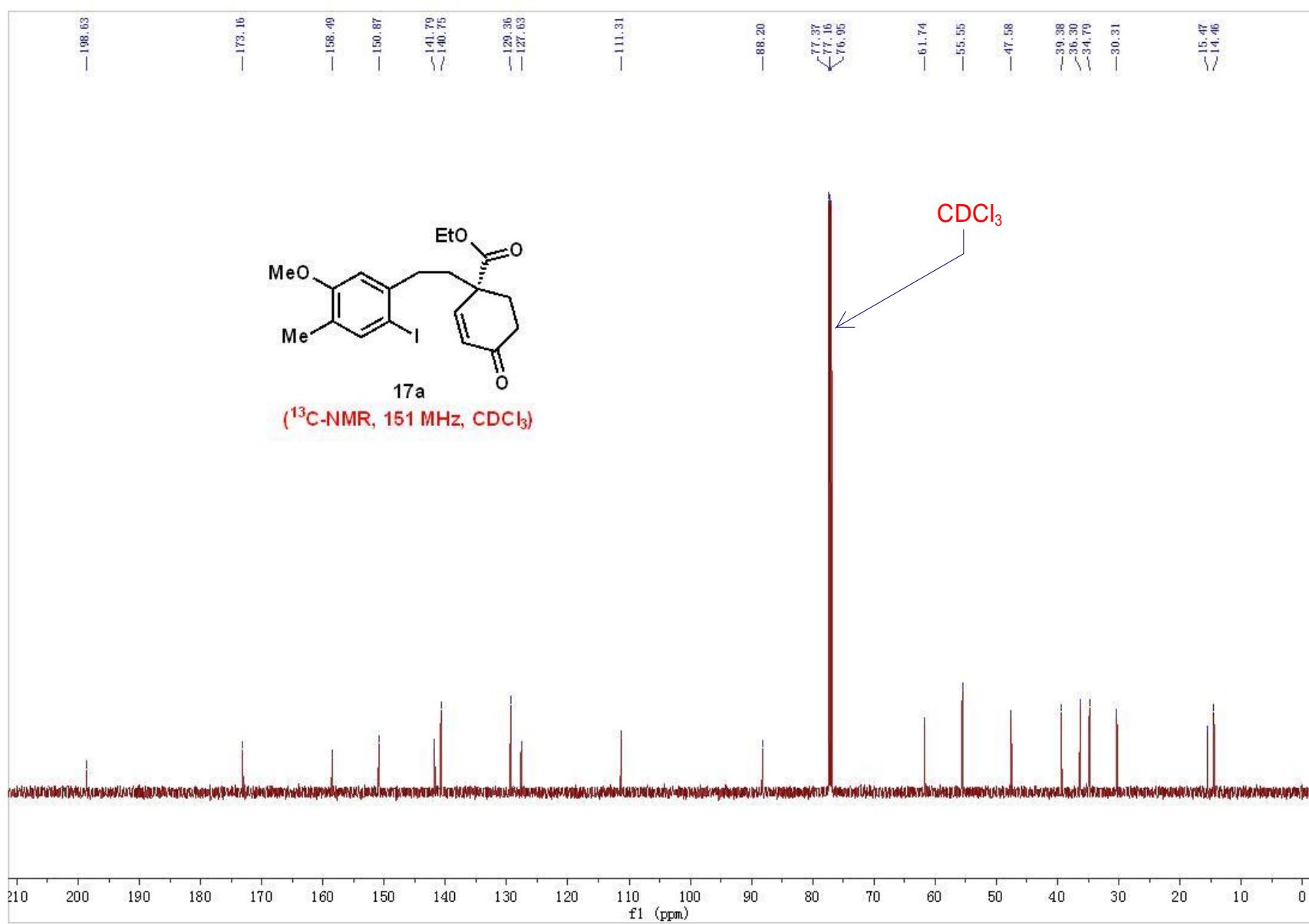


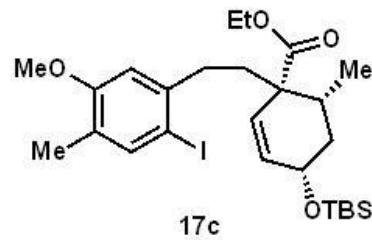




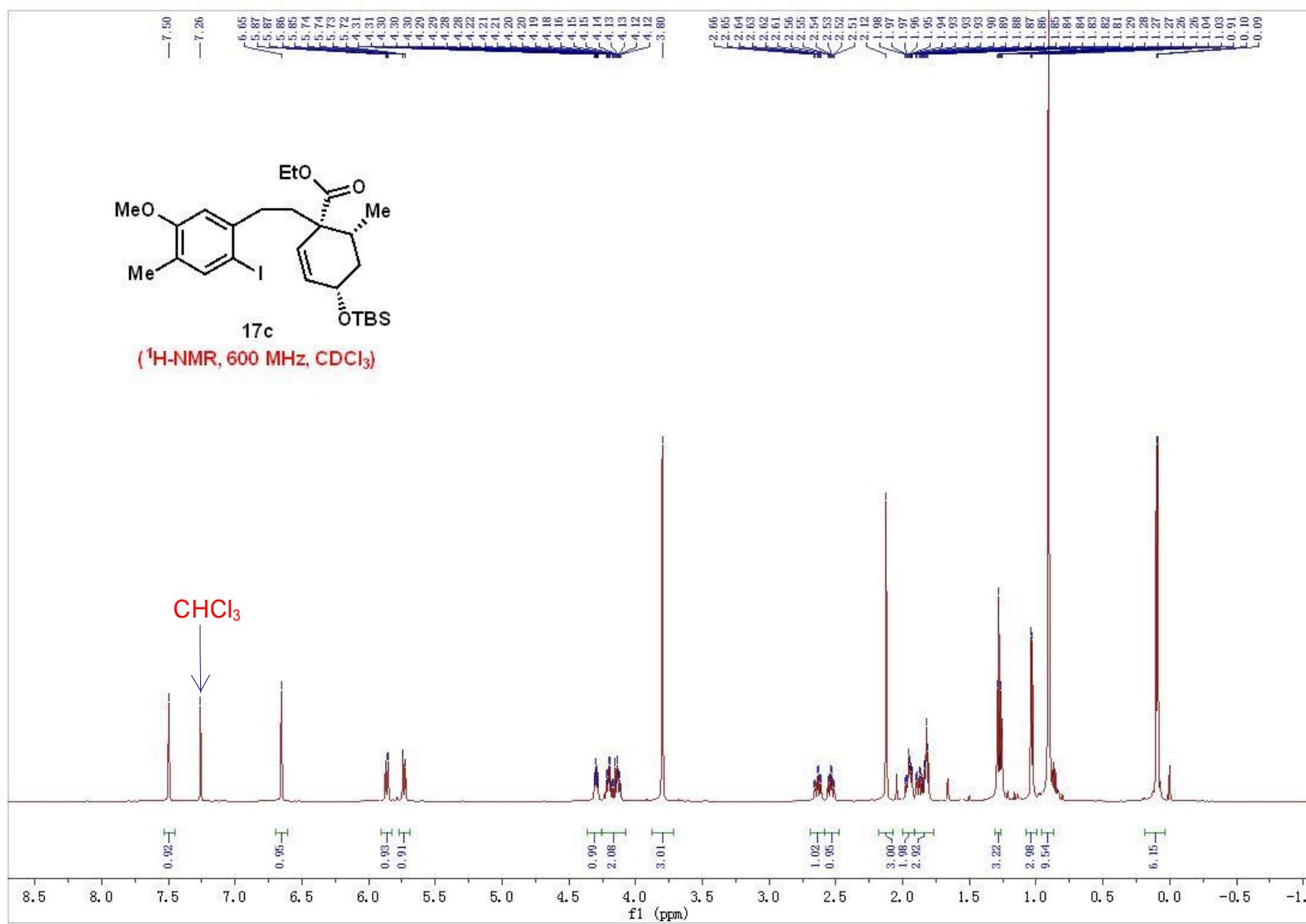
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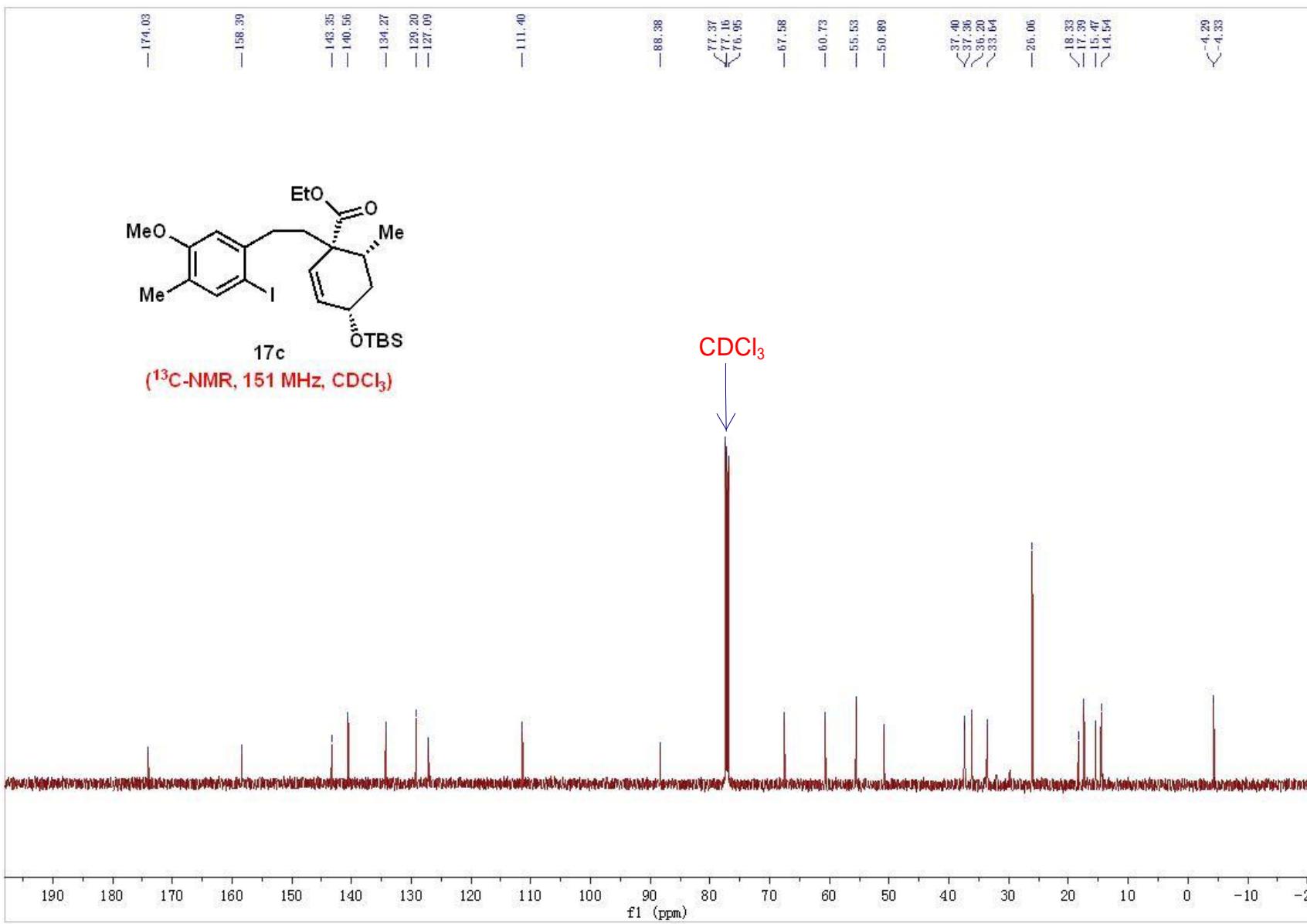


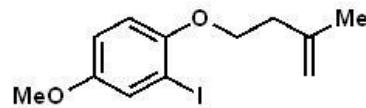




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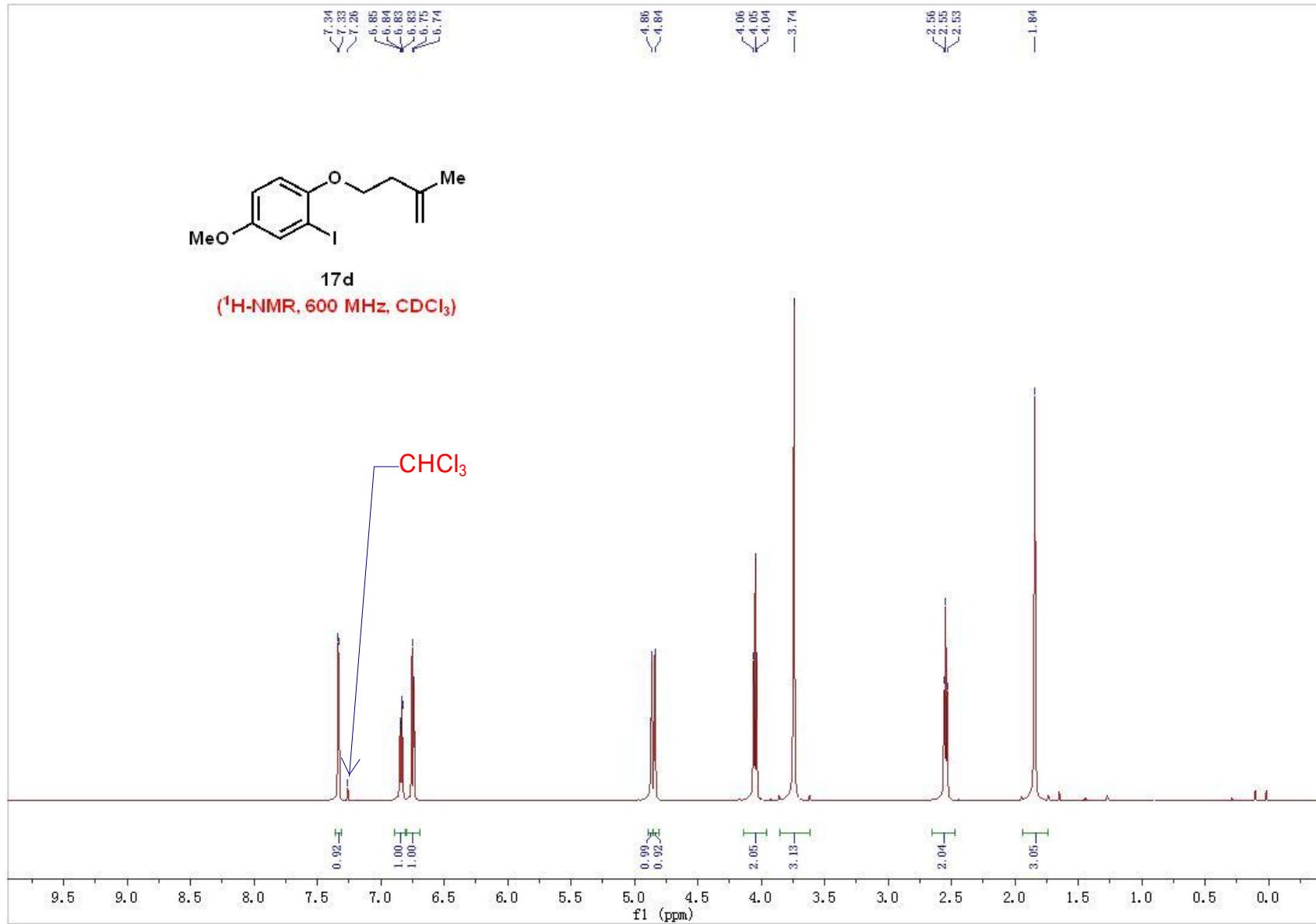


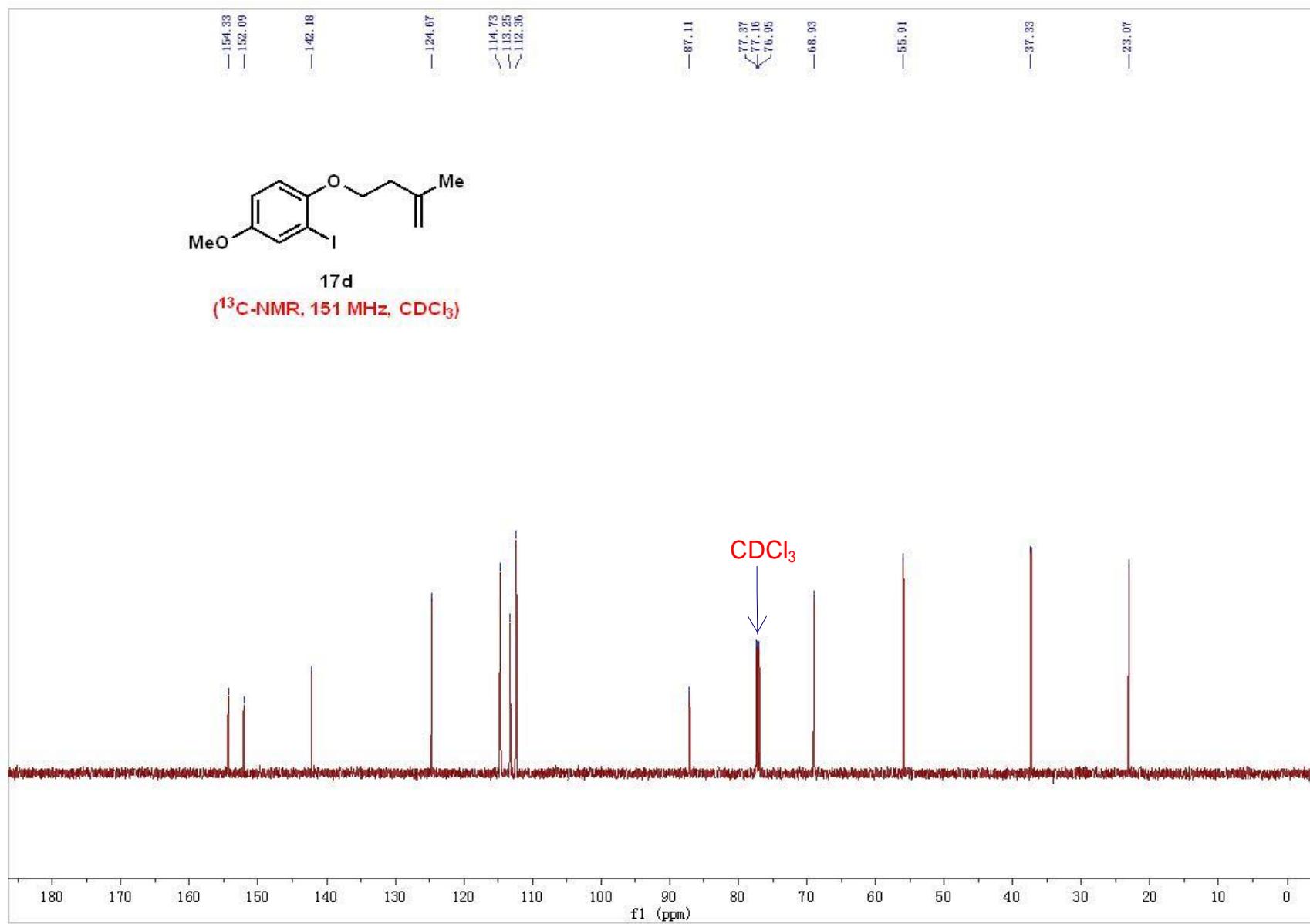


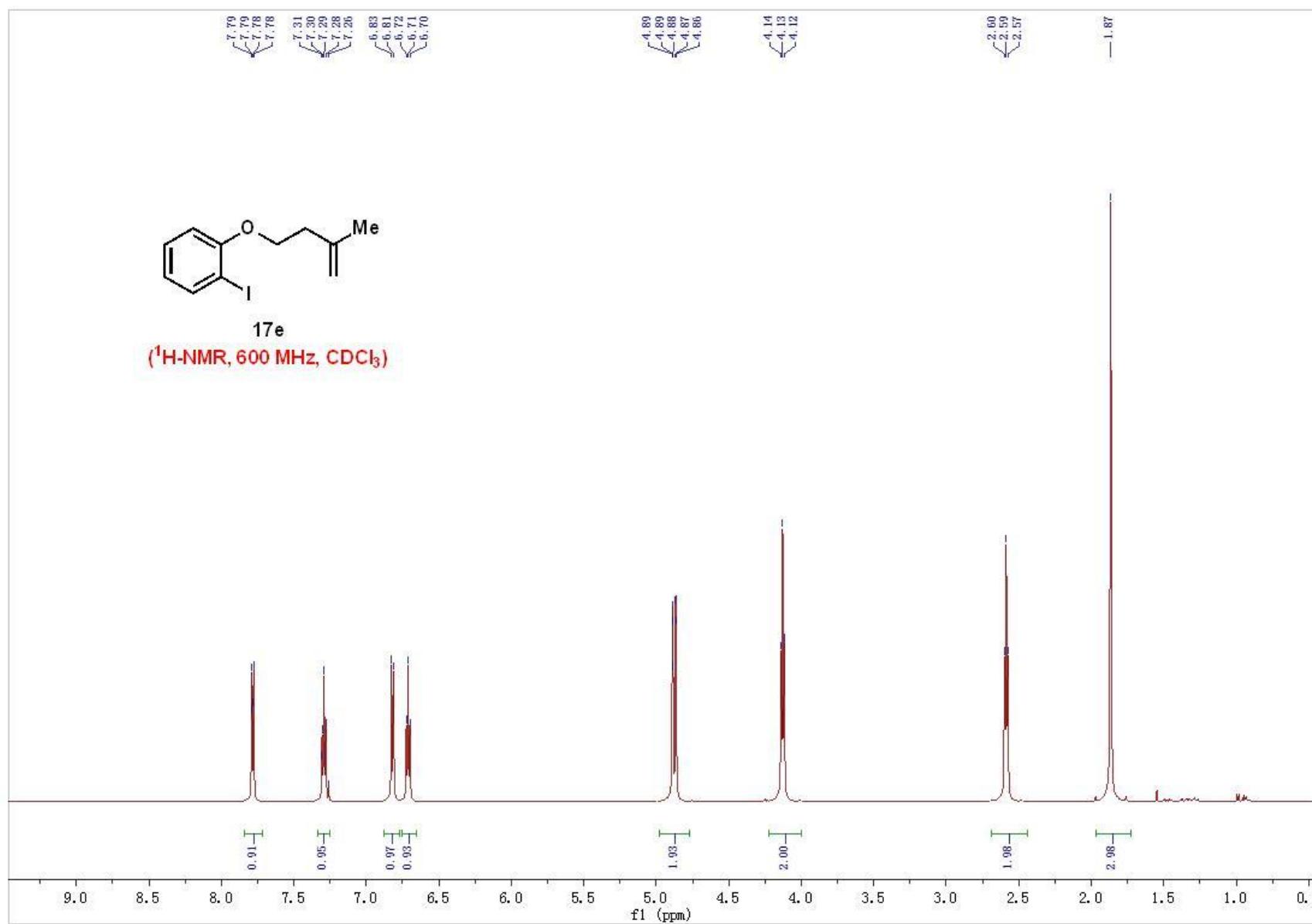


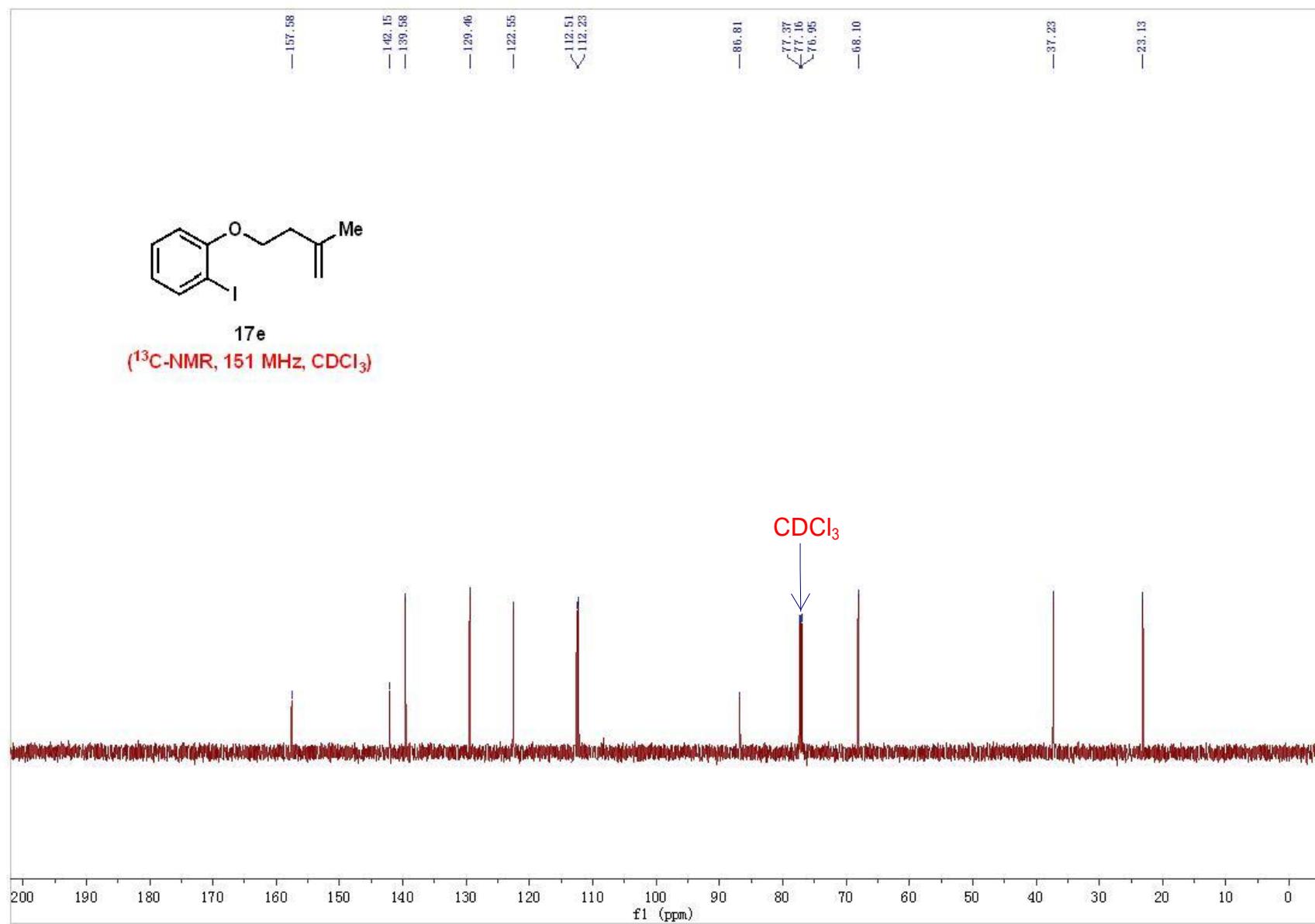
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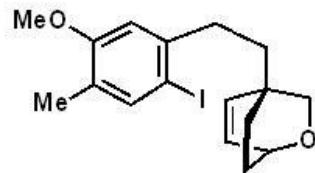
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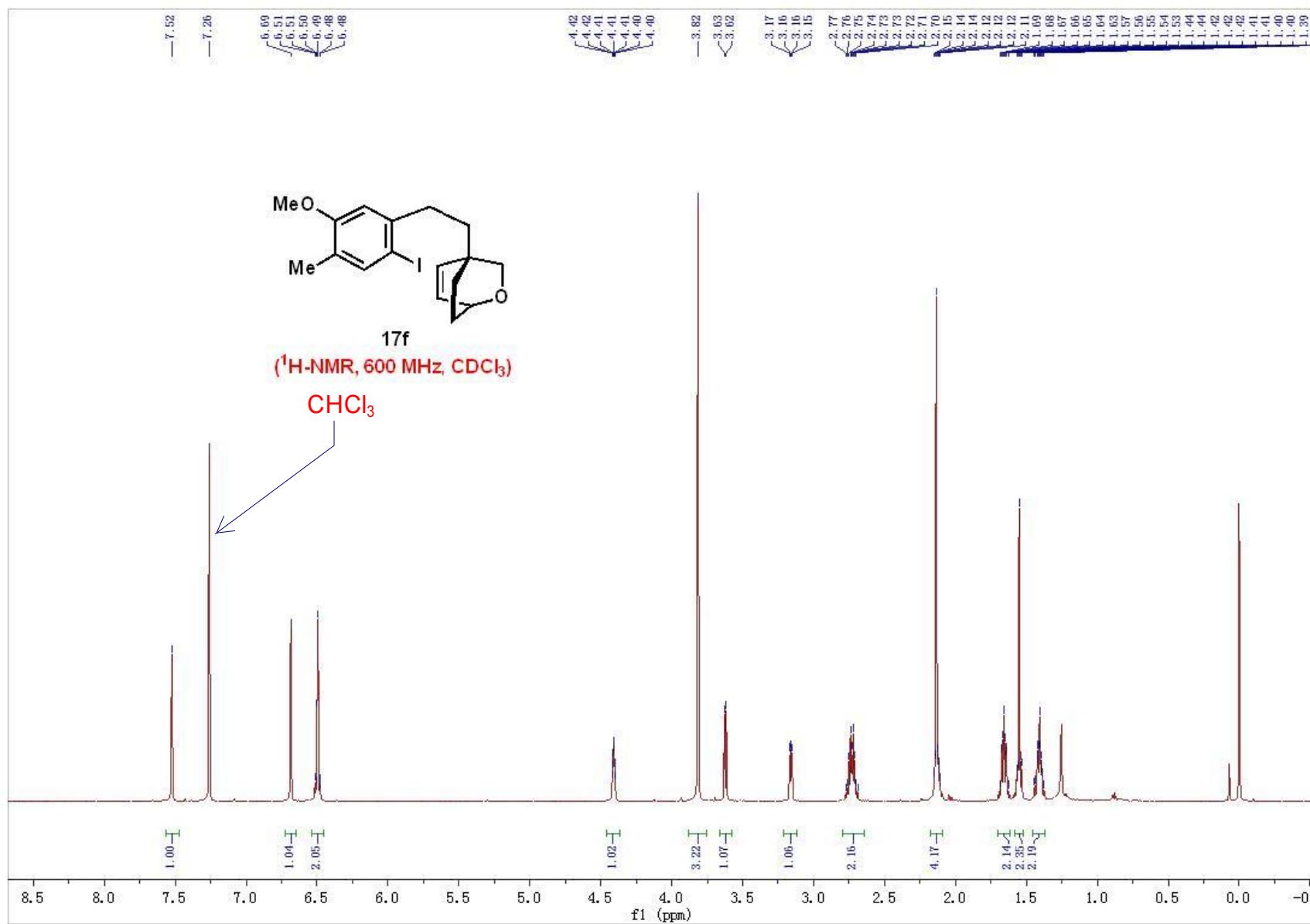


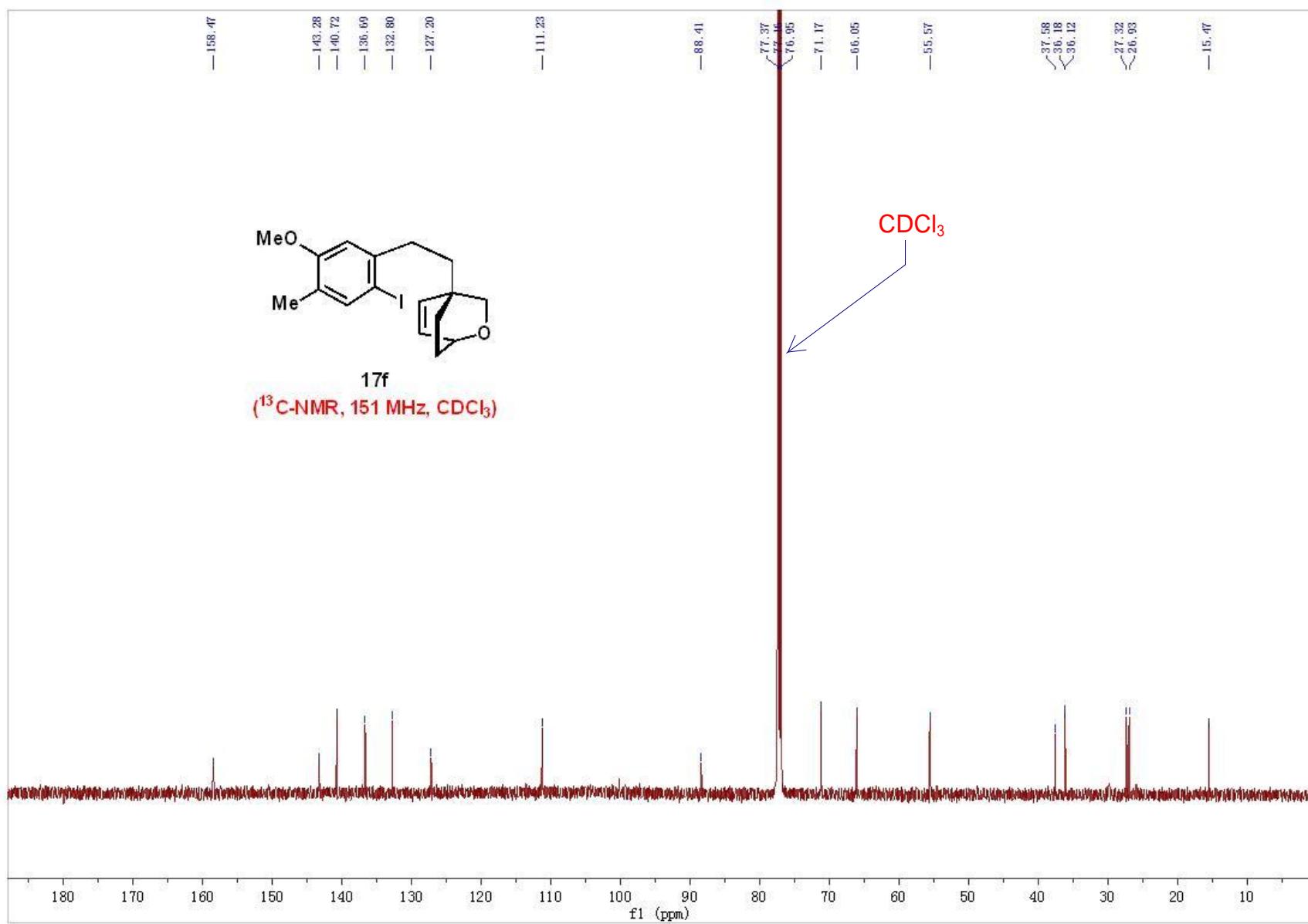


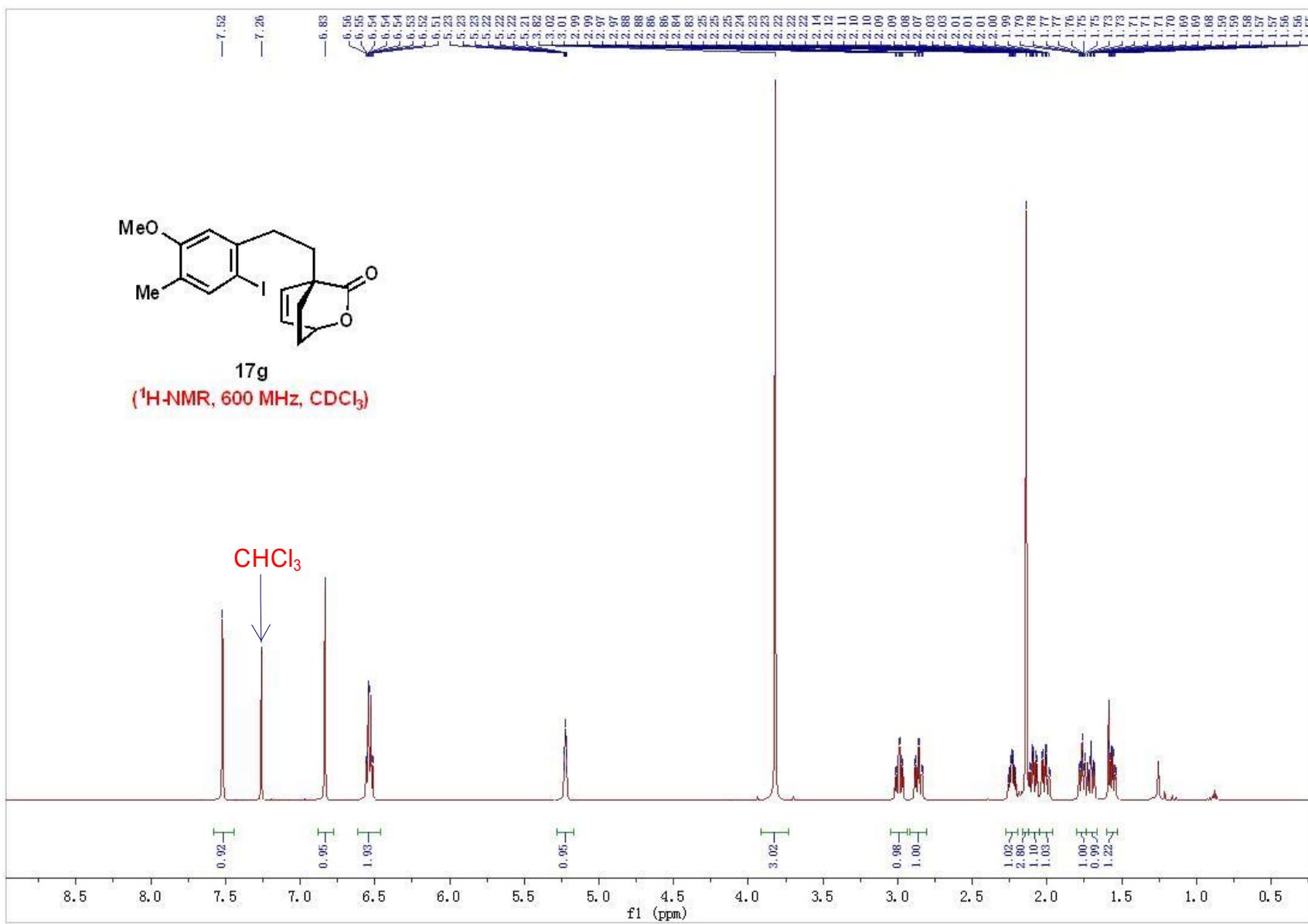


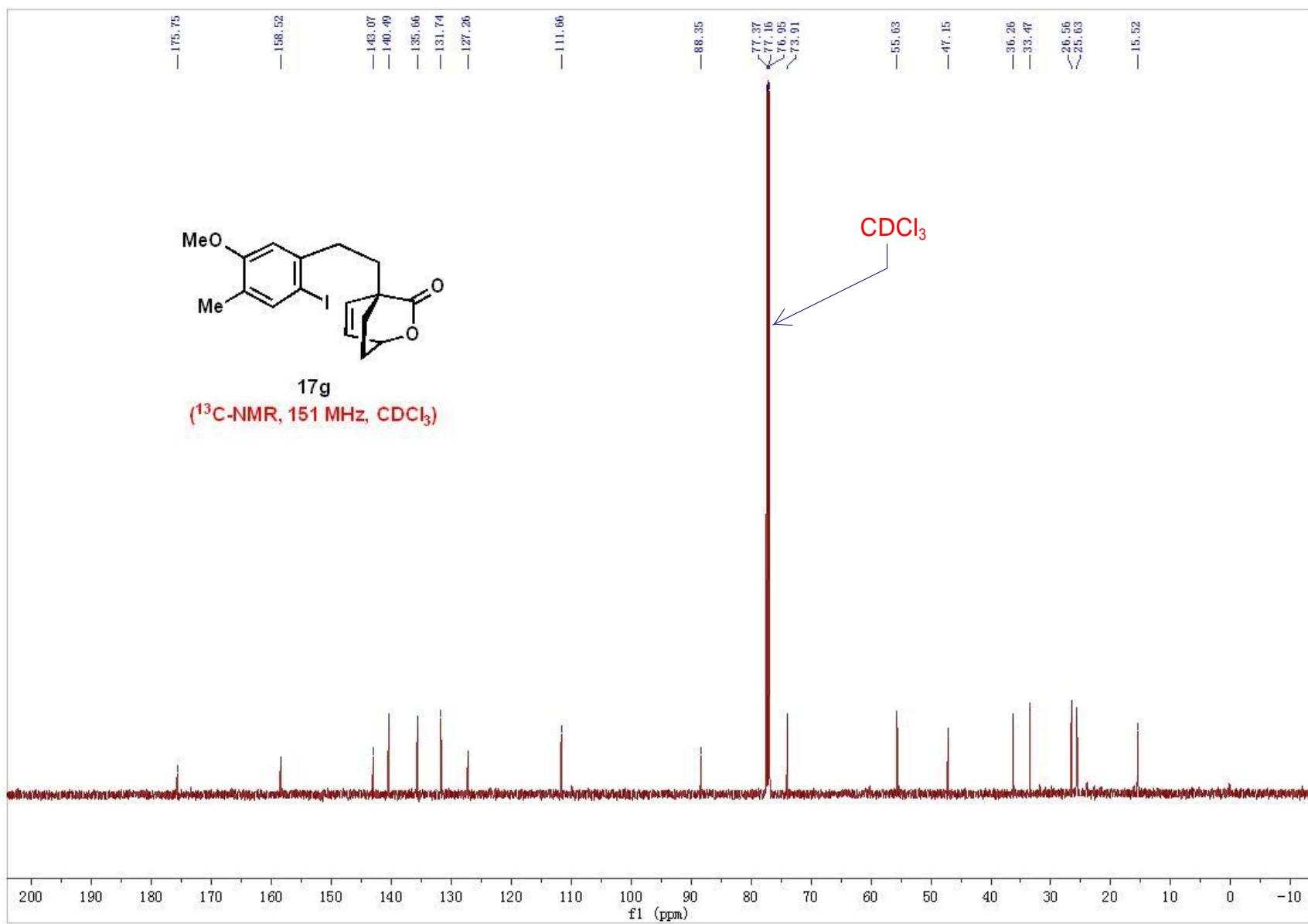
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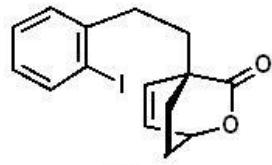
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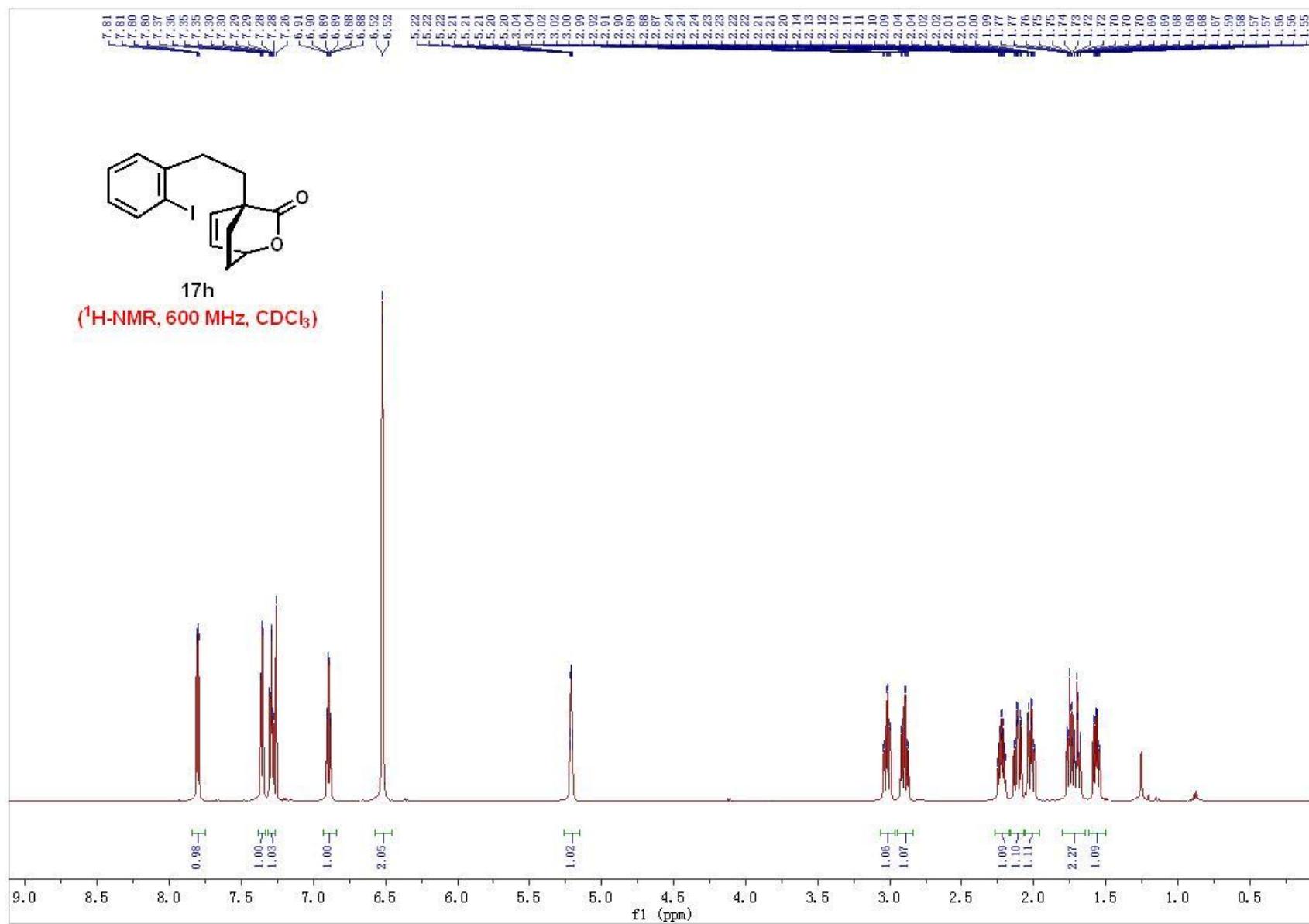


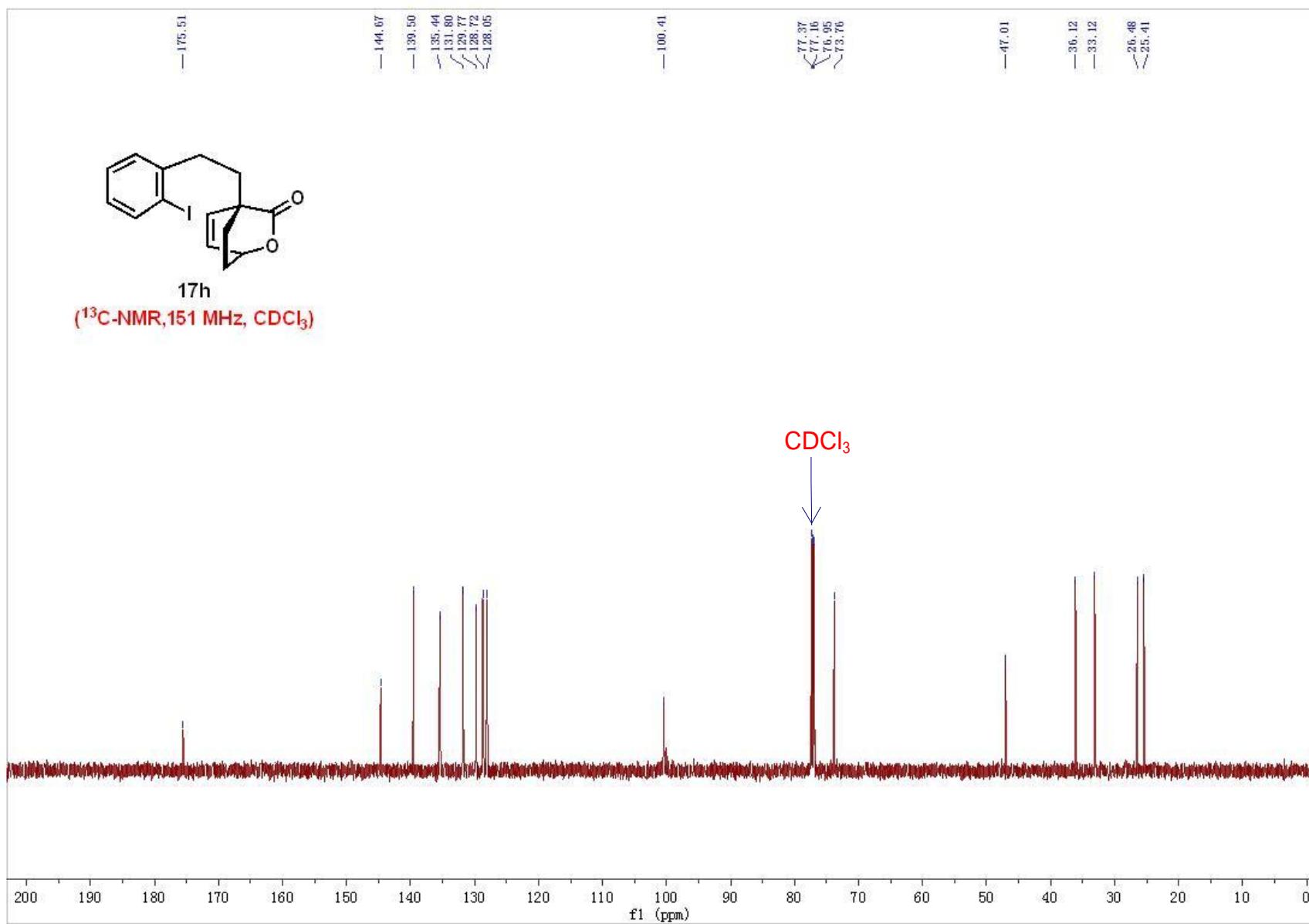


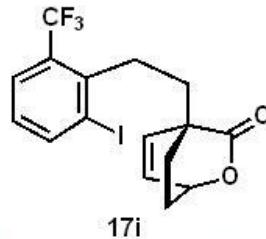




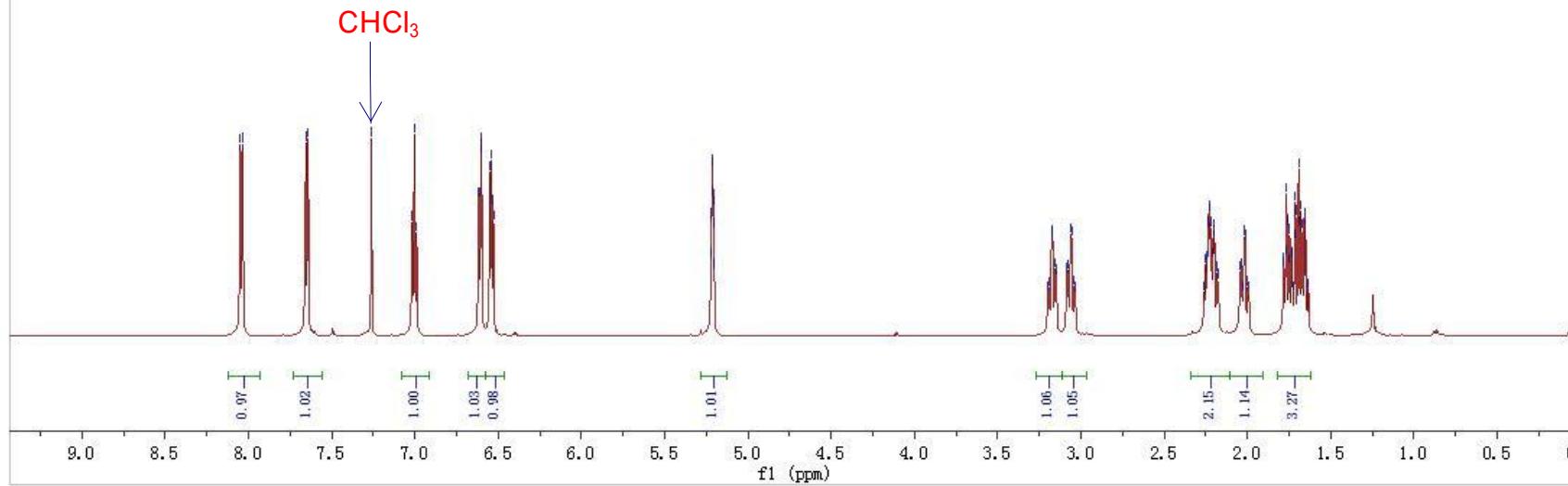
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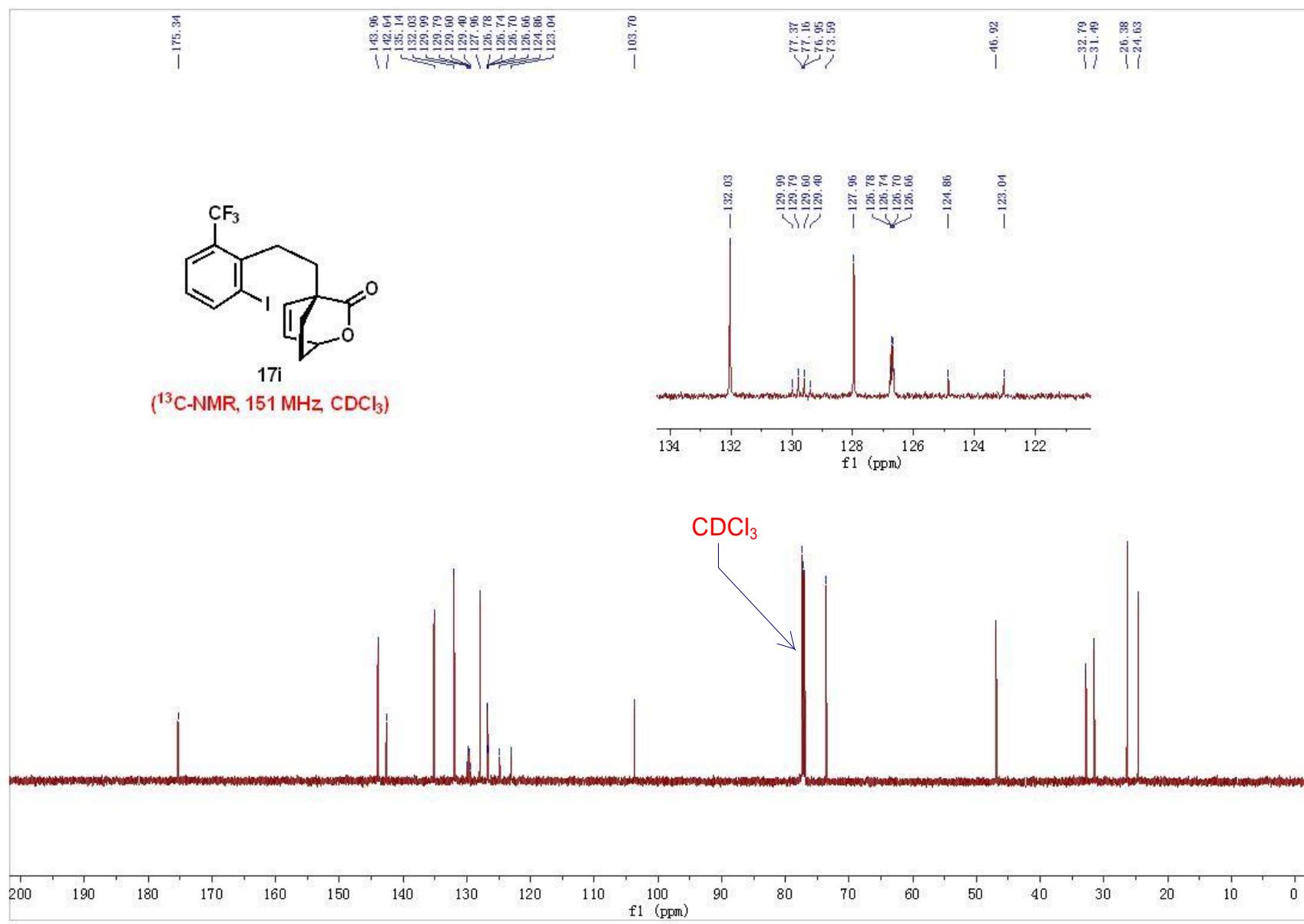


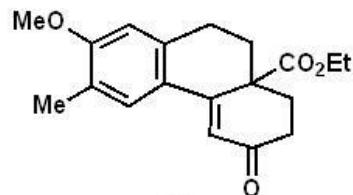




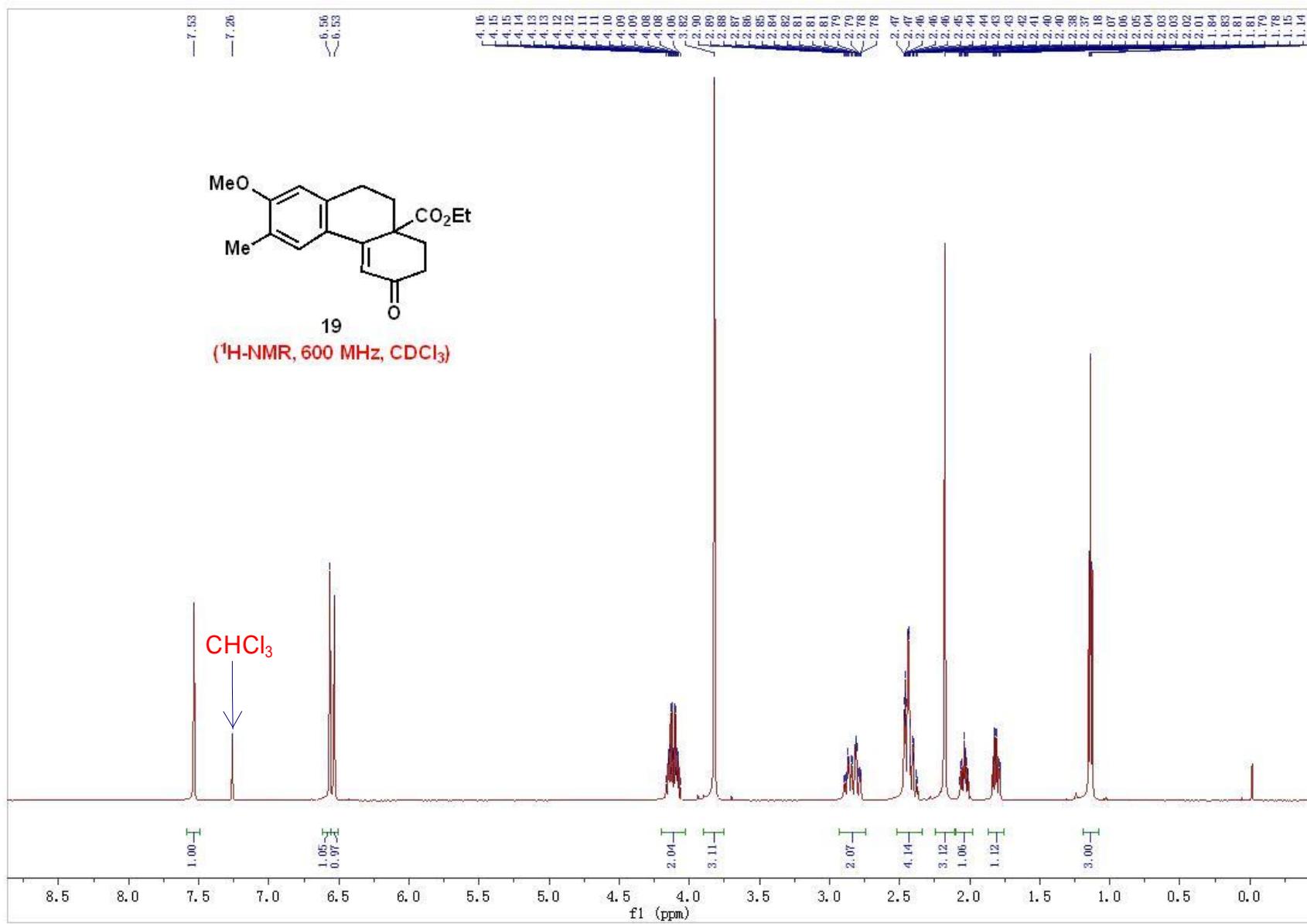
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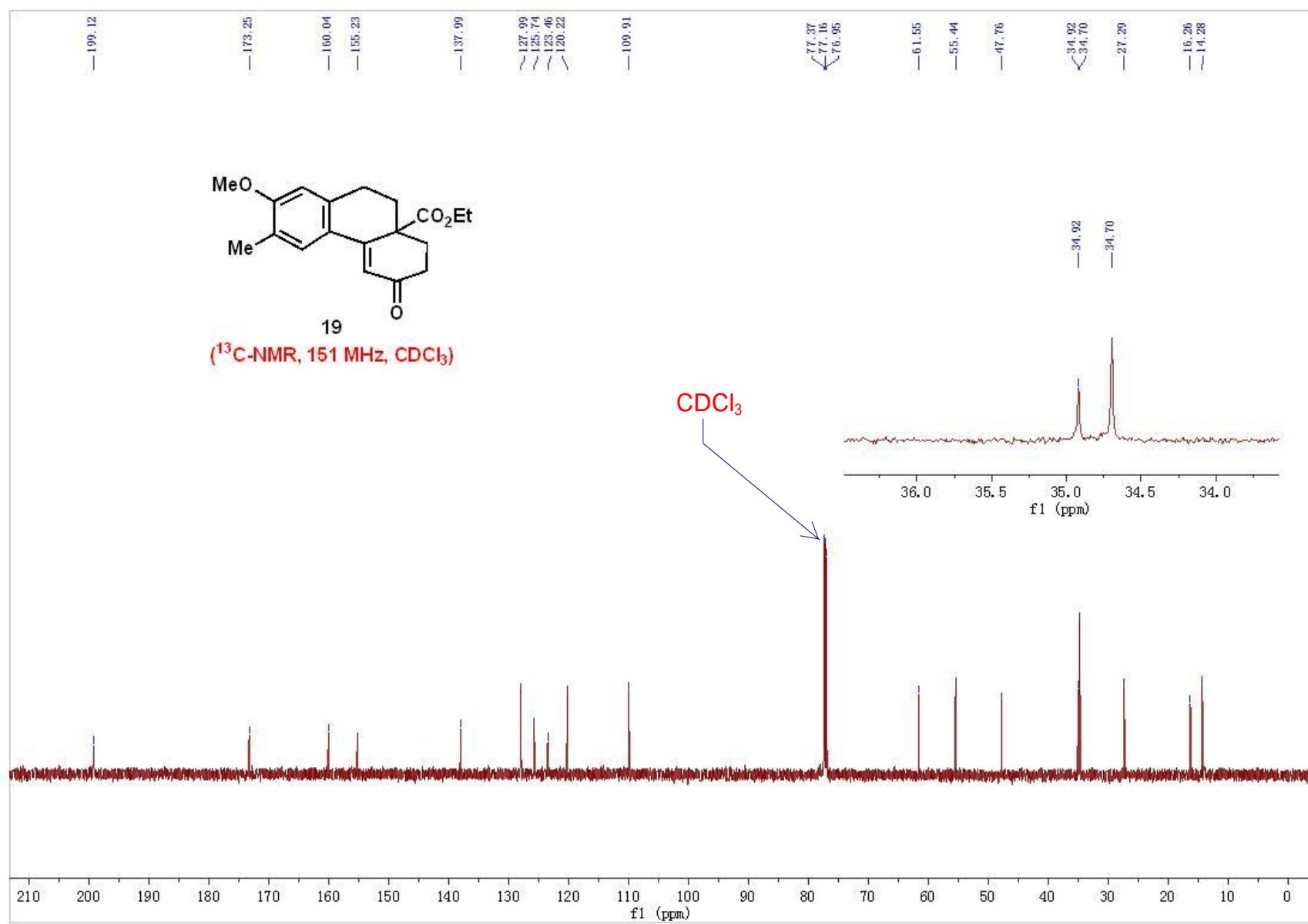


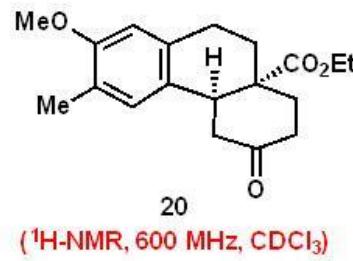




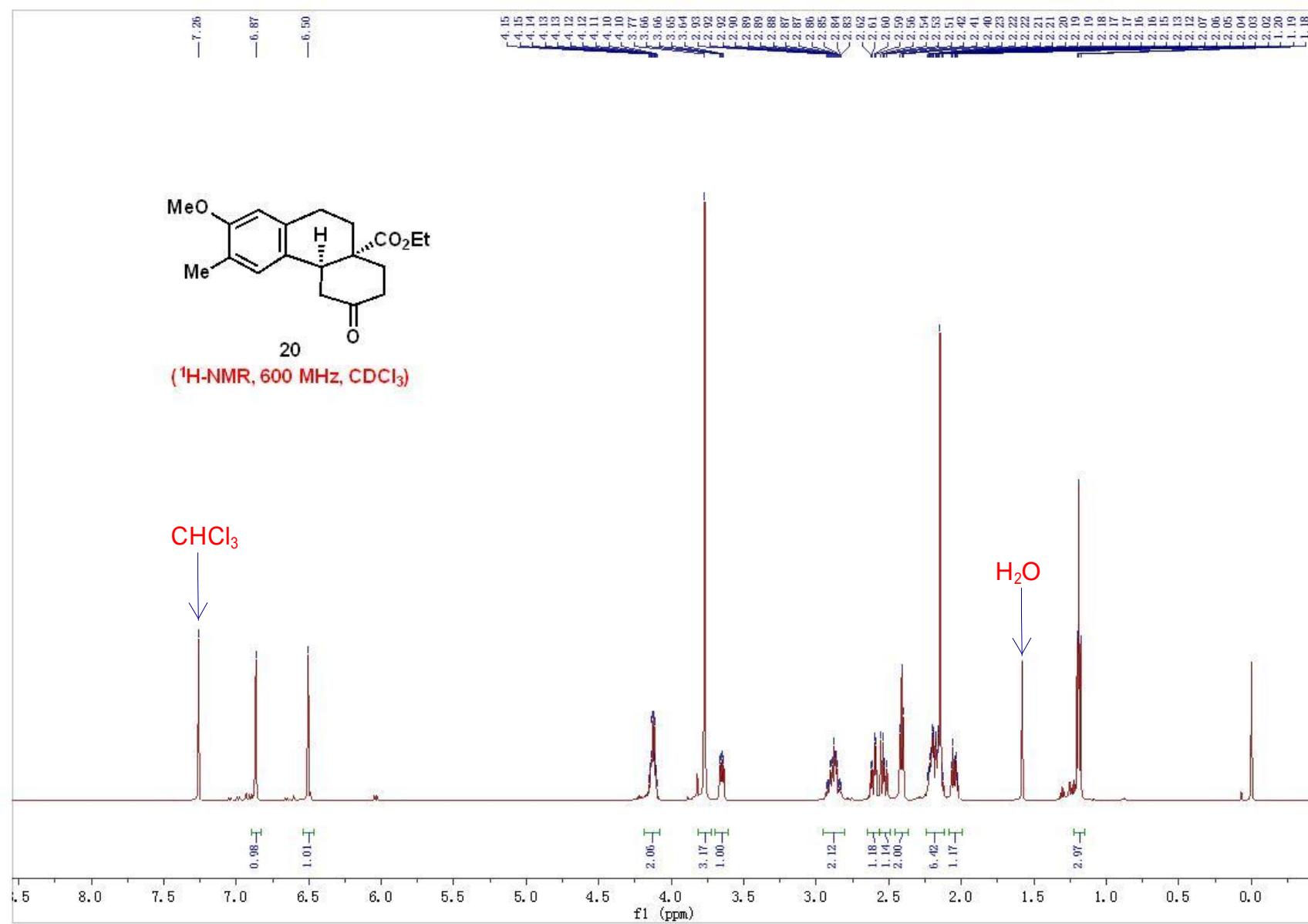
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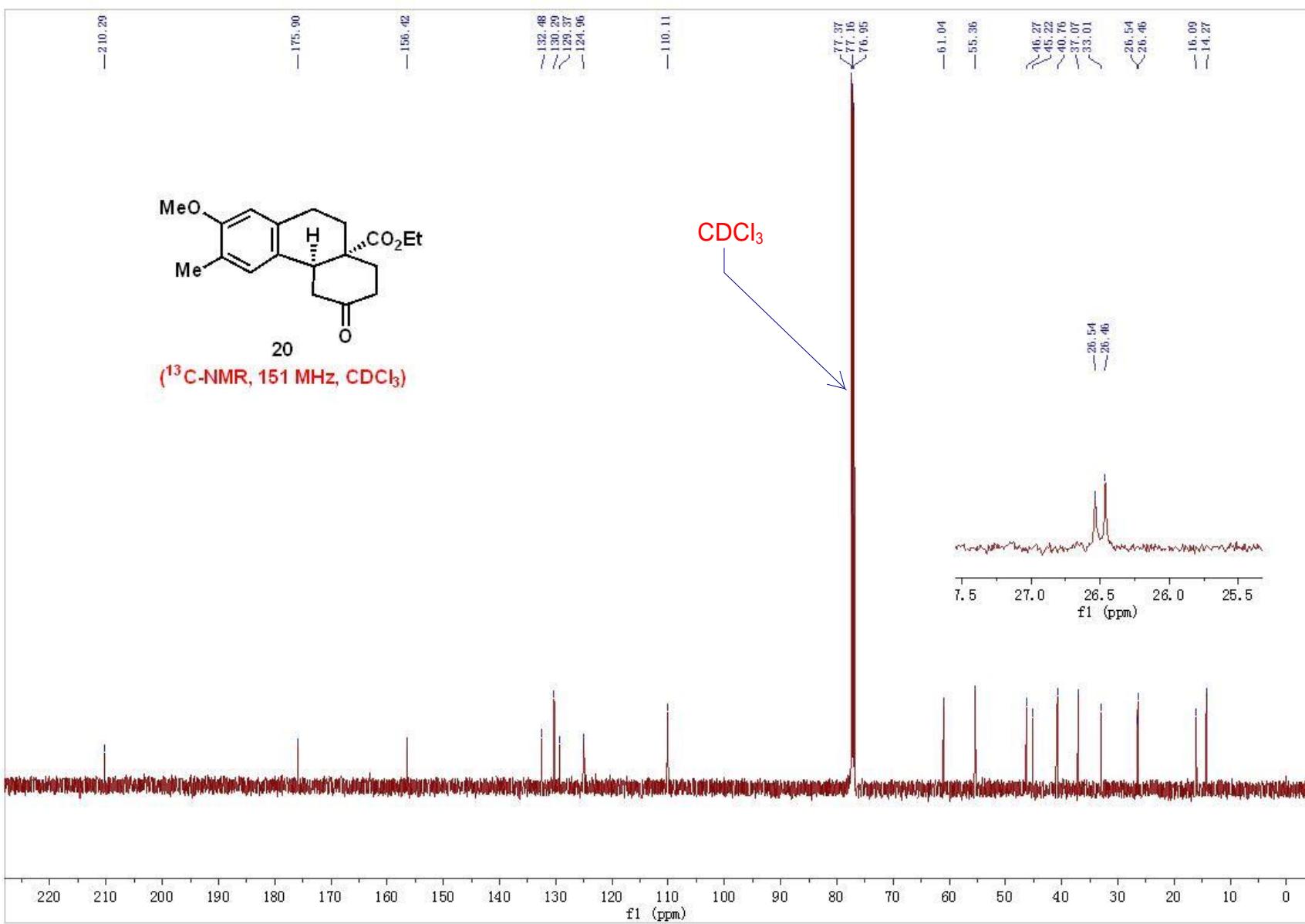


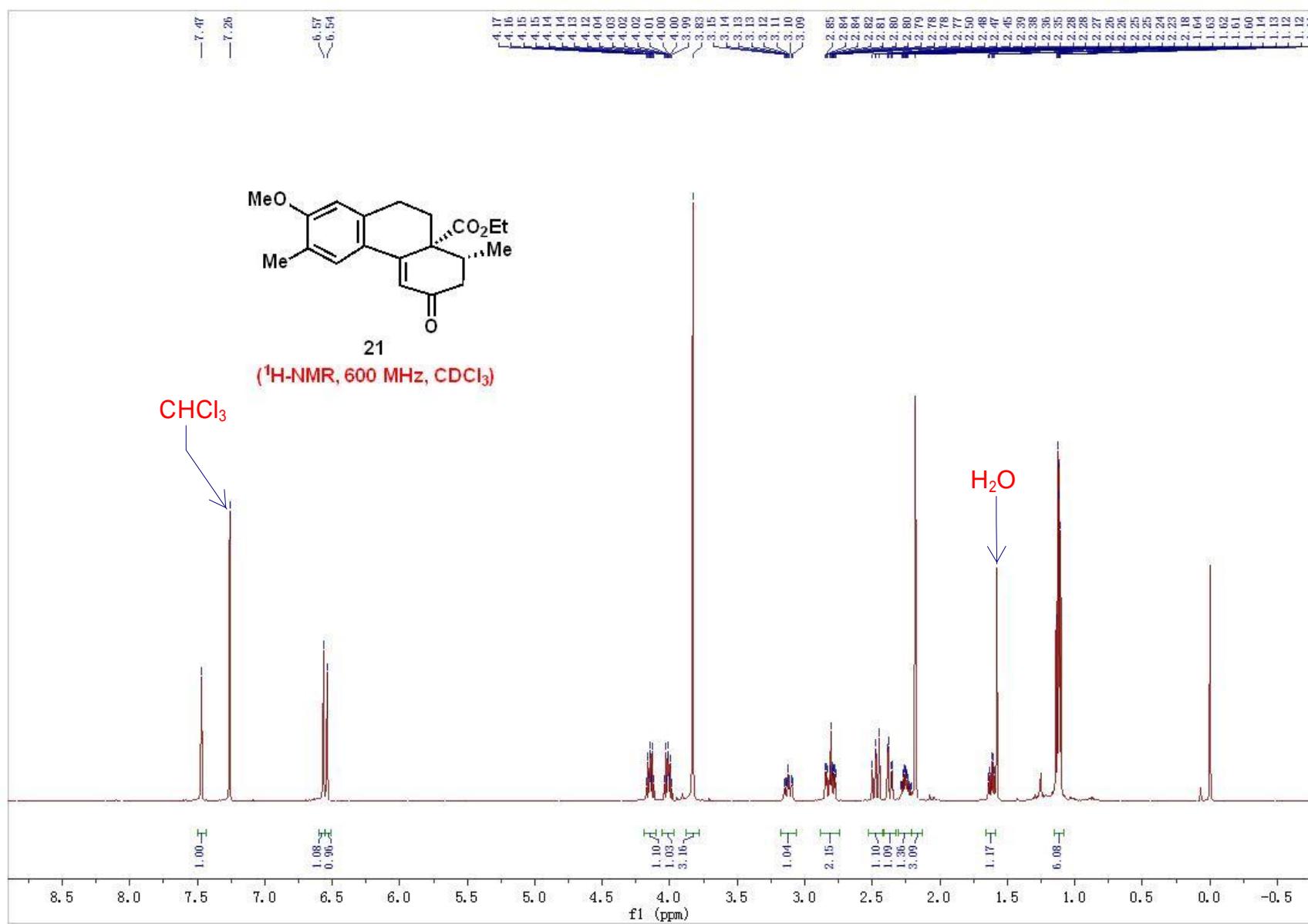


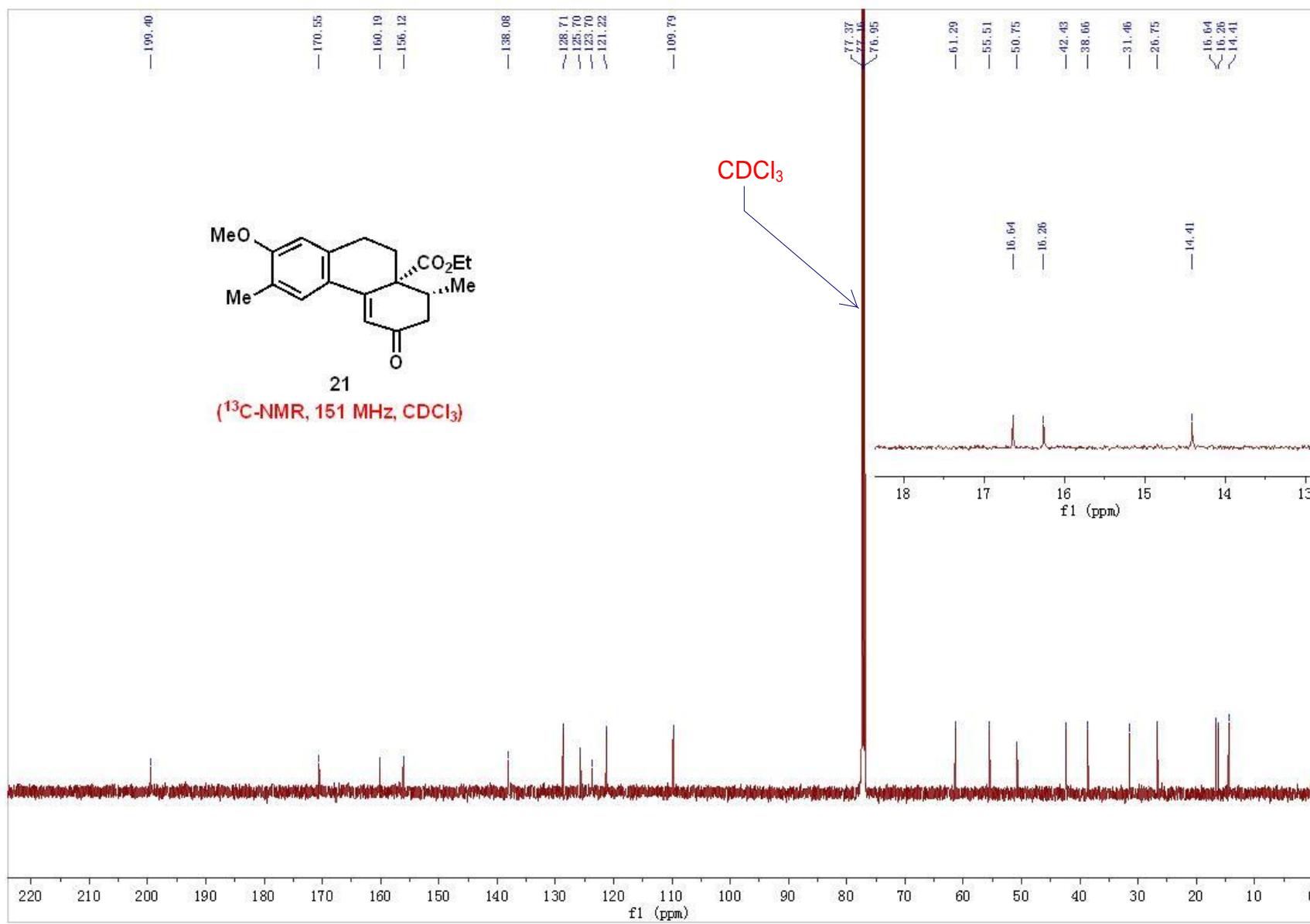


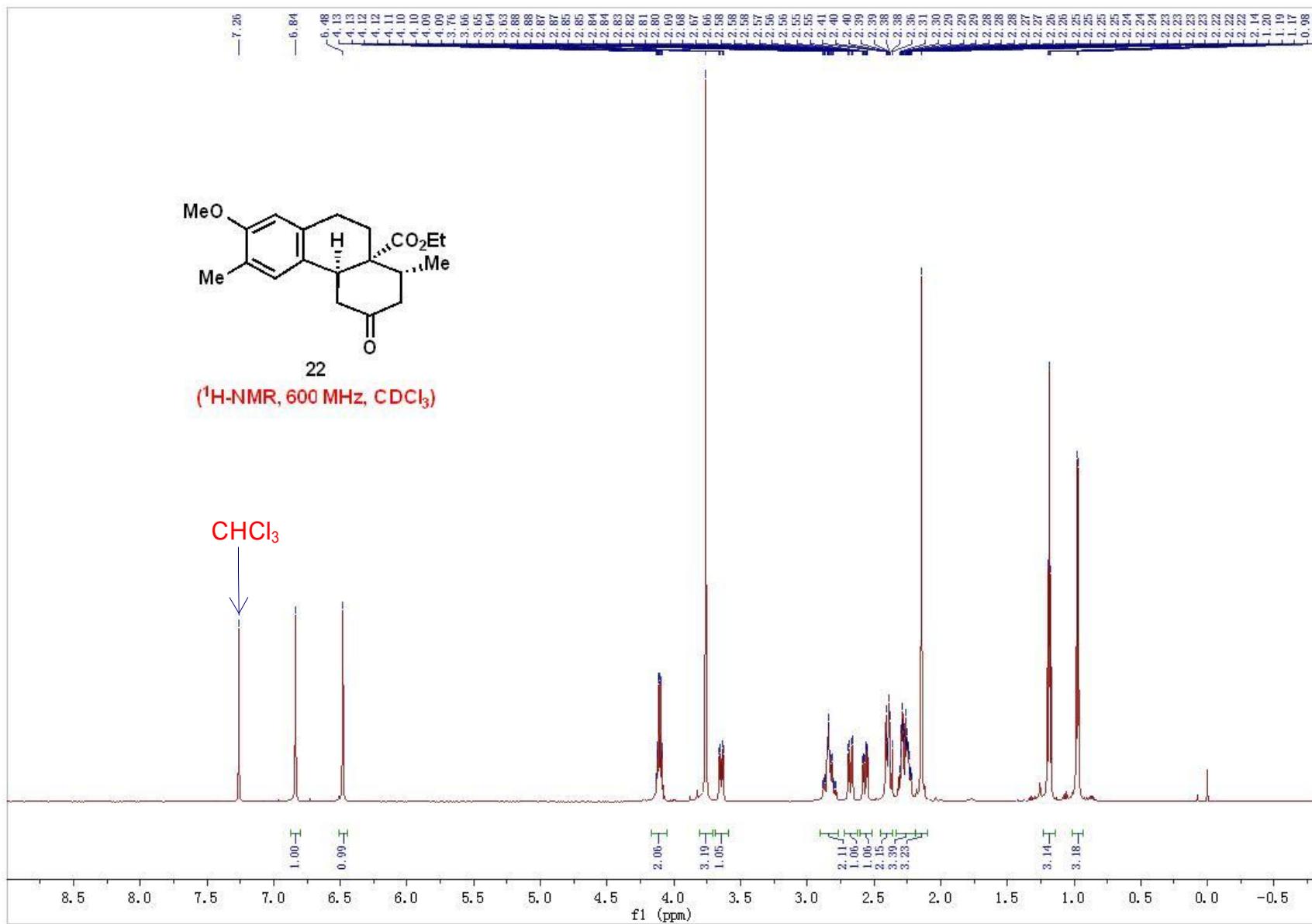
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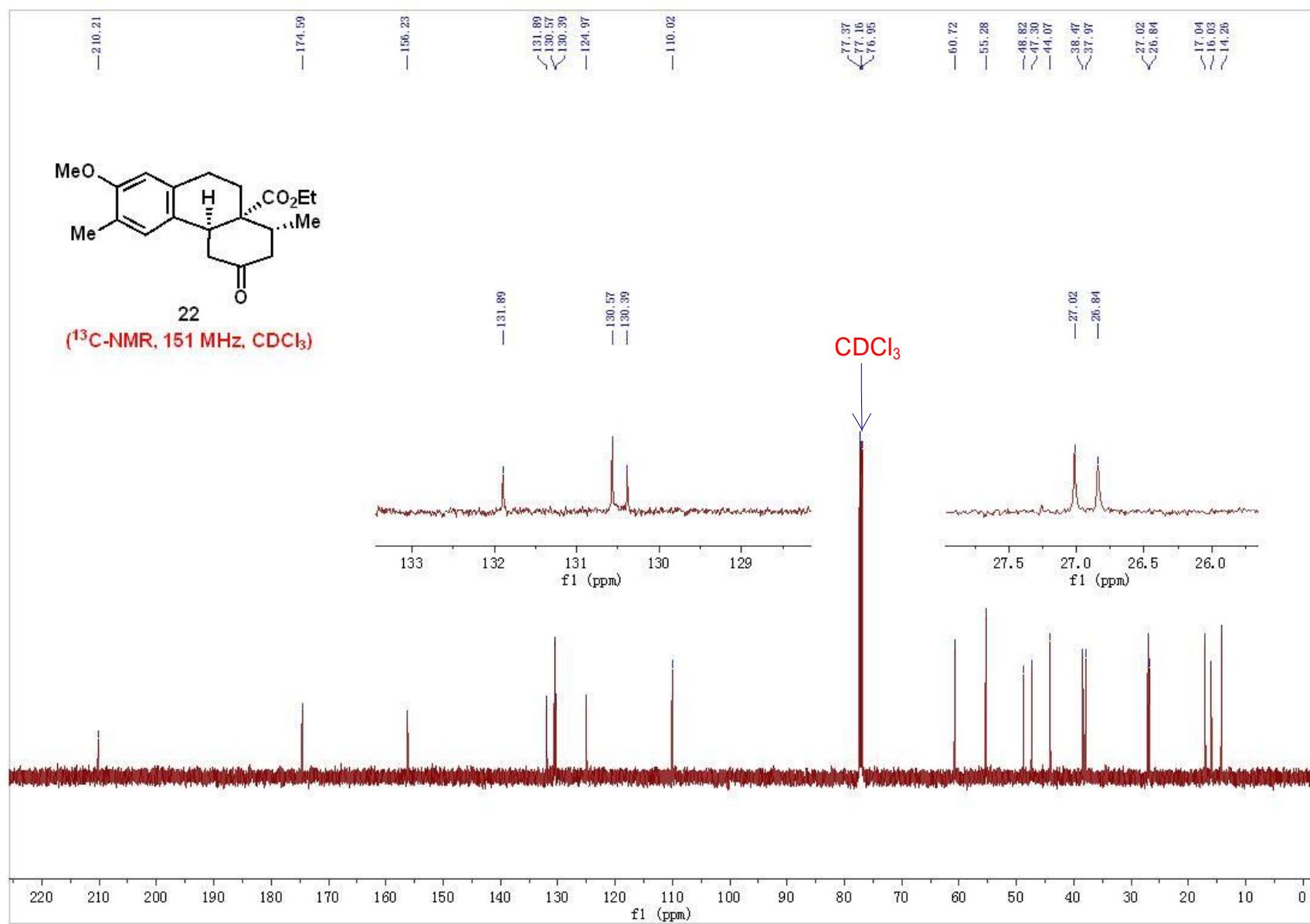


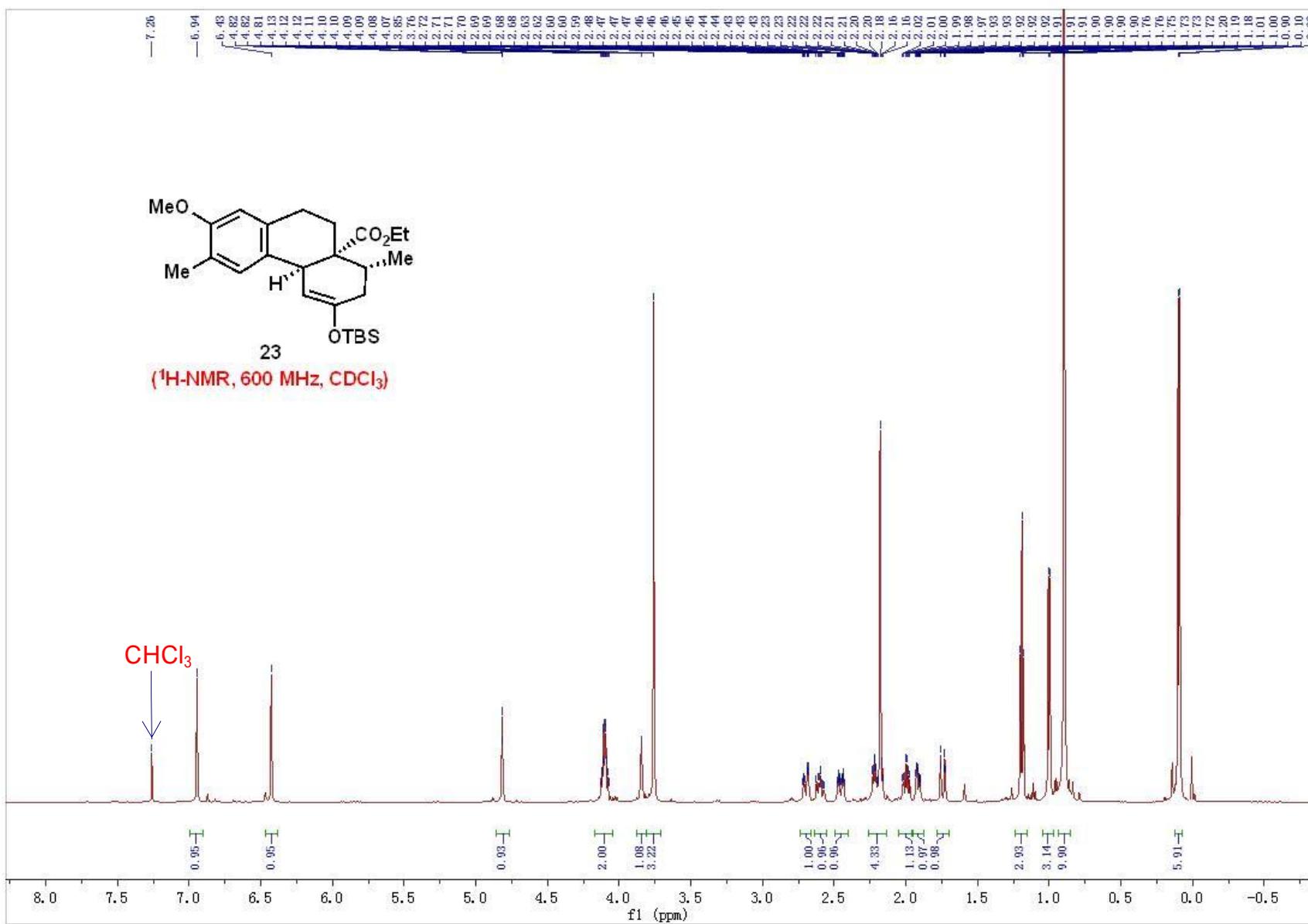


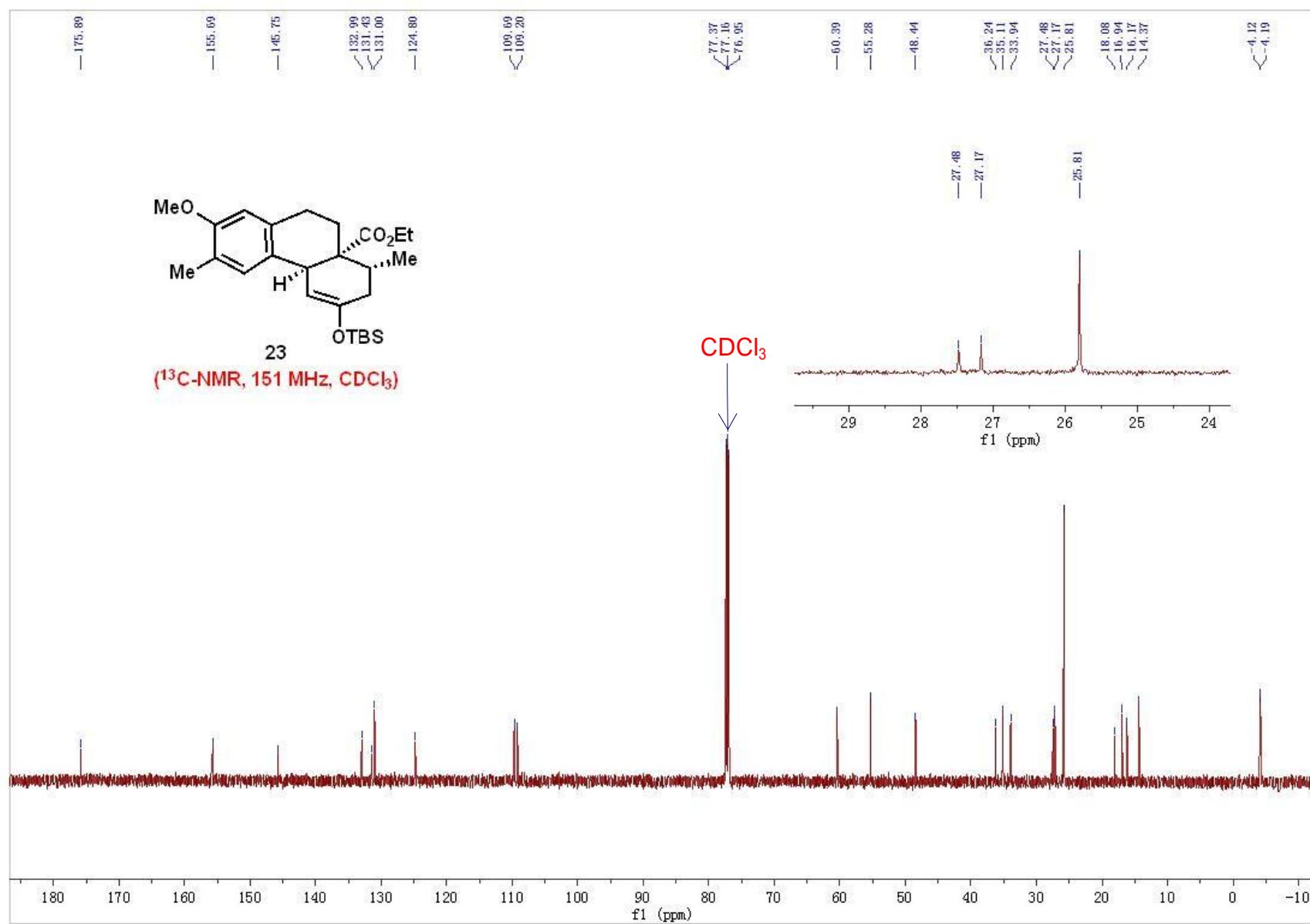


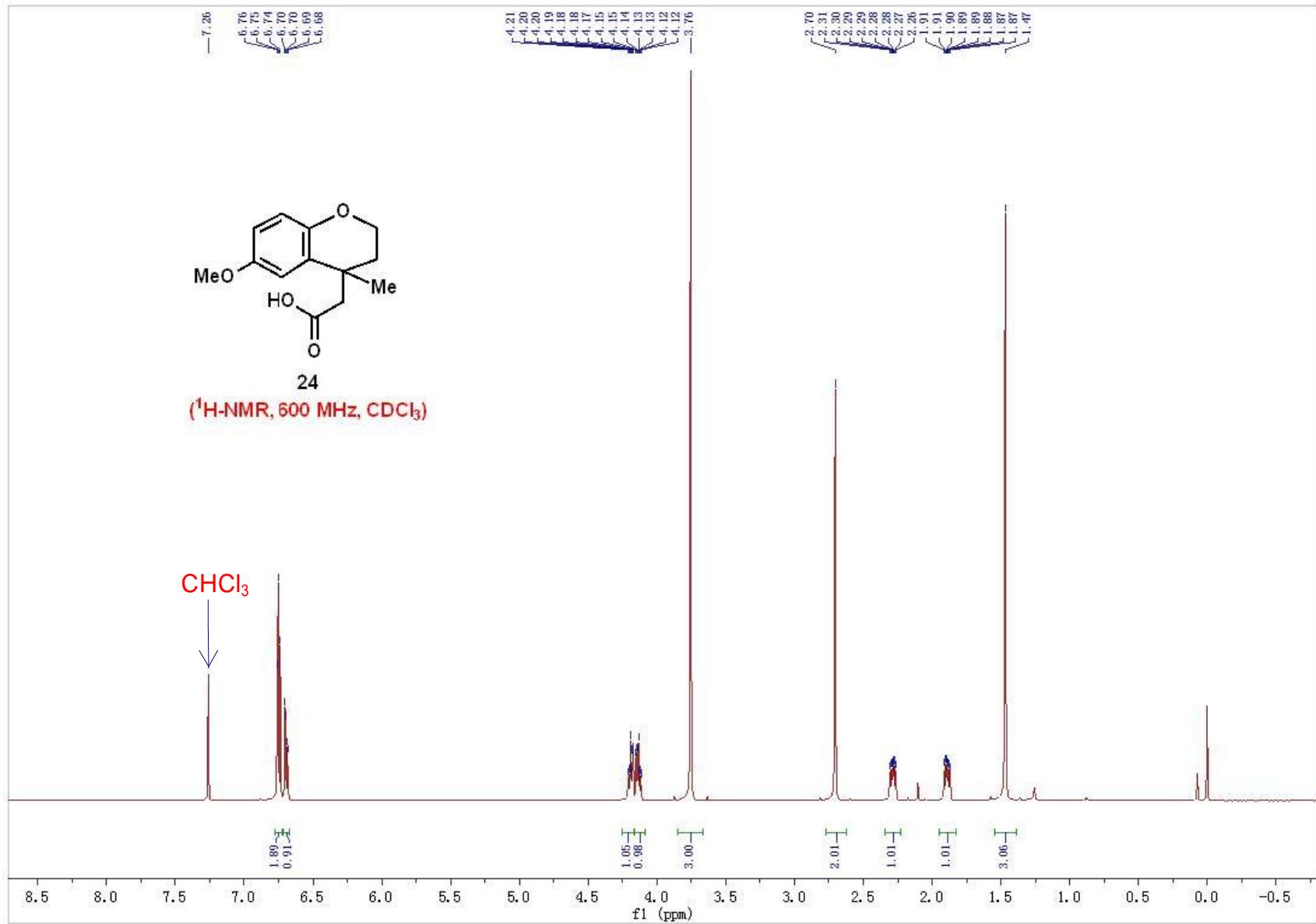


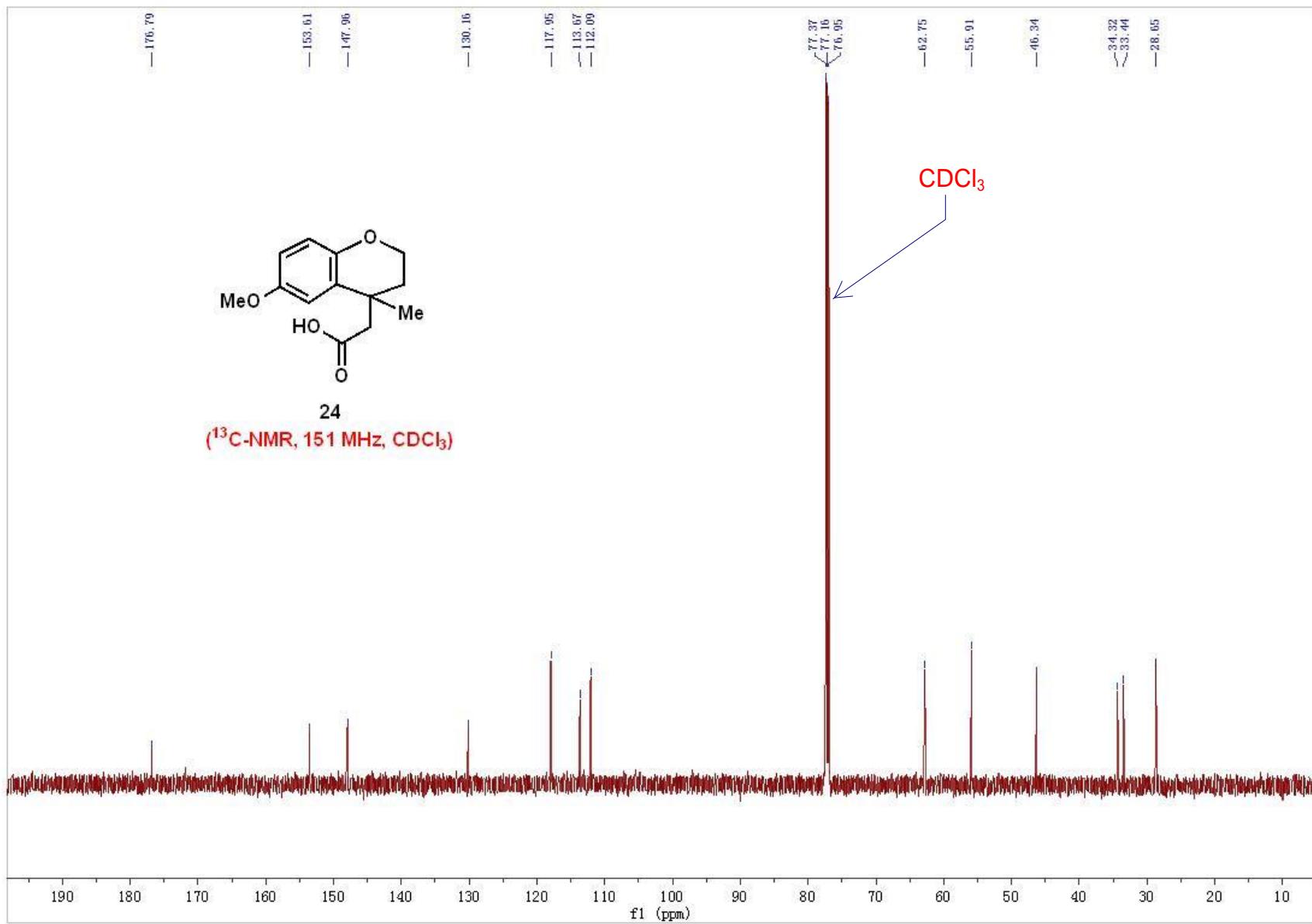


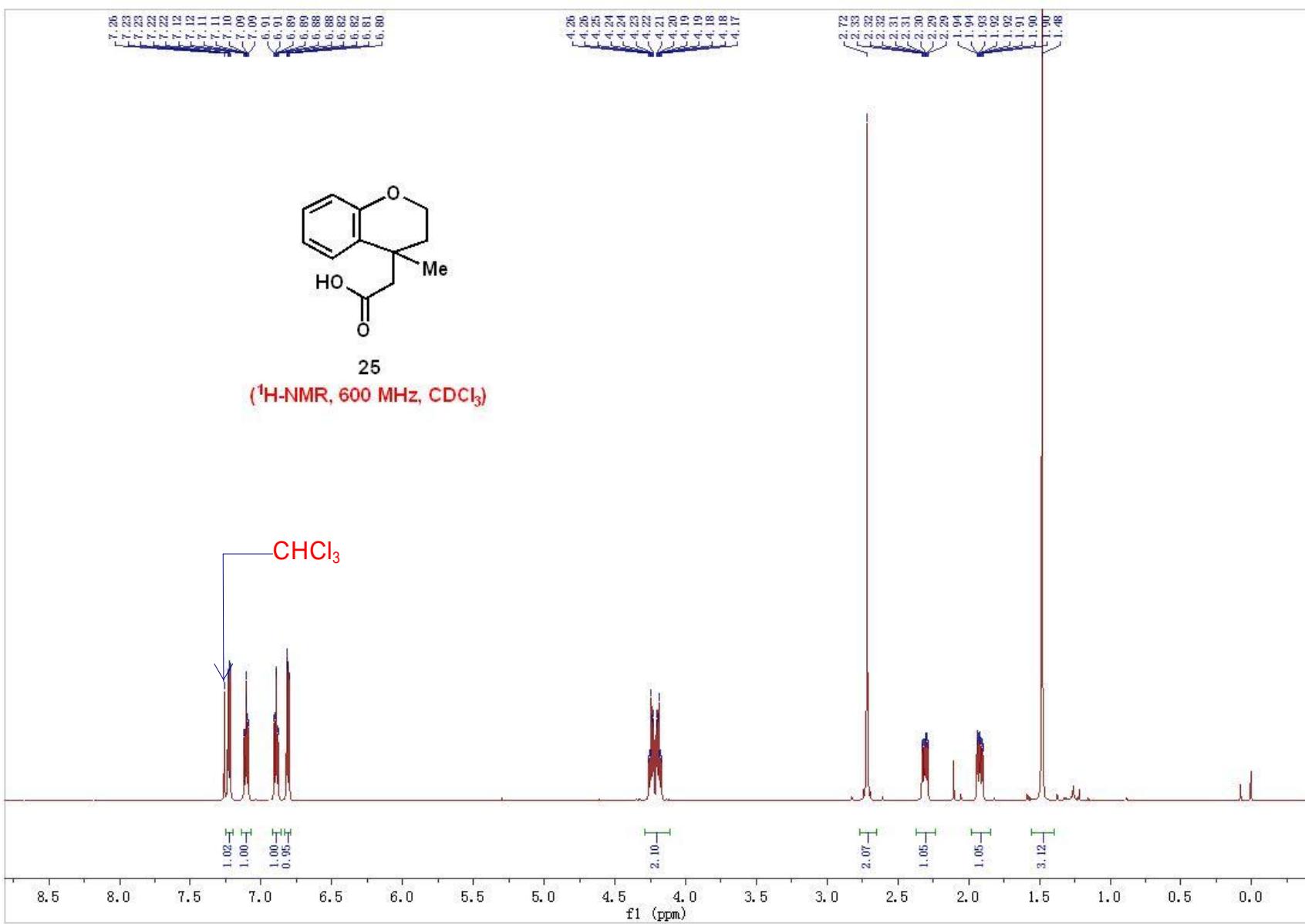


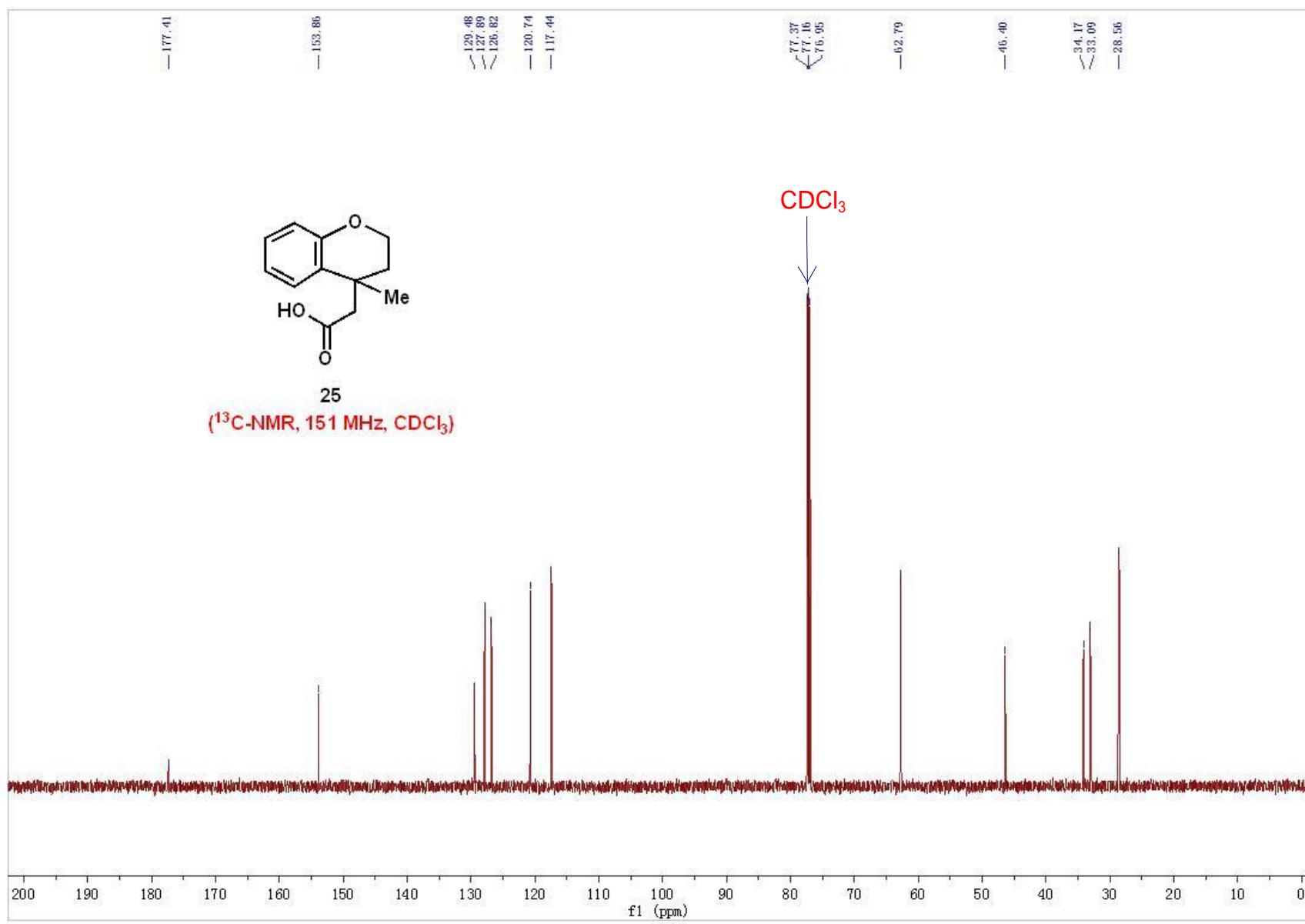


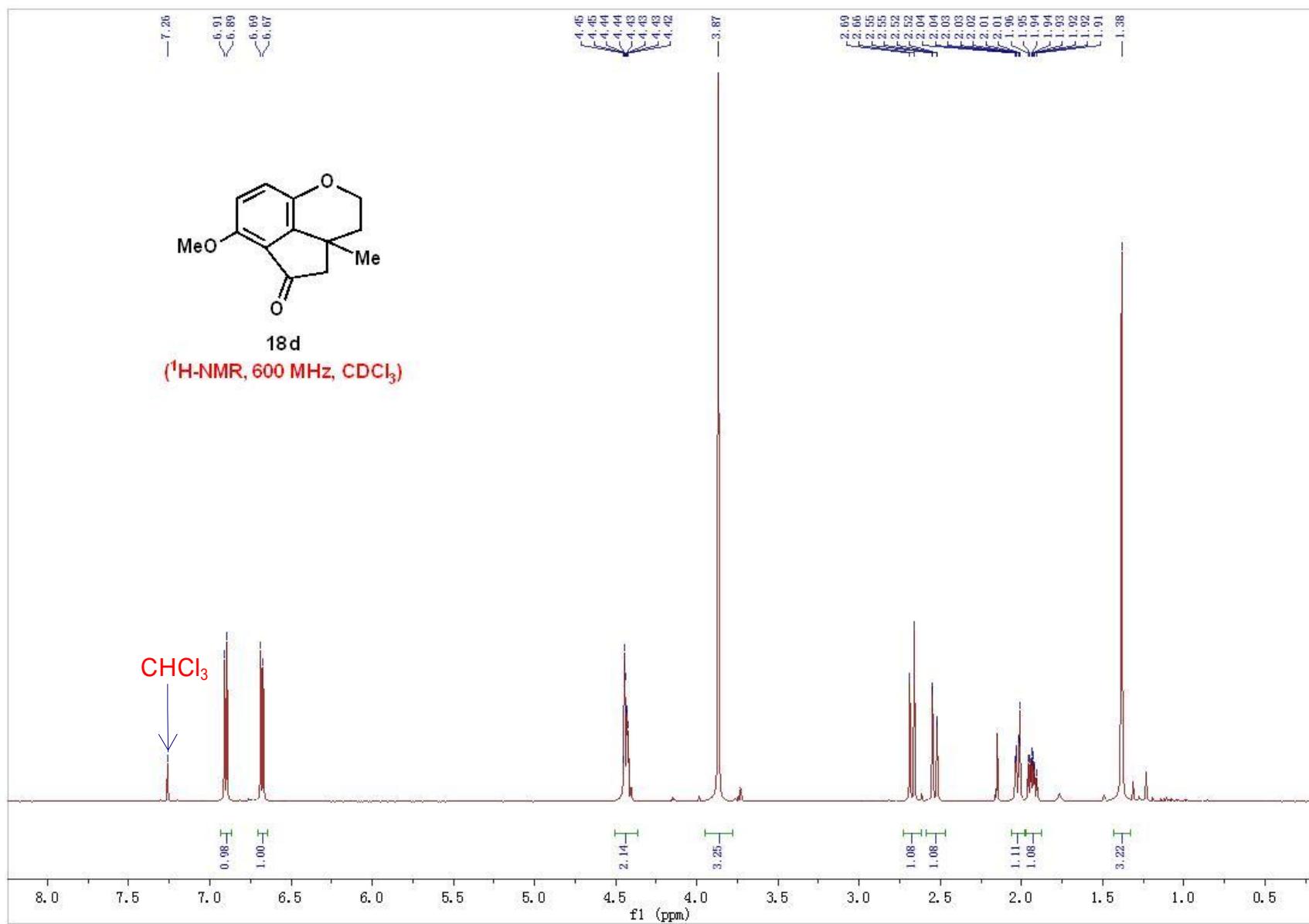


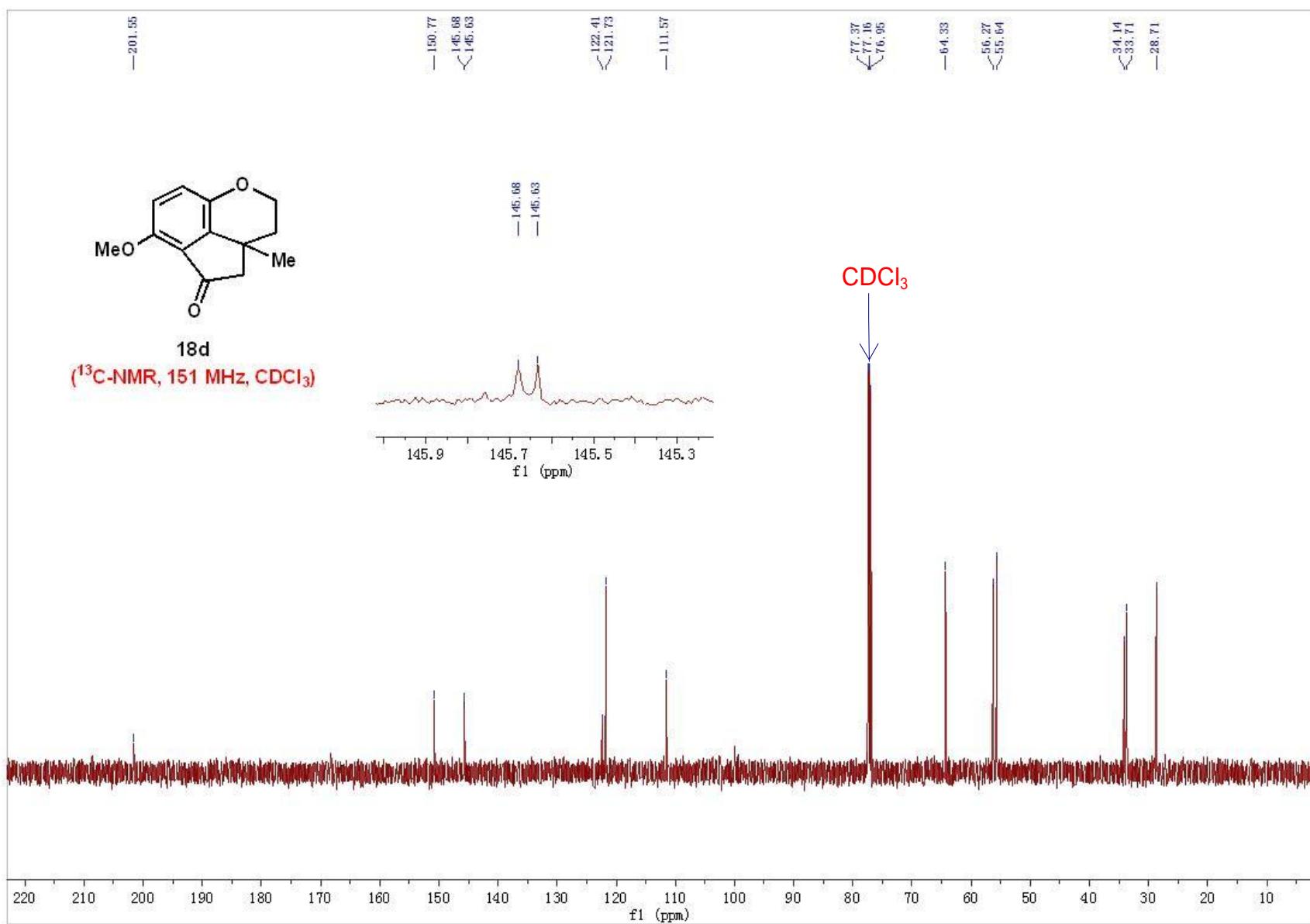


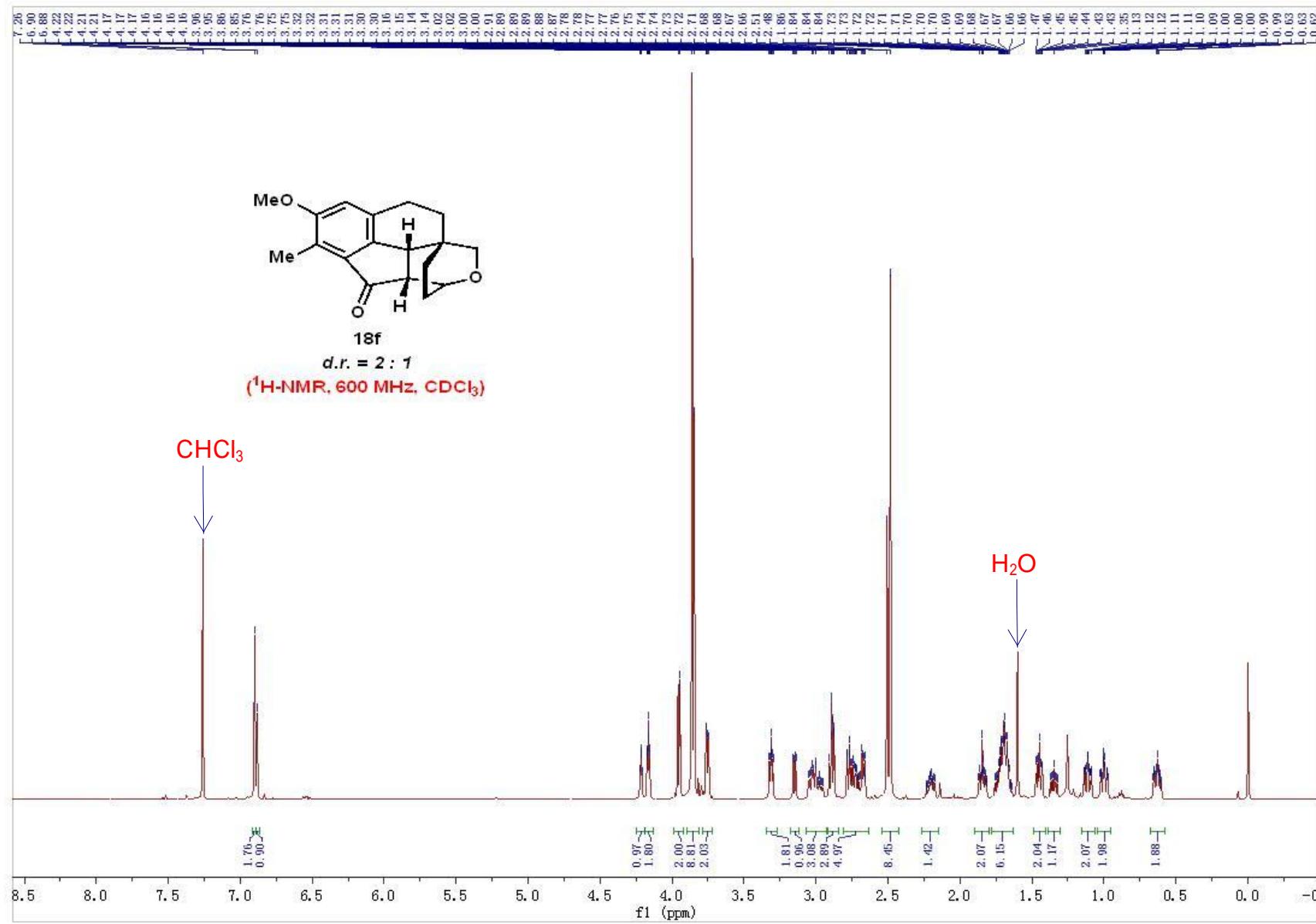


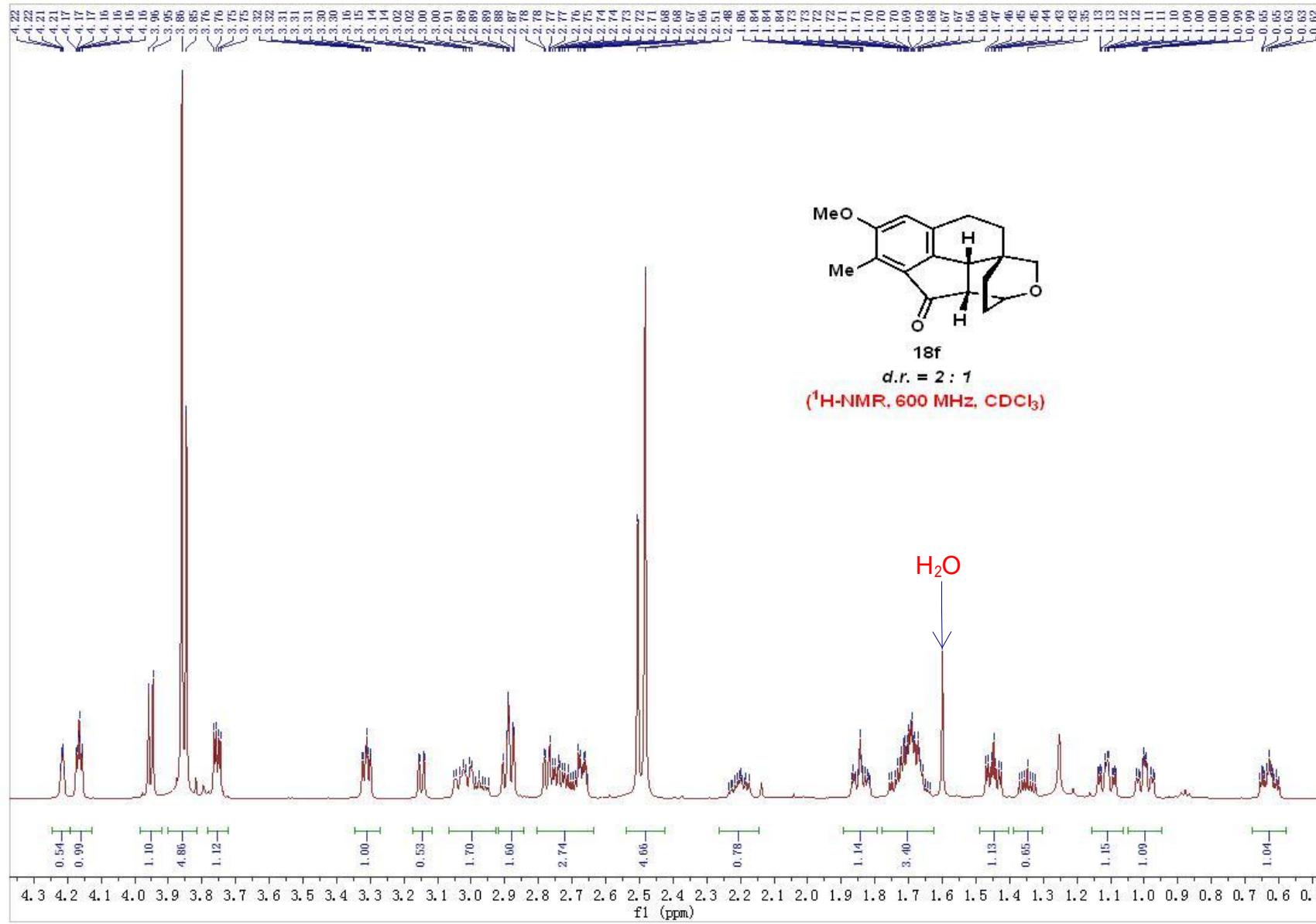


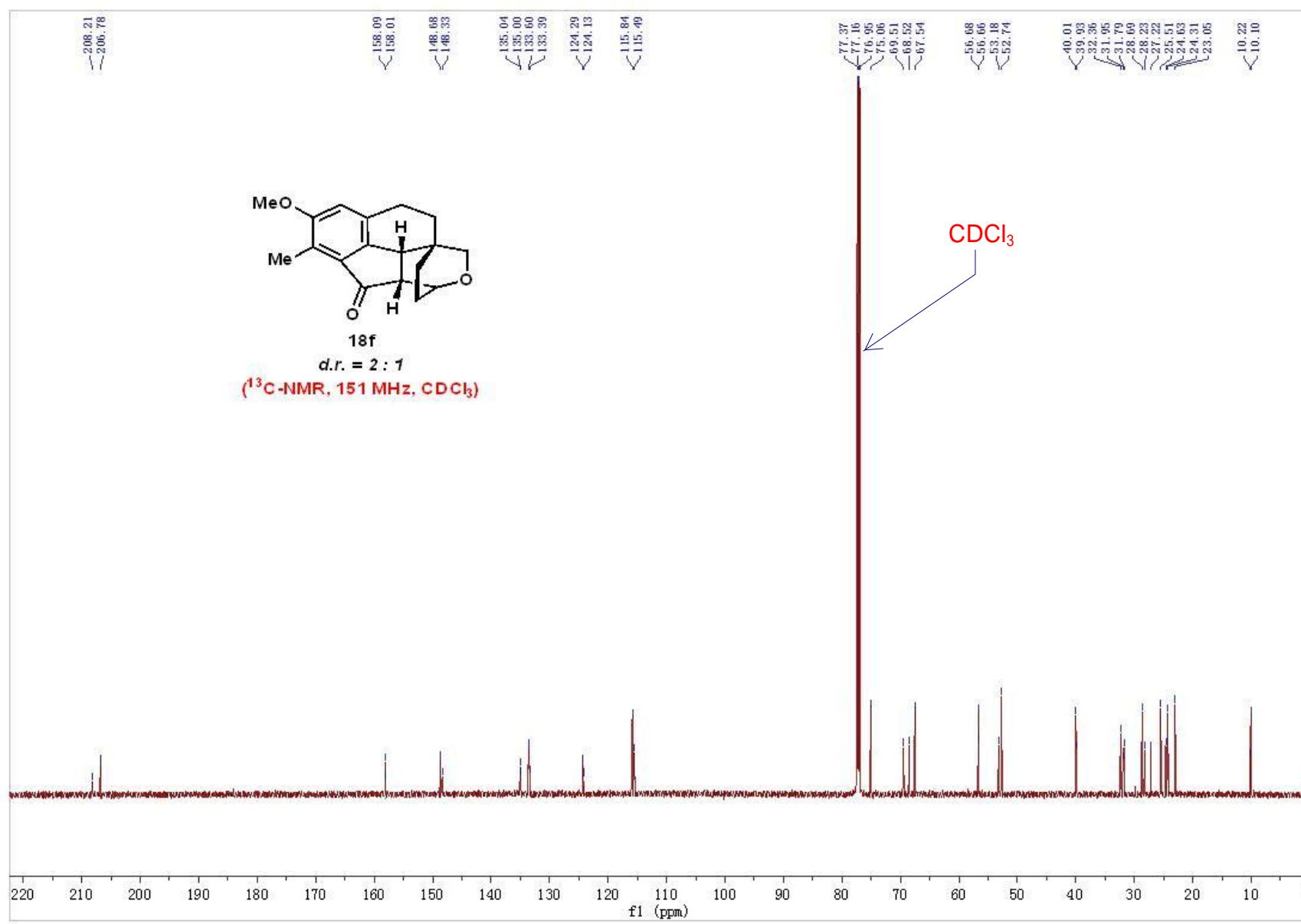


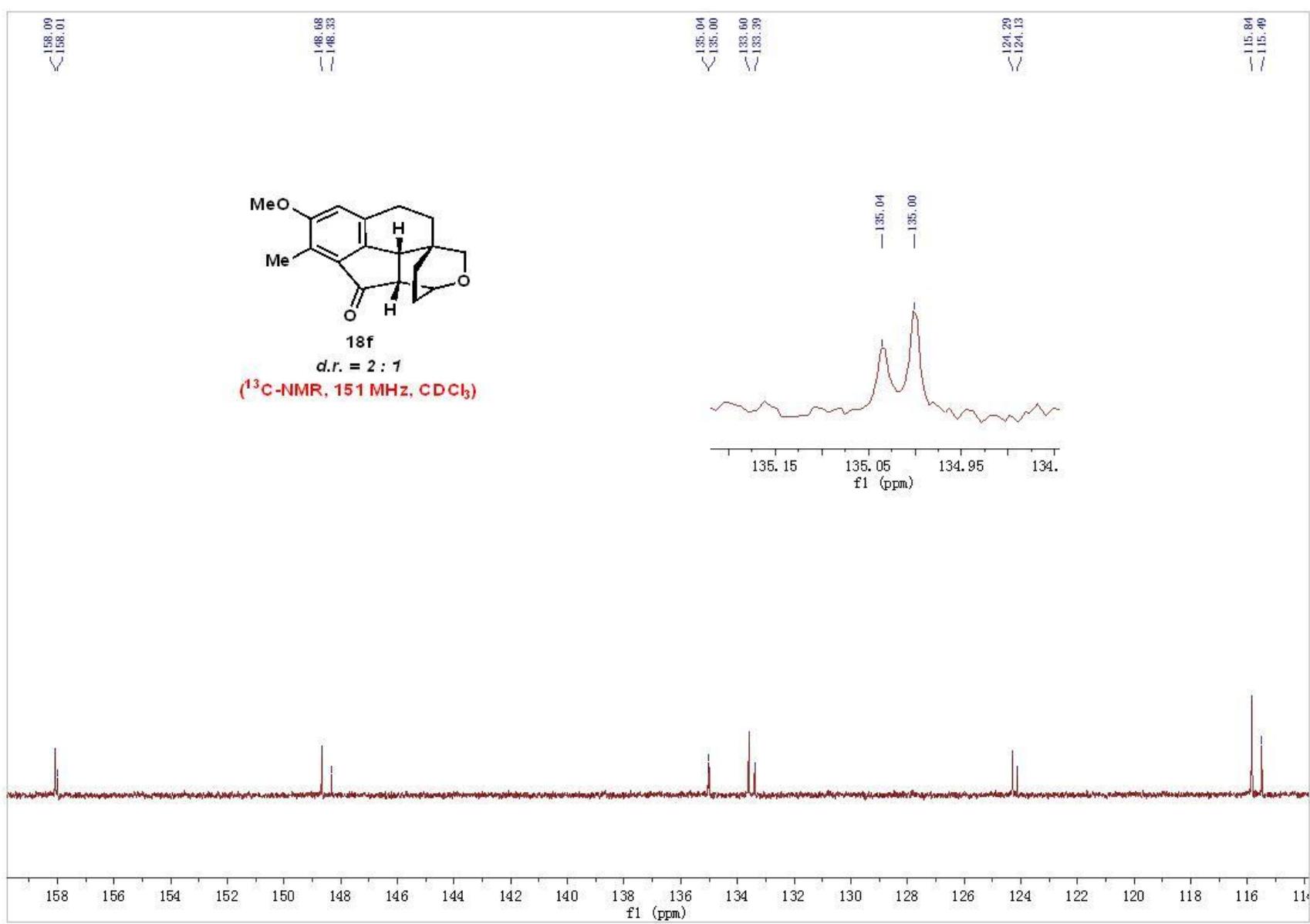


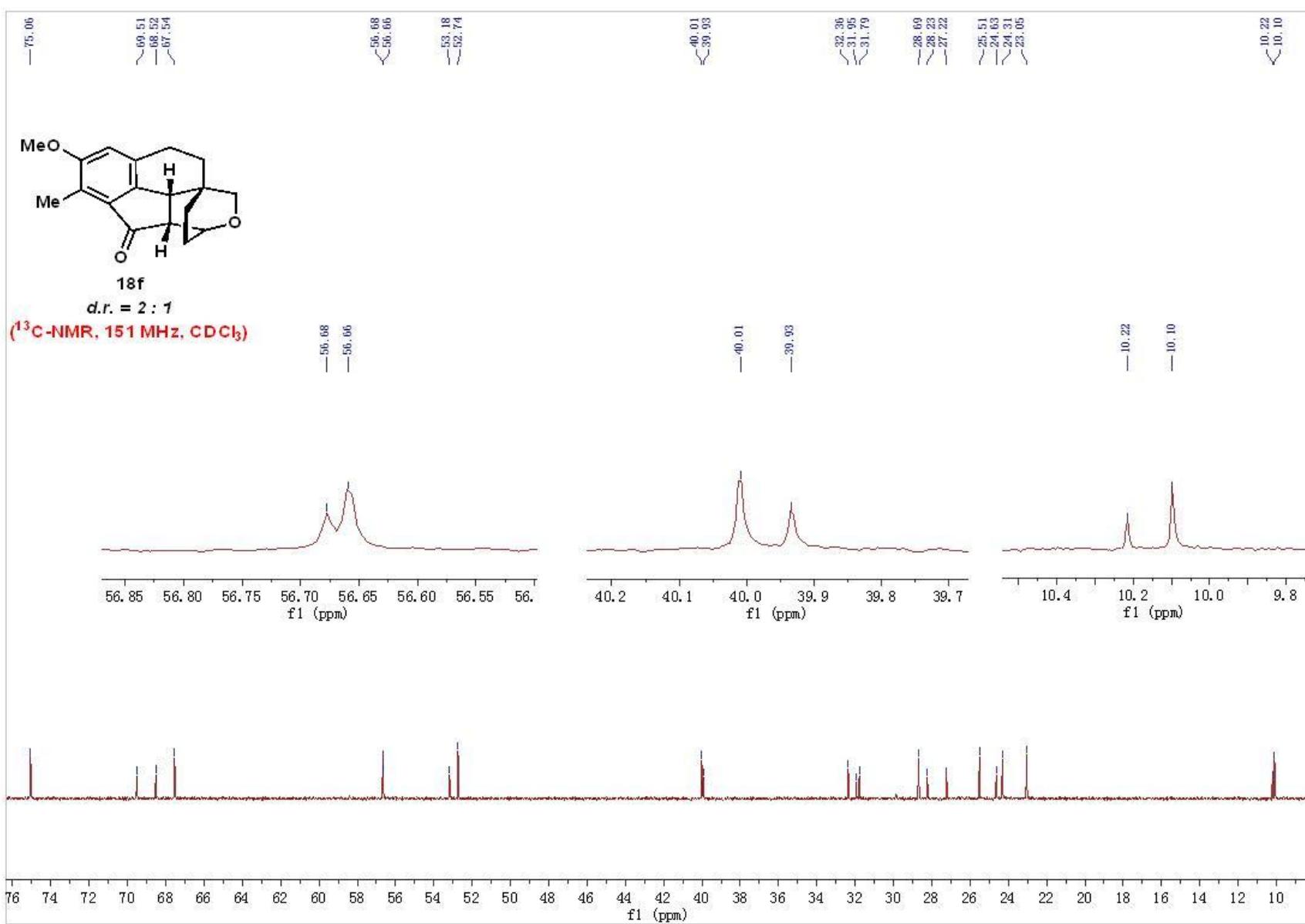


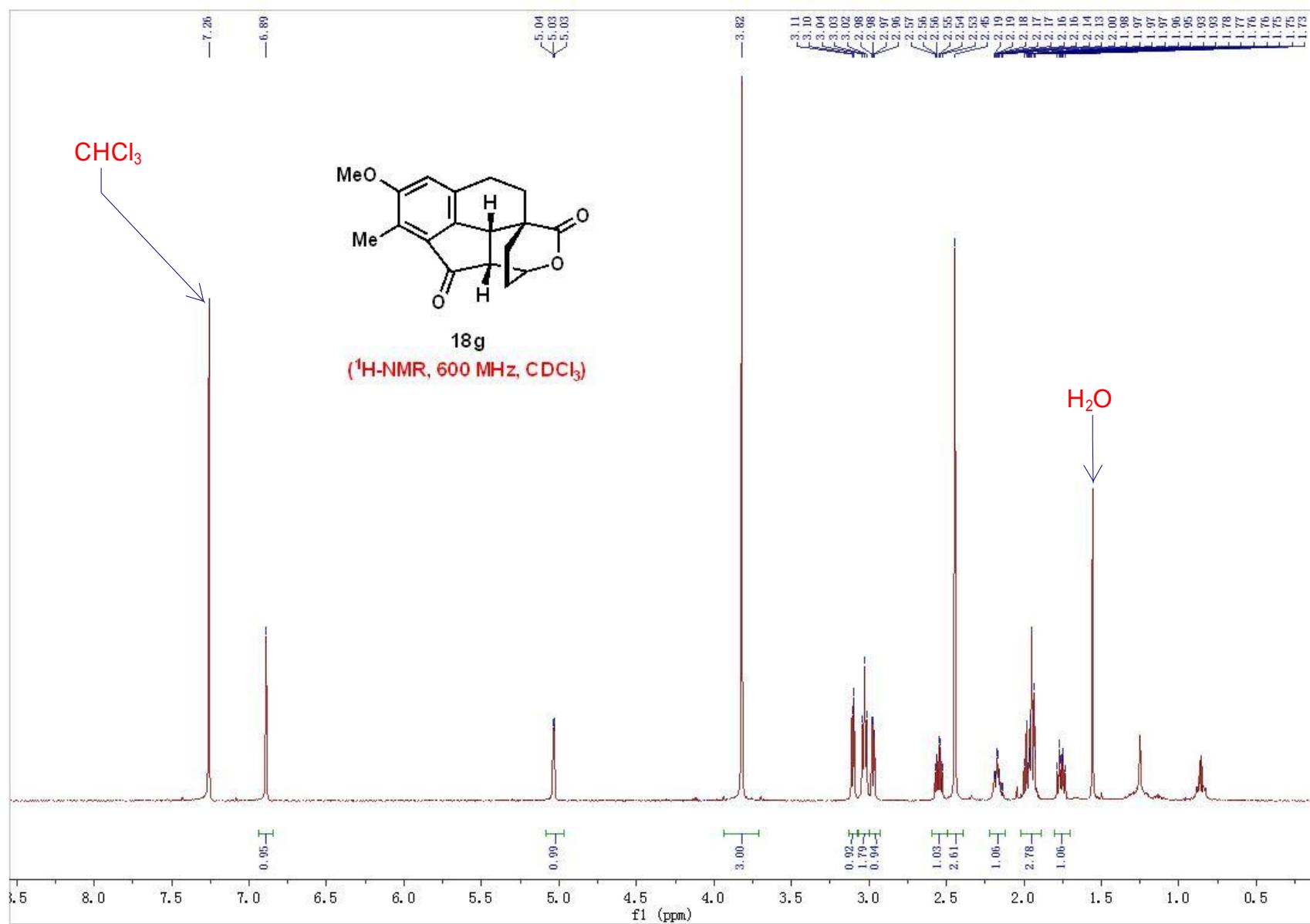


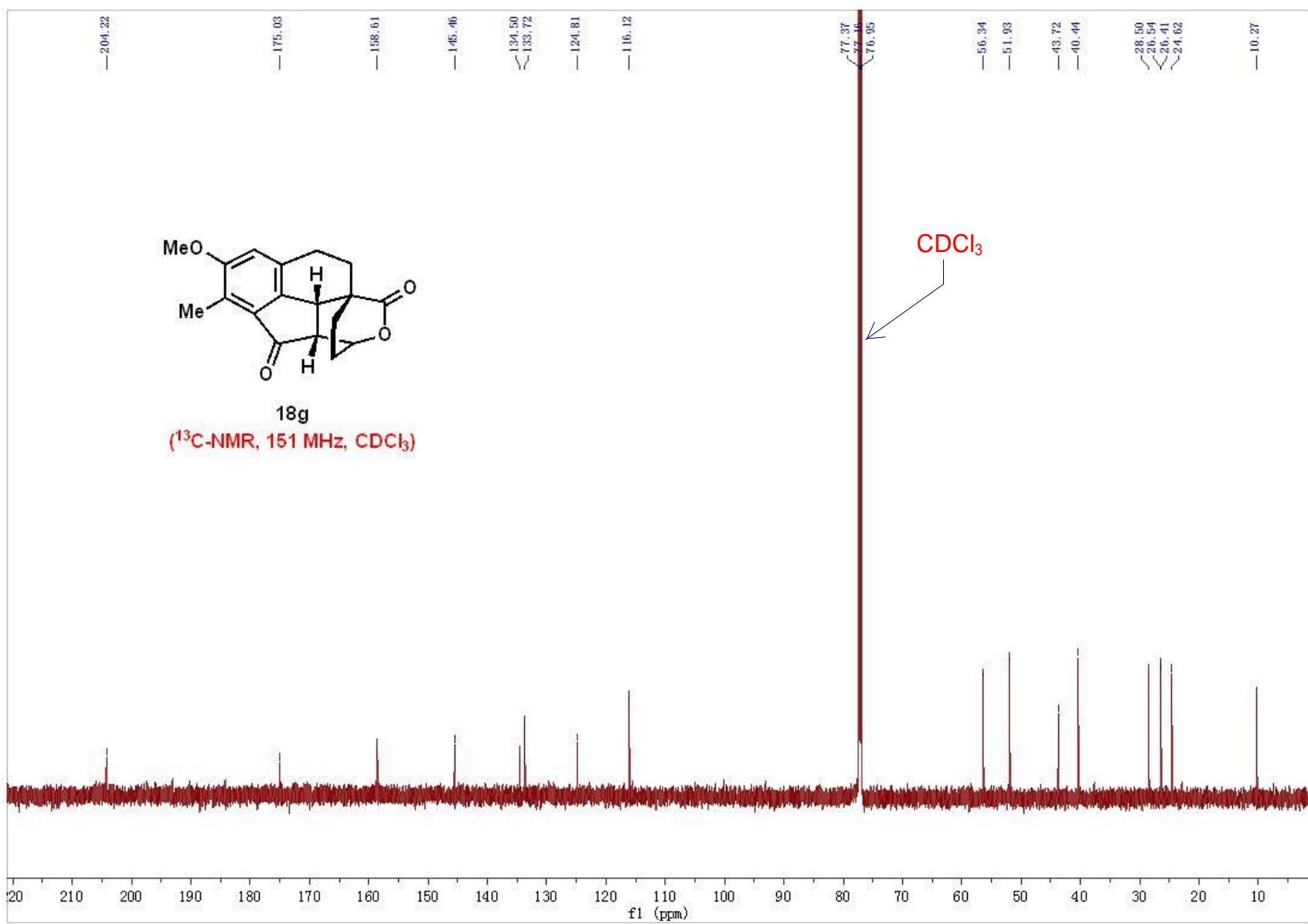


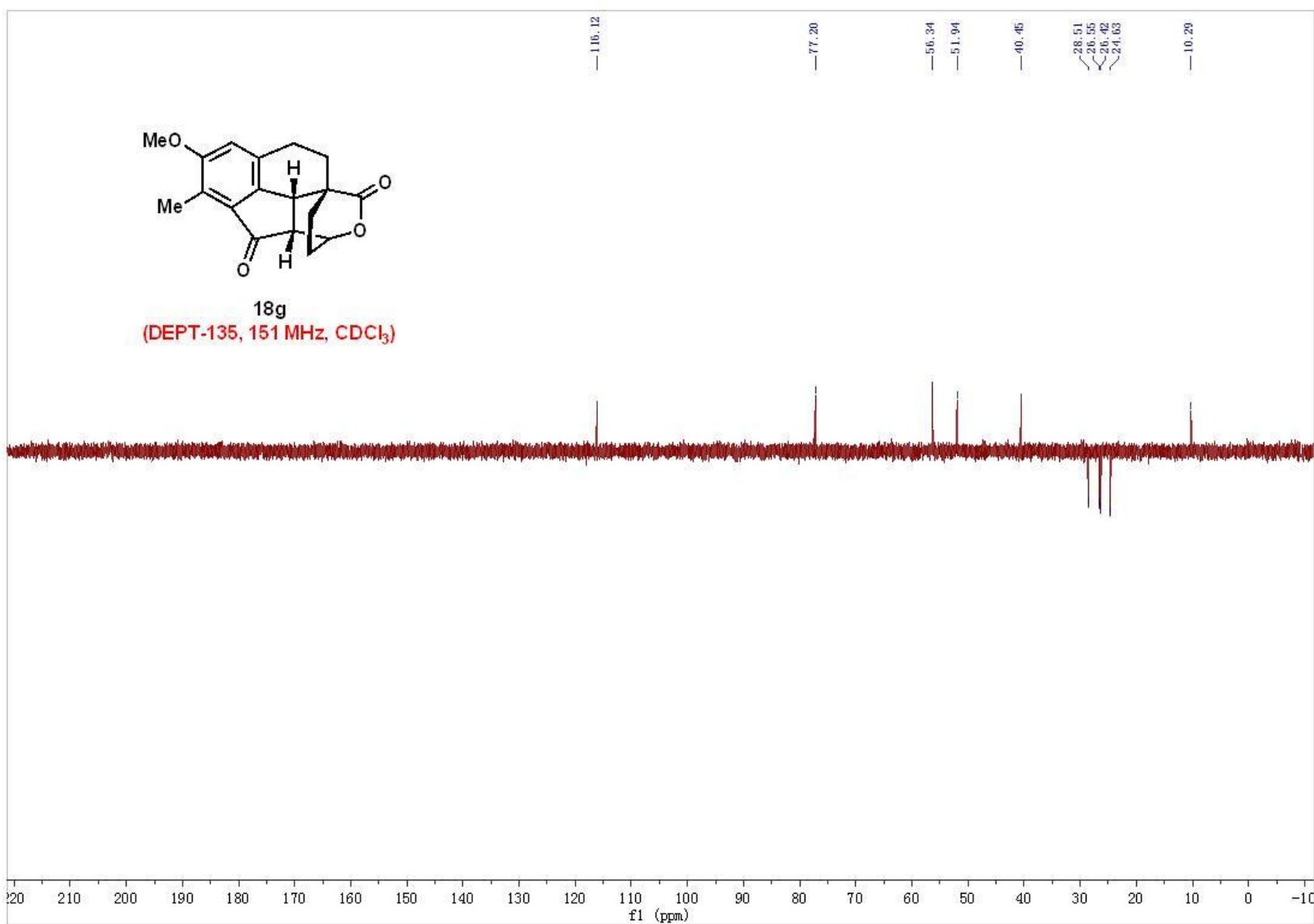


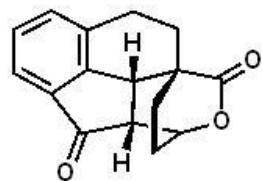




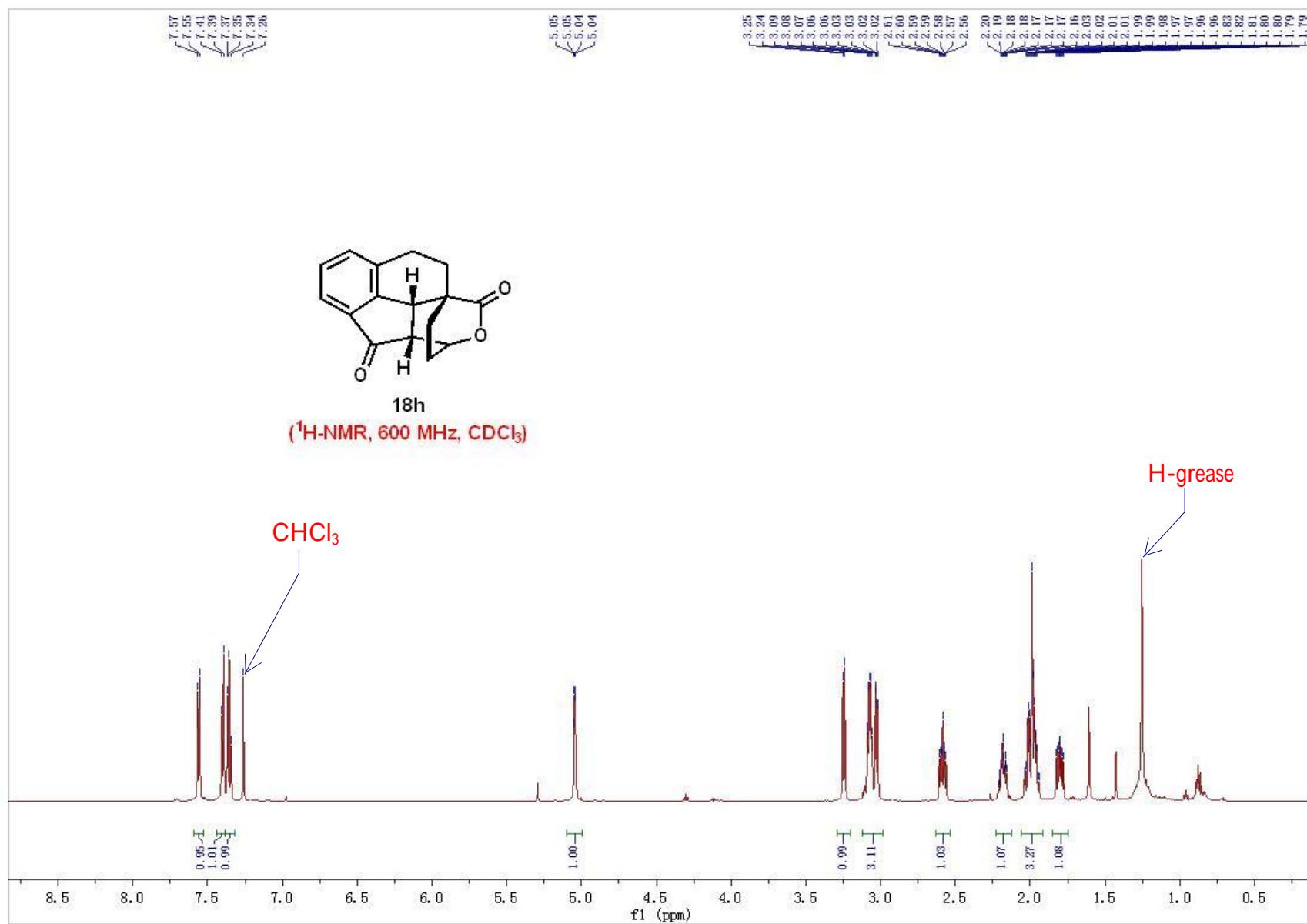


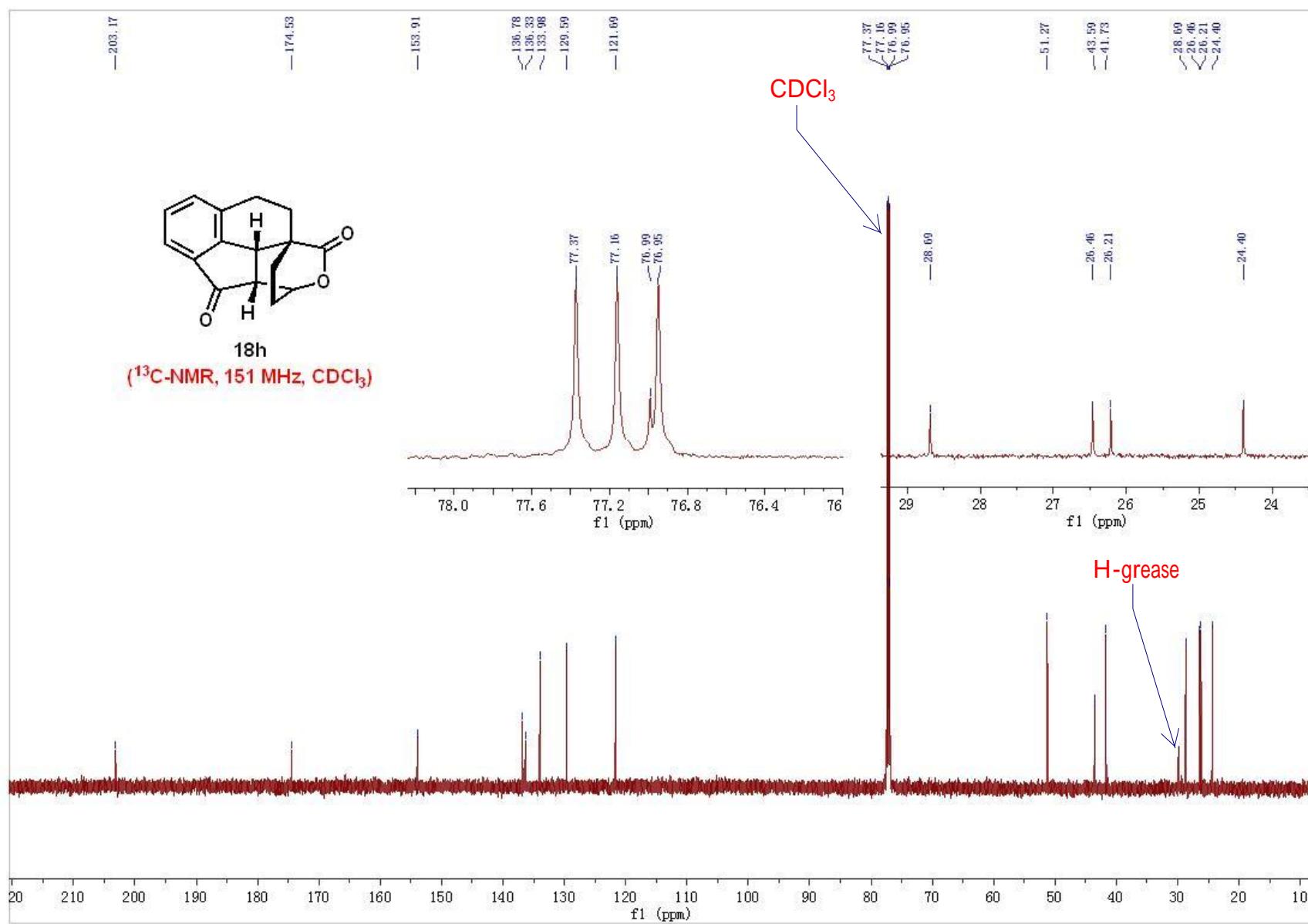


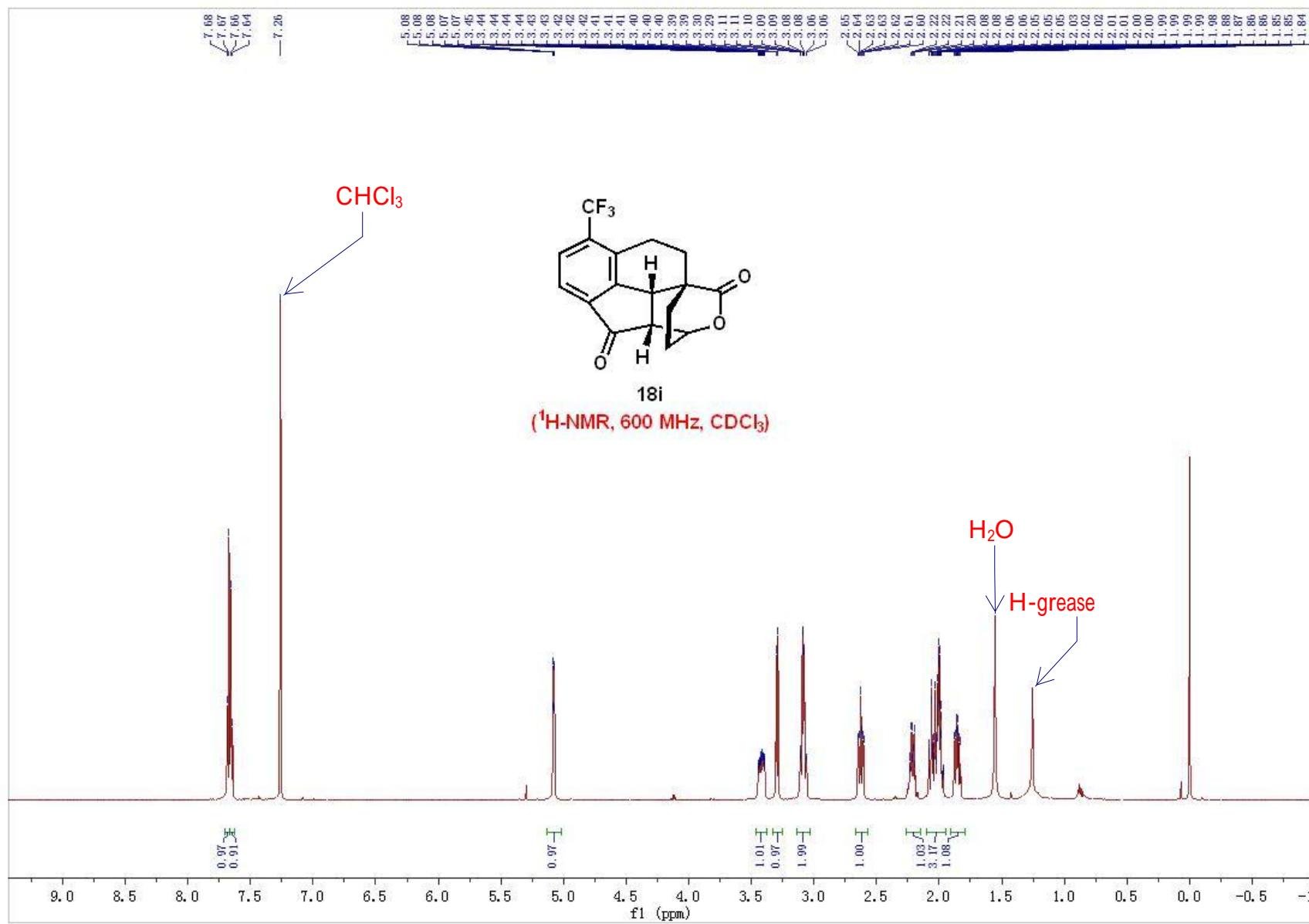




<sup>1H</sup>NMR, 600 MHz, CDCl<sub>3</sub>)









( $^{13}\text{C}$ -NMR, 151 MHz,  $\text{CDCl}_3$ )

