

## Supporting Information

# Site-Selective Functionalization of Unactivated Allylic C-H Bonds via Direct Deprotonation with KTMP: Application to the Formal Total Synthesis of (+)-Artemisinin from Amorphadiene

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**1. General Information:** All reactions were performed under an atmosphere of nitrogen unless otherwise noted. Reaction progress was monitored by TLC and/or HPLC analysis. TLC analysis was performed on Silica Gel 60, aluminum-backed TLC plates. LC/MS analysis was performed on an Agilent 1200/6130 Series LC/MS equipped with a ZORBAX Eclipse XDB-C18 analytical column from Agilent (4.6 x 150 m, 5  $\mu$ m, Part #: 993967-902). Quantitative HPLC analysis was performed on an Agilent 1260 instrument also equipped with a ZORBAX Eclipse XDB-C18 analytical column from Agilent (4.6 x 150 m, 5  $\mu$ m, Part #: 993967-902). Column chromatography was performed using 230-400 Mesh silica gel.  $^1\text{H}$  and  $^{13}\text{C}$  NMR analyses were performed on a Bruker AVIII 500 MHz, or a Bruker AVIII 300 MHz NMR. All peaks reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), qd (quartet of doublets), tq (triplet of quartets), ddd (doublet of doublets of doublets), ddt (doublet of doublets of triplets), ddq (doublet of doublets of quartets). HRMS analysis was performed on a Thermo Scientific Orbitrap Exploris 120 equipped with an ESI ion source or a quadrupole-time of flight (qTOF) mass spectrometer. All reagents were purchased from commercial sources without further purification unless otherwise stated. 2,2,6,6-tetramethylpiperidine (TMP) and *N,N,N',N'*-tetramethylethylene diamine (TMEDA) were distilled from potassium hydroxide prior to use. All solvents used in this study were dried and stored over 3Å molecular sieves. High purity solid potassium tert-butoxide (trace-metals basis, 99.99%) was purchased from Sigma-Aldrich, stored in the desiccator, and used without further purification. The concentration of *n*BuLi solution was determined according to the method of Ghiviriga et al.<sup>1</sup>

## 2. Synthetic procedures:

**a. Method A: Deprotonation of allylic C-H bonds by KTMP in THF:** A flame-dried round bottom flask under nitrogen and equipped with a magnetic stir bar and thermocouple was charged with THF (10.0 mL) and KO*t*Bu solution (1 M in THF, 2.0 mL, 2.0 mmol). The mixture was cooled to -78 °C and *n*BuLi (2.4-2.7 M in hexane, 2.0 mmol) was added dropwise while maintaining internal reaction temperature of < -72 °C. The resulting yellow solution was stirred for 15 minutes at -78 °C. 2,2,6,6-tetramethylpiperidine (TMP, 0.34 mL, 2.0 mmol) was added dropwise while maintaining internal reaction temperature of < -72 °C and then stirred for an additional 15 minutes at -78 °C. The terpene-based substrate (1.0 mmol) was then added via syringe and the reaction was stirred for 1 hour at -78 °C. Triisopropylborate (0.46 mL, 2.0 mmol) was added via syringe and the reaction was allowed to warm to room temperature over 30 minutes. Hydrogen peroxide (30% aqueous, 0.40 mL, 4.0 mmol) was added slowly to maintain the internal temperature < 30 °C (**CAUTION: Exothermic step**). The reaction was stirred for an additional 30 minutes. The reaction is then diluted with water (20 mL) and transferred to a separatory funnel. The organic layer was extracted with 3 portions of MTBE (20 mL), washed twice with HCl (20 mL), and followed by brine (20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation. The crude products were purified by flash silica gel chromatography.

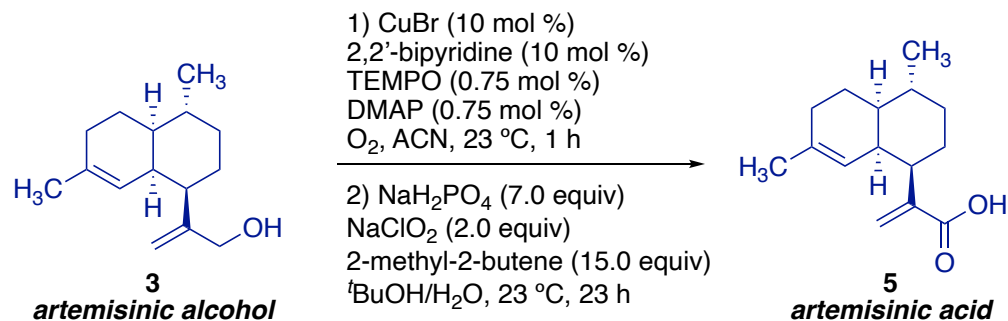
**b. Deprotonation of amorphadiene (AD) with KTMP in heptane:** A flame-dried 10 mL Schlenk flask equipped with a magnetic stir bar was charged with potassium *tert*-butoxide (1.5 mmol). The flask was placed under high vacuum at 120 °C for 30 minutes, then was backfilled with nitrogen. Heptane (5 mL) was added, and the suspension was stirred for 15 minutes. *n*BuLi (2.5 M solution, 0.60 mL, 1.5 mmol) was added dropwise and the mixture was stirred for an

additional 15 minutes. TMP (0.26 mL, 1.5 mmol) was added dropwise, and the mixture was stirred for an additional 15 minutes. Over this time the suspension partially dissolved followed by the formation of a new precipitate. AD (102 mg, 0.50 mmol) was then added via syringe and the reaction was stirred for 24 hours at room temperature (~22-24 °C). The flask was then cooled to 0 °C, triisopropyl borate (0.34 mL, 1.5 mmol) was added, and the reaction was stirred for an additional hour while allowing to warm back to room temperature. Hydrogen peroxide (30% aqueous, 0.16 mL, 1.5 mmol) was added slowly to maintain the internal temperature < 30 °C (**CAUTION: Exothermic step**) and the resulting colorless solution was stirred for 15 minutes. The mixture was diluted with water (10 mL) and extracted with diethyl ether (3x10 mL). The organic layer was concentrated by rotary evaporation to afford the crude artemisinic alcohol **3**. Conversion and yield were determined by <sup>1</sup>H NMR analysis.

**c. Deprotonation of amorphadiene (AD) with alkyllithium and TMEDA:** A flame-dried 10 mL Schlenk flask equipped with a magnetic stir bar under nitrogen was charged with hexanes (0.3 mL) and *N,N,N',N'*-tetramethylethylenediamine (0.18 mmol). The solution was cooled to 0 °C and either a 2.5 M solution of *n*BuLi (0.27 mL, 0.67 mmol) or 1.6 M solution of *sec*-BuLi (0.42 mL, 0.67 mmol) and the mixture was stirred for 15 min, then AD (204 mg, 1.00 mmol) was added. The next day, the reaction was cooled to -40 ° and triisopropylborate (0.25 mmol) was added. After stirring for 1 h, 30% aqueous hydrogen peroxide (0.25 mmol) was added slowly to maintain the internal temperature < 30 °C (**CAUTION: Exothermic step**) and stirred for an additional 15 min. The reaction was then worked up as described for the deprotonation with KTMP in heptane to afford the crude artemisinic alcohol **3**. Conversion and yield were determined by <sup>1</sup>H NMR analysis.

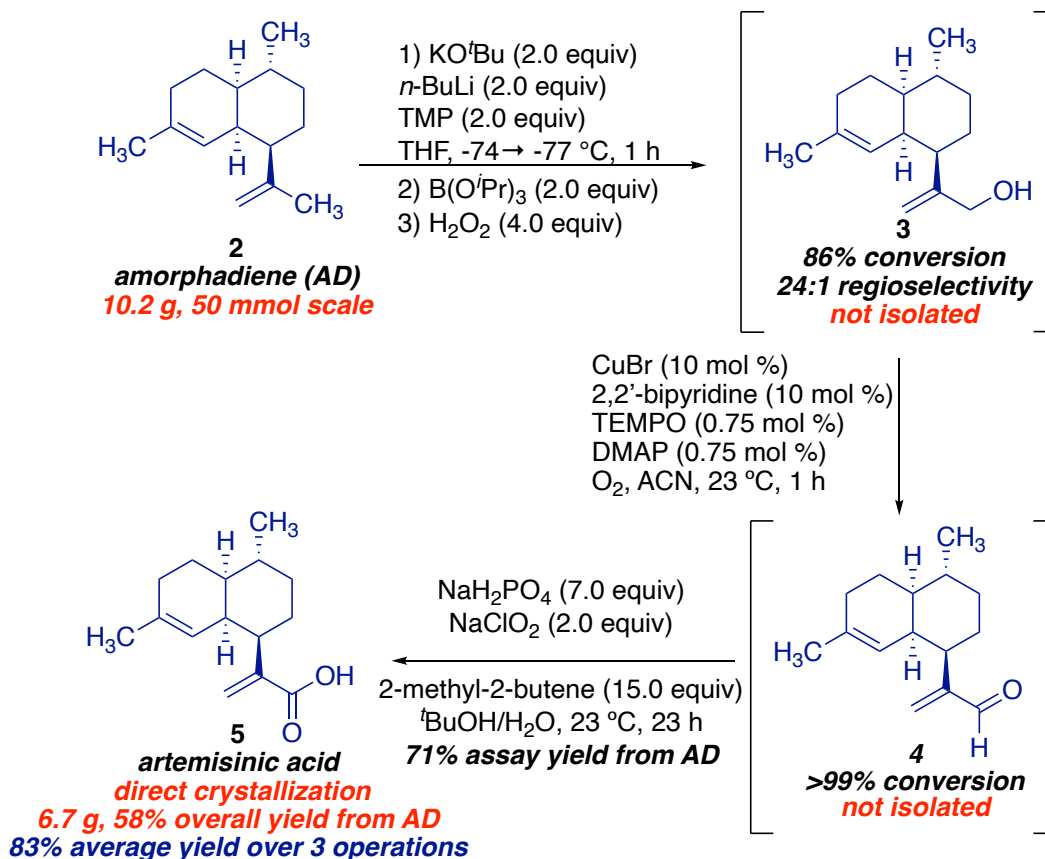
**d. Deprotonation of amorphadiene (AD) with *n*BuLi and KO<sup>t</sup>Bu in hexanes:** A flame-dried flask equipped with a magnetic stir bar was charged with potassium *tert*-butoxide (224 mg, 2.0 mmol). The flask was placed under high vacuum at 120 °C for 30 minutes, then was backfilled with nitrogen. Hexanes (6 mL) was added, and the suspension was stirred for 15 minutes. The solution was cooled to 0 °C and a 2.55 M solution of *n*BuLi (0.78 mL, 2.0 mmol) was added and the mixture was stirred for an additional 15 min. AD (408 mg, 2.00 mmol) was added and the reaction was stirred for 24 hours. After stirring for 1 h, the reaction 30% aqueous hydrogen peroxide (0.25 mmol) was added slowly to maintain the internal temperature < 30 °C (**CAUTION: Exothermic step**) and stirred for an additional 15 min. The reaction was then worked up as described for the deprotonation with KTMP in heptane to afford the crude artemisinic alcohol **3**.

**e. Small-scale oxidation of artemisinic alcohol to artemisinic acid:**



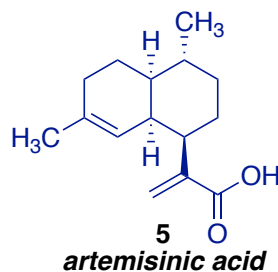
To a round bottom flask equipped with a magnetic stirring bar was added, CuBr (14.6 mg, 10 mol %), 2,2'-bipyridine (15.6 mg, 10 mol %), TEMPO (1.17 mg, 0.75 mol %), and DMAP (1.83 mg, 0.75 mol%). The flask was charged with 7.5 mL of acetonitrile then evacuated and backfilled with oxygen for three cycles and placed under a balloon to maintain oxygen atmosphere. Artemisinic alcohol (220 mg, 1.00 mmol) was added via syringe, and the reaction was stirred until complete conversion to artemisinic aldehyde, observed by HPLC assay, (about 1 hour). At this time, the flask was opened to air, and *t*BuOH (7.5 mL), 2-methyl-2-butene (1.59 mL, 15.0 mmol), and a 0.865 M solution of NaH<sub>2</sub>PO<sub>4</sub> (8.09 mL, 7 mmol) were added sequentially. A 1.28 M solution of NaClO<sub>2</sub> (1.56 mL, 2.00 mmol) was then added dropwise. The reaction was allowed to stir overnight at room temperature open to air, until judged complete by HPLC assay. Upon completion, the reaction was quenched by the addition of Na<sub>2</sub>SO<sub>3</sub> (31.5 mg, 0.25 mmol) and stirred for an additional 5 minutes. The mixture was then diluted with saturated ammonium chloride. The aqueous layer was extracted with MTBE (3x10 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated by rotary evaporation. The crude material then dissolved in acetonitrile (2 mL) and crystallized by the slow addition of water (2 mL). The solids were filtered and washed with additional water (1 mL) to afford the desired artemisinic acid as a white powder in 87% yield (224 mg).

**f. 50 mmol-scale process for the direct conversion of amorphadiene (AD) to artemisinic acid (AA)**



A flame-dried, 3-neck round bottom flask equipped with an addition funnel and thermocouple was placed under a nitrogen atmosphere and charged with 400 mL of THF. A solution of potassium *tert*-butoxide in THF (1 M, 100 mL, 100 mmol) was added and the flask was cooled to -77 °C (internal temperature). A solution of *n*BuLi in hexanes (2.83 M, 35.3 mL, 100 mmol) was added while maintaining an internal temperature of < -74 °C and then allowed to stir for an additional 15 minutes. 2,2,6,6-tetramethylpiperidine (TMP, 14.23 g, 16.9 mL, 100 mmol) was added while maintaining an internal temperature of < -74 °C and the resulting solution was also stirred for an additional 15 minutes. 4,11-amorphadiene (amorphadiene (AD), 10.22 g, 50 mmol) was then added slowly via syringe (no noticeable temperature change during addition) and the reaction was stirred for an hour at -77 °C. After 1-hour, triisopropyl borate (18.18 g, 23.1 mL, 100 mmol) was added slowly and the flask was allowed to warm to room temperature over 30 minutes. The flask was then cooled to 0 °C and a 30% aqueous hydrogen peroxide (20.4 mL, 200 mmol) (**CAUTION: Exothermic step**) was added while maintaining an internal temperature of <15 °C and the reaction was stirred for an additional 30 minutes. After this time, the crude material was then diluted with water (100 mL) and extracted with MTBE in 3 portions (100 mL). The solution was then washed 2 times with 1M HCl (100 mL), dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to yield the crude alcohol **3** (84% conversion by NMR). To a round bottom flask was added CuBr (731.9 mg, 10 mol %), 2,2'-bipyridine (781.0 mg, 10 mol %), TEMPO (58.59 mg, 0.75 mol %), and DMAP (91.63 mg, 0.75 mol%) along with a magnetic stir bar (all charges made based on starting 50 mmol of AD). The flask was then charged with acetonitrile (375 mL) and then evacuated and backfilled with oxygen for three cycles and ultimately placed under a balloon to maintain oxygen atmosphere. The crude alcohol **3** was added via syringe, and the reaction was stirred under oxygen atmosphere until complete conversion to artemisinic aldehyde **4** was observed by HPLC assay. At this time, the flask was opened to the air followed by the addition of *t*BuOH (375 mL), 2-methyl-2-butene (79.5 mL, 15.0 equiv.), and a 0.865 M solution of NaH<sub>2</sub>PO<sub>4</sub> (404.6 mL, 7.0 equiv.) added sequentially. A 1.28 M solution of NaClO<sub>2</sub> (78.13 mL, 2.0 equiv.) was then added dropwise. The reaction was allowed to stir overnight at room temperature open to air, until judged complete by quantitative HPLC analysis. Upon completion, the reaction was quenched by the addition of Na<sub>2</sub>SO<sub>3</sub> (1.576 g, 0.25 eq.) and stirred for an additional 5 minutes. The mixture was then diluted with saturated ammonium chloride. The aqueous layer was extracted with MTBE (3 x 200 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated by rotary evaporation. The crude material then dissolved in acetonitrile (70 mL) and crystallized by the slow addition of water (70 mL). The solids were filtered and washed with additional water (22 mL) to afford the desired artemisinic acid **5** as white powder in 58% yield (6.74 g) from the starting amorphadiene.

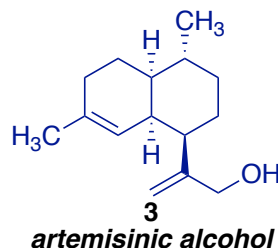
## Artemisinic Acid (5)<sup>2</sup>



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.17 (s, 1H), 6.47 (s, 1H), 5.58 (s, 1H), 5.01 (s, 1H), 2.72 (dt, *J* = 12.3, 3.8 Hz, 1H), 2.63 (s, 1H), 2.01 – 1.84 (m, 2H), 1.84 – 1.70 (m, 2H), 1.62 (s, 3H), 1.60 – 1.53 (m, 1H), 1.50 – 1.33 (m, 4H), 1.09 (qd, *J* = 12.3, 4.1 Hz, 1H), 0.92 (d, *J* = 5.8 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 171.8, 142.5, 135.0, 126.6, 120.1, 42.1, 41.4, 37.9, 35.2, 27.6, 26.4, 25.9, 25.6, 23.7, 19.8. HRMS (ESI-Orbitrap, negative mode) *m/z*: [M-H]<sup>-</sup> Calcd for [C<sub>15</sub>H<sub>21</sub>O<sub>2</sub>]<sup>-</sup> 233.1536; Found 233.1545. Compound was isolated as a white crystalline powder.

### 3. Characterization data on artemisinin related products:

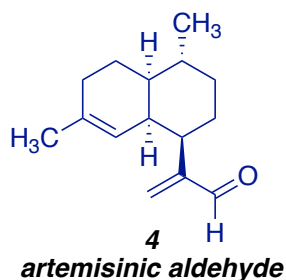
#### Artemisinic Alcohol (3)<sup>3</sup>



General procedure A was followed for this substrate. The crude product was purified by flash silica gel chromatography (10-30% EtOAc/hexanes) to afford the artemisinic alcohol in 81% yield (178 mg) isolated as a clear oil. NMR data matched what has been previously reported.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.22 (p, *J* = 1.4 Hz, 1H), 5.08 (h, *J* = 1.5 Hz, 1H), 4.87 (p, *J* = 1.4 Hz, 1H), 4.21 – 4.09 (m, 2H), 2.56 – 2.44 (m, 1H), 2.24 (d, *J* = 12.2 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.83 – 1.76 (m, 1H), 1.72 (dq, *J* = 12.9, 3.5 Hz, 1H), 1.62 (s, 3H), 1.61 – 1.31 (m, 6H), 1.03 (dtd, *J* = 13.0, 11.6, 3.5 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 151.1, 135.1, 120.5, 109.9, 65.7, 43.5, 41.7, 37.8, 35.3, 27.8, 26.4, 25.8, 25.7, 23.7, 19.8. HRMS (ESI-Orbitrap, positive mode) *m/z*: [M+H]<sup>+</sup> Calcd for [C<sub>15</sub>H<sub>25</sub>O]<sup>+</sup> 221.1900; Found: 221.1896.

### Artemisinic Aldehyde (**4**)<sup>3</sup>

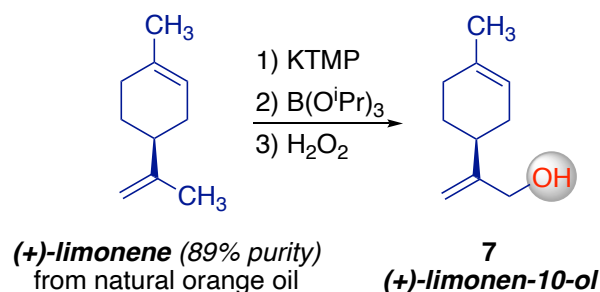


To a round bottom flask, CuBr (36.6 mg, 10 mol %), 2,2'-bipyridine (39.0 mg, 10 mol %), TEMPO (2.9 mg, 0.75 mol %), and DMAP (4.6 mg, 0.75 mol%) were added along with a magnetic stir bar. The flask was then charged with acetonitrile (12 mL), evacuated, and backfilled with oxygen for three cycles and ultimately placed under an oxygen balloon to maintain an oxygen atmosphere. The alcohol **3** (551.0 mg, 2.5 mmol) was added via syringe, and the reaction was stirred under oxygen atmosphere until complete conversion to artemisinic aldehyde **4** was observed by HPLC assay (~1 hour). The subsequent material was purified by column chromatography to afford a 69% yield (374.4 mg). The compound was isolated as a clear crystalline solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.55 (s, 1H), 6.20 (s, 1H), 6.15 (s, 1H), 4.91 (s, 1H), 2.73 (dd, *J* = 12.3, 3.9 Hz, 1H), 2.55 (s, 1H), 1.98 – 1.85 (m, 2H), 1.82 – 1.70 (m, 2H), 1.60 (s, 3H), 1.59 – 1.53 (m, 1H), 1.52 – 1.35 (m, 4H), 1.10 (qd, *J* = 12.2, 3.9 Hz, 1H), 0.92 (d, *J* = 6.1 Hz, 3H).  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.7, 152.5, 135.2, 134.7, 120.1, 41.3, 39.6, 37.4, 35.2, 27.6, 26.4, 25.5, 25.4, 23.7, 19.8. HRMS (ESI-Orbitrap, positive mode) *m/z*: [M+H]<sup>+</sup> Calcd for [C<sub>15</sub>H<sub>23</sub>O]<sup>+</sup> 219.1743; Found: 219.1744.

### 4. Site-selective functionalization of terpene-based natural products.

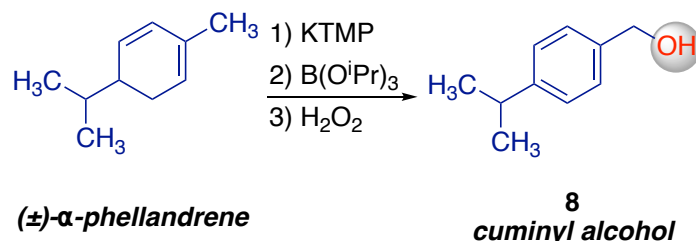
#### (+)-limonen-10-ol (**7**)<sup>4</sup>



General procedure A was followed for this substrate using 136 mg of orange oil (89 wt% limonene, 121 mg, 0.89 mmol). The crude product was purified by flash silica gel chromatography (10-30% EtOAc/hexanes) to afford (+)-limonen-10-ol in 77% yield (104 mg). NMR data matched what has been reported previously. Compound isolated as a yellow oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.45 – 5.35 (m, 1H), 5.09 – 5.01 (m, 1H), 4.97 – 4.86 (m, 1H), 4.14 (s, 2H), 2.23 – 2.11 (m, 2H), 2.11 – 2.02 (m, 1H), 2.01 – 1.88 (m, 2H), 1.87 – 1.77 (m, 2H), 1.66 (s, 3H), 1.52 (dtd,  $J = 12.8, 11.3, 5.6$  Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  153.7, 133.8, 120.4, 107.9, 65.2, 36.9, 31.4, 30.5, 28.2, 23.5.

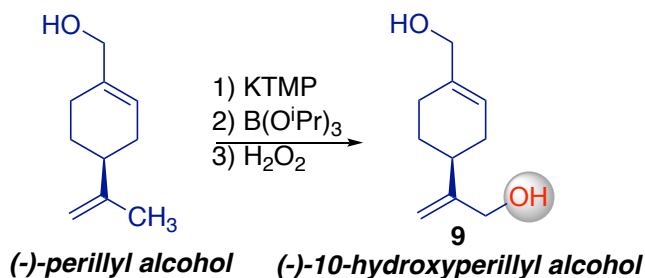
### Cuminyln alcohol (8)



General procedure A was followed for this substrate. The crude product was purified by flash silica gel chromatography (10-30% EtOAc/hexanes) to afford the aromatized cuminyln alcohol in 48% yield (73 mg). NMR data matched an authentic commercial sample. Compound isolated as a clear oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J = 7.8$  Hz, 2H), 7.26 (d,  $J = 7.8$  Hz, 2H), 4.69 (d,  $J = 5.3$  Hz, 2H), 2.94 (hept,  $J = 7.0$  Hz, 1H), 1.64 – 1.55 (m, 1H), 1.28 (d,  $J = 6.9$  Hz, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  148.5, 138.3, 127.2, 126.7, 65.3, 33.9, 24.0 (2  $\text{CH}_3$ 's).

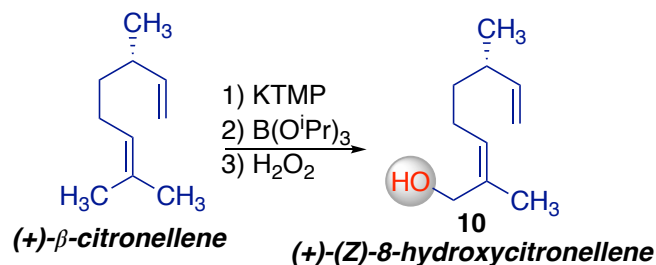
### (-)-10-hydroxyperillyl alcohol (9)<sup>5</sup>



General procedure A was followed using 2.5 equiv. each of  $n\text{BuLi}$ ,  $\text{KO}^t\text{Bu}$ ,  $\text{TMP}$ , and  $\text{B}(\text{O}^i\text{Pr})_3$  and increasing to 5 equiv. of  $\text{H}_2\text{O}_2$ . The crude product was purified by flash silica gel chromatography (10-30% EtOAc/hexanes) to afford (-)-10-hydroxyperillyl alcohol in 70% average yield (**experiment #1**: 74%, 125 mg, **experiment #2**: 65%, 109 mg). NMR data matched what has been reported previously. Compound isolated as an off yellow oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.76 – 5.67 (m, 1H), 5.13 – 5.04 (m, 1H), 4.97 – 4.90 (m, 1H), 4.17 (s, 2H), 4.07 – 3.96 (m, 2H), 2.31 – 2.20 (m, 2H), 2.18 – 2.09 (m, 2H), 2.05 – 1.96 (m, 1H), 1.96 – 1.89 (m, 1H), 1.70 (s, 1H), 1.61 – 1.50 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 137.3, 122.2, 108.2, 67.2, 65.2, 36.9, 30.9, 27.8, 26.1. HRMS (ESI-Orbitrap, positive mode)  $m/z$ :  $[\text{M}+\text{Na}^+]^+$  Calcd for  $[\text{C}_{10}\text{H}_{16}\text{O}_2\text{Na}]^+$  191.1043; Found: 191.1038.

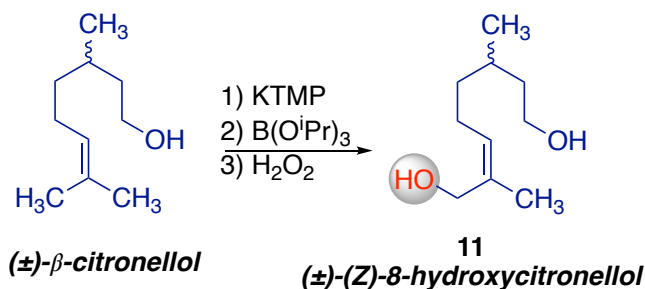
**(+)-(Z)-8-hydroxycitronellene (10)**



General procedure A was followed for this substrate. The crude product was purified by flash silica gel chromatography (0 to 20% EtOAc/hexanes) to afford (+)-(Z)-8-hydroxycitronellene in 61% yield (94 mg) and 86:14 *Z:E* stereoselectivity. Compound isolated as a clear oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.70 (ddd, *J* = 17.7, 10.2, 7.7 Hz, 1H), 5.30 (t, *J* = 7.4 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.14 (s, 2H), 2.14 (p, *J* = 6.9 Hz, 1H), 2.09 – 2.01 (m, 2H), 1.84 – 1.77 (m, 3H), 1.39 – 1.32 (m, 2H), 1.17 (s, 1H), 1.01 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 144.5, 134.2, 128.6, 112.8, 61.7, 37.4, 36.8, 25.3, 21.3, 20.3. HRMS (ESI-Orbitrap, positive mode) *m/z*: [M+H]<sup>+</sup> Calcd for [C<sub>10</sub>H<sub>19</sub>O]<sup>+</sup> 155.1430; Found: 155.1428.

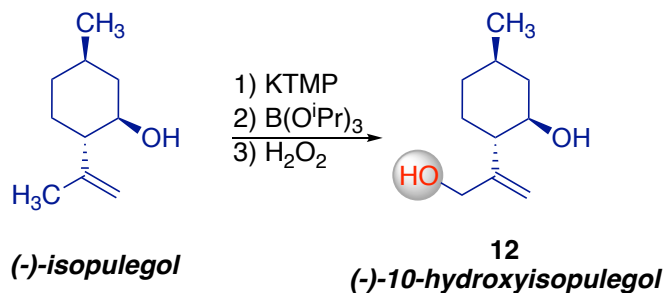
**(±)-(Z)-8-hydroxycitronellol (11)<sup>6</sup>**



General procedure A was followed using 3 equiv. each of *n*BuLi, KO<sup>*t*</sup>Bu, TMP, and B(O<sup>*i*</sup>Pr)<sub>3</sub> and increasing to 6 equiv. of H<sub>2</sub>O<sub>2</sub>. The crude product was purified by flash silica gel chromatography (17-80% EtOAc/hexanes) to afford (±)-(Z)-8-hydroxycitronellol in 91% yield (84:16 *Z:E* 156 mg). NMR data matched what has been reported previously. Compound isolated as a clear oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.29 (t, *J* = 7.4 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 4.08 (d, *J* = 11.8 Hz, 1H), 3.78 – 3.63 (m, 2H), 2.18 (dq, *J* = 15.4, 7.8 Hz, 1H), 2.04 (dq, 1H), 1.72 – 1.56 (m, 3H), 1.55 – 1.44 (m, 1H), 1.41 – 1.31 (m, 2H), 1.26 (ddt, *J* = 13.5, 8.6, 6.8 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 134.4, 128.6, 61.5, 60.9, 39.2, 37.1, 28.5, 24.9, 21.3, 19.7.

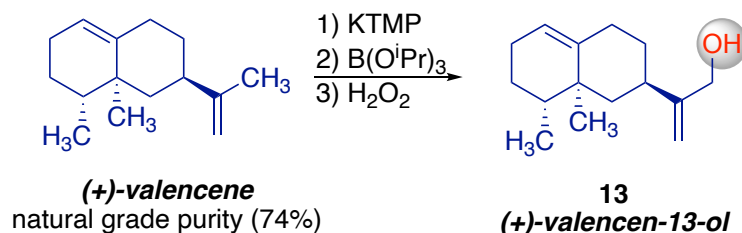
**(-)-10-hydroxyisopulegol (12)<sup>7,8</sup>**



General procedure A was followed using 2.5 equiv. each of *n*BuLi, KO*t*Bu, TMP, and B(O<sup>*i*</sup>Pr)<sub>3</sub> and increasing to 5 equiv. of H<sub>2</sub>O<sub>2</sub>. The crude product was purified by flash silica gel chromatography (20-100% EtOAc/hexanes) to afford (-)-10-hydroxyisopulegol in 93% yield (159 mg). NMR data matched what has been reported previously. Compound isolated as a white powder.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.29 – 5.17 (m, 1H), 5.07 (s, 1H), 4.14 (q, *J* = 12.9 Hz, 2H), 3.57 (td, *J* = 10.5, 4.2 Hz, 1H), 2.37 – 2.14 (m, 2H), 2.04 (dtd, *J* = 12.3, 3.9, 1.9 Hz, 1H), 1.97 (ddd, *J* = 13.1, 10.0, 3.6 Hz, 1H), 1.80 – 1.65 (m, 2H), 1.60 – 1.49 (m, 1H), 1.37 (qd, *J* = 12.9, 3.4 Hz, 1H), 1.04 (q, 1H), 1.00 – 0.89 (m, 4H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 150.8, 112.5, 73.2, 65.8, 50.1, 43.5, 34.5, 31.5, 31.3, 22.2. HRMS (ESI-Orbitrap, positive mode) *m/z*: [M+Na]<sup>+</sup> Calcd for [C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>Na]<sup>+</sup> 193.1199; Found: 193.1194.

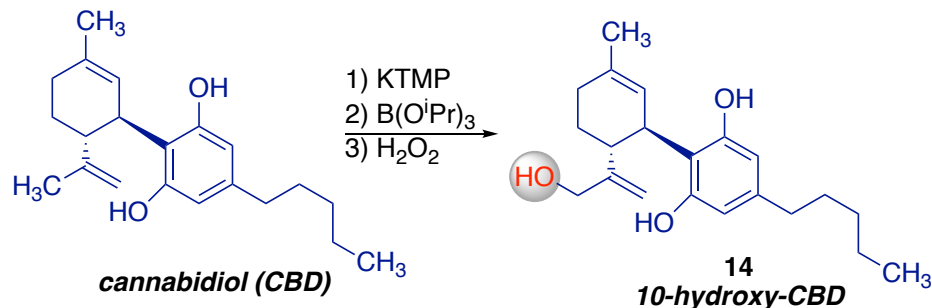
**Valencene-13-ol (13)<sup>9</sup>**



General procedure A was followed using 204 mg of natural grade valencene (74 wt% valencene, 151 mg, 0.74 mmol). The crude product was purified by flash silica gel chromatography (0 to 20% EtOAc/hexanes) to afford (+)-valencen-13-ol as a clear oil in 77% yield (126 mg). NMR data matched what has been reported previously.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.39 – 5.31 (m, 1H), 5.06 – 5.02 (m, 1H), 4.92 – 4.88 (m, 1H), 4.15 (m, 2H), 2.33 (tq, *J* = 11.9, 2.7 Hz, 2H), 2.12 (ddd, *J* = 14.1, 4.1, 2.5 Hz, 1H), 2.08 – 2.01 (m, 1H), 2.00 – 1.88 (m, 2H), 1.84 (ddq, *J* = 12.8, 5.1, 2.7 Hz, 1H), 1.66 – 1.53 (m, 1H), 1.49 – 1.40 (m, 3H), 1.35 (t, *J* = 6.2 Hz, 1H), 1.24 (dtd, *J* = 13.8, 12.3, 4.1 Hz, 1H), 1.02 (t, *J* = 12.8 Hz, 1H), 0.98 (s, 2H), 0.91 – 0.88 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 154.1, 142.8, 120.4, 107.9, 65.3, 45.5, 40.9, 38.0, 36.7, 33.6, 32.7, 27.1, 25.9, 18.4, 15.7.

## 10-hydroxycannabidiol (14)<sup>10</sup>

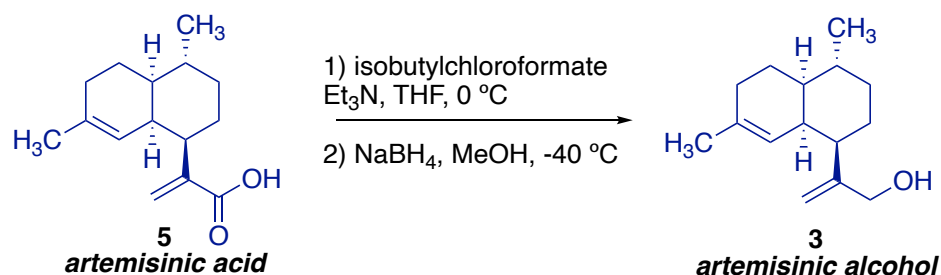


General procedure A was followed using 4 equiv. each of *n*BuLi, KO<sup>t</sup>Bu, TMP, and B(O<sup>i</sup>Pr)<sub>3</sub> and increasing to 8 equiv. of H<sub>2</sub>O<sub>2</sub>. The crude product was purified by flash silica gel chromatography (10-100% EtOAc/hexanes) to afford 10-hydroxy-cannabidiol in 52% yield (172 mg) isolated as a clear oil. <sup>1</sup>H NMR data matched what has been reported previously but <sup>13</sup>C NMR has not been published to the best of our knowledge.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.71 (s, 1H), 6.31 (s, 1H), 6.23 (s, 1H), 5.96 (s, 1H), 5.65 – 5.55 (m, 1H), 4.97 – 4.89 (m, 1H), 4.69 – 4.59 (m, 1H), 4.31 (d, *J* = 12.2 Hz, 1H), 2.69 (s, 1H), 2.54 (td, *J* = 11.3, 3.3 Hz, 1H), 2.50 – 2.40 (m, 2H), 2.34 – 2.22 (m, 1H), 2.18 – 2.11 (m, 1H), 2.05 – 1.86 (m, 2H), 1.82 (s, 3H), 1.69 (s, 1H), 1.58 (p, *J* = 7.5 Hz, 2H), 1.38 – 1.25 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 156.0, 154.0, 148.6, 143.3, 140.1, 124.0, 115.6, 113.3, 109.6, 108.7, 65.0, 44.5, 38.1, 35.5, 31.5, 30.7, 30.3, 27.4, 23.7, 22.6, 14.1. HRMS (ESI-Orbitrap, positive mode) *m/z*: [M+H<sup>+</sup>]<sup>+</sup> Calcd for [C<sub>21</sub>H<sub>31</sub>O<sub>3</sub>]<sup>+</sup> 331.2268; Found: 331.2262

## 5. Modified synthesis of amorphadiene

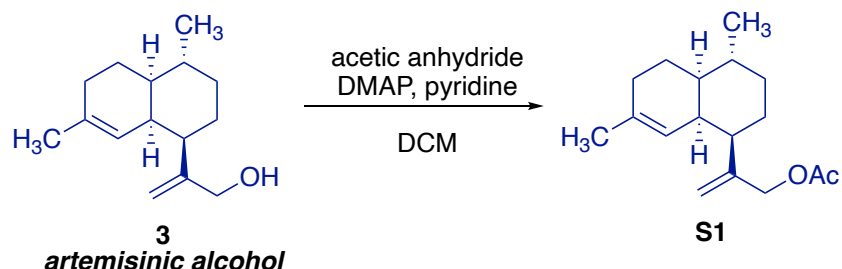
### Artemisinic alcohol (3) from artemisinic acid (5).



Isobutyl chloroformate (3.47 g, 3.29 mL, 25.38 mmol) was added to a chilled (0 °C) solution of Artemisinic acid **5** (5.0 g, 21.15 mmol) in THF (90 mL). After stirring 5 min, TEA (3.21 g, 4.42 mL, 31.73 mmol) was added dropwise and the mixture stirred for 1 h, before filtering through Celite. The mixed anhydride solution was added in one portion to pre-cooled MeOH (90 mL) at -40 °C, and the mixture was stirred for 5 min before adding NaBH<sub>4</sub> (3.2 g, 84.6 mmol) in one portion. The reaction mixture was then allowed to warm to room temperature and monitored for reaction completion (TLC: 10% EtOAc in hexanes + 2% TEA), before quenching with aqueous NH<sub>4</sub>Cl (5% (w/w), 150 mL), and the mixture was then extracted with EtOAc (3 x 150 mL). The organic layers were separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to

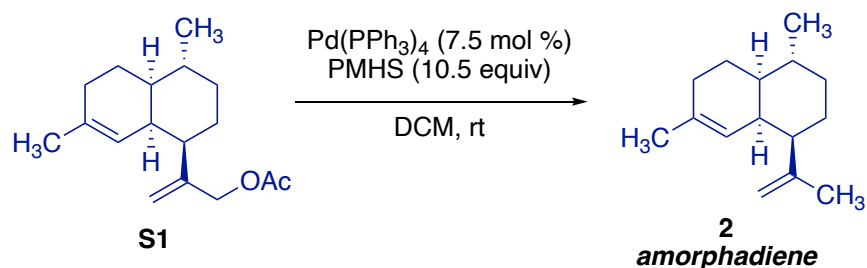
recover 6.7 g crude **2**, which was subsequently purified by chromatography (column: 40 g silica gel; eluent: gradient EtOAc 0 →25% in hexane) to isolate 3.81 g (81%) of pure **3** as a clear oil. Characterization conforms to previously reported data.<sup>11</sup>

**2-[(1R,4R,4aS,8aR)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl]prop-2-en-1-yl acetate (S1)**<sup>11</sup>



Acetic anhydride (15.01 g, 13.9 mL, 147.03 mmol) was added to a solution of pyridine (12.92 g, 13.21 mL, 163.35 mmol) and **2** (7.2 g, 32.67 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL) at room temperature. The mixture was stirred until determined to be complete by TLC (10% EtOAc in hexanes, ca ~16 h), whereupon the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed sequentially with aqueous citric acid (5% (w/w), 2 x 150 mL), NH<sub>4</sub>OH (10% (w/w), 2 x 150 mL), H<sub>2</sub>O (1 x 150 mL) and brine (1 x 150 mL). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to recover 9.35 g crude **S1** which was subsequently purified by chromatography (column: 40 g silica gel; eluent: gradient EtOAc 0 →15% in hexane) to isolate 7.43 g (87%) of pure **S1** as a clear oil. Characterization conforms to previously reported data. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.22 (s, 1H), 5.06 (s, 1H), 4.93 (s, 1H), 4.62 (d, *J* = 13.3 Hz, 1H), 4.54 (d, *J* = 13.3 Hz, 1H), 2.51 (s, 1H), 2.20 (d, *J* = 12.5 Hz, 1H), 2.12 (s, 3H), 2.01 – 1.94 (m, 1H), 1.94 – 1.85 (m, 1H), 1.80 (dd, *J* = 17.3, 6.0 Hz, 1H), 1.72 (dq, *J* = 12.6, 3.4 Hz, 1H), 1.62 (s, 3H), 1.60 – 1.49 (m, 2H), 1.48 – 1.26 (m, 3H), 1.03 (qd, *J* = 12.9, 3.2 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.9, 146.0, 135.1, 120.2, 112.5, 66.5, 43.7, 41.6, 37.7, 35.3, 27.8, 26.4, 25.70, 25.67, 23.7, 21.0, 19.8.

**Amorpha-4,11-diene (2).**<sup>12</sup>



A solution of **S1** (1.95 g, 7.24 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.42 g, 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) was de-gassed by evacuating the headspace of the reaction vessel under vacuum and back-filling with nitrogen (3 x), before adding polymethylhydrosiloxane (PMHS) (3.05 g, 3.03 mL, 50.68 mmol) in one portion at room temperature. The reaction was stirred for 6 h, whereupon additional Pd(PPh<sub>3</sub>)<sub>4</sub> (0.21 g, 0.18 mmol) and PMHS (1.51 g, 1.5 mL, 25.09 mmol) was added and the reaction continued to stir until determined complete by TLC (2% EtOAc in hexanes, ca. ~6-48

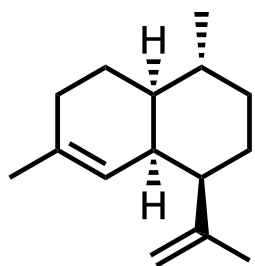
h). The reaction was concentrated to a residue under reduced pressure and dissolved in hexanes (80 mL) before adding aqueous NaOH (20% (w/w), 80 mL) and the mixture stirred for an additional 16 h. The organic layers were separated and washed with H<sub>2</sub>O (2 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude material was then purified by chromatography (column: 12 g silica gel; eluent: 100% hexane) to isolate 1.42 g (96%) of pure **2** as a clear oil. Characterization conforms to previously reported data.<sup>12</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.08 (s, 1H), 4.89 (s, 1H), 4.67 (s, 1H), 2.58 (s, 1H), 2.06 – 1.85 (m, 3H), 1.81 (dd, *J* = 14.0, 4.1 Hz, 1H), 1.77 (s, 3H), 1.70 (dq, *J* = 12.7, 3.6 Hz, 1H), 1.63 (d, *J* = 2.5 Hz, 3H), 1.61 – 1.48 (m, 2H), 1.48 – 1.38 (m, 1H), 1.38 – 1.24 (m, 2H), 1.00 (qd, *J* = 12.5, 3.4 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 148.0, 134.6, 120.9, 109.8, 47.6, 41.8, 37.6, 35.4, 27.9, 26.5, 26.1, 25.8, 23.7, 22.6, 19.8.

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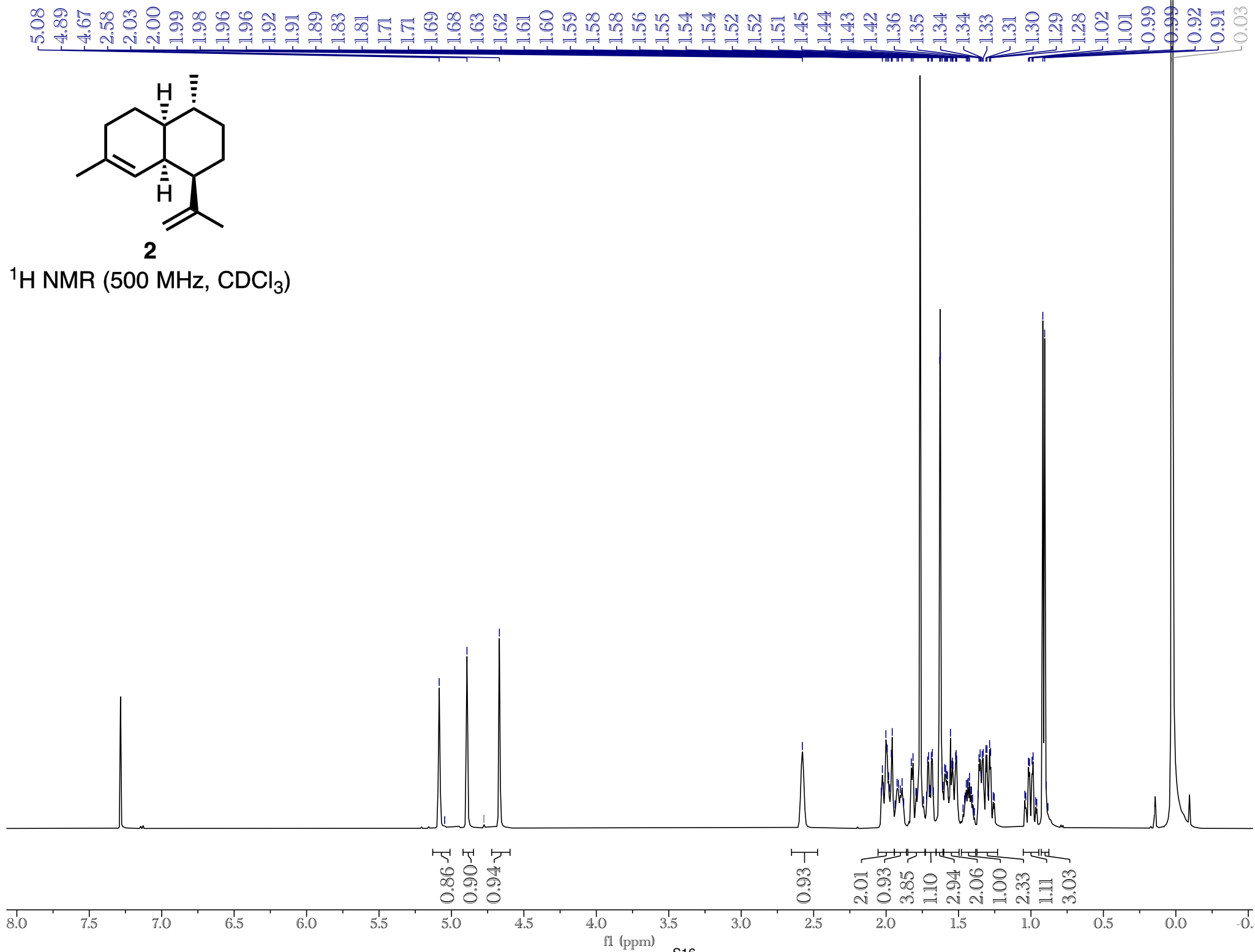
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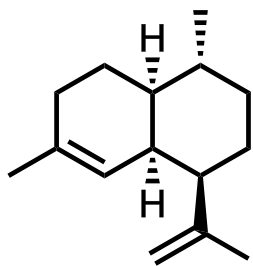
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2

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)





**2**

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

-148.0

-134.6

-120.9

-109.8

47.6

41.8

37.6

35.4

27.9

26.5

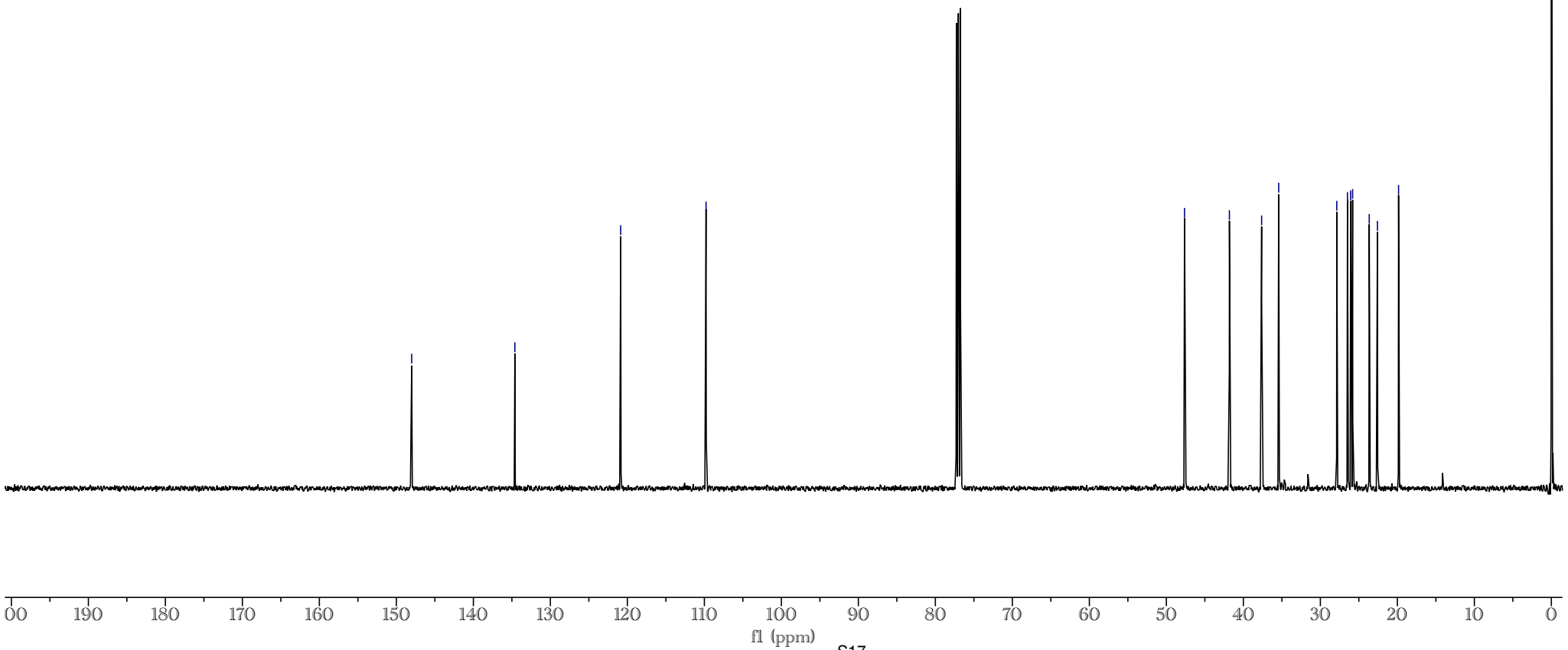
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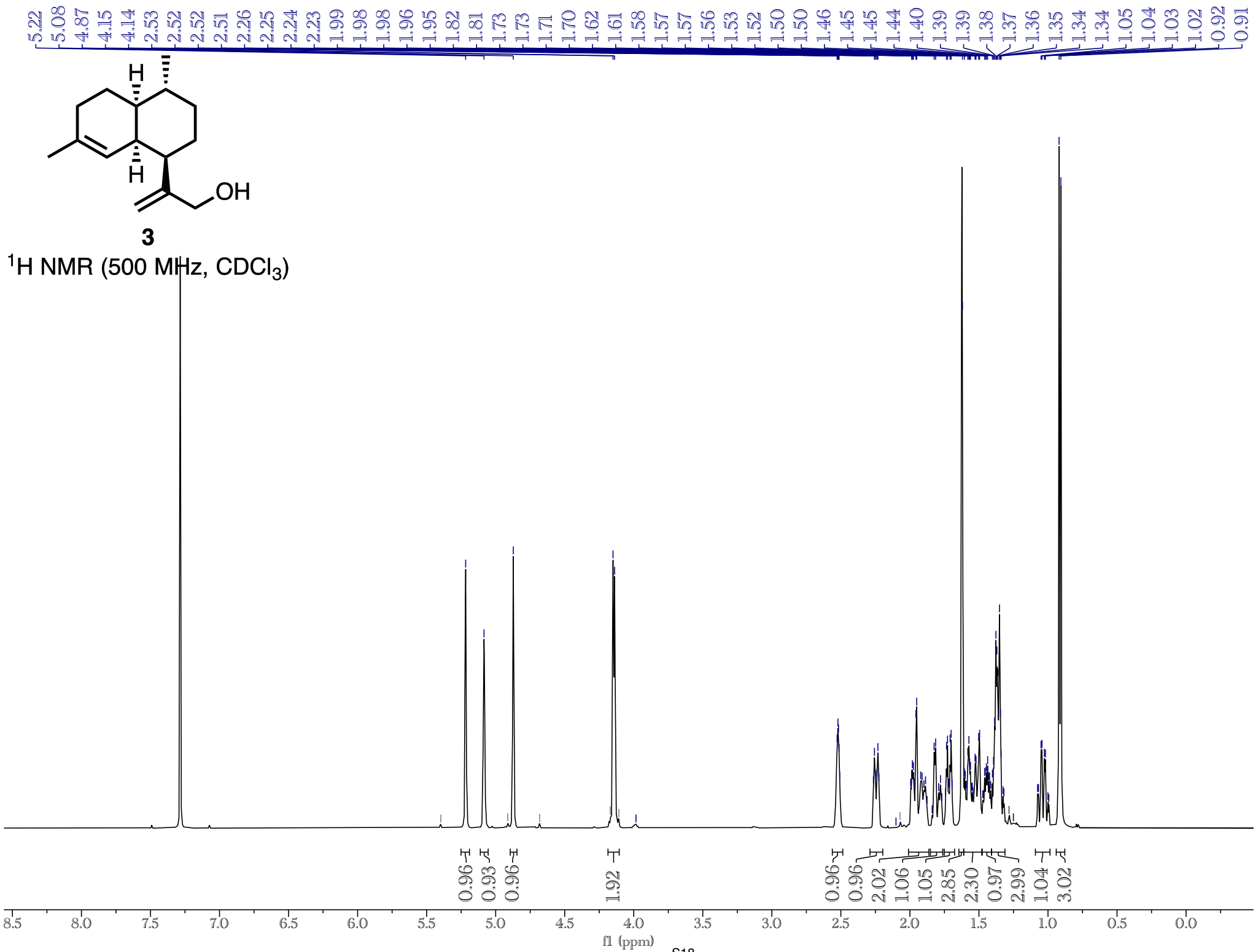
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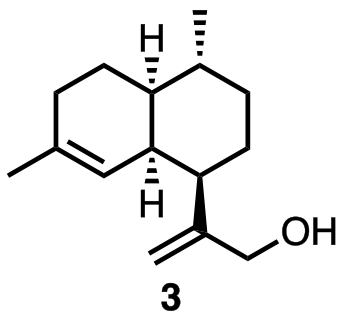
23.7

22.6

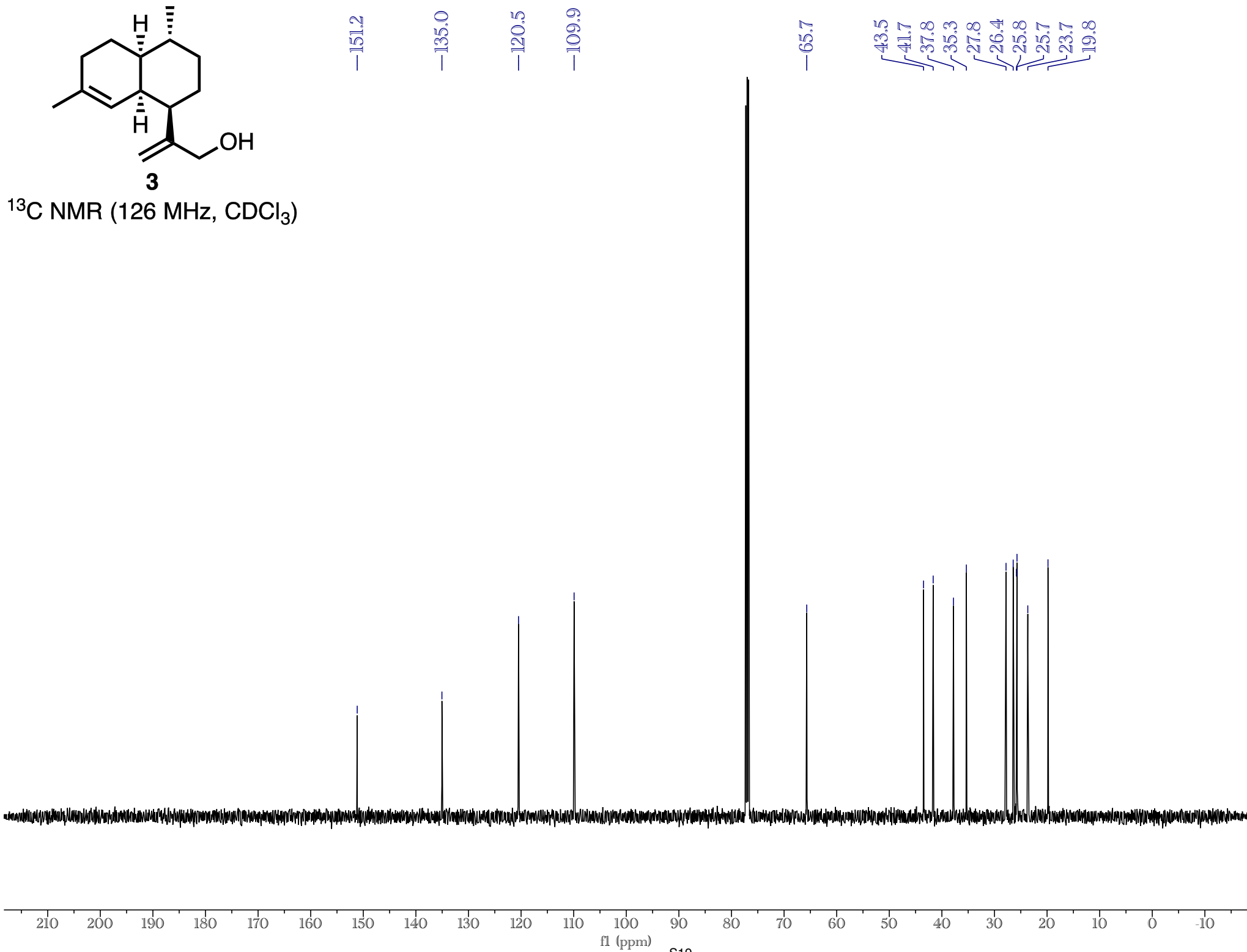
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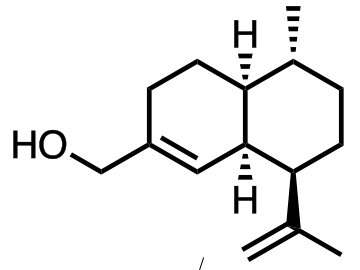
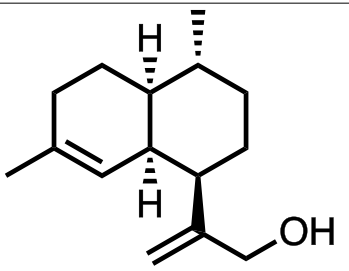
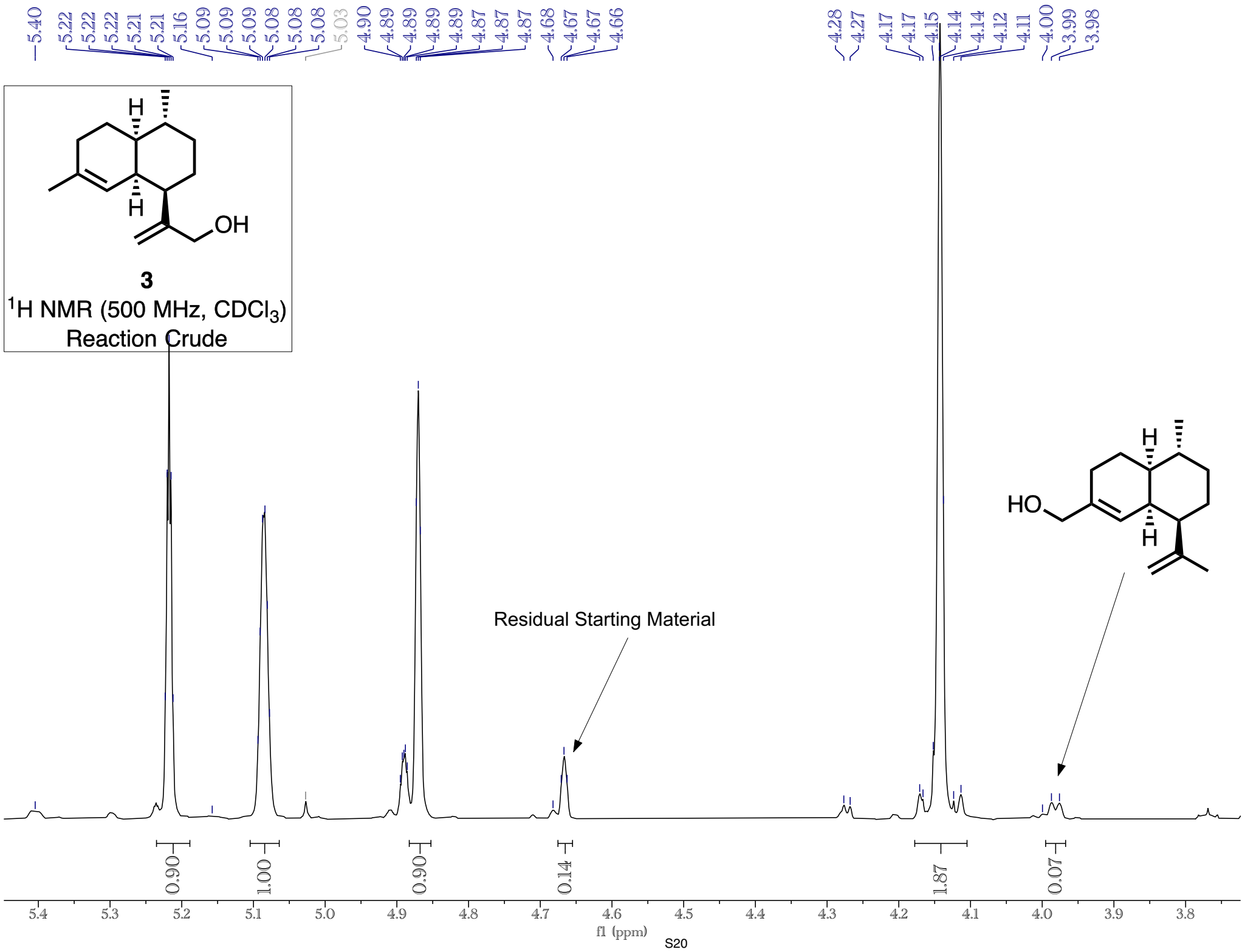


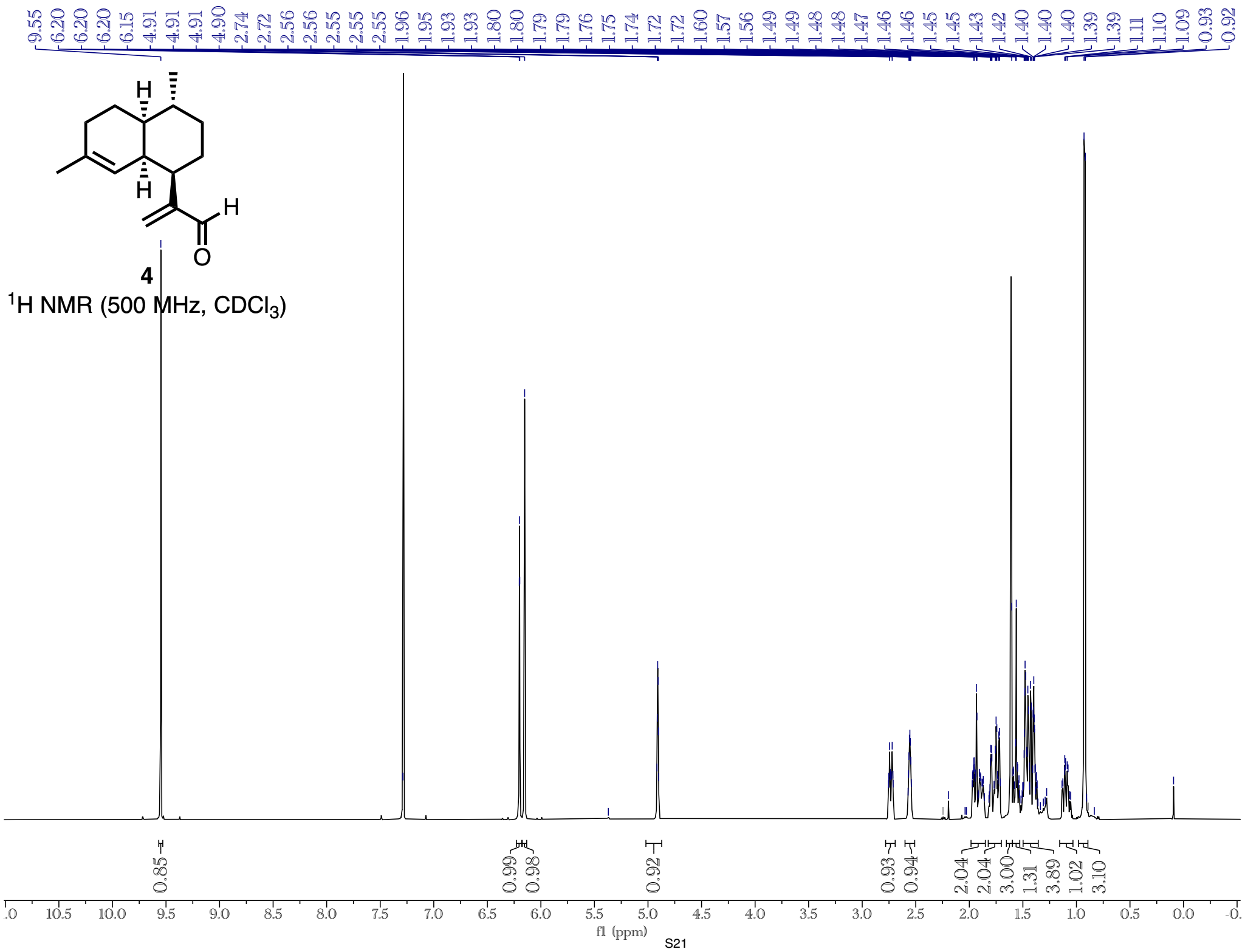


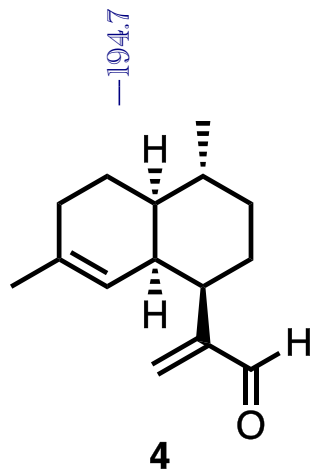


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )









4

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

194.7

152.5

135.2

134.7

120.1

41.3

39.6

37.4

35.2

27.6

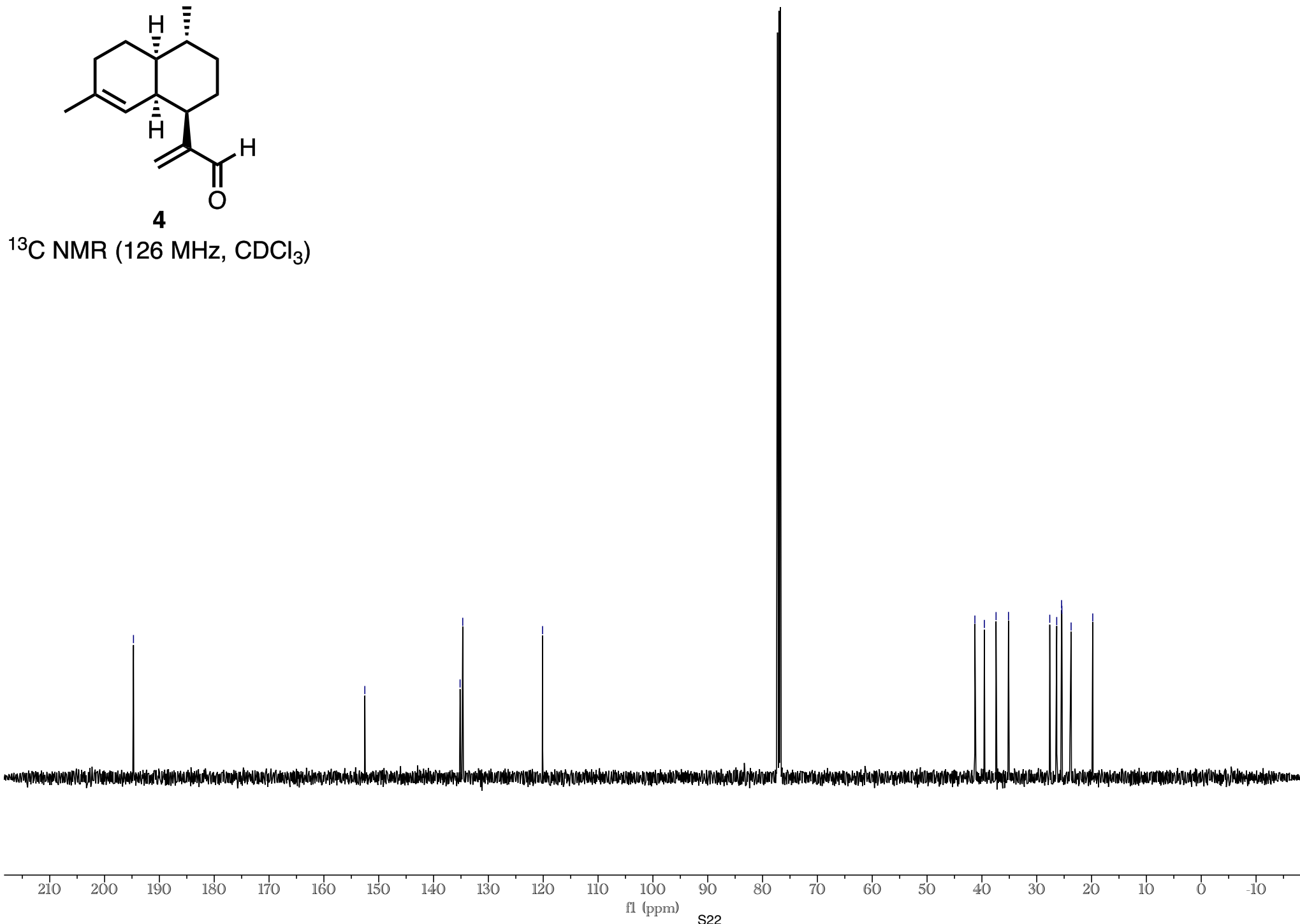
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25.5

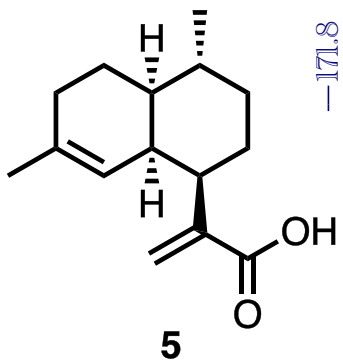
25.4

23.7

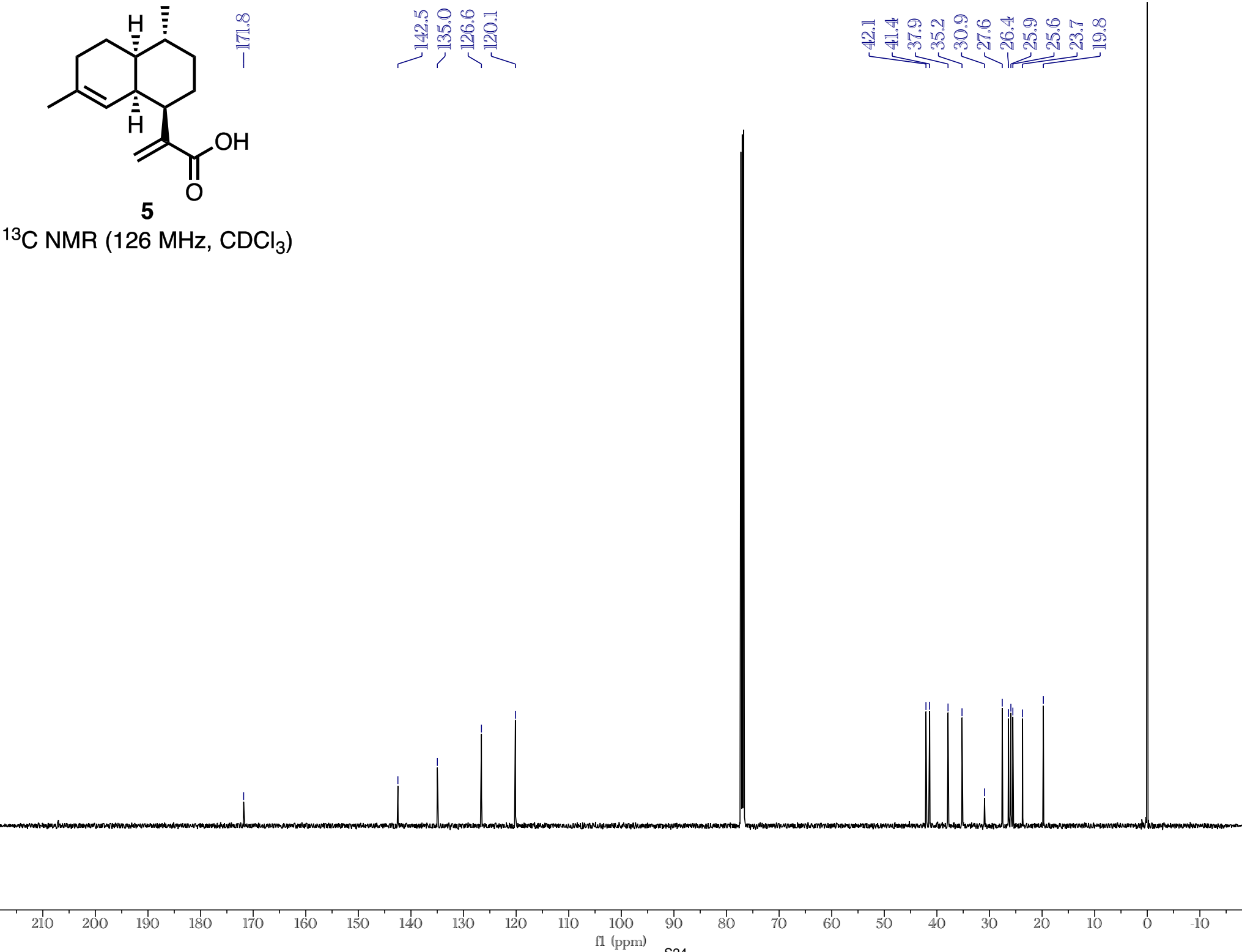
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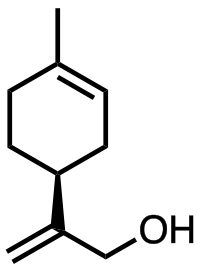






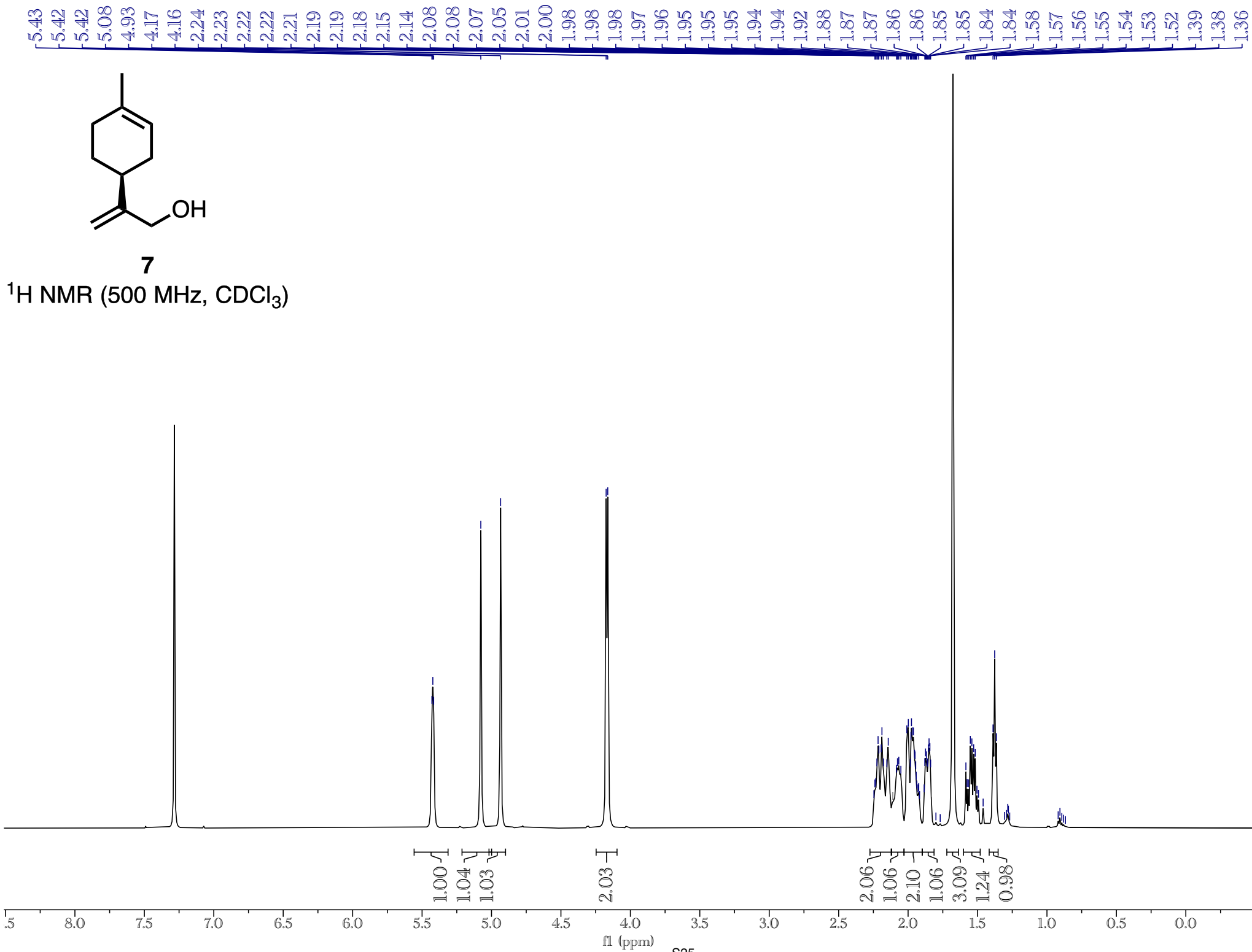
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

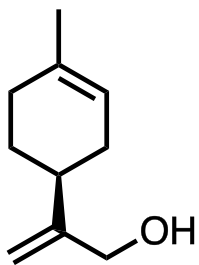




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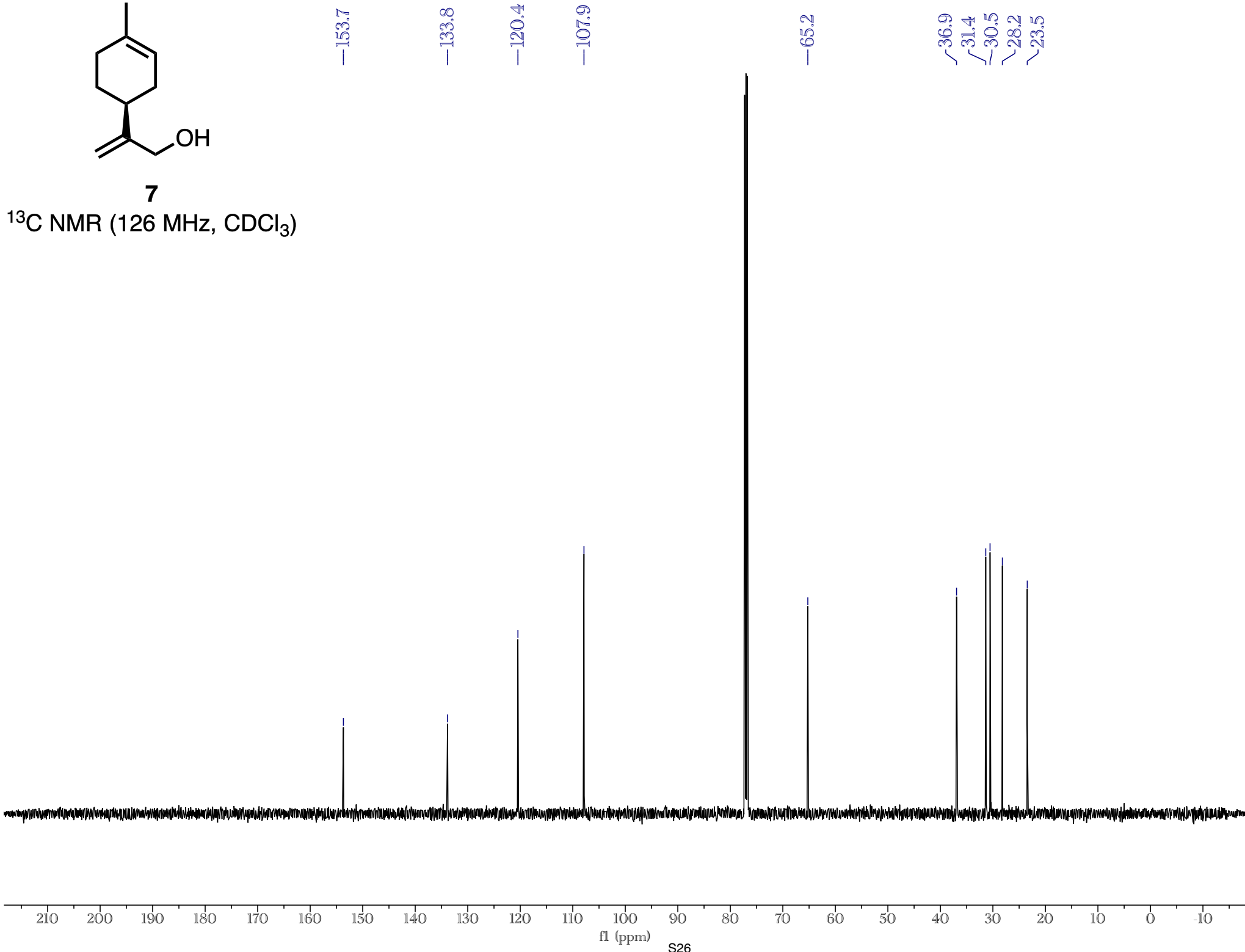
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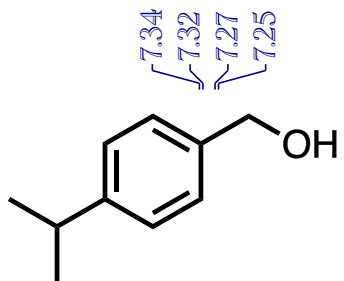




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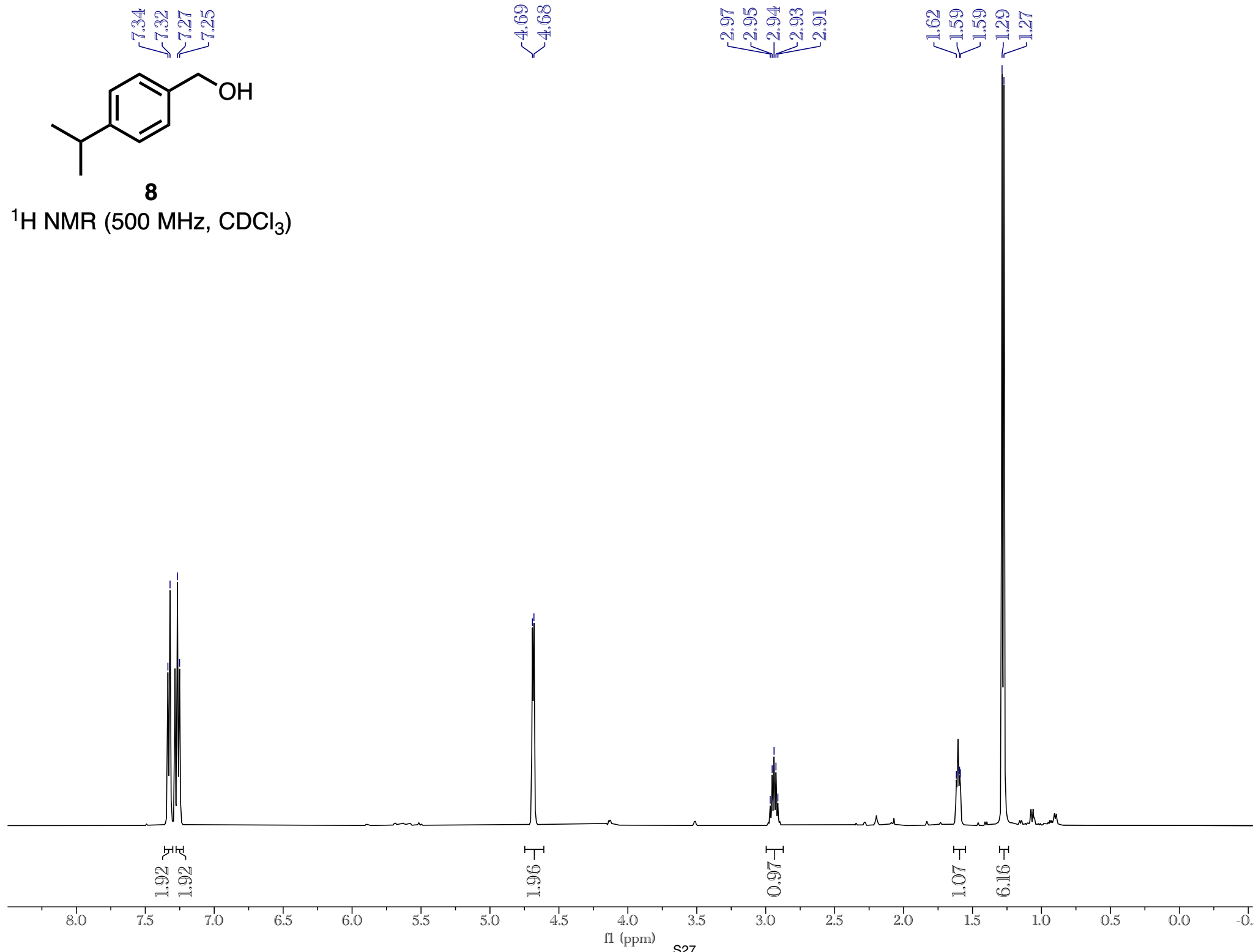
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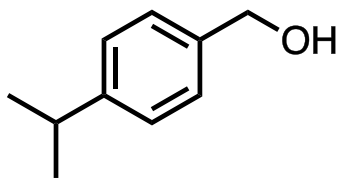




**8**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )





**8**

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

—148.5

—138.3

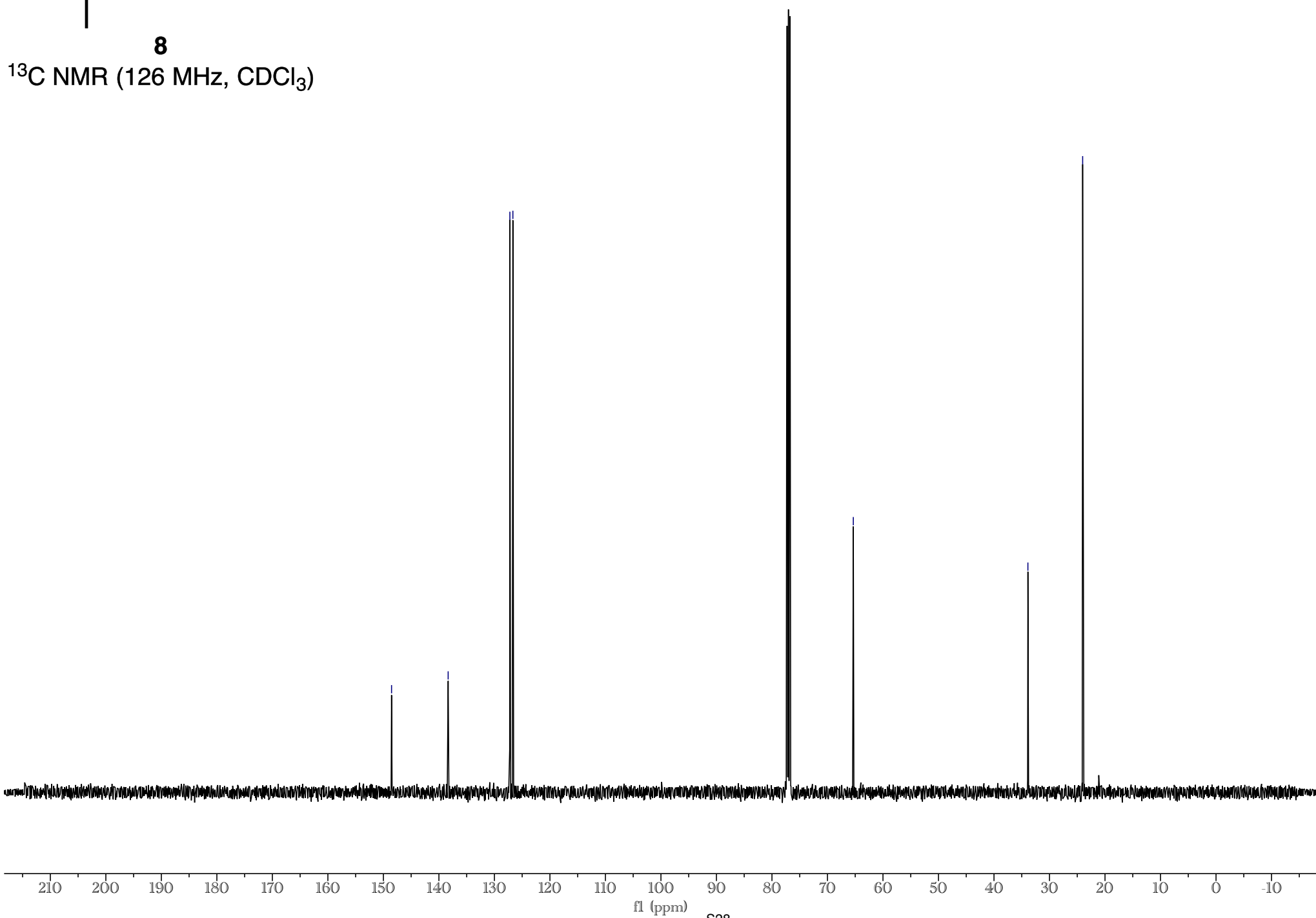
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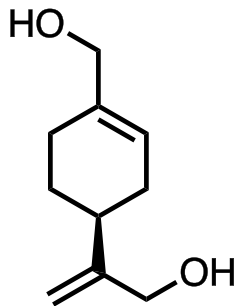
—126.7

—65.3

—33.9

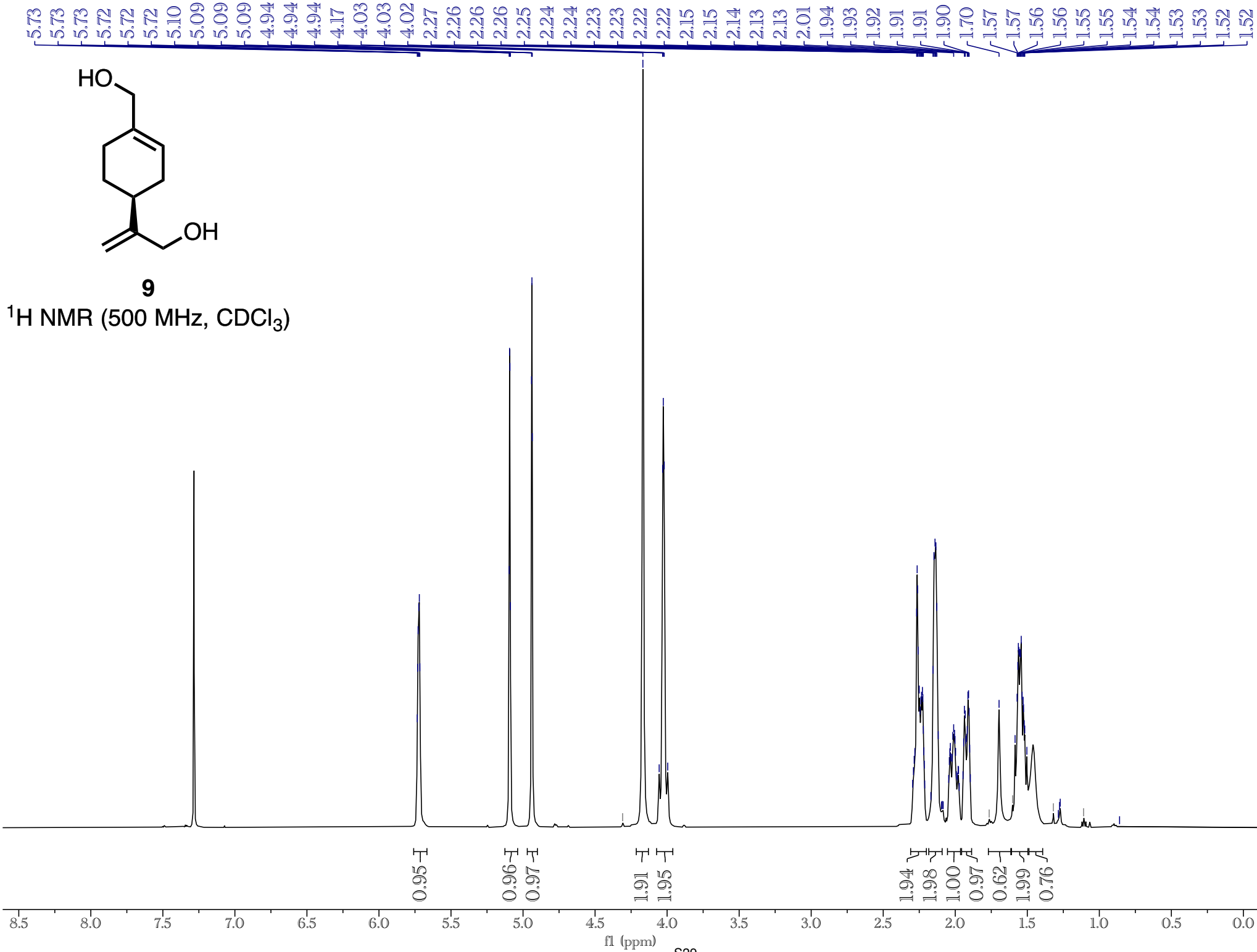
—24.0

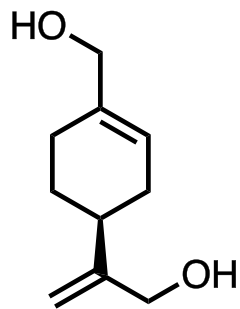




**9**

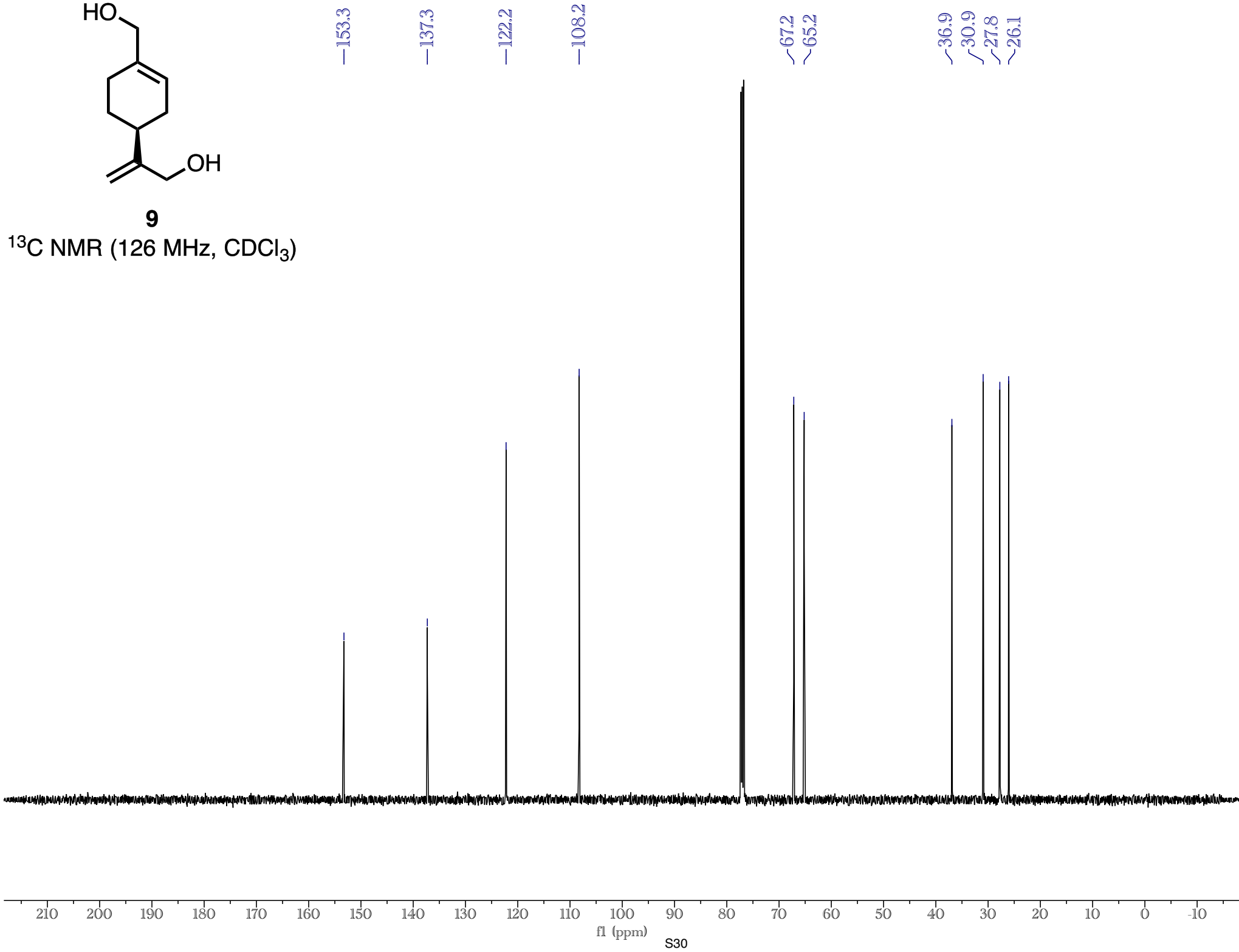
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



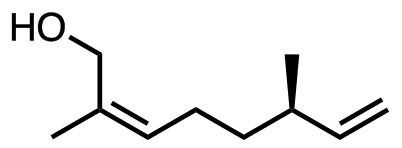


**9**

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

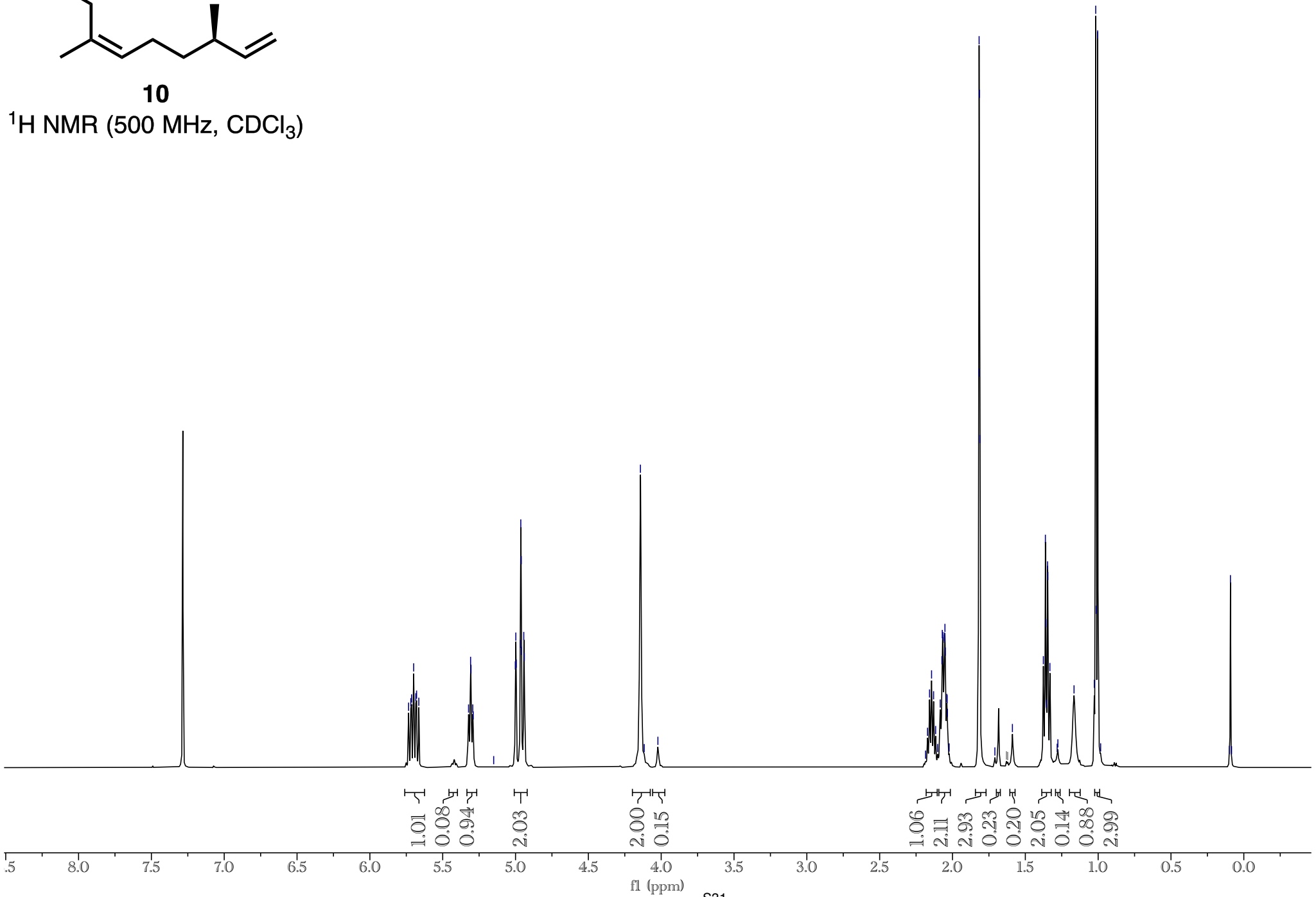


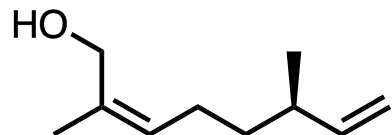
5.73  
5.72  
5.71  
5.70  
5.68  
5.68  
5.66  
5.32  
5.31  
5.31  
5.29  
5.29  
5.00  
5.00  
5.00  
4.97  
4.96  
4.96  
4.96  
4.94  
4.94  
4.14  
2.16  
2.14  
2.13  
2.08  
2.07  
2.07  
2.07  
2.06  
2.06  
2.05  
2.05  
2.04  
2.04  
2.03  
1.82  
1.82  
1.81  
1.81  
1.38  
1.36  
1.36  
1.35  
1.35  
1.35  
1.33  
1.17  
1.03  
1.02  
1.01  
1.00  
0.09



**10**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)





**10**

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

—144.5

—134.2

—128.6

—112.8

—61.7

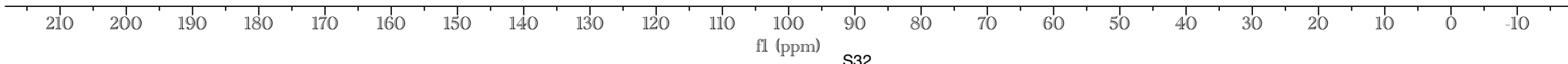
—37.4

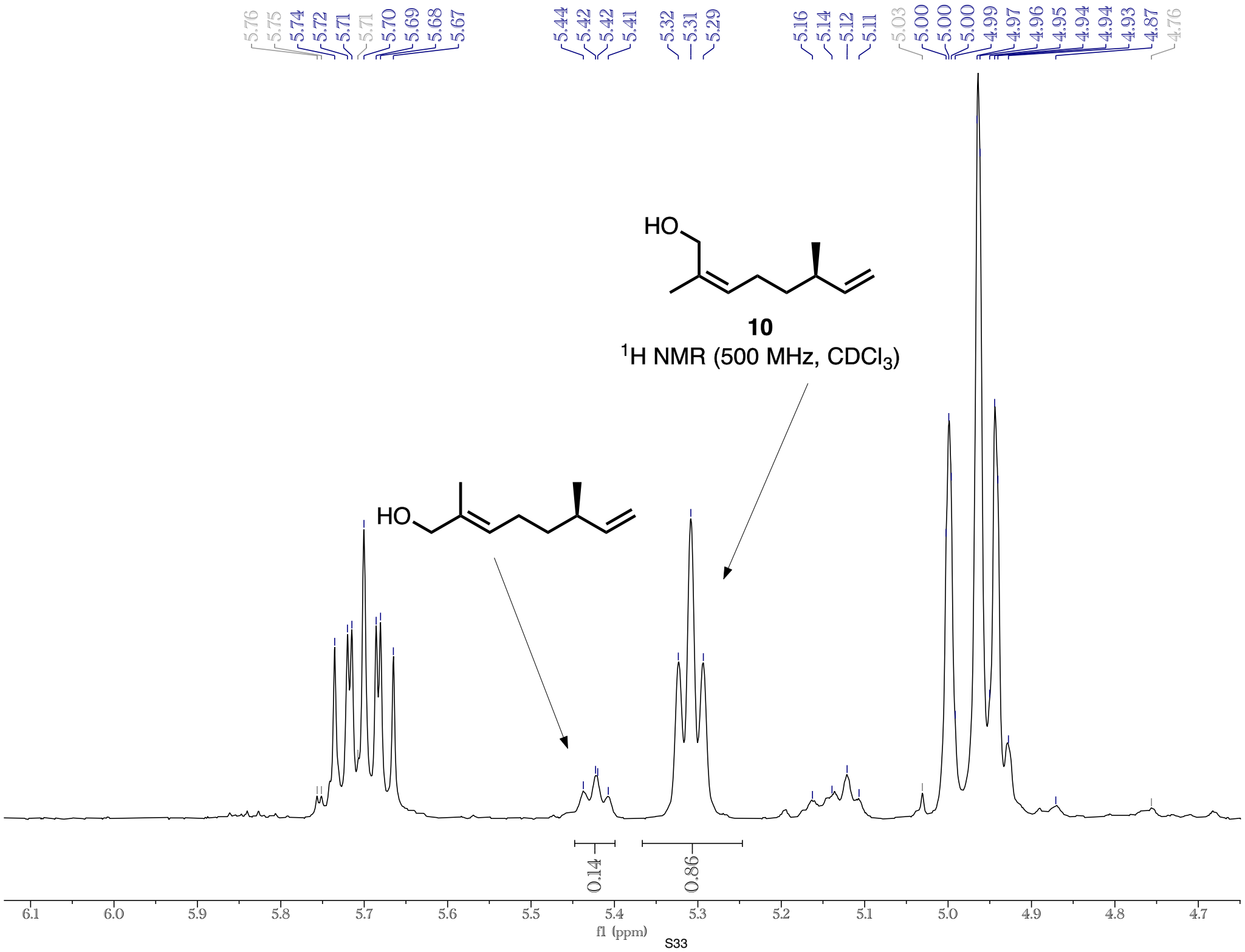
—36.8

—25.3

—21.3

—20.3



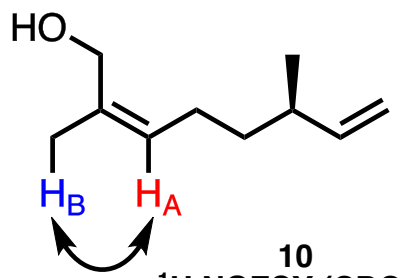


5.73  
5.73  
5.72  
5.71  
5.70  
5.69  
5.69  
5.67  
5.67  
5.31  
5.30  
5.28

4.14

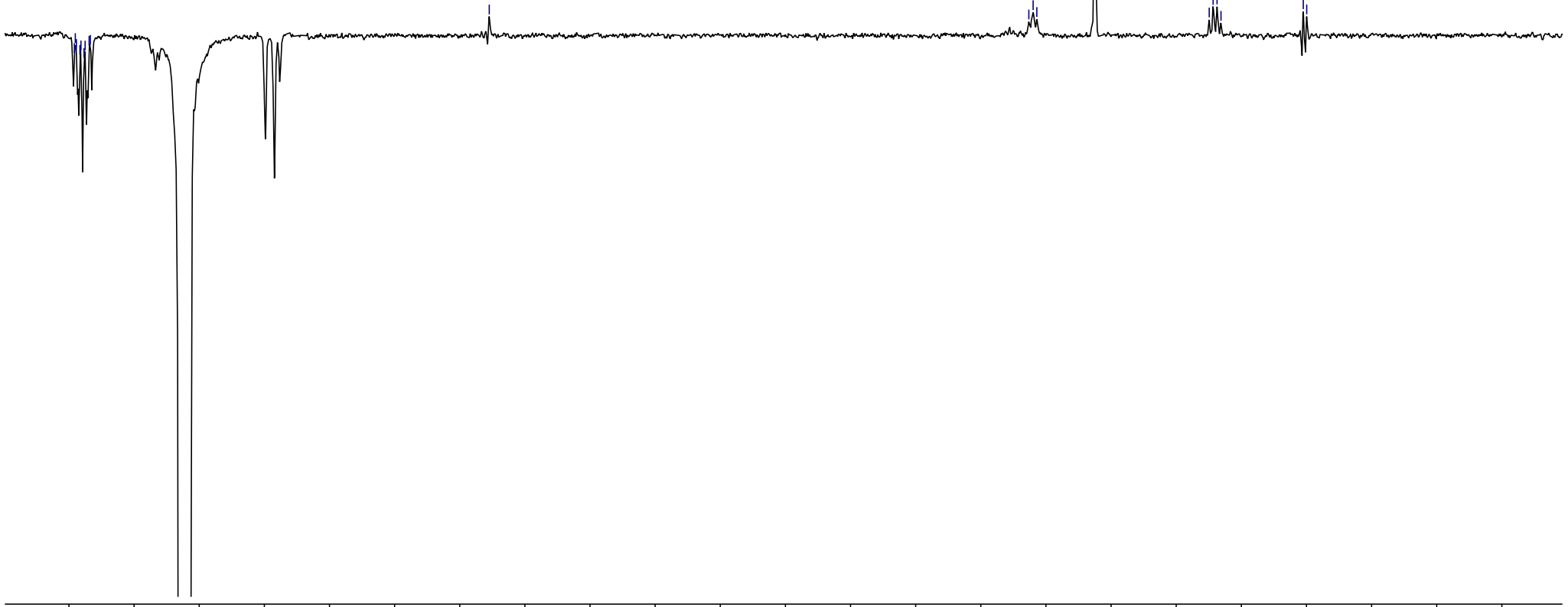
2.07  
2.05  
2.04

1.37  
1.36  
1.34  
1.33  
1.01  
1.00



H<sub>A</sub>

H<sub>B</sub>



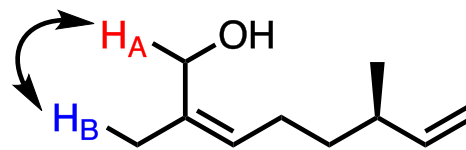
fl (ppm)

S34

4.19  
4.18  
4.16  
4.15  
4.13  
4.12  
4.10  
4.10

2.08  
2.07  
2.05  
2.03

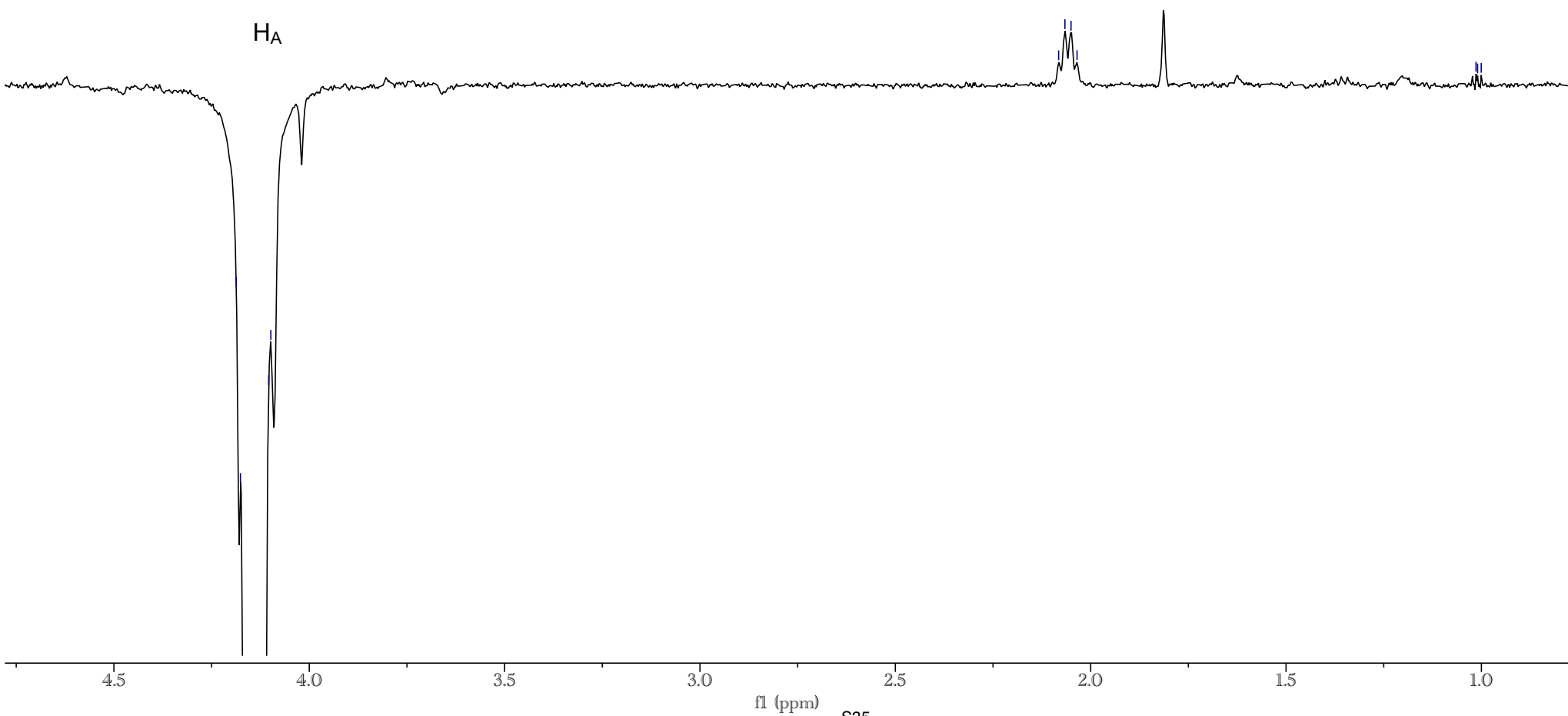
1.01  
1.01  
1.00



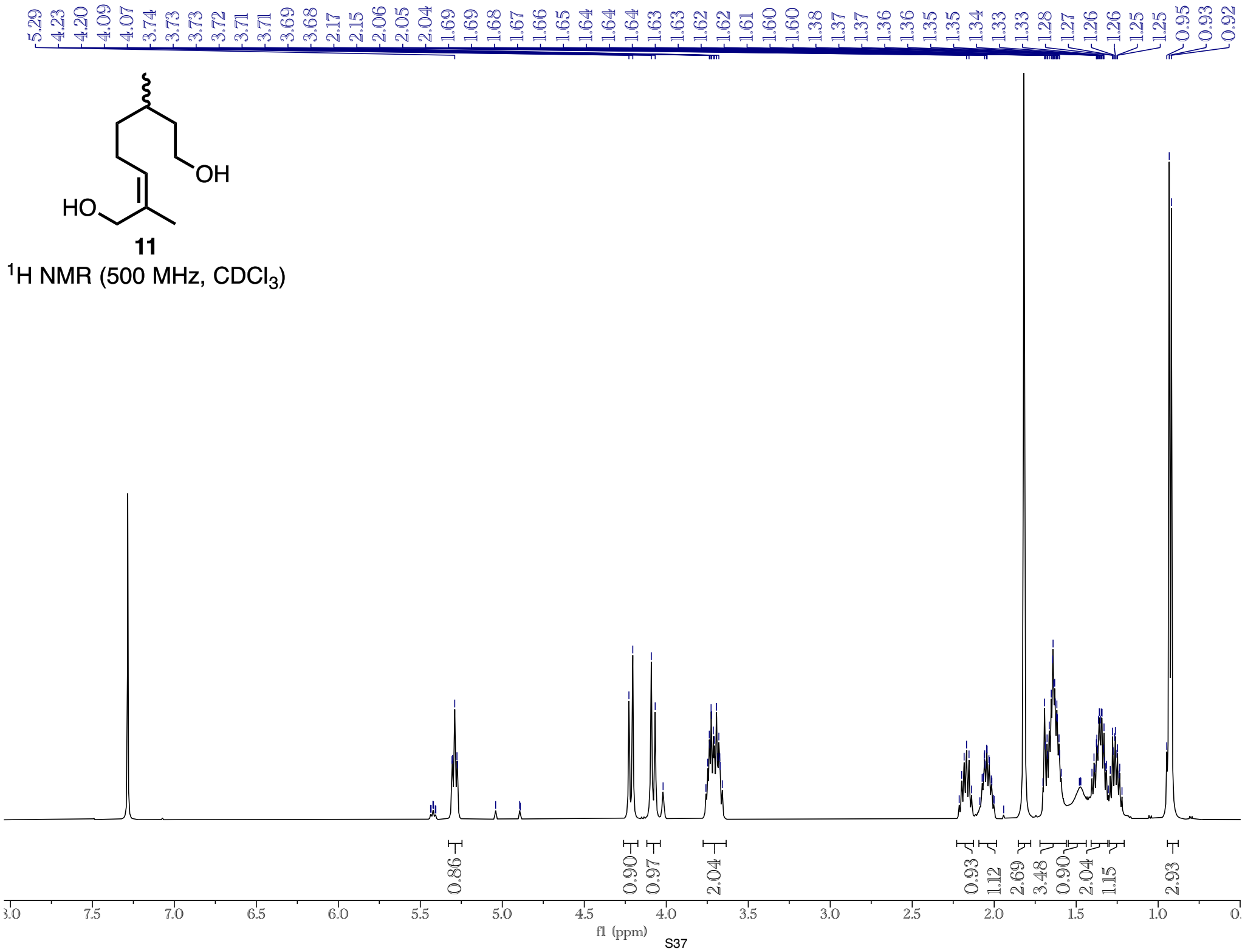
10  
<sup>1</sup>H NOESY (CDCl<sub>3</sub>)

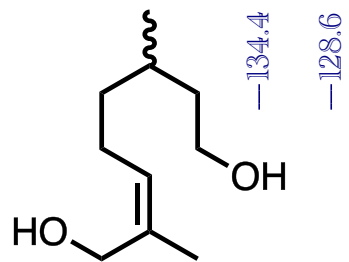
H<sub>B</sub>

H<sub>A</sub>



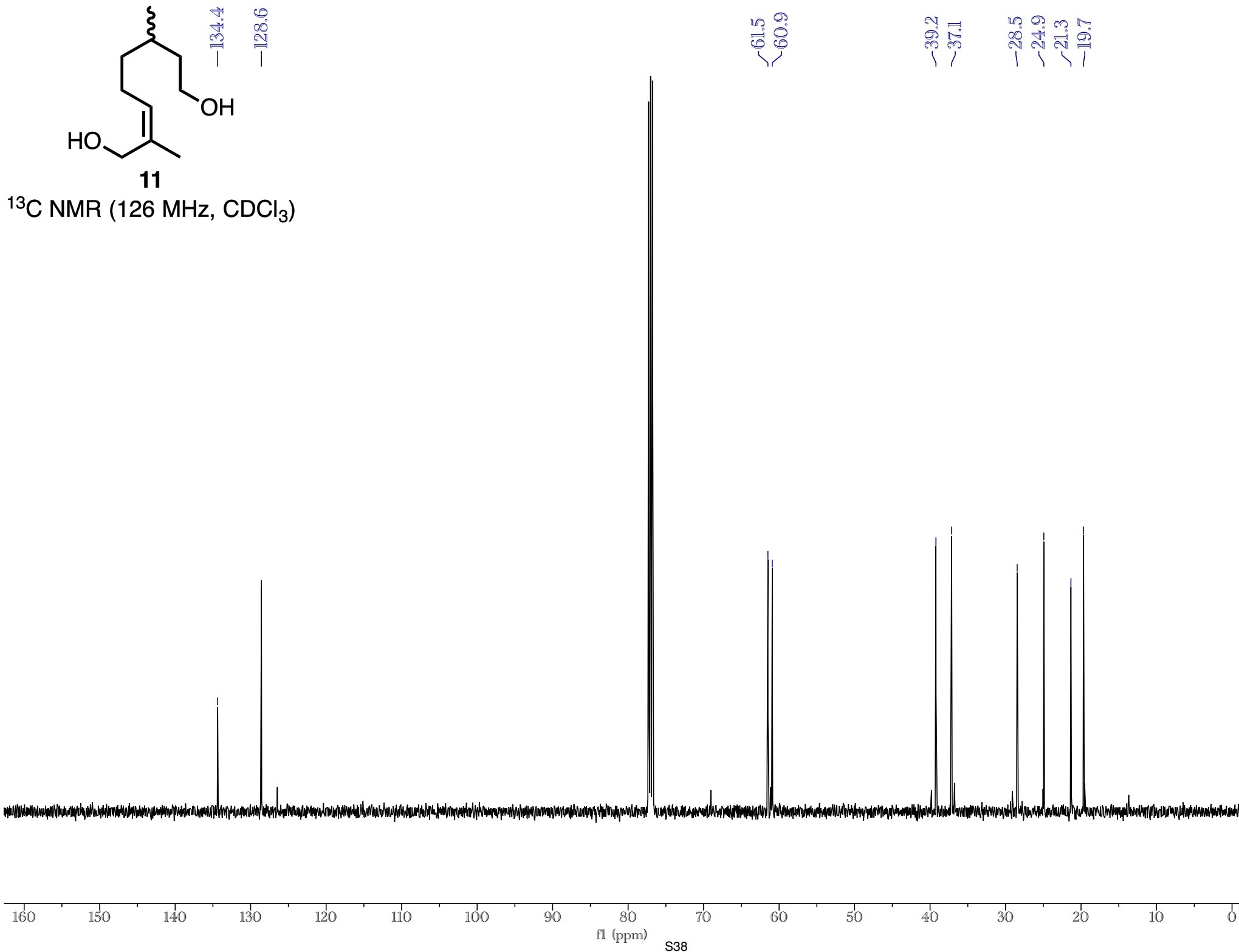


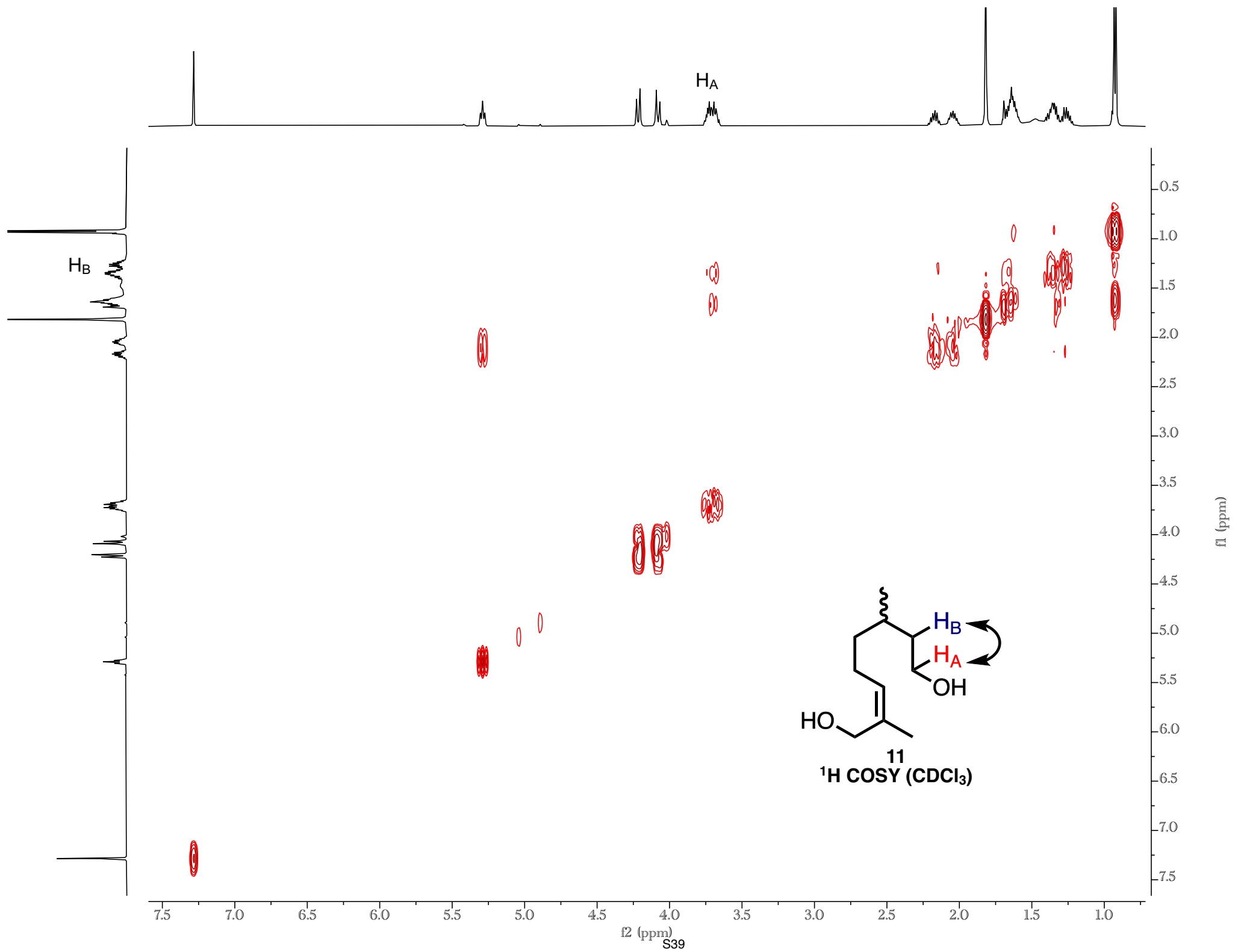


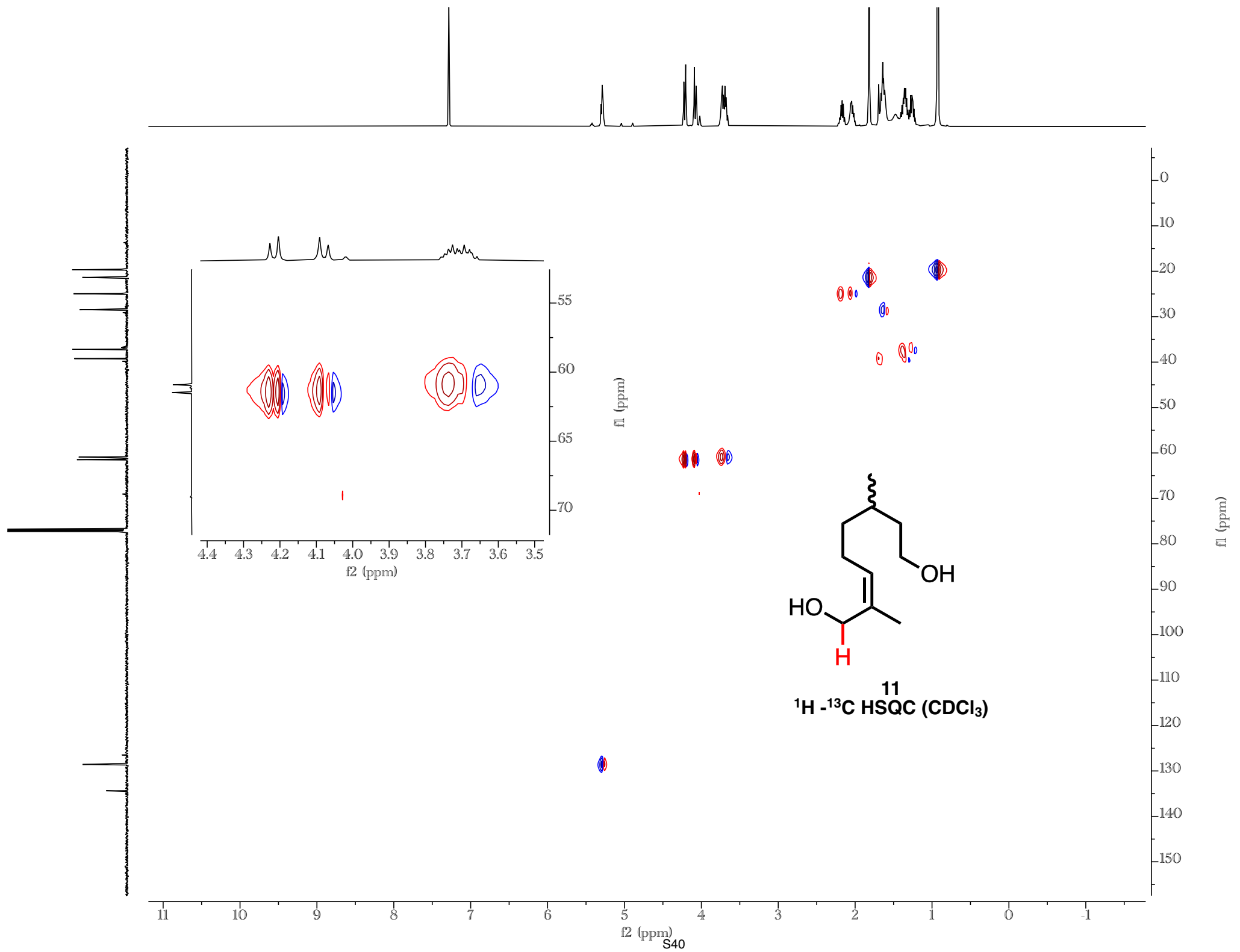


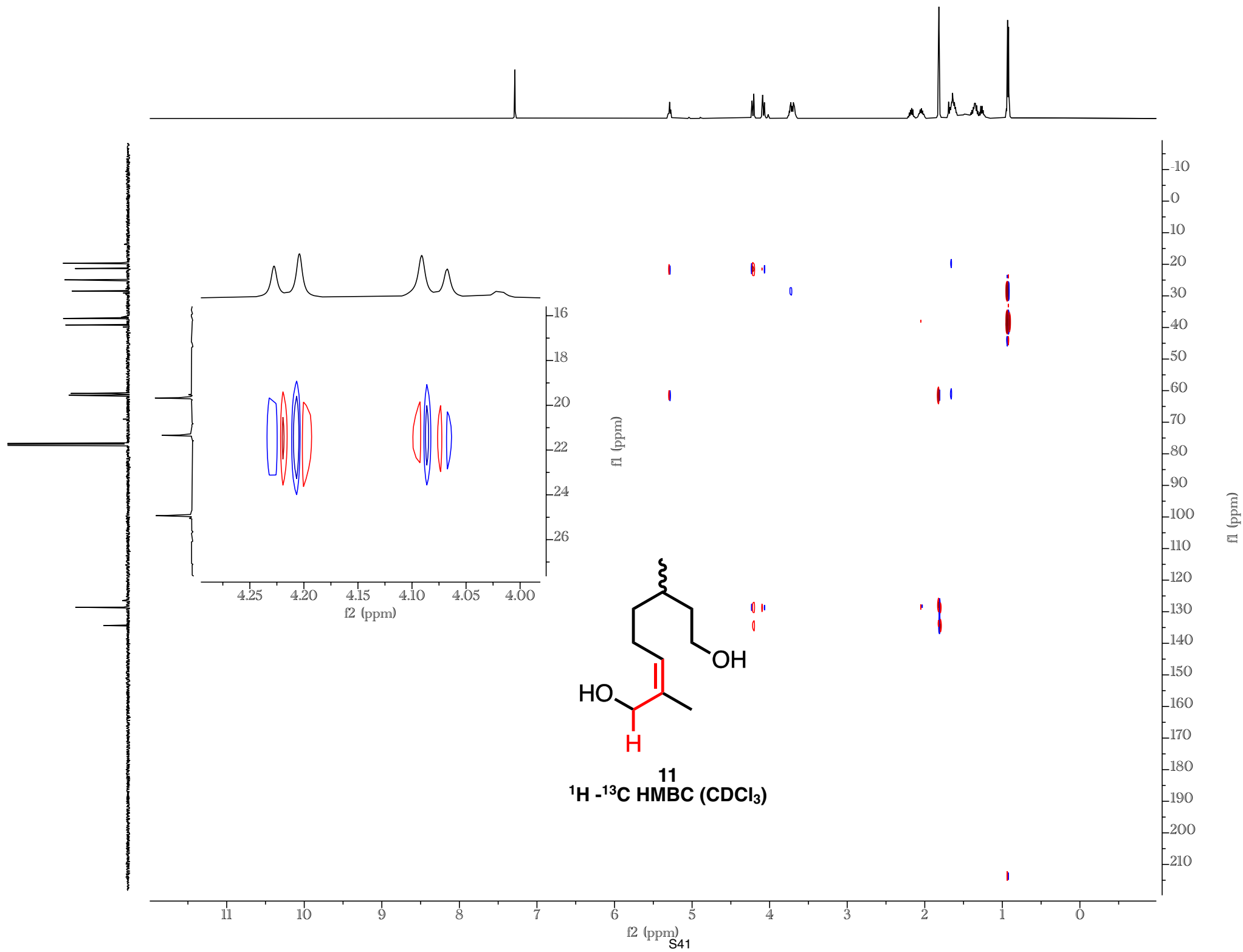
11

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



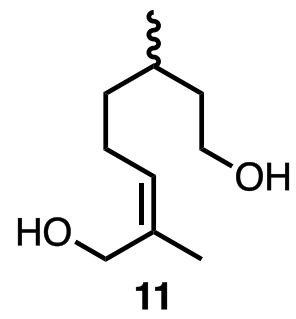




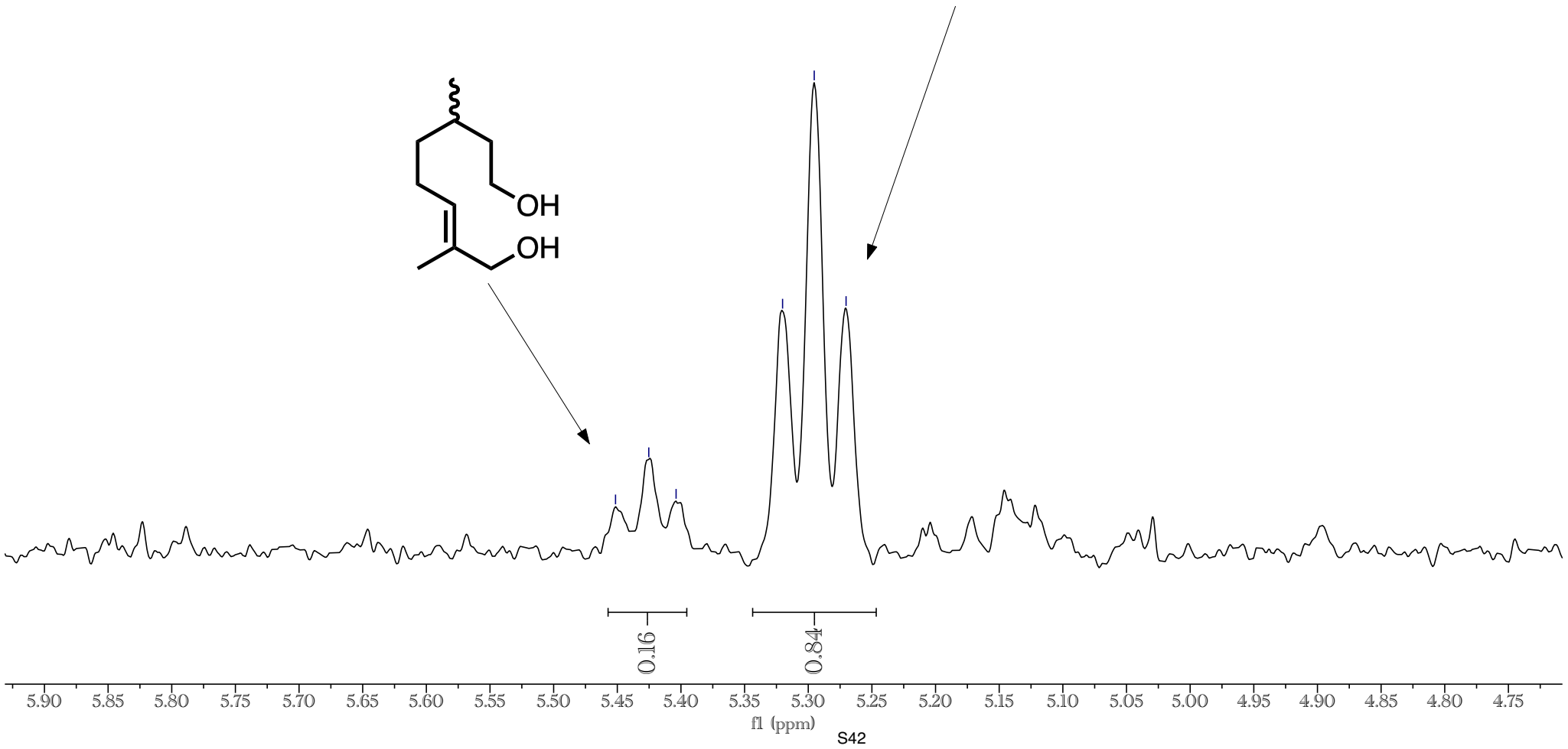
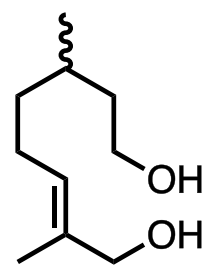


~5.45  
~5.43  
~5.40

~5.32  
~5.30  
~5.27

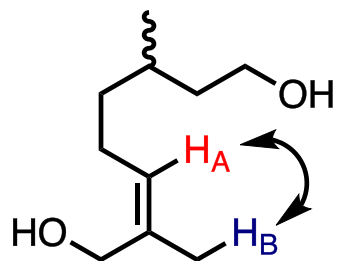


<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



5.31  
5.30  
5.28  
5.27

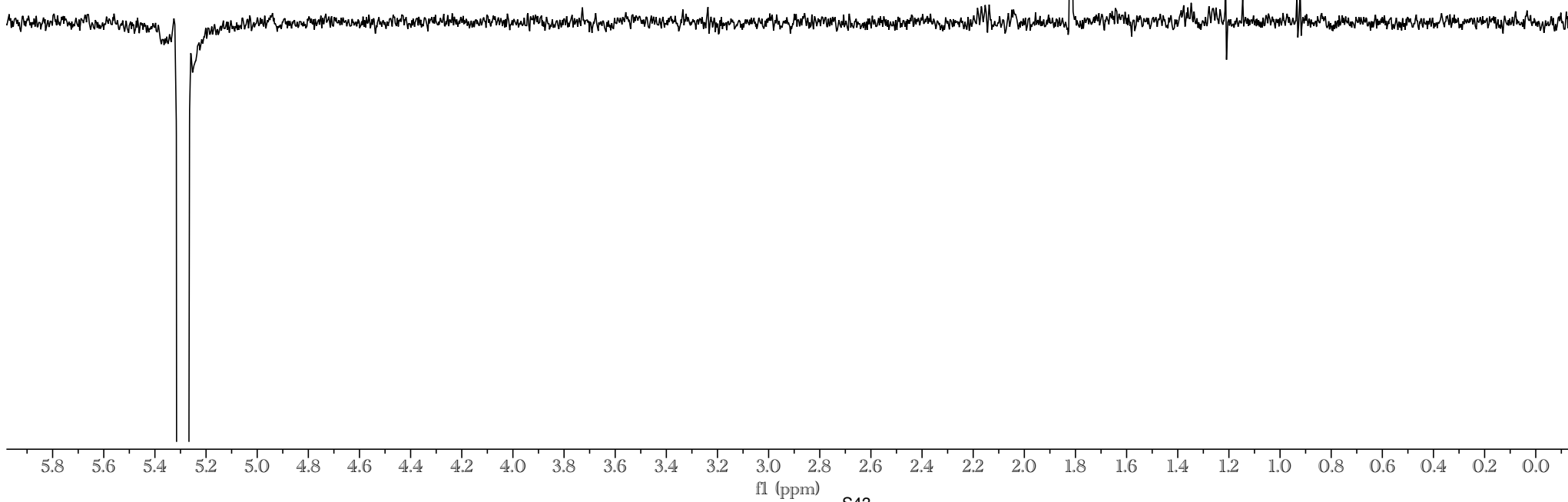
-1.21  
0.93  
0.92

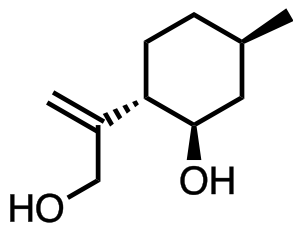


11  
 $^1\text{H}$  NOESY ( $\text{CDCl}_3$ )

$H_A$

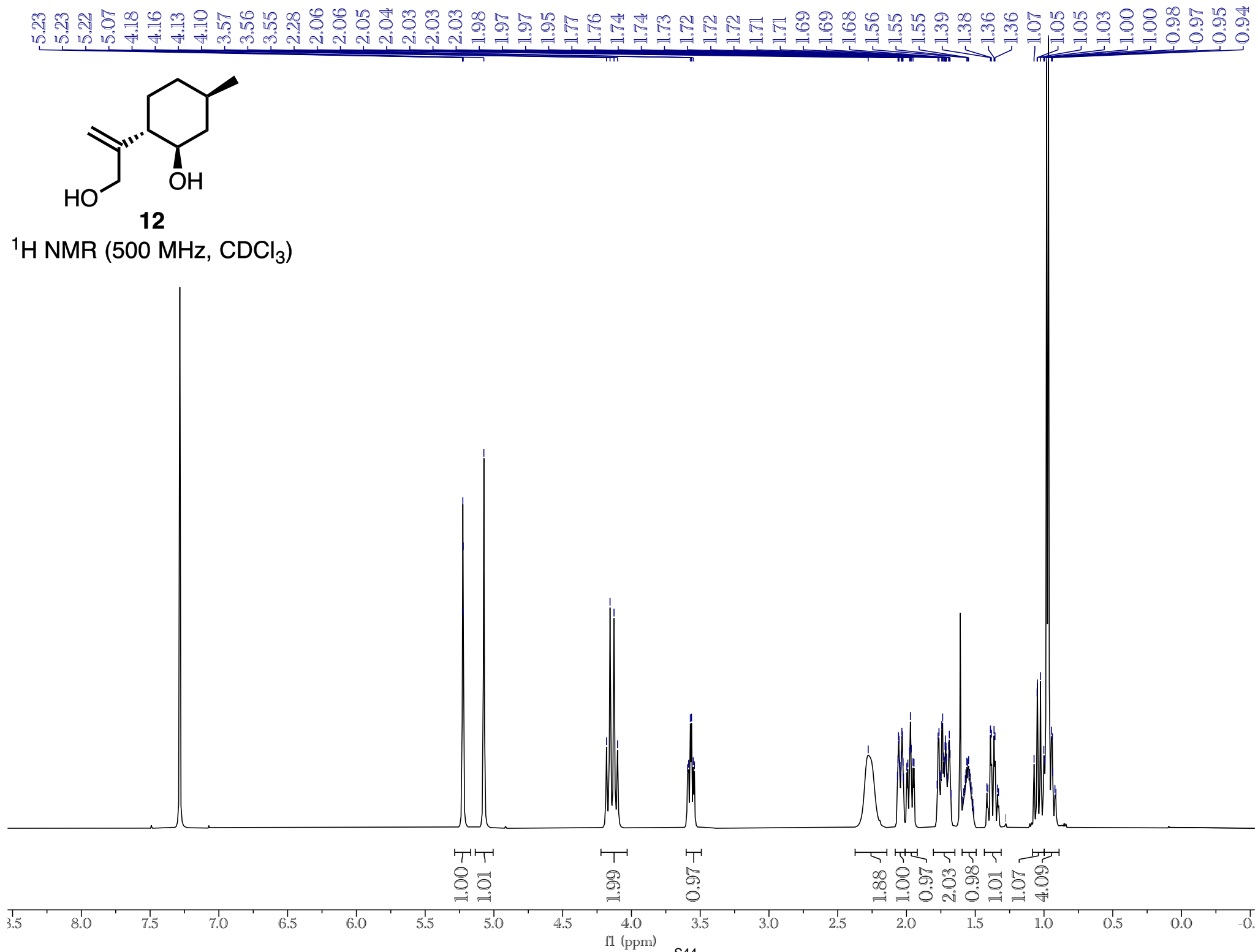
$H_B$

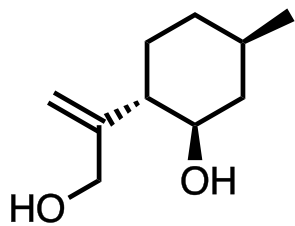




**12**

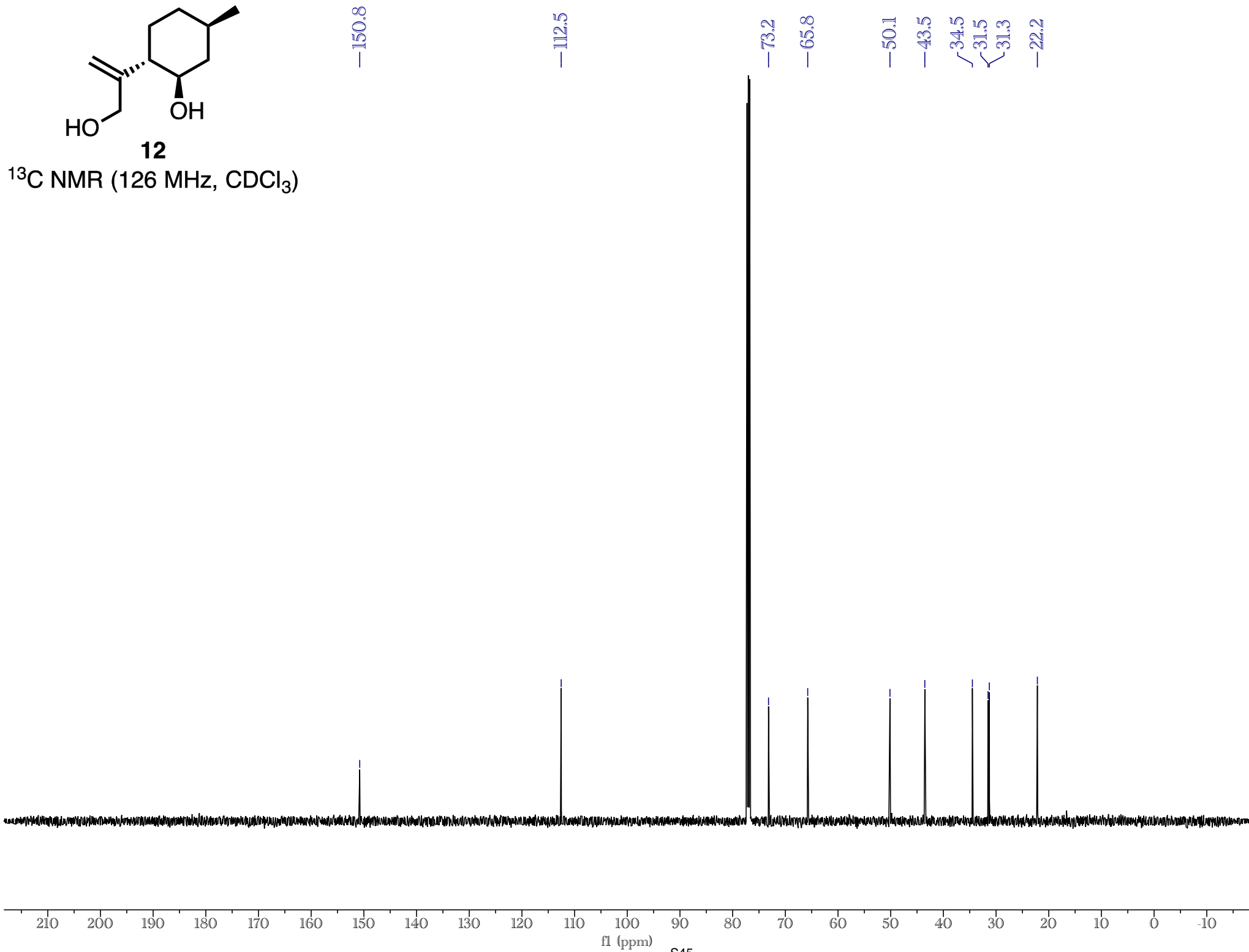
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

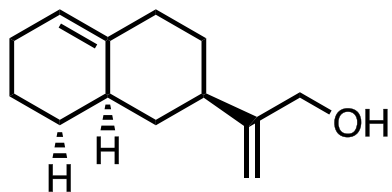




12

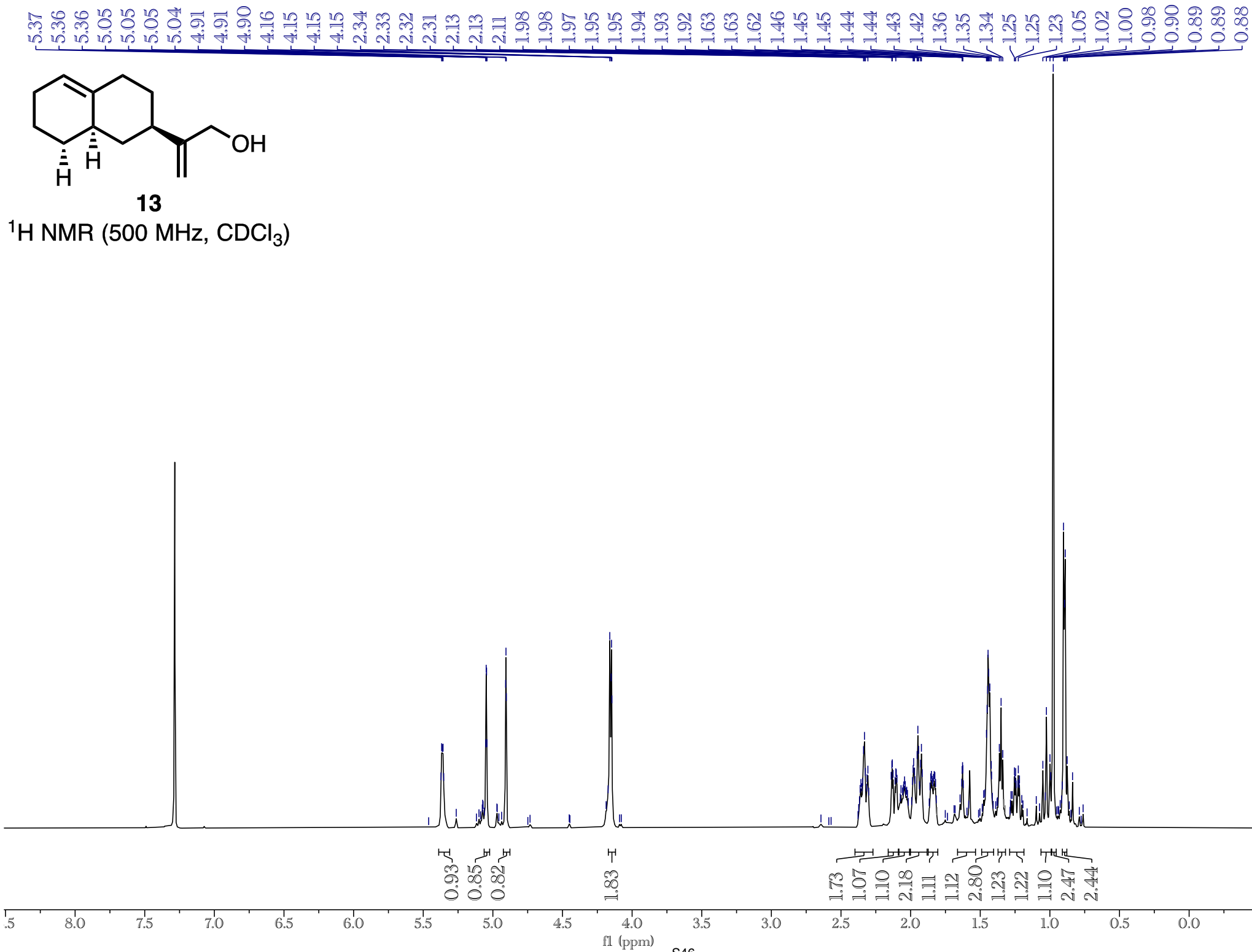
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

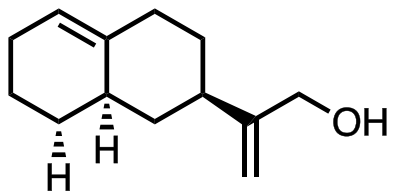




**13**

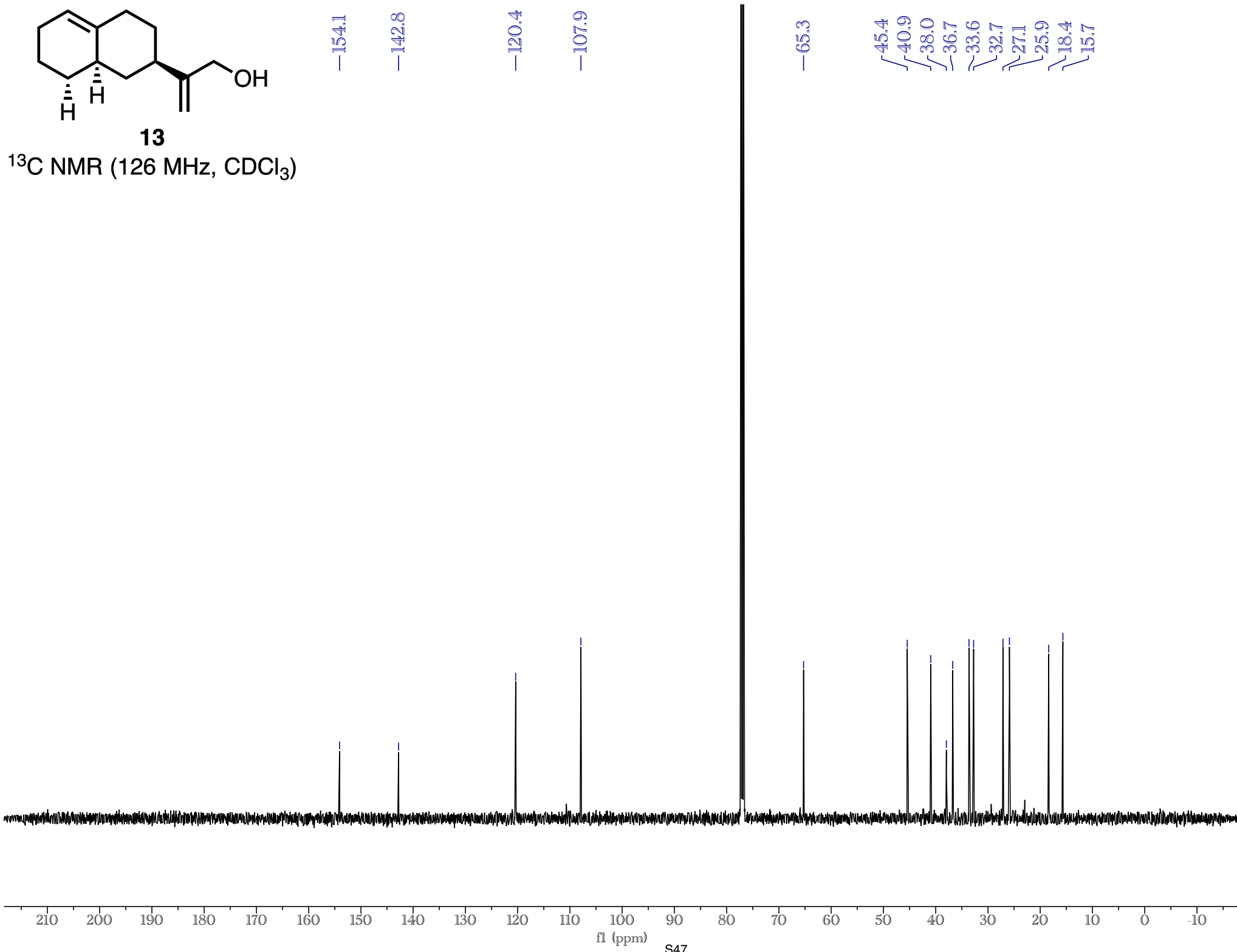
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

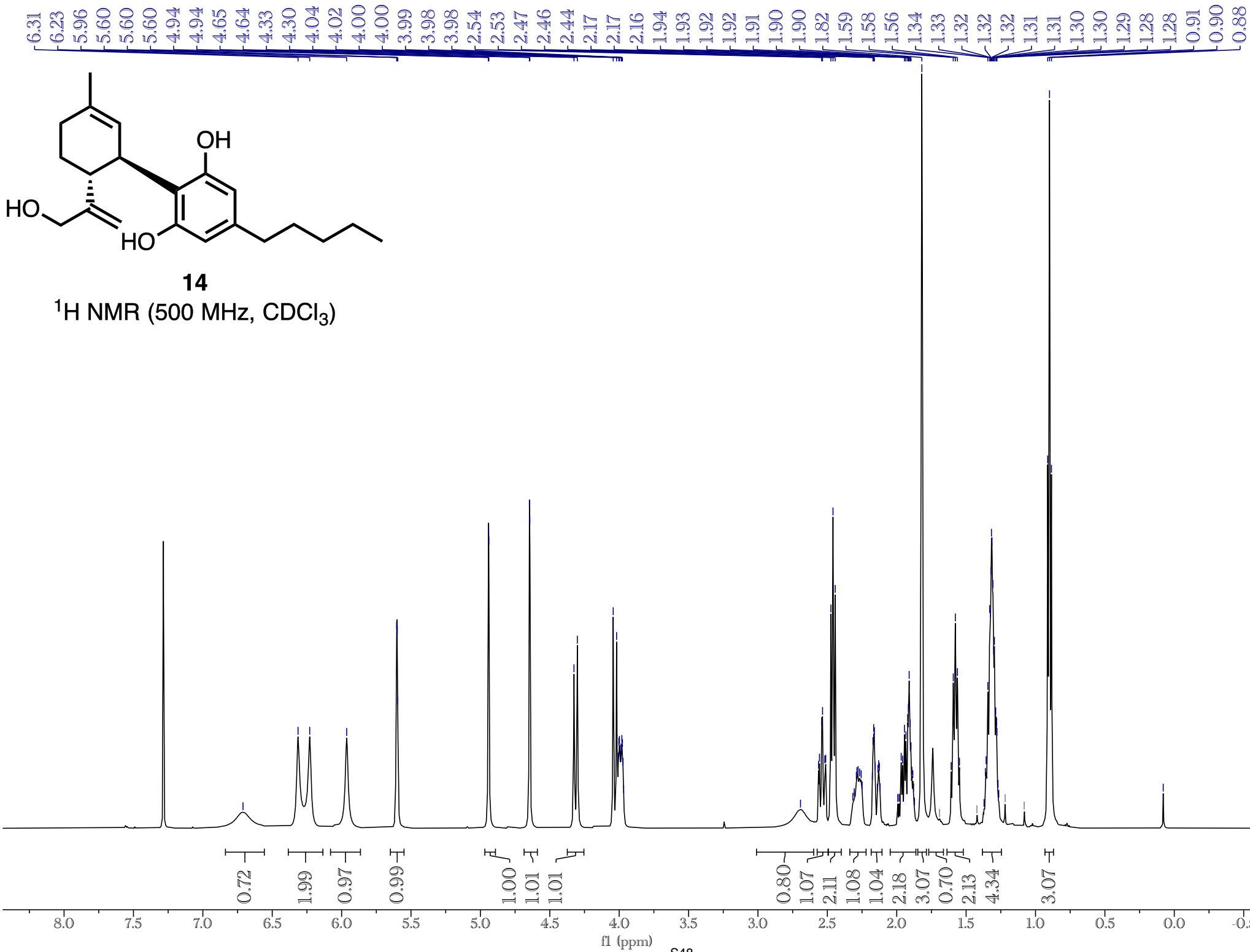


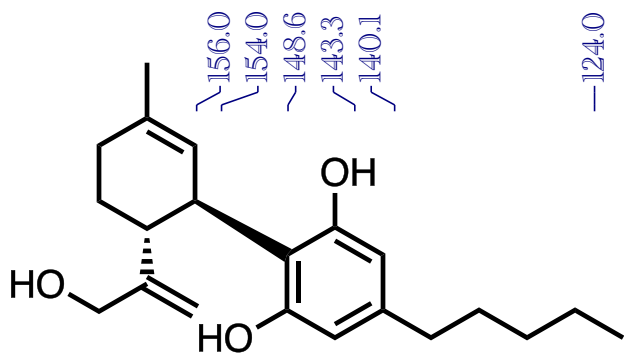


**13**

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

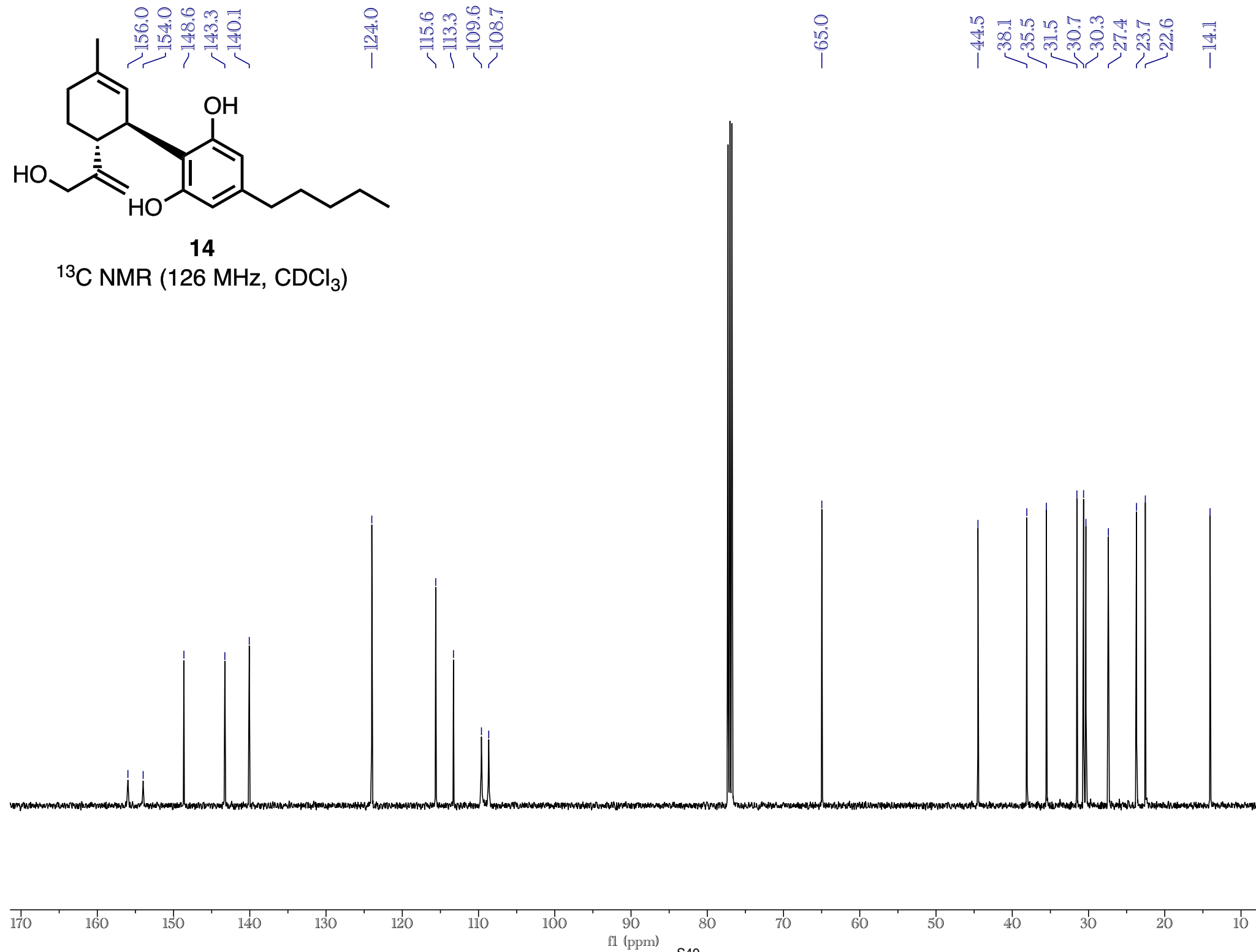


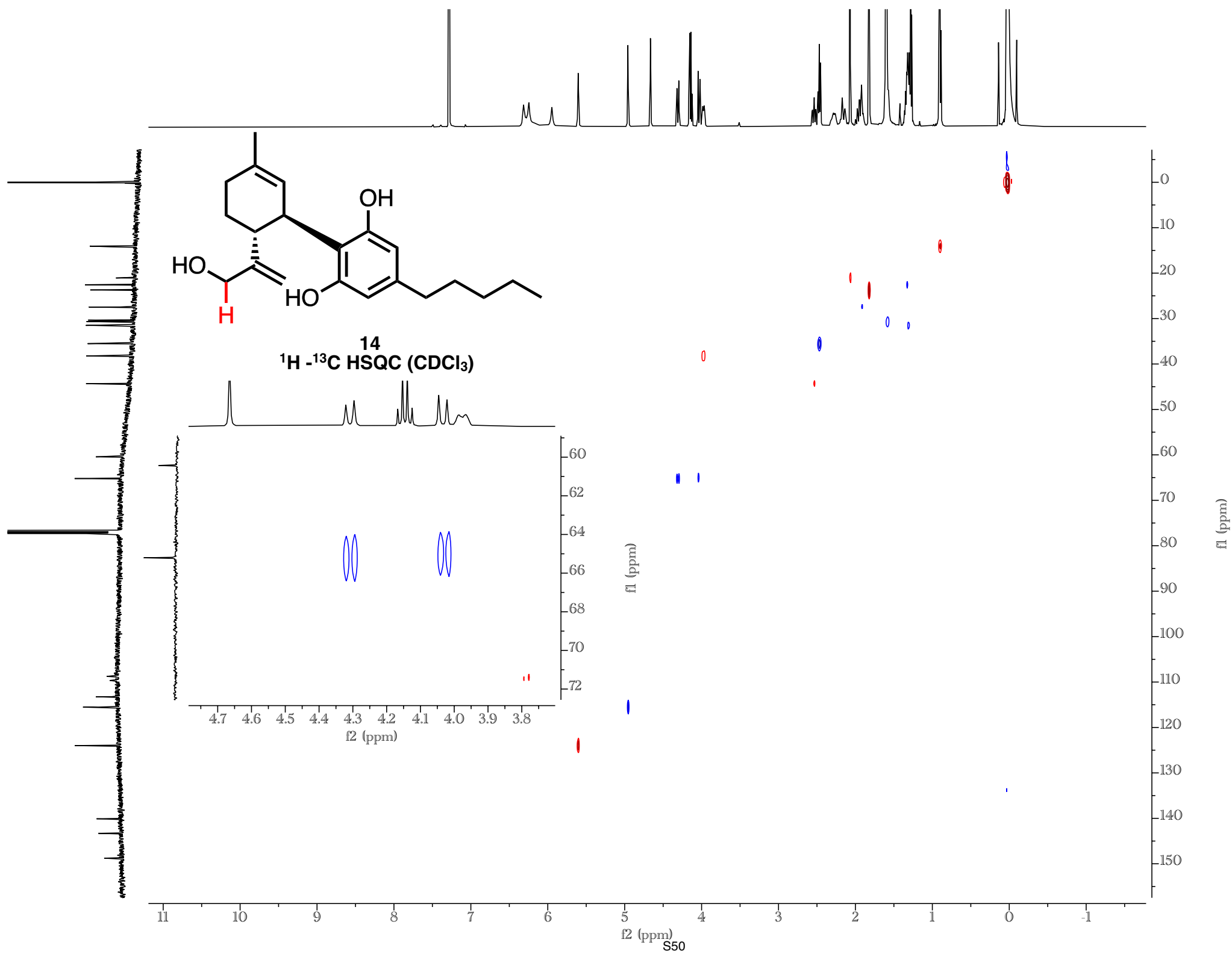


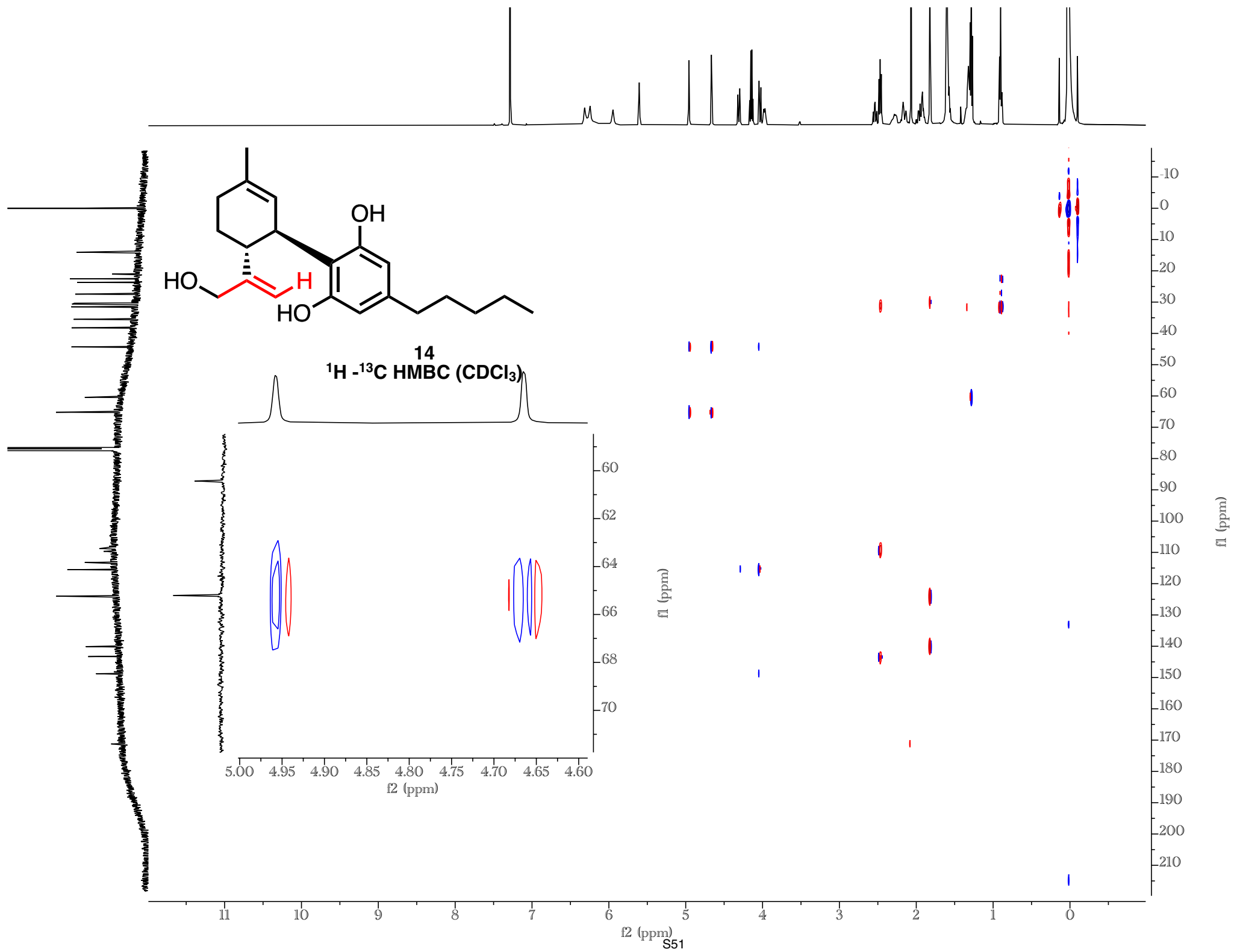


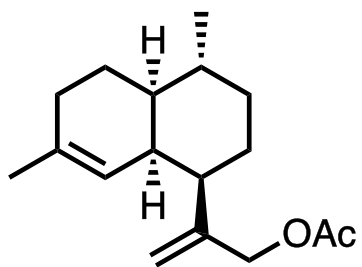
14

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



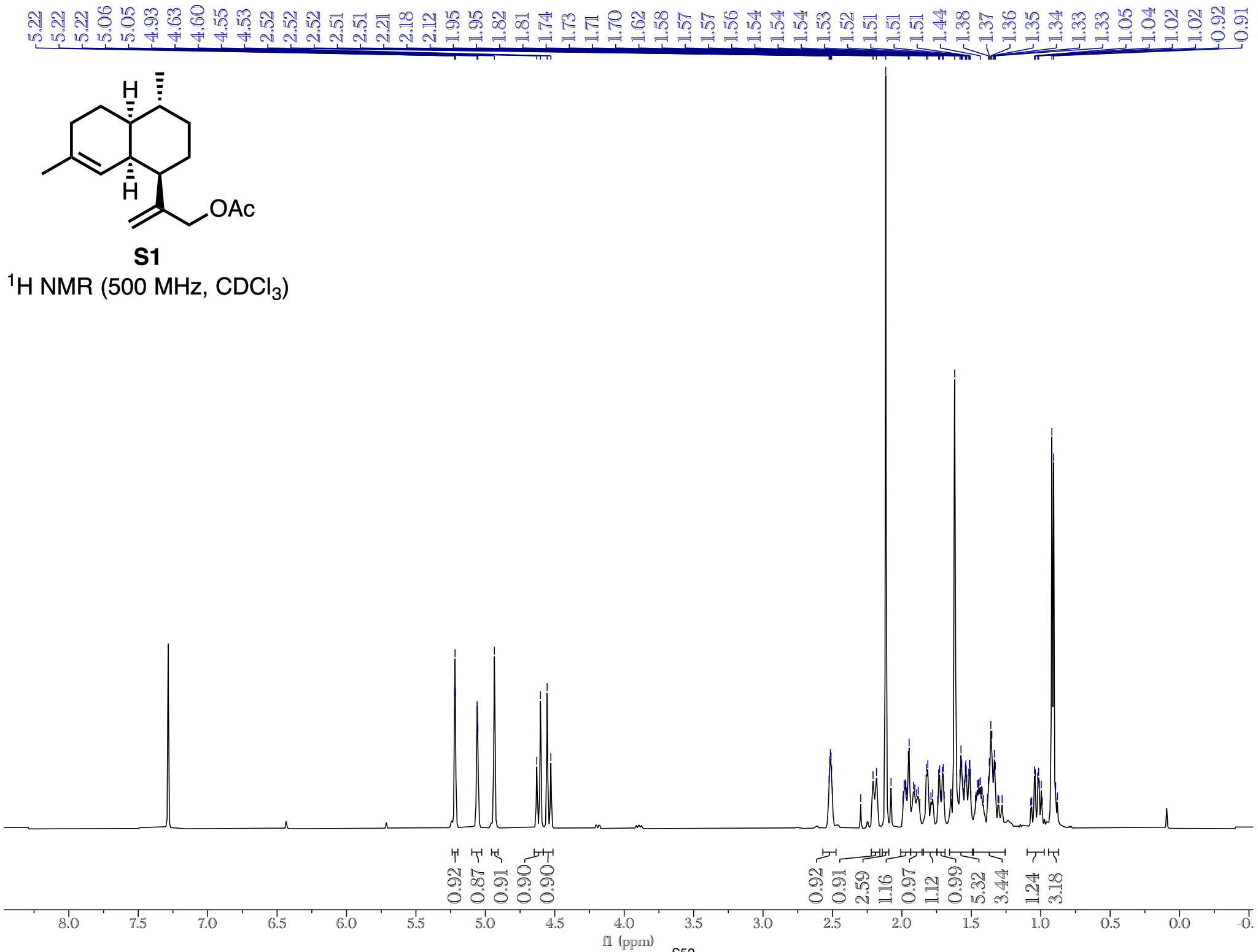


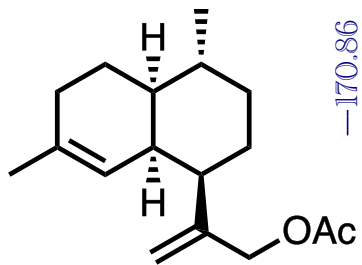




**S1**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )





**S1**

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

