

*Supplementary Information for*

## **Concise syntheses of (+)-maximumins B and C and (+)- ottensinin**

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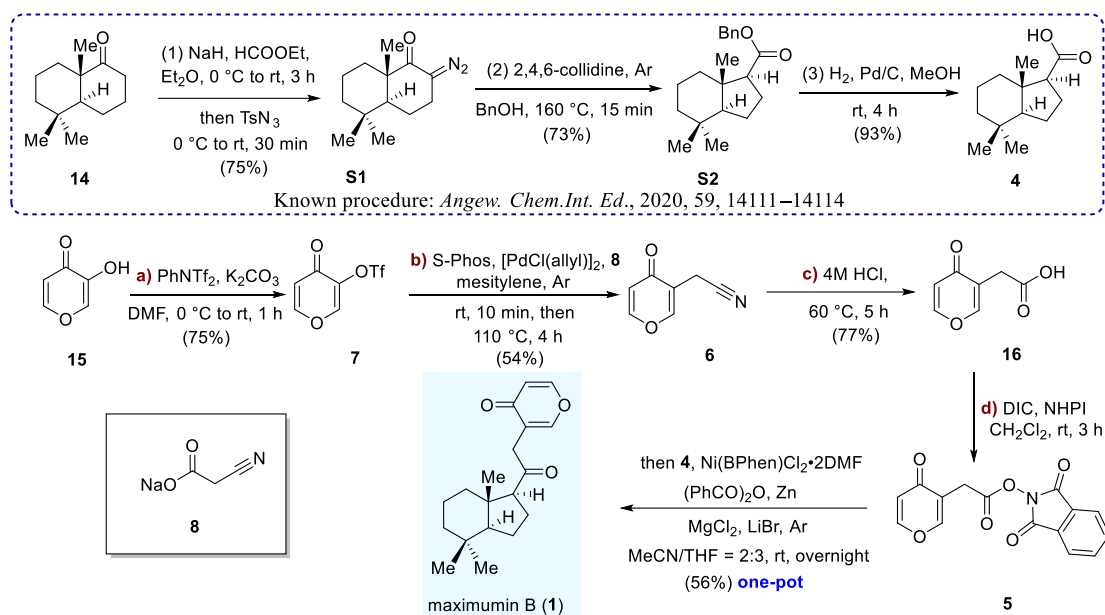
## General experimental

Unless otherwise stated, all reactions were carried out under anhydrous conditions. Super-dried solvents and reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) or LC/MS. TLC was performed using precoated silica gel 60 F254 (Merck), using short-wave UV light as the visualizing agent, and cerium molybdate (CAM or Hanessian's stain), phosphomolybdic acid (PMA), or KMnO<sub>4</sub> and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). NMR data were obtained on Bruker AVANCE III 400, AVANCE III 500, Ascend 600 and/or Ascend 800 NMR spectrometers referenced to deuterated solvent peaks ( $\delta_{\text{H}}$  7.26 in CDCl<sub>3</sub> or 4.87 in CD<sub>3</sub>OD,  $\delta_{\text{C}}$  77.16 in CDCl<sub>3</sub>, 49.00 in CD<sub>3</sub>OD).

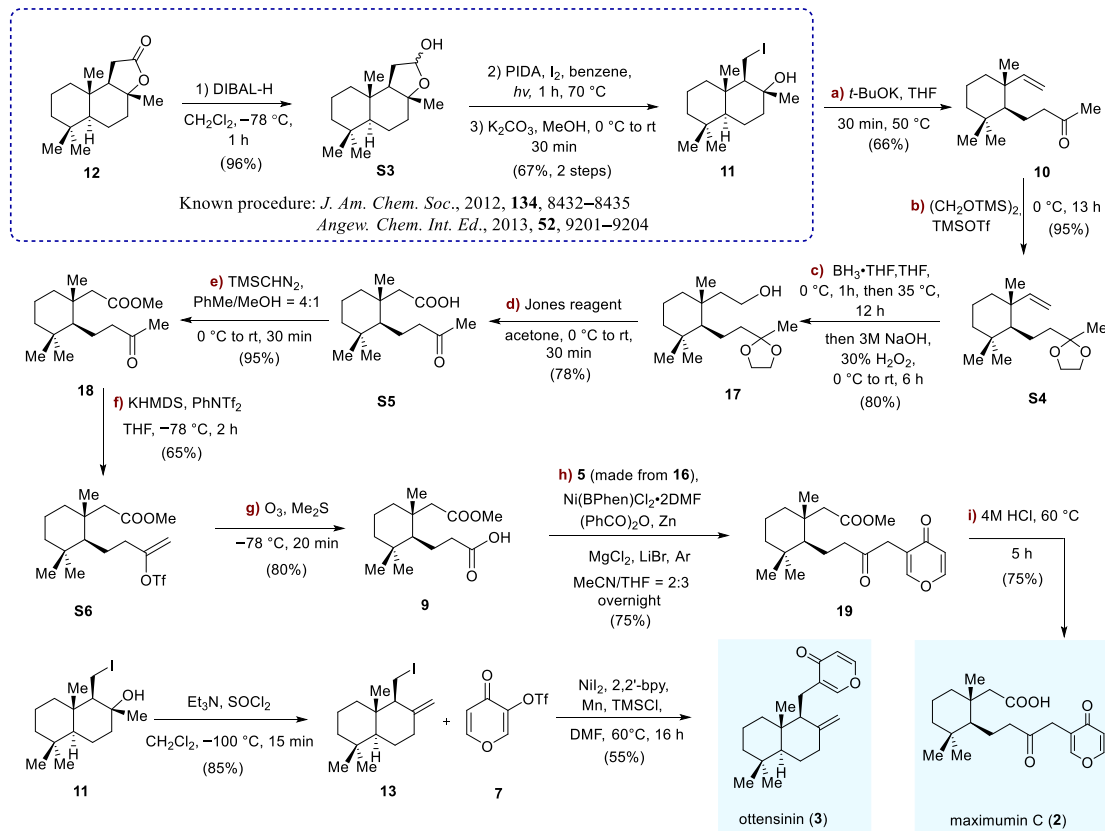
The X-ray diffraction analysis was performed on a Bruker SMART CCD detector employing graphite monochromated Cu-K $\alpha$  radiation. Melting points were recorded on an SGM X-4 apparatus. ESIMS and HRESIMS were implemented on a Bruker Daltonics Esquire 3000 plus and Waters-Micromass Q-TOF Ultima Global mass spectrometer, respectively.

# Full synthetic sequence

## Synthesis of (+)-maximumin B (1)

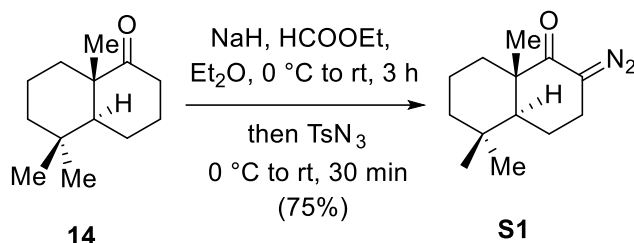


## Syntheses of (+)-maximumin C (2) and ottensinin (3)



## Experimental procedures and characterization data for new compounds

### Compound S1



**Experimental:** To a stirred suspension of NaH (29 mg, 0.727 mmol, 60% dispersed in oil, 3 equiv) in 2 mL Et<sub>2</sub>O was added **14** (47 mg, 0.242 mmol, 1 equiv) in 2 mL Et<sub>2</sub>O at 0 °C. HCO<sub>2</sub>Et (54 mg, 0.727 mmol, 3 equiv) and 2 drops of EtOH were then added. The mixture was warmed to room temperature. After stirring for 3 hours, the mixture was cooled to 0 °C and a solution of TsN<sub>3</sub> (238 mg, 1.21 mmol, 5 equiv) in 1 mL Et<sub>2</sub>O was added dropwise and stirred for 30 min under the same temperature. Upon reaction completion (monitored by TLC), the reaction was quenched with 10% NaOH (1 mL), and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Concentration *in vacuo* afforded a crude residue, which was purified by column chromatography (PE : EA = 20 : 1) to provide **S1** (40 mg, 75% yield) as a yellow oil.

**Physical state:** yellow oil;

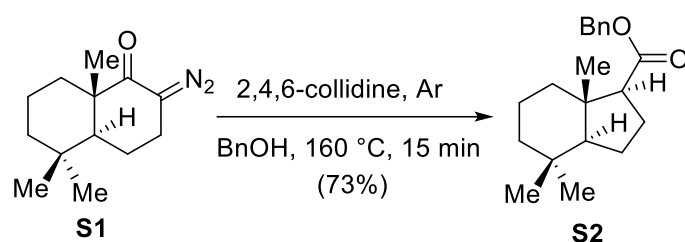
**TLC:** R<sub>f</sub> = 0.20 (PE : EA = 20 : 1);

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 2.77 – 2.65 (m, 2H), 2.11 – 2.05 (m, 1H), 1.90 – 1.83 (m, 1H), 1.63 – 1.52 (m, 3H), 1.47 – 1.40 (m, 1H), 1.31 – 1.22 (m, 3H), 1.19 – 1.13 (m, 4H), 0.94 (s, 3H), 0.88 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 201.4, 77.4, 77.2, 76.9, 61.3, 49.0, 46.3, 41.5, 34.6, 33.8, 33.1, 22.0, 21.2, 19.6, 18.4, 18.0.;

**HRMS(ESI-TOF):** calc'd for C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>ONa [M + Na]<sup>+</sup>: 243.1468, found: 243.1469.

## Compound S2



**Experimental:** The solution of **S1** (30.6 mg, 0.139 mmol) in 2,4,6-collidine (0.5 mL) and BnOH (0.5 mL) was purged with argon for 15 min. Then, the mixture was heated to 160 °C, and stirred for 30 min before being cooled to room temperature and diluted with EtOAc (7 mL). The organic layer was washed sequentially with 1M HCl (5 mL) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. Concentration *in vacuo* afforded a crude residue, which was purified via column chromatography (PE:EA = 100:1) to provide **S2** (30.5 mg, 0.101 mmol, 73% yield) as a colorless oil.

**Physical state:** colorless oil;

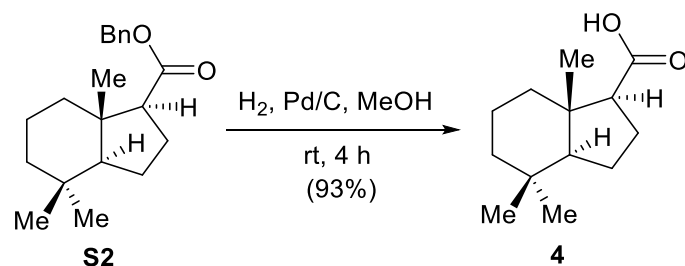
**TLC:** R<sub>f</sub> = 0.20 (PE:EA = 100:1);

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.37 – 7.28 (m, 5H), 5.15 – 5.08 (m, 2H), 2.36 (t, *J* = 9.6 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.92 (d, *J* = 12.9 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.68 – 1.61 (m, 1H), 1.60 – 1.54 (m, 1H), 1.52 – 1.42 (m, 3H), 1.23 – 1.16 (m, 2H), 1.09 – 1.02 (m, 1H), 0.86 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 174.1, 136.5, 128.6, 128.3, 128.1, 66.1, 58.4, 57.1, 44.5, 41.6, 39.4, 33.5, 33.4, 22.7, 21.1, 20.7, 19.9, 14.9;

**HRMS(ESI-TOF):** calc'd for C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup>: 323.1982, found: 323.1983.

## Compound 4



**Experimental:** Compound **S2** (30.4 mg, 0.1 mmol) was dissolved in 10 mL MeOH followed by addition of Pd/C (10 mg). The mixture was evacuated and backfilled with

hydrogen (3 times), and stirred at room temperature for 4 hours. Upon reaction completion (monitored by TLC), the resulting mixture was filtered over a pad of celite, and then concentrated *in vacuo*. The crude residue was purified via column chromatography (PE:EA = 10:1) to provide **4** (19.8 mg, 0.093 mmol, 93% yield) as a white solid.

**Physical state:** white solid;

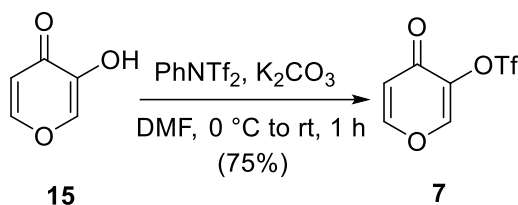
**TLC:**  $R_f = 0.20$  (PE:EA = 20:1);

**$^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  2.36 (t,  $J = 9.5$  Hz, 1H), 2.09 – 1.98 (m, 2H), 1.84 – 1.75 (m, 1H), 1.69 – 1.64 (m, 1H), 1.64 – 1.60 (m, 1H), 1.60 – 1.55 (m, 1H), 1.53 – 1.42 (m, 2H), 1.23 – 1.16 (m, 2H), 1.10 – 1.03 (m, 1H), 0.87 (s, 6H), 0.81 (s, 3H).

**$^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  178.7, 58.4, 56.8, 44.4, 41.5, 39.2, 33.5, 33.4, 22.5, 21.1, 20.8, 19.9, 14.8.

**HRMS(ESI-TOF):** calc'd for  $\text{C}_{13}\text{H}_{23}\text{O}_2$   $[\text{M} + \text{H}]^+$ : 211.1693, found: 211.1690.

## Compound 7



**Experimental:** To a solution of compound **15** (200.0 mg, 1.78 mmol, 1.0 equiv) in 10 mL DMF was added  $\text{K}_2\text{CO}_3$  (492 mg, 3.56 mmol, 2.0 equiv) at 0 °C. After stirring for 5 min,  $\text{PhNTf}_2$  (701 mg, 1.962 mmol, 1.1 equiv) was added. The mixture was allowed to stir at room temperature for 1 h (monitored by TLC). Then, the mixture was diluted with water and extracted with EtOAc (3×15 mL). The organic phase was sequentially washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and then evaporated under reduced pressure. Chromatography purification of the residue on silica gel using petroleum ether and ethyl acetate (PE:EA = 5:1 to 2:1) as the eluent to afford **7** (325 mg) in 75% yield.

**Physical state:** white solid;

**TLC:**  $R_f = 0.20$  (PE:EA = 5:1);

**$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.11 (d,  $J = 0.9$  Hz, 1H), 7.81 (dd,  $J = 5.8, 0.9$  Hz, 1H),

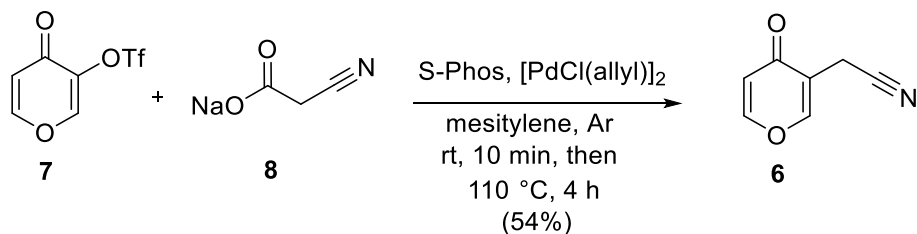


6.58 (d,  $J = 5.7$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.4, 155.6, 150.0, 141.8, 118.8.

HRMS(ESI-TOF): calc'd for  $\text{C}_6\text{H}_4\text{O}_5\text{S}$   $[\text{M} + \text{H}]^+$ : 244.9726, found: 244.9727.

### Compound 6



**Experimental:** An oven-dried 10 mL round-bottomed flask equipped with a stir bar was charged with **7** (50 mg, 0.205 mmol, 1 equiv), allyl palladium (II) chloride dimer (7.5 mg, 0.0205 mmol, 0.1 equiv), S-Phos (9.9 mg, 0.062 mmol, 0.3 equiv), and sodium 2-cyanoacetate (**8**, 33 mg, 0.308 mmol, 1.5 equiv). The mixture was evacuated and backfilled with argon (3 times). Then, 1 mL degassed mesitylene was added to the mixture. The flask was capped, and the reaction mixture was stirred at room temperature for 10 minutes before submerging in an oil bath that was preheated to 110 °C. The reaction mixture was stirred for another 4 h. At this point, the starting material was completely consumed, and the nitrile **6** was generated, as indicated by TLC. The mixture was then cooled to room temperature and diluted with EtOAc and 1M HCl. The mixture was extracted with EtOAc (3×4 mL), and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and filtered. Concentration *in vacuo* afforded a crude residue, which was purified by column chromatography (PE:EA=2:1), affording **6** (15 mg, 0.11 mmol, 54% yield) as a yellow solid.

**Physical state:** yellow solid;

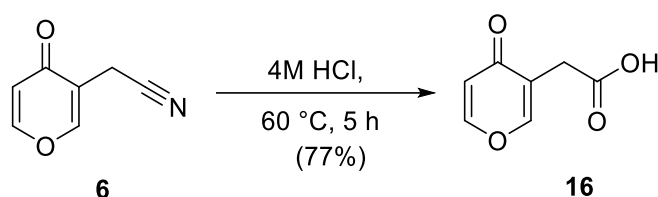
**TLC:**  $R_f = 0.20$  (PE:EA = 1:1);

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 (d,  $J = 1.6$  Hz, 1H), 7.82 (dd,  $J = 5.8, 0.9$  Hz, 1H), 6.42 (d,  $J = 5.8$  Hz, 1H), 3.51 (dd,  $J = 1.4, 0.7$  Hz, 2H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.0, 156.1, 153.2, 121.3, 116.6, 116.2, 14.7.

HRMS(ESI-TOF): calc'd for  $\text{C}_7\text{H}_6\text{O}_2$   $[\text{M} + \text{H}]^+$ : 136.0393, found: 211.136.0391.

## Compound 16



**Experimental:** Nitrile **6** (15.0 mg, 0.11 mmol) was dissolved in 5 mL 4M HCl. The reaction was heated to 60 °C and stirred for 5 hours. Then, the mixture was cooled to room temperature and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH=20:1, 0.3% HCOOH), affording **16** (13.2 mg, 77%) as a yellow solid.

**Physical state:** yellow solid;

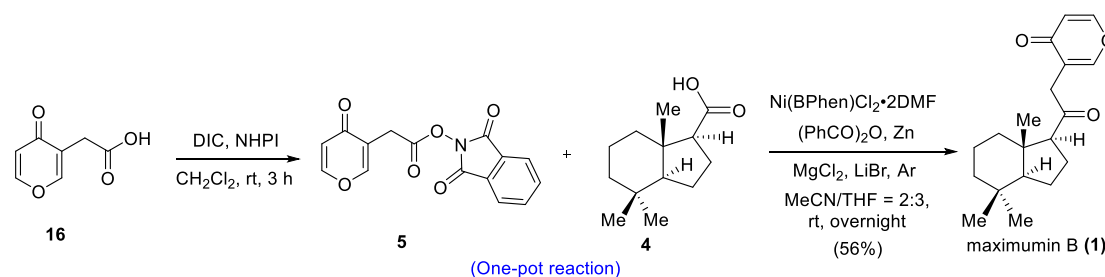
**TLC:** R<sub>f</sub> = 0.50 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 10:1, 0.1% HCOOH);

**<sup>1</sup>H NMR (500 MHz, MeOD):** δ 8.11 (s, 1H), 8.05 (dd, *J* = 5.8, 1.0 Hz, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 3.35 (d, *J* = 0.9 Hz, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 180.2, 173.9, 158.6, 156.9, 125.7, 117.0, 31.4.

**HRMS(ESI-TOF):** calc'd for C<sub>7</sub>H<sub>6</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 177.0158, found: 177.0161.

## Compound 1



**Experimental:** A flask was charged with acid **16** (10 mg, 0.065 mmol, 1 equiv) and *N*-hydroxyphthalimide (NHPI, 11.3 mg, 0.069 mmol, 1.05 equiv). 3 mL CH<sub>2</sub>Cl<sub>2</sub> was added, and the mixture was stirred vigorously. Then, *N,N'*-diisopropylcarbodiimide (DIC, 9.9 mg, 0.078 mmol, 1.1 equiv) was added dropwise via syringe, and the mixture was allowed to stir for 3 h. Upon reaction completion, the solvent was removed on a rotary evaporator at 35 °C under reduced pressure and dried on a high-vacuum line for at least 5 minutes to remove residual CH<sub>2</sub>Cl<sub>2</sub>. Next, acid **4** (27.3 mg, 0.13 mmol, 2 equiv), Ni(BPhen)Cl<sub>2</sub>·2DMF (12 mg, 0.02 mmol, 30 mol%), Zn (12.8 mg, 0.195 mmol,

3 equiv), benzoic anhydride (32.4 mg, 0.143 mmol, 2.2 equiv), MgCl<sub>2</sub> (9.3 mg, 0.098 mmol, 1.5 equiv), and LiBr (5.6 mg, 0.065 mmol, 1 equiv) were added to the same flask, which was evacuated and backfilled with argon (three times). Subsequently, 3 mL of anhydrous and deoxygenated mixture of MeCN/THF (1 : 1.5) was added using a syringe. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (3×5 mL), washed with HCl (1 M), K<sub>2</sub>CO<sub>3</sub> (1 M), and dried over Na<sub>2</sub>SO<sub>4</sub>. Upon filtration, the organic layer was concentrated under reduced pressure, and the residue was purified by flash column chromatography to afford the desired product **1** (11.0 mg, 56%).

**Physical state:** white solid;

**TLC:** R<sub>f</sub> = 0.20 (PE : EA = 1 : 1);

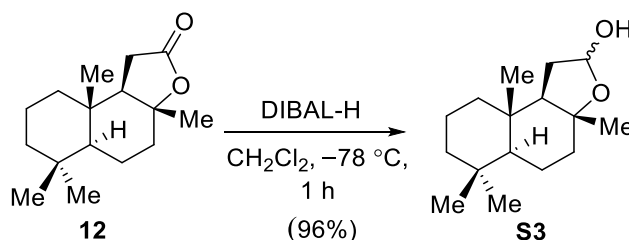
**Specific rotation:**  $[\alpha]_{\text{D}}^{18} = +150$  ( $c = 0.045$ , MeOH);

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  7.74 (s, 1H), 7.71 (d,  $J = 5.7$  Hz, 1H), 6.33 (d,  $J = 5.7$  Hz, 1H), 3.38 (s, 2H), 2.67 (t,  $J = 8.9$  Hz, 1H), 2.19 – 2.14 (m, 1H), 2.14 – 2.11 (m, 1H), 1.70 – 1.66 (m, 1H), 1.65 – 1.63 (m, 1H), 1.63 – 1.54 (m, 2H), 1.48 – 1.45 (m, 1H), 1.46 – 1.43 (m, 1H), 1.40 (td,  $J = 12.9, 4.2$  Hz, 1H), 1.28 (dd,  $J = 13.2, 6.5$  Hz, 1H), 1.10 (td,  $J = 13.4, 4.4$  Hz, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.74 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  207.3, 177.6, 155.4, 154.1, 124.7, 116.8, 64.9, 59.0, 44.9, 41.4, 39.9, 39.7, 33.5, 33.5, 22.2, 21.1, 20.8, 20.1, 14.8.

**HRMS(ESI-TOF):** calc'd for C<sub>19</sub>H<sub>27</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 303.1955, found: 303.1956.

### Compound S3

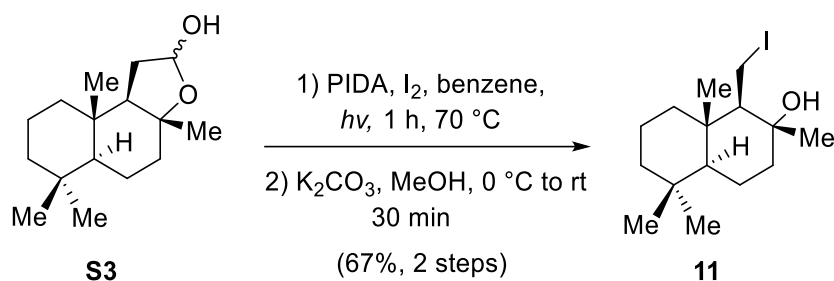


**Experimental:** To a solution of (+)-sclareolide (**12**, 12.0 g, 48.0 mmol, 1.0 equiv) in 300 mL CH<sub>2</sub>Cl<sub>2</sub> at -78 °C was added DIBAL-H (1.5 M in heptane, 38.4 mL, 57.6 mmol, 1.2 equiv) dropwise over 10 min via syringe along the wall of the flask. The reaction

mixture was then stirred for additional 60 min. A saturated aqueous solution of Rochelles salt was slowly added to the reaction mixture, and then was warmed to room temperature and stirred overnight. The mixture was sequentially extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×100 mL), washed with brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*, affording **S3** (11.6 g, 96%) as a white solid.

The characterization data are consistent with reported reference: *J. Am. Chem. Soc.* 2012, **134**, 8432-8435

### Compound 11



**Experimental:** A solution of **S3** (12.1 g, 48.0 mmol, 1.0 equiv) in 480 mL benzene was treated with PIDA (21.6 g, 67.2 mmol, 1.4 equiv) and I<sub>2</sub> (14.6 g, 57.6 mmol, 1.2 equiv). The purple reaction mixture was vigorously stirred at 70 °C (clear oil bath) with simultaneous irradiation using a 150-watt flood lamp for 1 h. Upon reaction completion (monitored by TLC), the reaction mixture was cooled to room temperature, concentrated *in vacuo*, diluted with brine, and extracted with EtOAc. The combined organic layers were washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was used directly for the next step without further purification.

The crude formate was dissolved in MeOH (30 mL). To this solution was added K<sub>2</sub>CO<sub>3</sub> (7.3 g, 52.8 mmol, 1.1 equiv) at 0 °C. The resulting mixture was warmed to room temperature, and stirred for 30 min before being quenched with saturated aq. NH<sub>4</sub>Cl solution (10 mL). The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent under vacuum, the residue was

subjected to flash column chromatography using PE:EA = (10:1) as the eluent to give **11** (11.3 g, 67 %) as a white solid.

**Physical state:** white solid;

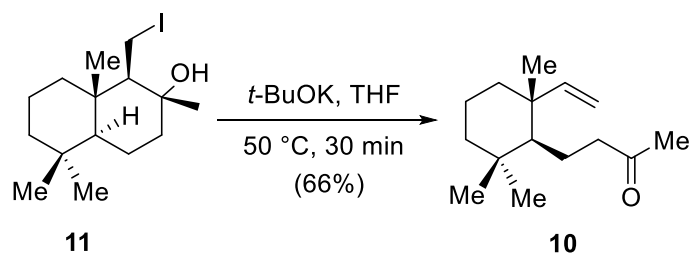
**TLC:**  $R_f = 0.30$  (PE:EA = 5:1);

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  3.47 (dd,  $J = 10.5, 3.4$  Hz, 1H), 3.11 (dd,  $J = 10.5, 4.5$  Hz, 1H), 2.00 (t,  $J = 3.9$  Hz, 1H), 1.91 – 1.84 (m, 2H), 1.66 (ddd,  $J = 13.9, 6.0, 3.4$  Hz, 1H), 1.61 – 1.47 (m, 2H), 1.45 – 1.41 (m, 2H), 1.40 – 1.36 (m, 1H), 1.33 – 1.21 (m, 2H), 1.20 – 1.14 (m, 1H), 1.12 (s, 3H), 0.97 (dd,  $J = 12.2, 2.4$  Hz, 1H), 0.86 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  74.7, 66.1, 56.0, 44.7, 41.8, 40.6, 39.9, 33.5, 33.4, 22.9, 21.6, 20.3, 18.6, 14.7, -1.6.

**HRMS(ESI-TOF):** calc'd for  $\text{C}_{15}\text{H}_{27}\text{IONa}$   $[\text{M} + \text{Na}]^+$ : 373.0999, found: 373.1000.

### Compound 10



**Experimental:** A 25 mL round-bottomed flask charged with  $t\text{-BuOK}$  (225.5 mg, 2.01 mmol, 2 equiv) was evacuated and backfilled with argon (3 times). Then a solution of **11** (352 mg, 1.005 mmol, 1 equiv) in THF (10 mL) was added dropwise at  $0\text{ }^\circ\text{C}$  by using syringe. The resulting mixture was heated in an oil bath that was preheated to  $50\text{ }^\circ\text{C}$  for 30 min. After the starting material was completely consumed (monitored by TLC), the reaction was quenched with aq.  $\text{NH}_4\text{Cl}$  and extracted with EtOAc ( $3 \times 15$  mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 50:1), affording **10** (147.4 mg, 66%) as a white solid.

**Physical state:** white solid;

**TLC:**  $R_f = 0.15$  (PE:EA = 20:1);

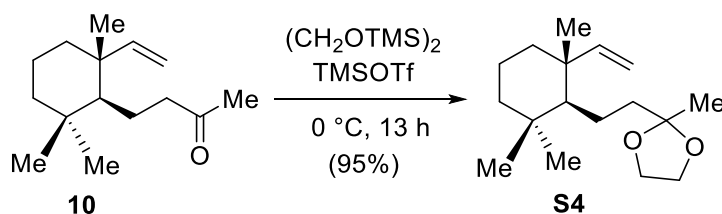
**Specific rotation:**  $[\alpha]_D^{18} = -22.67$  ( $c = 0.15$ , MeOH);

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.61 (dd,  $J = 17.7, 10.4$  Hz, 1H), 4.89 (d,  $J = 1.7$  Hz, 1H), 4.87 (dd,  $J = 5.0, 1.2$  Hz, 1H), 2.44 (ddd,  $J = 16.8, 11.4, 5.4$  Hz, 1H), 2.36 (ddd,  $J = 16.8, 11.5, 5.3$  Hz, 1H), 2.06 (s, 3H), 1.63 – 1.46 (m, 2H), 1.43 – 1.35 (m, 3H), 1.33 – 1.28 (m, 1H), 1.27 – 1.21 (m, 1H), 1.19 – 1.12 (m, 1H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  209.4, 151.5, 110.6, 53.0, 47.3, 42.2, 41.5, 40.3, 34.6, 33.7, 29.8, 22.0, 21.1, 18.8, 17.2.

**HRMS(ESI-TOF):** calc'd for  $\text{C}_{15}\text{H}_{27}\text{O}$   $[\text{M} + \text{H}]^+$ : 223.2056, found: 223.2059.

### Compound S4



**Experimental:** To a cooled and nitrogen filled round bottom flask charged with **10** (145 mg, 0.653 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (13.2 mL) was added  $(\text{CH}_2\text{OTMS})_2$  (2.02 g, 9.8 mmol, 15 equiv) and TMSOTf (22.2 mg, 0.1 mmol, 0.15 equiv). The reaction mixture was stirred at  $0\text{ }^\circ\text{C}$  for 13 h. Saturated  $\text{NaHCO}_3$  was added to quench the reaction and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give compound **S4** (165 mg, 95%) as a colorless oil.

**Physical state:** white solid;

**TLC:**  $R_f = 0.20$  (PE:EA = 20:1);

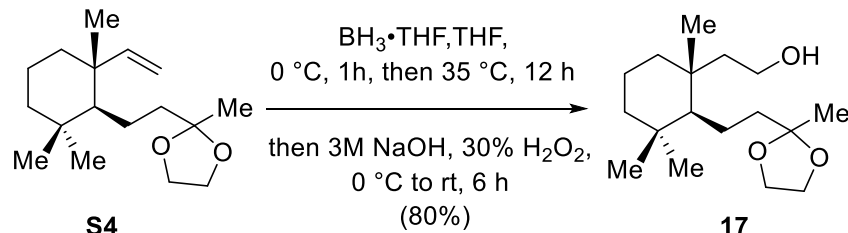
**Specific rotation:**  $[\alpha]_D^{18} = -7.78$  ( $c = 0.167$ , MeOH);

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.76 – 5.60 (m, 1H), 4.91 (d,  $J = 1.0$  Hz, 1H), 4.88 (dt,  $J = 6.2, 1.2$  Hz, 1H), 3.99 – 3.83 (m, 4H), 1.68 – 1.62 (m, 1H), 1.60 – 1.53 (m, 2H), 1.45 – 1.38 (m, 2H), 1.35 – 1.29 (m, 5H), 1.27 – 1.25 (m, 1H), 1.25 – 1.21 (m, 1H), 1.17 (td,  $J = 13.5, 4.1$  Hz, 1H), 1.00 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.83 (t,  $J = 4.1$  Hz, 1H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 151.7, 110.4, 110.2, 64.6, 64.6, 53.5, 42.3, 42.2, 41.7, 40.2, 34.8, 33.7, 23.5, 22.2, 21.5, 18.9, 17.5.

**HRMS(ESI-TOF):** calc'd for C<sub>17</sub>H<sub>31</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 267.2319, found: 267.2321.

### Compound 17



**Experimental:** To a stirred solution of compound **S4** (178.0 mg, 0.67 mmol, 1 equiv) in dry THF (10 mL) at 0 °C was added 1M BH<sub>3</sub>•THF in THF (3.35 mL, 3.35 mmol, 5 equiv). The mixture was stirred at 0 °C for 1 h and then 35 °C for 12 h. After the starting material was completely consumed (monitored by TLC), a solution of NaOH (1.33 mL, 3 M) was slowly added at 0 °C followed by a H<sub>2</sub>O<sub>2</sub> solution (1.33 mL, 30%). The mixture was stirred for another 6 h, and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (PE:EA = 10:1) to furnish **17** (152 mg, 80%).

**Physical state:** colorless oil;

**TLC:** R<sub>f</sub> = 0.20 (PE:EA = 10:1);

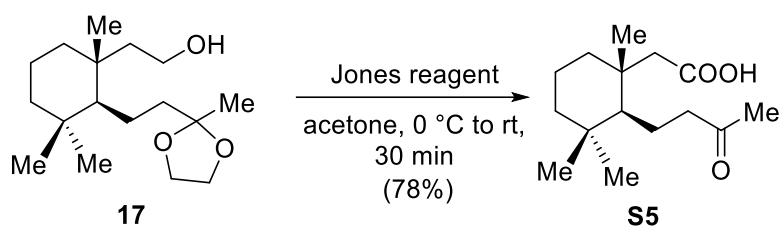
**Specific rotation:** [α]<sub>D</sub><sup>18</sup> = +5.00 (c = 0.2, MeOH);

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 3.98 – 3.90 (m, 4H), 3.68 (dd, *J* = 8.5, 7.0 Hz, 2H), 1.72 – 1.66 (m, 2H), 1.53 (dt, *J* = 13.7, 3.3 Hz, 1H), 1.46 (dq, *J* = 5.4, 3.0 Hz, 1H), 1.43 – 1.38 (m, 3H), 1.38 – 1.34 (m, 2H), 1.32 (s, 3H), 1.19 – 1.09 (m, 2H), 0.88 (s, 6H), 0.86 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 110.3, 64.8, 64.7, 59.4, 55.0, 46.9, 42.9, 42.2, 38.7, 37.4, 35.3, 33.6, 23.7, 22.1, 21.0, 19.5, 18.9.

**HRMS(ESI-TOF):** calc'd for C<sub>17</sub>H<sub>32</sub>NaO<sub>2</sub> [M + Na]<sup>+</sup>: 307.2244, found: 307.2248.

## Compound S5



**Experimental:** To a solution of **17** (36.6 mg, 0.129 mmol) in 2 mL acetone was added 0.13 mL Jones reagent (3M) dropwise at 0 °C. The mixture was warmed to room temperature, stirred for 30 min, and then cooled to 0 °C. Upon reaction completion (monitored by TLC), the reaction was quenched with isopropyl alcohol and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 5:1) to furnish **S5** (25.5 mg, 78%).

**Physical state:** colorless oil;

**TLC:** R<sub>f</sub> = 0.20 (PE:EA = 5:1, 0.1% HCOOH);

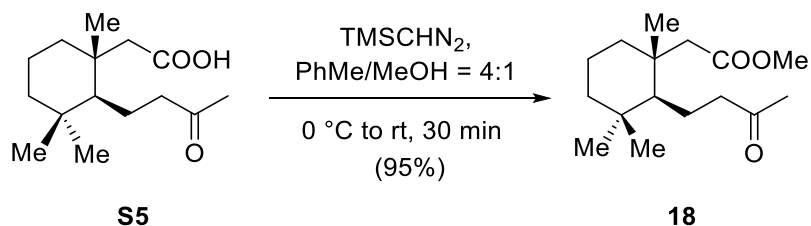
**Specific rotation:**  $[\alpha]_D^{18} = +9.00$  (*c* = 0.1, MeOH);

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 2.62 – 2.45 (m, 2H), 2.26 (d, *J* = 13.1 Hz, 1H), 2.16 (d, *J* = 13.1 Hz, 1H), 2.13 (s, 3H), 1.65 – 1.50 (m, 4H), 1.48 – 1.43 (m, 1H), 1.42 (s, 1H), 1.38 (d, *J* = 3.5 Hz, 1H), 1.36 – 1.28 (m, 1H), 1.19 – 1.09 (m, 1H), 1.02 (s, 3H), 0.99 (d, *J* = 3.9 Hz, 1H), 0.90 (s, 3H), 0.85 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 209.3, 178.1, 53.4, 48.2, 47.2, 41.9, 38.5, 38.4, 35.4, 33.7, 30.1, 21.9, 20.5, 19.8, 18.7.

**HRMS(ESI-TOF):** calc'd for C<sub>15</sub>H<sub>26</sub>NaO<sub>3</sub> [M + Na]<sup>+</sup>: 277.1774, found: 277.1772.

## Compound 18



**Experimental:** To a solution of **S5** (10.2 mg, 0.04 mmol, 1 equiv) in 2.5 mL



toluene/MeOH (4:1) was added 0.2 mL TMSCHN<sub>2</sub>(1M in THF, 5 equiv) at 0 °C. The mixture was warmed to room temperature and stirred for 30min. Upon reaction completion (monitored by TLC), the reaction was quenched with 2 drops AcOH and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 10:1) to furnish **18** (10.2 mg, 95%).

**Physical state:** colorless oil;

**TLC:** R<sub>f</sub> = 0.15 (PE:EA = 10:1);

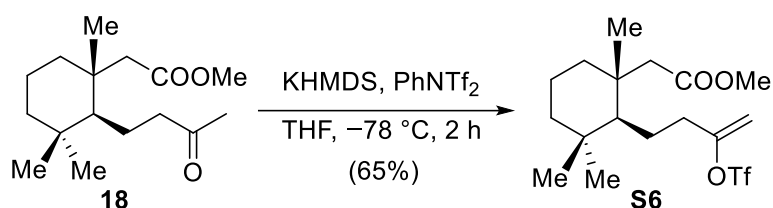
**Specific rotation:**  $[\alpha]_D^{18} = +25.67$  (*c* = 0.2, MeOH);

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 3.63 (s, 3H), 2.63 – 2.45 (m, 2H), 2.23 (d, *J* = 13.1 Hz, 1H), 2.13 (d, *J* = 13.1 Hz, 1H), 2.13 (s, 3H), 1.58 – 1.48 (m, 4H), 1.44 – 1.40 (m, 2H), 1.37 (t, *J* = 2.9 Hz, 1H), 1.13 (td, *J* = 13.4, 4.1 Hz, 1H), 1.00 (t, *J* = 4.0 Hz, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 209.2, 172.8, 53.1, 51.3, 48.2, 47.3, 41.9, 38.5, 38.5, 35.4, 33.7, 30.1, 21.9, 20.5, 19.9, 18.7.

**HRMS(ESI-TOF):** calc'd for C<sub>16</sub>H<sub>29</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 269.2111, found: 269.2112.

### Compound S6



**Experimental:** To a solution of **18** (55 mg, 0.205 mmol, 1 equiv), *N*-Phenyl-bis(trifluoromethanesulfonyl)imide (80.7 mg, 0.226 mmol, 1.1 equiv) in 7 mL THF at -78 °C under argon was added dropwise 226 μL KHMDS (1.0 M in THF, 1.1 equiv). The mixture was stirred for 2 h until the starting material was consumed (monitored by TLC). The reaction was quenched with NH<sub>4</sub>Cl and extracted EtOAc (3×7 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column

chromatography (PE:EA = 20:1) to furnish **S6** (53.4 mg, 65%).

**Physical state:** colorless oil;

**TLC:**  $R_f = 0.25$  (PE:EA = 10:1);

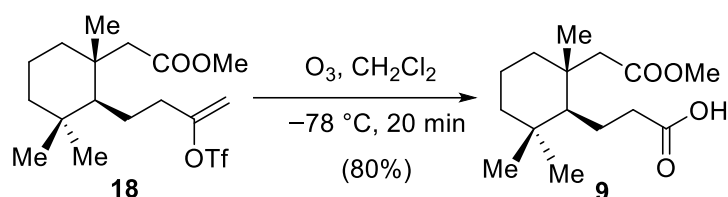
**Specific rotation:**  $[\alpha]_D^{18} = +15.00$  ( $c = 0.06$ , MeOH);

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.09 (dd,  $J = 3.6, 1.1$  Hz, 1H), 4.95 (dd,  $J = 3.5, 1.3$  Hz, 1H), 3.64 (s, 3H), 2.47 – 2.33 (m, 2H), 2.24 (d,  $J = 13.2$  Hz, 1H), 2.14 (d,  $J = 13.3$  Hz, 1H), 1.53 (dt,  $J = 16.3, 3.9$  Hz, 3H), 1.50 – 1.43 (m, 2H), 1.42 – 1.34 (m, 2H), 1.16 (td,  $J = 13.4, 3.7$  Hz, 1H), 1.05 (t,  $J = 3.9$  Hz, 1H), 0.99 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta$  172.5, 157.2, 104.0, 53.1, 51.3, 48.0, 41.8, 38.4, 38.4, 36.9, 35.3, 33.5, 23.9, 22.0, 20.0, 18.7.

**HRMS(ESI-TOF):** calc'd for  $\text{C}_{17}\text{H}_{28}\text{F}_3\text{O}_5$   $[\text{M} + \text{H}]^+$ : 401.1604, found: 401.1605.

### Compound 9



**Experimental:** To a stirred solution of **18** (49 mg, 0.133 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was bubbled through  $\text{O}_3$  at  $-78$  °C for 20 min before being quenched with  $\text{Me}_2\text{S}$  (0.5 mL). Then, the mixture was warmed to room temperature, stirred for 1 h, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 20:1, 0.3% HCOOH) to afford **9** (26.5 mg, 80%).

**Physical state:** colorless oil;

**TLC:**  $R_f = 0.20$  (PE:EA = 5:1, 0.1% HCOOH);

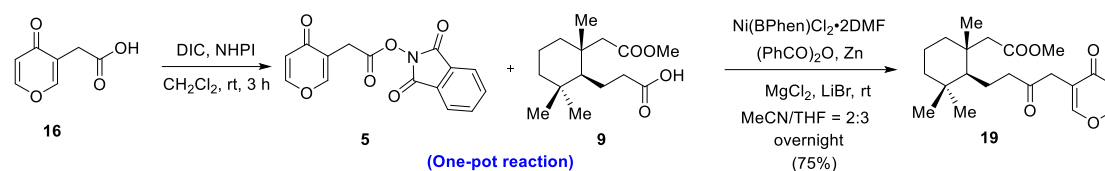
**Specific rotation:**  $[\alpha]_D^{18} = +16.13$  ( $c = 0.125$ , MeOH);

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  3.64 (s, 3H), 2.51 – 2.37 (m, 2H), 2.28 (d,  $J = 13.2$  Hz, 1H), 2.16 (d,  $J = 13.1$  Hz, 1H), 1.71 – 1.59 (m, 2H), 1.59 – 1.51 (m, 2H), 1.46 – 1.32 (m, 3H), 1.15 (td,  $J = 13.1, 3.7$  Hz, 1H), 1.03 (t,  $J = 4.0$  Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  179.1, 172.7, 53.3, 51.3, 48.2, 41.9, 38.5, 38.5, 37.0, 35.4, 33.6, 22.0, 22.0, 19.9, 18.7.

HRMS(ESI-TOF): calc'd for  $\text{C}_{15}\text{H}_{27}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 271.1904, found: 271.1904.

### Compound 19



**Experimental:** A flask was charged with acid **16** (0.075 mmol, 11.5 mg, 1 equiv) and *N*-hydroxyphthalimide (NHPI, 13.1 mg, 0.08 mmol, 1.07 equiv). 3 mL  $\text{CH}_2\text{Cl}_2$  was added, and the mixture was stirred vigorously. Then, *N,N'*-diisopropylcarbodiimide (DIC, 11.9 mg, 0.094 mmol, 1.25 equiv) was added dropwise via syringe, and the mixture was allowed to stir for 3 h (monitored by TLC). The solvent was removed on a rotary evaporator at 35 °C under reduced pressure and dried on a high-vacuum line for at least 5 minutes to remove residual  $\text{CH}_2\text{Cl}_2$ . Next, carboxylic acid **9** (40.5 mg, 0.15 mmol, 2 equiv),  $\text{Ni}(\text{BPhen})\text{Cl}_2 \cdot 2\text{DMF}$  (13.7 mg, 0.023 mmol, 30 mol%), Zn (14.7 mg, 0.225 mmol, 3 equiv), benzoic anhydride (50.9 mg, 0.225 mmol, 2.2 equiv),  $\text{MgCl}_2$  (10.5 mg, 0.11 mmol, 1.5 equiv), and LiBr (6.5 mg, 0.075 mmol, 1 equiv) were added to the same flask. The tube was evacuated and backfilled with argon (three times). Subsequently, 3 mL of anhydrous and deoxygenated mixture of  $\text{MeCN}/\text{THF}$  (1 : 1.5) was added via a syringe. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with  $\text{EtOAc}$  (3×5 mL), washed with HCl (1 M),  $\text{K}_2\text{CO}_3$  (1 M), and dried over  $\text{Na}_2\text{SO}_4$ . Upon filtration, the organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford **19** (20.3 mg, 75%).

**Physical state:** colorless oil;

**TLC:**  $R_f = 0.20$  (PE : EA = 1 : 1);

**Specific rotation:**  $[\alpha]_D^{18} = +15.00$  ( $c = 0.1$ , MeOH);

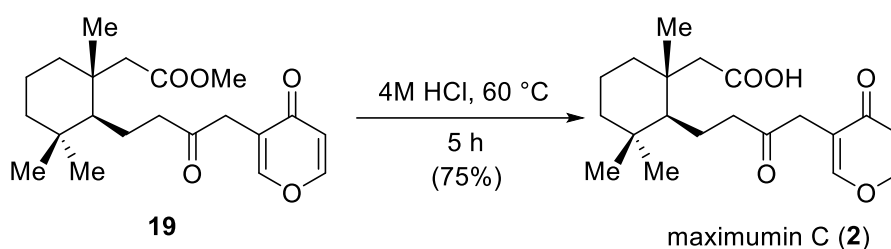
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.77 (d,  $J = 1.1$  Hz, 1H), 7.73 (dd,  $J = 5.8, 1.1$  Hz, 1H),

6.35 (d,  $J = 5.8$  Hz, 1H), 3.64 (s, 3H), 3.46 – 3.37 (m, 2H), 2.69 (ddd,  $J = 9.9, 8.0, 6.3$  Hz, 2H), 2.24 (d,  $J = 13.1$  Hz, 1H), 2.16 (d,  $J = 13.1$  Hz, 1H), 1.67 – 1.60 (m, 1H), 1.56 – 1.53 (m, 1H), 1.52 – 1.49 (m, 1H), 1.45 – 1.32 (m, 4H), 1.14 (td,  $J = 12.9, 3.4$  Hz, 1H), 1.03 (t,  $J = 3.9$  Hz, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.7, 177.6, 172.8, 155.5, 154.1, 124.6, 116.8, 53.2, 51.3, 48.2, 46.6, 42.0, 38.6, 38.5, 38.3, 35.4, 33.7, 22.0, 20.5, 20.0, 18.8.

HRMS(ESI-TOF): calc'd for  $\text{C}_{21}\text{H}_{31}\text{O}_5$   $[\text{M} + \text{H}]^+$ : 363.2166, found: 301.2166.

### Compound 2



**Experimental:** Compound **19** (15 mg, 0.11 mmol) was dissolved in 5 mL 4M HCl. The reaction mixture was heated to 60 °C, and stirred for 5 hours before being cooled to room temperature and concentrated under reduced pressure. The resulting crude residue was purified via column chromatography ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1, 0.3% HCOOH), affording **2** (10.8 mg, 75%) as a white solid.

**Physical state:** white solid;

**TLC:**  $R_f = 0.10$  (PE:EA = 1:1, 0.1% HCOOH);

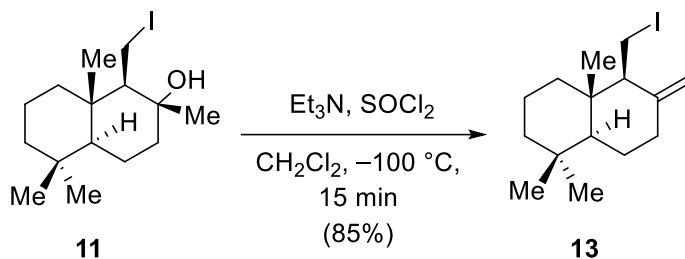
**Specific rotation:**  $[\alpha]_D^{18} = +10.00$  ( $c = 0.1$ , MeOH);

$^1\text{H}$  NMR (800 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.79 (s, 1H), 7.76 (d,  $J = 5.8$  Hz, 1H), 6.39 (d,  $J = 5.8$  Hz, 1H), 3.45 (d,  $J = 16.6$  Hz, 1H), 3.39 (d,  $J = 16.6$  Hz, 1H), 2.77 – 2.64 (m, 2H), 2.27 (d,  $J = 13.4$  Hz, 1H), 2.19 (d,  $J = 13.5$  Hz, 1H), 1.63 – 1.61 (m, 2H), 1.61 – 1.59 (m, 1H), 1.57 (qt,  $J = 13.1, 3.1$  Hz, 1H), 1.46 – 1.44 (m, 1H), 1.44 – 1.42 (m, 1H), 1.42 – 1.38 (m, 1H), 1.16 (td,  $J = 13.2, 3.5$  Hz, 1H), 1.06 (t,  $J = 4.0$  Hz, 1H), 1.03 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H).

$^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.8, 178.0, 175.5, 155.7, 154.3, 124.7, 116.8, 53.5, 48.0, 46.6, 42.0, 38.8, 38.6, 38.4, 35.4, 33.7, 22.0, 20.5, 19.9, 18.7.

**HRMS(ESI-TOF):** calc'd for C<sub>20</sub>H<sub>29</sub>O<sub>5</sub> [M + H]<sup>+</sup>: 349.2010, found: 349.2009.

### Compound 13



**Experimental:** To a stirred solution of **11** (1.0 g, 2.86 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was sequentially added Et<sub>3</sub>N (870 mg, 8.58 mmol, 3 equiv) and SOCl<sub>2</sub> (1.53 g, 1.53 g, 12.87 mmol, 1.5 equiv) at -100 °C. The reaction mixture was stirred at the same temperature for 15 min before being quenched with saturated aq. NaHCO<sub>3</sub> solution (5 mL). Then, the resulting mixture was extracted with EtOAc (3×25 mL), and the combined organic phases were washed with brine (100 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and removal of the solvent under vacuum, the residue was purified by flash column chromatography eluted with pentane to give homoallylic iodide **13** (806 mg, 85%) as a white solid.

**Physical state:** white solid;

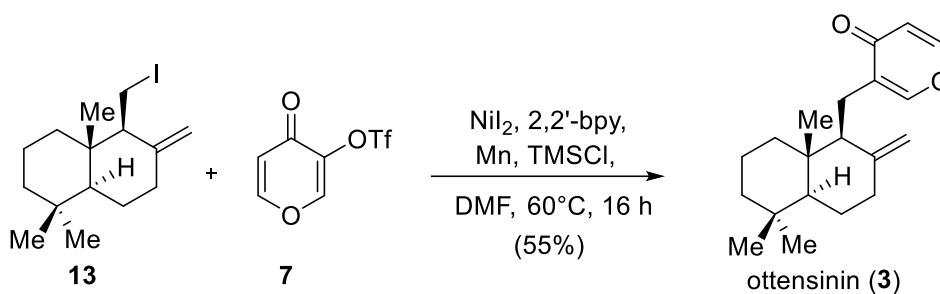
**TLC:** R<sub>f</sub> = 0.95 (PE);

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 5.00 (s, 1H), 4.64 (s, 1H), 3.65 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.03 (dd, *J* = 10.5, 9.8 Hz, 1H), 2.46 – 2.40 (m, 1H), 2.17 (d, *J* = 11.3 Hz, 1H), 2.08 (td, *J* = 13.1, 5.1 Hz, 1H), 1.78 – 1.69 (m, 2H), 1.59 – 1.49 (m, 2H), 1.40 (dq, *J* = 13.8, 2.1 Hz, 1H), 1.36 – 1.28 (m, 1H), 1.27 – 1.16 (m, 2H), 1.11 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.88 (s, 3H), 0.80 (s, 3H), 0.69 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 146.0, 108.2, 60.5, 55.3, 42.0, 41.8, 39.3, 37.7, 33.7, 33.7, 24.4, 21.8, 19.4, 13.9, 2.6.

**HRMS(ESI-TOF):** calc'd for C<sub>15</sub>H<sub>26</sub>I [M + H]<sup>+</sup>: 333.1074, found: 373.1076.

### Compound 3



**Experimental:** Homoallylic iodide **13** (73.5 mg, 0.21 mmol, 2.0 equiv), vinyl triflate **7** (25.5 mg, 0.105 mmol, 1.0 equiv), Mn (17.3 mg, 0.315 mmol, 3.0 equiv), and NiI<sub>2</sub> (6.6 mg, 0.021 mmol, 20 mol %), 2,2'-bipyridine (3.3 mg, 0.021 mmol, 20 mol %), TMSCl (2.3 mg, 0.021 mmol, 0.2 equiv) were placed in a flask under an argon atmosphere, and the flask was evacuated and backfilled with argon (3 times). Afterward, anhydrous and deoxygenated DMF (1.5 mL) was added, and the mixture was stirred for 16 h at 60 °C. The mixture was diluted with 0.5M HCl (5.0 mL), and the resulting black solution was extracted with EtOAc (3×5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Ottensinin (**3**) was obtained (17.2 mg, 55%) as a white solid after column chromatography (PE:EA = 5:1).

**Physical state:** white solid;

**TLC:** R<sub>f</sub> = 0.20 (PE:EA = 5:1);

**Specific rotation:**  $[\alpha]_D^{18} = +34$  ( $c = 0.125$ , MeOH);

**Melting point:** 120–121 °C;

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  7.66 (dd,  $J = 5.7, 1.1$  Hz, 1H), 7.52 (dd,  $J = 2.4, 1.1$  Hz, 1H), 6.30 (d,  $J = 5.7$  Hz, 1H), 4.81 (dd,  $J = 2.8, 1.4$  Hz, 1H), 4.46 (dd,  $J = 2.7, 1.3$  Hz, 1H), 2.69 (dt,  $J = 16.4, 1.8$  Hz, 1H), 2.44 (dd,  $J = 16.3, 11.3$  Hz, 1H), 2.38 (ddd,  $J = 12.8, 4.3, 2.4$  Hz, 1H), 2.02 (d,  $J = 11.0$  Hz, 1H), 1.97 (dd,  $J = 13.0, 5.2$  Hz, 1H), 1.90 – 1.85 (m, 1H), 1.75 (dddd,  $J = 12.8, 5.0, 2.5, 2.5$  Hz, 1H), 1.62 – 1.57 (m, 1H), 1.57 – 1.48 (m, 1H), 1.43 – 1.38 (m, 1H), 1.34 (dddd,  $J = 12.9, 12.9, 4.3$  Hz, 1H), 1.24 – 1.20 (m, 1H), 1.20 – 1.18 (m, 1H), 1.17 – 1.15 (m, 1H), 0.88 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**  $\delta$  178.8, 154.7, 153.0, 147.8, 130.0, 116.5, 107.9, 55.7,

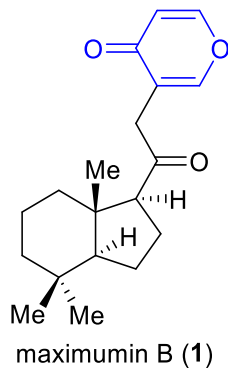
54.1, 42.2, 40.1, 39.2, 38.2, 33.8, 24.5, 21.9, 19.7, 19.5, 14.5.

**HRMS(ESI-TOF):** calc'd for  $C_{20}H_{29}O_2$   $[M + H]^+$ : 301.2162, found: 301.2161.

## NMR data comparison of synthetic and natural maximumins

### B/C and ottensinin

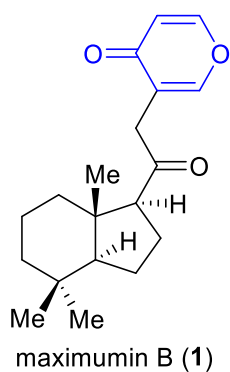
#### <sup>1</sup>H NMR data comparison of synthetic and natural maximumin B



No.	Synthetic maximumin B (600 MHz)	Natural maximumin B (500 MHz)	Err(Natural- Synthetic) $\Delta\delta$ (ppm)
1 $\alpha$	1.40 (1H, td, $J = 12.9, 4.2$ Hz)	1.40 td ( $J=12.6, 3.9$ Hz)	0
1 $\beta$	2.14–2.11 (1H, m)	2.13 (1H, m)	-
2 $\alpha$	1.63–1.54 (2H, m)	1.59 (2H, m)	-
3 $\alpha$	1.10 (1H, td, $J = 13.4, 4.4$ Hz)	1.10 td ( $J=13.5, 4.5$ Hz)	0
3 $\beta$	1.48–1.45 (1H, m)	1.47 m	-
5	1.28 (1H, dd, $J=13.2, 6.5$ Hz)	1.29(1H, dd, $J = 13.2, 6.4$ Hz)	0.01
6 $\alpha$	1.65–1.63 (1H, m)	1.65 (1H, m)	-
6 $\beta$	1.46–1.43 (1H, m)	1.44(1H, m)	-
7 $\alpha$	1.70–1.66 (1H, m)	1.68(1H, m)	-
7 $\beta$	2.19–2.14 (1H, m)	2.17 m (1H, m)	-
8	2.67 (1H, t, $J = 8.9$ Hz)	2.67 (1H, t, $J = 8.9$ Hz)	0
11 $\alpha$	3.38 (2H, s)	3.39 s (2H, s)	0.01
14	6.33 (1H d, $J = 5.7$ Hz)	6.34 (1H, d, $J = 5.7$ Hz)	0.01
15	7.71 (1H, d, $J = 5.7$ Hz)	7.72 (1H, d, $J = 5.7$ Hz)	0.01
16	7.74 (1H, s)	7.75 (1H, s)	0.01
18	0.87 (3H, s)	0.87 (3H, s)	0
19	0.86 (3H, s)	0.86 (3H, s)	0
20	0.74 (3H, s)	0.74 (3H, s)	0

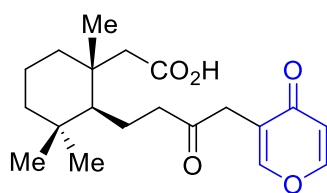


### <sup>13</sup>C NMR data comparison of synthetic and natural maximumin B



No.	Synthetic maximumin B (150 MHz)	Natural maximumin B (125 MHz)	Err (Natural- Synthetic) $\Delta\delta$ (ppm)
1	39.9	39.9	0
2	20.1	20.1	0
3	41.4	41.4	0
4	33.5	33.5	0
5	59.0	59.0	0
6	21.1	21.1	0
7	22.2	22.2	0
8	64.9	64.9	0
9	207.3	207.3	0
10	44.9	45.0	0.1
11	39.7	39.7	0
12	124.7	124.7	0
13	177.6	177.6	0
14	116.8	116.8	0
15	155.4	155.4	0
16	154.1	154.2	0.1
18	33.5	33.6	0.1
19	20.8	20.8	0
20	14.8	14..8	0

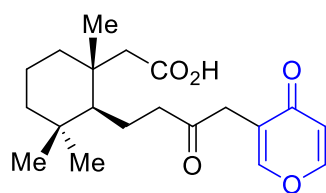
### <sup>1</sup>H NMR data comparison of synthetic and natural maximumin C



maximumin C (2)

No.	Synthetic maximumin C (800 MHz in CDCl <sub>3</sub> )	Natural maximumin C (500 MHz CDCl <sub>3</sub> )	Err (Natural- Synthetic) Δδ (ppm)
1α	1.46–1.44 (1H, m)	1.44 (1H, m)	-
1β	1.61–1.59 (1H, m)	1.58 (1H, m)	-
2α	1.44–1.42 (1H, m)	1.41 (1H, m)	-
2β	1.57 (1H, qt J=13.1,3.1Hz)	1.55 qt (1H, J = 13.1,3.1 Hz)	-0.02
3α	1.16 td (1H J = 13.2, 3.5 Hz)	1.16 td (1H, J=13.1, 3.1 Hz)	0
3β	1.42-1.38 m	1.38 m	-
5	1.06 (1H, t, J = 4.0 Hz)	1.07 (1H, t, J = 3.7 Hz)	0.01
6α	1.63–1.61 (2H, m)	1.61 m (2H, m)	-
7α	2.77–2.64 (2H, m)	2.71 (2H, m)	-
9α	2.27 d (1H, J = 13.4 Hz)	2.25 d (1H, J = 13.5 Hz)	-0.02
9β	2.19 d (1H, J = 13.5 Hz)	2.20 d (1H, J = 13.5 Hz)	0.01
14	6.39 d (1H, J = 5.8 Hz)	6.41 d (1H, J = 5.5 Hz)	0.02
15	7.76 d (1H, J = 5.8 Hz)	7.77 d (1H, J = 5.5 Hz)	0.01
16	7.79, (1H, s)	7.80, (1H, s)	0.01
17α	3.45 d (1H, J = 16.6 Hz)	3.46 d (1H, J = 16.6 Hz)	0.01
17β	3.39 d (1H, J = 16.6 Hz)	3.38 d (1H, J = 16.6 Hz)	-0.01
18	0.88 (3H, s)	0.87 (3H, s)	0
19	0.91 (3H, s)	0.90 (3H, s)	0
20	1.03 (3H, s)	1.02 (3H, s)	0

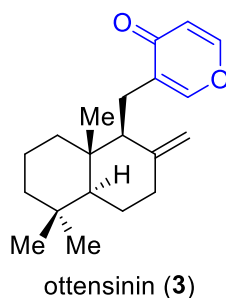
### <sup>13</sup>C NMR data comparison of synthetic and natural maximumin C



maximumin C (2)

No.	Synthetic maximumin C (200 MHz)	Natural maximumin C (125 MHz)	Err(Natural- Synthetic) $\Delta\delta$ (ppm)
1	38.8	38.7	-0.1
2	18.7	18.8	0.1
3	42.0	42.0	0
4	35.4	35.4	0
5	53.5	53.3	-0.2
6	20.5	20.5	0
7	46.6	46.6	0
8	206.8	206.8	0
9	48.0	48.1	0.1
10	38.6	38.6	0
11	175.5	175.9	0.4
12	124.7	124.7	0
13	178.0	178.	0.1
14	116.8	116.8	0
15	155.7	155.9	0.2
16	154.3	154.5	0.2
17	38.4	38.4	0
18	38.8	38.7	0.1
19	22.0	22.0	0
20	19.9	20.1	0.2

**<sup>1</sup>H NMR data comparison of synthetic and natural ottensinin**

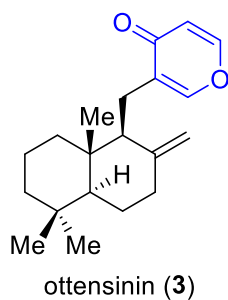


No.	Synthetic ottensinin (500 MHz)	Natural ottensinin (500 MHz)	Err (Natural- Synthetic) $\Delta\delta$ (ppm)
1 $\beta$	1.90–1.85 (1H, m)	1.88 (1H, m)	-
1 $\alpha$	1.20–1.18 (1H, m)	1.18 (1H, br ddd, $J = 13, 13, 4$ Hz)	-
2 $\beta$	1.62–1.57 (1H, m)	1.60 (1H, ddddd, $J = 13 \times 3, 3 \times 2$ Hz)	-
2 $\alpha$	1.57–1.48 (1H, m)	1.53 (1H, m)	-
3 $\beta$	1.43–1.38 (1H, m)	1.41 (1H, dddd, $J = 13, 3 \times 2, 2$ Hz)	-
3 $\alpha$	1.24–1.20 (1H, m)	1.20 (1H, br, ddd, $J = 13 \times 2, 4$ Hz)	-
5	1.20–1.18 (1H, m)	1.17 (1H, dd, $J = 13, 3$ Hz)	-
6 $\beta$	1.34 (1 H, dddd, 12.9, 12.9, 4.3, 4.3 Hz)	1.36 (1H, dddd, $J = 13 \times 3, 4$ Hz),	0.02
6 $\alpha$	1.75 (1H, dddd, $J = 12.8, 5.0, 2.5, 2.5$ Hz)	1.76 (1H, dddd, $J = 13, 5, 3 \times 2$ Hz)	0.01
7 $\beta$	2.38 (1H, ddd, $J = 12.8, 4.3, 2.4$ Hz)	2.38 (1H, ddd, $J = 13, 4, 2$ Hz),	0
7 $\alpha$	1.97 (1H, dd, $J = 13.0, 5.2$ Hz)	1.99 (1H, br ddd, $J = 13 \times 2, 5$ Hz)	0.02
9	2.02 (1H, d, $J = 11.0$ Hz)	2.01 (1H, brd, $J = 12$ Hz)	-0.01
11	2.69 (1H, dt, $J = 16.4, 1.8$ Hz), 2.44 (1H, dd, $J = 16.3, 11.3$ Hz)	2.69 (1H, ddd, $J = 16, 2, 1$ Hz), 2.45 (1H, ddd, $J = 16, 12.1$ Hz)	0.01
14	6.30 (1H, d, $J = 5.7$ Hz)	6.31 (1H, d, $J = 5.5$ Hz)	0.01
15	7.66 (1H, dd, $J = 5.7, 1.1$ Hz)	7.67 (1H, dd, $J = 6, 1$ Hz)	0.01
16	7.52 (1H, dd, $J = 2.4, 1.1$ Hz)	7.52 (1H, ddd, $J = 1 \times 3$ Hz)	0
17	4.81 (1H, dd, $J = 2.8, 1.4$ Hz) 4.46 (1H, dd, $J = 2.7, 1.3$ Hz)	4.82 (1H, br d, $J = 1$ Hz), 4.46 (1H, br d, $J = 1$ Hz)	0.01
18	0.88 (3H, s)	0.88 (3H, s)	0

19	0.82 (3H, s)	0.82 (3H, s)	0
20	0.78 (3H, s)	0.78 (3H, s)	0

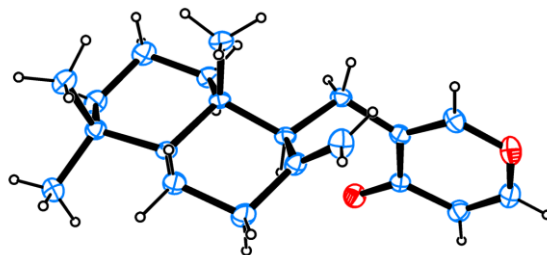
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### <sup>13</sup>C NMR data comparison of synthetic and natural ottensinin



No.	Synthetic ottensinin (125 MHz CDCl <sub>3</sub> )	Natural ottensinin (125 MHz in CDCl <sub>3</sub> )	Err(Natural-Synthetic) Δδ (ppm)
1	39.2	39.0	-0.2
2	19.5	19.4	-0.1
3	42.2	42.0	-0.2
4	33.8	33.6	-0.2
5	55.7	55.5	-0.2
6	24.5	24.4	-0.1
7	38.2	38.1	-0.1
8	147.8	147.7	-0.1
9	54.1	53.9	-0.2
10	40.1	40.0	-0.1
11	19.7	19.5	-0.2
12	130.0	129.8	-0.2
13	178.8	178.8	0
14	116.5	116.4	-0.1
15	154.7	154.6	-0.1
16	153.0	153.0	0
17	107.9	107.8	-0.1
18	33.8	33.6	-0.2
19	21.9	21.7	-0.2
20	14.5	14.4	-0.1

## X-ray crystallographic data for ottensinin (3)



**Table S1.** Crystallographic data of ottensinin (3).

Identification code	mj24051_0m
Empirical formula	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>
Formula weight	300.42
Temperature/K	296
Crystal system	triclinic
Space group	P1
a/Å	6.3767(4)
b/Å	7.3447(4)
c/Å	20.6781(11)
α/°	90.948(2)
β/°	98.205(2)
γ/°	114.304(2)
Volume/Å <sup>3</sup>	870.54(9)
Z	2
ρ <sub>calc</sub> /cm <sup>3</sup>	1.146
μ /mm <sup>-1</sup>	0.355
F(000)	328.0
Crystal size/mm <sup>3</sup>	0.17 × 0.15 × 0.05
Radiation	GaKα (λ = 1.34139)
2θ range for data collection/°	7.542 to 109.712
Index ranges	-7 ≤ h ≤ 7, -8 ≤ k ≤ 8, -25 ≤ l ≤ 25
Reflections collected	30267
Independent reflections	6470 [R <sub>int</sub> = 0.0678, R <sub>sigma</sub> = 0.0518]
Data/restraints/parameters	6470/3/404
Goodness-of-fit on F <sup>2</sup>	1.049
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0431, wR <sub>2</sub> = 0.1175
Final R indexes [all data]	R <sub>1</sub> = 0.0487, wR <sub>2</sub> = 0.1226
Largest diff. peak/hole / e Å <sup>-3</sup>	0.15/-0.13
Flack parameter	0.07(19)

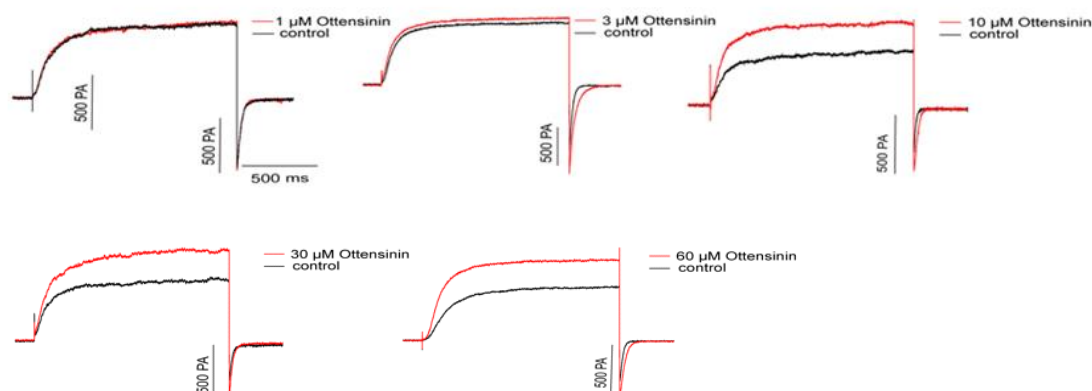
## Biological activities assays

### Ottensinin

**Table S2.** Effects of ottensinin (**3**) on current of KCNQ2 channel at different concentrations

Concentration ( $\mu\text{M}$ )	$I_{\text{drug}}/I_{\text{control}}^a$	n
1	$1.01 \pm 0.01$	3
3	$1.13 \pm 0.05$	4
10	$1.77 \pm 0.07$	3
30	$1.99 \pm 0.10$	4
60	$2.03 \pm 0.19$	6

<sup>a</sup>The amplitude change of the outward current:  $I_{\text{control}}$ , amplitude of the outward current without the compound;  $I_{\text{drug}}$ , amplitude of the outward current with the compound;  $I_{\text{drug}}/I_{\text{control}}$ , effect of compound on the amplitude of the outward current of KCNQ2 channel.



**Figure S1.** Representative current traces of the ottensinin on human KCNQ2 channels.

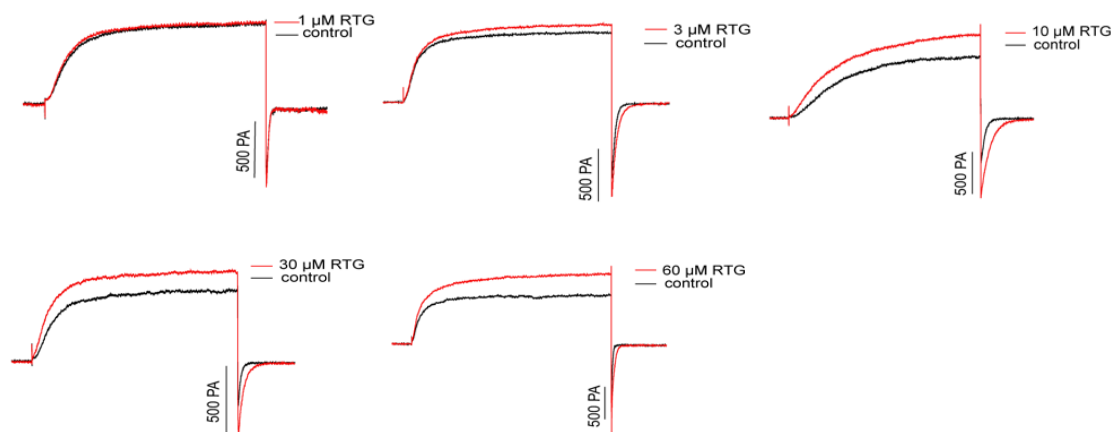
### Retigabine

**Table S3.** Effects of Retigabine on current of KCNQ2 channel at different concentrations

Compound ( $\mu\text{M}$ )	$I_{\text{drug}}/I_{\text{control}}^a$	n
1	$1.05 \pm 0.03$	3
3	$1.24 \pm 0.09$	4
10	$1.50 \pm 0.10$	4
30	$1.54 \pm 0.09$	5
60	$1.57 \pm 0.08$	5

<sup>a</sup>The amplitude change of the outward current:  $I_{\text{control}}$ , amplitude of the outward current without the compound;  $I_{\text{drug}}$ , amplitude of the outward current with the compound;  $I_{\text{drug}}/I_{\text{control}}$ , effect of compound on the amplitude of the outward current of KCNQ2 channel.





**Figure S2.** Representative current traces of the RTG on human KCNQ2 channels.

**Table S4.** Effects of ottensinin on current of KCNQ2 channel kinetics

		Control	ottensinin (10 $\mu$ M)
Activation	$V_{1/2}$ (mv)	$-9.53 \pm 1.91$	$-12.26 \pm 3.23$
	$k$	$18.73 \pm 1.13$	$24.05 \pm 2.99$
	$\tau$ activation	$247.75 \pm 35.03$	$237.56 \pm 30.32$
	$\tau$ deactivation	$12.81 \pm 0.73$	$14.92 \pm 0.18$

### Electrophysiological recordings

Whole cell voltage clamp recording was performed with cultured CHO cells at room temperature using an Axopatch-200B amplifier (Molecular Devices, Sunnyvale, CA). The borosilicate glass capillaries (World Precision Instruments, Sarasota, FL) were prepared as glass electrodes for infusion of internal buffer liquid by electrode drawing instrument with the resistance of 3-5M $\Omega$ . The pipette solution contained the following (mM): 145 KCl, 10 HEPES, 1 MgCl<sub>2</sub>, 5 EGTA, 1 CaCl<sub>2</sub>, and 10 HEPES (pH 7.2 adjusted by KOH), bath or extracellular solution contained the following (mM): 140 NaCl, 5KCl, 2 CaCl<sub>2</sub>, 1 MgCl<sub>2</sub>, 10 glucose, and 10 HEPES (pH 7.4 adjusted by NaOH). The cells were clamped to a holding potential of  $-80$  mV, and then depolarization to  $-10$  mV, duration 1500 ms, recording potassium current. For perfusion testing, the BPS perfusion system (ALA Scientific Instruments, Westburg, NY) was used to continuously infuse the bath solution. The Axopatch-200B amplifier (Axon Instruments,

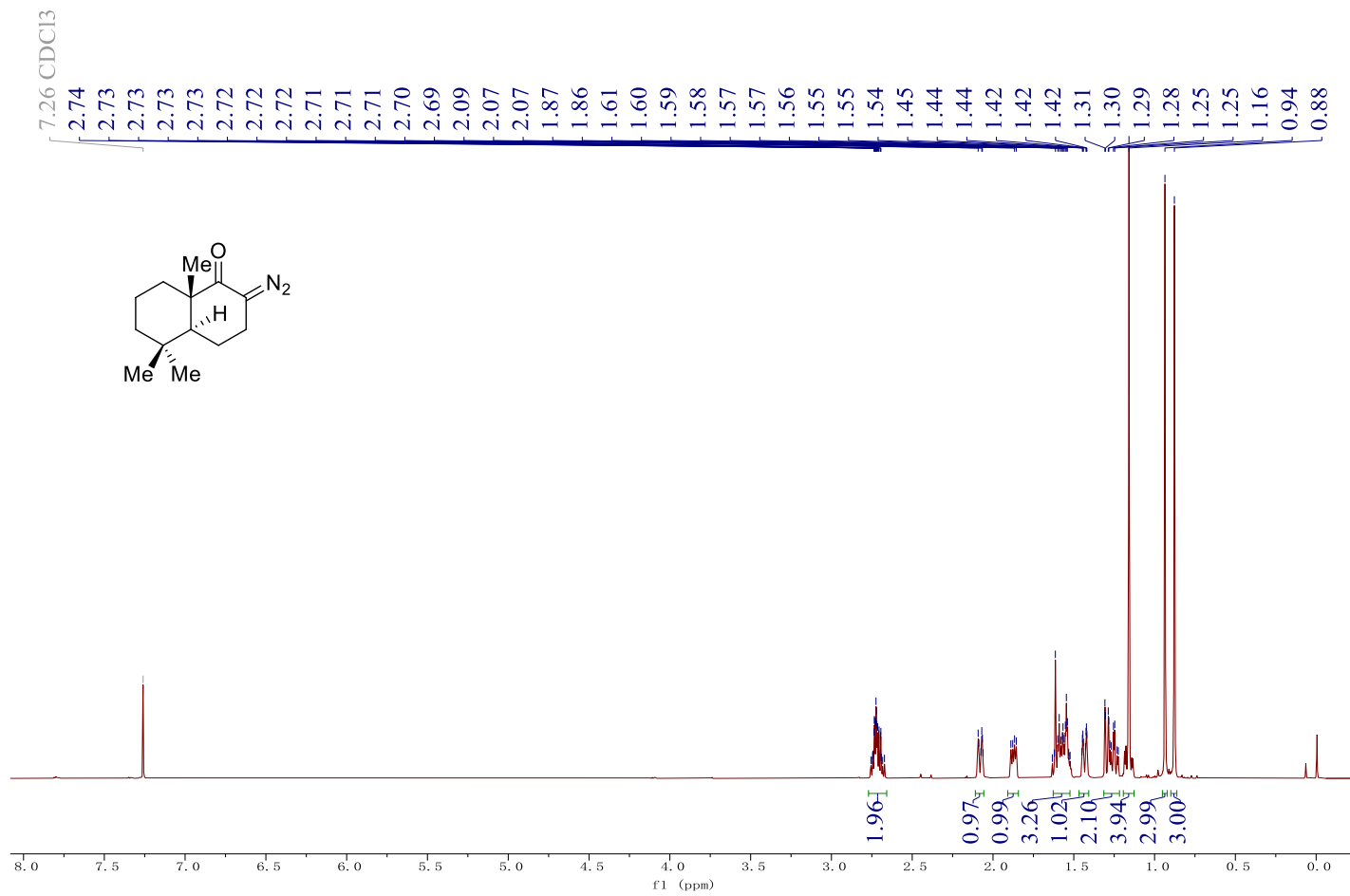
Burlingame, CA, USA) was used for data acquisition at room temperature, filtering at 2 kHz, and digitizing at 50 kHz using the Digidata 1440A interface (Axon Instruments, Burlingame, CA, USA).

### **Patch clamp data Analysis**

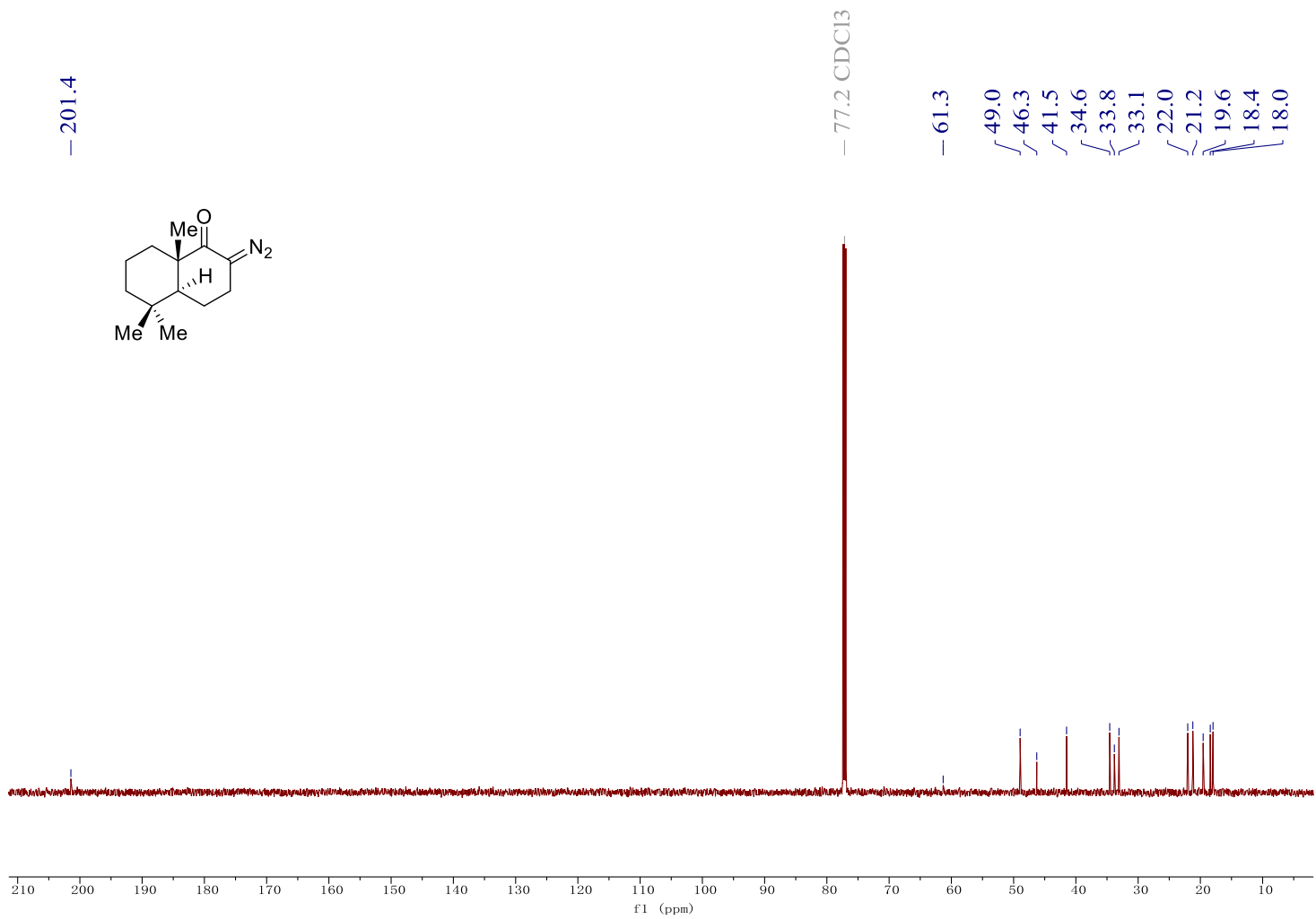
Patch clamp data were processed using Clampfit 10.6 (Molecular Devices, Sunnyvale, CA, USA) and then analyzed using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). The data were presented as mean  $\pm$  SEM. The significance was estimated using unpaired two-tailed Student's t test or one-way ANOVA with Tukey's post hoc procedure. Statistical significance: \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$ .

# NMR Spectra

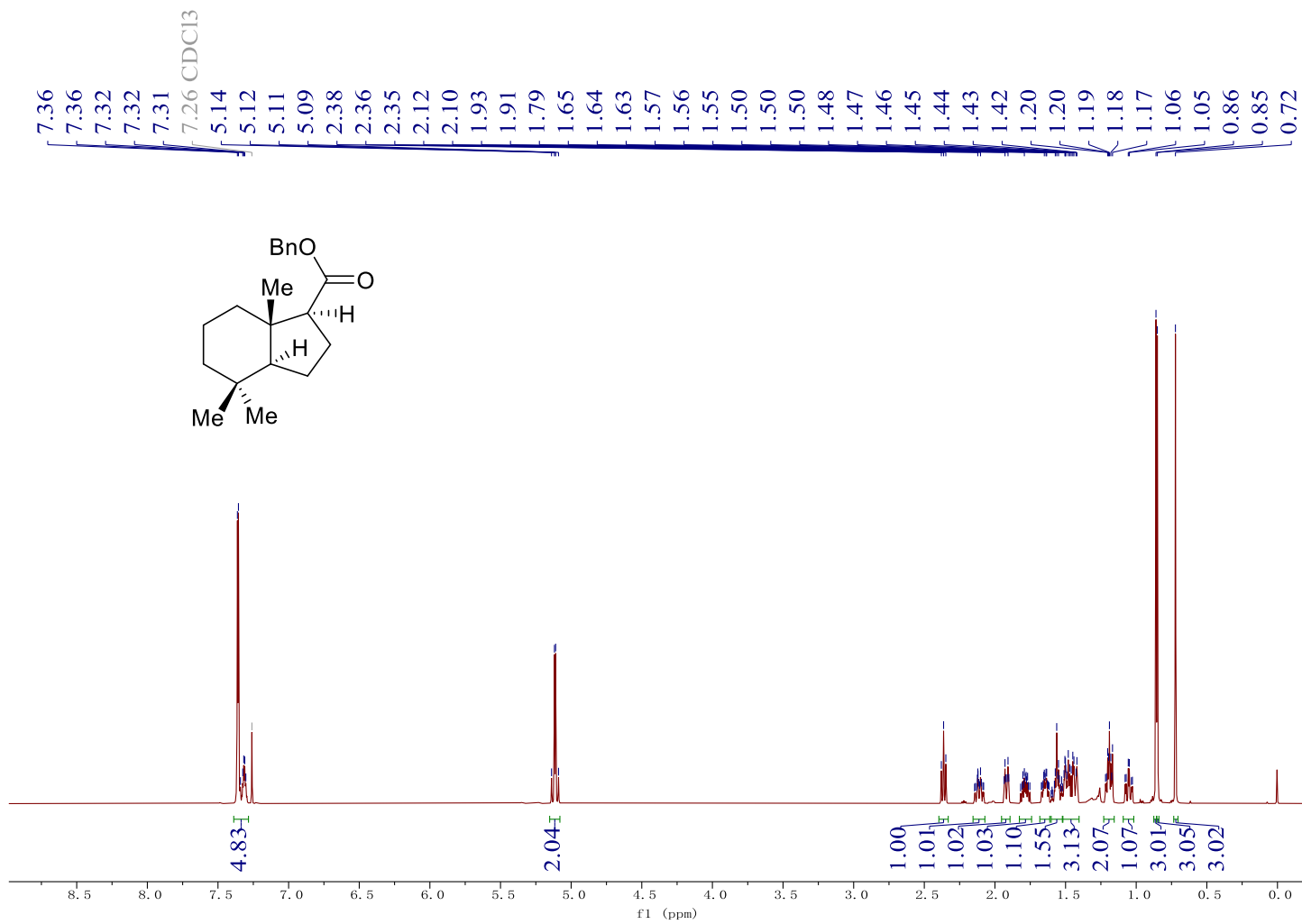
## Compound S1 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



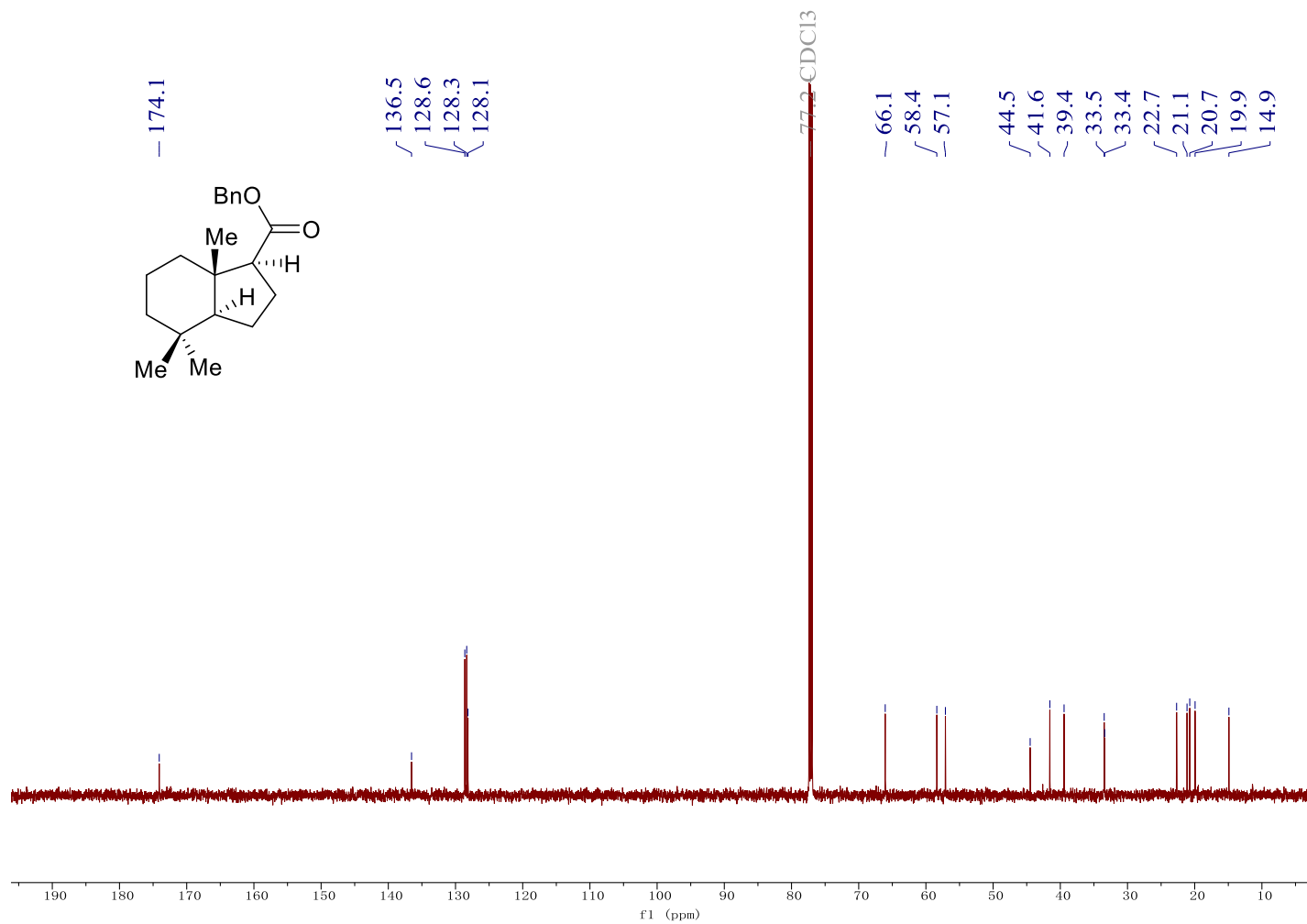
Compound S1 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



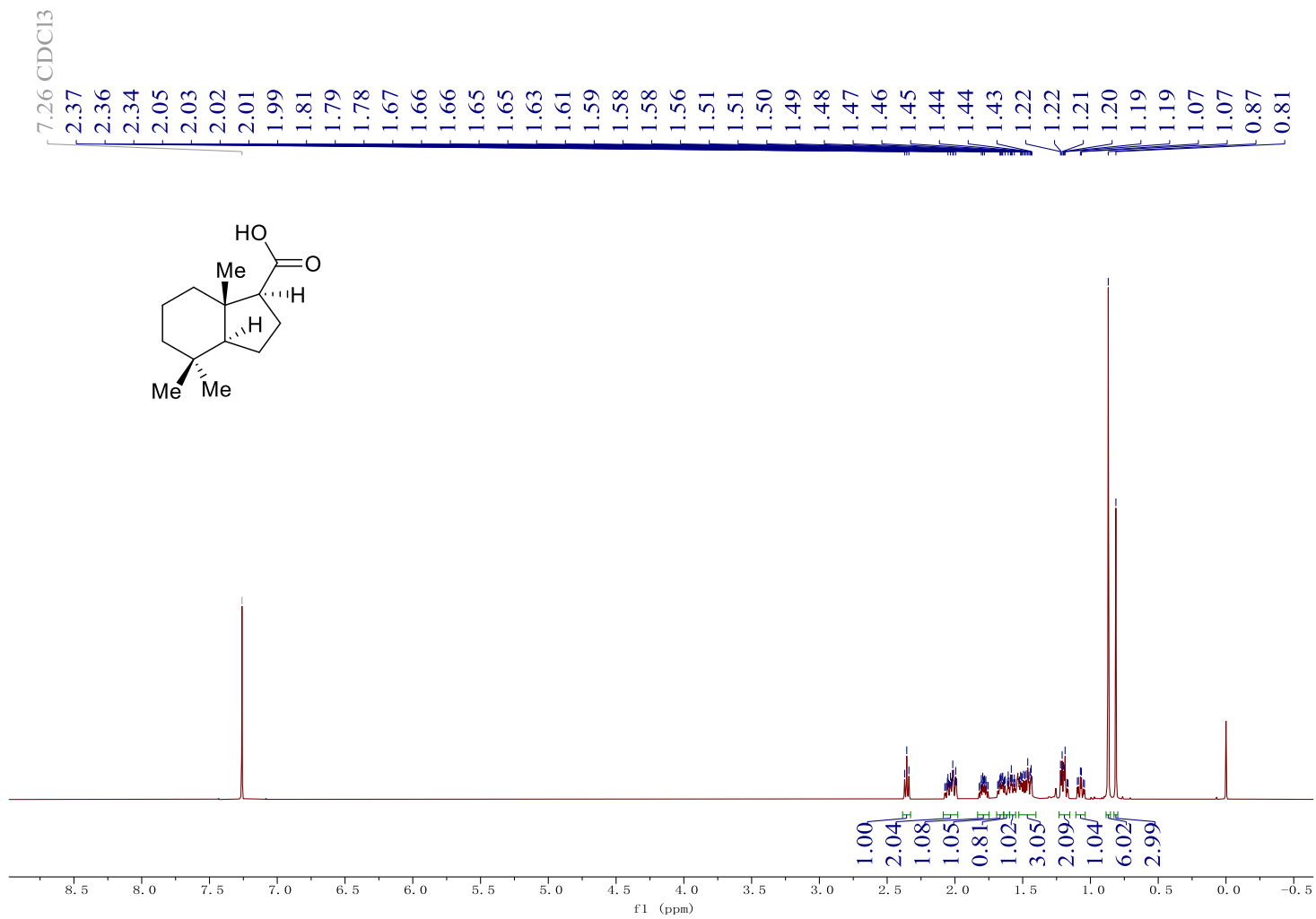
Compound S2 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



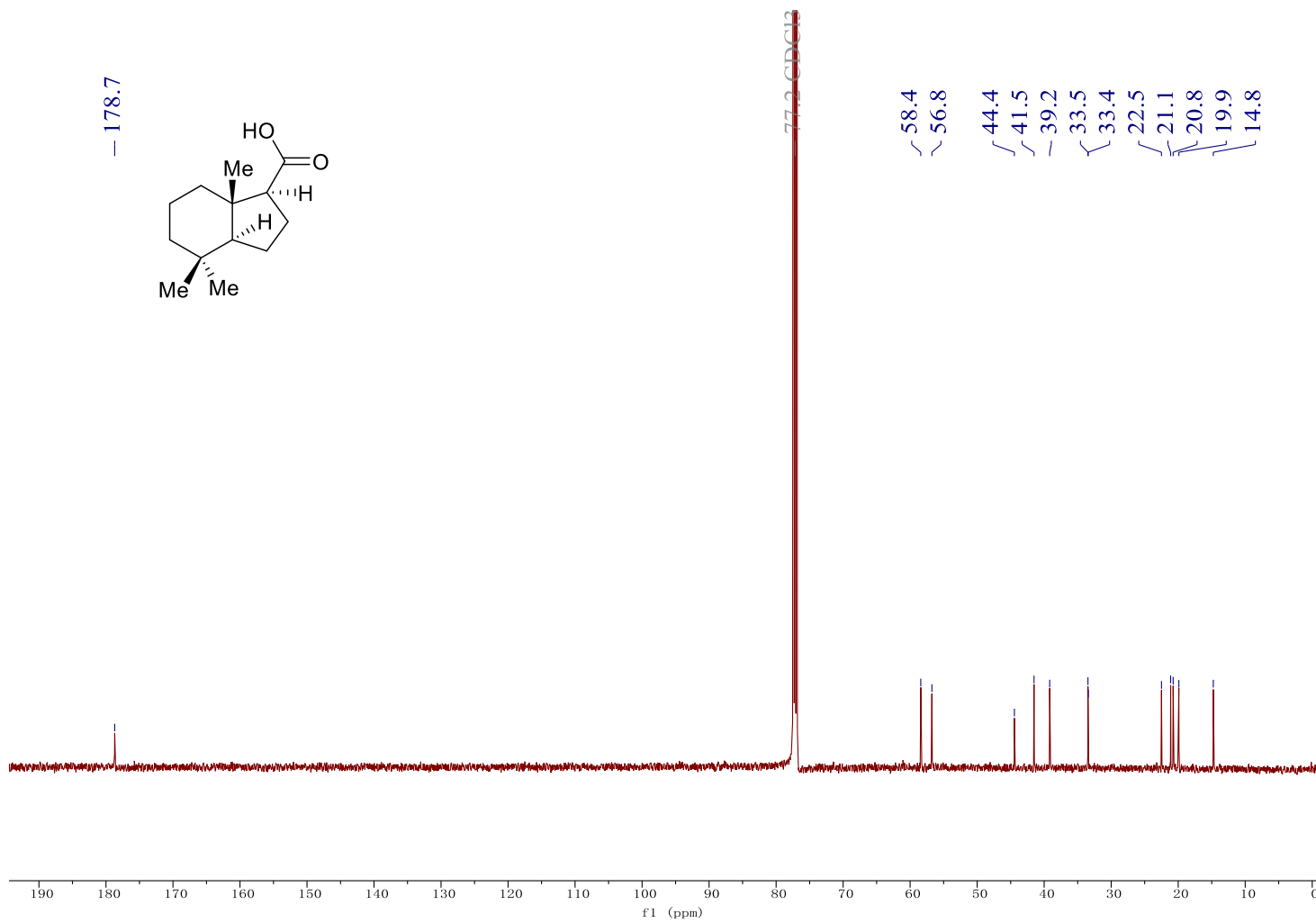
Compound S2 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



# Compound 4 <sup>1</sup>H NMR (CDCl<sub>3</sub>)

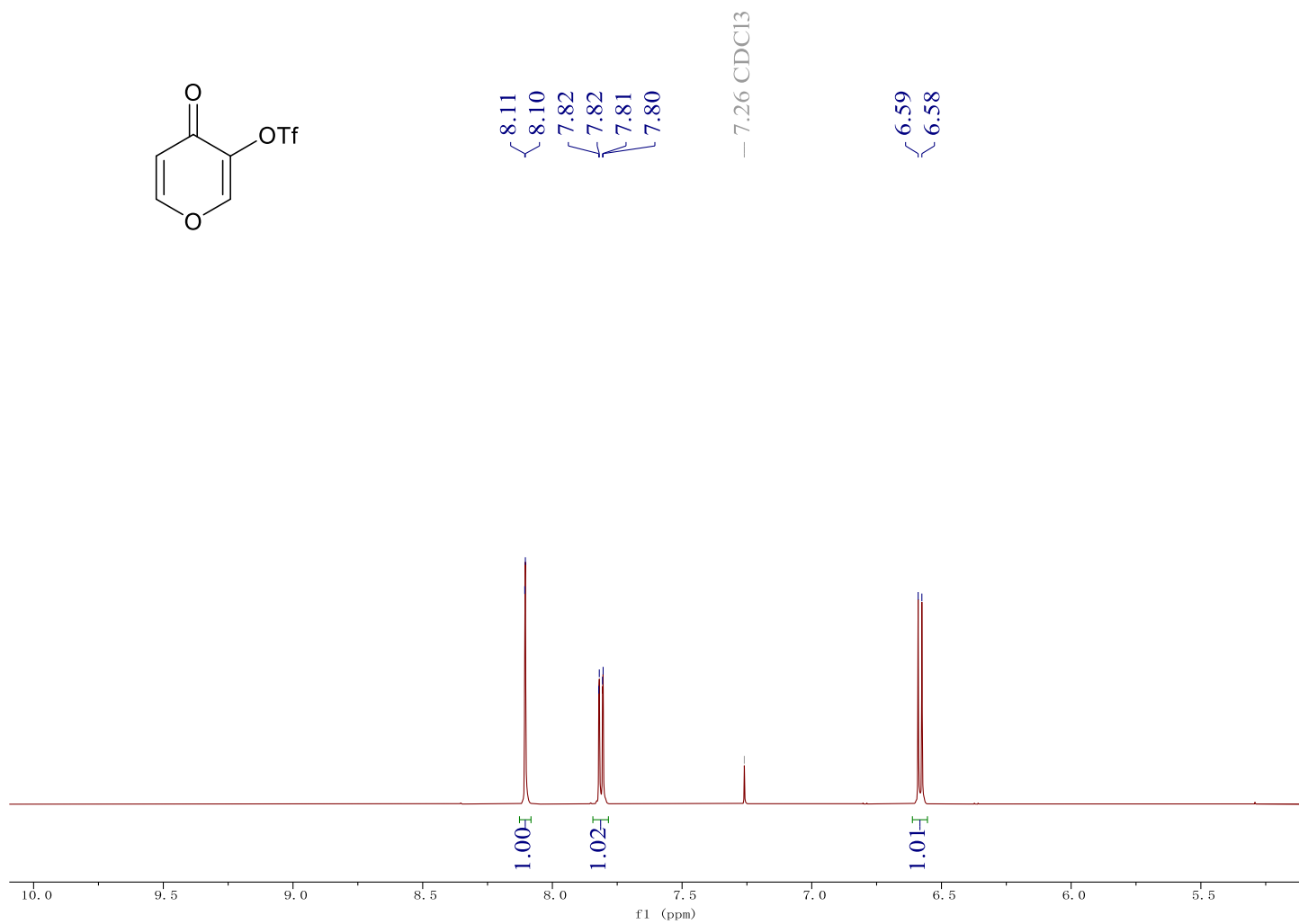
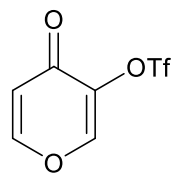


# Compound 4 <sup>13</sup>C NMR (CDCl<sub>3</sub>)

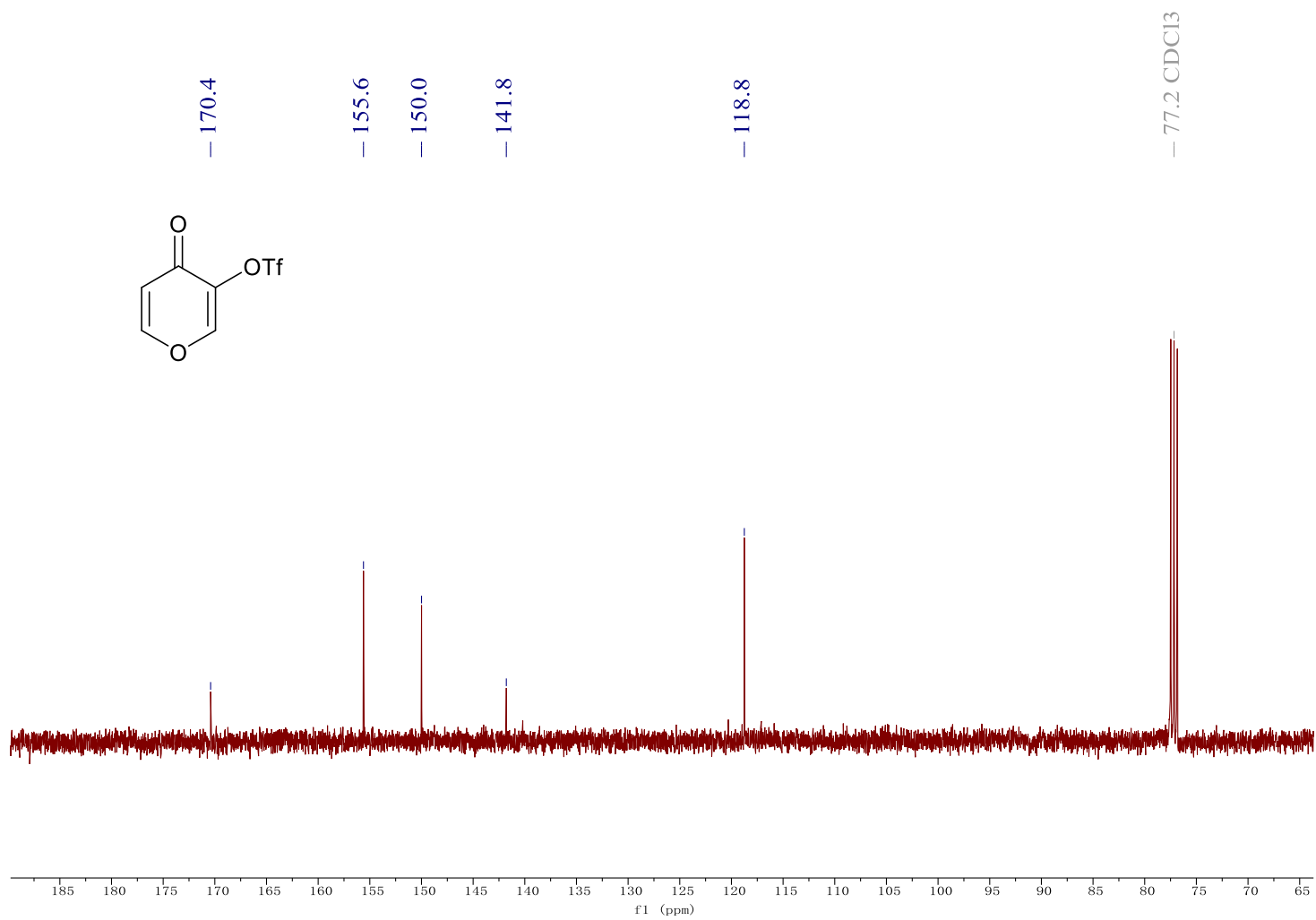




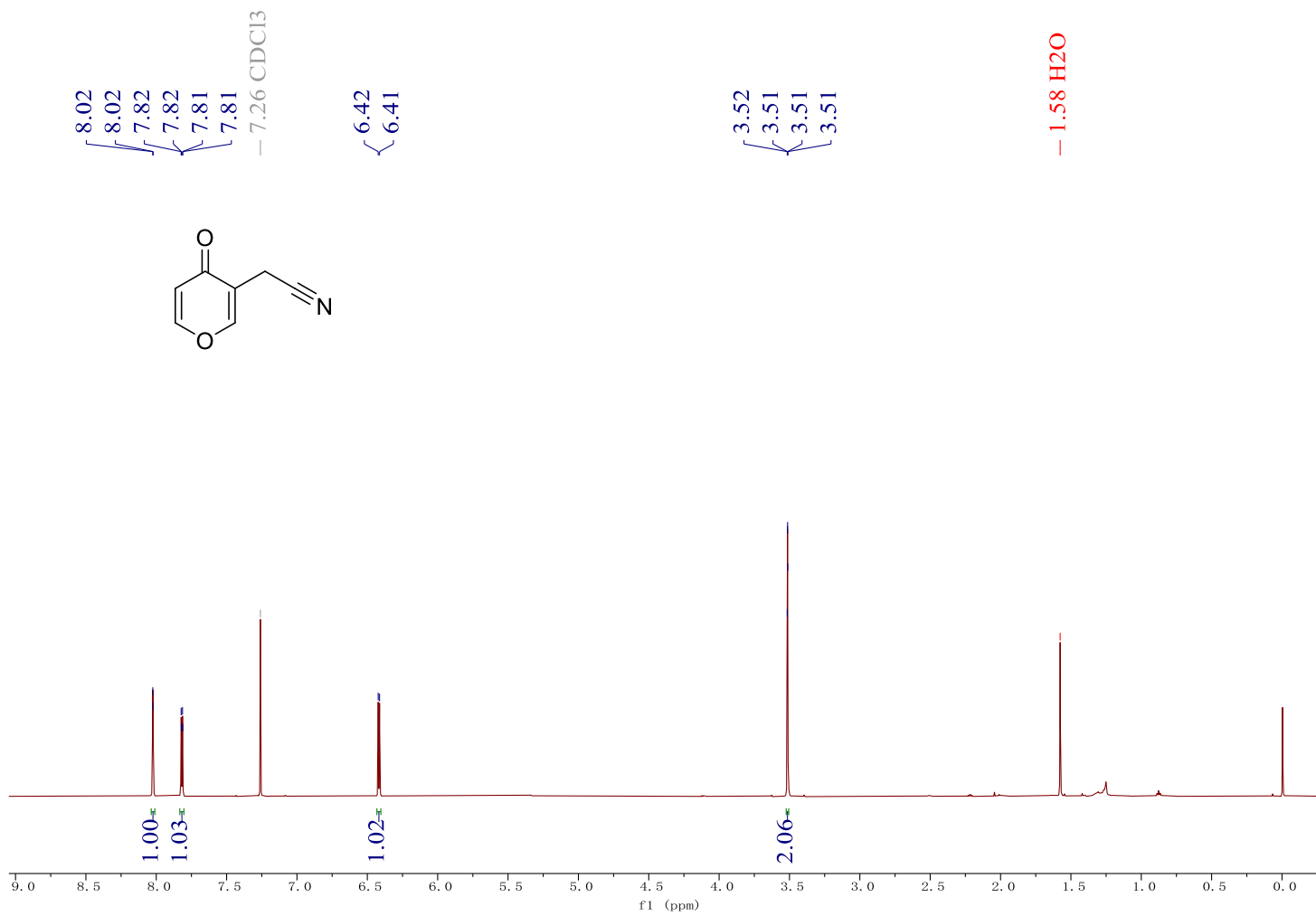
Compound 7  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )



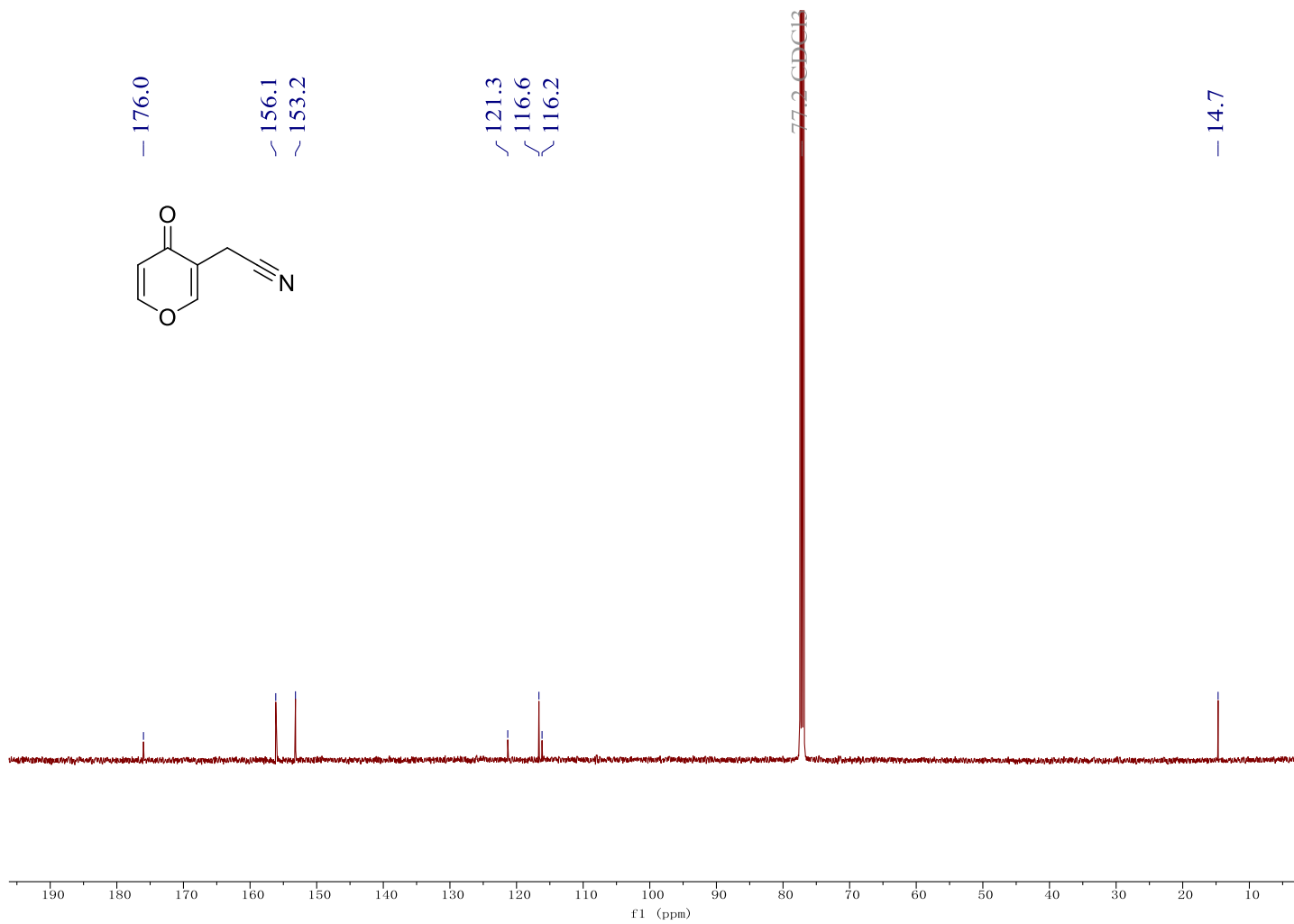
Compound 7 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



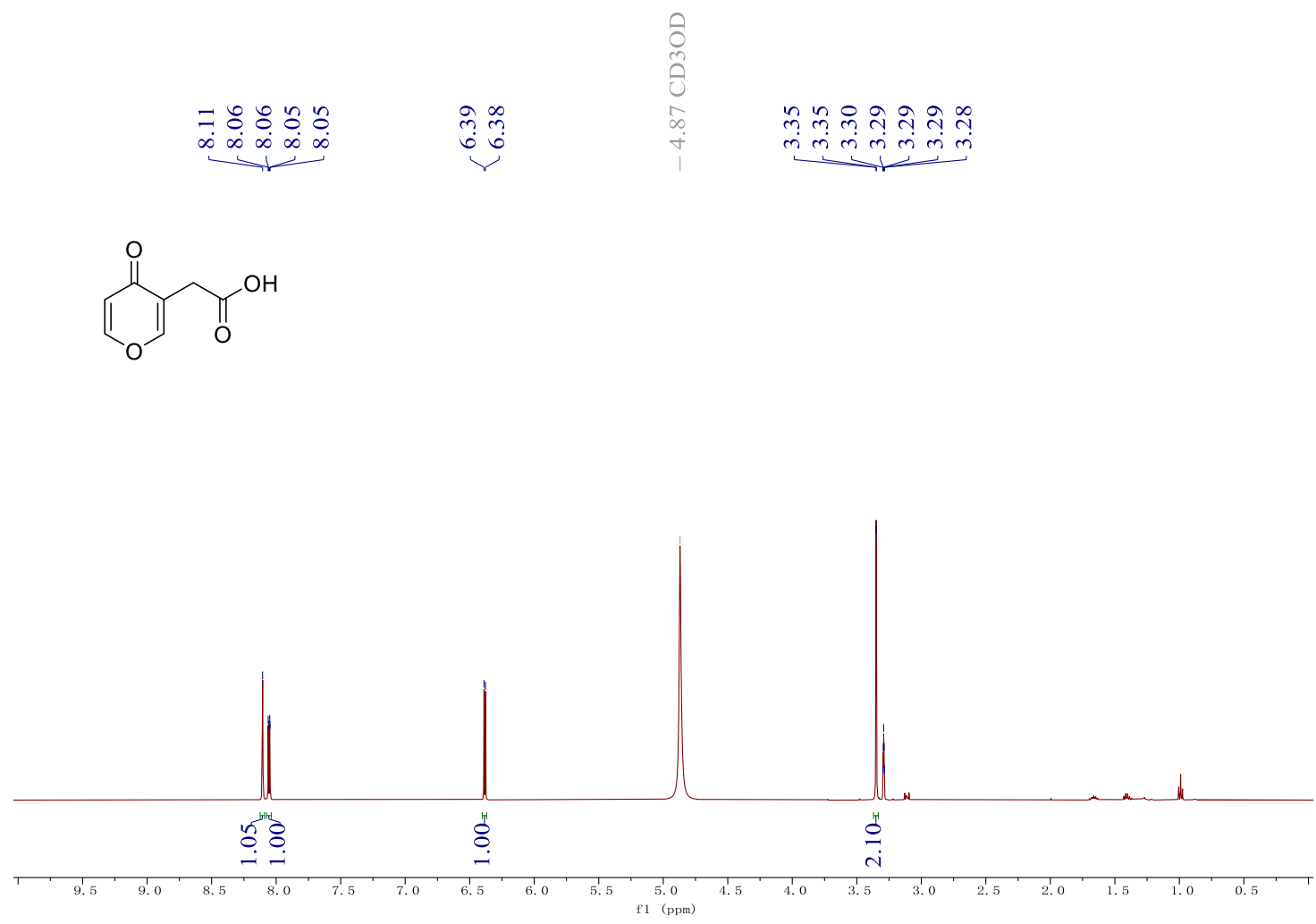
Compound 6 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



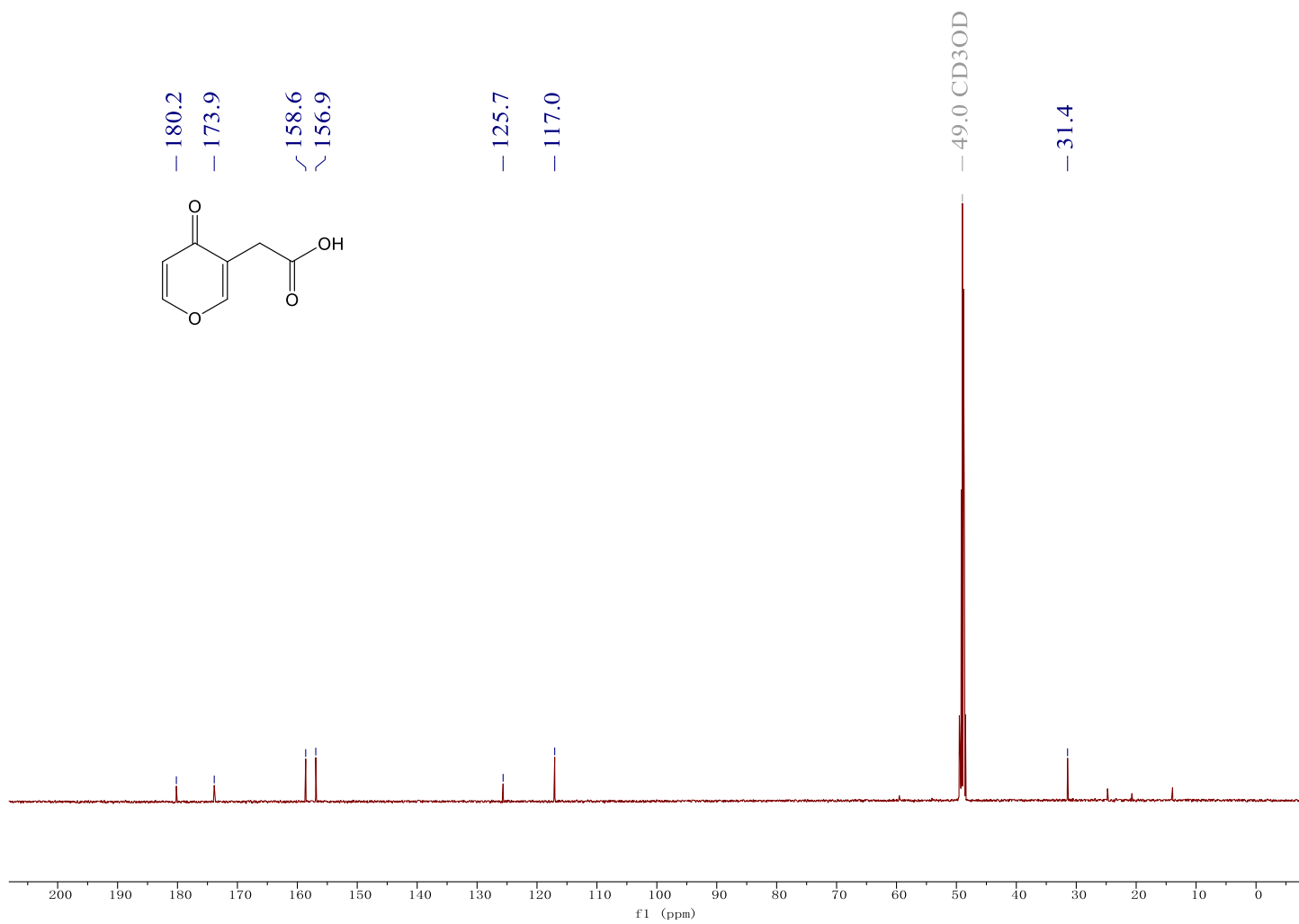
Compound 6 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



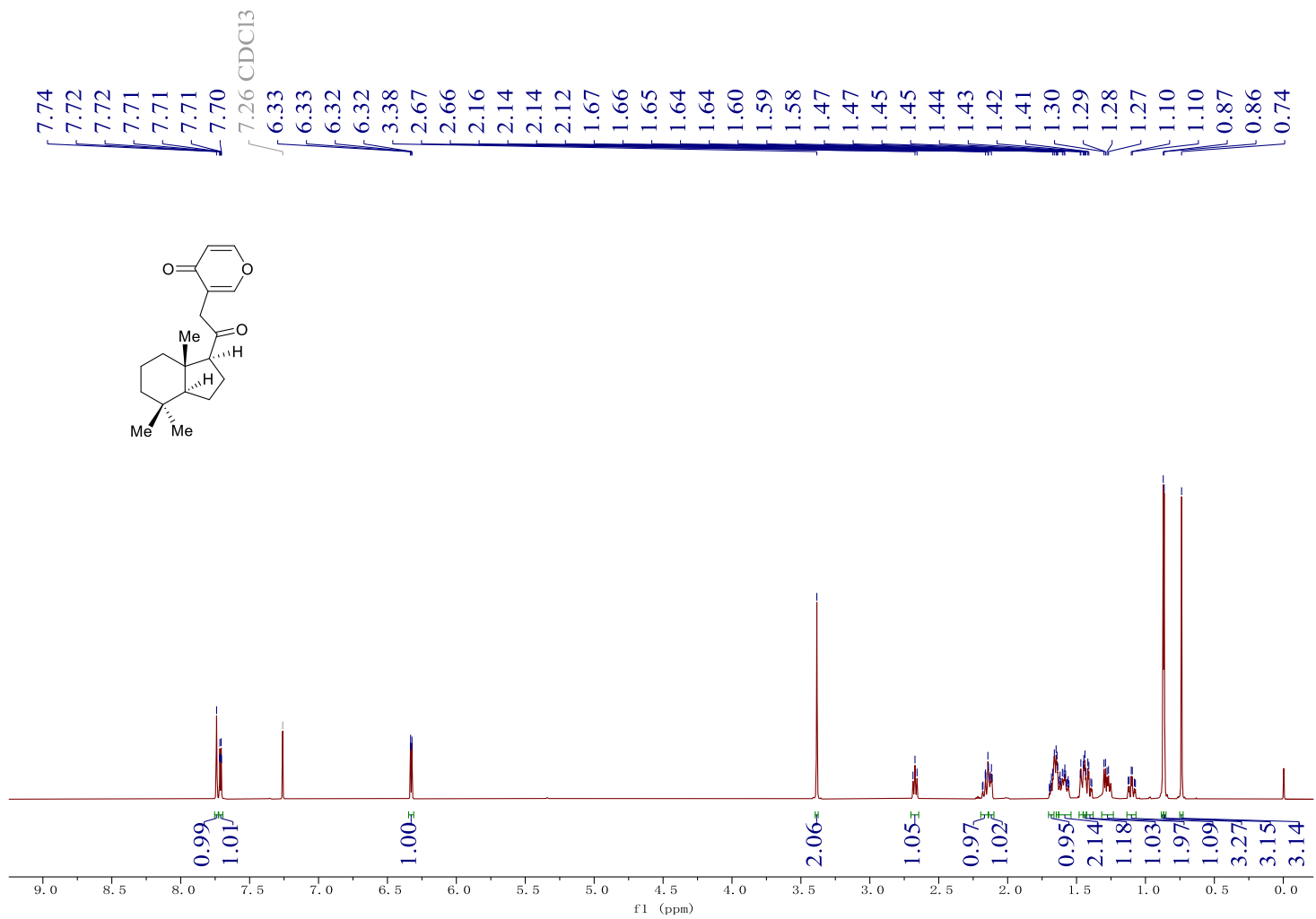
Compound 16 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



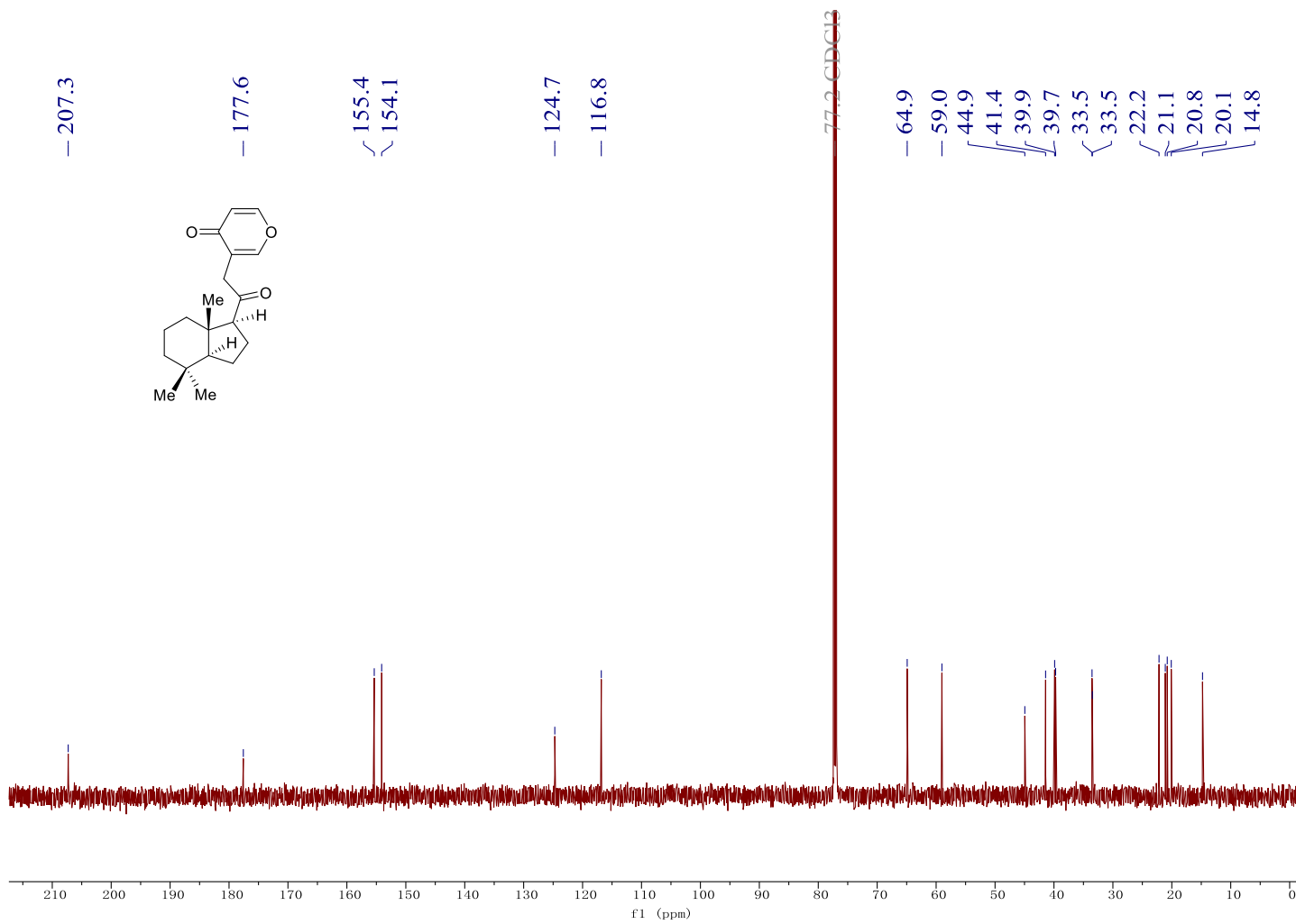
Compound 16  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )



Compound 1 <sup>1</sup>H NMR (CDCl<sub>3</sub>)

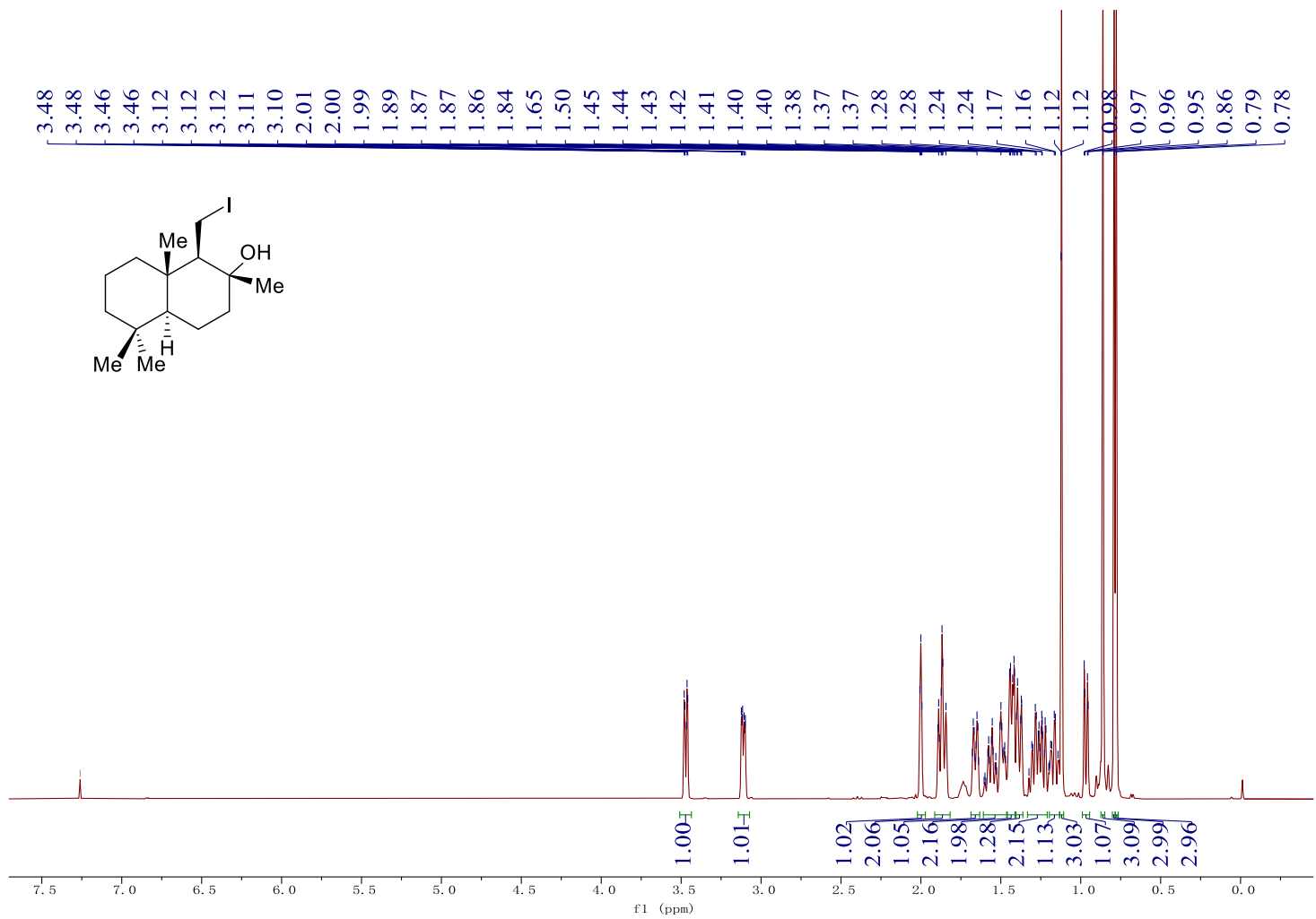


# Compound 1 <sup>13</sup>C NMR (CDCl<sub>3</sub>)

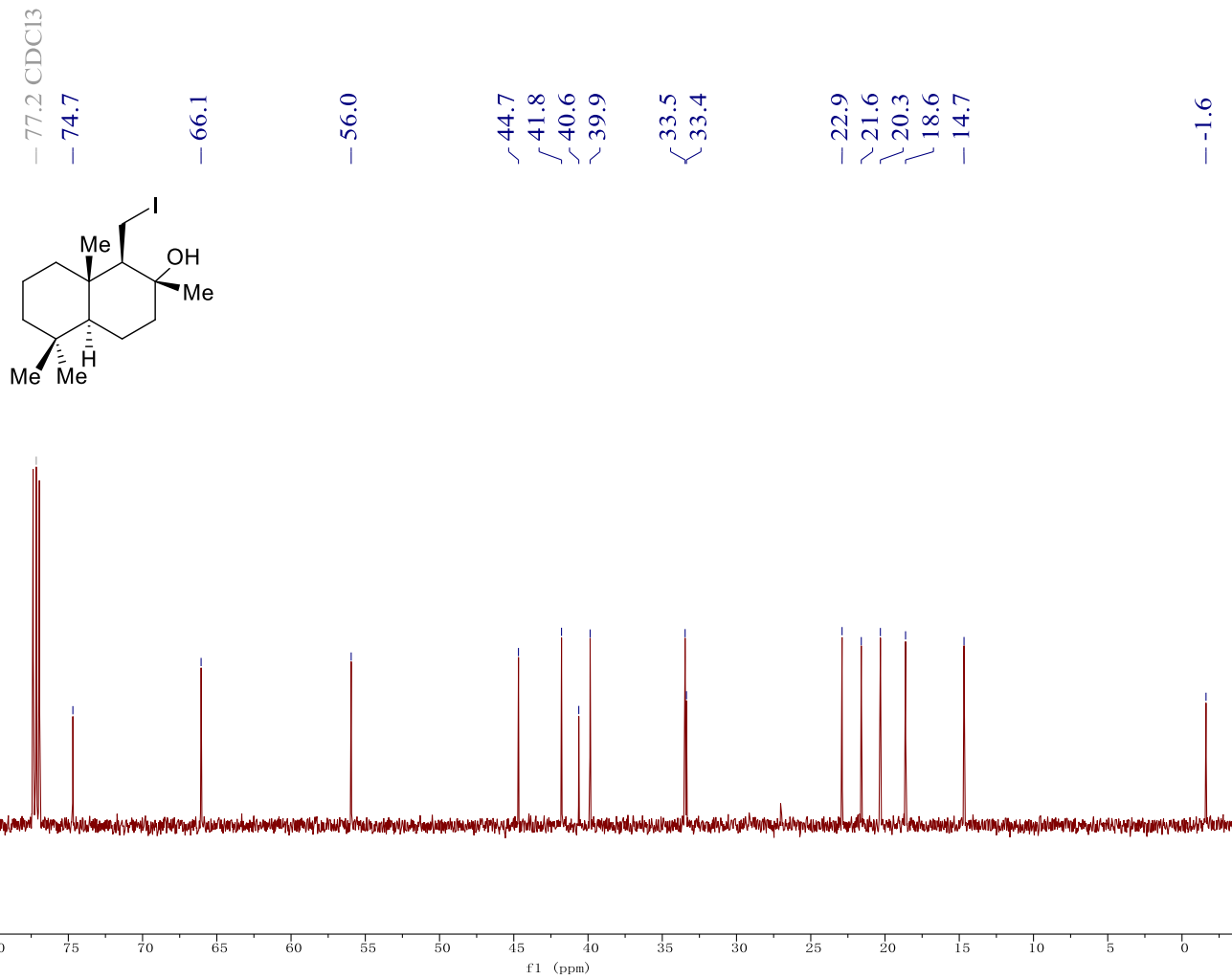




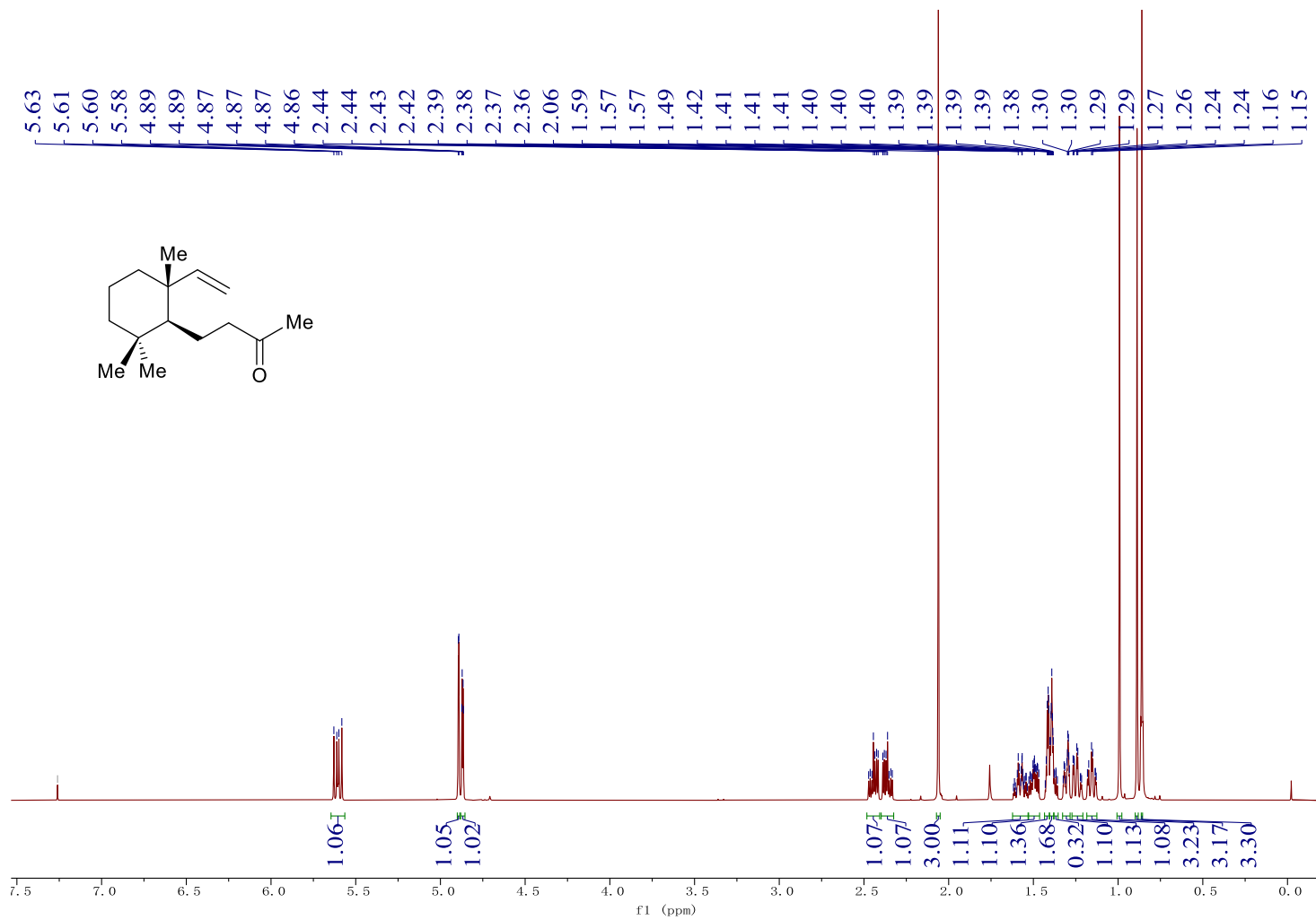
Compound 11  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )



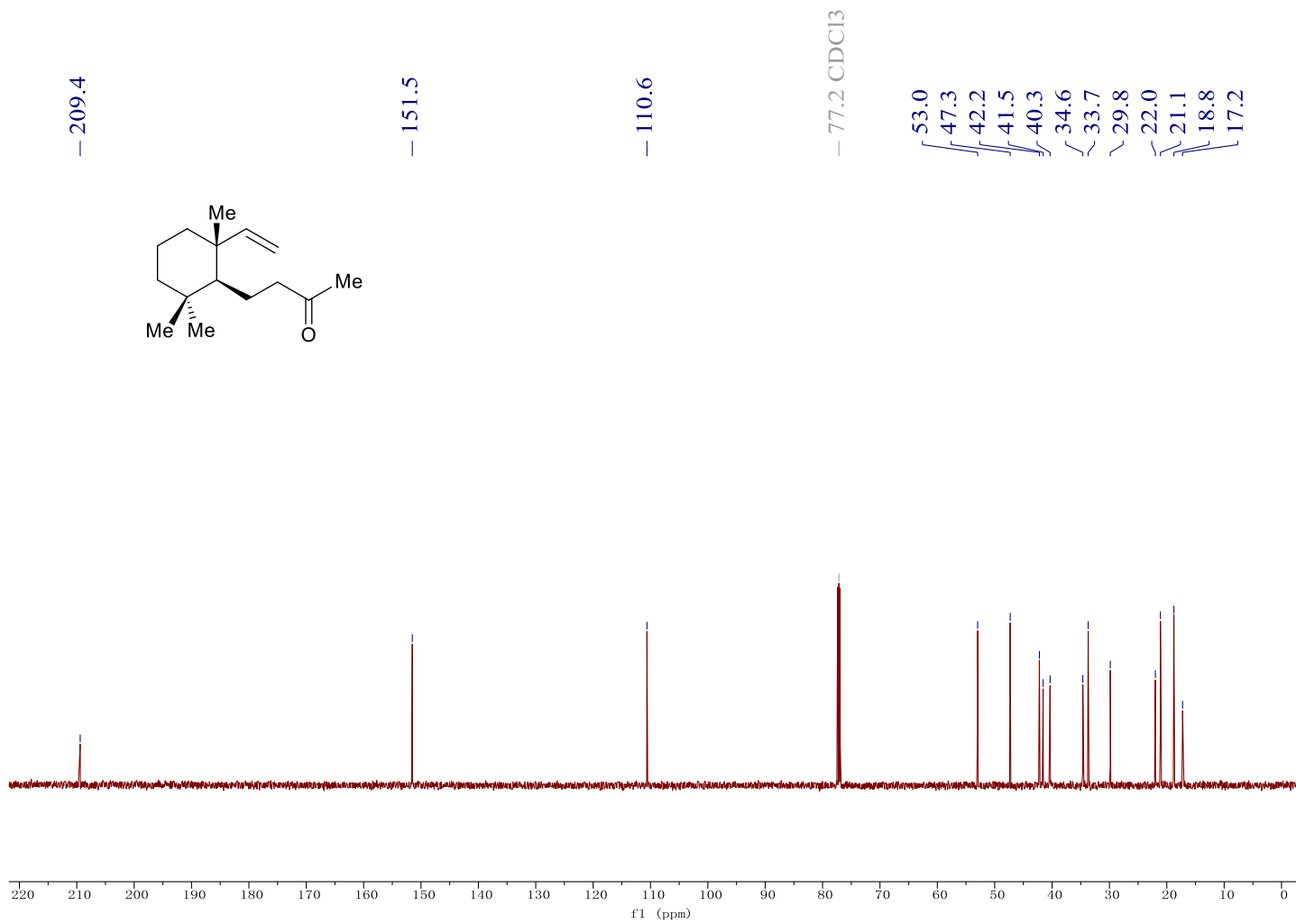
# Compound 11 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



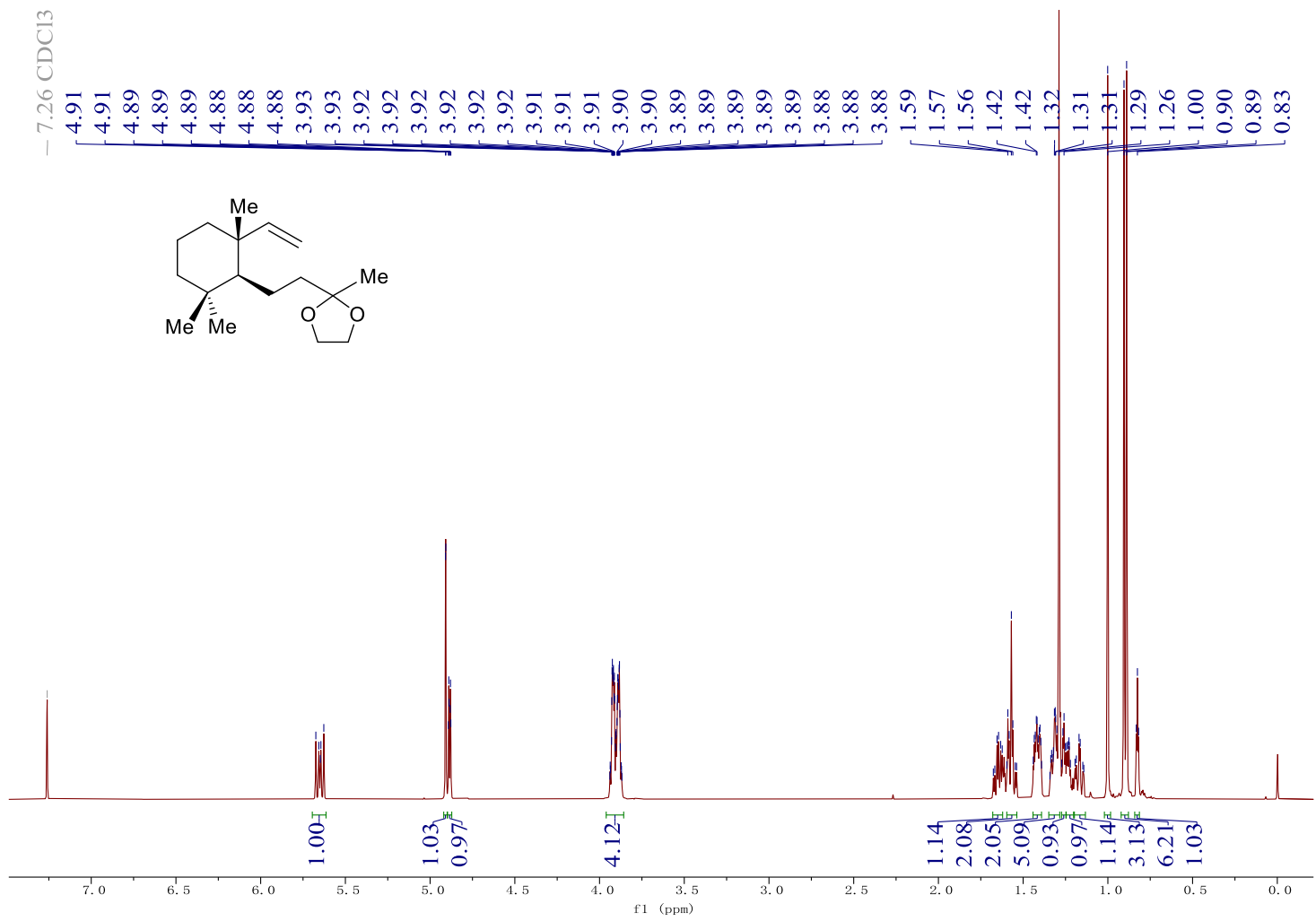
Compound 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



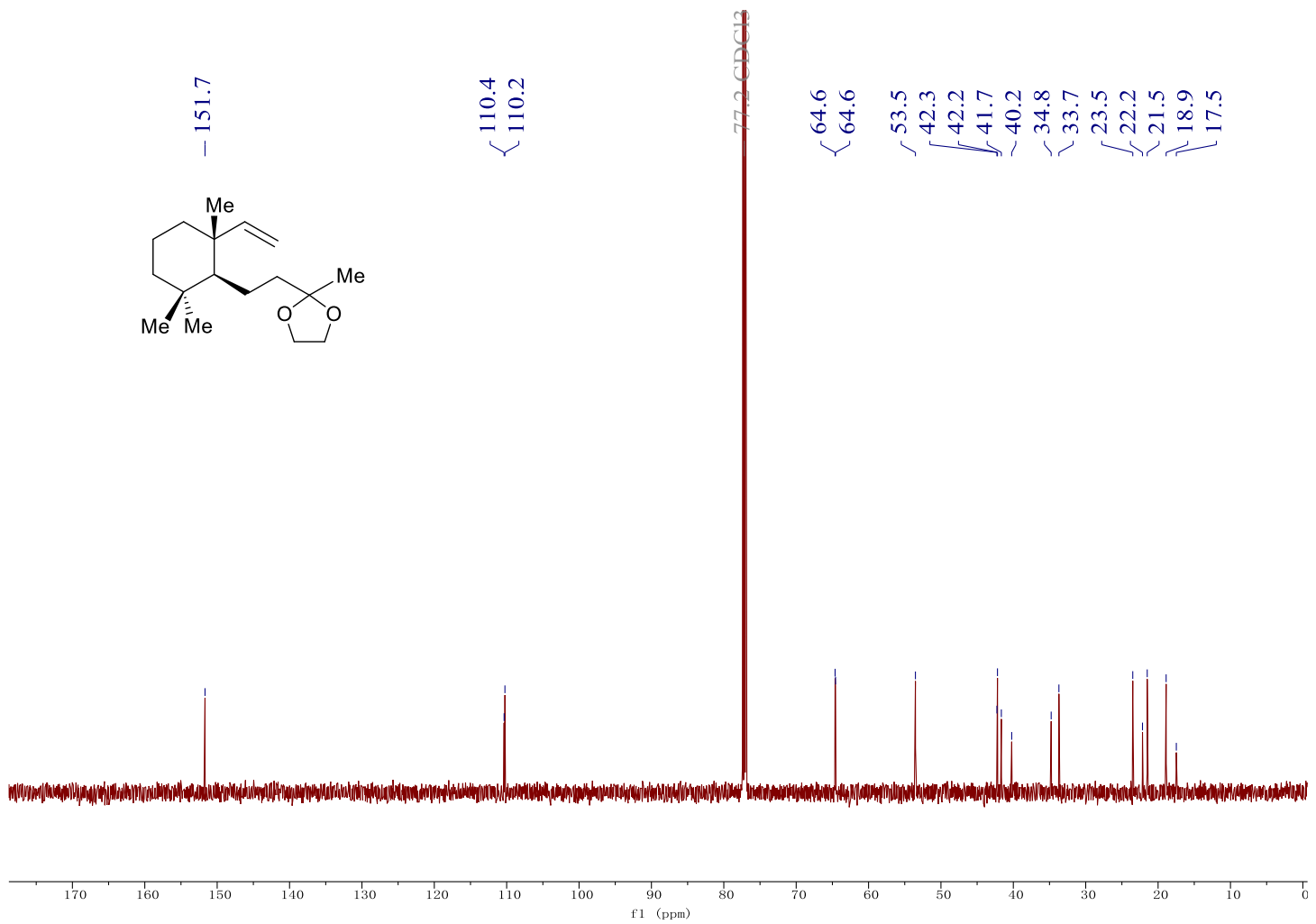
# Compound 10 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



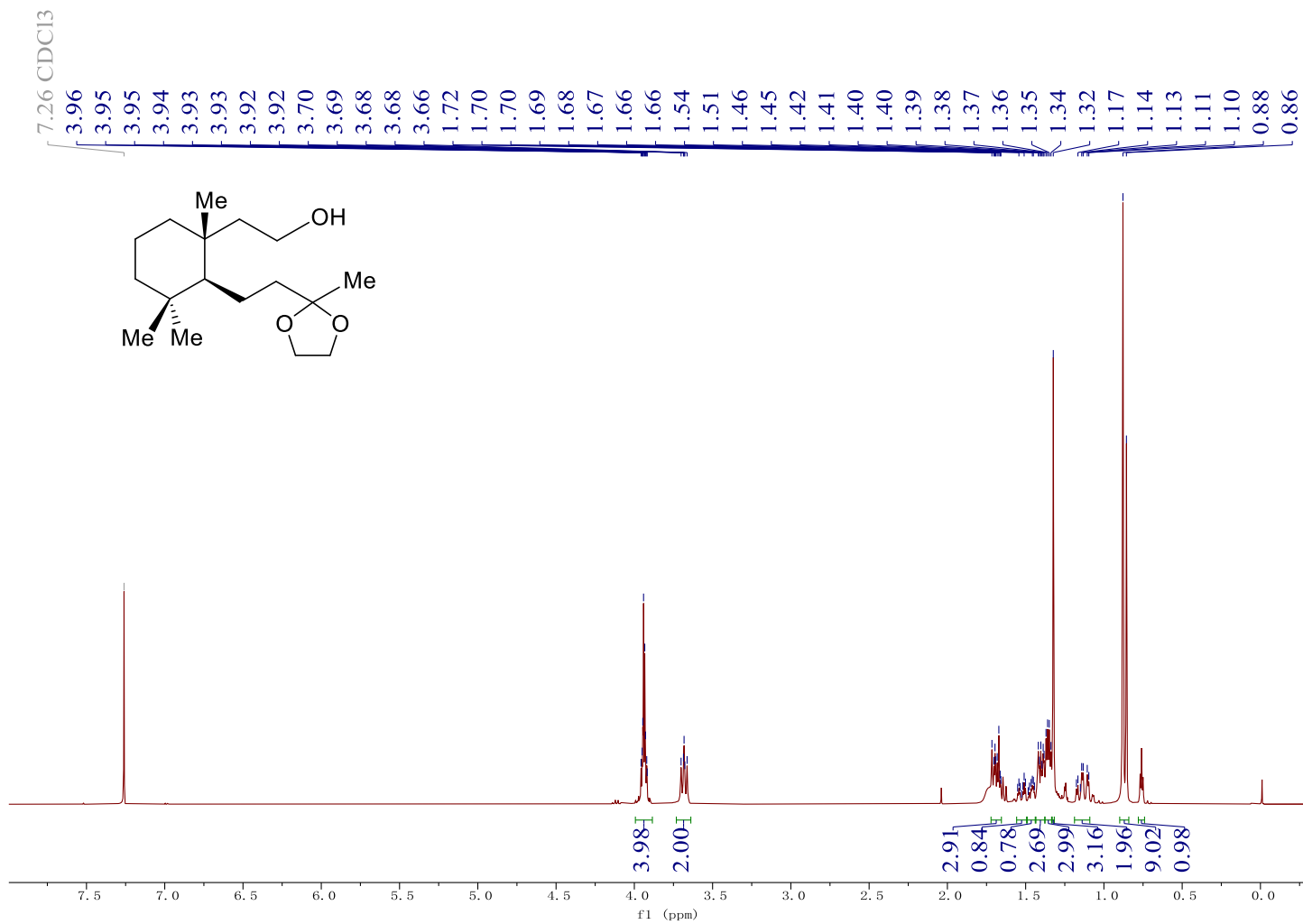
Compound S4 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



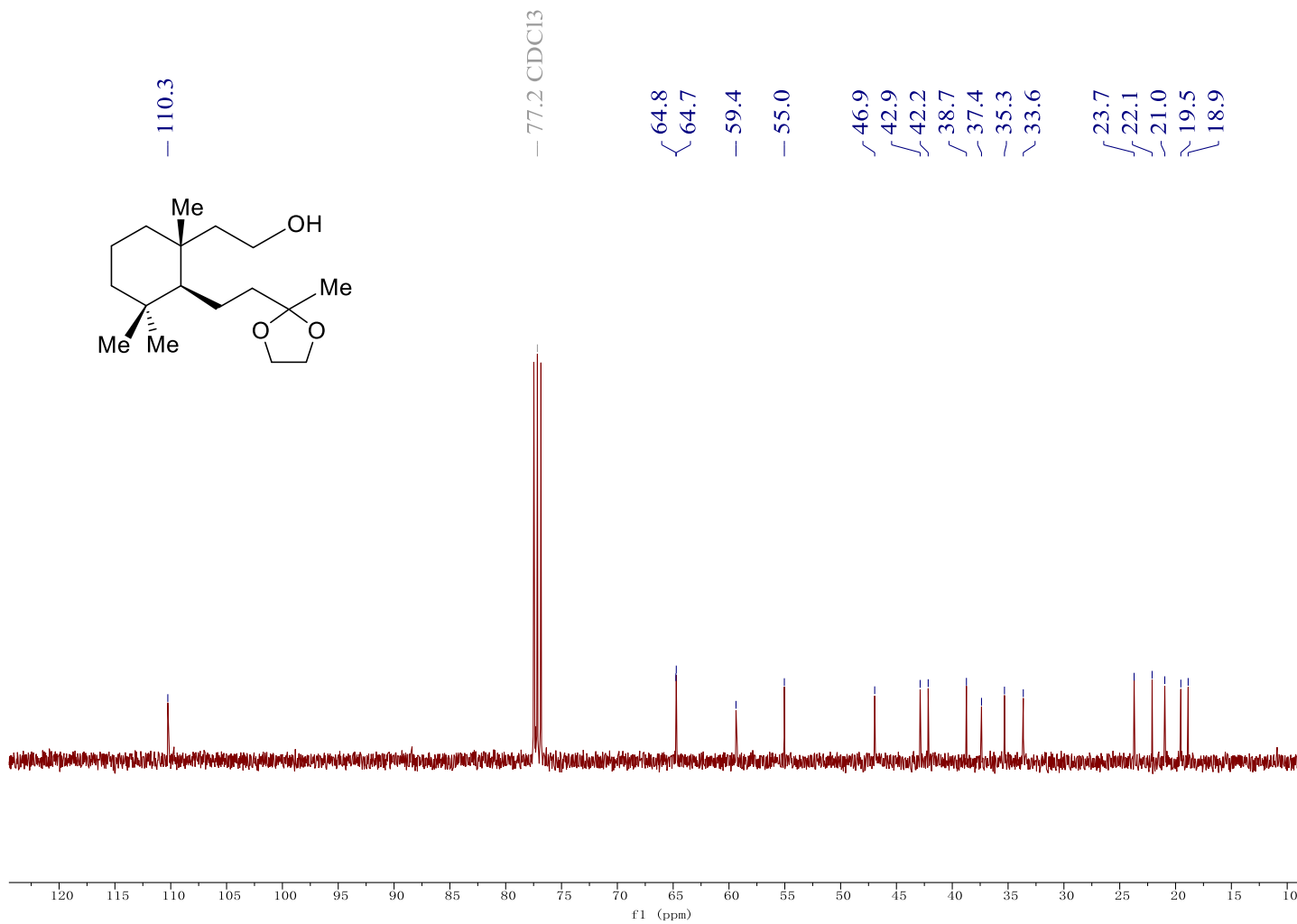
Compound S4 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



# Compound 17 <sup>1</sup>H NMR (CDCl<sub>3</sub>)

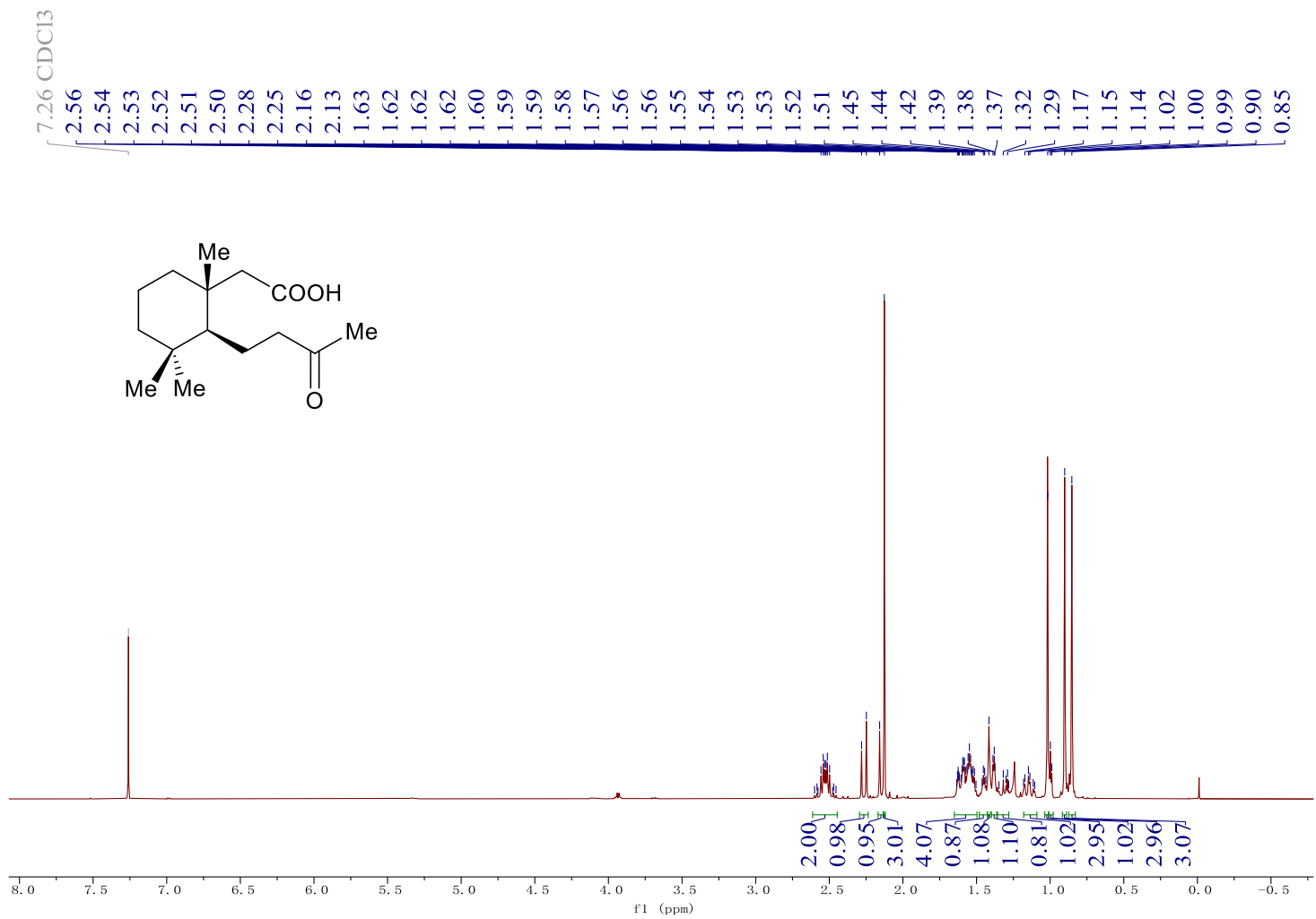


Compound 17 <sup>13</sup>C NMR (CDCl<sub>3</sub>)

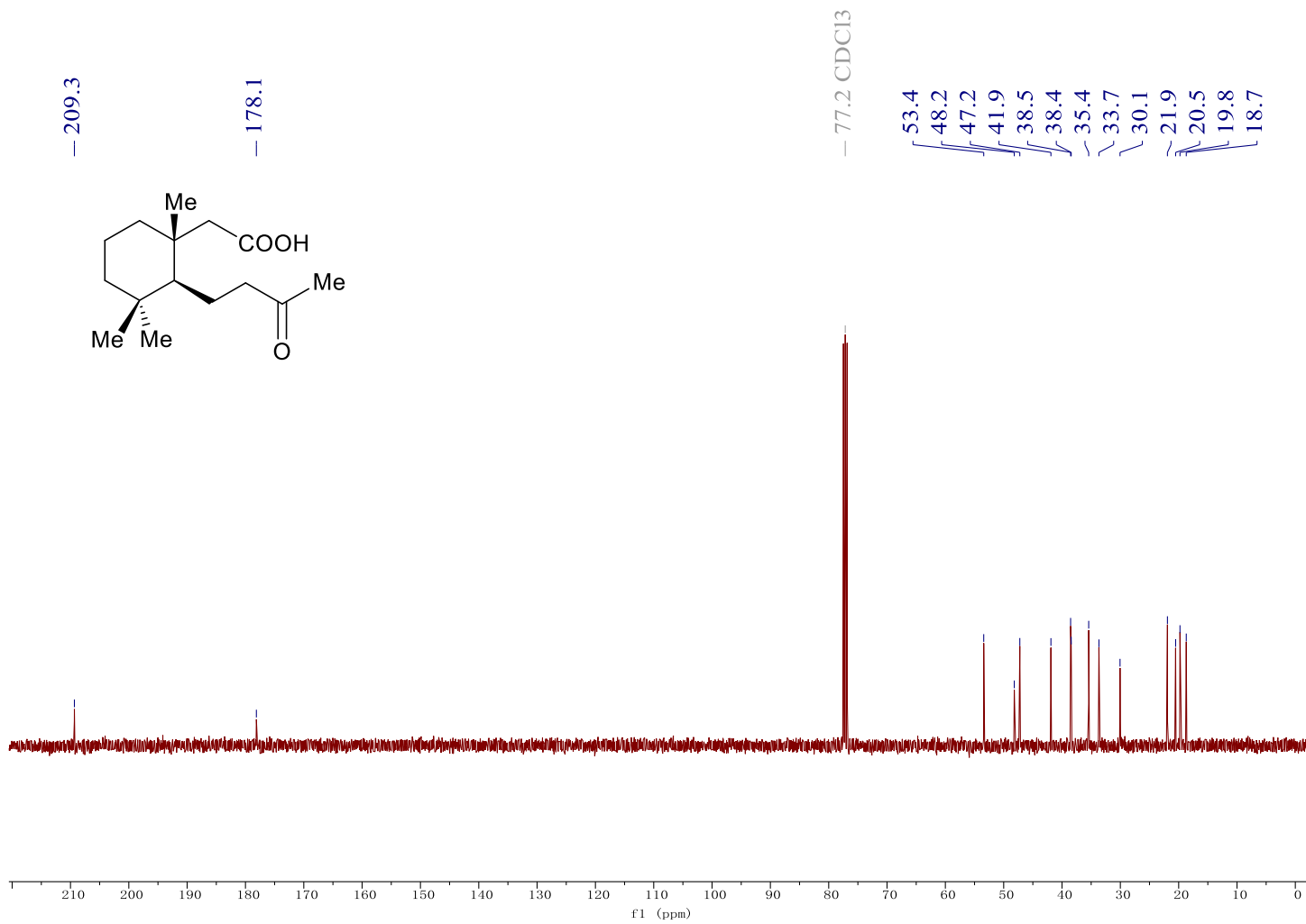




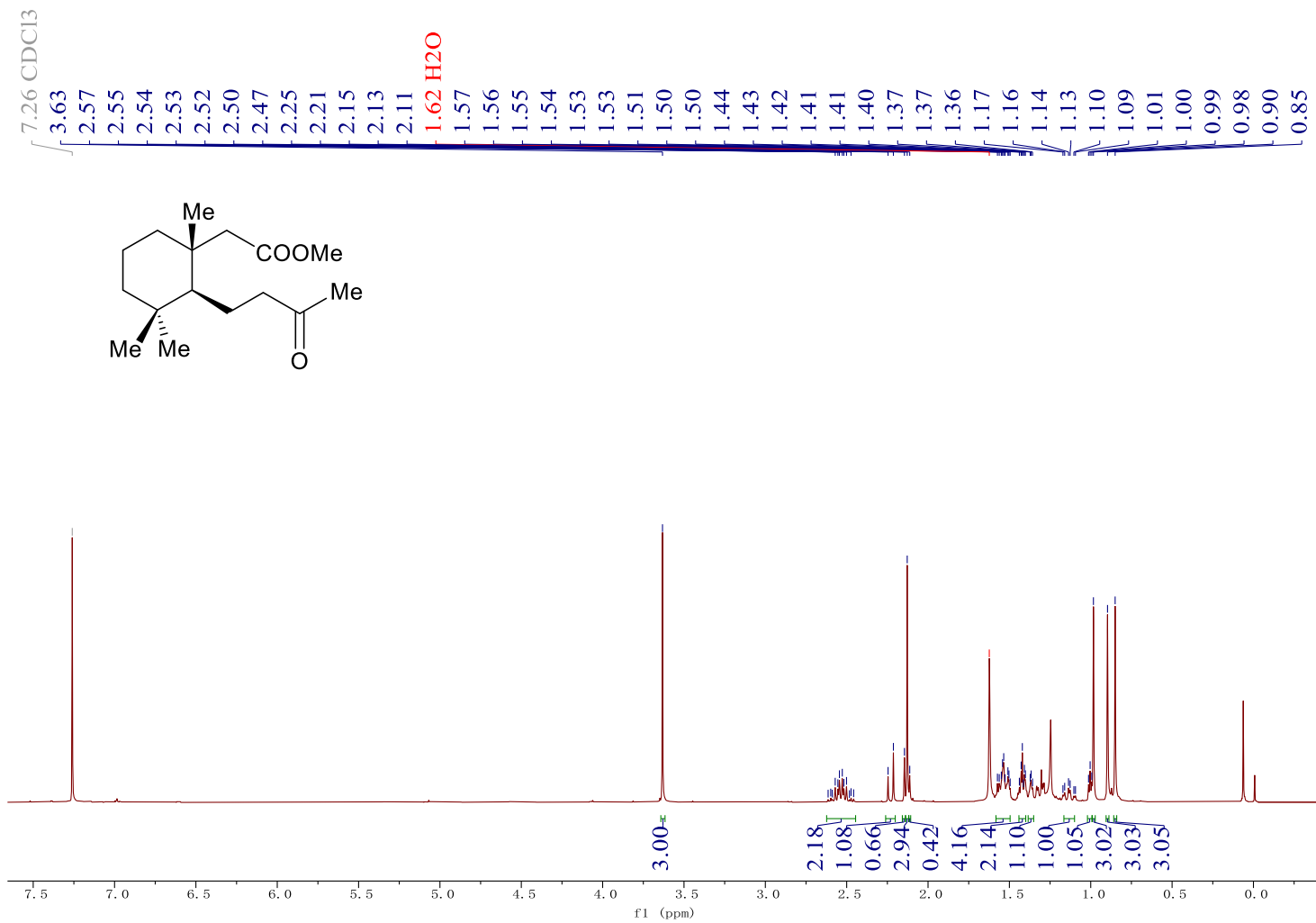
Compound S5 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



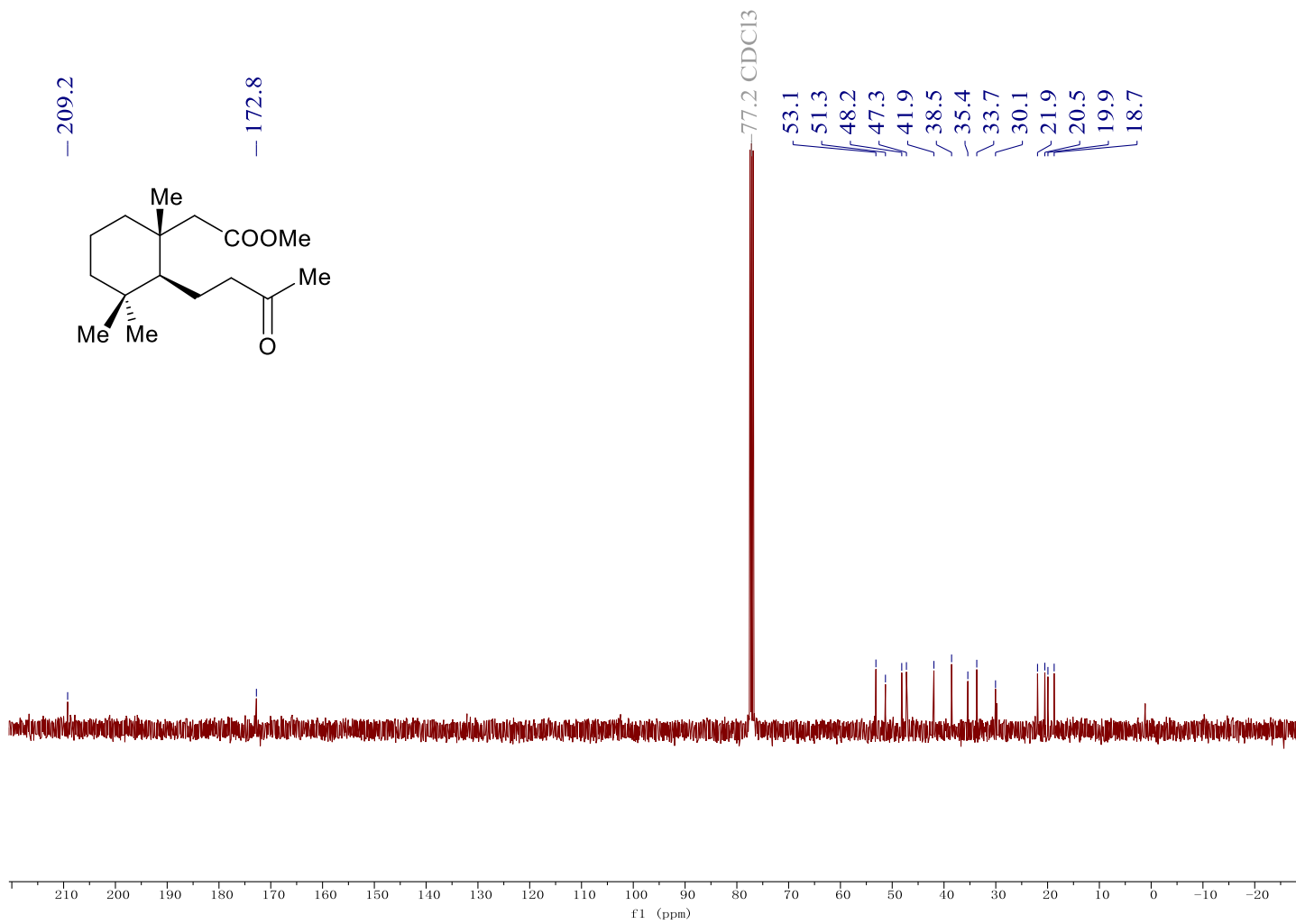
Compound S5 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



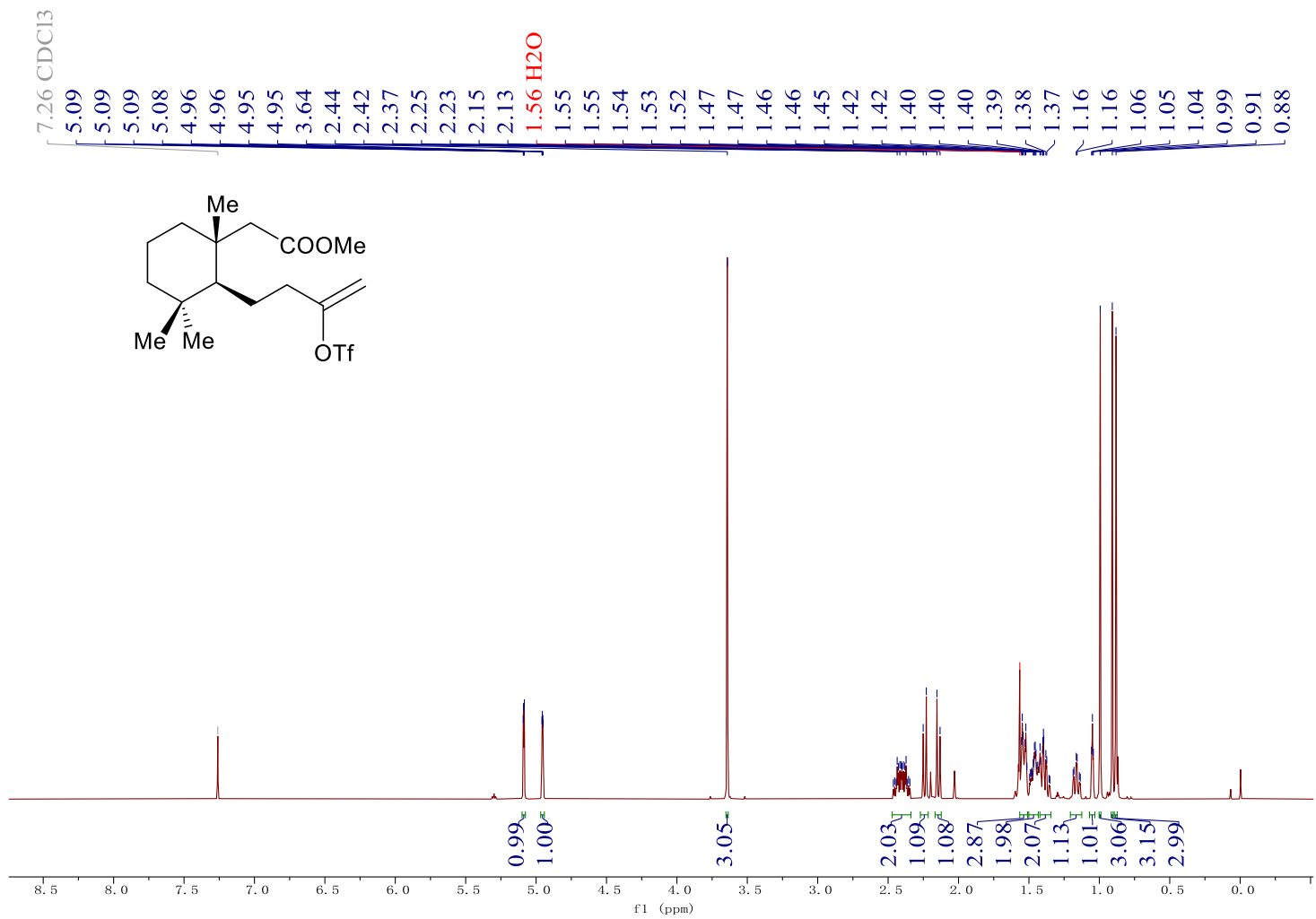
Compound 18 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



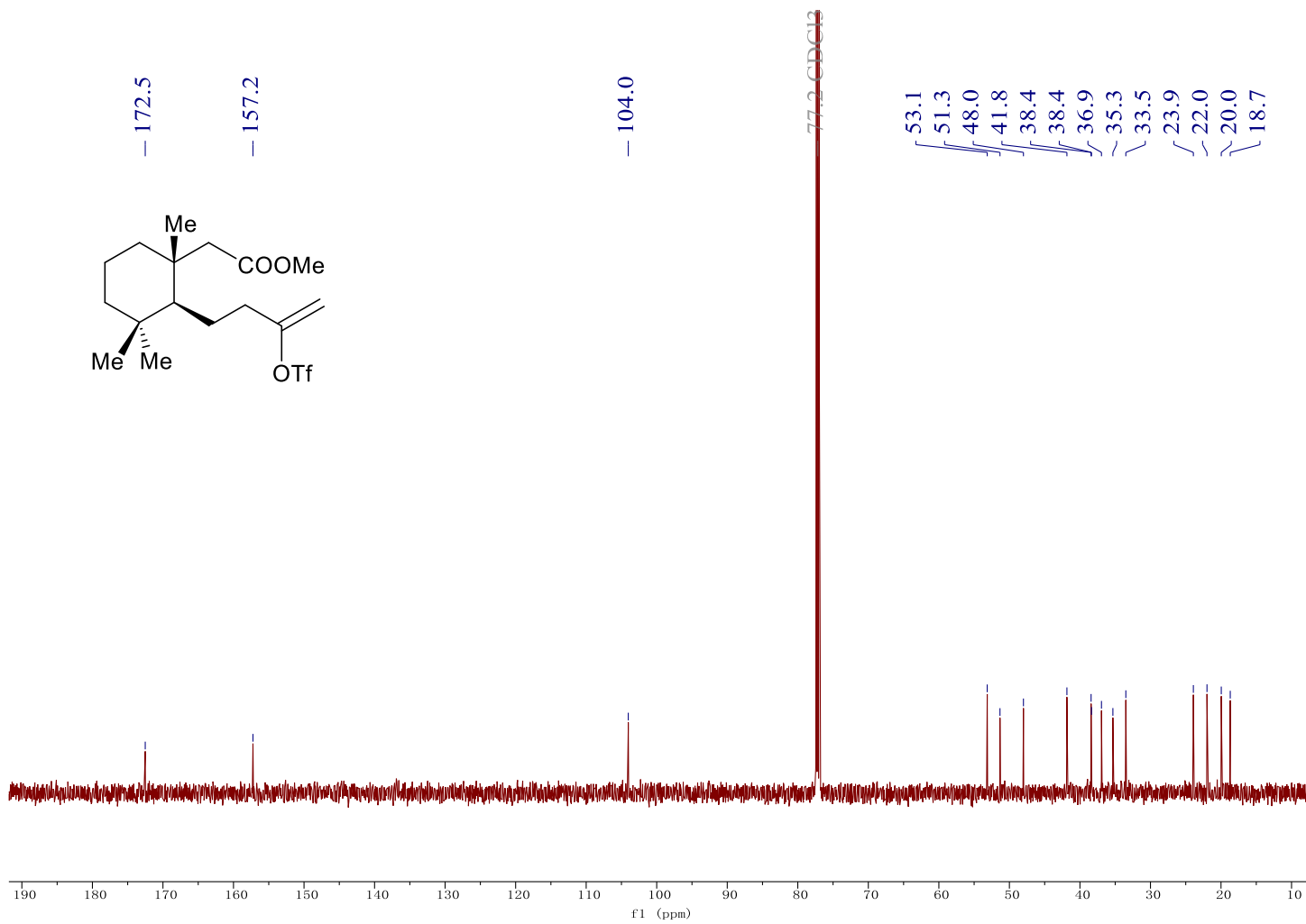
Compound 18 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



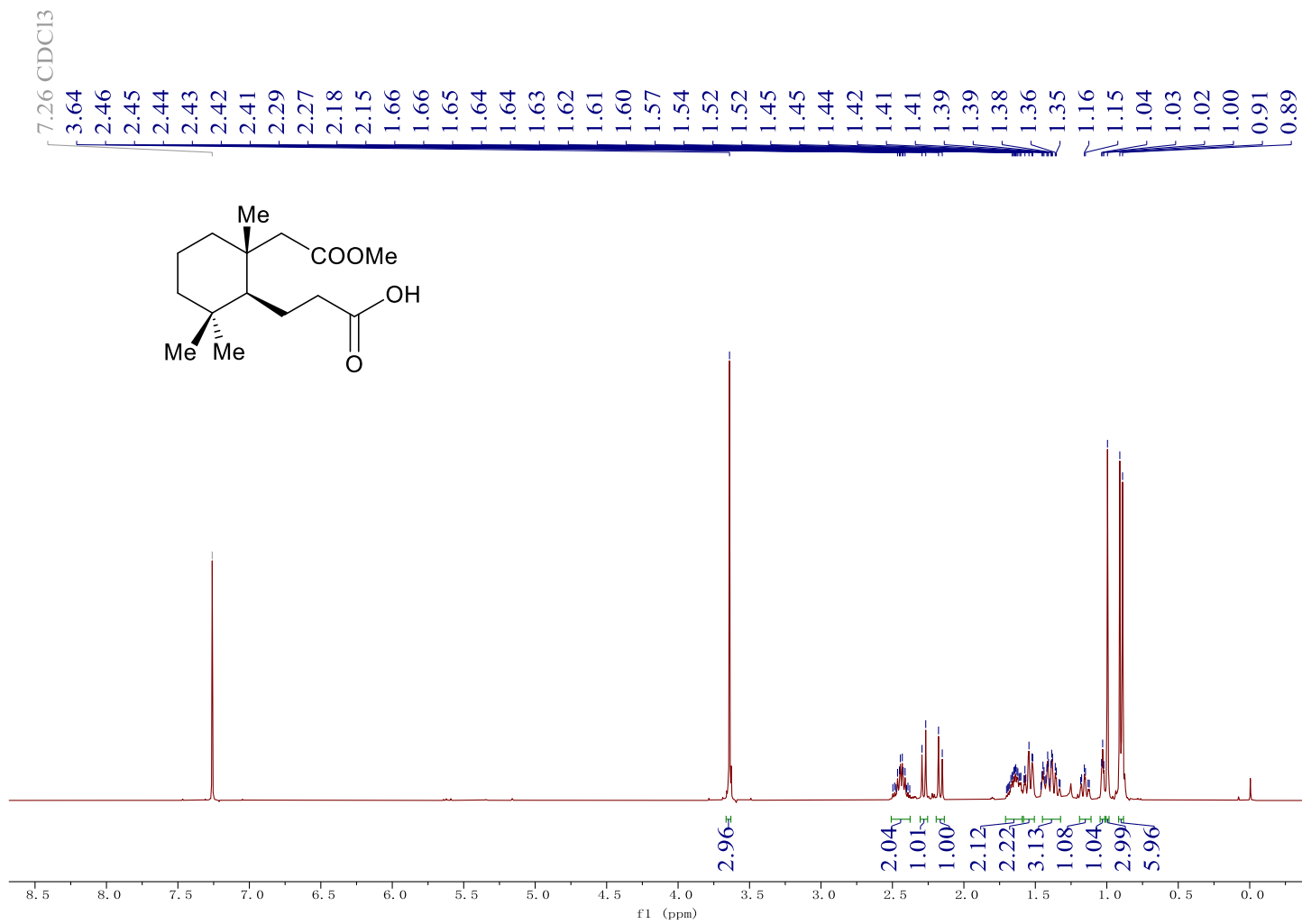
Compound S6 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



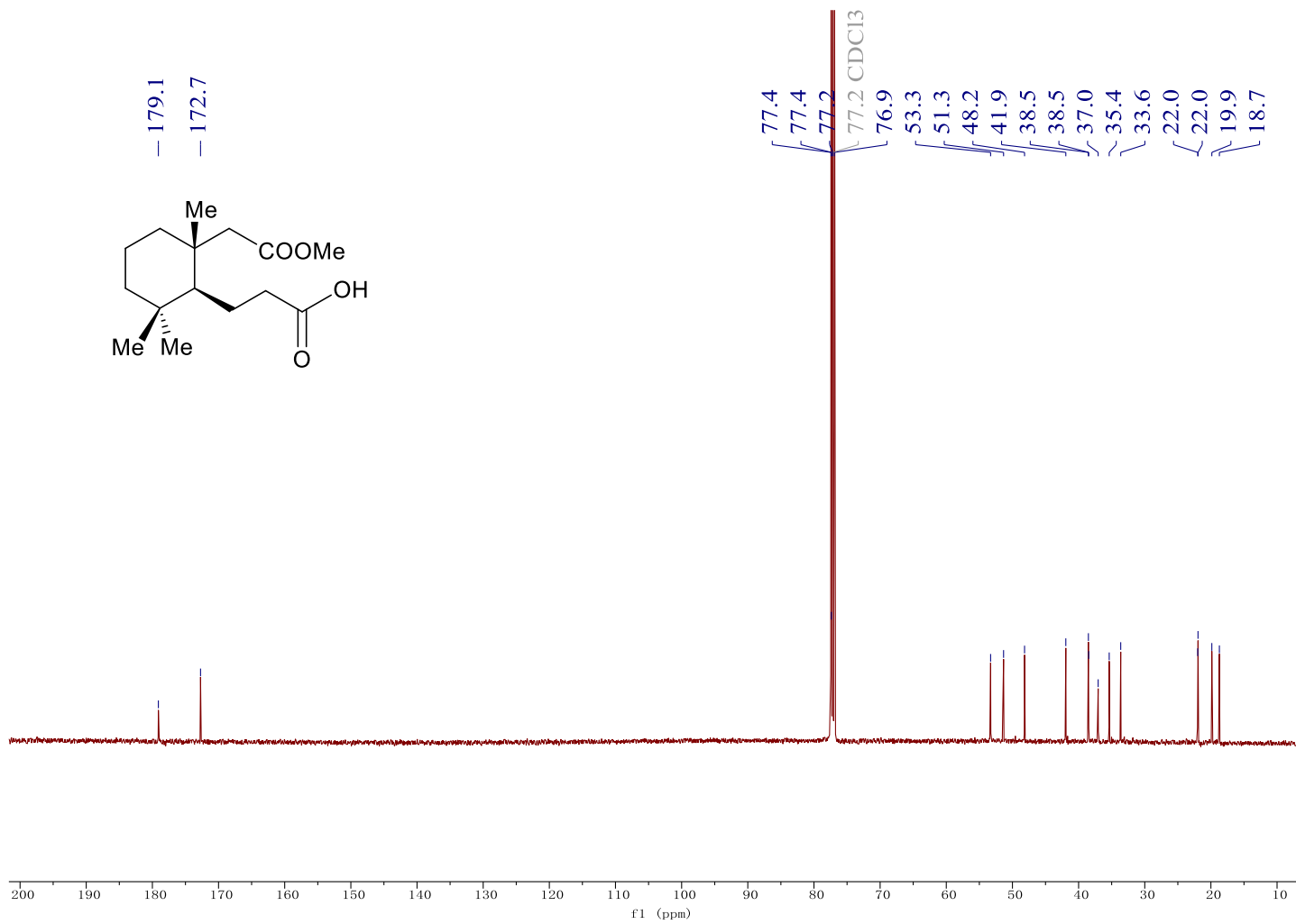
Compound S6 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



Compound 9 <sup>1</sup>H NMR (CDCl<sub>3</sub>)

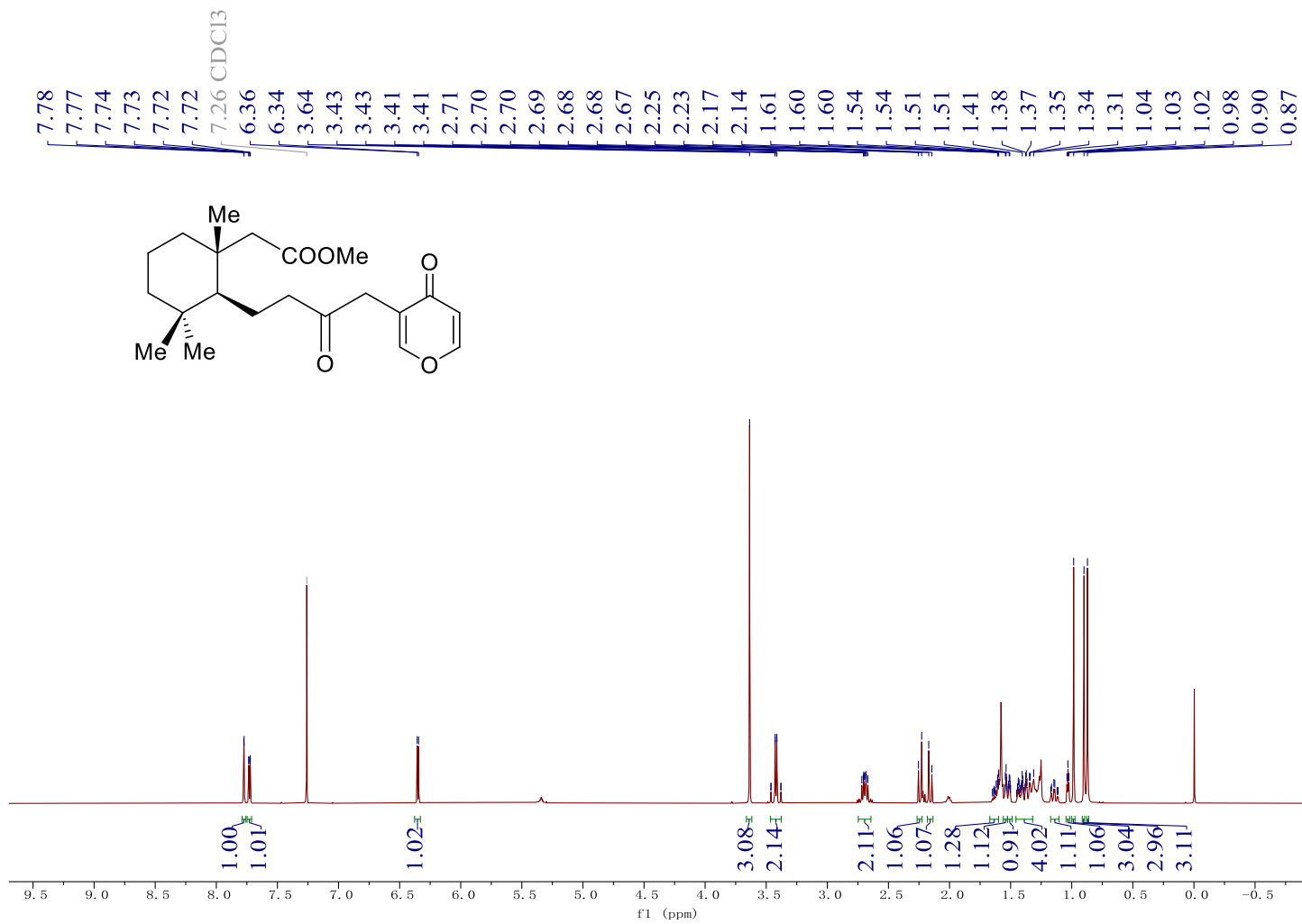


Compound 9 <sup>13</sup>C NMR (CDCl<sub>3</sub>)

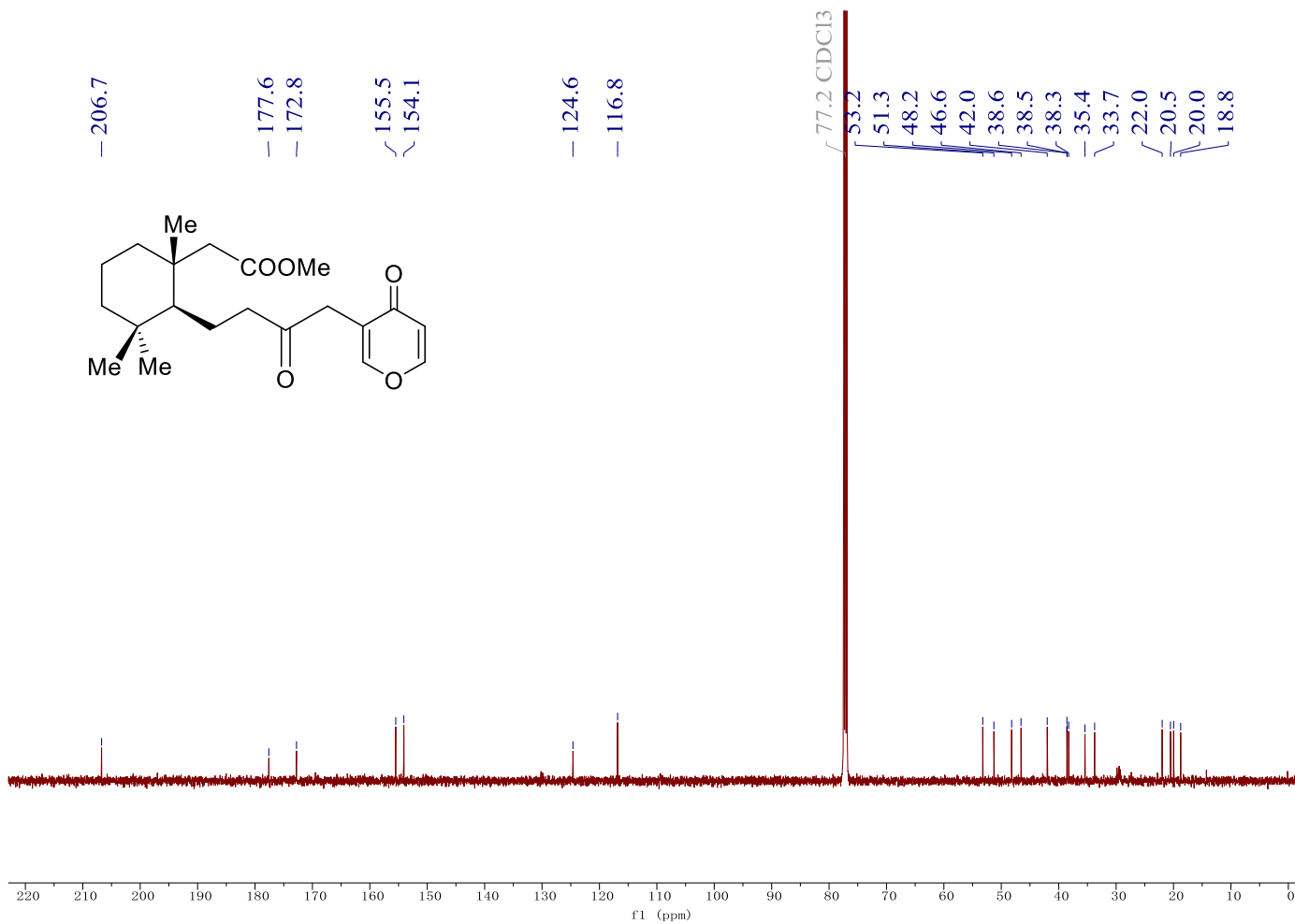




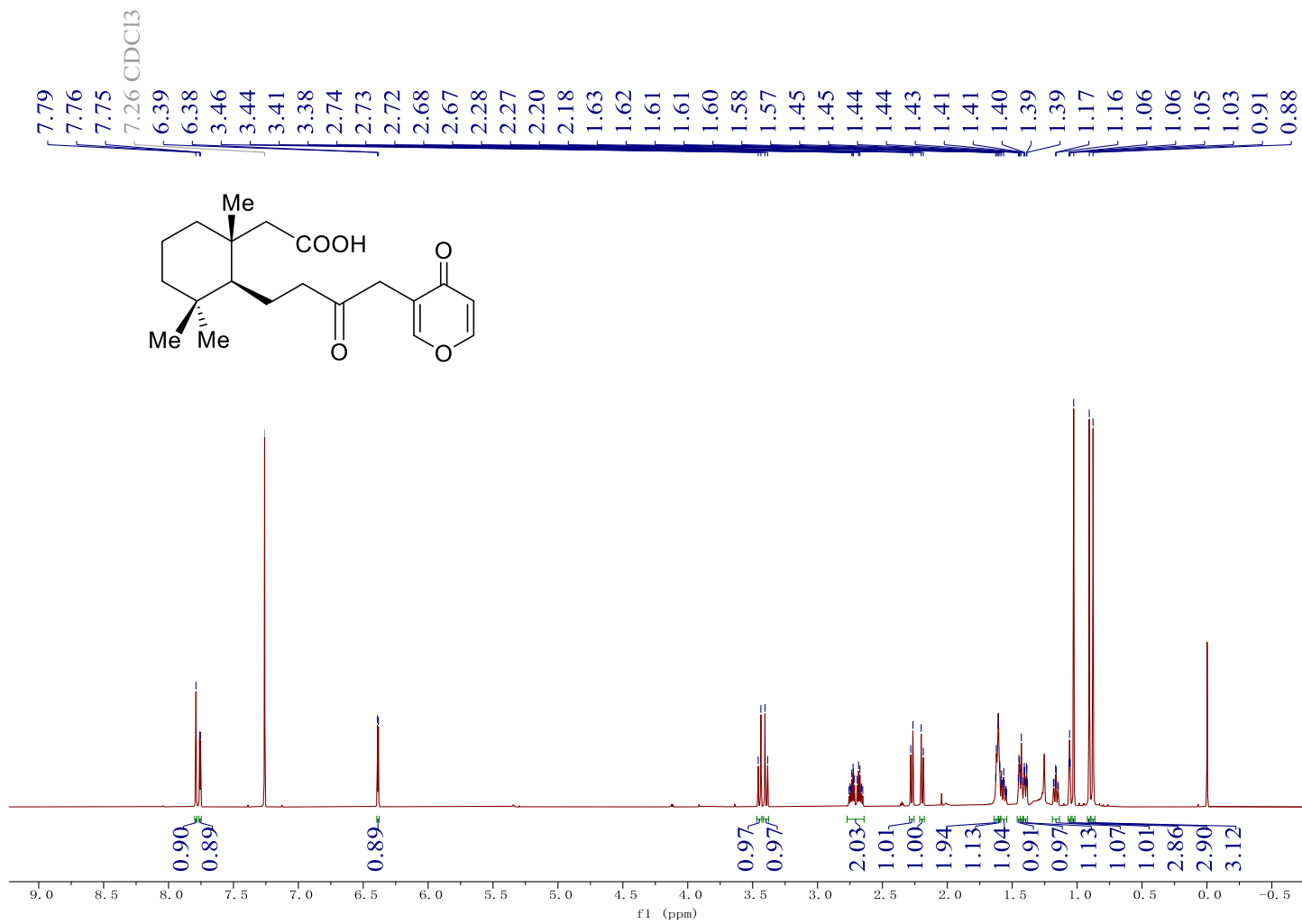
Compound 19 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



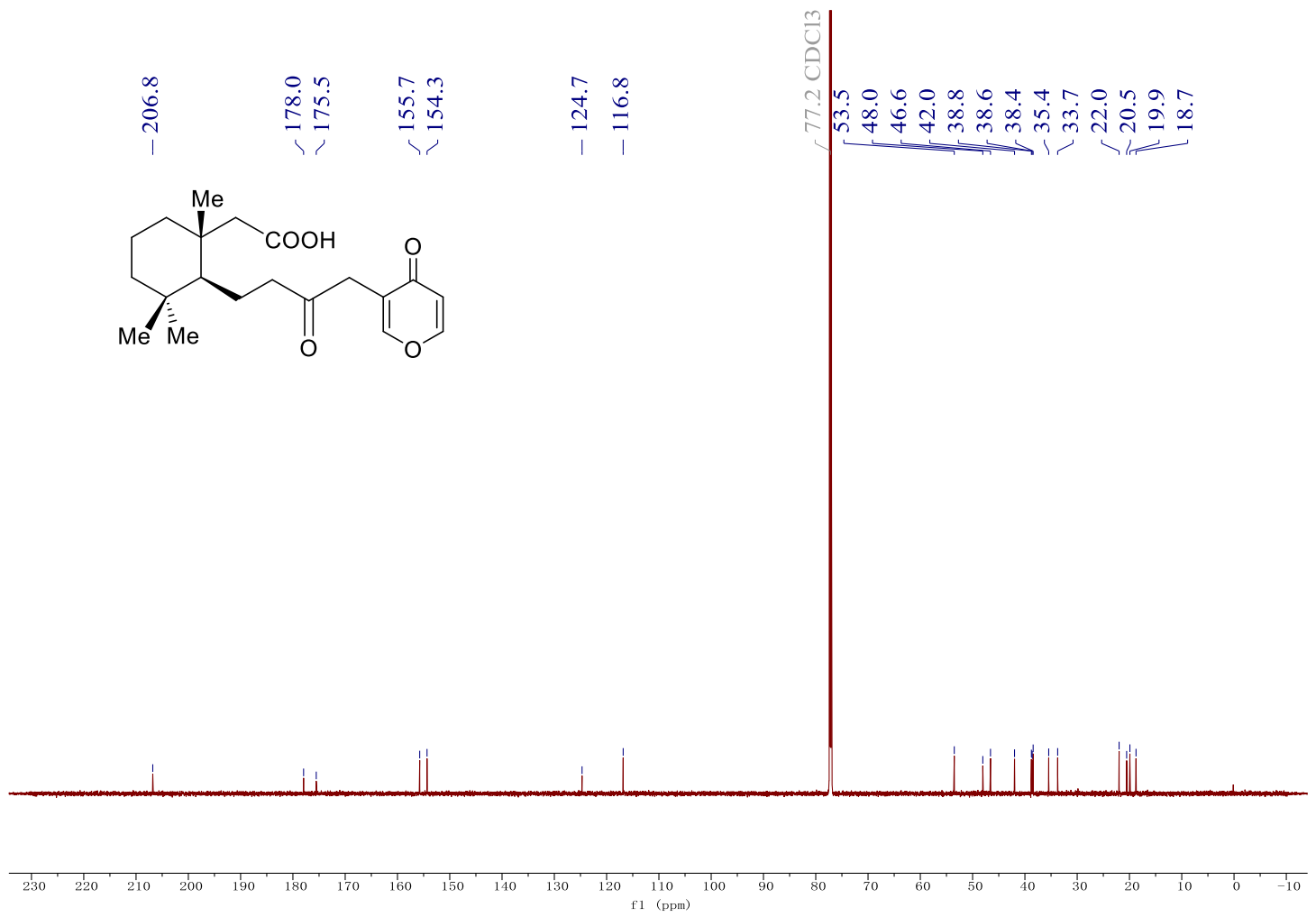
# Compound 19 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



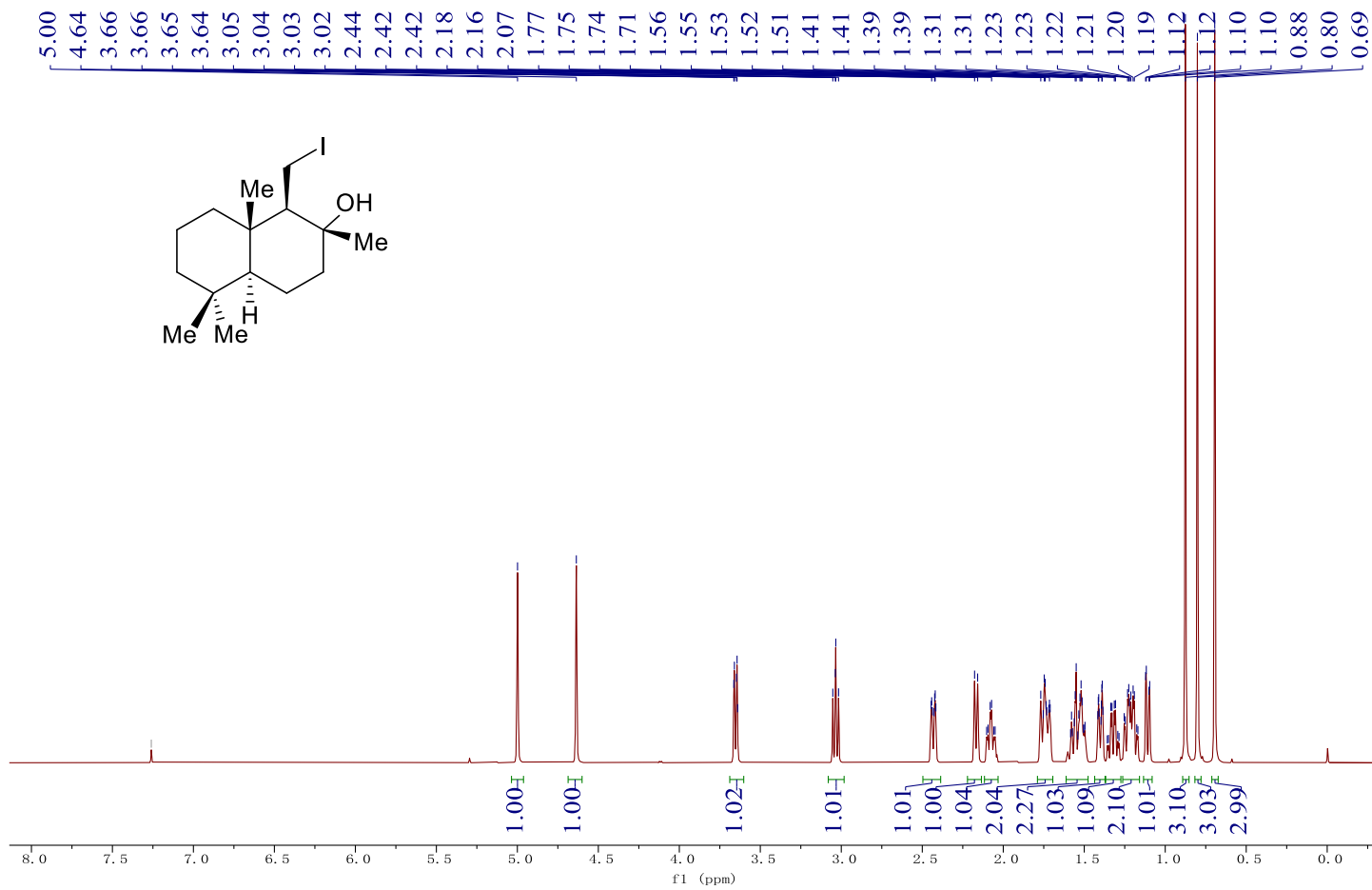
Compound 2 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



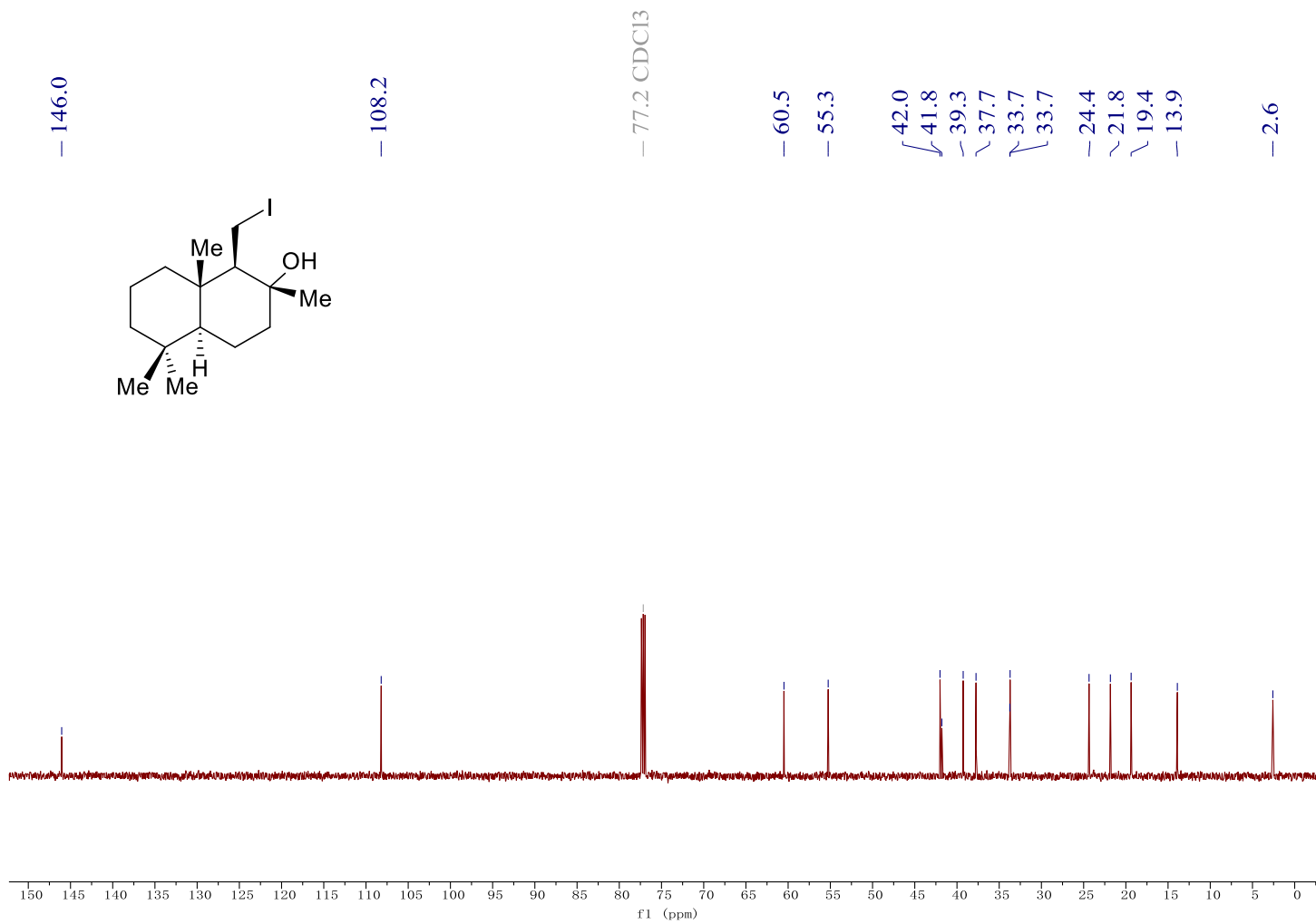
Compound 2 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



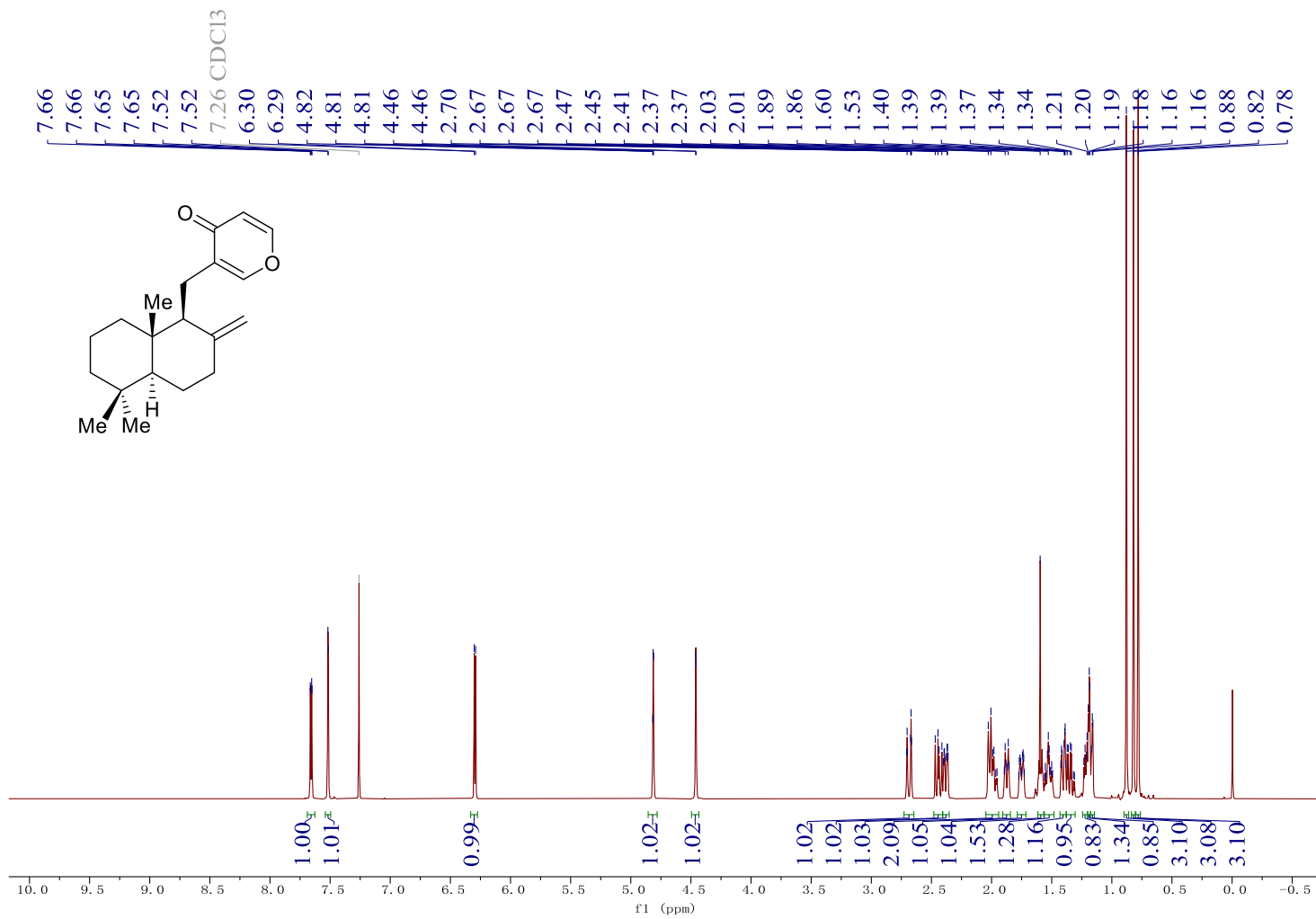
Compound 13 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



# Compound 13 <sup>13</sup>C NMR (CDCl<sub>3</sub>)



# Compound 3 <sup>1</sup>H NMR (CDCl<sub>3</sub>)



# Compound 3 <sup>13</sup>C NMR (CDCl<sub>3</sub>)

