



## Supporting Information

### **Total Synthesis of (+)-Cochlearol B by an Approach Based on a Catellani Reaction and Visible-Light-Enabled [2+2] Cycloaddition**

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**Table of Contents**

<b>1. General Information</b>	3
<b>2. Experimental Procedures</b>	
2.1 Synthesis of chromanone <b>11</b>	4
2.2 Model Systems and Initial Route	5 – 9
2.3 Investigation into the asymmetric synthesis of <b>11</b>	10 – 11
2.4 Synthesis of (–)- <b>11</b> through a chiral resolution	12 – 13
2.5 Total synthesis of (+)-cochlearol B	14 – 20
<b>3. HPLC Spectra</b>	21 – 22
<b>4. X-ray Crystallographic Data</b>	23 – 25
<b>5. References</b>	26
<b>6. NMR Spectra</b>	27 – 72

## 1. General Information

### 1.1. General Laboratory Procedures

All air- or moisture-sensitive reaction were carried out in flame-dried glassware under an atmosphere of nitrogen. Thin-layer chromatography (TLC) was performed on *Merck* silica gel 60 F<sub>254</sub> plates using UV light (254 or 366 nm), KMnO<sub>4</sub> or CAM stain for visualization. Flash chromatography was performed using silica gel Silia Flash® 40-63 micron (230-400 mesh) from Silicycle unless otherwise noted.

### 1.2. Materials and Instrumentation

All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, and Strem were used as received unless otherwise stated. THF, DCM, Et<sub>2</sub>O, MeOH, MeCN, DMF, DMSO were dried by being passed through a column of activated alumina under argon using a JC- Meyer Solvent Systems. [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> was prepared according to the procedure described by Stephenson.<sup>1</sup> Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on Varian MR400, Bruker Avance Neo 500, Varian Vnmrs 500, Varian Vnmrs 600, and Varian Vnmrs 700 spectrometers and are referenced to the residual NMR solvent signal (CHCl<sub>3</sub>: δ 7.26 ppm; C<sub>6</sub>H<sub>6</sub>: δ 7.16 ppm; (CH<sub>3</sub>)<sub>2</sub>SO: δ 2.50 ppm; (CH<sub>3</sub>)<sub>2</sub>CO: δ 2.05 ppm). Data for <sup>1</sup>H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration. Carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on Bruker Avance Neo 500, Varian Vnmrs 500, Varian Vnmrs 600, and Varian Vnmrs 700 spectrometers and are referenced to the carbon resonances of the NMR solvent (CDCl<sub>3</sub>: δ 77.16 ppm; C<sub>6</sub>D<sub>6</sub>: δ 128.06 ppm; (CD<sub>3</sub>)<sub>2</sub>S<sub>2</sub>O: δ 39.52 ppm; (CD<sub>3</sub>)<sub>2</sub>CO: δ 29.84 ppm). High-resolution mass spectrometry (HRMS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent 6230 TOF HPLC-MS (ESI) or Micromass AutoSpec Ultima Magnetic Sector mass spectrometer (ESI, EI). Infrared (IR) spectra were obtained using a PerkinElmer Frontier FT-IR spectrometer. IR data are represented as frequency of absorption (cm<sup>-1</sup>). Chiral HPLC analysis was performed on a Agilent Infinity 1260 equipped with a Daicel Chiralpak OJ-H column (5 μm, 4.6 mm x 250 mm) or a Daicel Chiralpak IC column (5 μm, 4.6 mm x 250 mm). Optical rotations were acquired on a Jasco P-2000 digital polarimeter and reported as *c* = g/100 mL at 589 nm (sodium D line) at room temperature and 10 cm path length. Stereochemistry indicators with asterisk (*R*\*, *S*\*) were used to indicate relative stereochemistry of diastereomers.

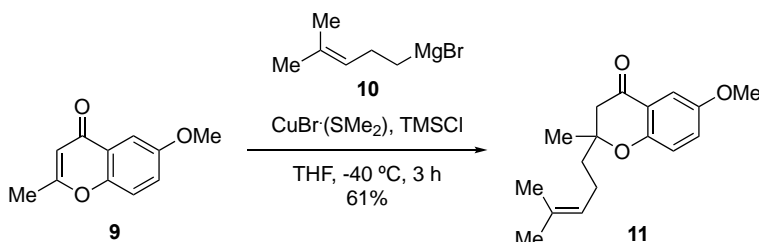
### 1.3. Abbreviations

CAM = ceric ammonium molybdate, THF = tetrahydrofuran, DCM = dichloromethane, Et<sub>2</sub>O = diethyl ether, MeOH = methanol, MeCN = acetonitrile, DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, EtOAc = ethyl acetate, ESI = electrospray ionization, EI = electron ionization, h = hours, min = minutes, rt = room temperature, TMSCl = trimethylsilyl chloride, NaHMDS = sodium bis(trimethylsilyl)amide, 9-BBN = 9-borabicyclo[3.3.1]nonane, Py·SO<sub>3</sub> = pyridine sulfur trioxide complex, NMMO = *N*-Methylmorpholine *N*-oxide, DMF-DMA = *N,N*-dimethylformamide dimethyl acetal, Tf<sub>2</sub>O = triflic anhydride

## 2. Experimental Procedures

### 2.1. Synthesis of chromanone 11

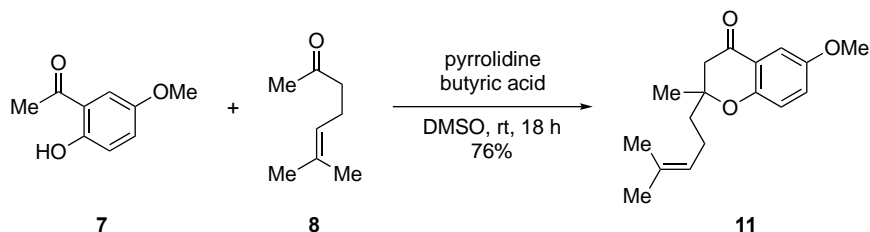
#### 6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-4-one (11)



**General Procedure A (GP-A):** Preparation of homoprenyl magnesium bromide (**10**): A flask was charged with acid washed magnesium (2.18 g, 89.6 mmol, 1.00 equiv) turnings and flame dried under vacuum. To the flask was added THF (128 mL) and a small crystal of iodine. Then 5-bromo-2-methylpent-2-ene (12.80 mL, 95.56 mmol, 1.07 equiv) was added slowly while stirring. The reaction mixture was left to react at room temperature for 1.5 h.

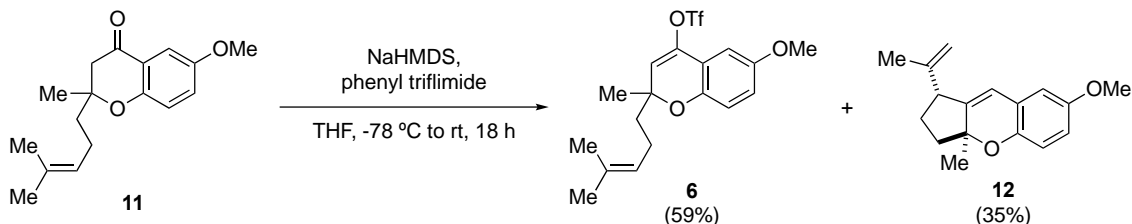
**Conjugate Addition:** A flame dried flask was charged with CuBr(SMe<sub>2</sub>) (1.228 g, 5.97 mmol, 0.10 equiv) and THF (200 mL). The mixture was cooled to -40 °C, the solution of **10** was added, and the mixture was left to stir for 30 min. TMS-Cl (12.98 g, 15.2 mL, 2.0 Eq, 119.5 mmol) was added to the reaction mixture followed by a solution of 6-methoxy-2-methyl-4H-chromen-4-one<sup>2</sup> (**9**) (11.36 g, 1 Eq, 59.7 mmol) in THF (50 mL). The mixture was left to react at -40 °C for 3 h. While the reaction was still cold, quenched with water. Diluted in diethyl ether and NH<sub>4</sub>Cl (aq., sat.). Stirred for 30 min while warming to room temperature. Then, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **11** as a yellow oil (10.00 g, 36.45 mmol, 61%).

R<sub>f</sub> = 0.29 (hexanes:EtOAc, 9:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.28 (d, J = 3.2 Hz, 1H), 7.08 (dd, J = 9.0, 3.2 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 5.06 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 2.77 (d, J = 16.5 Hz, 1H), 2.65 (d, J = 16.5 Hz, 1H), 2.17 – 2.05 (m, 2H), 1.85 – 1.74 (m, 1H), 1.71 – 1.60 (m, 4H), 1.57 (s, 3H), 1.40 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 192.8, 154.6, 153.7, 132.4, 125.4, 123.5, 120.2, 119.8, 107.1, 81.0, 55.9, 47.6, 39.2, 25.8, 24.0, 22.4, 17.7.; IR (neat) 2971, 2933, 2915, 2859, 2836, 1686, 1619, 1485, 1430, 1282, 1218, 1052, 1034, 802, 701; HRMS (ESI) *m/z* calculated for C<sub>17</sub>H<sub>22</sub>O<sub>3</sub>H<sup>+</sup> ([M+H]<sup>+</sup>) 275.1642, found 275.1637.



**General Procedure B (GP-B):** Charged a flame dried flask with pyrrolidine (1.50 mL, 18.13 mmol, 3.00 equiv), DMSO (12.0 mL), and butyric acid (0.55 mL, 6.05 mmol, 1.00 equiv). After the mixture was stirred for 10 min, ketone **8** (984 μL, 6.65 mmol, 1.10 equiv) was added dropwise. After stirring for an additional 15 min, acetophenone **7** (1.005 g, 6.05 mmol, 1.00 equiv) was added in one portion. The resulting reaction mixture was stirred at room temperature for 18 hours. Then, the reaction mixture was diluted with water (600 mL) and EtOAc (300 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with 1 N HCl (300 mL) and brine (300 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:DCM, 19:1 to 3:2) afforded **11** as a yellow oil (1.261 g, 4.60 mmol, 76%).<sup>3</sup>

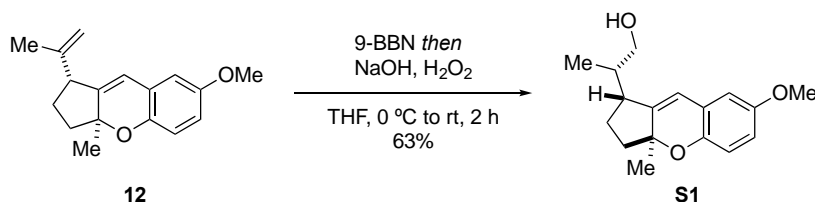
## 2.2 Model Systems and Initial Route

**6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-4-yl trifluoromethanesulfonate (6) and (1*R*\*,3*aS*\*)-7-methoxy-3*a*-methyl-1-(prop-1-en-2-yl)-1,2,3,3*a*-tetrahydrocyclopenta[*b*]chromene (12)**

Charged a flame dried flask with **11** (1.092 g, 3.98 mmol, 1.00 equiv) and THF (15 mL) and cooled to -78 °C. In a separate flame dried flask, NaHMDS (1.094 g, 5.97 mmol, 1.50 equiv) was dissolved in THF (5 mL). This mixture was then added dropwise to the solution chromanone **11** at -78 °C. After stirring at -78 °C for 1 hour, phenyl triflimide (1.706 g, 4.78 mmol, 1.20 equiv) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Then, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with NH<sub>4</sub>Cl (aq. sat.), brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:DCM, 19:1 to 3:2) afforded **6** as a colorless oil (956 mg, 2.35 mmol, 59%) and **12** as a yellow oil (359 mg, 1.40 mmol, 35%).

**(6)** *R<sub>f</sub>* = 0.38 (hexanes:DCM, 3:2); **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 6.83 – 6.74 (m, 3H), 5.61 (s, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 2.19 – 2.06 (m, 2H), 1.84 – 1.77 (m, 1H), 1.73 – 1.68 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.45 (s, 3H); **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 154.0, 147.7, 142.6, 132.5, 123.5, 118.7 (q, *J* = 320 Hz), 118.6, 117.7, 117.3, 116.6, 106.4, 80.0, 55.9, 41.0, 26.1, 25.8, 22.8, 17.7; **IR** (neat) 2972, 2929, 2859, 2837, 1661, 1615, 1579, 1488, 1424, 1207, 1139, 1040, 1020, 1010, 868, 848, 815, 784, 760, 706; **HRMS** (ESI) *m/z* calculated for C<sub>18</sub>H<sub>21</sub>F<sub>3</sub>O<sub>5</sub>S<sup>+</sup> ([M]<sup>+</sup>) 406.1062, found 406.1059.

**(12)** *R<sub>f</sub>* = 0.26 (hexanes:DCM, 3:2); **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 6.78 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.60 (d, *J* = 2.9 Hz, 1H), 6.13 (d, *J* = 1.84 Hz, 1H), 4.85 (d, *J* = 56.0 Hz, 2H), 3.76 (s, 3H), 3.45 (t, *J* = 8.7 Hz, 1H), 2.11 – 2.02 (m, 3H), 1.75 (s, 3H), 1.67 – 1.58 (m, 1H), 1.30 (s, 3H); **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 154.2, 146.2, 146.2, 146.0, 124.4, 117.7, 117.0, 113.3, 111.7, 111.2, 82.9, 55.8, 48.8, 38.8, 28.3, 22.1, 20.2.; **IR** (neat) 2965, 2871, 2832, 1645, 1610, 1578, 1484, 1268, 1212, 1178, 1159, 1038, 882, 798, 762, 692; **HRMS** (ESI) *m/z* calculated for C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>H<sup>+</sup> ([M+H]<sup>+</sup>) 257.1536, found 257.1533.

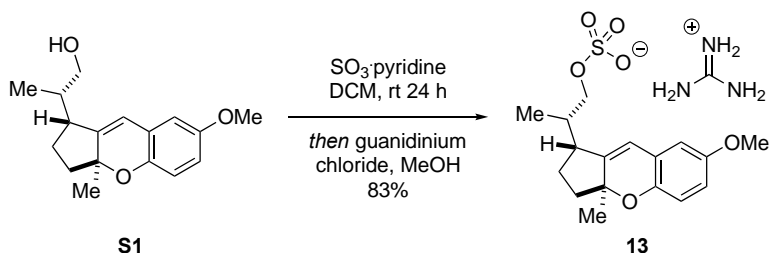
**(S\*)-2-((1*R*\*,3*aS*\*)-7-methoxy-3*a*-methyl-1,2,3,3*a*-tetrahydrocyclopenta[*b*]chromen-1-yl)propan-1-ol (S1)**

Charged flame dried flask with **12** (133 mg, 519 μmol, 1.00 equiv) and THF (3.00 mL), then cooled this solution to 0 °C. Added 9-BBN (1.04 mL, 0.5 M in THF, 519 μmol, 1.00 equiv) and stirred the reaction mixture at room temperature for 1 h. Returned the reaction to 0 °C then added NaOH (0.5 mL, 2 M) followed by H<sub>2</sub>O<sub>2</sub> (53 μL, 30% w/w in water, 519 μmol, 1.00 equiv). Stirred this mixture at room temperature for 1 h. Then, diluted the reaction with water and Et<sub>2</sub>O. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (x3). The combined organic layers were

washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography over silica (hexanes:EtOAc, 9:1 to 1:1) afforded **S1** as a colorless oil (90 mg, 328  $\mu\text{mol}$ , 63%).

**Rf** = 0.42 (hexanes:EtOAc, 1:1);  **$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.75 (d,  $J$  = 8.6 Hz, 1H), 6.64 (dd,  $J$  = 8.7, 2.8 Hz, 1H), 6.58 (d,  $J$  = 2.8 Hz, 1H), 6.24 – 6.13 (d,  $J$  = 1.5 Hz, 1H), 3.76 (m, 4H), 3.58 – 3.51 (m, 1H), 2.84 (q,  $J$  = 7.4 Hz, 1H), 2.07 – 1.93 (m, 3H), 1.85 (dt,  $J$  = 13.4, 6.8 Hz, 1H), 1.54 (m, 1H), 1.34 (t,  $J$  = 5.1 Hz, 1H), 1.27 (s, 3H), 1.09 (d,  $J$  = 6.8 Hz, 3H);  **$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.2, 146.6, 146.1, 124.3, 117.4, 116.9, 113.3, 111.6, 83.1, 66.3, 55.8, 43.4, 39.7, 38.7, 26.1, 22.2, 15.4; **IR** (neat) 3434, 2960, 2875, 2834, 1733, 1485, 1465, 1269, 1214, 1183, 1159, 1036, 971, 877, 813, 756; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{22}\text{O}_3^+$  ( $[\text{M}]^+$ ) 274.1569, found 274.1561.

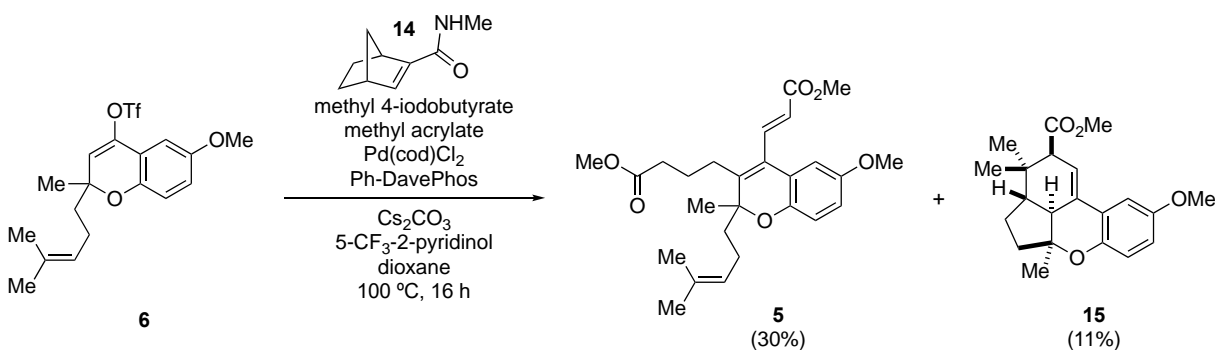
**Guanidinium (S\*)-2-((1R\*,3aS\*)-7-methoxy-3a-methyl-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-1-yl)propyl sulfate (13)**



A flame dried flask was charged with  $\text{Py}\cdot\text{SO}_3$  (26 mg, 166  $\mu\text{mol}$ , 1.3 equiv). Added a solution of **S1** (35 mg, 128  $\mu\text{mol}$ , 1.00 equiv) in DCM (0.6 mL) and stirred this mixture at room temperature for 18 hours. Then, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. To this residue was added guanidinium chloride (12 mg, 128  $\mu\text{mol}$ , 1.00 equiv) and methanol (2.0 mL). Slow evaporation of this homogeneous solution afforded **13** as a yellow crystalline solid (44 mg, 106  $\mu\text{mol}$ , 83%).<sup>4</sup>

In accordance with the literature,<sup>3</sup>  $^1\text{H}$ ,  $^{13}\text{C}$ , and IR data is provided for the intermediate pyridinium sulfate **S2**.  **$^1\text{H NMR}$**  (500 MHz,  $(\text{CD}_3)_2\text{SO}$ )  $\delta$  9.29 (d,  $J$  = 5.8 Hz, 6H), 8.89 (d,  $J$  = 4.3 Hz, 5H), 8.66 (t,  $J$  = 7.6 Hz, 3H), 8.51 (s, 2H), 8.14 (t,  $J$  = 6.7 Hz, 6H), 8.00 (s, 5H), 6.73 – 6.66 (m, 1H), 6.61 (dd,  $J$  = 8.7, 2.8 Hz, 1H), 6.24 (s, 1H), 3.77 (dd,  $J$  = 9.5, 5.0 Hz, 1H), 3.68 (m, 4H), 2.78 (q,  $J$  = 7.8 Hz, 1H), 2.00 – 1.79 (m, 4H), 1.56 – 1.42 (m, 1H), 1.15 (s, 3H), 0.96 (d,  $J$  = 6.8 Hz, 3H);  **$^{13}\text{C NMR}$**  (500 MHz,  $(\text{CD}_3)_2\text{SO}$ )  $\delta$  153.59, 146.98, 146.18, 145.41, 144.92, 143.21, 140.15, 127.98, 126.80, 123.90, 116.77, 116.37, 113.25, 111.19, 82.43, 68.70, 55.27, 42.48, 38.03, 36.45, 25.54, 21.81, 15.09; **IR** (neat) 3455, 3074, 2964, 2889, 1620, 1545, 1488, 1216, 1156, 1023, 971, 848, 750, 680; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{17}\text{H}_{21}\text{O}_6\text{S}^-$  (M-H)<sup>-</sup> 353.1064, found 353.1068.

**Methyl (E)-4-(6-methoxy-4-(3-methoxy-3-oxoprop-1-en-1-yl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-3-yl)butanoate (5) and methyl (2S\*,3aS\*,3a<sup>1</sup>S\*,5aS\*)-9-methoxy-3,3,5a-trimethyl-3,3a,3a<sup>1</sup>,4,5,5a-hexahydro-2H-indeno[1,7-*bc*]chromene-2-carboxylate (15)**

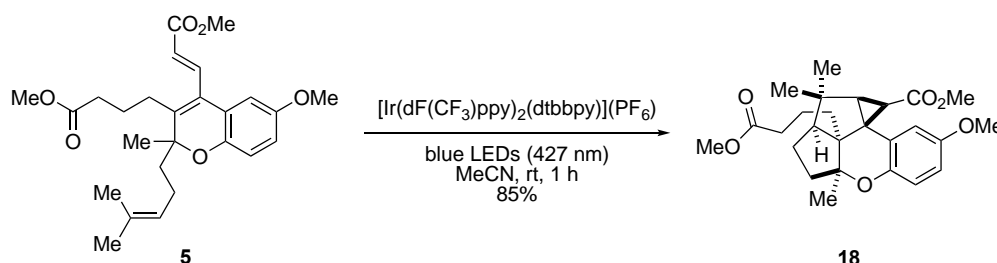


In a glovebox, Pd(cod)Cl<sub>2</sub> (8.4 mg, 29.5 μmol, 0.10 equiv) and Ph-DavePhos (11.3 mg, 29.5 μmol, 0.10 equiv) were dissolved in a vial in 1,4-dioxane (1 mL). This mixture was stirred for 1 min. Vinyl triflate **6** (120 mg, 295 μmol, 1.00 equiv), methyl 4-iodobutanoate (120 μL, 886 μmol, 3.00 equiv), methyl acrylate (40 μL, 443 μmol, 1.50 equiv), N-methylbicyclo[2.2.1]hept-2-ene-2-carboxamide<sup>5</sup> (22.3 mg, 148 μmol, 0.50 equiv), 5-(trifluoromethyl)-2-pyridinol (9.6 mg, 59.1 μmol, 0.20 equiv), Cs<sub>2</sub>CO<sub>3</sub> (289 mg, 886 μmol, 3.00 equiv), and additional 1,4-dioxane (5 mL) were added to the reaction mixture. The vial was sealed, removed from the glovebox, and stirred at 100 °C for 16 h. Then, the mixture was filtered through a thin pad of silica eluting with EtOAc. The combined filtrate was concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 4:1) afforded **5** as a colorless oil (40 mg, 91 μmol, 31%) and **15** as a colorless oil (11 mg, 32 μmol, 11%).

(**5**) R<sub>f</sub> = 0.23 (hexanes:EtOAc, 4:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.61 (d, *J* = 16.2 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 2.8 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.15 (d, *J* = 16.2 Hz, 1H), 4.99 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 2.45 – 2.35 (m, 3H), 2.29 – 2.17 (m, 1H), 2.13 – 2.02 (m, 2H), 1.85 – 1.76 (m, 2H), 1.75 – 1.68 (m, 1H), 1.63 (s, 3H), 1.52 (s, 3H), 1.51 – 1.46 (m, 4H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 173.5, 167.3, 153.8, 146.3, 143.6, 140.3, 132.0, 126.4, 123.9, 123.8, 123.1, 117.5, 113.8, 111.1, 80.0, 55.9, 51.9, 51.8, 37.4, 34.1, 29.4, 25.8, 25.4, 23.0, 22.3, 17.7; IR (neat) 2951, 2880, 1735, 1721, 1631, 1491, 1435, 1271, 1194, 1168, 1040, 987, 870, 816, 775, 722; HRMS (ESI) *m/z* calculated for C<sub>26</sub>H<sub>34</sub>O<sub>6</sub>Na<sup>+</sup> ([M+Na]<sup>+</sup>) 465.2247; found 465.2243.

(**15**) R<sub>f</sub> = 0.26 (hexanes:EtOAc, 9:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.89 (d, *J* = 3.0 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.05 (t, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.96 (t, *J* = 2.5 Hz, 1H), 2.19 – 2.15 (m, 2H), 1.96 (dt, *J* = 12.3, 2.1 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.49 – 1.38 (m, 1H), 1.29 (s, 3H), 1.15 (s, 3H), 0.92 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.08, 154.75, 147.64, 137.39, 125.42, 119.46, 114.99, 108.16, 82.93, 55.84, 54.84, 53.84, 51.69, 51.08, 42.19, 35.10, 27.15, 26.95, 24.86, 24.31; IR (neat) 2959, 2874, 2835, 1732, 1483, 1432, 1258, 1208, 1156, 1038, 923, 868, 847, 820, 791, 736; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>H<sup>+</sup> ([M+H]<sup>+</sup>) 343.1904; found 343.1898.

**Methyl (1*R*\*,1*aR*\*,2*a*<sup>1</sup>*S*\*,4*aS*\*,9*bS*\*)-8-methoxy-2*a*<sup>1</sup>-(4-methoxy-4-oxobutyl)-2,2,4*a*-trimethyl-1,1*a*,2,2*a*,2*a*<sup>1</sup>,3,4,4*a*-octahydrocyclopropa[5,6]pentaleno[1,6-*bc*]chromene-1-carboxylate (**18**)**



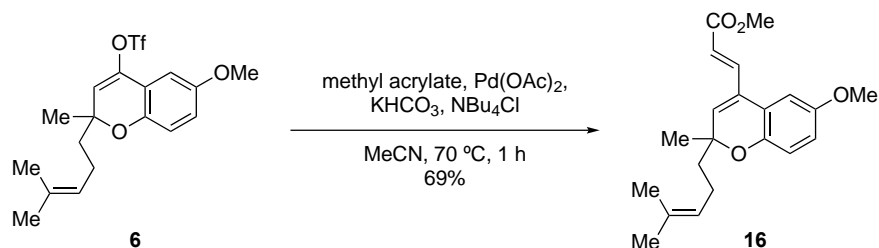
Charged a flame dried flask with **5** (15 mg, 34 μmol, 1.00 equiv), MeCN (0.400 mL) and Ir[(dF(CF<sub>3</sub>)ppy)<sub>2</sub>dtbbpy]PF<sub>6</sub> (0.3 mg, 0.34 μmol, 0.01 equiv). The reaction mixture was degassed by sparging with nitrogen gas for 30 min. The flask was placed approximately 5 cm in front of two 40 W PR160-427 nm Kessil lights. The lights were set to 100% intensity, a fan was used for cooling, and the reaction was stirred for 1 h. Then, the reaction mixture was concentrated *in vacuo* and purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **18** as a colorless solid (13 mg, 29 μmol, 85%).

R<sub>f</sub> = 0.23 (hexanes:EtOAc, 4:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.69 (d, *J* = 8.7 Hz, 1H), 6.62 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.51 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 3.31 (s, 3H), 2.60 (q, *J* = 11.1 Hz, 1H), 2.43 (d, *J* = 2.6 Hz, 1H), 2.26 – 2.18 (m, 2H), 2.17 – 2.06 (m, 2H), 2.00 (dd, *J* = 13.7, 8.6 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.71 – 1.62 (m, 2H), 1.50 – 1.38 (m, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.22 (td, *J* = 14.2, 13.4, 5.6 Hz, 1H), 1.16 (s, 3H), 1.10 (m, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 173.8, 170.2, 152.5, 151.0, 125.3, 115.8, 112.8, 112.5, 92.7, 59.0, 55.8, 51.6, 51.5, 48.5, 48.5, 45.9, 40.9, 36.9, 35.8, 34.1, 33.0, 30.7, 26.8, 24.2, 24.2, 22.8; IR (neat) 2958, 1728, 1464, 1429, 1269, 1209,



1159, 1140, 1032, 927, 888, 874, 848, 814, 783; **HRMS** (ESI)  $m/z$  calculated for  $C_{26}H_{34}O_6H^+$  ( $[M+H]^+$ ) 443.2438, found 443.2424.

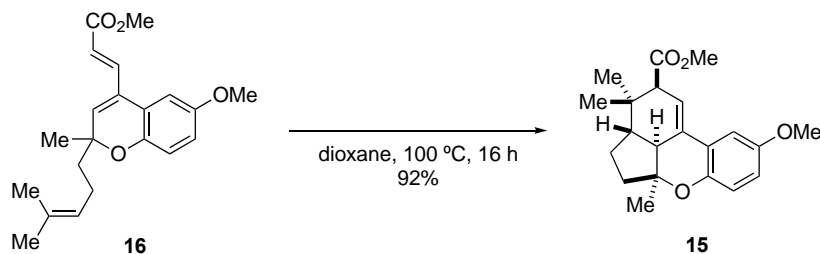
### Methyl (E)-3-(6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-4-yl)acrylate (**16**)



Charged a flamed dried flask with potassium bicarbonate (185 mg, 1.85 mmol, 3.00 equiv), palladium(II) acetate (2.07 mg, 9.23  $\mu$ mol, 0.015 equiv) and tetrabutylammonium chloride (205 mg, 738  $\mu$ mol, 1.20 equiv). A solution of **6** (250 mg, 615  $\mu$ mol, 1.00 equiv) in MeCN (5.00 mL) was then added, followed by methyl acrylate (223  $\mu$ L, 2.46 mmol, 4.00 equiv). The reaction mixture was stirred at 70 °C for 1 h. The mixture was concentrated *in vacuo*, re-dissolved in DCM, and diluted with water. The organic layer was separated, and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over  $Na_2SO_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 17:3) afforded **16** as a colorless oil (145 mg, 423  $\mu$ mol, 69%).

$R_f$  = 0.27 (hexanes:EtOAc, 9:1);  **$^1H$  NMR** (600 MHz,  $CDCl_3$ )  $\delta$  7.57 (d,  $J$  = 15.9 Hz, 1H), 6.83 (d,  $J$  = 2.9 Hz, 1H), 6.79 (d,  $J$  = 8.7 Hz, 1H), 6.74 (dd,  $J$  = 8.7, 2.9 Hz, 1H), 6.29 (d,  $J$  = 15.9 Hz, 1H), 5.94 (s, 1H), 5.07 (t,  $J$  = 7.1 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.15 – 2.05 (m, 2H), 1.76 – 1.67 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.38 (s, 3H);  **$^{13}C$  NMR** (151 MHz,  $CDCl_3$ )  $\delta$  167.2, 154.0, 147.0, 141.3, 132.6, 132.1, 129.7, 124.0, 121.3, 120.9, 117.7, 114.9, 109.8, 77.7, 56.0, 51.9, 40.2, 25.8, 25.2, 22.8, 17.8; **IR** (neat) 2969, 2949, 2925, 2857, 2845, 2838, 1719, 1486, 1429, 1308, 1262, 1168, 1039, 979, 821, 737; **HRMS** (ESI)  $m/z$  calculated for  $C_{21}H_{26}O_4H^+$  ( $[M+H]^+$ ) 343.1904, found 343.1903.

### Methyl (2*S*\*,3*aS*\*,3*a*<sup>1</sup>*S*\*,5*aS*\*)-9-methoxy-3,3,5*a*-trimethyl-3,3*a*,3*a*<sup>1</sup>,4,5,5*a*-hexahydro-2*H*-indeno[1,7-*bc*]chromene-2-carboxylate (**15**)



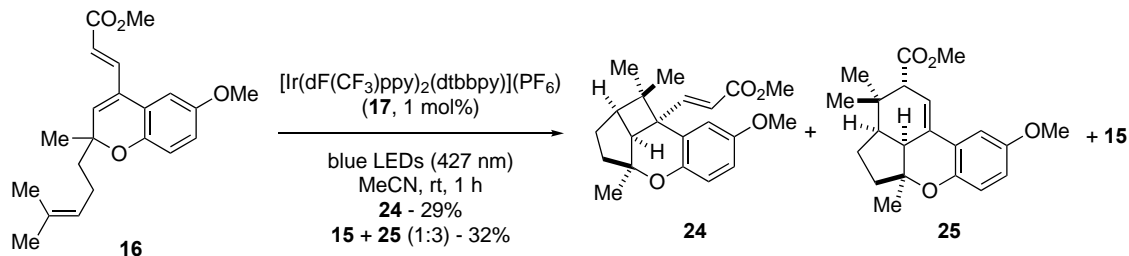
Charged a flame dried flask with **16** (34 mg, 99  $\mu$ mol, 1.00 equiv) and dioxane (3.0 mL). The reaction mixture was degassed by sparging with nitrogen gas for 15 mins. The reaction mixture was stirred at 100 °C for 16 h. Then, the reaction mixture was concentrated *in vacuo* and purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **15** as a colorless oil (31 mg, 91  $\mu$ mol, 92%).

$R_f$  = 0.26 (hexanes:EtOAc, 9:1);  **$^1H$  NMR** (600 MHz,  $CDCl_3$ )  $\delta$  6.89 (d,  $J$  = 3.0 Hz, 1H), 6.80 (d,  $J$  = 8.7 Hz, 1H), 6.72 (dd,  $J$  = 8.7, 3.0 Hz, 1H), 6.05 (t,  $J$  = 2.9 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.96 (t,  $J$  = 2.5 Hz, 1H), 2.19 – 2.15 (m, 2H), 1.96 (dt,  $J$  = 12.3, 2.1 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.49 – 1.38 (m, 1H), 1.29 (s, 3H), 1.15 (s, 3H), 0.92 (s, 3H);  **$^{13}C$  NMR** (151 MHz,  $CDCl_3$ )  $\delta$  174.1, 154.8, 147.6, 137.4, 125.4, 119.5 (2C), 115.0, 108.2, 82.9, 55.8, 54.8, 53.8, 51.7,



51.1, 42.2, 35.1, 27.1, 26.95, 24.86, 24.31; **IR** (neat) 2959, 2874, 2835, 1732, 1483, 1432, 1258, 1208, 1156, 1038, 923, 868, 847, 820, 791, 736; **HRMS** (ESI)  $m/z$  calculated for  $C_{21}H_{26}O_4H^+$  ( $[M+H]^+$ ) 343.1904; found 343.1898.

methyl (*E*)-3-((1*aR*\*,1*a*<sup>1</sup>*S*\*,3*aS*\*,8*bS*\*)-7-methoxy-1,1,3*a*-trimethyl-1,1*a*,1*a*<sup>1</sup>,2,3,3*a*-hexahydro-8*bH*-4-oxabenzof[*f*]cyclobuta[*cd*]inden-8*b*-yl)acrylate (**22**) and methyl (2*S*\*,3*aS*\*,3*a*<sup>1</sup>*S*\*,5*aS*\*)-9-methoxy-3,3,5*a*-trimethyl-3,3*a*,3*a*<sup>1</sup>,4,5,5*a*-hexahydro-2*H*-indeno-[1,7-*bc*]chromene-2-carboxylate (**15**) and methyl (2*R*\*,3*aR*\*,3*a*<sup>1</sup>*S*\*,5*aS*\*)-9-methoxy-3,3,5*a*-trimethyl-3,3*a*,3*a*<sup>1</sup>,4,5,5*a*-hexahydro-2*H*-indeno[1,7-*bc*]chromene-2-carboxylate (**24**)



Charged a flame dried flask with **16** (97 mg, 283  $\mu$ mol, 1.00 equiv), MeCN (90 mL) and Ir[(dF(CF<sub>3</sub>)ppy)<sub>2</sub>dtbbpy]PF<sub>6</sub> (3.2 mg, 2.83  $\mu$ mol, 0.01 equiv). The reaction mixture was degassed by sparging with nitrogen gas for 30 min. The flask was placed approximately 5 cm in front of two 40 W PR160-427 nm Kessil lights. The lights were set to 100% intensity, a fan was used for cooling, and the reaction was stirred for 1 h. Then, the reaction mixture was concentrated *in vacuo* and purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **23** as a colorless oil (28 mg, 82  $\mu$ mol, 29%) and **15** + **24** as a colorless oil (1:3, 31 mg, 91  $\mu$ mol, 32%).

(**21**) **R<sub>f</sub>** = 0.23 (hexanes:EtOAc, 9:1); **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 (d, *J* = 15.6 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.69 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.46 (d, *J* = 2.9 Hz, 1H), 5.68 (d, *J* = 15.6 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.76 (d, *J* = 8.2 Hz, 1H), 2.31 (t, *J* = 8.0 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.75 – 1.68 (m, 1H), 1.66 – 1.47 (m, 2H), 1.43 (s, 3H), 1.24 (s, 3H), 0.87 (s, 3H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  167.5, 154.1, 153.4, 147.2, 126.7, 119.4, 118.4, 114.8, 113.1, 84.7, 55.8, 51.6, 46.0, 46.0, 45.1, 43.5, 36.8, 29.7, 27.8, 25.5, 22.1; **IR** (neat) 2952, 2866, 2835, 1721, 1640, 1492, 1463, 1436, 1376, 1297, 1267, 1176, 1129, 1040, 809, 771; **HRMS** (ESI)  $m/z$  calculated for  $C_{21}H_{26}O_4H^+$  ( $[M+H]^+$ ) 343.1904, found 343.1903.

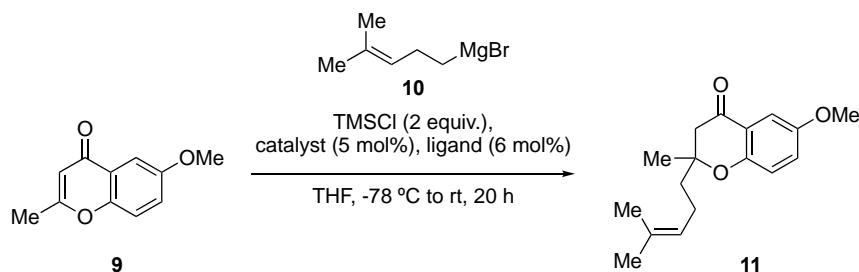
(**15** + **24**) **R<sub>f</sub>** = 0.26 (hexanes:EtOAc, 9:1); **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 – 6.87 (m, 1.3H), 6.81 – 6.71 (m, 2.6H), 6.05 (s, 0.3H), 6.02 (s, 1H), 3.77 (s, 3.9H), 3.74 (s, 0.9H), 3.68 (s, 3H), 3.07 (s, 1H), 2.96 (s, 0.3H), 2.35 (s, 1H), 2.19 – 2.15 (m, 0.6H), 2.05 (d, *J* = 7.5 Hz, 1H), 2.00 – 1.9 (m, 2.3H), 1.77 – 1.70 (m 0.6H), 1.66 – 1.57 (m, 1H), 1.55 – 1.49 (m, 1H), 1.49 – 1.41 (m, 3.3H), 1.30 (s, 0.9H), 1.20 – 1.15 (m, 3.9H), 1.06 (s, 3H), 0.92 (s, 0.9H); **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$  174.2, 174.1, 154.7, 153.5, 147.6, 146.9, 137.4, 129.7, 125.4, 121.8, 119.5 (2C), 119.0, 117.8, 116.1, 115.0, 108.6, 108.1, 84.3, 82.9, 56.0, 55.8, 54.8, 53.8, 51.7, 51.7, 51.4, 51.0, 46.8, 42.5, 42.2, 35.2, 35.1, 33.9, 32.9, 27.1 (2C), 27.0, 25.5, 24.9, 24.3, 20.8; **IR** (neat) 2959, 2874, 2835, 1732, 1483, 1432, 1258, 1208, 1156, 1038, 923, 868, 847, 820, 791, 736; **HRMS** (ESI)  $m/z$  calculated for  $C_{21}H_{26}O_4H^+$  ( $[M+H]^+$ ) 343.1904; found 343.1898.

### 2.3. Investigation into the asymmetric synthesis of 11

An asymmetric copper-catalyzed conjugate addition between **9** and **10** was explored using chiral ligands **L1-L5**. The catalyst and ligand were pre-stirred in THF at rt for 30 min, then cooled to -78 °C. Each reaction was subsequently completed according to *GP-A*, with any modifications indicated in Table S1.

**Table S1.** (A) Evaluation of asymmetric conjugate addition conditions. (B) Control reaction without copper.

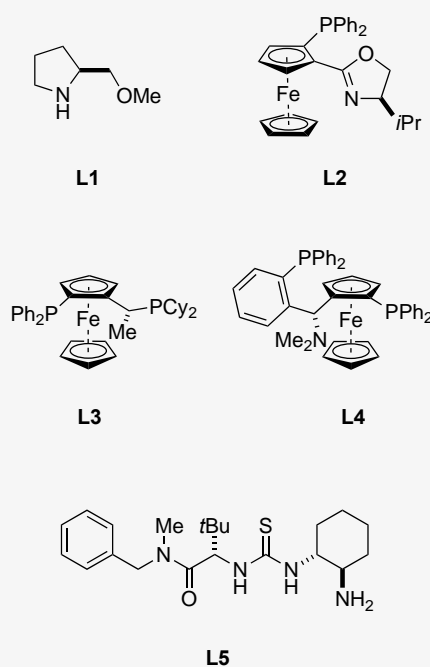
**A.** Conditions evaluated for an asymmetric copper-catalyzed conjugate addition



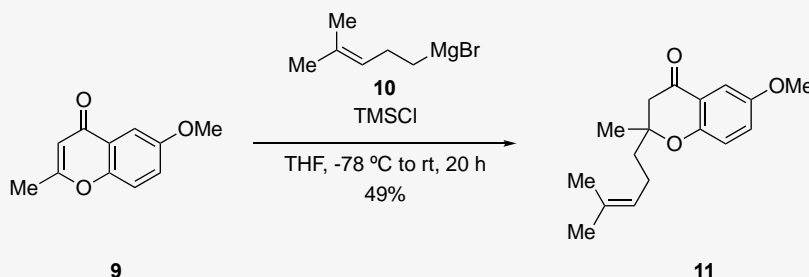
Entry	Catalyst	Ligand	ee (%)
1	CuBr(SMe <sub>2</sub> )	L1	0
2	CuI	L1	0
3	CuBr(SMe <sub>2</sub> )	L2	0
4	CuBr(SMe <sub>2</sub> )	L3	0
5	CuI	L4	0
6	CuBr(SMe <sub>2</sub> )	L5	0
7 <sup>a</sup>	CuBr(SMe <sub>2</sub> )	L1	0
8 <sup>a</sup>	CuI	L1	0
9 <sup>a</sup>	CuBr(SMe <sub>2</sub> )	L2	0
10 <sup>a</sup>	CuI	L2	0
11 <sup>a</sup>	CuBr(SMe <sub>2</sub> )	L3	0
12 <sup>a</sup>	CuI	L3	0
13 <sup>a</sup>	CuBr(SMe <sub>2</sub> )	L4	0
14 <sup>a</sup>	CuI	L4	0

<sup>a</sup> Reaction performed without TMSCl

Ligands:

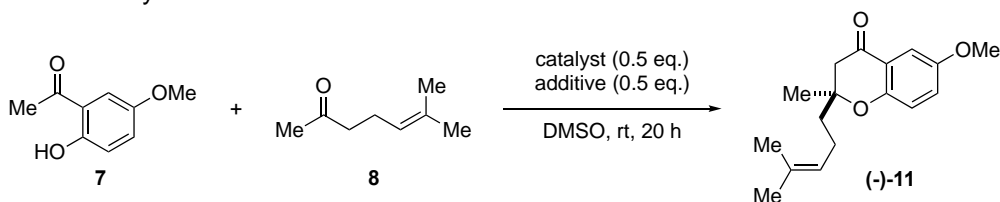


**B.** Background reactivity likely responsible for racemic product observed



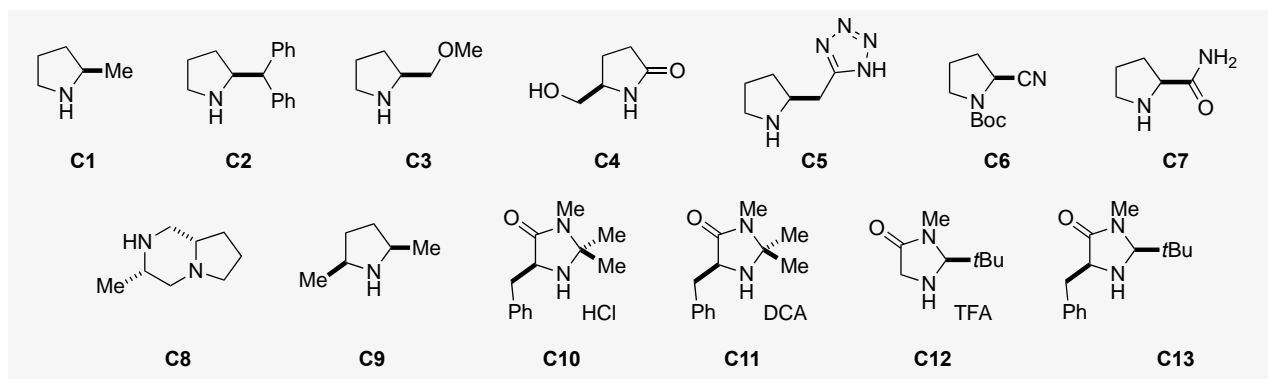
In addition, an asymmetric Kabbe condensation between **7** and **8** was explored using chiral catalysts **C1-C13**. Each reaction was completed according to *GP-B*, with any modifications indicated in Table S2.

**Table S2.** Evaluation of asymmetric Kabbe condensation conditions.



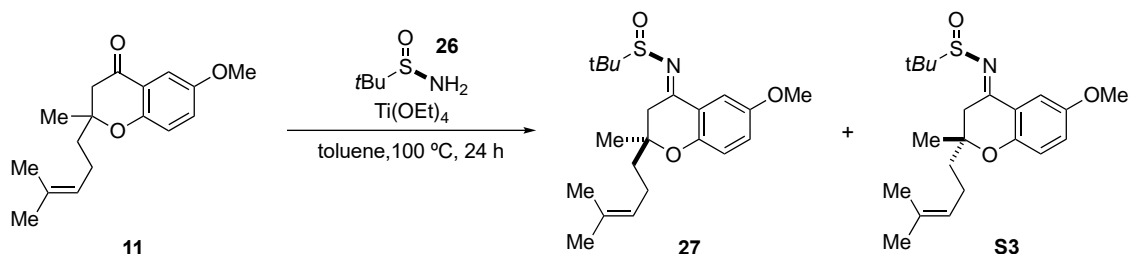
Entry	Catalyst	Additive	Yield (%)	ee (%)
1	(R)-2-methylpyrrolidine ( <b>C1</b> )	butyric acid	5	23
2	(S)-2-diphenylmethylpyrrolidine ( <b>C2</b> )	butyric acid	NR	-
3	(S)-2-(methoxymethyl)pyrrolidine ( <b>C3</b> )	butyric acid	NR	-
4	(R)-5-(hydroxymethyl)-2-pyrrolidine ( <b>C4</b> )	butyric acid	NR	-
5	(S)-5-(2-pyrrolidinyl)-1H-tetrazole ( <b>C5</b> )	butyric acid	NR	-
6	(S)-1-boc-2-pyrrolidinecarbonitrile ( <b>C6</b> )	butyric acid	NR	-
7	L-prolinamide ( <b>C7</b> )	butyric acid	7	7
8	(3S,8aS)-3-methyloctahydropyrrolo[1,2-a]pyrazine ( <b>C8</b> )	butyric acid	NR	-
9	(2S,5R)-2,5-dimethylpyrrolidine ( <b>C9</b> )	butyric acid	NR	-
10	(S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one monohydrochloride ( <b>C10</b> )	-	NR	-
11	(S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid ( <b>C11</b> )	-	NR	-
12	(S)-2-(tertbutyl)-3-methylimidazolidin-4-one trifluoroacetic acid ( <b>C12</b> )	-	NR	-
13	(2S,5S)-5-benzyl-2-(tertbutyl)-3-methylimidazolidin-4-one ( <b>C13</b> )	butyric acid	NR	-
14 <sup>a</sup>	(R)-2-methylpyrrolidine ( <b>C1</b> )	butyric acid	19	0
15 <sup>b</sup>	(S)-2-(methoxymethyl)pyrrolidine ( <b>C3</b> )	butyric acid	26	12
16 <sup>b</sup>	(R)-2-methylpyrrolidine ( <b>C1</b> )	butyric acid	30	9
17 <sup>b</sup>	(S)-2-diphenylmethylpyrrolidine ( <b>C2</b> )	butyric acid	3	16

<sup>a</sup> Reaction performed at 50 °C. <sup>b</sup> 3 eq. of the catalyst and 1 eq. of the additive were used. NR = no reaction.



## 2.4. Synthesis of (-)-11 through a chiral resolution

### (R)-N-((S,E)-6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-4-ylidene)-2-methylpropane-2-sulfinamide (**27**) and (R)-N-((R,E)-6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-4-ylidene)-2-methylpropane-2-sulfinamide (**S3**)

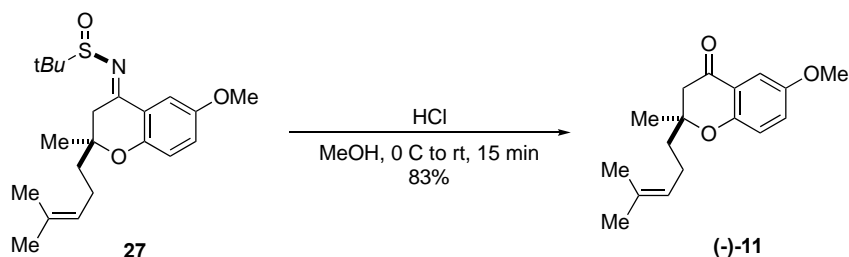


Charged a flame dried flask with chromanone **11** (2.28 g, 8.31 mmol, 1.00 equiv), toluene (16.6 mL), titaniummethoxide (3.79 g, 16.6 mmol, 2.00 equiv), and (R)-(+)-2-methylpropane-2-sulphinamide (**26**) (1.01 g, 8.31 mmol, 1.00 equiv). The resulting mixture was stirred at 100 °C for 24 hours. Then, the reaction mixture was diluted in THF and quenched with 24% NaCl (aq.). The mixture was filtered through celite and the filtrate was washed with brine. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 4:1) afforded **S3** as a yellow oil (1.06 g, 2.81 mmol, 34%) followed by **27** as a yellow oil (1.05 g, 2.78 mmol, 34%).

(**S3**) *R<sub>f</sub>* = 0.48 (hexanes:EtOAc, 7:3);  $[\alpha]_D^{24} = +15.6$  (*c* = 0.10, MeOH); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.42 (d, *J* = 3.2 Hz, 1H), 7.00 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 5.07 – 5.02 (m, 1H), 3.78 (s, 3H), 3.42 (d, *J* = 16.7 Hz, 1H), 3.09 (d, *J* = 16.7 Hz, 1H), 2.19 – 2.02 (m, 2H), 1.79 – 1.70 (m, 1H), 1.67 – 1.61 (m, 4H), 1.57 (s, 3H), 1.35 (s, 3H), 1.32 (s, 9H).; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 170.30, 153.46, 151.78, 132.23, 123.60, 122.87, 120.22, 119.54, 108.19, 78.62, 57.93, 55.81, 39.86, 38.94, 25.78, 23.96, 22.76, 22.29, 17.76; IR (neat) 2967, 2913, 2870, 2834, 1740, 1622, 1594, 1487, 1426, 1285, 1220, 1199, 1068, 1032, 895, 688; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>31</sub>NO<sub>3</sub>S<sup>+</sup>H ([M+H]<sup>+</sup>) 378.2098, found 378.2094.

(**27**) *R<sub>f</sub>* = 0.43 (hexanes:EtOAc, 7:3);  $[\alpha]_D^{24} = -139.6$  (*c* = 0.10, MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 3.1 Hz, 1H), 7.00 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 5.05 (t, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 3.35 (d, *J* = 16.6 Hz, 1H), 3.19 (d, *J* = 16.6 Hz, 1H), 2.16 – 2.01 (m, 2H), 1.75 – 1.69 (m, 1H), 1.66 (s, 3H), 1.64 – 1.58 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.32 (s, 9H).; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.24, 153.47, 151.73, 132.32, 123.59, 122.80, 120.30, 119.55, 108.22, 78.70, 58.00, 55.83, 39.74, 38.63, 25.80, 24.22, 22.79, 22.48, 17.74.; IR (neat) 2975, 2924, 2865, 2835, 1740, 1590, 1485, 1427, 1284, 1214, 1086, 1037, 890, 823, 735, 694; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>31</sub>NO<sub>3</sub>S<sup>+</sup>H ([M+H]<sup>+</sup>) 378.2098, found 378.2092.

### (S)-6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-4-one [(-)-11]

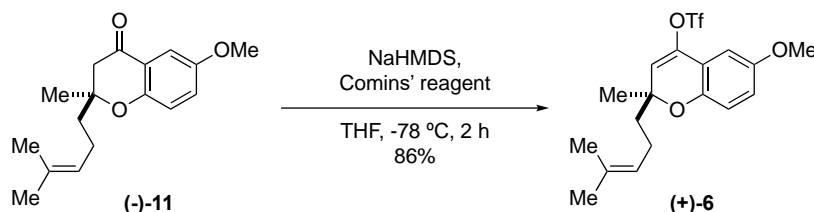


Charged a flask with **27** (1.44 g, 3.81 mmol, 1.00 equiv) and methanol (8.80 mL). The resulting mixture was cooled to 0 °C in an ice bath, then a solution of HCl (aq.) (556 mg, 1.27 mL, 12 molar, 15.3 mmol, 4.00 equiv) was added

dropwise while stirring. The mixture was removed from the cold bath and allowed to warm to room temp. for 15 minutes. The reaction was quenched with NaHCO<sub>3</sub> (sat. aq.) and diluted with DCM. The organic layer was separated, and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 17:3) afforded (-)-**11** as a yellow oil (866 mg, 3.16 mmol, 83%).

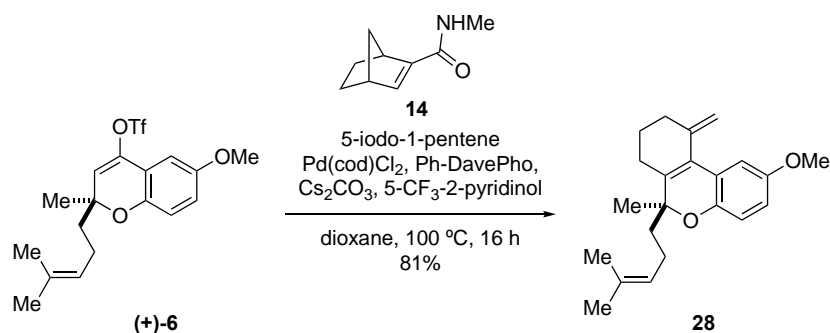
**R<sub>f</sub>** = 0.29 (hexanes:EtOAc, 9:1); [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -43.6 (c = 0.10, MeOH); **HPLC** (Daicel Chiralpak OJ-H, hexanes:isopropanol 99.9:0.1 to 99.7:0.3) 13.3 min (minor), 23.2 min (major); **<sup>1</sup>H NMR** (401 MHz, CDCl<sub>3</sub>):  $\delta$  7.28 (d, J = 3.2 Hz, 1H), 7.08 (dd, J = 9.0, 3.2 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 5.06 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 2.77 (d, J = 16.5 Hz, 1H), 2.65 (d, J = 16.5 Hz, 1H), 2.17 – 2.05 (m, 2H), 1.85 – 1.74 (m, 1H), 1.71 – 1.60 (m, 4H), 1.57 (s, 3H), 1.40 (s, 3H); **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  192.8, 154.6, 153.7, 132.4, 125.4, 123.5, 120.2, 119.8, 107.1, 81.0, 55.9, 47.6, 39.2, 25.8, 24.0, 22.4, 17.7.; **IR** (neat) 2971, 2933, 2915, 2859, 2836, 1686, 1619, 1485, 1430, 1282, 1218, 1052, 1034, 802, 701; **HRMS** (ESI) *m/z* calculated for C<sub>17</sub>H<sub>22</sub>O<sub>3</sub>H<sup>+</sup> ([M+H]<sup>+</sup>) 275.1642, found 275.1637.

## 2.5. Total synthesis of (+)-cochlearol B

**(S)-6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-4-yl trifluoromethanesulfonate [(+)-6]**

Charged a flame dried flask with NaHMDS (2.16 g, 11.8 mmol, 1.10 equiv) and THF (24 mL), then cooled this mixture to -78 °C. A solution of **11** (2.94 g, 10.7 mmol, 1.00 equiv) in THF (8 mL) was then added. After stirring for 1 h at -78 °C, a solution of Comins' reagent (4.63 g, 11.8 mmol, 1.10 equiv) in THF (8 mL) was added and the mixture was stirred at -78 °C for 2 h. Then, the reaction mixture was quenched with water and diluted with diethyl ether and NaHCO<sub>3</sub> (aq. sat.). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:DCM, 19:1 to 3:2) afforded **(+)-6** as a yellow oil (3.75 g, 9.23 mmol, 86%).

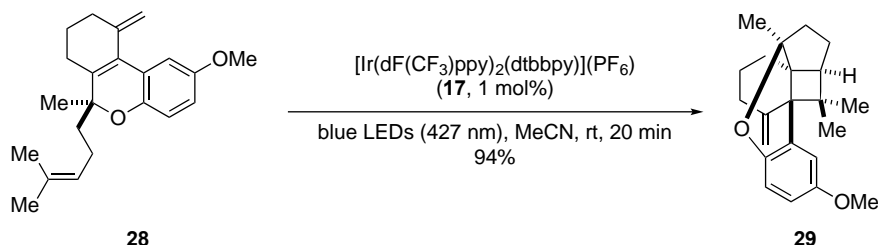
$R_f = 0.54$  (hexanes:EtOAc, 9:1);  $[\alpha]_D^{23} = +109.7$  ( $c = 0.10$ , MeOH); **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$  6.83 – 6.74 (m, 3H), 5.61 (s, 1H), 5.08 (t,  $J = 7.0$  Hz, 1H), 3.77 (s, 3H), 2.19 – 2.06 (m, 2H), 1.84 – 1.77 (m, 1H), 1.73 – 1.68 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.45 (s, 3H); **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$  154.0, 147.7, 142.6, 132.5, 123.5, 118.7 (q,  $J = 320$  Hz), 118.6, 117.7, 117.3, 116.6, 106.4, 80.0, 55.9, 41.0, 26.1, 25.8, 22.8, 17.7; **IR** (neat) 2972, 2929, 2859, 2837, 1661, 1615, 1579, 1488, 1424, 1207, 1139, 1040, 1020, 1010, 868, 848, 815, 784, 760, 706; **HRMS** (ESI)  $m/z$  calculated for C<sub>18</sub>H<sub>21</sub>F<sub>3</sub>O<sub>5</sub>S<sup>+</sup> ( $[M]^+$ ) 406.1062, found 406.1059.

**(S)-2-methoxy-6-methyl-10-methylene-6-(4-methylpent-3-en-1-yl)-7,8,9,10-tetrahydro-6H-benzo-[c]chromene (28)**

In a glovebox, Pd(cod)Cl<sub>2</sub> (70 mg, 246  $\mu$ mol, 0.10 equiv) and Ph-DavePhos (94 mg, 246  $\mu$ mol, 0.10 equiv) were dissolved in 1,4-dioxane (10 mL). This mixture was stirred for 1 min. Vinyl triflate **(+)-6** (1.00 g, 2.46 mmol, 1.00 equiv), 5-iodopent-1-ene (923  $\mu$ L, 7.38 mmol, 3.00 equiv), N-methylbicyclo[2.2.1]hept-2-ene-2-carboxamide<sup>5</sup> (186 mg, 1.23 mmol, 0.50 equiv), 5-(trifluoromethyl)-2-pyridinol (80 mg, 492  $\mu$ mol, 0.20 equiv), Cs<sub>2</sub>CO<sub>3</sub> (2.41 g, 7.38 mmol, 3.00 equiv), and additional 1,4-dioxane (36 mL) were added to the reaction mixture. The flask was sealed with a rubber septum, removed from the glovebox, and stirred at 100 °C for 16 h. Then, the mixture was filtered through a thin pad of silica eluting with EtOAc. The combined filtrate was concentrated *in vacuo*. Purification by flash column chromatography over silica gel (hexanes:EtOAc, 49:1 to 4:1) followed by purification by flash chromatography over C-18 silica (Water:MeCN, 1:4 to 0:1) afforded **28** as a colorless oil (647 mg, 1.99 mmol, 81%).

$R_f = 0.57$  (hexanes:EtOAc, 9:1) and on C-18 silica  $R_f = 0.19$  (Water/MeCN, 1:4);  $[\alpha]_D^{23} = +65.8$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (d,  $J = 3.0$  Hz, 1H), 6.81 (d,  $J = 8.6$  Hz, 1H), 6.67 (dd,  $J = 8.7, 3.0$  Hz, 1H), 5.18 (d,  $J = 53.8$  Hz, 2H), 5.03 (t,  $J = 7.8$  Hz, 1H), 3.76 (s, 3H), 2.45 – 2.34 (m, 2H), 2.25 (qt,  $J = 18.5, 6.3$  Hz, 2H), 2.16 – 1.99 (m, 2H), 1.92 – 1.80 (m, 2H), 1.71 – 1.59 (m, 4H), 1.56 – 1.48 (m, 4H), 1.35 (s, 3H).;  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.2, 151.8, 148.3, 130.6, 118.3, 115.9, 112.3, 110.9, 86.1, 55.7, 53.6, 50.6, 47.4, 42.3, 38.8, 33.8, 30.1, 29.8, 23.8, 23.7, 23.5, 19.9.; **IR** (neat) 2987, 2966, 2930, 2856, 2831, 1632, 1610, 1574, 1486, 1454, 1424, 1375, 1272, 1226, 1166, 1045, 882, 849, 765, 740; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{28}\text{O}_2\text{H}^+$  ( $[\text{M}+\text{H}]^+$ ) 325.2162; found 325.2160.

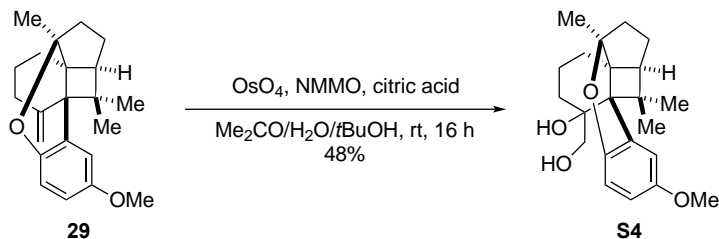
**(4a*S*,5*S*,7a*S*,12*bS*)-11-methoxy-7a,13,13-trimethyl-1-methylene-1,2,3,4,5,6,7,7a-octahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromene (26)**



Charged a flame dried flask with **28** (300 mg, 925  $\mu\text{mol}$ , 1.00 equiv), MeCN (90 mL) and  $\text{Ir}[(\text{dF}(\text{CF}_3)\text{ppy})_2\text{dtbbpy}]\text{PF}_6$  (10.4 mg, 9.25  $\mu\text{mol}$ , 0.01 equiv). The reaction mixture was degassed by sparging with nitrogen gas for 20 min. The flask was placed approximately 5 cm in front of two 40 W PR160-427 nm Kessil lights. The lights were set to 100% intensity, a fan was used for cooling, and the reaction was stirred for 1 h. Then, the reaction mixture was concentrated *in vacuo* and purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **29** as a colorless oil (283 mg, 872  $\mu\text{mol}$ , 94%).

$R_f = 0.48$  (hexanes:EtOAc, 9:1);  $[\alpha]_D^{23} = -117.7$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (700 MHz,  $\text{CDCl}_3$ )  $\delta$  6.72 – 6.68 (m, 2H), 6.65 (dd,  $J = 8.7, 2.6$  Hz, 1H), 4.86 (d,  $J = 35.7$  Hz, 2H), 3.73 (s, 3H), 2.13 – 2.06 (m, 1H), 2.05 – 1.99 (m, 1H), 1.95 – 1.86 (m, 1H), 1.86 – 1.80 (m, 2H), 1.73 – 1.64 (m, 3H), 1.60 – 1.45 (m, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 0.93 (s, 3H).;  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 147.0, 140.8, 139.5, 131.8, 126.7, 124.3, 123.4, 117.7, 112.9, 112.2, 111.5, 79.6, 55.8, 37.0, 33.6, 26.0, 25.8, 23.9, 23.0, 22.4, 17.7.; **IR** (neat) 2945, 2865, 2831, 1489, 1455, 1374, 1267, 1229, 1210, 1137, 1043, 848, 802, 784, 773, 722; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{28}\text{O}_2\text{H}^+$  ( $[\text{M}+\text{H}]^+$ ) 325.2162, found 325.2157.

**(4a*S*,5*S*,7a*S*,12*bR*)-1-(hydroxymethyl)-11-methoxy-7a,13,13-trimethyl-1,2,3,4,5,6,7,7a-octahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromen-1-ol (S4)**



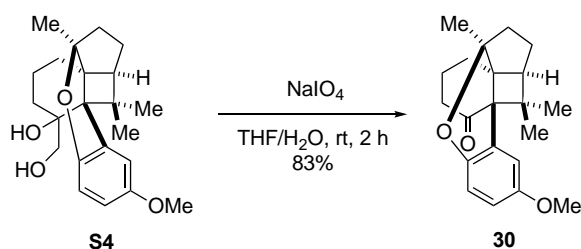
Charged a flask with **29** (485 mg, 1.49 mmol, 1.00 equiv) and acetone:water (3:1, 16 mL). To this mixture was added osmium tetroxide (3.04 g, 3.8 mL, 2.5% wt in *t*BuOH, 299  $\mu\text{mol}$ , 0.20 equiv), citric acid (574 mg, 2.99 mmol, 2.00 equiv), and *N*-Methylmorpholine *N*-oxide (350 mg, 2.99 mmol, 2.00 equiv). This solution was stirred at room temperature for 16 h. Then, the reaction mixture was diluted with  $\text{Na}_2\text{SO}_4$  (aq. sat.) and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with



brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 9:1 to 2:3) afforded **S4** as an off-white foam (247 g, 715  $\mu\text{mol}$ , 48%).

$R_f = 0.18$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{23} = +72.1$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (700 MHz,  $\text{CDCl}_3$ )  $\delta$  6.81 (d,  $J = 8.5$  Hz, 1H), 6.76 – 6.73 (m, 1H), 6.53 (s, 1H), 3.78 – 3.73 (m, 4H), 3.51 (d,  $J = 10.9$  Hz, 1H), 2.20 – 2.13 (m, 2H), 2.09 – 2.00 (m, 2H), 2.00 – 1.85 (m, 3H), 1.59 (dd,  $J = 13.9, 7.6$  Hz, 1H), 1.50 – 1.42 (m, 1H), 1.41 (s, 3H), 1.38 (dd,  $J = 13.0, 6.2$  Hz, 1H), 1.34 (s, 3H), 0.95 (s, 3H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.3, 150.1, 127.1, 119.5, 118.1, 113.7, 87.2, 77.2, 69.7, 55.8, 52.0, 48.8, 47.7, 39.1, 37.3, 29.9, 29.3, 26.3, 24.8, 24.4, 24.1, 17.8; **IR** (neat) 3473, 3468, 2950, 2881, 2834, 1489, 1414, 1376, 1265, 1219, 1137, 1039, 860, 807, 784, 733, 703; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{30}\text{O}_4\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 381.2036; Found: 381.2034.

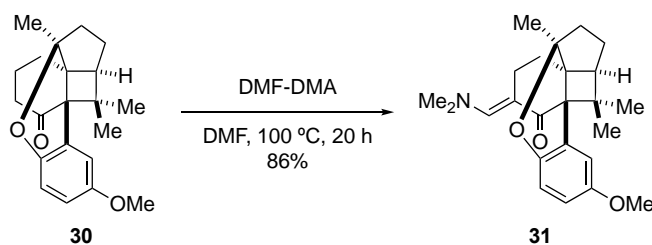
**(4a*S*,5*S*,7a*S*,12*bR*)-11-methoxy-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromen-1(2*H*)-one (30)**



Charged a flask with **S4** (586 mg, 1.63 mmol, 1.00 equiv) and THF:water (1:1, 8.5 mL). Added sodium periodate (699 mg, 3.27 mmol, 2.00 equiv) to this solution and stirred at room temperature for 2 h. Then, the reaction mixture diluted with  $\text{Na}_2\text{SO}_4$  (aq. sat.) and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 9:1) afforded **30** as a white powder (440 mg, 1.35 mmol, 83%).

$R_f = 0.31$  (hexanes:EtOAc, 9:1);  $[\alpha]_D^{23} = -53.1$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.31 (d,  $J = 3.0$  Hz, 1H), 6.92 (d,  $J = 8.8$  Hz, 1H), 6.71 (dd,  $J = 8.8, 3.0$  Hz, 1H), 3.39 (s, 3H), 2.18 – 2.02 (m, 2H), 1.90 (dt,  $J = 17.7, 6.6$  Hz, 1H), 1.76 – 1.67 (m, 2H), 1.65 (d,  $J = 7.9$  Hz, 1H), 1.41 – 1.33 (m, 3H), 1.31 (s, 3H), 1.27 – 1.17 (m, 5H), 0.86 (s, 3H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  210.5, 154.3, 148.4, 123.5, 119.2, 115.3, 115.2, 86.0, 55.8, 55.2, 51.9, 48.4, 42.6, 39.0, 38.1, 32.5, 31.0, 24.0 (2C), 22.1, 19.7; **IR** (neat) 2990, 2975, 2952, 2937, 2873, 2831, 1691, 1609, 1493, 1271, 1227, 1134, 1038, 858, 815, 810, 744, 711, 688; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{21}\text{H}_{26}\text{O}_3\text{H}^+$  ( $[\text{M}+\text{H}]^+$ ) 327.1955, found 327.1955.

**(4a*S*,5*S*,7a*S*,12*bR*,*E*)-2-((dimethylamino)methylene)-11-methoxy-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromen-1(2*H*)-one (31)**

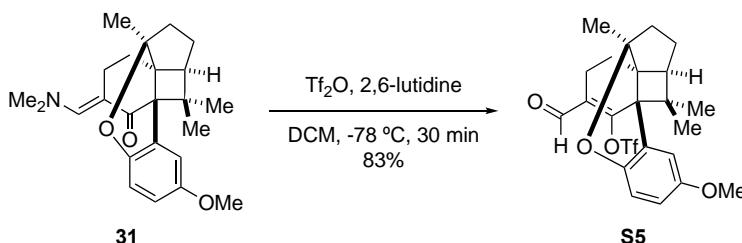


Charged oven dried vial with **30** (200 mg, 613  $\mu\text{mol}$ , 1.00 equiv), DMF-DMA (730 mg, 814  $\mu\text{L}$ , 6.13 mmol, 10 equiv.), and DMF (1.20 mL). The vial was sealed, and the reaction mixture was stirred at 100  $^\circ\text{C}$  for 20 h. Then, the reaction was diluted with water and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc

(x3). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 9:1 to 2:3) afforded **31** as a yellow solid (201 mg, 527  $\mu\text{mol}$ , 86%).

$R_f = 0.17$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{23} = +23.3$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (700 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 (s, 1H), 7.08 (d,  $J = 2.6$  Hz, 1H), 6.69 – 6.61 (m, 2H), 3.74 (s, 3H), 2.95 (s, 6H), 2.65 (dt,  $J = 13.7, 3.6$  Hz, 1H), 2.59 (t,  $J = 13.3$  Hz, 1H), 2.33 (dt,  $J = 14.0, 3.5$  Hz, 1H), 2.12 – 2.05 (m, 1H), 1.88 (d,  $J = 7.3$  Hz, 1H), 1.81 (td,  $J = 13.5, 3.1$  Hz, 1H), 1.58 – 1.49 (m, 2H), 1.49 – 1.44 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 0.92 (s, 3H);  $^{13}\text{C NMR}$  (176 MHz,  $\text{CDCl}_3$ )  $\delta$  198.9, 153.1, 148.5, 147.8, 126.4, 118.1, 115.2, 113.7, 105.3, 85.9, 55.6, 53.4, 52.2, 47.6, 43.2, 41.9, 38.1, 32.3, 32.3, 24.4, 23.6, 22.5, 22.5; **IR** (neat) 2975, 2952, 2914, 2861, 1648, 1550, 1488, 1429, 1230, 1198, 1130, 1088, 1041 922, 870, 806, 780, 703; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{24}\text{H}_{31}\text{NO}_3\text{H}^+$  ( $[\text{M}+\text{H}]^+$ ) 382.2377, found 382.2373.

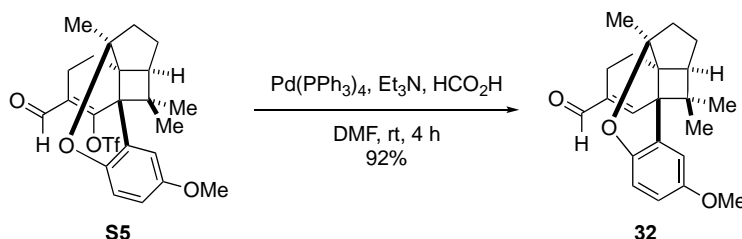
**(4a*S*,5*S*,7a*S*,12*bR*)-2-formyl-11-methoxy-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromen-1-yl trifluoromethanesulfonate (**S5**)**



Charged a flame dried flask with **31** (183 mg, 480  $\mu\text{mol}$ , 1.00 equiv) and DCM (15 mL) and cooled this solution to  $-78$   $^{\circ}\text{C}$ . To this flask was added 2,6-lutidine (514  $\mu\text{L}$ , 4.80 mmol, 10.00 equiv) then triflic anhydride (405  $\mu\text{L}$ , 2.40 mmol, 5.00 equiv). The mixture was stirred at  $-78$   $^{\circ}\text{C}$  for 30 min. Then, the reaction quenched with  $\text{NaHCO}_3$  (aq. sat.). The organic layer was separated, and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 17:3) afforded **S5** as a pale yellow powder (193 mg, 397  $\mu\text{mol}$ , 83%).

$R_f = 0.30$  (hexanes:EtOAc, 9:1);  $[\alpha]_D^{24} = +9.0$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.87 (s, 1H), 6.91 (s, 1H), 6.85 – 6.71 (m, 2H), 3.78 (s, 3H), 3.02 (dt,  $J = 16.9, 4.2$  Hz, 1H), 2.29 (ddd,  $J = 16.7, 11.7, 4.7$  Hz, 1H), 2.05 (td,  $J = 13.4, 7.6$  Hz, 1H), 1.97 (d,  $J = 7.3$  Hz, 1H), 1.76 (dt,  $J = 13.6, 4.1$  Hz, 1H), 1.72 – 1.56 (m, 3H), 1.45 (dd,  $J = 12.9, 7.2$  Hz, 1H), 1.38 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.2, 159.9, 153.2, 148.3, 133.6, 122.1, 119.4, 118.7 (q,  $J = 320$  Hz), 117.8, 115.2, 87.6, 55.7, 51.1, 50.4, 49.6, 45.4, 36.1, 28.7, 25.2, 24.9, 24.4, 22.8, 22.0; **IR** (neat) 2995, 2966, 2924, 2873, 1688, 1496, 1395, 1382, 1213, 1135, 1037, 951, 888, 816, 766, 748, 701, 673; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{23}\text{H}_{25}\text{F}_3\text{O}_6\text{S}^+$  ( $[\text{M}]^+$ ) 486.1324, found 486.1336.

**(4a*S*\*,5*S*\*,7a*S*\*,12*bS*\*)-11-methoxy-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromene-2-carbaldehyde (**32**)**

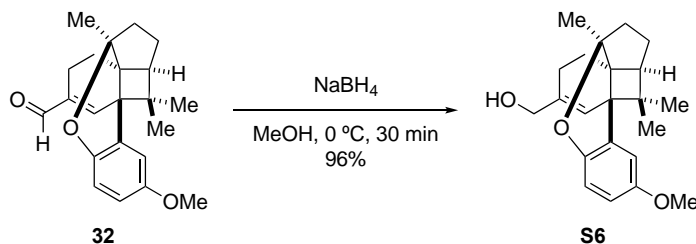


Charged a flame dried flask with **S5** (180 mg, 370  $\mu\text{mol}$ , 1.00 equiv), THF (8.0 mL), triethylamine (464  $\mu\text{L}$ , 3.33 mmol, 9.00 equiv), and formic acid (84  $\mu\text{L}$ , 2.22 mmol, 6.00 equiv). This solution was then degassed by sparging with nitrogen

gas for 10 mins. This mixture was then added to a separate flask containing Pd(PPh<sub>3</sub>)<sub>4</sub> (43 mg, 37.0 μmol, 0.10 equiv). The reaction was stirred at room temperature for 4 h. Then, the reaction mixture was diluted with NaHCO<sub>3</sub> (aq. sat.) and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 99:1 to 17:3) afforded **32** as a colorless, viscous oil (116 mg, 341 μmol, 92%).

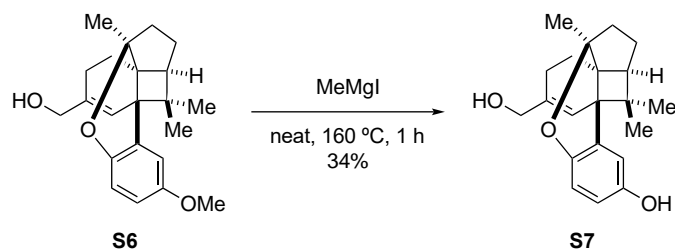
$R_f = 0.19$  (hexanes:EtOAc, 9:1);  $[\alpha]_D^{23} = +23.9$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (600 MHz, CDCl<sub>3</sub>)  $\delta$  9.48 (s, 1H), 6.88 (d,  $J = 2.3$  Hz, 1H), 6.80 (d,  $J = 8.7$  Hz, 1H), 6.72 (dd,  $J = 8.7, 2.9$  Hz, 1H), 6.68 (d,  $J = 2.9$  Hz, 1H), 3.80 (s, 3H), 2.73 (dt,  $J = 16.6, 4.2$  Hz, 1H), 2.19 – 2.10 (m, 1H), 2.08 – 1.97 (m, 2H), 1.77 – 1.70 (m, 1H), 1.66 – 1.56 (m, 3H), 1.41 (ddd,  $J = 13.3, 11.8, 4.7$  Hz, 1H), 1.31 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H);  $^{13}\text{C NMR}$  (151 MHz, CDCl<sub>3</sub>)  $\delta$  193.3, 156.5, 154.0, 147.5, 141.5, 128.3, 119.4, 113.6, 112.6, 87.0, 55.9, 49.6, 47.4, 45.7, 44.9, 38.4, 29.0, 26.0, 24.3, 23.8, 21.8, 19.1; **IR** (neat) 2947, 2912, 2864, 2851, 2834, 1737, 1679, 1636, 1493, 1460, 1375, 1267, 1210, 1182, 1134, 1041, 874, 812, 775, 723; **HRMS** (ESI)  $m/z$  calculated for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>H<sup>+</sup> ( $[\text{M}+\text{H}]^+$ ) 339.1955, found 339.1955.

**((4a*S*,5*S*,7a*S*,12*bS*)-11-methoxy-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12*b*-methanobenzo[*c*]cyclopenta[*b*]chromen-2-yl)methanol (**S6**)**



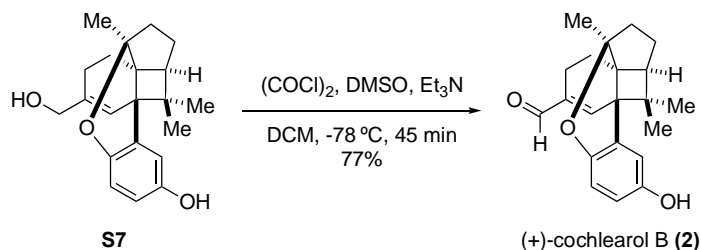
Charged a flask with **32** (114 mg, 337 μmol, 1.00 equiv) and methanol (3.00 mL). Cooled this solution to 0 °C then added NaBH<sub>4</sub> (12.7 mg, 337 μmol, 1.00 equiv). This mixture was stirred at room temperature for 30 min. Then, the reaction was quenched with NH<sub>4</sub>Cl (aq. sat.) and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexanes:EtOAc, 19:1 to 7:3) afforded **S6** as a pale yellow solid (110 mg, 320 μmol, 96%).

$R_f = 0.32$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25} = +71.5$  ( $c = 0.10$ , MeOH);  $^1\text{H NMR}$  (700 MHz, CDCl<sub>3</sub>)  $\delta$  6.76 (d,  $J = 8.7$  Hz, 1H), 6.66 (dd,  $J = 8.7, 2.9$  Hz, 1H), 6.64 (d,  $J = 2.9$  Hz, 1H), 5.81 (s, 1H), 4.12 (d,  $J = 13.2$  Hz, 1H), 4.09 (d,  $J = 13.1$  Hz, 1H), 3.77 (s, 3H), 2.25 (dt,  $J = 16.1, 4.0$  Hz, 1H), 2.14 – 2.02 (m, 2H), 1.95 (d,  $J = 6.2$  Hz, 1H), 1.74 – 1.66 (m, 1H), 1.62 – 1.51 (m, 3H), 1.45 (td,  $J = 12.5, 4.7$ , 1H), 1.29 (s, 3H), 0.98 (s, 3H), 0.81 (s, 3H);  $^{13}\text{C NMR}$  (176 MHz, CDCl<sub>3</sub>)  $\delta$  153.8, 147.2, 138.7, 130.8, 129.0, 118.9, 113.7, 112.0, 86.8, 67.5, 55.8, 49.4, 46.4, 43.6, 43.5, 38.4, 29.2, 26.8, 24.2, 23.9, 23.7, 21.8; **IR** (neat) 3411, 3402, 2944, 2924, 2910, 2863, 2845, 1491, 1459, 1265, 1221, 1206, 1135, 1042, 952, 867, 811, 783, 774; **HRMS** (ESI)  $m/z$  calculated for C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>H<sup>+</sup> ( $[\text{M}+\text{H}]^+$ ) 341.2111, found 341.2110.

**(4a*S*,5*S*,7a*S*,12b*S*)-2-(hydroxymethyl)-7a,13,13-trimethyl-3,4,5,6,7,7a-hexahydro-5,12b-methanobenzo[*c*]cyclopenta[*b*]chromen-11-ol (S6)**

Charged a flame dried flask with **S6** (93 mg, 0.27 mmol, 1.00 equiv) and diethyl ether (5.00 mL). Cooled this solution to 0 °C then added MeMgI (2.7 mL, 3.0 molar in Et<sub>2</sub>O, 8.2 mmol, 30.0 equiv). After gently removing diethyl ether under vacuum, the resulting residue was heated to 160 °C under vacuum for 1 h. After cooling to room temperature, then back to 0 °C, the residue was diluted in diethyl ether. Then, the reaction mixture was carefully quenched with water then NH<sub>4</sub>Cl (aq. sat.). The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography over silica (hexanes:EtOAc, 9:1 to 2:3) afforded **S7** as a pale yellow powder (30 mg, 92 μmol, 34%).

**R<sub>f</sub>** = 0.18 (hexanes:EtOAc, 1:1);  $[\alpha]_{\text{D}}^{23} = +17.9$  (*c* = 0.10, MeOH); **<sup>1</sup>H NMR** (700 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 7.73 (s, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.81 (s, 1H), 4.09 – 3.98 (m, 2H), 3.77 (t, *J* = 5.8 Hz, 1H), 2.21 (dt, *J* = 16.1, 4.0 Hz, 1H), 2.11 – 2.06 (m, 1H), 2.04 – 1.99 (m, 1H), 1.97 (dd, *J* = 8.5, 2.2 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.65 – 1.58 (m, 1H), 1.58 – 1.50 (m, 2H), 1.36 (td, *J* = 12.5, 4.8 Hz, 1H), 1.23 (s, 3H), 0.96 (s, 3H), 0.79 (s, 3H); **<sup>13</sup>C NMR** (151 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 151.9, 146.6, 139.6, 131.5, 128.0, 119.2, 114.9, 114.3, 86.9, 66.3, 49.8, 47.1, 43.8, 43.8, 38.9, 29.3, 27.2, 24.4, 24.1, 23.7, 21.8; **IR** (neat) 3429, 3212, 3212, 2988, 2967, 2924, 2879, 2846, 2540, 2400, 1494, 1442, 1377, 1210, 1182, 1143, 1131, 997, 952, 944, 869, 810, 758, 740; **HRMS** (ESI) *m/z* calculated for C<sub>21</sub>H<sub>26</sub>O<sub>3</sub>Na<sup>+</sup> ([M+Na]<sup>+</sup>) 349.1774, found 349.1778.

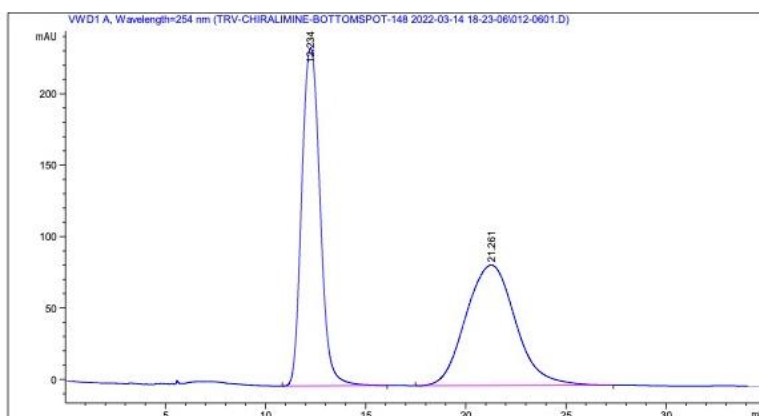
**(+)-Cochlearol B (2)**

Charged a flame dried flask with oxalyl chloride (2.36 μL, 27.0 μmol, 1.10 equiv) and DCM (0.3 mL), then cooled to -78 °C. To this solution was added DMSO (3.83 μL, 53.9 μmol, 2.20 equiv). The resulting mixture was stirred at -78 °C for 15 mins. Next, a solution of **S7** (0.008 g, 24.5 μmol, 1.00 eq.) in DCM:DMSO (10:1, 0.33 mL) was added. After stirring for 15 min at -78 °C, triethylamine (17.1 μL, 123 μmol, 5.0 equiv) was added. Following an additional 15 min of stirring, the reaction mixture was quenched with water and diluted in EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexanes:EtOAc, 19:1 to 7:3) afforded (+)-cochlearol B (**2**) as a pale yellow solid (6.1 mg, 19 μmol, 77%).

**R<sub>f</sub>** = 0.17 (hexanes:EtOAc, 4:1);  $[\alpha]_{\text{D}}^{25} = +112.8$  (*c* = 0.10, MeOH); **HPLC** (Daicel Chiralpak IC, hexanes:ethanol 75:25) 4.6 min (minor), 6.9 min (major). **<sup>1</sup>H NMR** (700 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 9.54 (s, 1H), 7.89 (s, 1H), 7.06 (d, *J* = 2.3 Hz, 1H),

6.79 (d,  $J = 2.1$  Hz, 1H), 6.71 – 6.58 (m, 2H), 2.64 (ddd,  $J = 16.5, 4.6, 3.7$  Hz, 1H), 2.15 – 2.10 (m, 1H), 2.07 (d,  $J = 1.9$  Hz, 1H), 2.04 – 1.98 (m, 1H), 1.76 – 1.71 (m, 1H), 1.70 – 1.58 (m, 3H), 1.37 (ddd,  $J = 13.4, 11.6, 4.7$  Hz, 1H), 1.28 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H);  **$^{13}\text{C}$  NMR** (176 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  193.4, 156.5, 152.3, 147.3, 142.0, 129.1, 119.9, 115.3, 115.0, 87.2, 50.2, 48.1, 46.1, 45.1, 39.0, 29.1, 26.7, 24.6, 23.9, 21.8, 19.5; **IR** (neat) 3375, 2951, 2928, 2859, 1679, 1663, 1492, 1445, 1209, 1182, 1134, 952, 882, 815, 789, 679; **HRMS** (ESI)  $m/z$  calculated for  $\text{C}_{21}\text{H}_{24}\text{O}_3\text{H}^+$  ( $[\text{M}+\text{H}]^+$ ) 325.1798, found 325.1794.

## 3. HPLC Spectra

Figure S1. HPLC traces of ( $\pm$ )-11 and (-)-11.

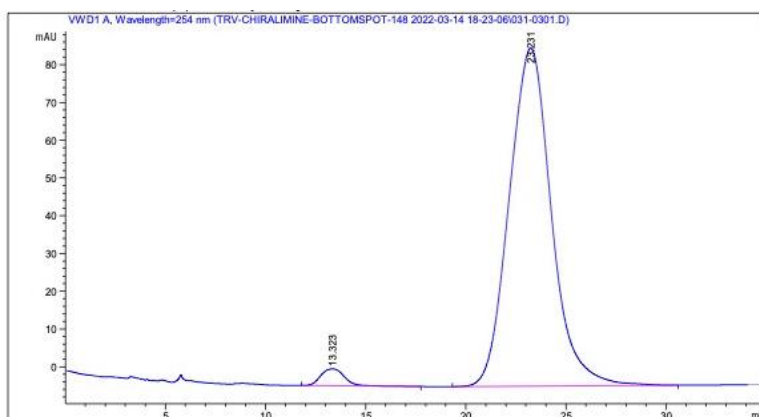
## Area Percent Report

Sorted By : Signal  
Multiplier : 1.0000  
Dilution : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.234	BB	1.0143	1.50214e4	236.71468	50.7720
2	21.261	BB	2.7131	1.45645e4	84.36419	49.2280

Totals : 2.95859e4 321.07887



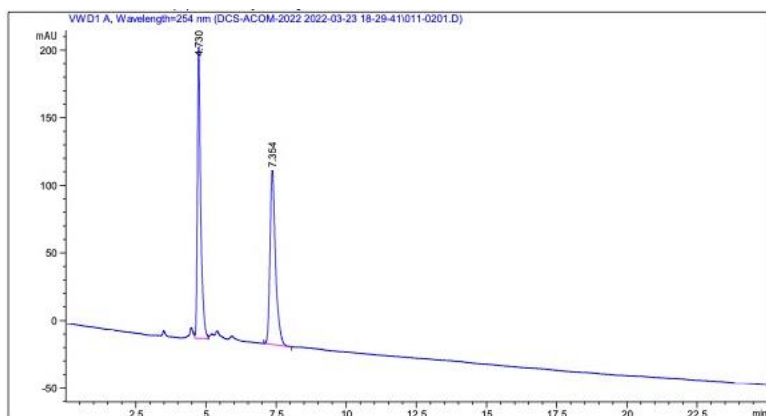
## Area Percent Report

Sorted By : Signal  
Multiplier : 1.0000  
Dilution : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.323	BB	0.9890	370.70453	4.46791	2.7525
2	23.231	BB	2.2520	1.30971e4	89.51569	97.2475

Totals : 1.34678e4 93.98360

Figure S2. HPLC traces of ( $\pm$ )-cochlearol B and (+)-cochlearol B.

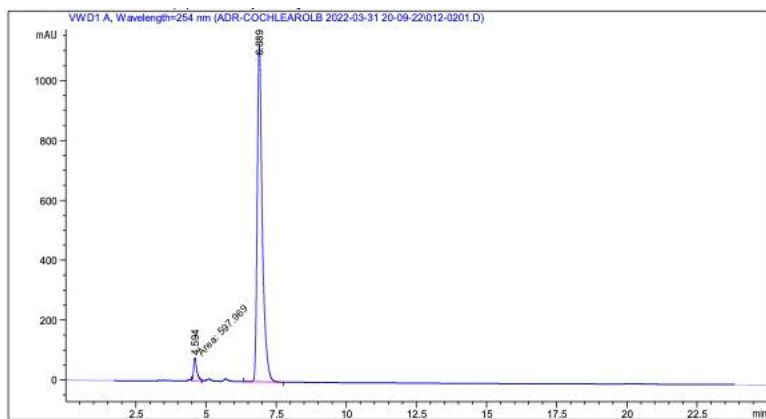
=====  
 Area Percent Report  
 =====

Sorted By : Signal  
 Multiplier : 1.0000  
 Dilution : 1.0000  
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.730	VV	0.1205	1764.70984	215.51315	50.1599
2	7.354	BB	0.2039	1753.46082	128.76698	49.8401

Totals : 3518.17065 344.28014



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 Area Percent Report  
 =====

Sorted By : Signal  
 Multiplier : 1.0000  
 Dilution : 1.0000  
 Use Multiplier & Dilution Factor with ISTDs

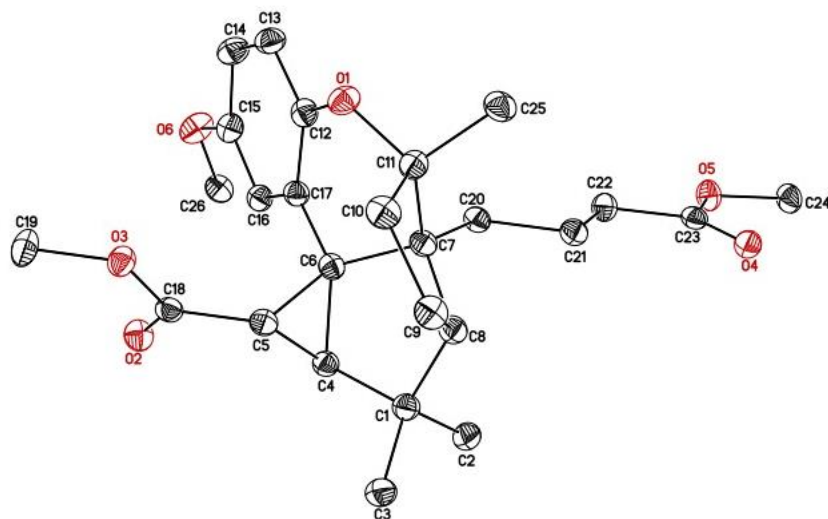
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.594	MM	0.1296	597.96875	76.89019	4.0682
2	6.889	BB	0.1868	1.41008e4	1120.88000	95.9318

Totals : 1.46988e4 1197.77020



## 4. X-ray Crystallographic Data



**Figure S3.** Crystal structure of **19**. X-ray crystallographic coordinates have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with the deposit number 2142344.

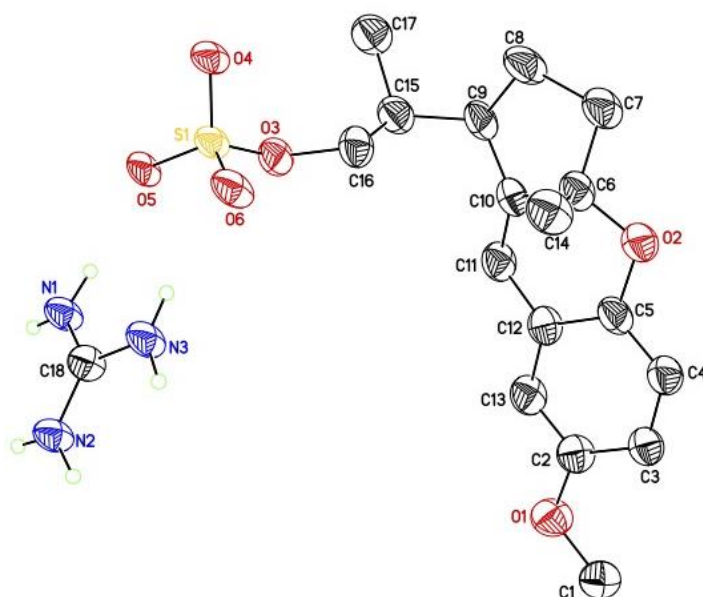
Colorless blocks of **19** were grown from an ethyl acetate solution of the compound at 20 deg. C. A crystal of dimensions 0.14 x 0.12 x 0.08 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode ( $\lambda = 1.54187$  Å) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in  $\omega$ . The exposure times were 1 sec. for the low angle images, 2 sec. for high angle. Rigaku d\*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 32993 reflections to a maximum  $2\theta$  value of 138.76° of which 4189 were independent and 4068 were greater than  $2\sigma(I)$ . The final cell constants (Table 1) were based on the xyz centroids of 18434 reflections above  $10\sigma(I)$ . Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group P2(1)/c with Z = 4 for the formula C<sub>26</sub>H<sub>34</sub>O<sub>6</sub>. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on  $F^2$  converged at  $R1 = 0.0433$  and  $wR2 = 0.1154$  [based on  $I > 2\sigma(I)$ ],  $R1 = 0.0448$  and  $wR2 = 0.1178$  for all data. Additional details are presented in Table S3 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

**Table S3.** Crystal data and structure refinement for **19**.

Empirical formula	C <sub>26</sub> H <sub>34</sub> O <sub>6</sub>
Formula weight	442.53
Temperature	85(2) K
Wavelength	1.54184 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 17.6211(3) Å    alpha = 90 deg. b = 8.05114(8) Å    beta = 118.0448(19) deg. c = 17.9615(3) Å    gamma = 90 deg.
Volume	2248.98(6) Å <sup>3</sup>
Z, Calculated density	4, 1.307 Mg/m <sup>3</sup>
Absorption coefficient	0.744 mm <sup>-1</sup>

F(000)	952
Crystal size	0.140 x 0.120 x 0.080 mm
Theta range for data collection	2.841 to 69.387 deg.
Limiting indices	-21 ≤ h ≤ 21, -9 ≤ k ≤ 9, -21 ≤ l ≤ 21
Reflections collected / unique	32993 / 4189 [R(int) = 0.0664]
Completeness to theta = 67.684	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.81148
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4189 / 0 / 296
Goodness-of-fit on F <sup>2</sup>	1.094
Final R indices [I > 2σ(I)]	R1 = 0.0433, wR2 = 0.1154
R indices (all data)	R1 = 0.0448, wR2 = 0.1178
Extinction coefficient	0.0064(4)
Largest diff. peak and hole	0.311 and -0.298 e.Å <sup>-3</sup>

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", *Acta Cryst.*, C71, 3-8 (Open Access).  
 CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA  
 77381-5209, Rigaku Tokyo, 196-8666, Japan.  
 CrysAlisPro 1.171.40.53 (Rigaku Oxford Diffraction, 2019).



**Figure S4.** Crystal structure of **13**. X-ray crystallographic coordinates have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with the deposit number 2142345.

Colorless plates of **13** were grown from a methanol solution of the compound at 25 deg. C. A crystal of dimensions 0.07 x 0.06 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode ( $\lambda = 1.54187$  Å) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in  $\omega$ . The exposure times were 1 sec. for the low angle images, 4 sec. for high angle. Rigaku d\*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 29002 reflections to a

maximum  $2\theta$  value of  $139.36^\circ$  of which 3765 were independent and 2703 were greater than  $2\sigma(I)$ . The final cell constants (Table 1) were based on the xyz centroids of 3313 reflections above  $10\sigma(I)$ . Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group  $P2(1)/c$  with  $Z = 4$  for the formula  $C_{18}H_{27}N_3O_6S$ . All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. Full matrix least-squares refinement based on  $F^2$  converged at  $R1 = 0.0851$  and  $wR2 = 0.2275$  [based on  $I > 2\sigma(I)$ ],  $R1 = 0.1118$  and  $wR2 = 0.2448$  for all data. Additional details are presented in Table S4 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

**Table S4.** Crystal data and structure refinement for **13**.

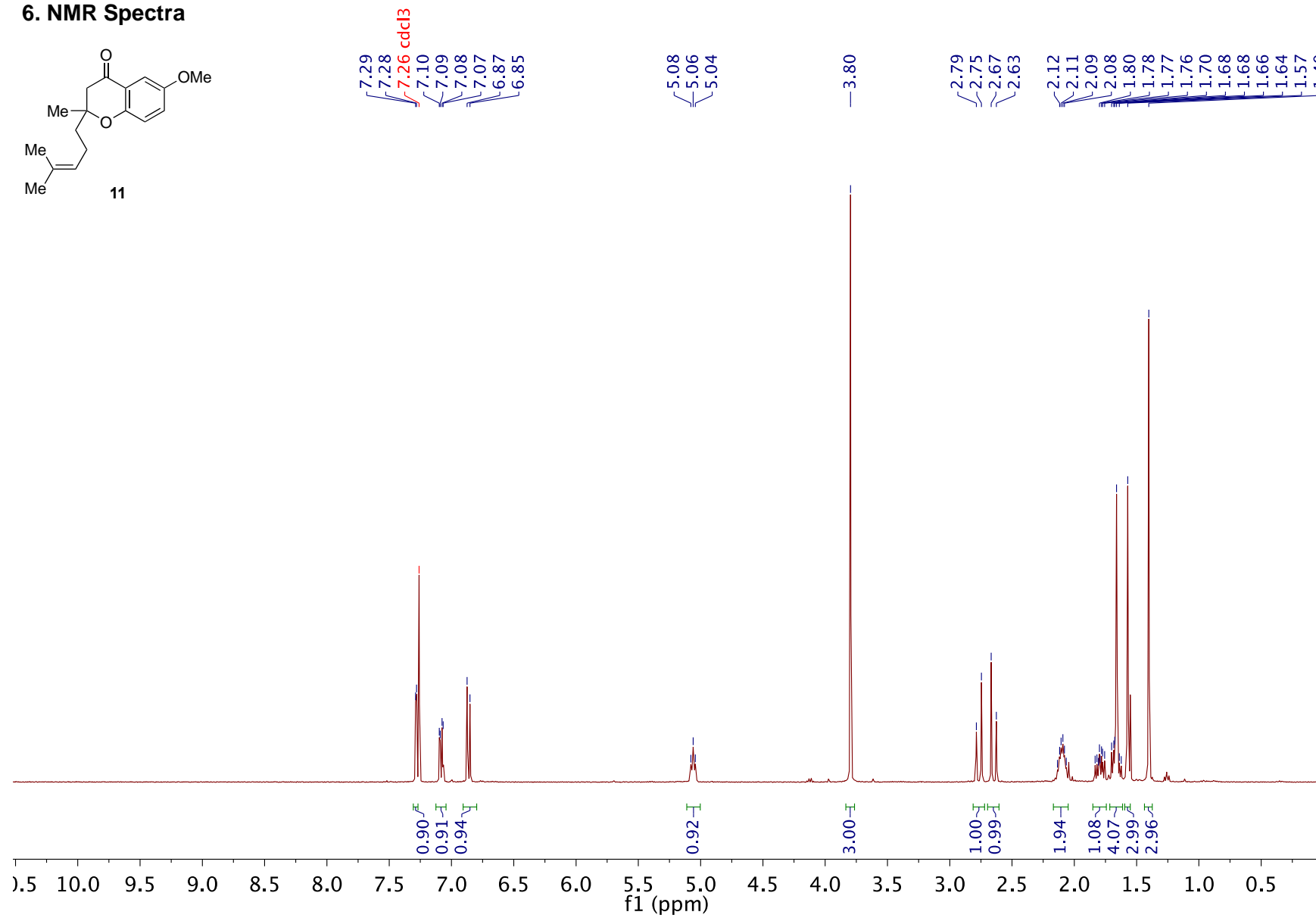
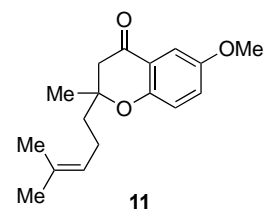
Empirical formula	$C_{18}H_{27}N_3O_6S$
Formula weight	413.48
Temperature	85(2) K
Wavelength	1.54184 Å
Crystal system, space group	Monoclinic, $P2(1)/c$
Unit cell dimensions	$a = 22.2228(16)$ Å $\alpha = 90$ deg. $b = 7.1175(4)$ Å $\beta = 100.377(5)$ deg. $c = 12.9942(5)$ Å $\gamma = 90$ deg.
Volume	$2021.7(2)$ Å <sup>3</sup>
Z, Calculated density	4, 1.358 Mg/m <sup>3</sup>
Absorption coefficient	$1.771$ mm <sup>-1</sup>
$F(000)$	880
Crystal size	0.070 x 0.060 x 0.020 mm
Theta range for data collection	4.045 to 69.679 deg.
Limiting indices	$-26 \leq h \leq 25$ , $-8 \leq k \leq 8$ , $-15 \leq l \leq 15$
Reflections collected / unique	29002 / 3765 [ $R(\text{int}) = 0.1067$ ]
Completeness to $\theta = 67.684$	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.63671
Refinement method	Full-matrix least-squares on $F^2$
Data / restraints / parameters	3765 / 15 / 280
Goodness-of-fit on $F^2$	1.115
Final R indices [ $I > 2\sigma(I)$ ]	$R1 = 0.0851$ , $wR2 = 0.2275$
R indices (all data)	$R1 = 0.1118$ , $wR2 = 0.2448$
Extinction coefficient	n/a
Largest diff. peak and hole	0.500 and -0.381 e.Å <sup>-3</sup>

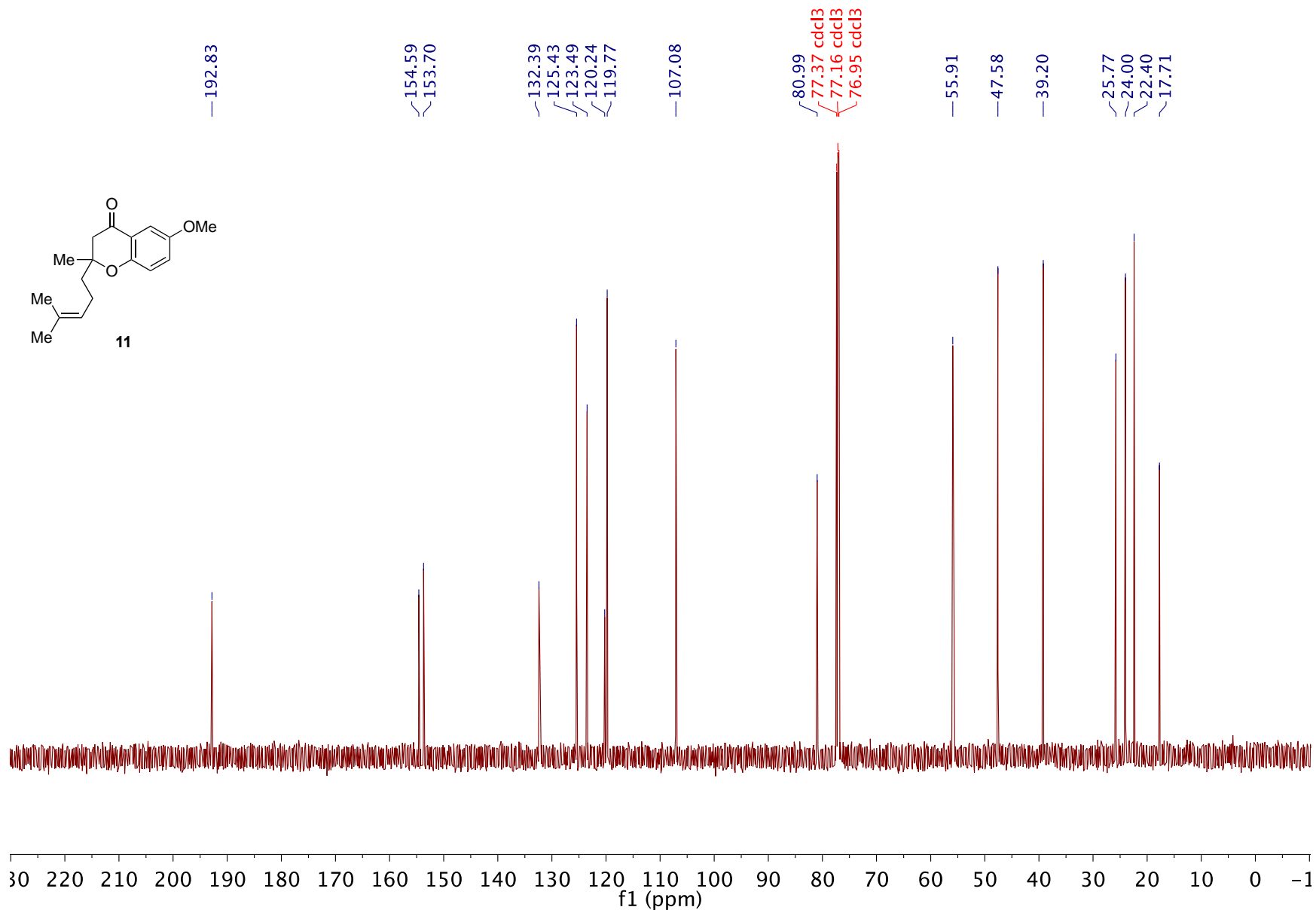
G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", *Acta Cryst.*, C71, 3-8 (Open Access).  
CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA  
77381-5209, Rigaku Tokyo, 196-8666, Japan.  
CrysAlisPro 1.171.40.53 (Rigaku Oxford Diffraction, 2019).

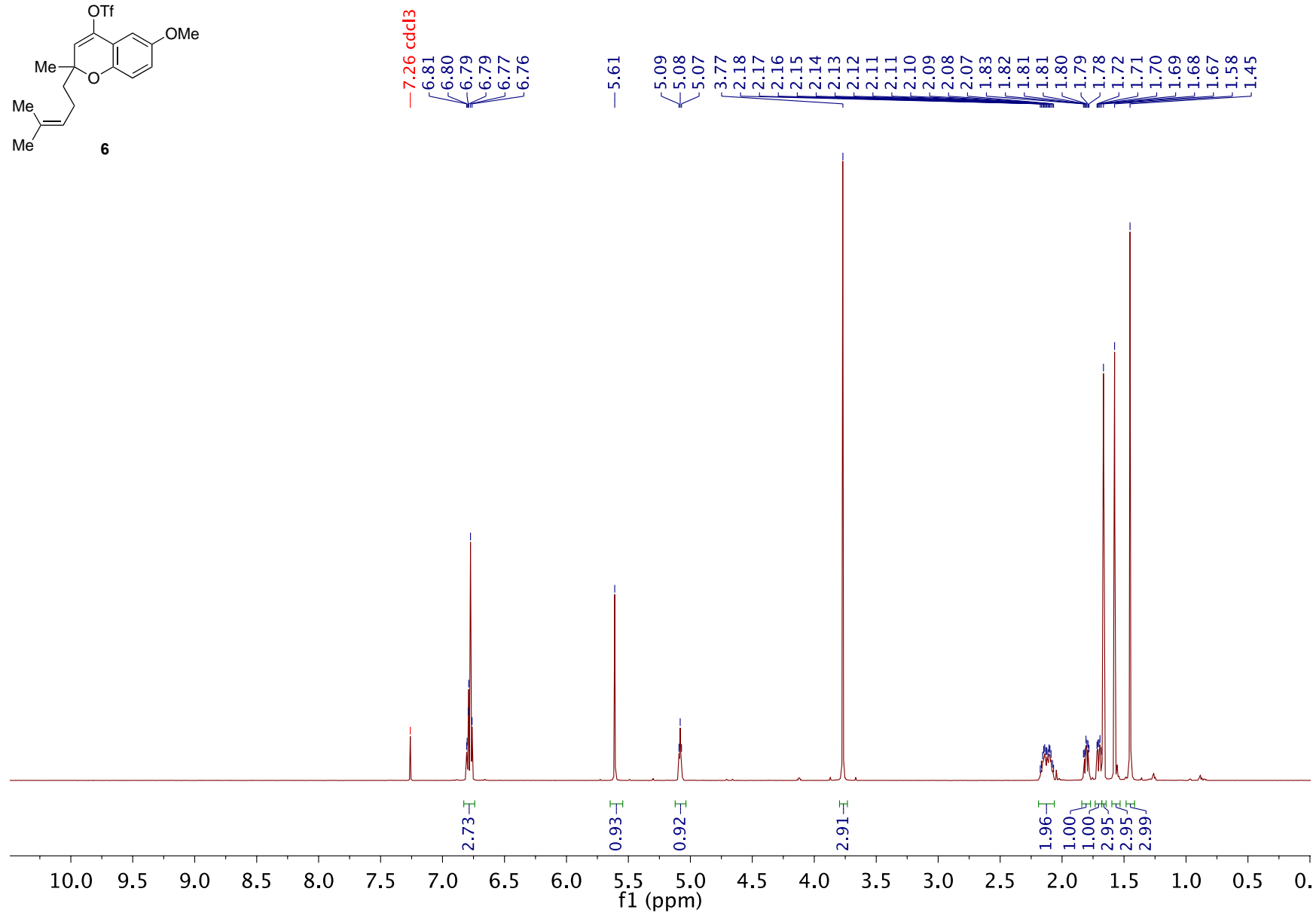
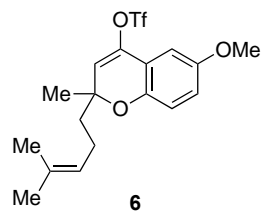
## 5. References

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5. J. Wang, Z. Dong, C. Yang, G. Dong, *Nat. Chem.* **2019**, *11*, 1106-1112.

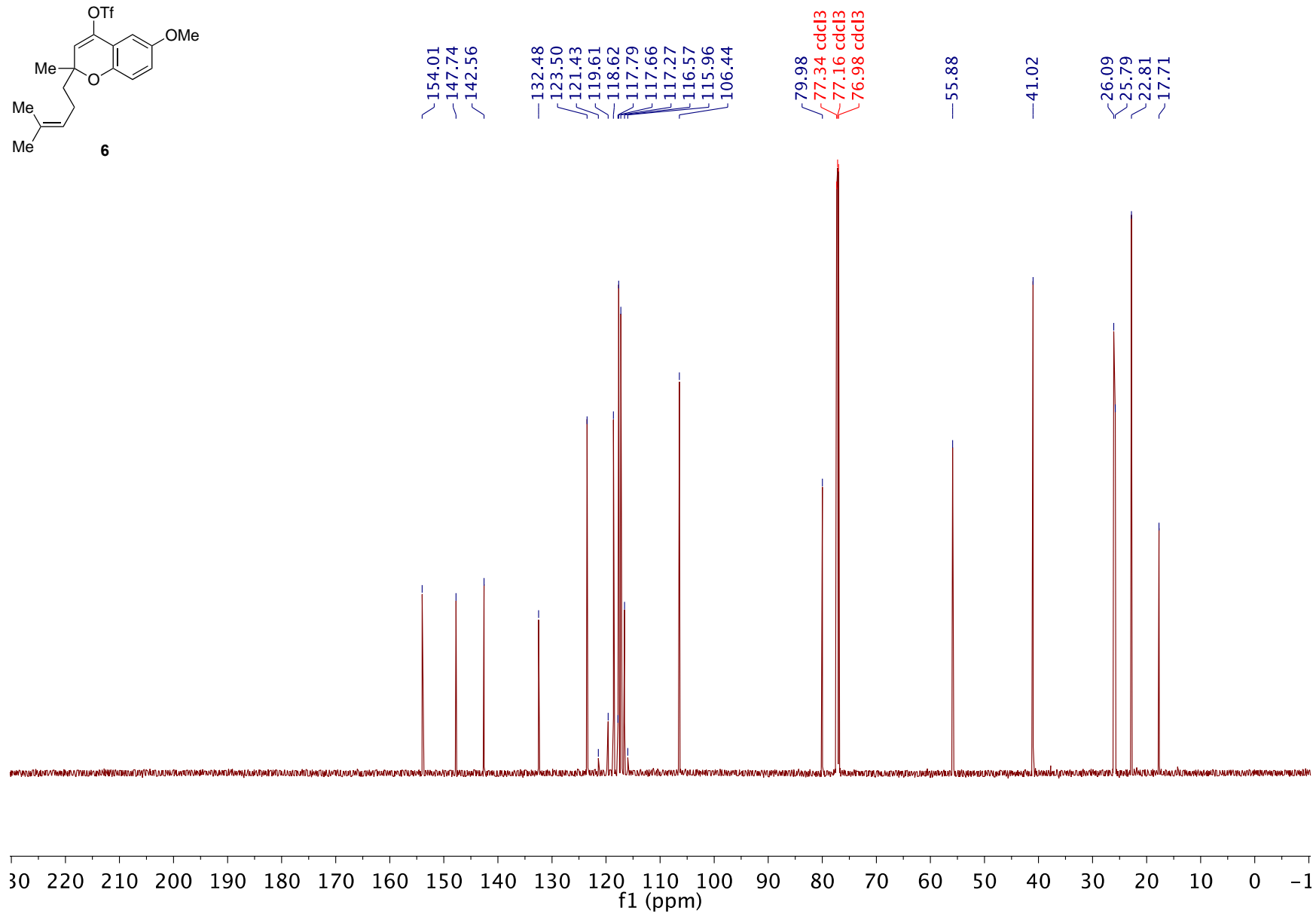
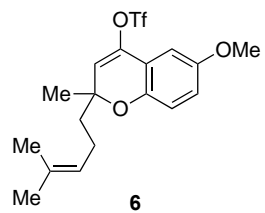
## 6. NMR Spectra

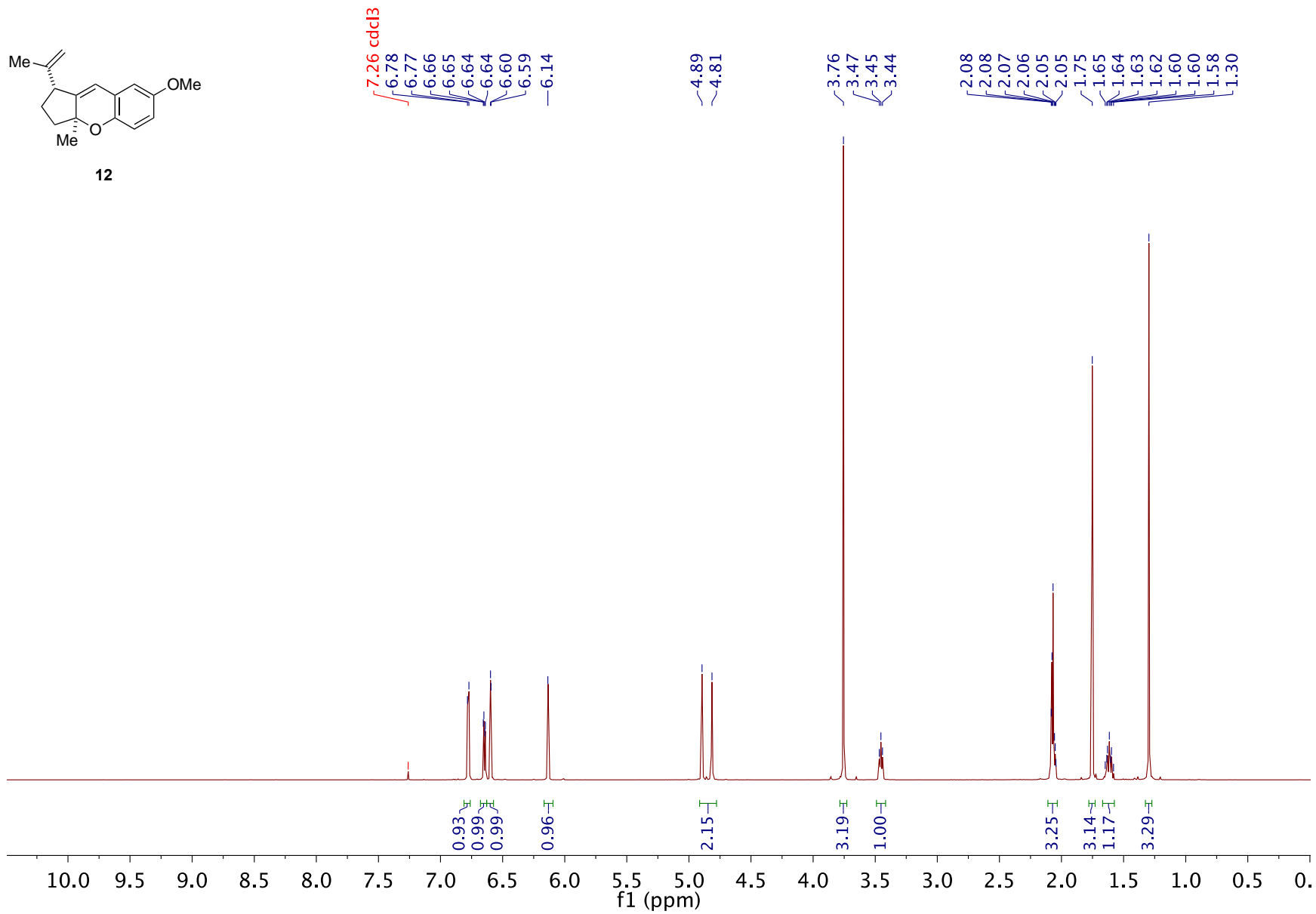


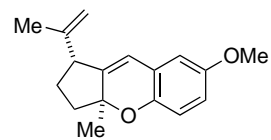




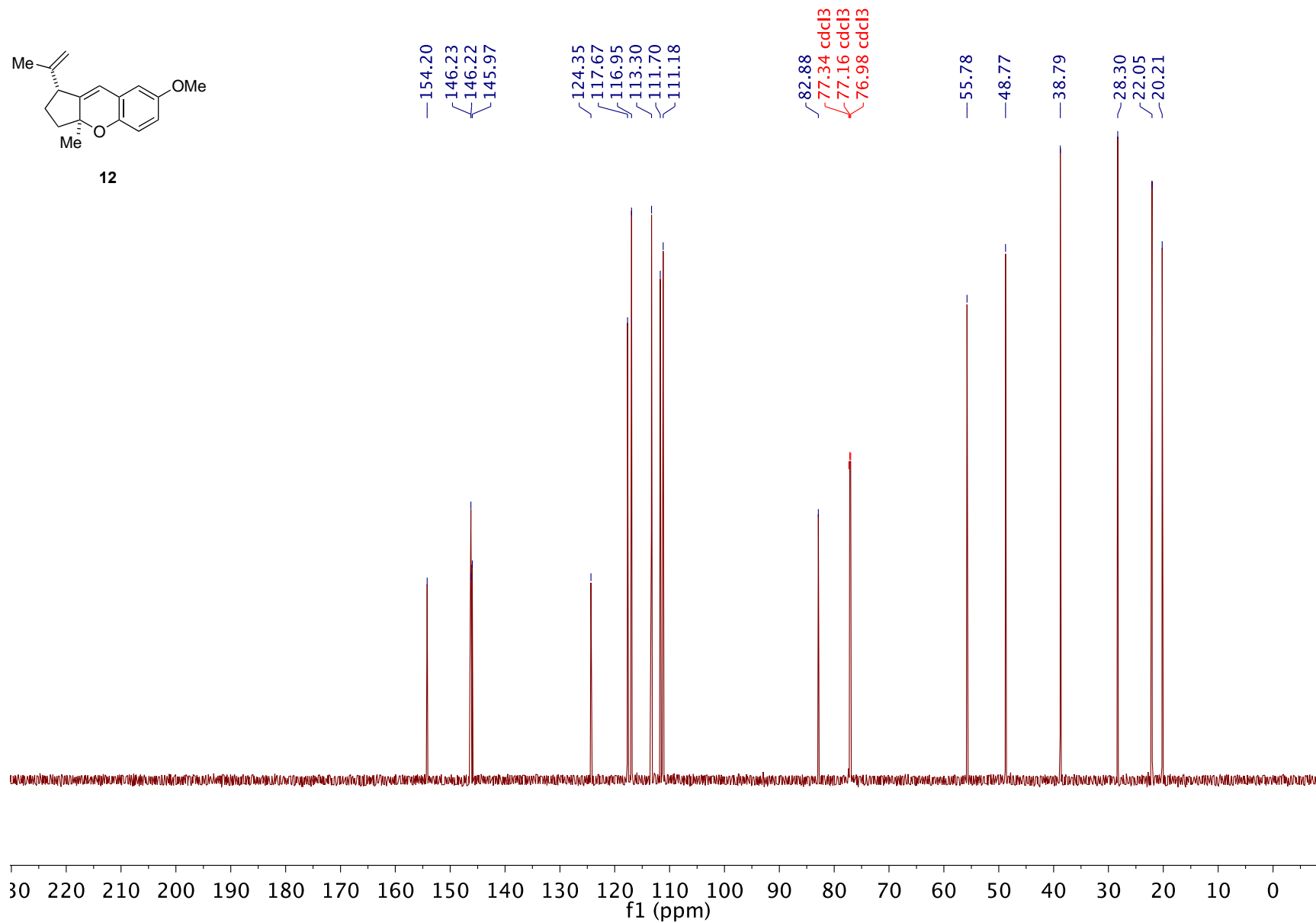


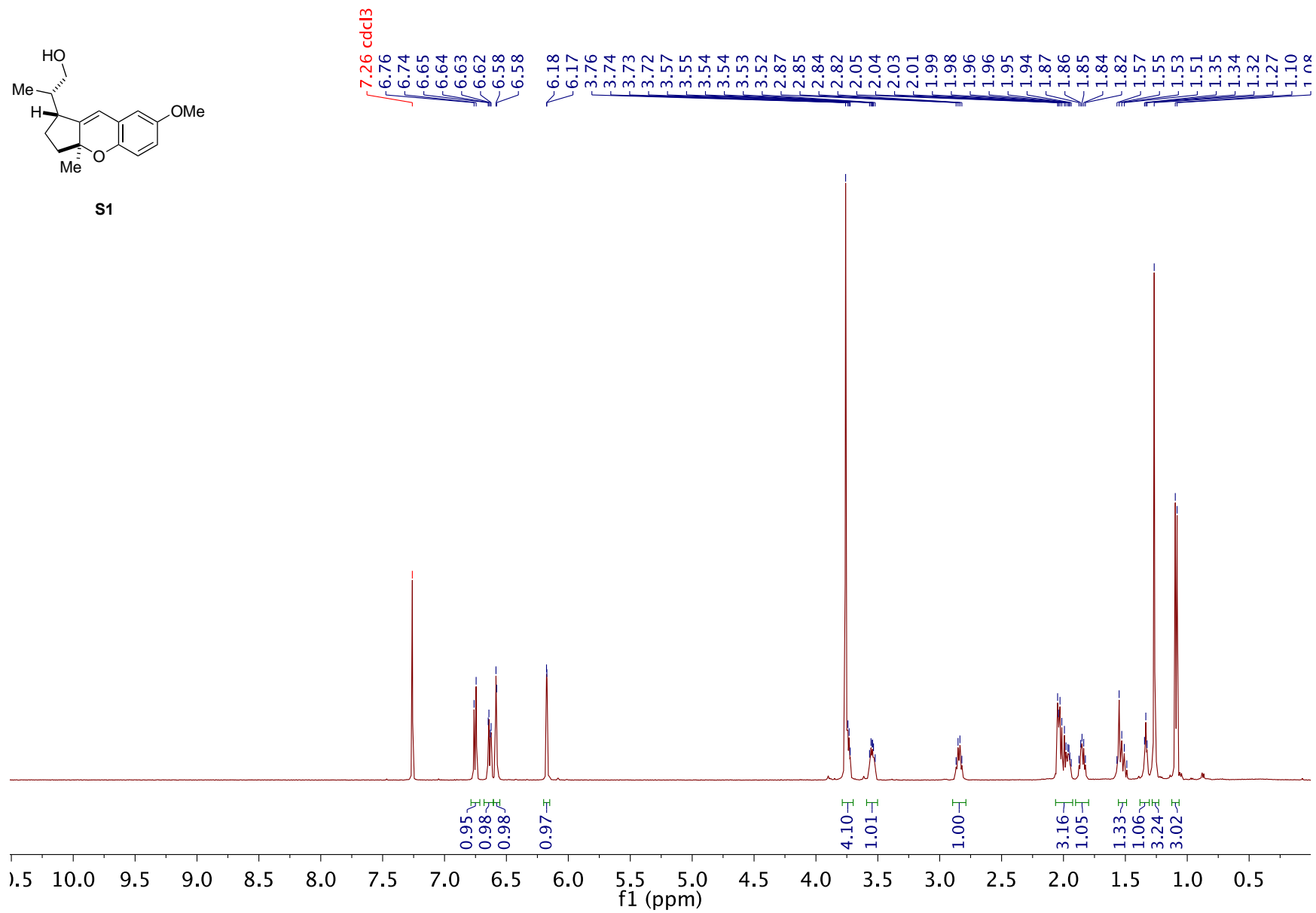


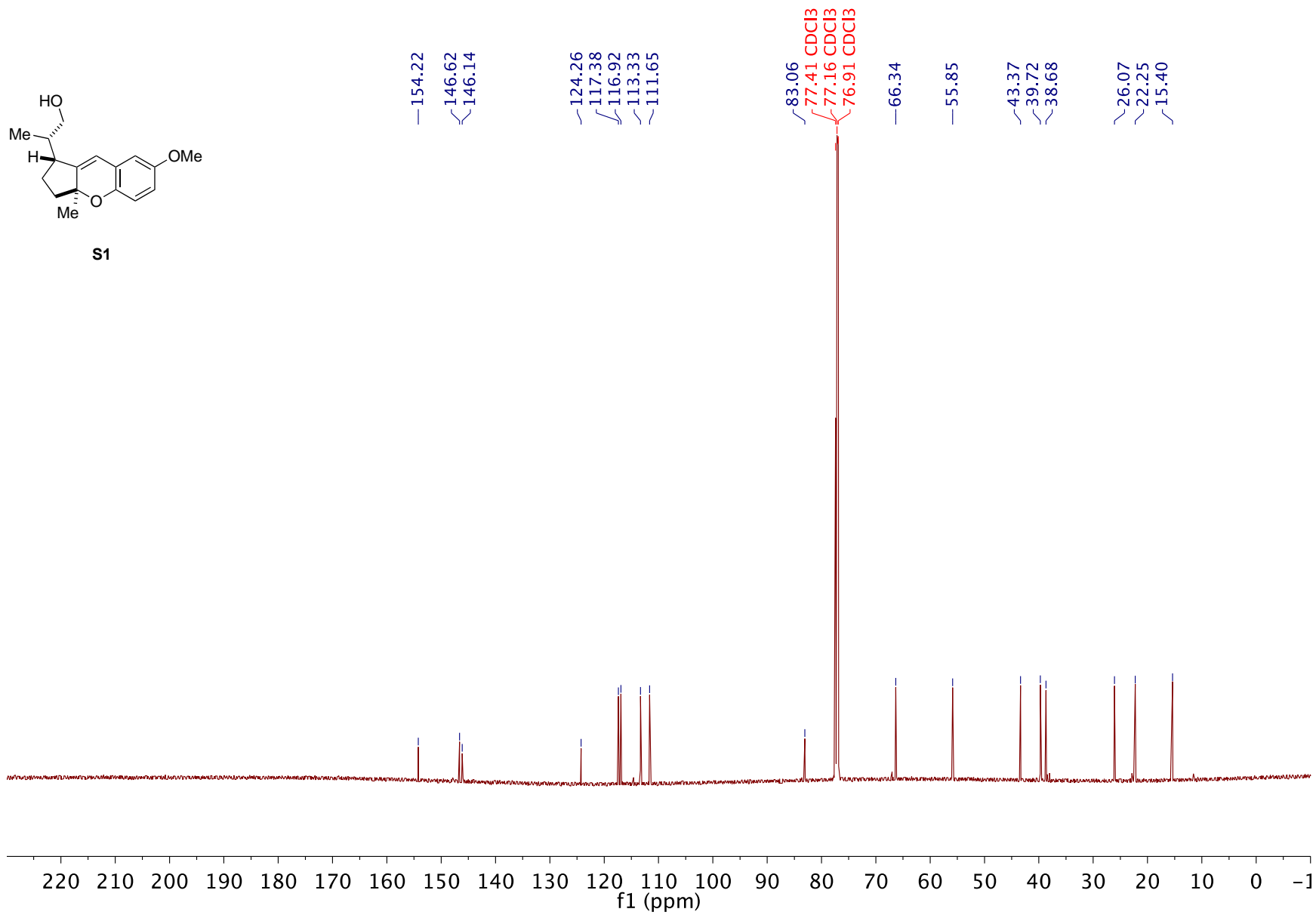


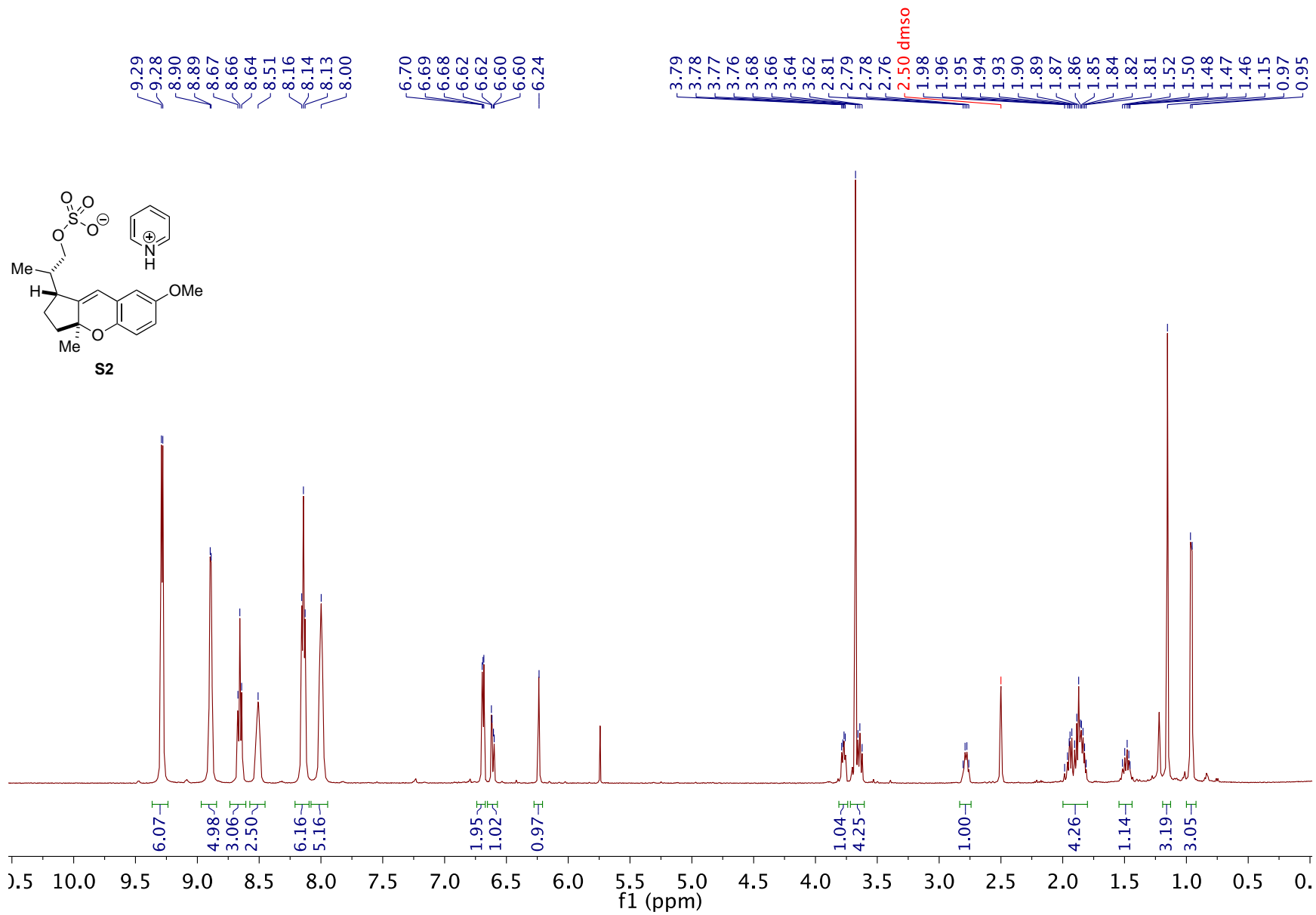


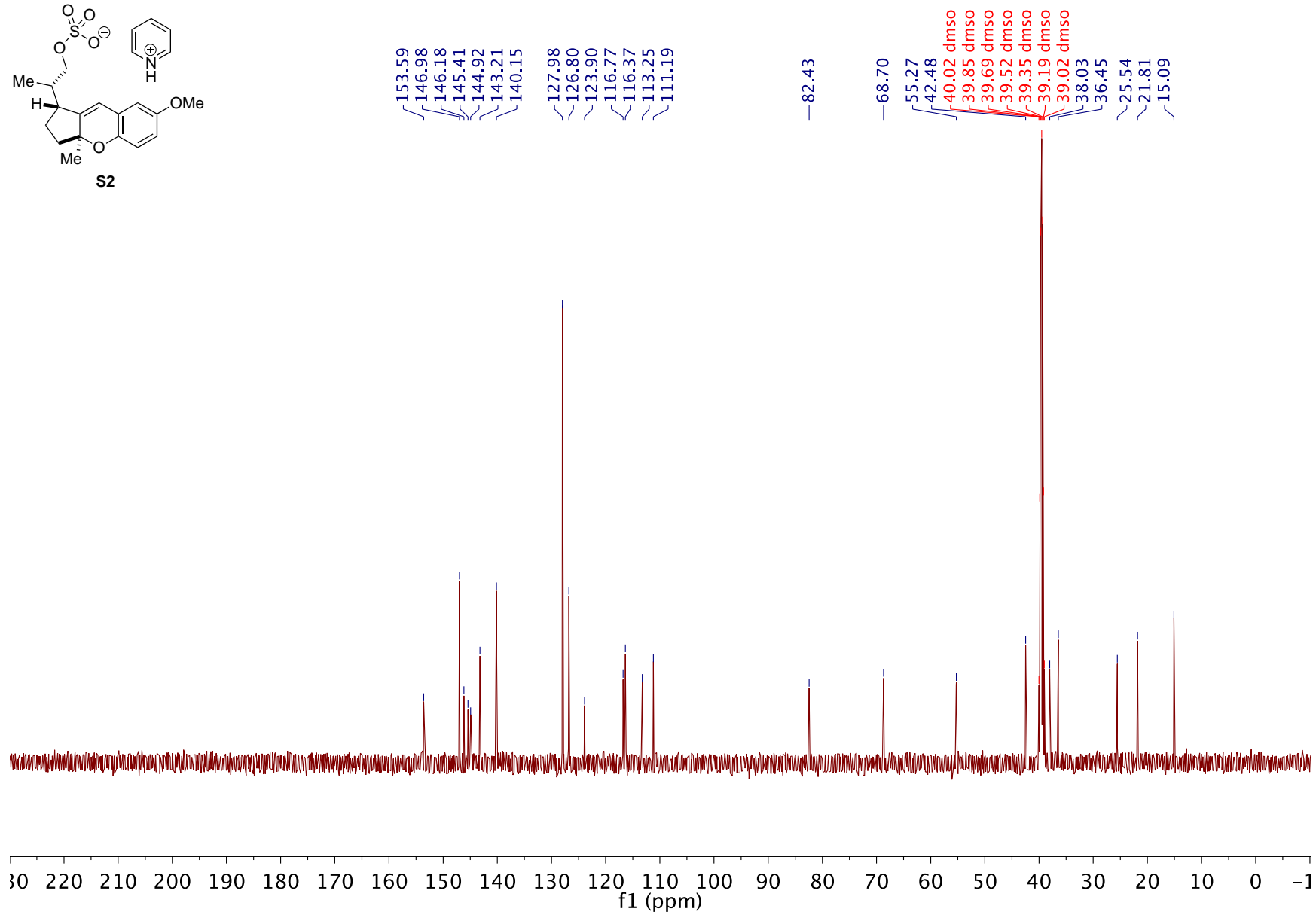
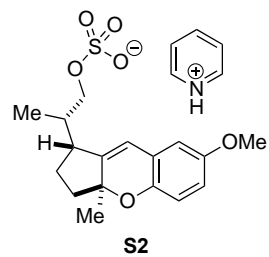
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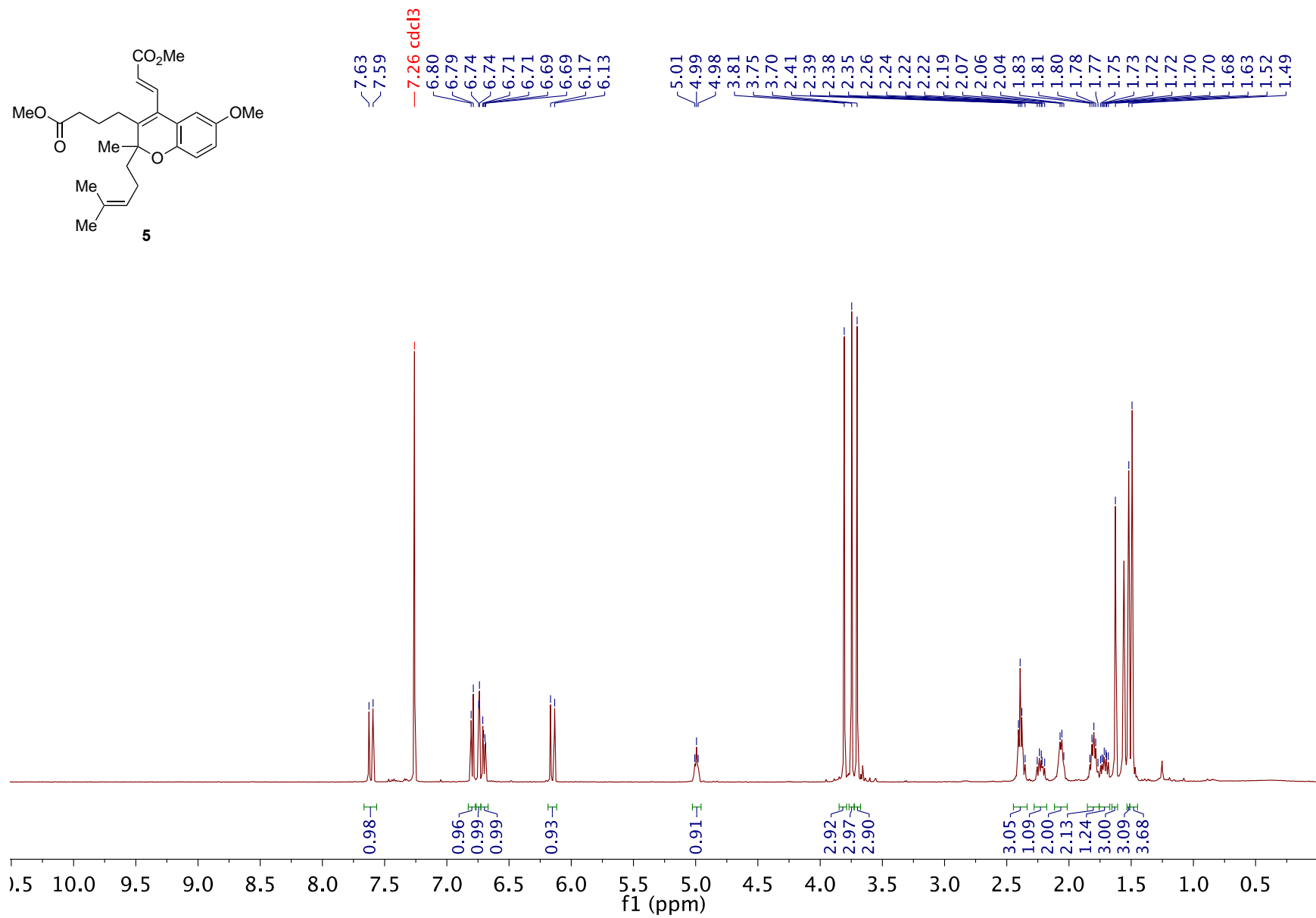


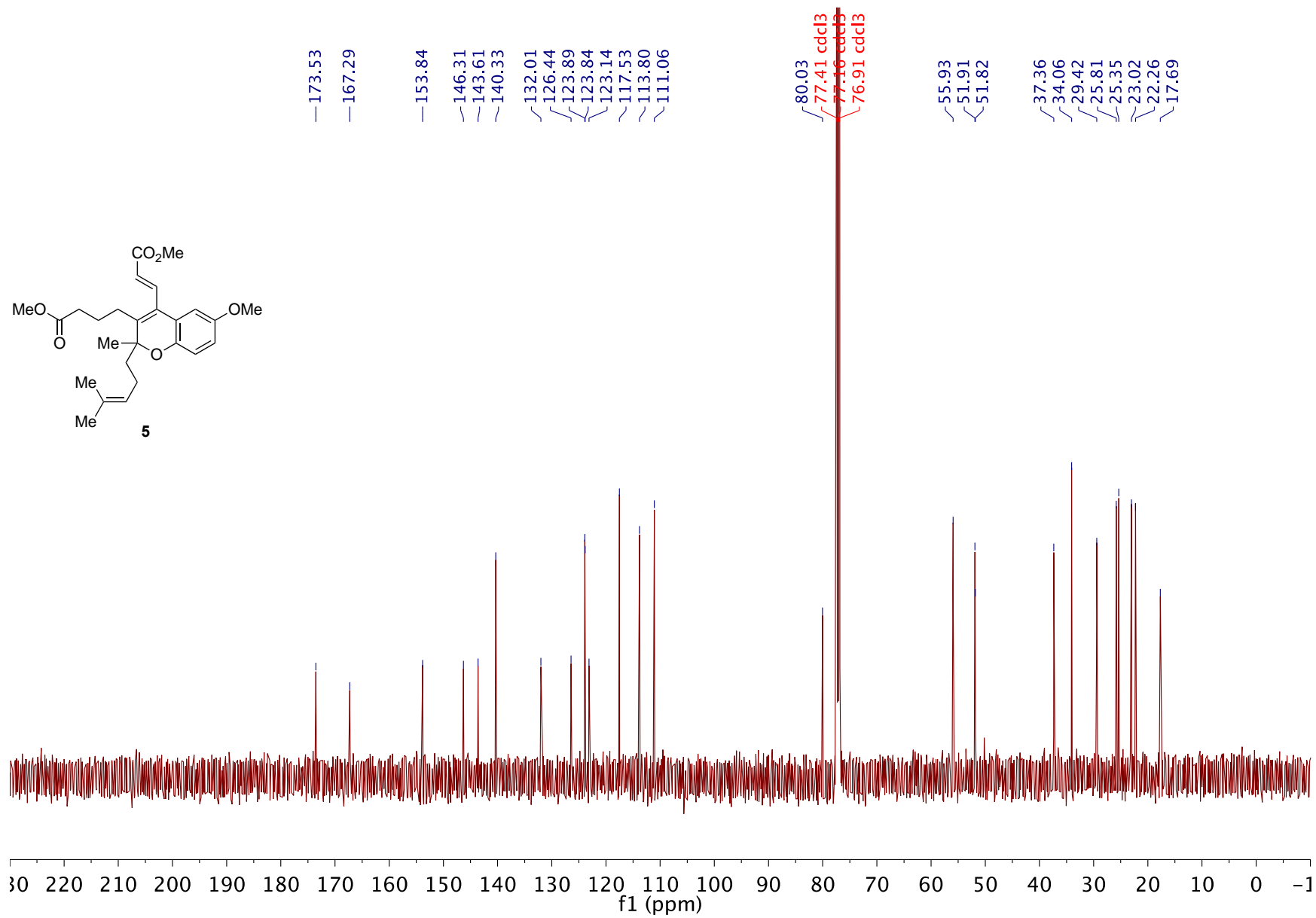


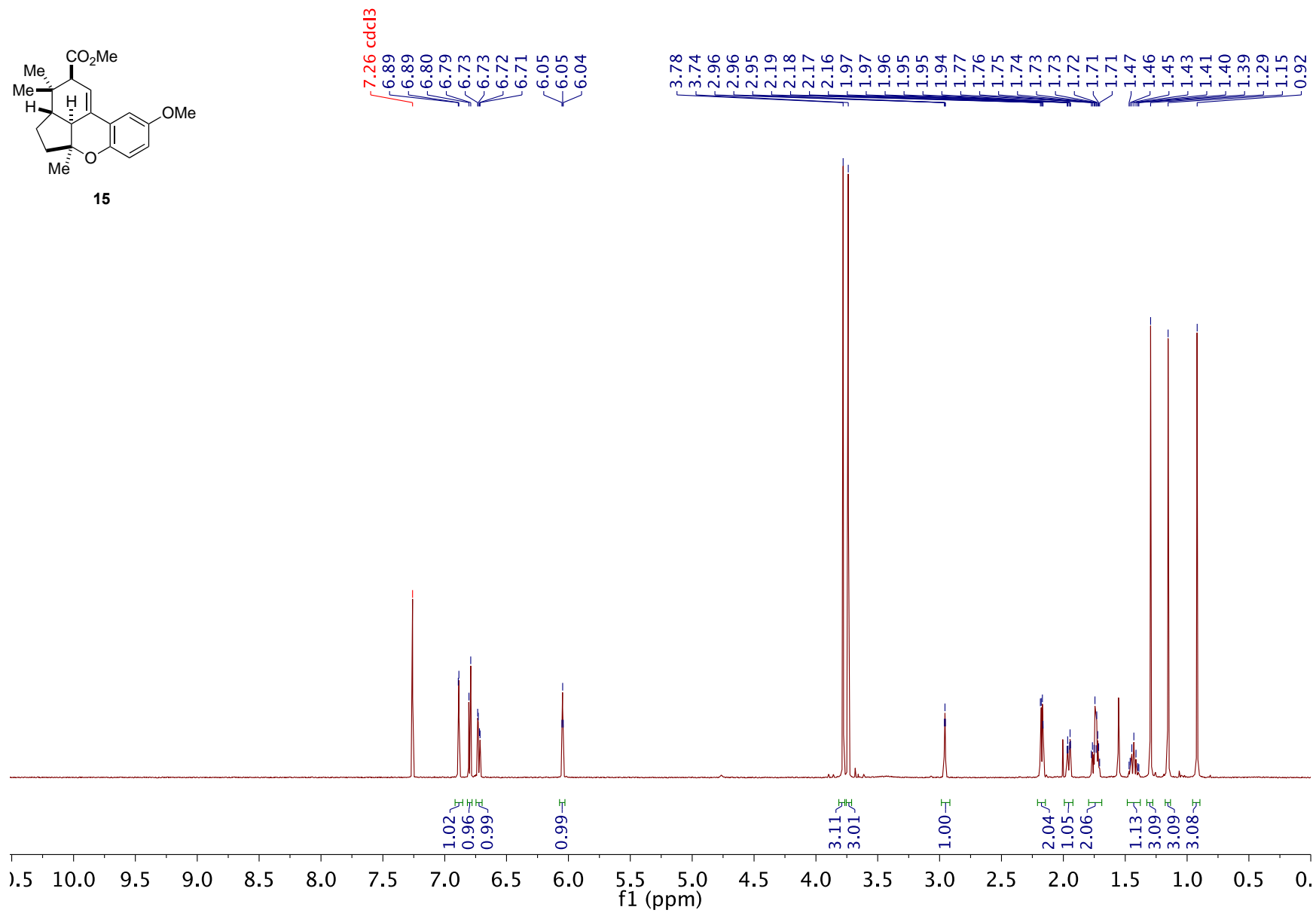


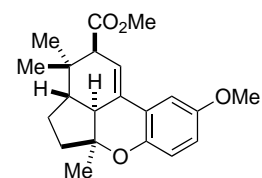




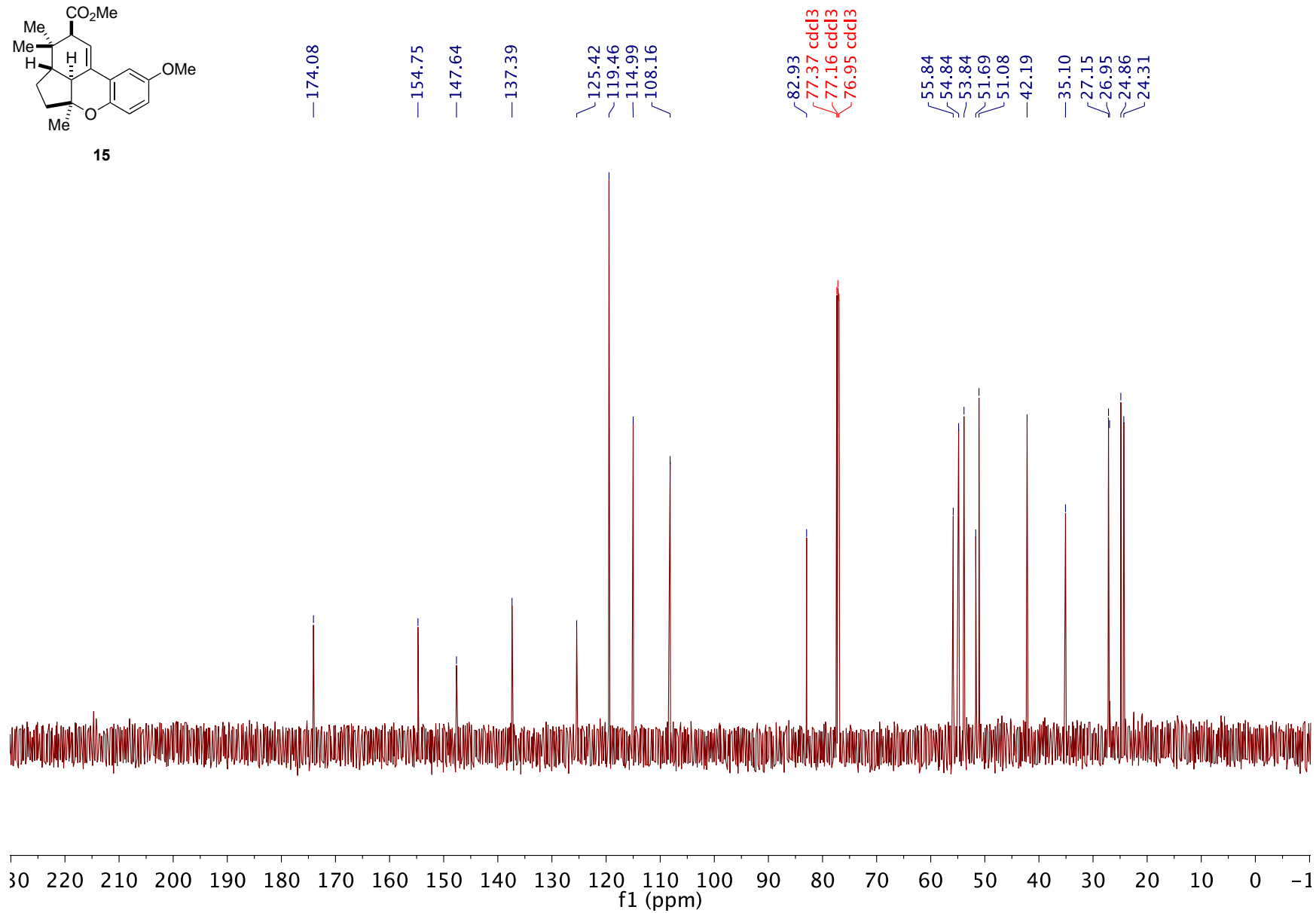


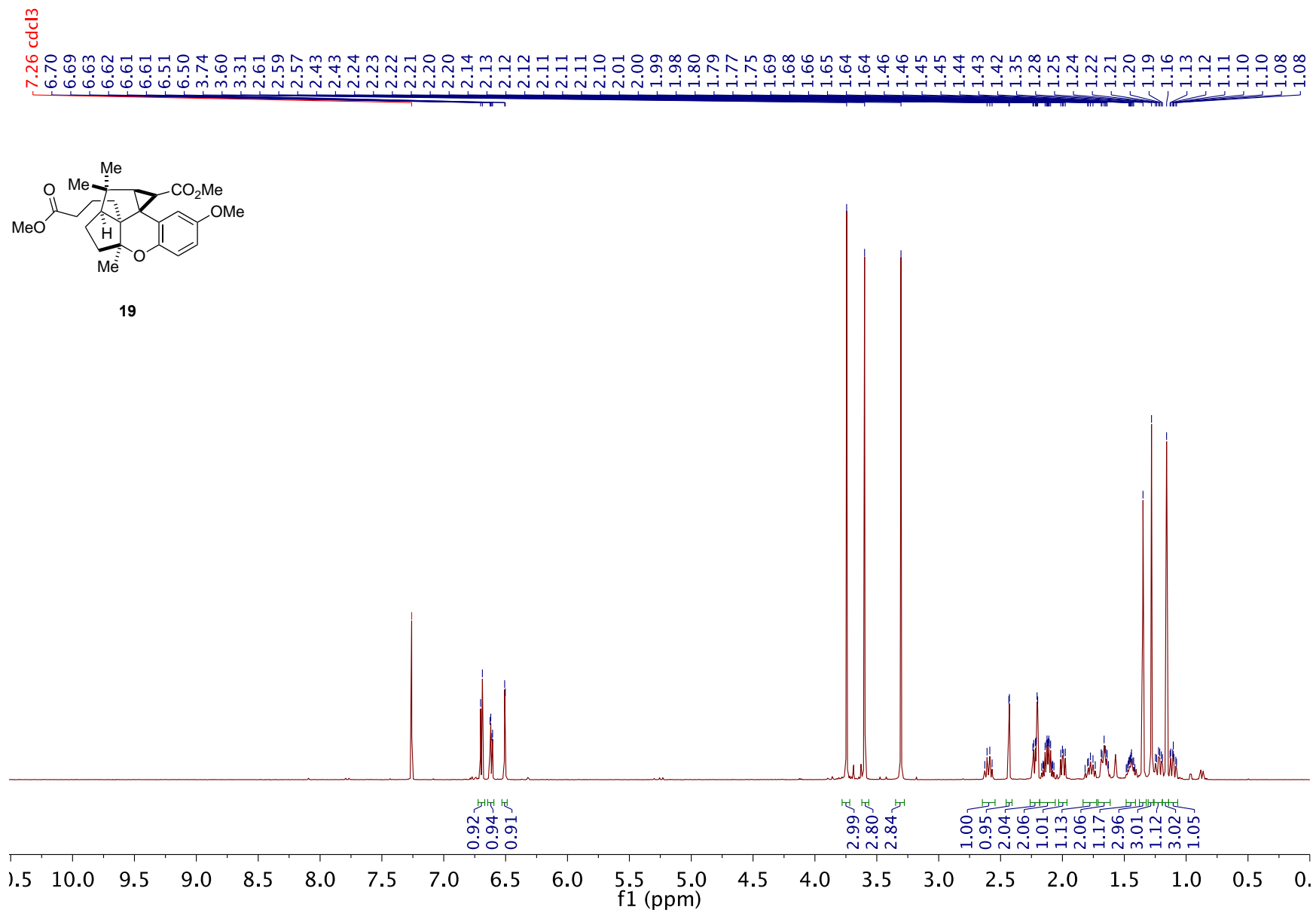


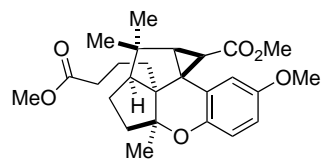




15







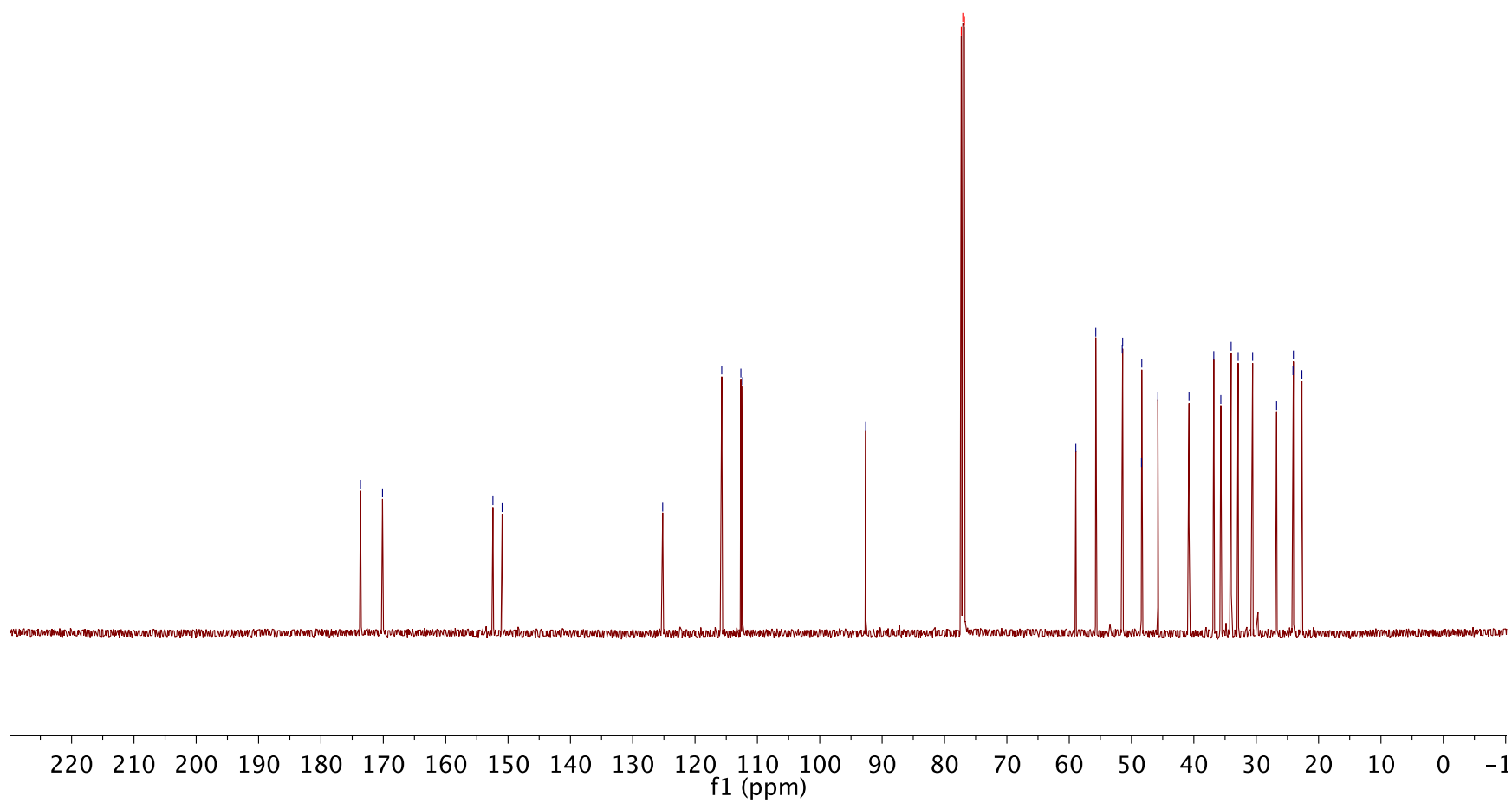
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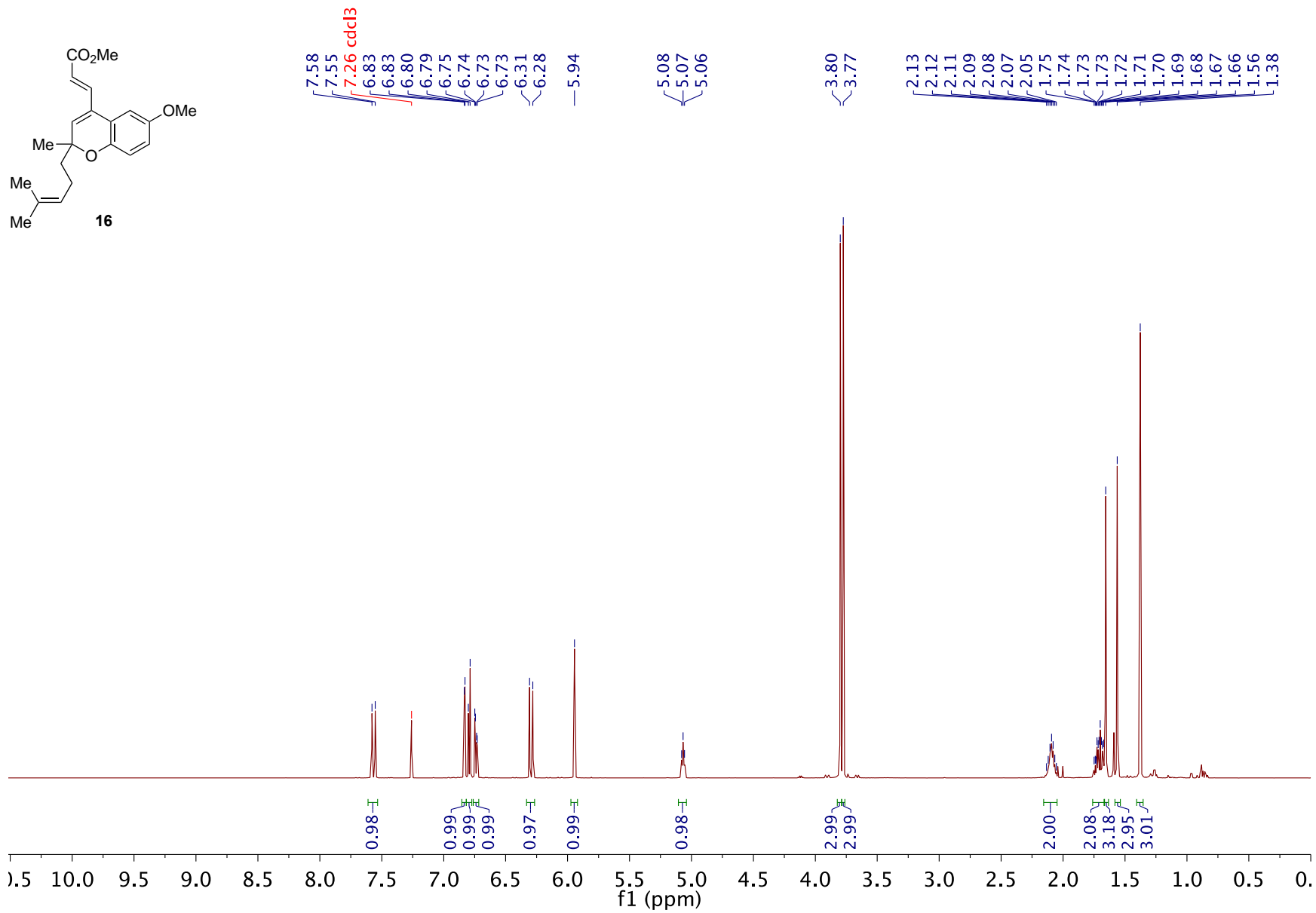
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—170.13—152.42  
—150.94

—125.19

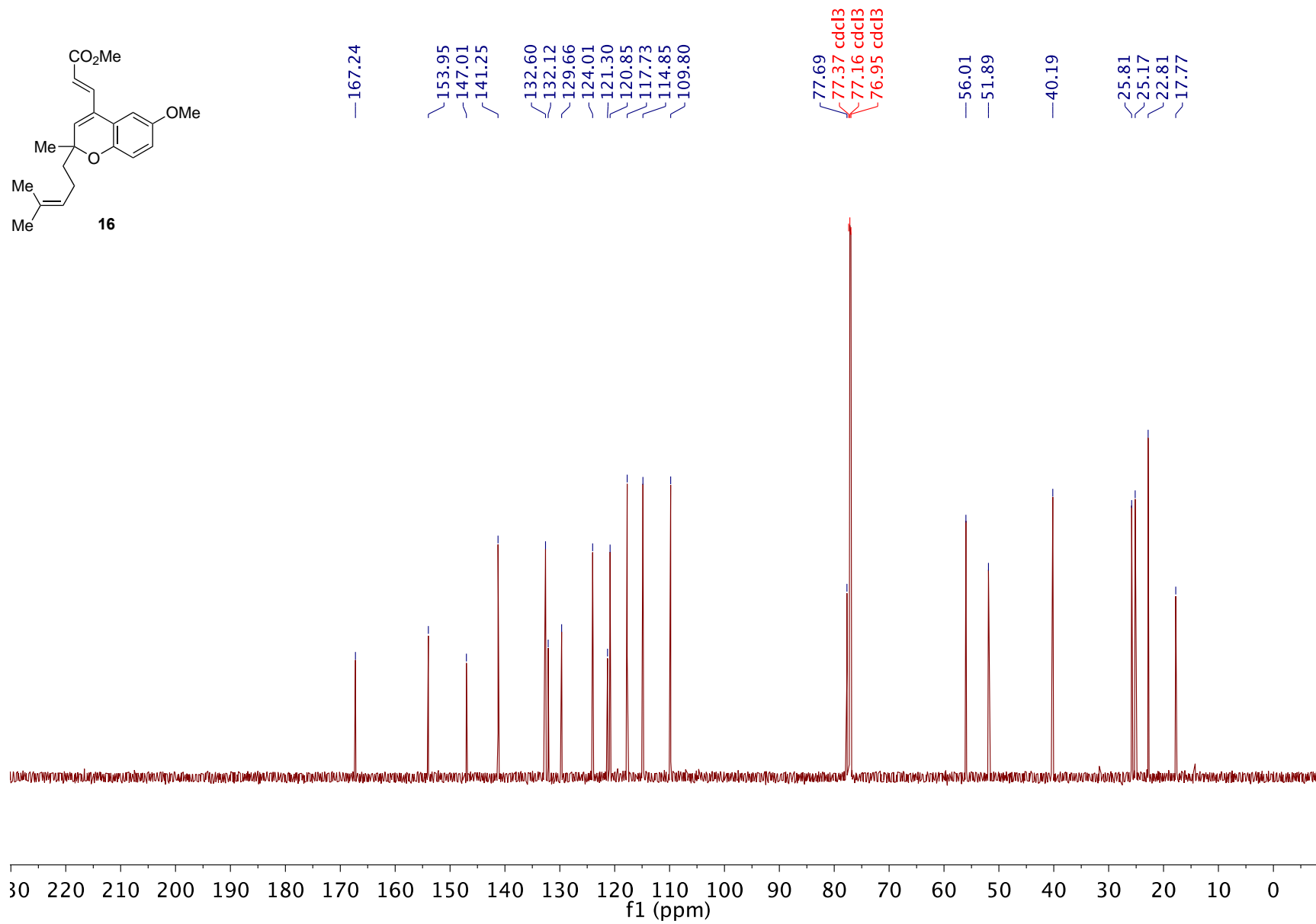
—115.73  
—112.66  
—112.38

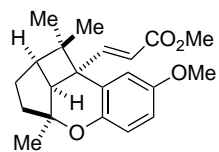
—92.62

77.30 CDC13  
77.05 CDC13  
76.79 CDC1358.92  
55.73  
51.49  
51.43  
48.39  
48.35  
45.76  
40.79  
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35.67  
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30.58  
26.73  
24.11  
24.04  
22.67

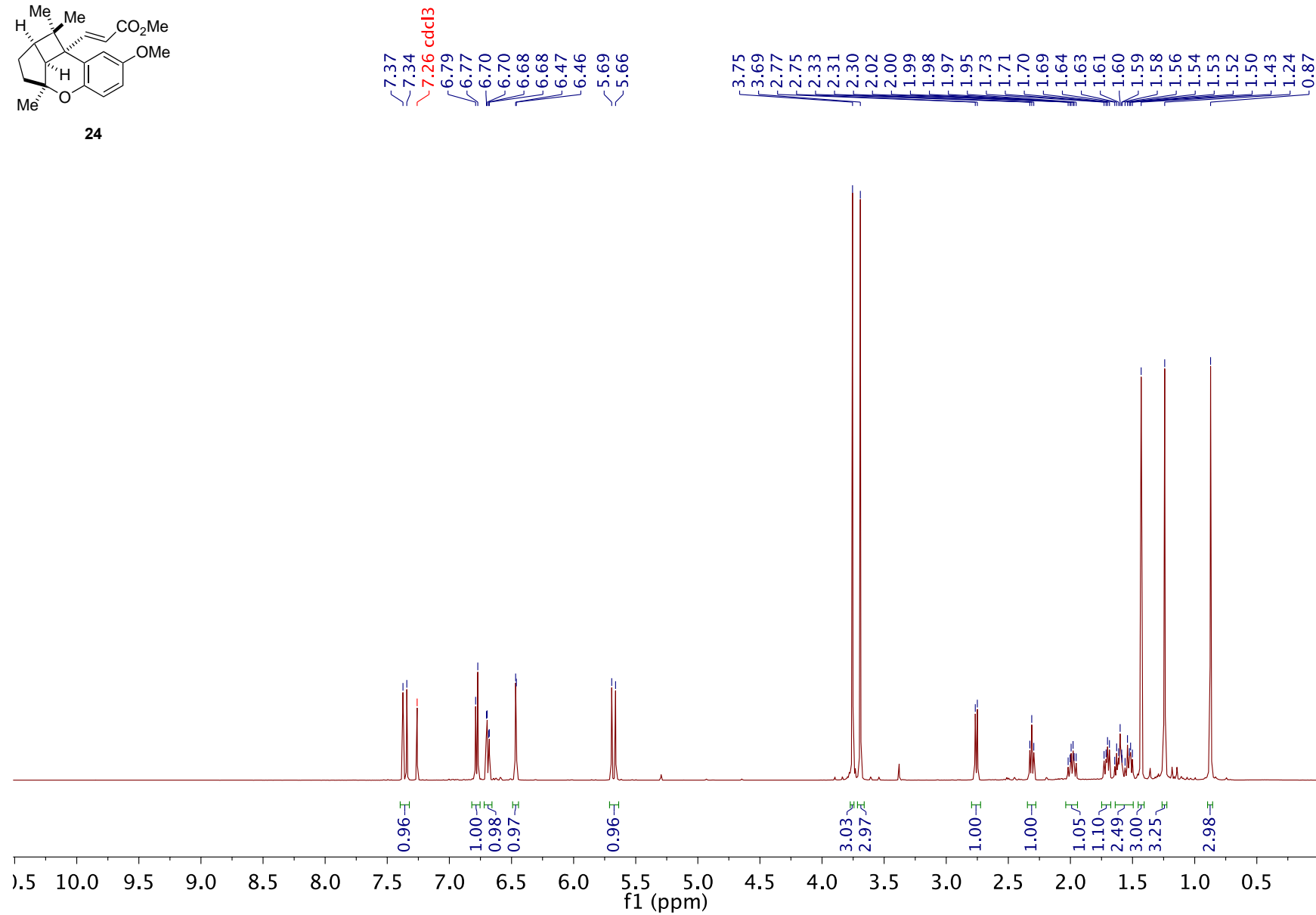


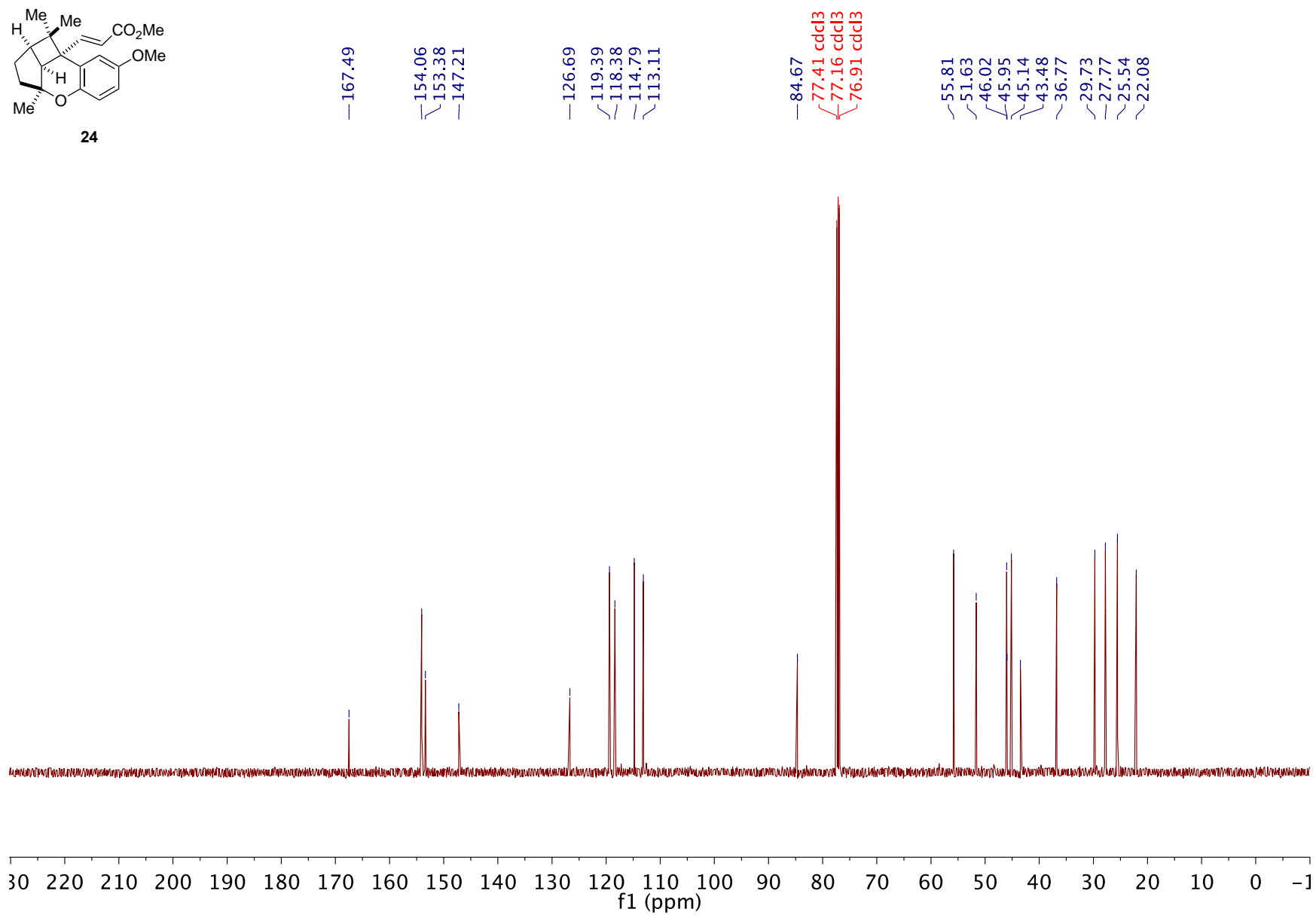
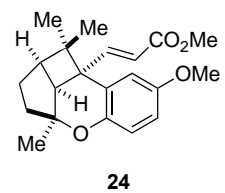


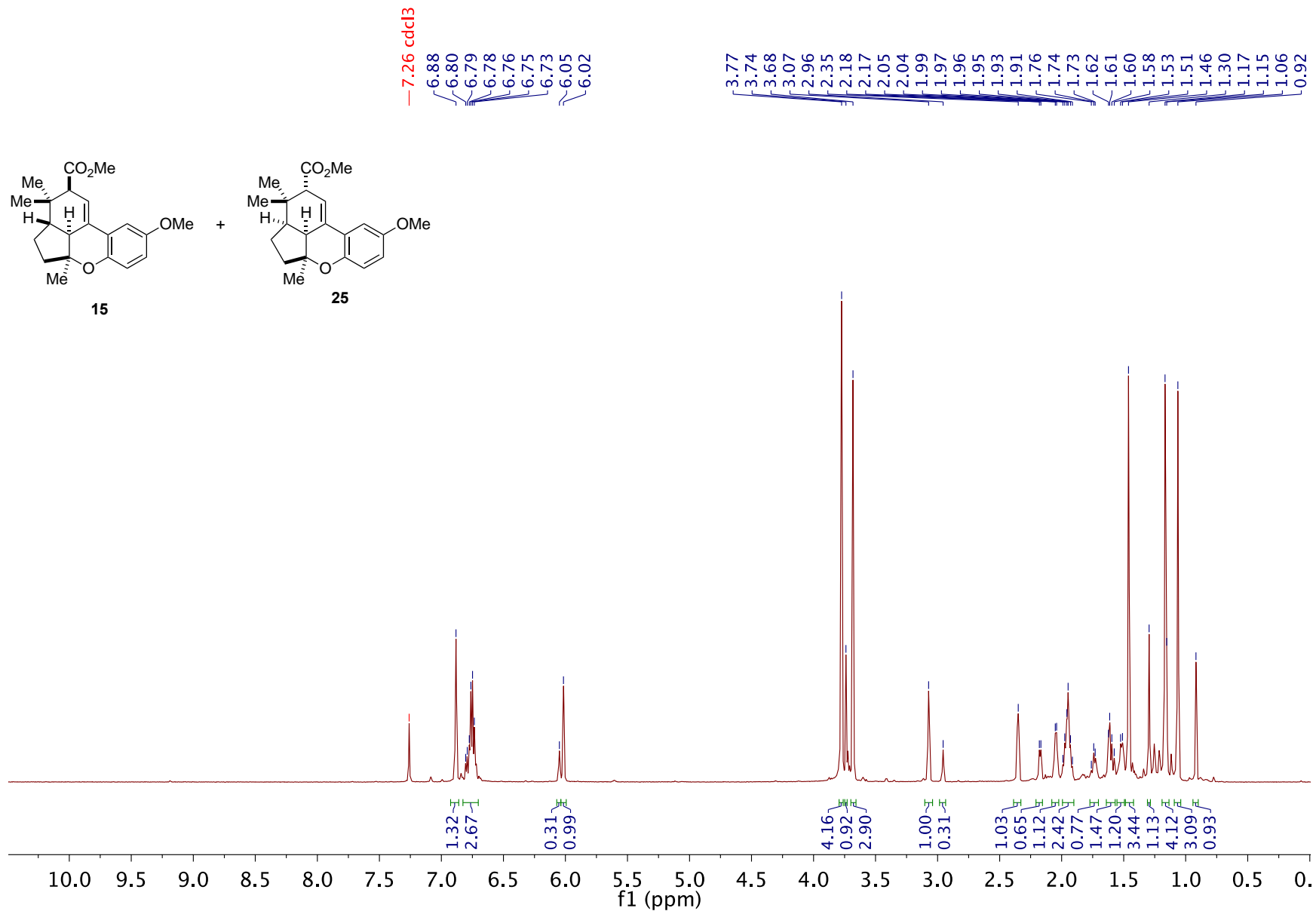


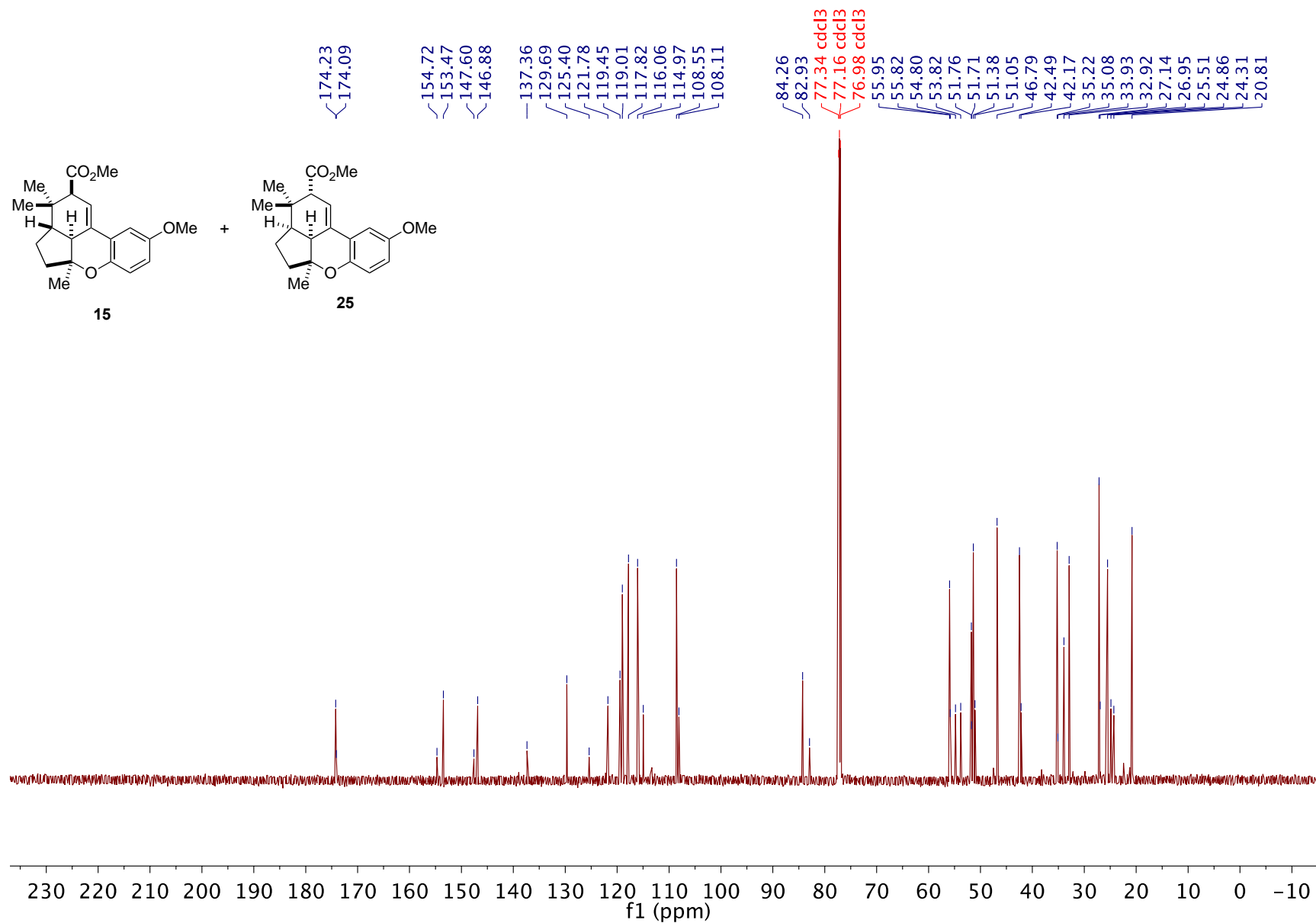


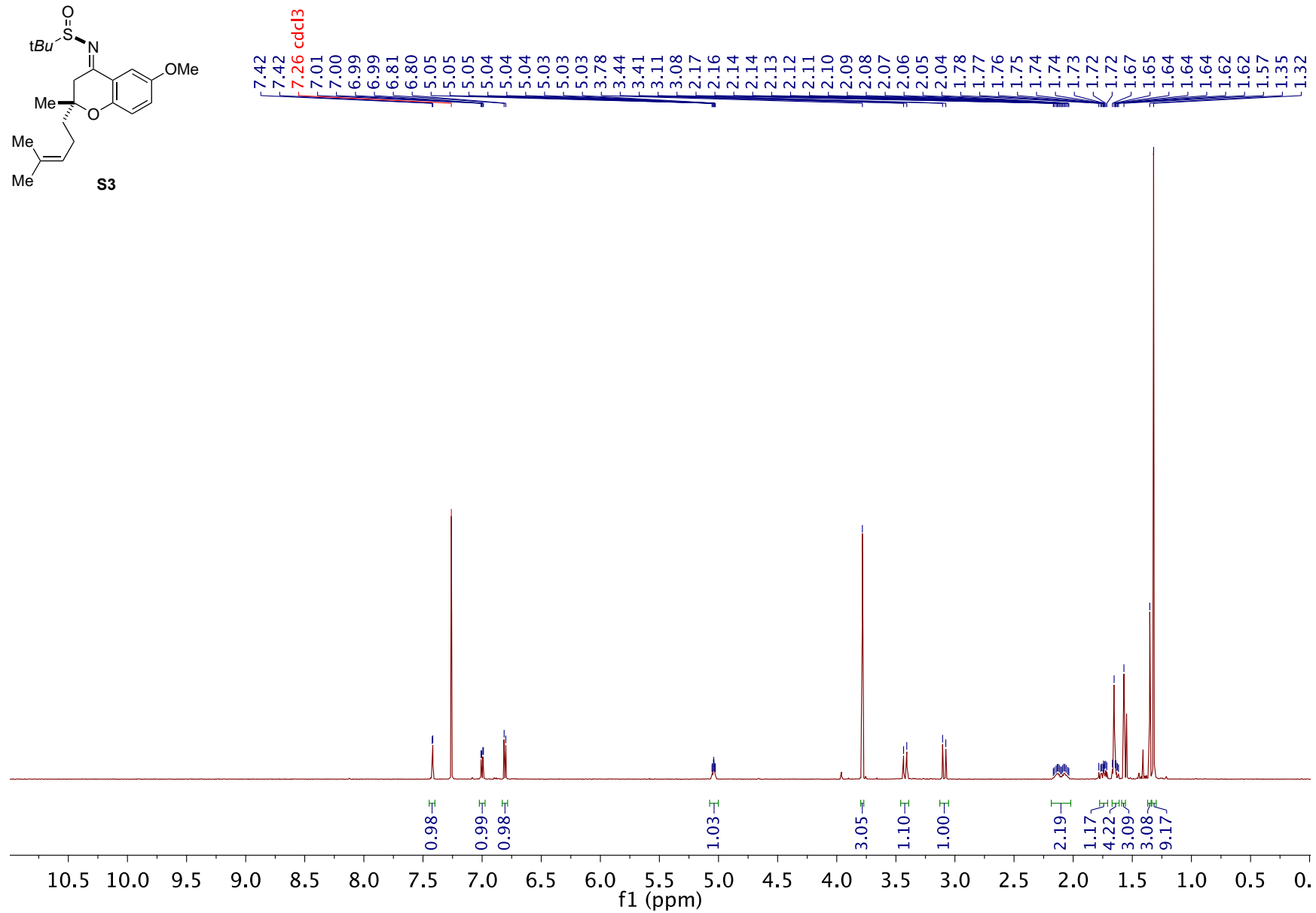
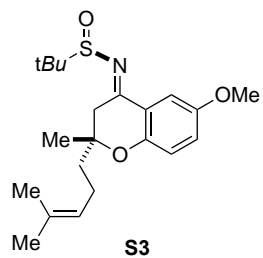
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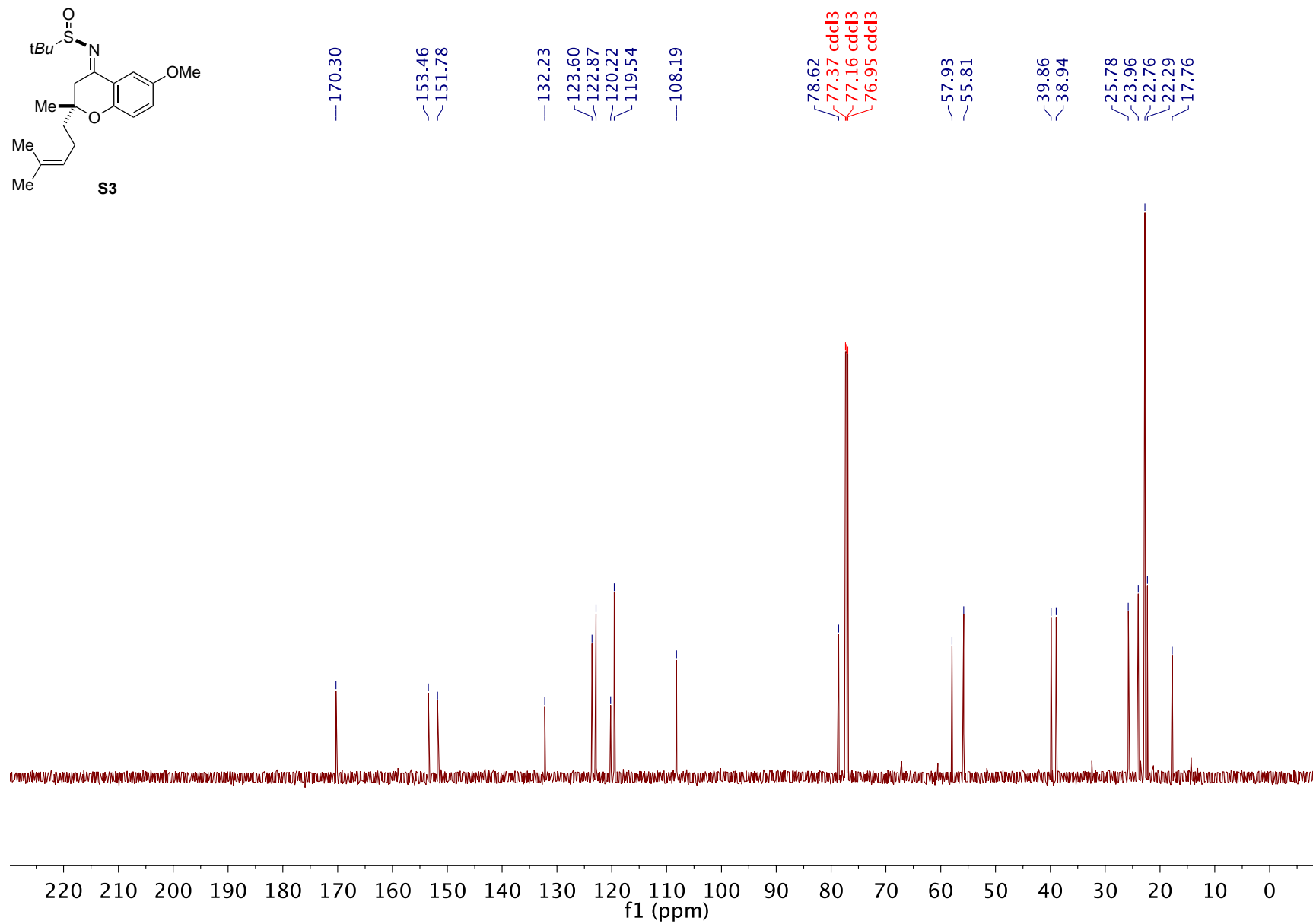
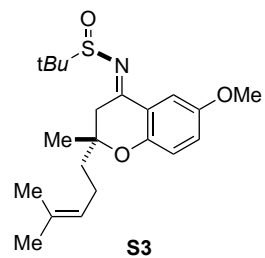


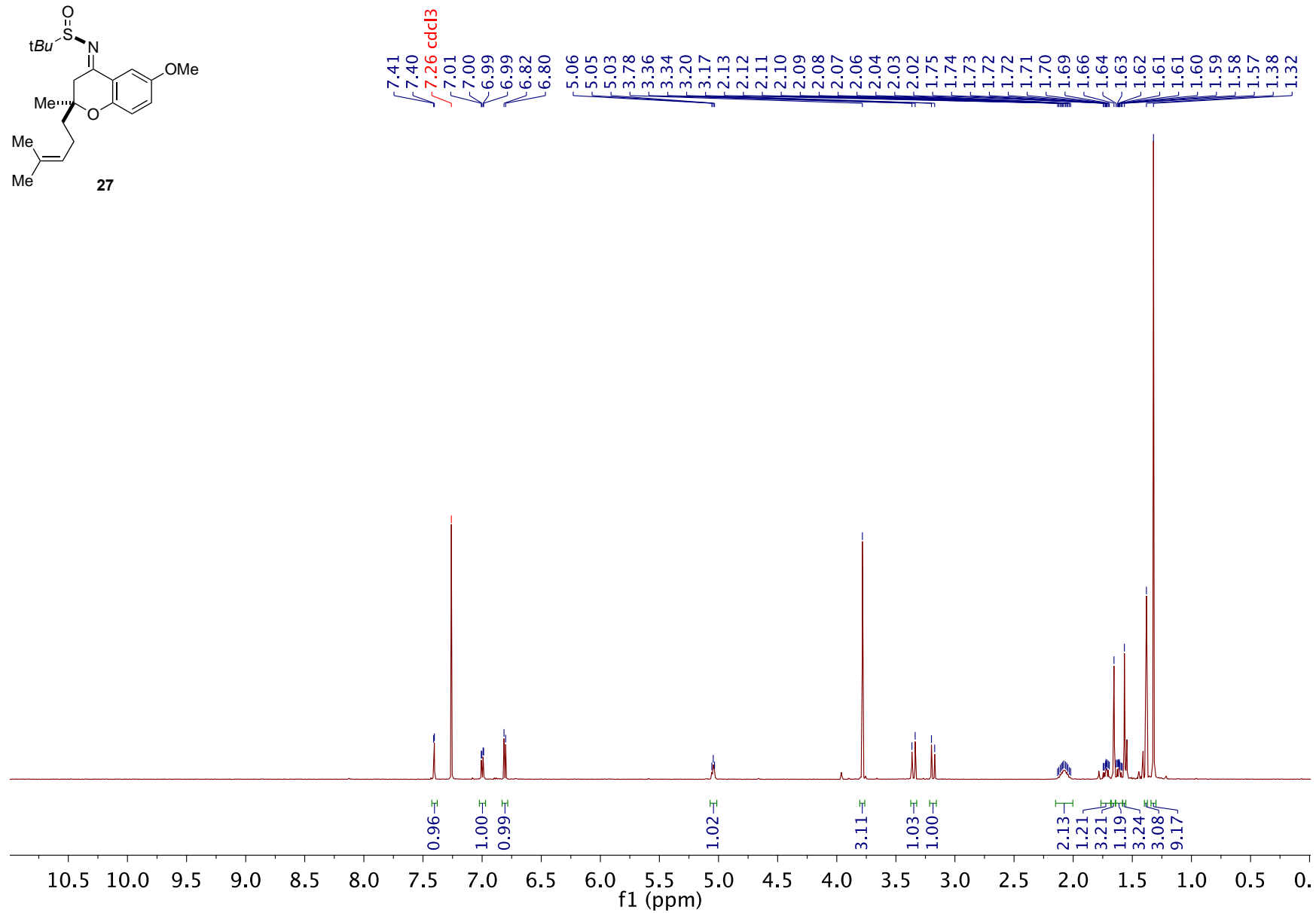
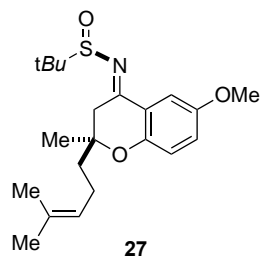




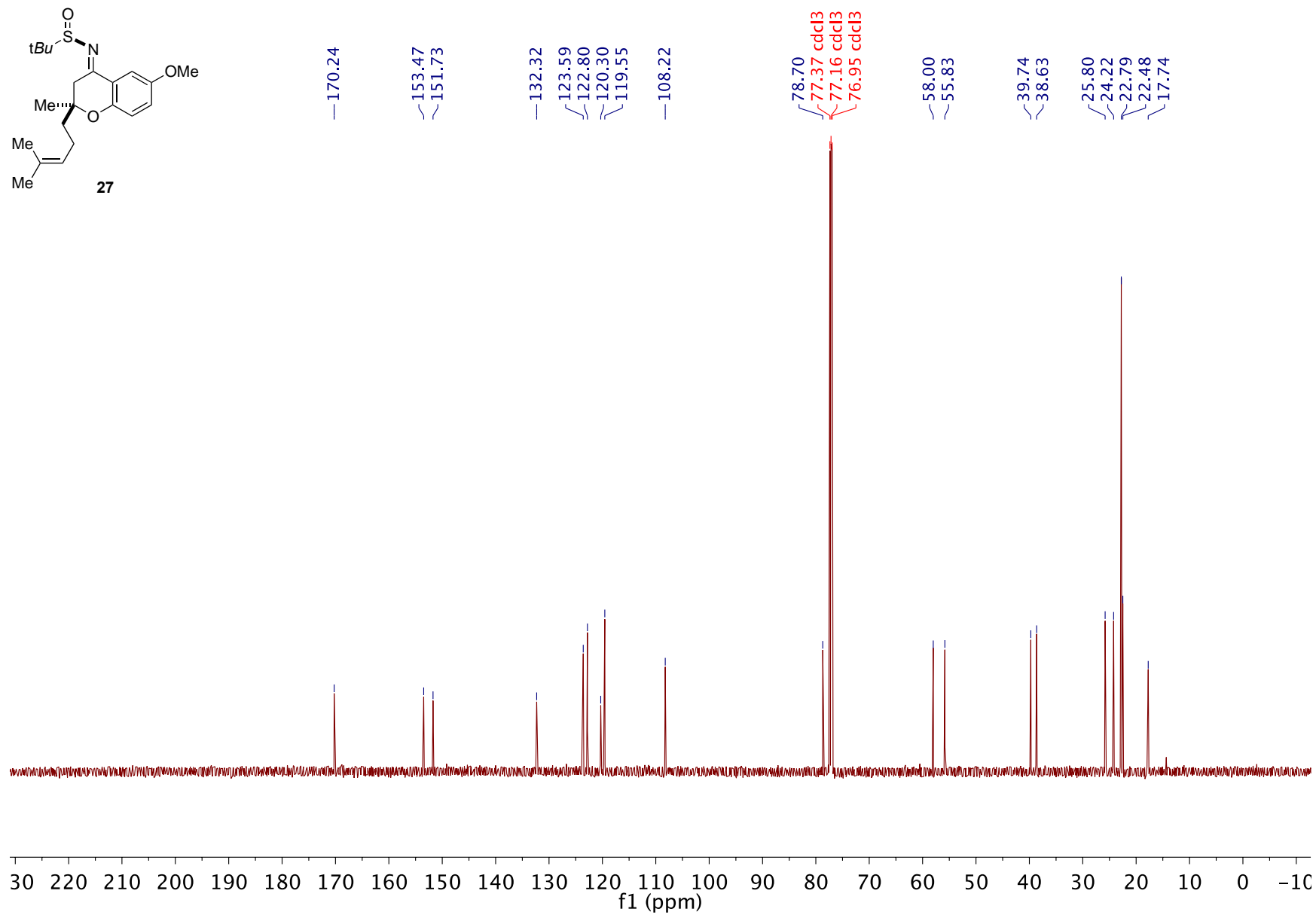


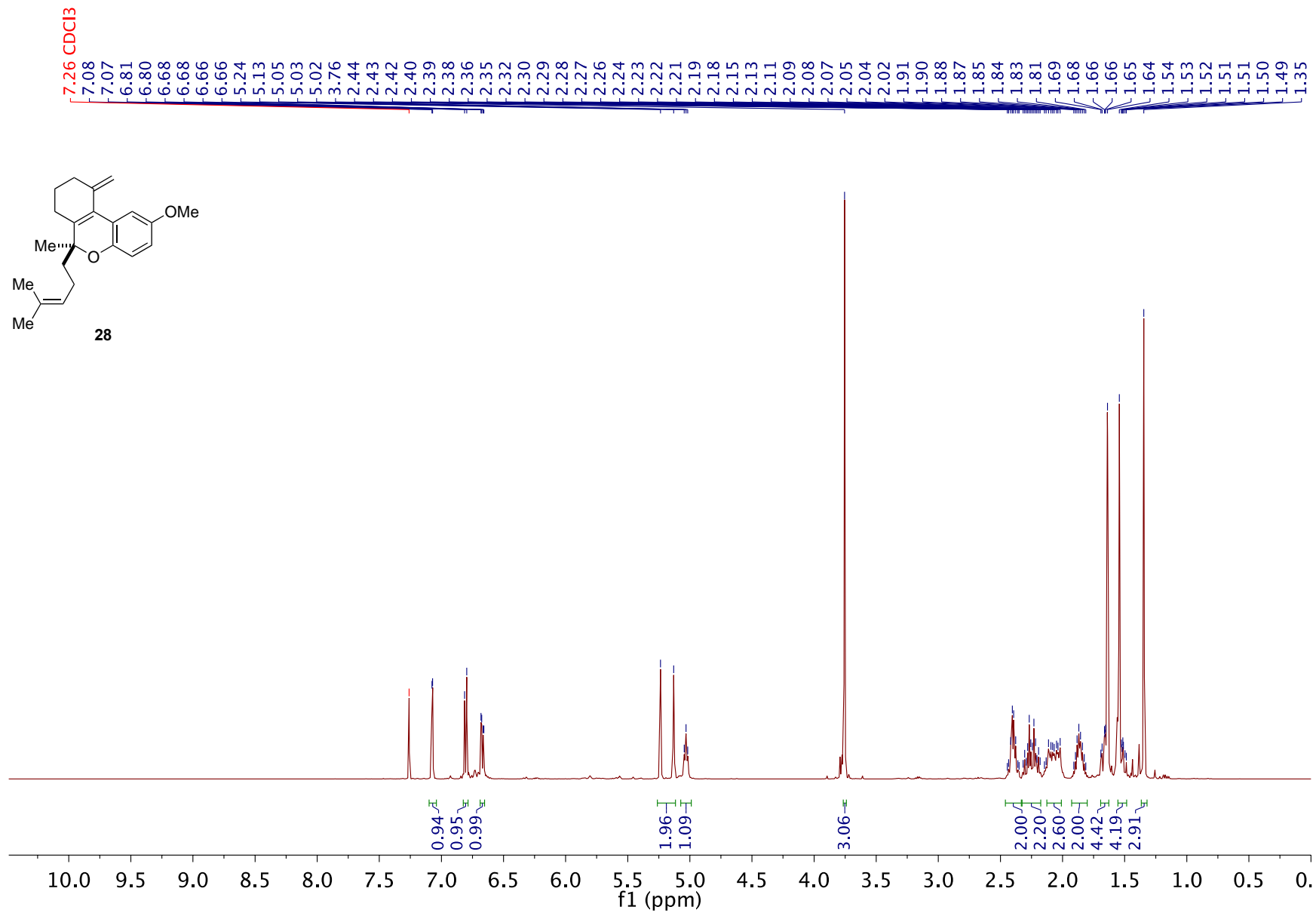


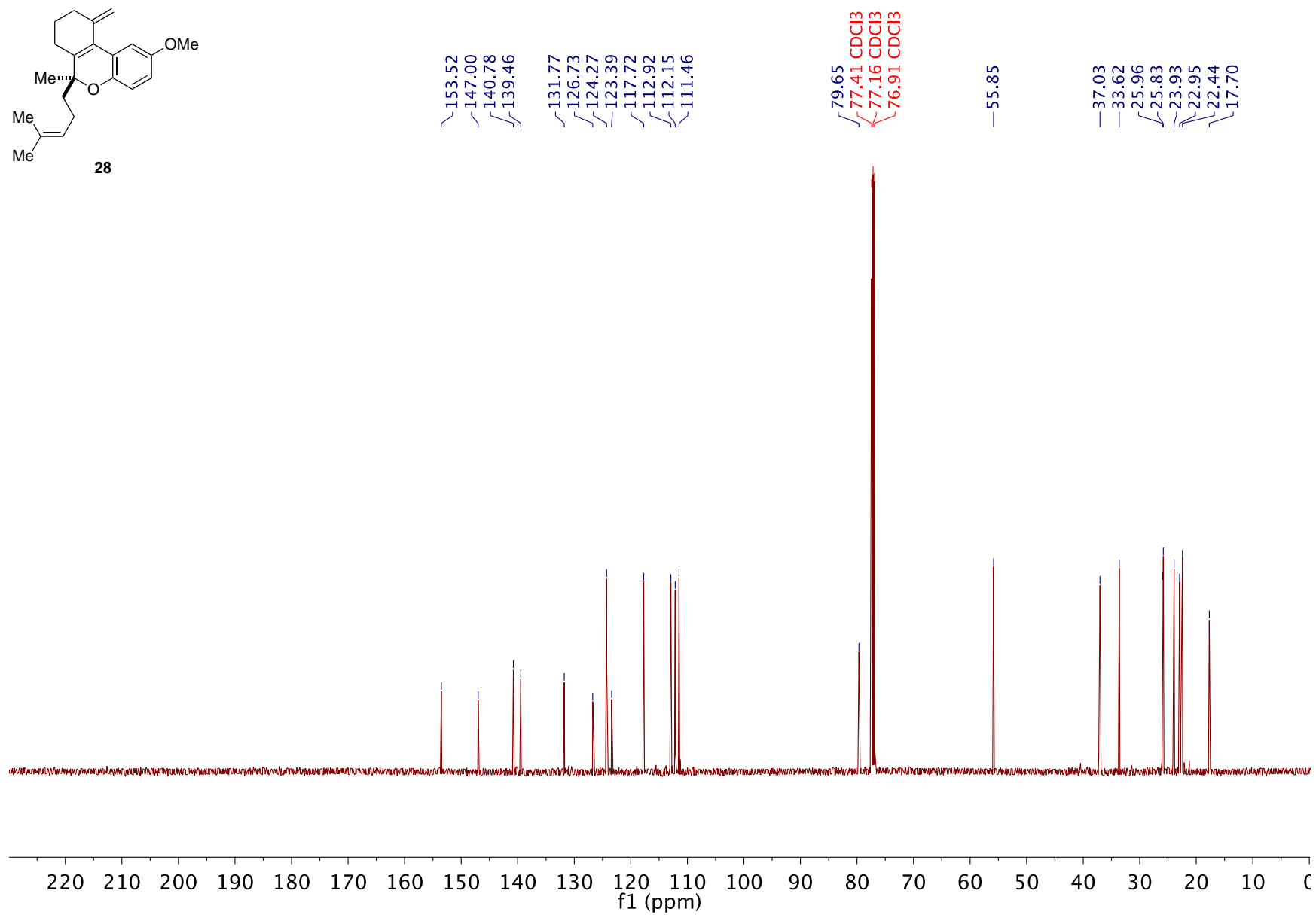
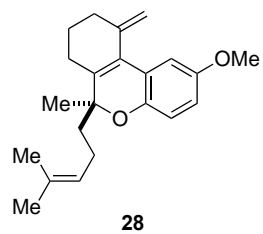


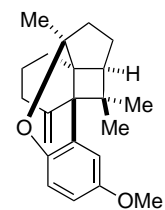












29

