

# Scalable Total Synthesis and Biological Evaluation of Haouamine A and Its Atropisomer

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## SUPPORTING INFORMATION

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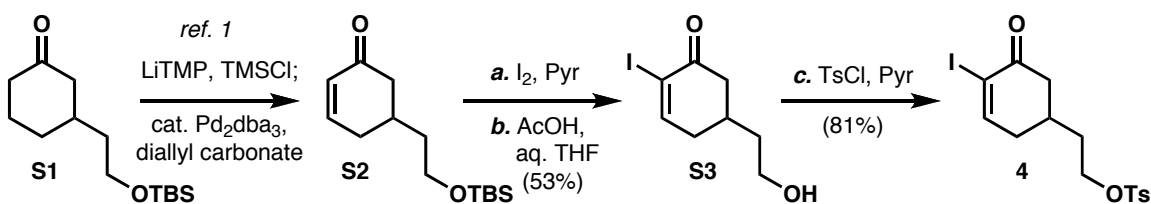
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**General Procedures.** All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), *N,N*-dimethylformamide (DMF), and triethylamine (Et<sub>3</sub>N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO<sub>4</sub>), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl<sub>3</sub> @ 7.26 ppm <sup>1</sup>H NMR, 77.00 ppm <sup>13</sup>C NMR, (CHD<sub>2</sub>)CO(CD<sub>3</sub>) @ 2.05 ppm <sup>1</sup>H NMR, 29.84 <sup>13</sup>C NMR).

The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.

### Scheme S1.



### Iodocyclohexenone alcohol (S3):

Compound **S2** was synthesized according to the procedure of Shea<sup>1</sup> beginning with 56.6 mmol **S1**. The product was crudely purified and this mixture (containing ca. 50 mmol **S2** along with small amounts of the regioisomeric enone and dba) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (125 mL, 0.4 M) and cooled to 0 °C. Pyridine (100 mL, 0.5 M) was added followed by iodine (31.7 g, 125 mmol, 2.5 equiv). The reaction flask was removed from the cooling bath, allowed to warm to room temperature, and stirred for 2 h. EtOAc (500 mL) was added, and the organics were washed successively with: sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 x 150 mL), H<sub>2</sub>O (150 mL), 10% aq. CuSO<sub>4</sub> (6 x 150 mL), H<sub>2</sub>O (150 mL), and brine (150 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated. This crude material was

<sup>1</sup> Zhu, L.; Lauchli, R.; Loo, M.; Shea, K. J. *Org. Lett.* **2007**, *9*, 2269.

then dissolved in a mixture of THF (50 mL, 1.0 M), H<sub>2</sub>O (50 mL, 1.0 M), and AcOH (150 mL, 0.33 M) and placed in a 50 °C oil bath. After stirring at this temperature for 2.5 h, the reaction mixture was allowed to cool to room temperature. Na<sub>2</sub>CO<sub>3</sub> (150 g, 1.42 mol) was dissolved in H<sub>2</sub>O (1.0 L), and this aqueous solution was *cautiously* combined with the reaction mixture. Once effervescence had ceased, the solution was extracted with EtOAc (500 mL). The organic layer was washed with brine (250 mL), and the combined aqueous phase was further extracted with EtOAc (3 x 500 mL). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 1:1 → 1:0 EtOAc/hexanes) afforded **S3** as a colorless oil (8.0 g, 53% over three steps);

**R<sub>f</sub>** = 0.31 (silica gel, 2:1 EtOAc/hexanes);

**IR** (film)  $\nu_{\max}$  3426, 2928, 2875, 1698, 1677, 1591, 1326, 1066, 1046 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.85 – 2.78 (m, 1H), 2.57 – 2.49 (m, 1H), 2.45 – 2.29 (m, 2H), 2.27 – 2.19 (m, 1H), 1.76 (br s, 1H), 1.70 – 1.57 (m, 2H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  192.4, 158.5, 103.4, 59.8, 43.2, 37.5, 36.1, 32.1;

**HRMS** (ESI) calcd. for C<sub>8</sub>H<sub>11</sub>IO<sub>2</sub> [M + Na<sup>+</sup>] 288.9696, found 288.9696.

#### **Tosyloxy iodocyclohexenone (4):**

Alcohol **S3** (8.0 g, 30.1 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (150 mL, 0.2 M) and to this solution was added pyridine (7.3 mL, 90.2 mmol, 3.0 equiv) and *p*-toluenesulfonyl chloride (11.5 g, 60.1 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 6 h and then diluted with EtOAc (600 mL). The organics

were washed successively with: 1 N HCl (3 x 150 mL), H<sub>2</sub>O (150 mL), and brine (150 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 3:1 → 2:1 hexanes/EtOAc) afforded **4** as a white solid (10.3 g, 81%);

**m.p.** 95–97 °C;

**R<sub>f</sub>** = 0.13 (silica gel, 3:1 hexanes/EtOAc);

**IR** (film)  $\nu_{\max}$  2920, 1681, 1595, 1352, 1188, 1172, 926 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 5.9 Hz, 3.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.13 – 4.02 (m, 2H), 2.70 – 2.64 (m, 1H), 2.49 – 2.41 (m, 1H), 2.46 (s, 3H), 2.36 – 2.12 (m, 3H), 1.80 – 1.67 (m, 2H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  191.2, 157.6, 145.1, 132.6, 129.9, 127.8, 103.4, 67.2, 42.5, 35.4, 33.8, 31.6, 21.6;

**HRMS** (ESI) calcd. for C<sub>15</sub>H<sub>17</sub>IO<sub>4</sub>S [M + H<sup>+</sup>] 420.9965, found 420.9982.

### **Cyclohexenones **7** and **8**:**

#### **Coupling procedure:**

Aryl bromide **5** (1.0 g, 1.69 mmol) was dried by azeotropic removal of water with benzene (2 x 10 mL) then dissolved in THF (11.3 mL, 0.15 M). The reaction flask was cooled to –78 °C and *n*-butyllithium (860  $\mu$ L, 2.16 M, 1.86 mmol, 1.1 equiv) was added at once. The resulting bright orange solution was stirred for 10 min at –78 °C. Trimethyl borate (386  $\mu$ L, 3.38 mmol, 2.0 equiv) was added, the flask was removed from the cooling bath, and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h at room temperature, water (3.10 mL, 0.55 M) was added and stirring was

continued for 10 min. A separate flask was charged with the following solids: tosyloxy iodocyclohexenone **4** (710 mg, 1.69 mmol, 1.0 equiv), bis(benzonitrile)dichloropalladium (65.2 mg, 0.17 mmol, 0.1 equiv), triphenylarsine (104 mg, 0.34 mmol, 0.2 equiv), and silver(I) oxide (627 mg, 2.70 mmol, 1.6 equiv). This flask was then evacuated and backfilled with argon three times. The aqueous THF solution of the boronic ester was then added via cannula to this flask using additional THF (13.7 mL) to ensure quantitative transfer and to give a final concentration of 0.06 M in 8:1 THF/H<sub>2</sub>O. The resulting black suspension was stirred in the dark at room temperature for 18 h. The reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl (30 mL), and the resulting solution was stirred for 1 h. The solution was then filtered through Celite, washing with EtOAc (50 mL). The organic layer was separated and washed with brine (30 mL), and the combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 3:1 → 2:1 hexanes/EtOAc) afforded diastereomeric mixture **6** as an off-white foam (1.05 g, 77%).

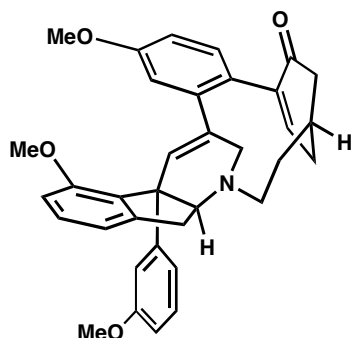
**Iodide formation:**

Coupled product **6** (1.0 g, 1.24 mmol) was dissolved in acetone (12.4 mL, 0.1 M) at room temperature. Sodium iodide (1.86 g, 12.4 mmol, 10.0 equiv) was added, and the reaction mixture was stirred at this temperature for 7 h. The solvent was removed on a rotary evaporator, EtOAc (150 mL) was added, and the organic layer was washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (50 mL) then brine (50 mL). The combined aqueous layers were extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over MgSO<sub>4</sub>, filtered,

and concentrated. Column chromatography (silica gel, 85:15 hexanes:EtOAc) afforded the alkyl iodide (906 mg, 96%) as a slightly yellow foam.

**Macrocyclization:**

This alkyl iodide (1.87 g, 2.46 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (49.2 mL, 0.05 M) and the resulting light yellow solution was cooled to 0 °C. Trifluoroacetic acid (2.46 mL, 1.0 M) was added dropwise, and the reaction flask was placed in a 5 °C cold room and stirred for 24 h. Benzene (25 mL) was then added, and the solvent was removed by a rotary evaporator. This process was repeated twice more with benzene (25 mL each) to ensure complete removal of the excess trifluoroacetic acid. The resulting dark oil was then dissolved in acetonitrile (1.23 L, 0.002 M) and treated with *N,N*-diisopropylethylamine (4.3 mL, 24.6 mmol, 10.0 equiv). The reaction mixture was heated to reflux and stirred for 26 h. After cooling to room temperature the solvent was removed by rotary evaporation. Sat. aq. NaHCO<sub>3</sub> (100 mL) was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 4:1 → 1:2 hexanes/EtOAc) afforded first **8** (423 mg as a ~4:1 mixture of isomers) and then the more polar **7** (614 mg as a ~10:1 mixture of isomers) (79% combined yield, 1.45:1 of **7**:**8**). [NOTE- This diastereomeric ratio implies a small amount of selectivity in either this or the previous coupling step.]



**Cyclohexenone 7:**

**m.p.** 227–230 °C;

**R<sub>f</sub>** = 0.29 (silica gel, 2:1 EtOAc/hexanes);

**IR** (film)  $\nu_{\max}$  2934, 2834, 1665, 1598, 1477, 1464, 1287, 1261, 1081, 1040  $\text{cm}^{-1}$ ;

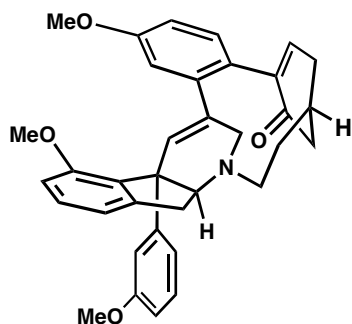
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) major isomer:  $\delta$  7.23 – 7.14 (m, 4H), 6.86 (d,  $J$  = 7.6 Hz, 1H), 6.84 (dd,  $J$  = 2.8 Hz, 8.5 Hz, 1H), 6.72 – 6.67 (m, 5H), 6.58 (d,  $J$  = 2.2 Hz, 1H), 3.88 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.56 (s, 3H), 3.23 (dd,  $J$  = 6.7 Hz, 17.1 Hz, 1H), 3.13 (dd,  $J$  = 9.0 Hz, 17.1 Hz, 1H), 3.03 (dd,  $J$  = 1.7 Hz, 16.1 Hz, 1H), 2.85 (d,  $J$  = 16.0 Hz, 1H), 2.77 – 2.67 (m, 2H), 2.61 – 2.43 (m, 5H), 2.07 (m, 1H), 1.23 (m, 1H);

**<sup>13</sup>C-APT NMR** (150 MHz, CDCl<sub>3</sub>) major isomer:  $\delta$  198.7, 159.4, 158.8, 156.5, 152.4, 149.4, 144.1, 143.4, 139.3, 136.7, 134.9, 131.24, 131.19, 128.8, 128.6, 126.2, 118.9, 116.8, 114.8, 112.8, 111.8, 110.1, 109.5, 73.7, 55.3, 55.2, 55.0, 54.9, 50.5, 47.6, 43.1, 33.3, 30.7, 30.0, 27.4;

**HRMS** (ESI) calcd. for C<sub>35</sub>H<sub>35</sub>NO<sub>4</sub> [M + H<sup>+</sup>] 534.2639, found 534.2637.

**[This compound (7) has also been verified by X-ray crystallography, see accompanying .cif files]**





**Cyclohexenone 8:**

**m.p.** 107–111 °C;

**R<sub>f</sub>** = 0.40 (silica gel, 2:1 EtOAc/hexanes);

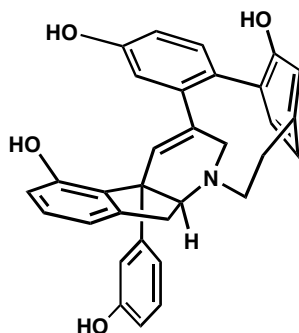
**IR** (film)  $\nu_{\max}$  2937, 2834, 1662, 1598, 1477, 1463, 1286, 1262, 1083, 1040  $\text{cm}^{-1}$ ;

**<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ) major isomer:  $\delta$  7.24 (d,  $J = 7.3$  Hz, 1H), 7.22 (d,  $J = 6.4$  Hz, 1H), 7.17 (t,  $J = 8.2$  Hz, 1H), 7.03 (d,  $J = 2.7$  Hz, 1H), 6.88 (d,  $J = 7.5$  Hz, 1H), 6.85 (dd,  $J = 2.8$  Hz, 8.5 Hz, 1H), 6.78 (m, 1H), 6.73 – 6.67 (m, 4H) 6.65 (m, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.60 (s, 3H), 3.38 (dd,  $J = 2.5$  Hz, 7.4 Hz, 1H), 3.28 (dd,  $J = 7.5$  Hz, 16.7 Hz, 1H), 3.11 (d,  $J = 14.2$  Hz, 1H), 3.03 (dd,  $J = 2.2$  Hz, 16.8 Hz, 1H), 2.75 (m, 1H), 2.60 (m, 2H), 2.50 (m, 2H), 2.38 (m, 2H), 2.17 (dt,  $J = 4.5$  Hz, 12.9 Hz, 1H), 1.86 (m, 1H), 1.45 (m, 1H);

**<sup>13</sup>C NMR** (125 MHz,  $\text{CDCl}_3$ ) both isomers:  $\delta$  199.0, 195.1, 159.7, 159.6, 159.3, 158.7, 156.6, 156.2, 151.9, 151.3, 148.7, 144.9, 144.4, 144.0, 143.8, 143.6, 143.4, 141.0, 135.3, 134.5, 133.6, 132.7, 131.7, 131.5, 130.0, 129.2, 129.0, 128.7, 128.5, 128.4, 126.1, 119.2, 118.9, 116.6, 116.4, 114.8, 114.5, 113.1, 111.89, 111.85, 111.4, 110.6, 109.5, 109.4, 75.6, 72.7, 60.3, 55.7, 55.4 (2C), 55.24, 55.22, 55.0 (2C), 50.1, 49.7, 48.0, 47.3, 44.0, 42.1, 36.6, 34.0, 33.2, 31.0, 30.8, 30.2, 29.9, 26.7;

**HRMS** (ESI) calcd. for  $\text{C}_{35}\text{H}_{35}\text{NO}_4$  [ $\text{M} + \text{H}^+$ ] 534.2639, found 534.2636.

[This compound (8) has also been verified by X-ray crystallography, see accompanying .cif files]



**Haouamine A (1):**

Macrocyclic **7** (1.05 g, 1.97 mmol) was dried by azeotropic removal of water with benzene (2 x 20 mL) then suspended in THF (19.7 mL, 0.1 M). A solution of lithium chloride in THF was added (19.7 mL, 0.5 M, 9.84 mmol, 5.0 equiv), and the reaction mixture was sonicated for 10 seconds to give a fine white suspension. The reaction flask was cooled to  $-78\text{ }^{\circ}\text{C}$  and then treated with freshly prepared lithium hexamethyldisilazide in THF (7.58 mL, 0.52 M, 3.94 mmol, 2.0 equiv). The reaction flask was then placed in a  $0\text{ }^{\circ}\text{C}$  cooling bath and stirred for 20 min. At this point a clear, light-orange solution was observed. The reaction mixture was again cooled to  $-78\text{ }^{\circ}\text{C}$ . Meanwhile a solution of *N*-*t*-butylbenzenesulfinimidoyl chloride<sup>2</sup> was prepared in THF (0.5 M). This reagent (5.12 mL, 2.56 mmol, 1.3 equiv) was then added rapidly down the side of the reaction flask and the reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1 minute. Sat. aq.  $\text{NH}_4\text{Cl}$  (75 mL) was then added and the biphasic solution was allowed to warm to room temperature while rapidly stirring. EtOAc (75 mL) was added and the organic layer was separated. The aqueous

<sup>2</sup> For preparation, see: Matsuo, J.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223.

layer was further extracted with EtOAc (2 x 75 mL) and the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 95:5 → 85:15 hexanes/EtOAc to elute the product, then 1:1 → 1:2 hexanes/EtOAc to elute the recovered starting material) afforded haouamine A trimethylether **9** (633 mg, 60%) as well as recovered macrocycle **7** (245 mg, 23%). Haouamine A trimethylether **9** (285 mg, 0.54 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (26.8 mL, 0.02 M) and cooled to -78 °C. Boron tribromide (3.75 mL, 1.0 M, 3.75 mmol, 7.0 equiv) was added dropwise and the reaction mixture was then removed from the cooling bath and placed in a 5 °C cold room. Stirring was continued at this temperature for 20 h, after which the reaction vessel was cooled to 0 °C and quenched by the careful addition of aq. KH<sub>2</sub>PO<sub>4</sub>/K<sub>2</sub>PO<sub>4</sub> (75 mL, 1.0 M, pH 7). EtOAc (100 mL) and MeOH (20 mL) were added and the resulting suspension was allowed to warm to room temperature and stir until dissolution of all solids. The layers were separated, and the aqueous layer was further extracted with EtOAc containing MeOH (2 x 100 mL EtOAc + 10 mL MeOH). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (silica gel, 99:1 → 98:2 CHCl<sub>3</sub>/MeOH) afforded haouamine A **1** (165 mg, 63%) as a white solid. Utilizing this route over 550 mg of (±)-**1** have been produced to date.

**R<sub>f</sub>** = 0.24 (silica gel, 9:1 CHCl<sub>3</sub>/MeOH);

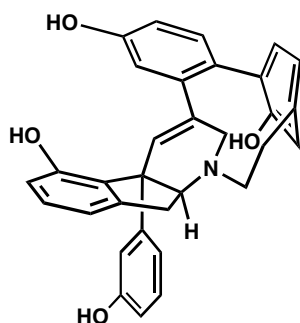
**IR** (film)  $\nu_{\max}$  3244, 1592, 1567, 1463, 1446, 1276, 1184 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>) [~3:2 isomeric ratio in this solvent]  $\delta$  7.42 (d, *J* = 8.2 Hz, 0.4H), 7.24 (d, *J* = 8.1 Hz, 0.6H), 7.12 (m, 1H), 7.07 (t, *J* = 7.9 Hz, 0.4H), 6.97 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 0.6H), 6.85 (d, *J* = 7.4 Hz, 0.6H), 6.79 (m, 2H), 6.75 (m, 1.6H), 6.72 – 6.59 (m, 2.6H), 6.53 (m, 0.6H), 6.48 – 6.42 (m, 1.6H), 6.13 (d, *J* = 2.5

Hz, 0.4H), 5.62 (d,  $J = 1.4$  Hz, 0.6H), 3.65 (0.4H, obscured by solvent), 3.16 (d,  $J = 4.6$  Hz, 0.6H), 3.02 (dd,  $J = 5.9$  Hz, 13.9 Hz, 0.6H), 2.98 – 2.87 (m, 1.4H), 2.85 – 2.69 (m, 1H), 2.61 (dd,  $J = 4.3$  Hz, 11.5 Hz, 0.6H), 2.53 (dd,  $J = 5.0$  Hz, 11.8 Hz, 0.4H), 2.39 (m, 0.4H), 2.33 (dd,  $J = 2.6$  Hz, 15.1 Hz, 0.6H), 2.24 (dd,  $J = 15.4$  Hz, 2.4 Hz, 0.4H), 2.18 (m, 0.6H), 2.04 (0.4H, obscured by solvent), 1.76 (ddd,  $J = 4.5$  Hz, 11.2 Hz, 14.3 Hz, 0.6H), 0.79 (d,  $J = 15.1$  Hz, 0.6H), 0.40 (d,  $J = 15.7$  Hz, 0.4H);

$^{13}\text{C}$  NMR (150 MHz, 10%  $\text{D}_2\text{O}/\text{Acetone-}d_6$ )  $\delta$  158.27, 157.98, 157.73, 156.95, 156.91, 156.26, 155.11, 154.78, 153.22, 147.91, 146.16, 145.73, 145.20, 144.58, 144.47, 144.16, 143.03, 141.10, 134.52, 133.22, 132.76, 132.35, 131.62, 130.60, 130.44, 129.57, 129.35, 129.17, 129.08, 129.05, 128.89, 128.80, 128.04, 127.89, 126.24, 125.18, 122.32, 118.78, 118.43, 117.76, 117.36, 116.66, 116.50, 116.30, 114.95, 114.68, 114.57, 114.12, 114.01, 113.55, 113.50, 112.89, 75.15, 73.57, 62.79, 58.88, 57.03, 56.64, 53.45, 44.71, 40.43, 38.51, 35.67;

HRMS (ESI) calcd. for  $\text{C}_{32}\text{H}_{27}\text{NO}_4$  [ $\text{M} + \text{H}^+$ ] 490.2013, found 490.2016.



**Atrop-Haouamine A (2):**

An identical procedure to that above was applied to macrocycle **10** (600 mg, 1.12 mmol) with the following exceptions: the starting material was fully soluble in THF prior to treatment with base, and the dienolate solution was cooled to  $-95$  °C (acetone/liq.  $\text{N}_2$ )

before being treated with *N*-*t*-butylbenzenesulfinimidoyl chloride. An identical workup as above was followed by column chromatography (silica gel, 95:5 → 85:15 hexanes/EtOAc) to afford atrop-haouamine A trimethylether **10** (365 mg, 61%). [**This compound (10) has been verified by X-ray crystallography, see accompanying .cif files**] No starting material could be recovered with this substrate. An identical ether cleavage procedure was performed with **10** (150 mg, 0.28 mmol) to afford after column chromatography (99:1 → 9:1 CHCl<sub>3</sub>/MeOH) atrop-haouamine A (**2**) (83 mg, 60%) as a white solid.

**R<sub>f</sub>** = 0.13 (silica gel, 9:1 CHCl<sub>3</sub>/MeOH);

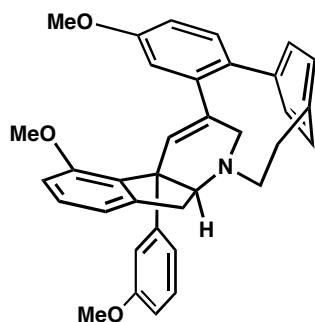
**IR** (film)  $\nu_{\max}$  3280, 1592, 1565, 1463, 1448, 1256, 1184 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>) [~7:3 isomeric ratio in this solvent]  $\delta$  7.36 (td, *J* = 1.3 Hz, 1.3 Hz, 8.6 Hz, 0.7H), 7.28 (d, *J* = 8.1 Hz, 0.3H), 7.09 (t, *J* = 7.7 Hz, 0.7H), 7.05 (t, *J* = 7.9 Hz, 0.3H), 6.99 (d, *J* = 7.9 Hz, 0.7H), 6.97 (d, *J* = 4.5 Hz, 0.3H), 6.95 (d, *J* = 7.7 Hz, 0.3H), 6.90 (td, *J* = 1.2 Hz, 7.8 Hz, 0.3H), 6.86 (dd, *J* = 1.5 Hz, 8.0 Hz, 0.3H), 6.82 (m, 1H), 6.79 – 6.73 (m, 2.4H), 6.69 (d, *J* = 1.5 Hz, 0.3H), 6.64 – 6.59 (m, 2.3H), 6.54 (m, 0.7H), 6.48 (d, *J* = 7.6 Hz, 0.7H), 6.45 (ddd, *J* = 1.0 Hz, 1.5 Hz, 1.7 Hz, 0.7H), 6.41 (m, 1.0H), 6.21 (d, *J* = 2.6 Hz, 0.3H), 5.55 (dd, *J* = 1.5 Hz, 7.7 Hz, 0.7H), 3.16 (d, *J* = 4.9 Hz, 0.7H), 3.02 (dd, *J* = 5.6 Hz, 14.0 Hz, 0.7H), 2.96 – 2.74 (m, 2.3H), 2.55 (m, 1H), 2.44 (m, 1H), 2.14 (m, 1.3H), 1.73 (ddd, *J* = 4.3 Hz, 11.4 Hz, 15.3 Hz, 0.7H), 0.83 (d, *J* = 15.1 Hz, 0.7H), 0.45 (dd, *J* = 0.9 Hz, 15.6 Hz, 0.3H);

**<sup>13</sup>C NMR** (150 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)  $\delta$  157.97, 157.68, 157.65, 157.43, 157.08, 156.90, 155.38, 154.77, 153.27, 147.55, 146.17, 146.09, 145.24, 145.03, 144.80, 143.97, 142.35, 140.93, 134.35, 133.76, 132.42, 130.64, 130.57, 130.38, 129.58, 129.52, 129.32,

128.99, 128.85, 128.63, 127.52, 125.21, 124.32, 121.91, 118.95, 118.70, 118.39, 117.07, 116.36, 116.16, 116.04, 115.12, 114.49, 114.16, 113.98, 113.60, 113.46, 113.01, 75.02, 73.46, 62.91, 59.25, 56.86, 56.83, 53.80, 44.68, 40.46, 38.38, 35.32, 30.86;

**HRMS** (ESI) calcd. for C<sub>32</sub>H<sub>27</sub>NO<sub>4</sub> [M + H<sup>+</sup>] 490.2013, found 490.2012.



**Reduced macrocycle (11):**

Compound **9** (5.0 mg, 0.0094 mmol) was placed in a small vial along with *N*-phenyl-bis(trifluoromethanesulfonimide) (17 mg, 0.047 mmol, 5.0 equiv) and cesium carbonate (31 mg, 0.094 mmol, 10 equiv). Acetonitrile (200  $\mu$ L, 0.047 M) was added and the reaction mixture was stirred at room temperature for 5 h. Sat. aq. NH<sub>4</sub>Cl (10 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. A crude purification was performed by passing the mixture through a plug of silica gel eluting with 4:1 hexanes/Et<sub>2</sub>O. After concentration, this crude material was placed in a small vial along with Pd(dppf)Cl<sub>2</sub> (3.8 mg, 0.0047 mmol, 0.5 equiv). The flask was then evacuated and backfilled with argon three times. DMF (200  $\mu$ L, 0.047 M) was added followed by triethylsilane (15.2  $\mu$ L, 0.094 mmol, 10.0 equiv). The reaction flask was then placed in an 80 °C oil bath and stirred for 4 h. Sat. aq. NaHCO<sub>3</sub> (20 mL) and EtOAc (20 mL) were then added. The layers were separated and the organic layer was washed with brine (5 x 10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated.

Preparative thin-layer chromatography (silica gel, 4:1 hexanes/Et<sub>2</sub>O) afforded **11** (2.5 mg, 51%) as a clear film. An identical procedure beginning with **10** (29.8 mg, 0.056 mmol) also afforded **11** (8.7 mg, 30%).

**R<sub>f</sub>** = 0.34 (silica gel, 4:1 hexanes/Et<sub>2</sub>O);

**IR** (film)  $\nu_{\text{max}}$  2935, 2834, 1598, 1562, 1477, 1465, 1438, 1284, 1259, 1080, 1048 cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) [ $\sim$  3:2 isomeric ratio in this solvent]  $\delta$  7.54 (d,  $J$  = 8.3 Hz, 0.4H), 7.51 (d,  $J$  = 8.2 Hz, 0.6H), 7.39 (dd,  $J$  = 1.2 Hz, 7.8 Hz, 0.4H), 7.30 (m, 1.4H), 7.23 – 7.11 (m, 3.2H), 6.96 (d,  $J$  = 7.3 Hz, 0.6H), 6.89 (m, 1.2H), 6.86 (m, 0.8H), 6.80 (m, 1.6H), 6.72 (m, 1.4H), 6.66 (d,  $J$  = 8.0 Hz, 0.4H), 6.60 (d,  $J$  = 2.7 Hz, 0.4H), 6.57 (m, 1H), 6.43 (d,  $J$  = 2.6 Hz, 0.6H), 6.15 (d,  $J$  = 2.6 Hz, 0.4H), 6.07 (d,  $J$  = 7.8 Hz, 0.6H), 3.84 (s, 1.8H), 3.81 (s, 1.2H), 3.75 (s, 1.2H), 3.71 (s, 1.8H), 3.69 (s, 1.8H), 3.55 (s, 1.2H), 3.24 (dd,  $J$  = 1.4 Hz, 4.3 Hz, 0.6H), 3.03 – 2.85 (m, 2.0H), 2.79 – 2.55 (m, 2.0H), 2.31 (m, 1H), 2.09 (dd,  $J$  = 2.6 Hz, 16.0 Hz, 0.4H), 1.94 (ddd,  $J$  = 5.6 Hz, 10.0 Hz, 13.3 Hz, 0.4H), 1.63 (ddd,  $J$  = 4.4 Hz, 11.2 Hz, 14.0 Hz, 0.6H), 0.37 (d,  $J$  = 15.4 Hz, 0.6H), –0.13 (dd,  $J$  = 0.9 Hz, 16.0 Hz, 0.4H);

**<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>)  $\delta$  159.45, 159.30, 158.64, 158.57, 157.18, 156.57, 152.50, 146.59, 145.38, 145.29, 144.21, 143.67, 142.11, 140.65, 140.52, 140.19, 140.14, 139.35, 135.38, 135.17, 134.74, 134.33, 134.31, 132.87, 132.28, 132.23, 130.11, 129.91, 128.98, 128.93, 128.71, 128.48, 128.42, 128.36, 128.23, 127.90, 125.61, 125.54, 119.73, 118.96, 117.39, 116.95, 116.06, 115.68, 113.72, 112.67, 111.56, 111.49, 110.71, 110.46, 109.39, 109.25, 74.32, 72.83, 62.52, 58.42, 56.44, 56.29, 55.39, 55.36, 55.31, 55.17, 55.08, 54.99, 52.75, 43.89, 39.68, 37.65, 34.85, 29.56;

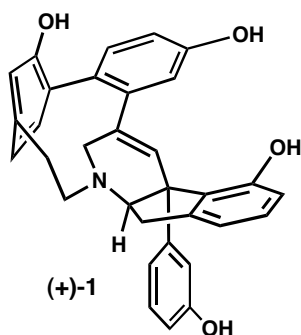
**HRMS** (ESI) calcd. for C<sub>35</sub>H<sub>33</sub>NO<sub>3</sub> [M + H<sup>+</sup>] 516.2533, found 516.2530.

### Failed oxidations of 7 and 8:

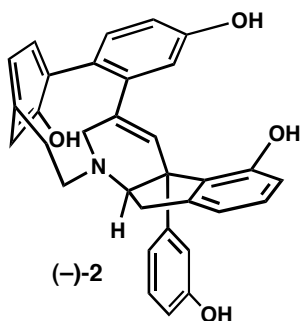
- $\alpha$ -Selenation-oxidation-elimination
- LDA;  $\text{Cp}_2\text{FePF}_6$
- $\text{CuCl}_2$ ,  $\text{LiCl}$ ,  $\Delta^3$
- $\alpha$ -Bromination, elimination
- Benzeneseleninic anhydride,  $\Delta^4$
- Pd/C, xylenes,  $\Delta$
- $\text{PdCl}_2$ ,  $\text{Na}_2\text{CO}_3$ , *t*-BuOH,  $\Delta^5$
- DDQ

### Enantioselective synthesis:

Enantiopure **5**<sup>6</sup> (200 mg) has also been carried through the above sequence with racemic **4** to deliver (+)-haouamine A [(+)-**1**] (14.6 mg) and (-)-atrop-haouamine A [(–)-**2**] (9.8 mg):



(+)-haouamine A  
[ $\alpha$ ]<sub>D</sub><sup>20</sup> +80.3 (c 0.4, MeOH)



(–)-atrop-haouamine A  
[ $\alpha$ ]<sub>D</sub><sup>20</sup> –143.3 (c 0.3, MeOH)

natural (–)-haouamine A:  
[ $\alpha$ ]<sub>D</sub><sup>27</sup> –50.2 (c 0.4, MeOH)

<sup>3</sup> Murase, M.; Hosaka, T.; Koike, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1989**, *37*, 1999.

<sup>4</sup> Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. C. S. Perkin I*, **1980**, 2209.

<sup>5</sup> Shan, S.; Ha, C. *Syn. Commun.* **2004**, *34*, 4005.

<sup>6</sup> Burns, N. Z.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 205.



**Biological Assay:**

**Tissue Culture.** Prostate cancer PC3 cells were obtained from American Tissue Type Culture collection (ATCC, VA) and maintained as recommended in full media supplemented with 10% fetal bovine serum. Cells were grown in an incubator at 37 °C / 5% CO<sub>2</sub>. Before each experiment, cell viability was assessed by using trypan-blue indicator on a Vi-Cell counter (Beckman Coulter, CA).

**Cell Proliferation Assay.** Cells were plated in white opaque-bottomed 384-well plates (Becton, Dickinson, NJ) and incubated for 24 h before each experiment. Compounds were dissolved as 10 mM stocks in DMSO and stored at –20 °C. Serial dilutions of compounds were prepared in full media and added to cells (in quadruplicate) for 24 h such that DMSO concentration did not exceed 1%. Cell viability was measured using Cell Titer Glo assay following manufacturer’s protocol (Promega, CA). Average signal was background subtracted and normalized to DMSO control. Data were processed using Kaleidagraph software and dose-titration points were fit by using a non-linear regression equation  $[(m1-m4)/(1+((m0/m3)^{m2}))]+m4$ ;  $m1=3.5$ ;  $m2=1$ ;  $m3=1.8$ ;  $m4=0.1$ ].  $R^2$  values were 0.996 – 0.998 range. IC<sub>50</sub> values were calculated accordingly from the fitted curves.

**Table S1.** Growth inhibitory activity of Haouamine A and analogues in PC3 cells

compound	IC <sub>50</sub> (μM)
haouamine A ( <b>1</b> )	29 ± 2
atrop-haouamine A ( <b>2</b> )	32 ± 3
dihydro-atrop-haouamine A	> 75
dihydro-haouamine A	>180

**Note on Biological Activity:**

Zubía and coworkers reported<sup>7</sup> that Haouamine A exhibits selective activity against HT-29 colon cancer cell lines ( $IC_{50} = 0.1 \text{ ug/ml}$ ,  $\sim 0.2 \text{ }\mu\text{M}$ ) without providing details about how these experiments were conducted or the  $IC_{50}$  values were measured. We obtained a minute quantity of natural **1** from the Zubía group which we tested in HT-29 cells and found that it exhibits only  $\sim 20 \%$  growth inhibition at  $10 \text{ }\mu\text{M}$  after 72 h treatment (which is not in agreement with their findings). On the other hand, we tested exhaustively the bioactivity and determined the mechanism of action of synthetic racemic **1** in a wide panel of cell lines which include HT-29, HCT-116, PC-3, MCF-7, A-549, HeLa, HUVEC, and RPE (Krylova *et al.*, manuscript in preparation).

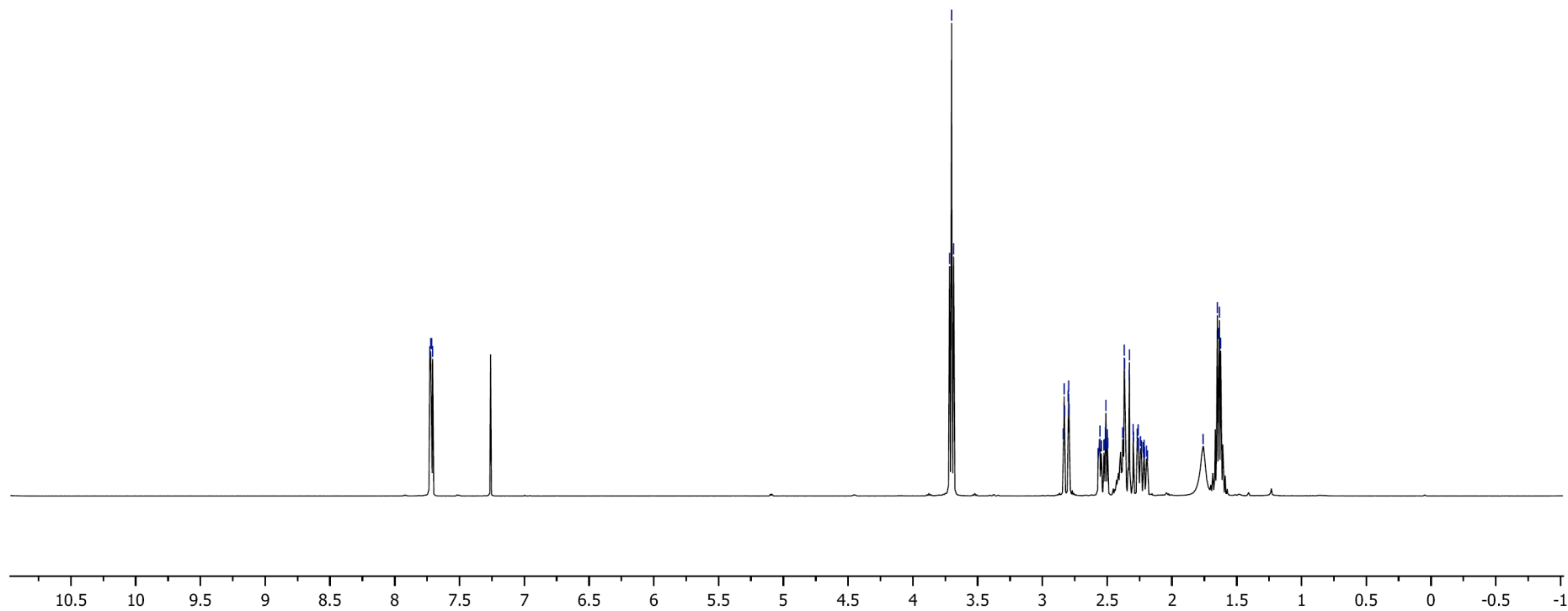
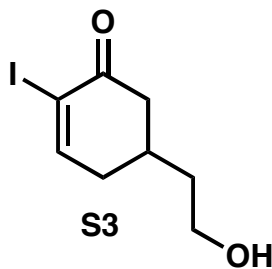
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<sup>7</sup> Garrido, L.; Zubía, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *68*, 293.

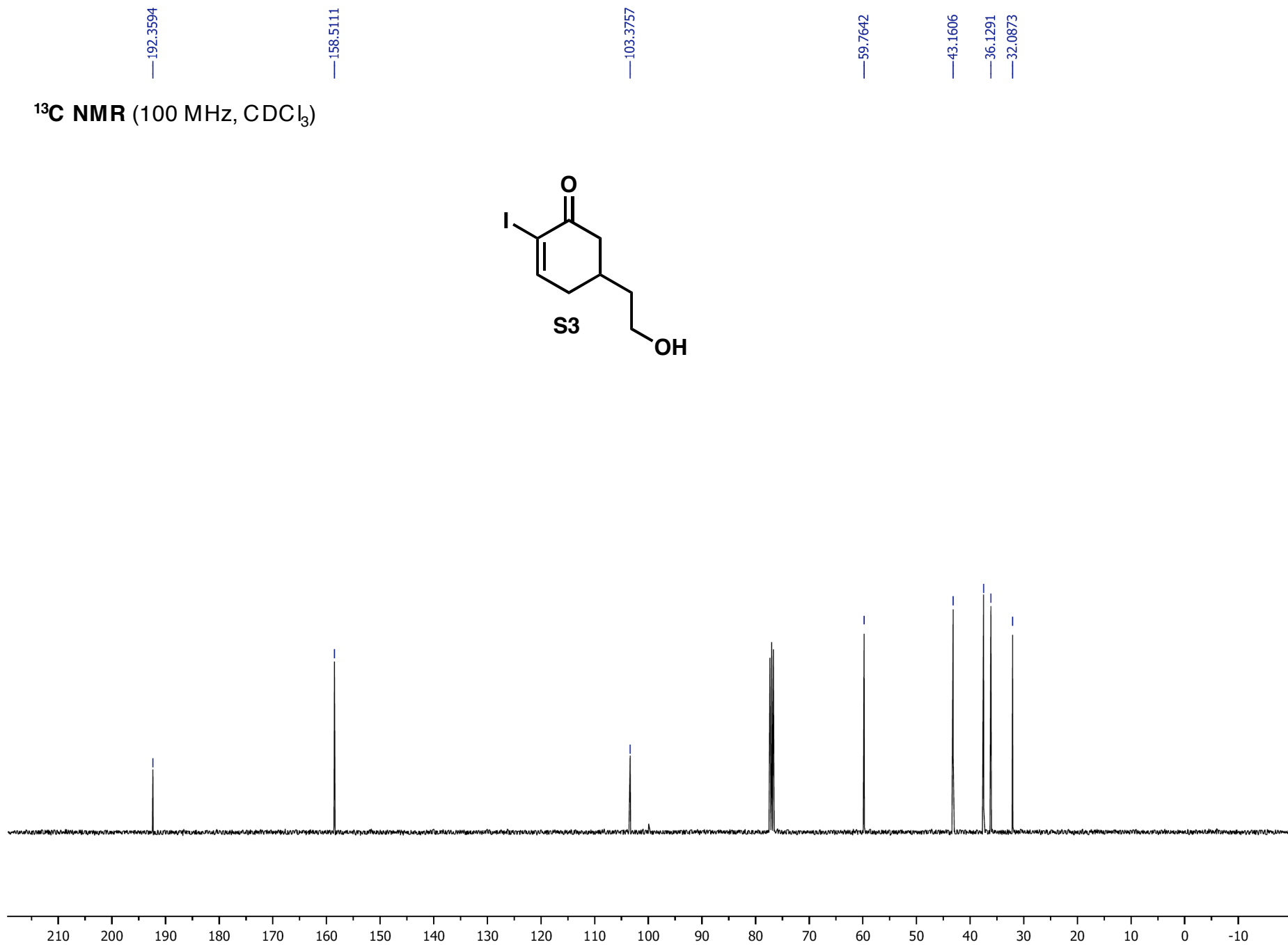
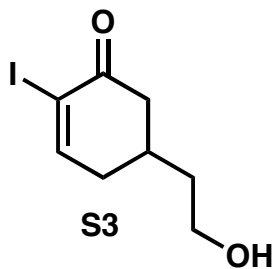
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2.7941  
2.4988  
2.2656  
2.2151  
1.7594  
1.6493  
1.6398  
1.6333  
1.6237

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**

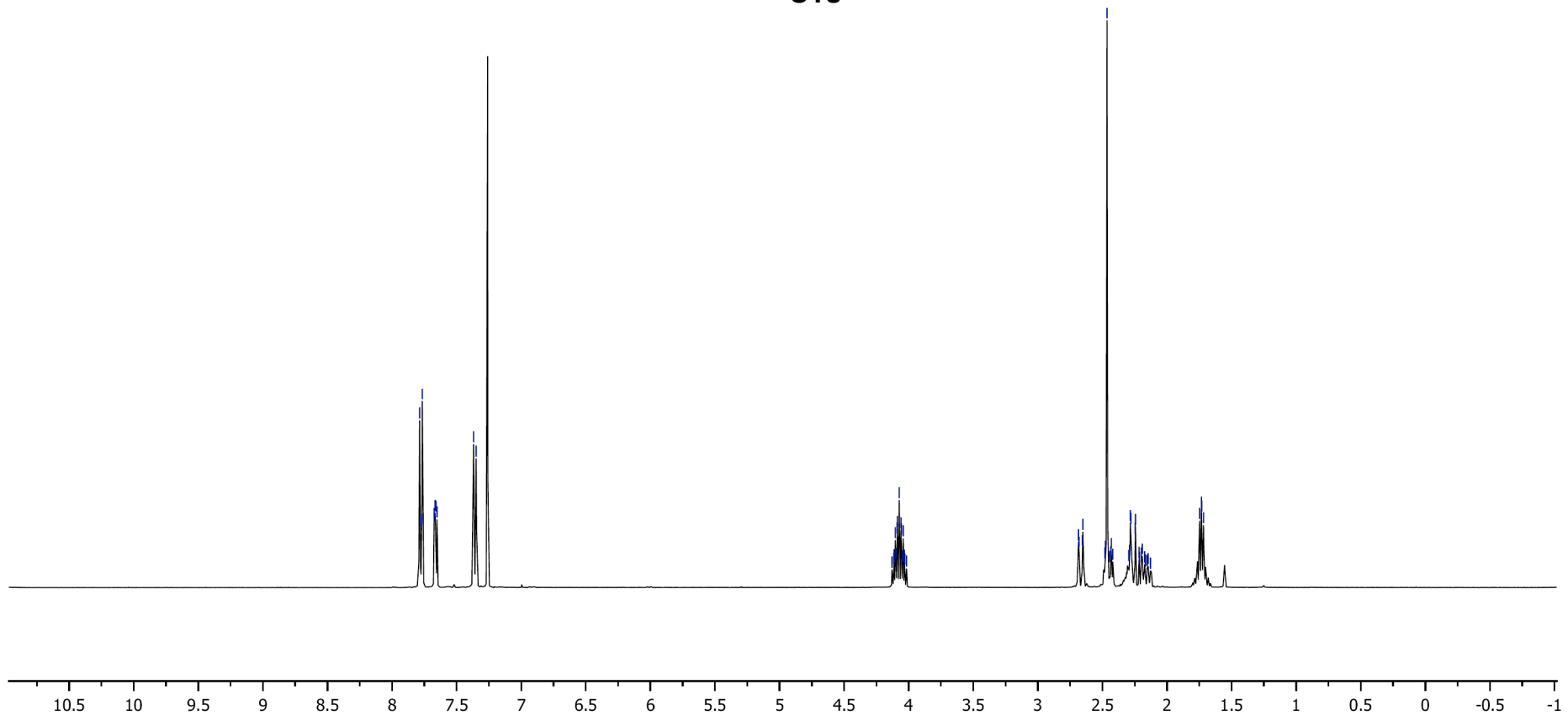
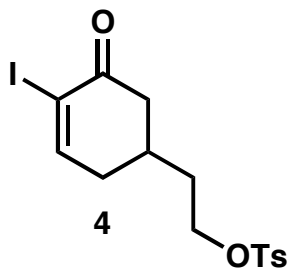


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7.6665  
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7.3487

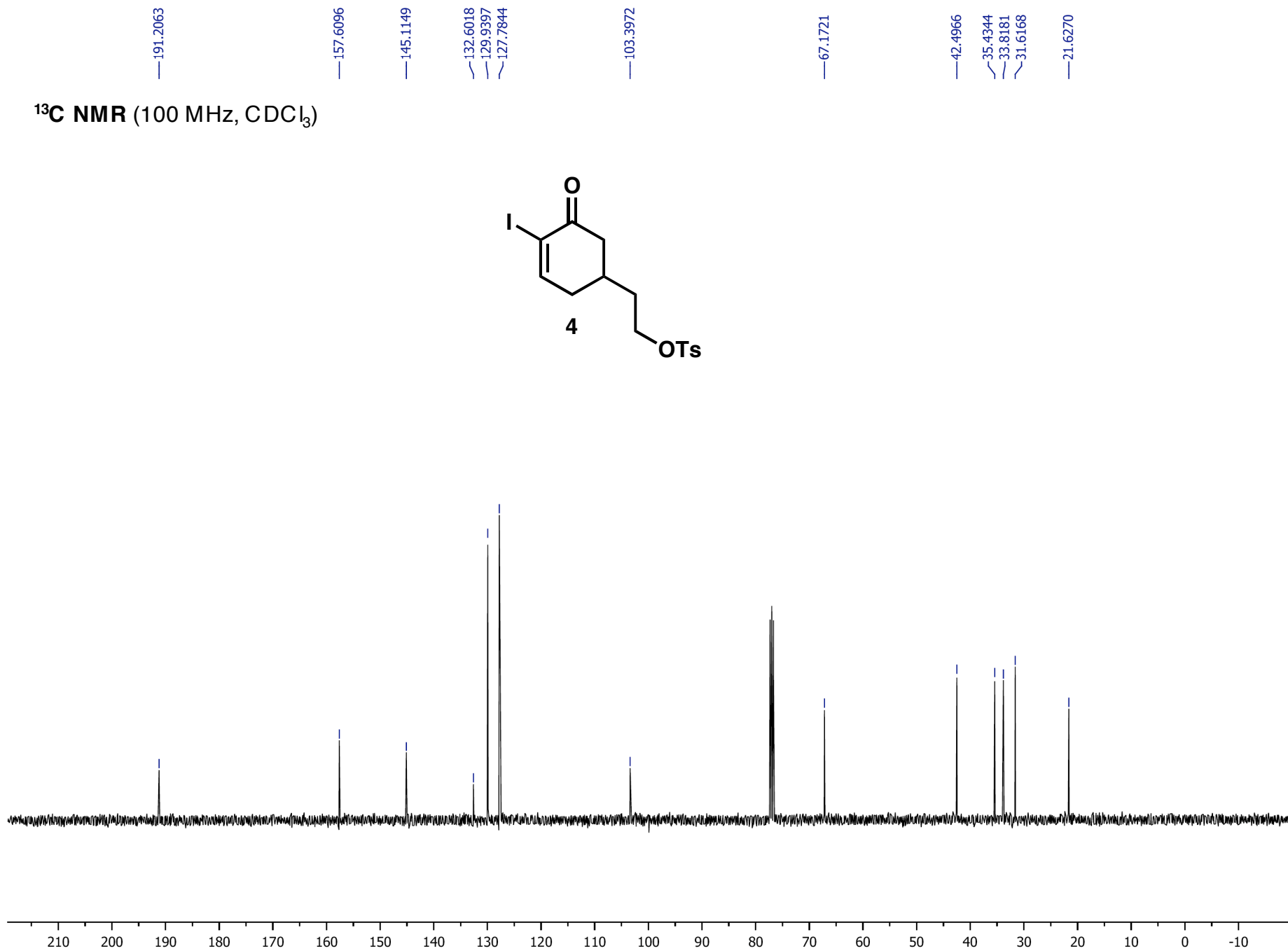
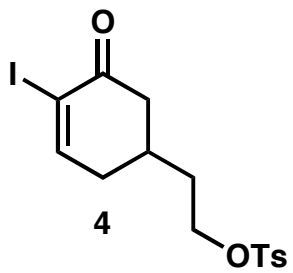
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4.0301  
4.0166

2.6857  
2.6818  
2.6553  
2.6514  
2.1993  
2.1461  
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1.7337  
1.7311  
1.7173

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )

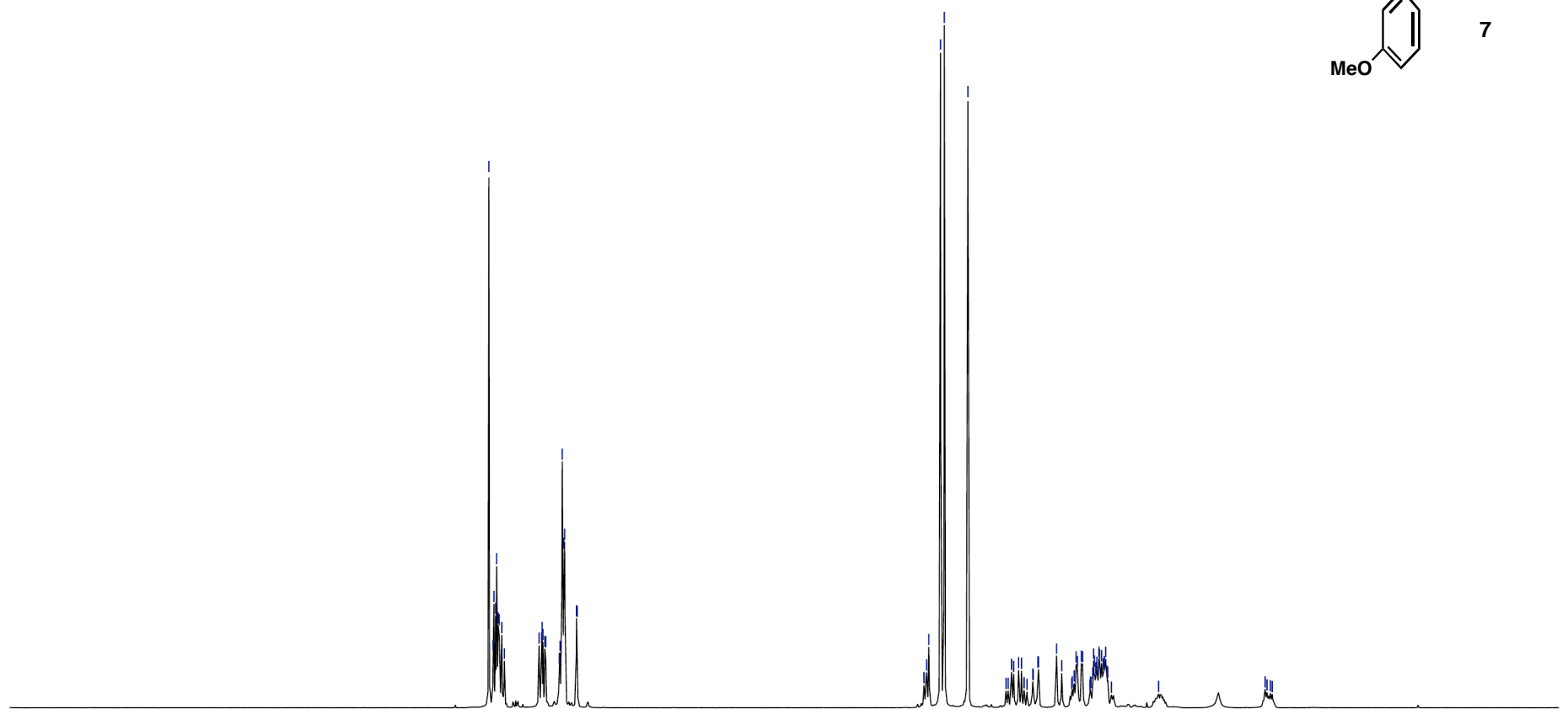
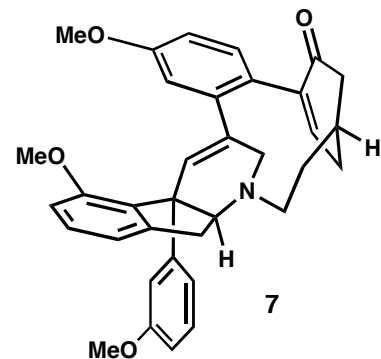


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

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7.2212  
7.2080  
7.2000  
7.1885  
7.1807  
7.1602  
7.1406  
6.8486  
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6.6924  
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6.5770

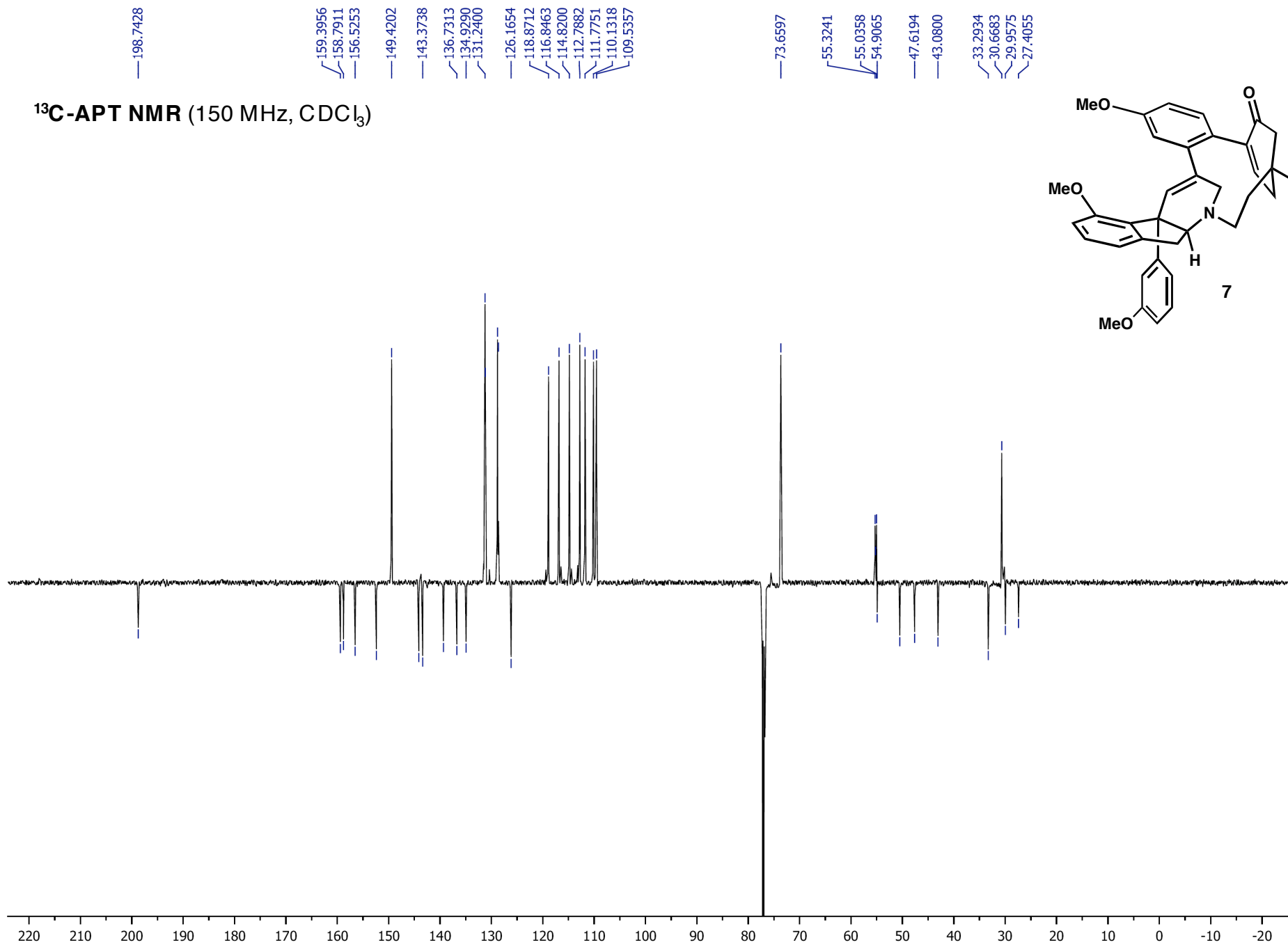
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2.0805

1.2568  
1.2425  
1.2160  
1.2018



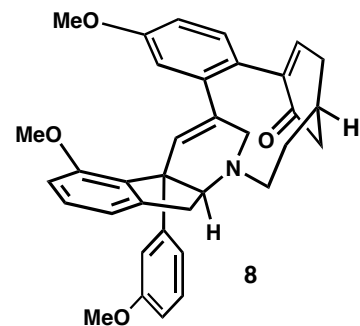
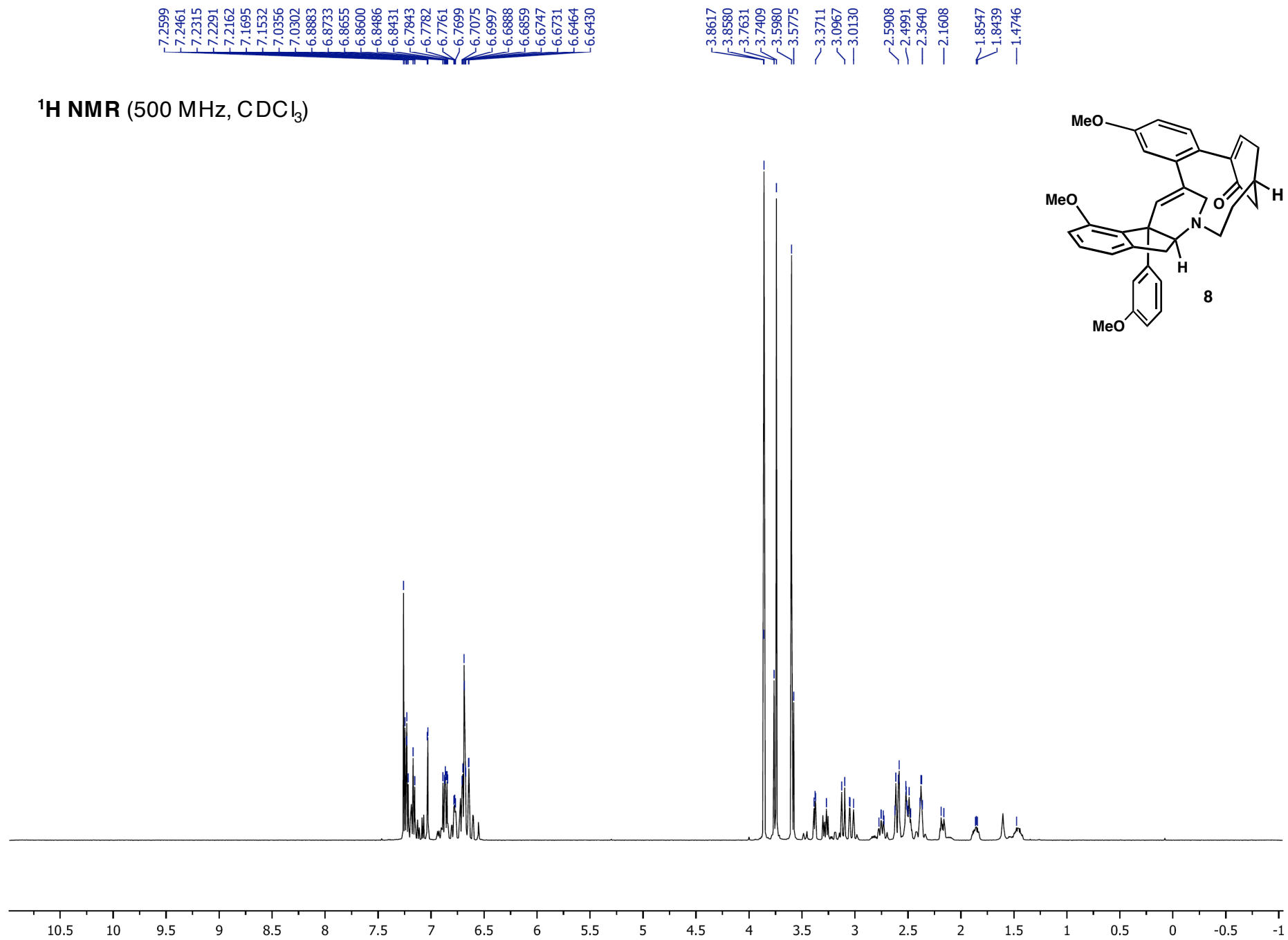
10.5 10 9.5 9 8.5 8 7.5 7 6.5 6 5.5 5 4.5 4 3.5 3 2.5 2 1.5 1 0.5 0 -0.5 -1

**$^{13}\text{C}$ -APT NMR (150 MHz,  $\text{CDCl}_3$ )**

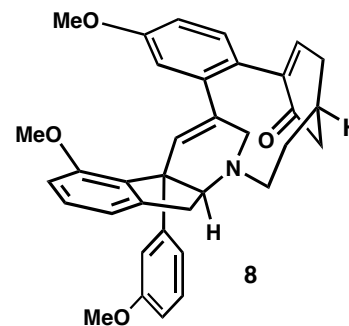
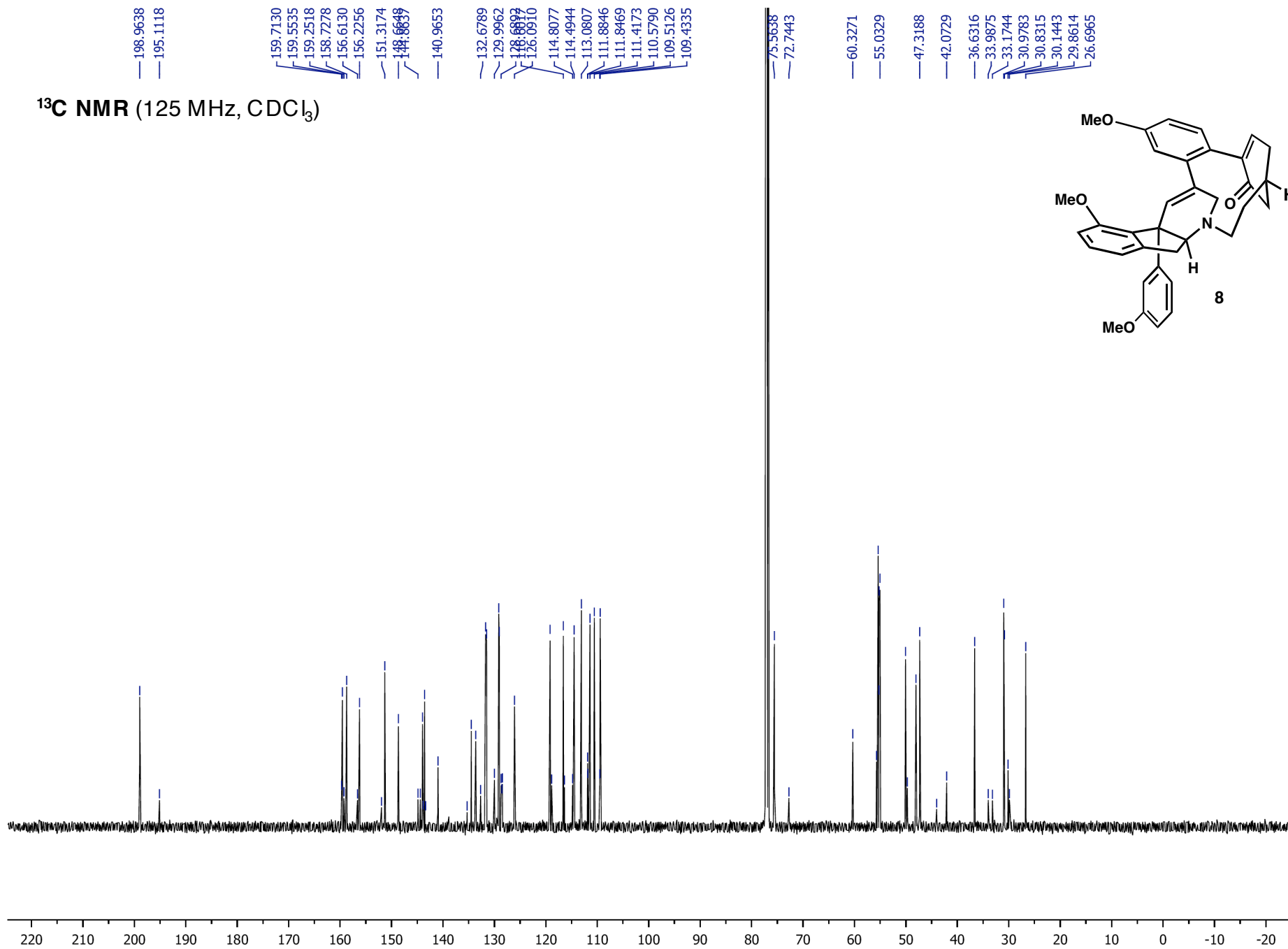




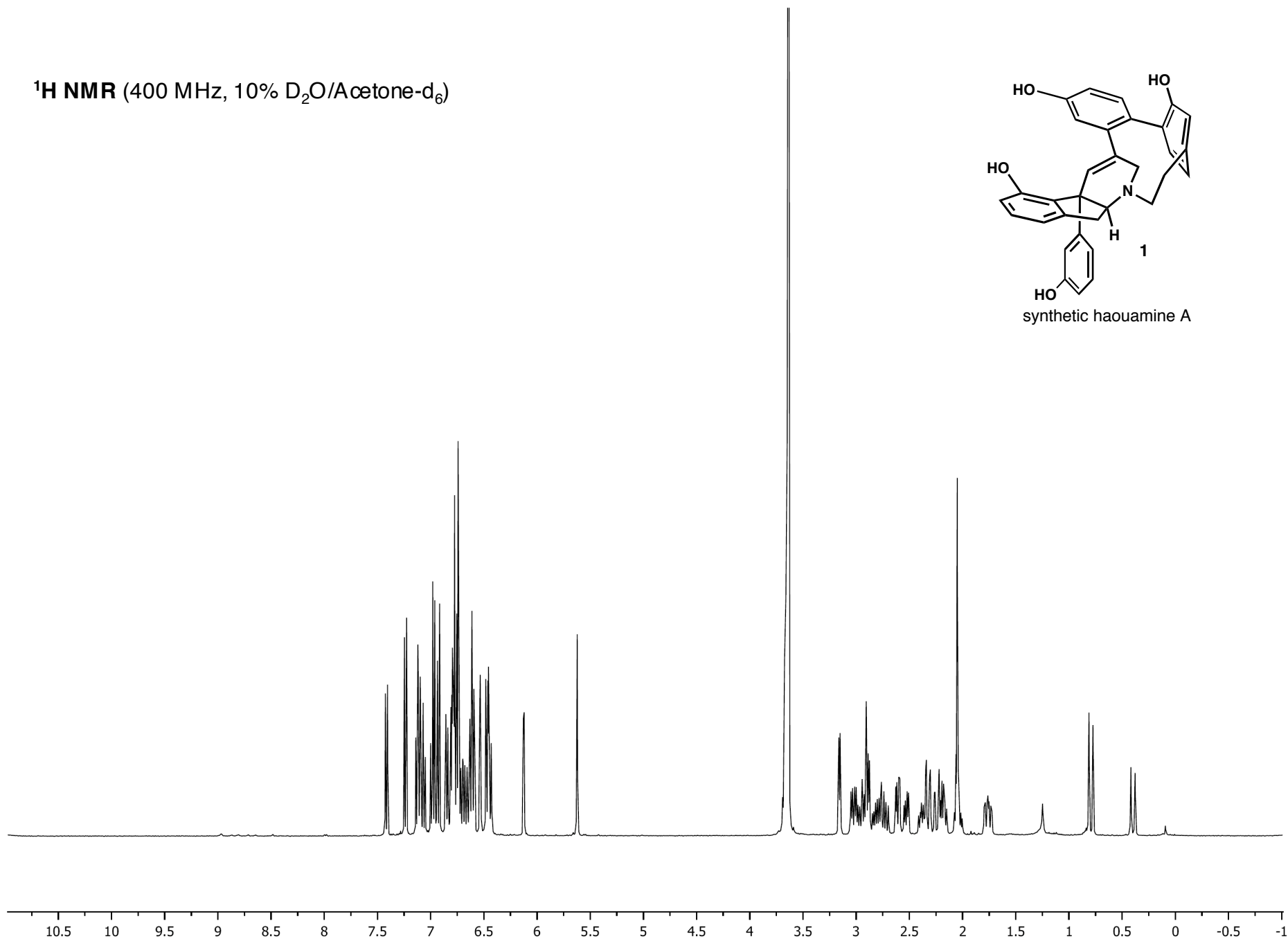
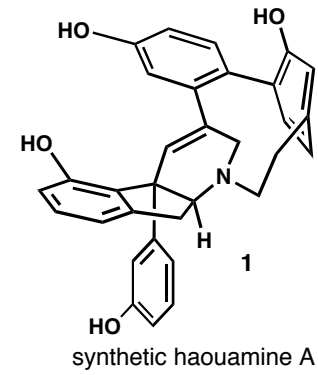
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



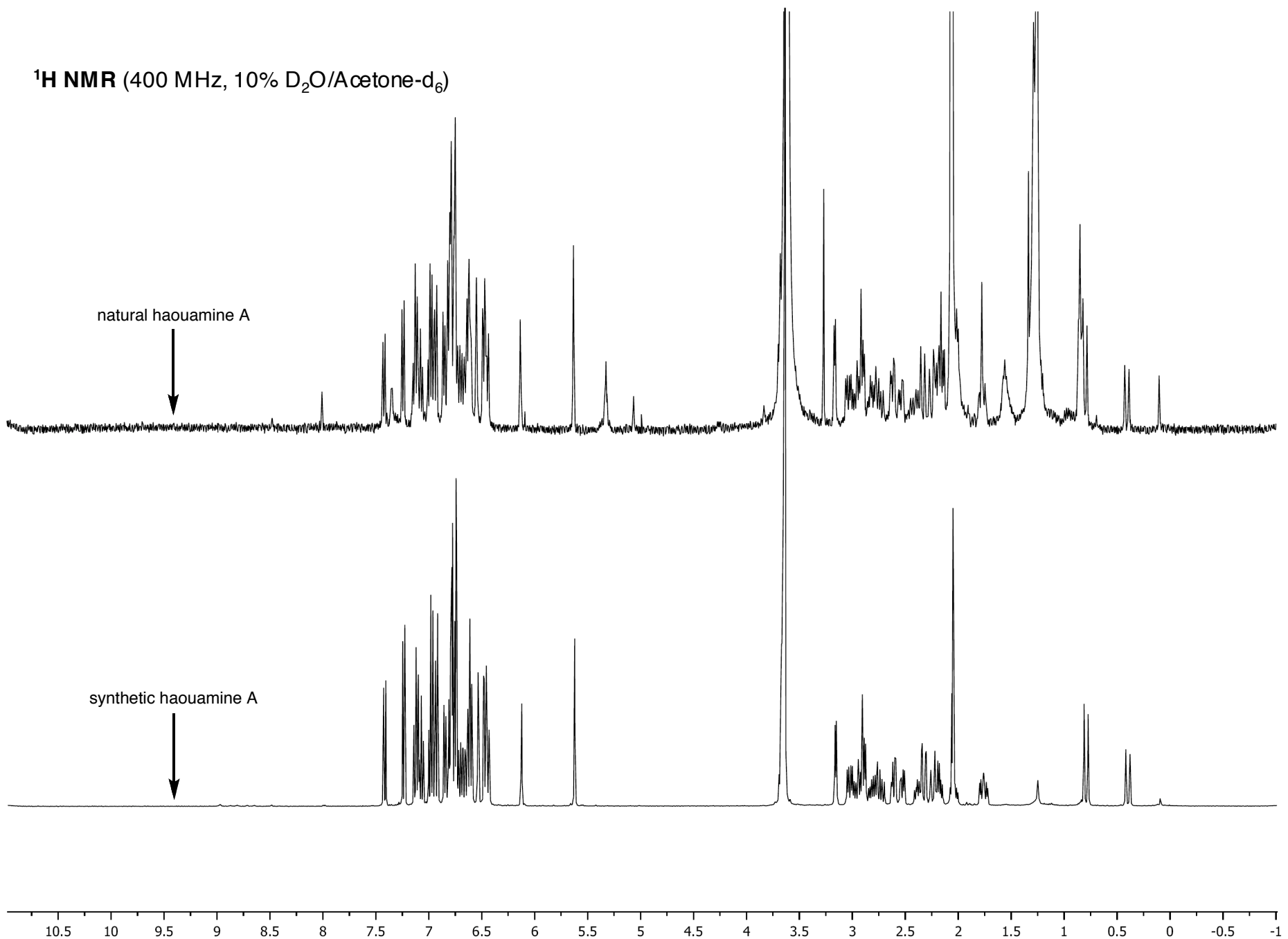
**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**



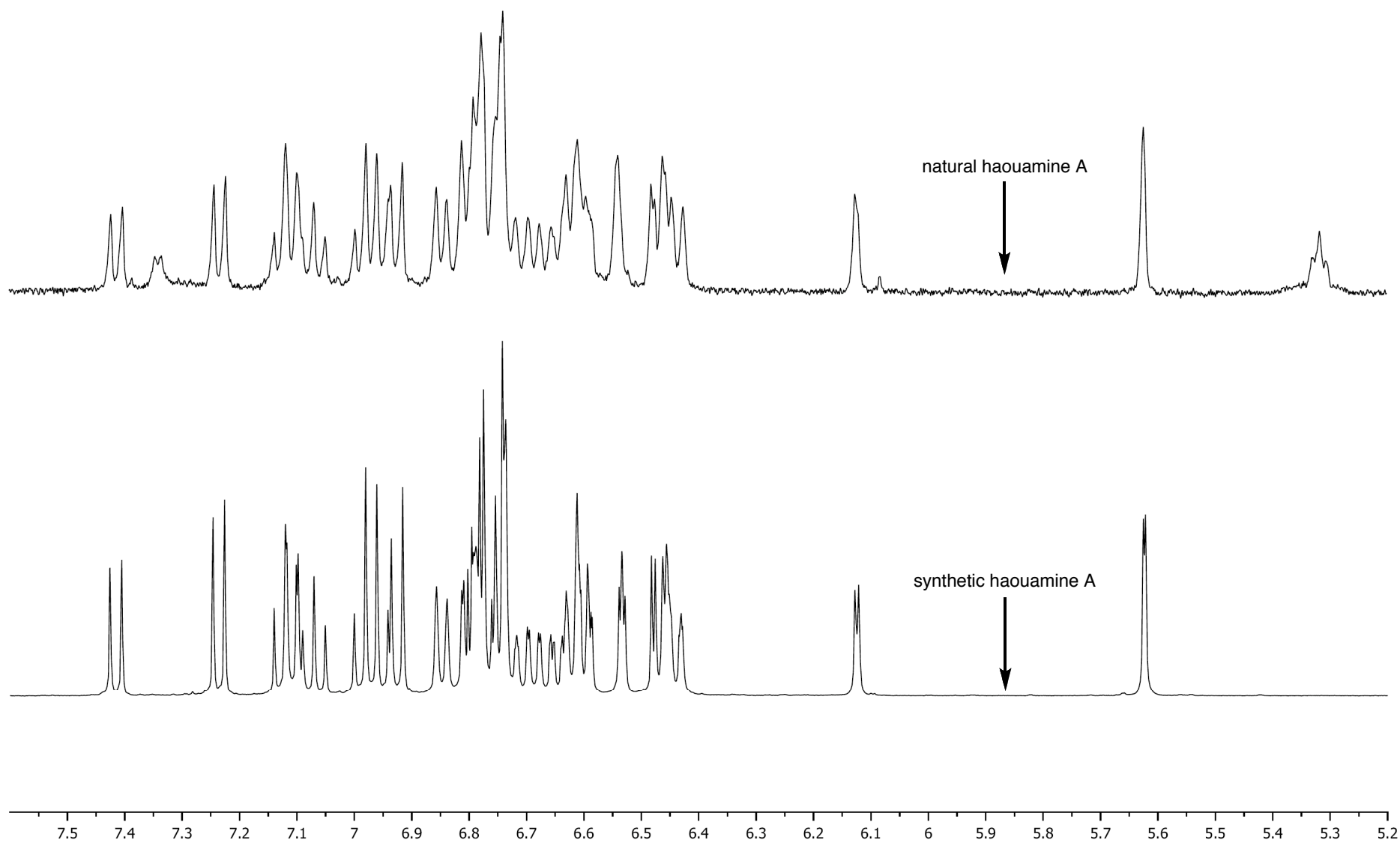
<sup>1</sup>H NMR (400 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)



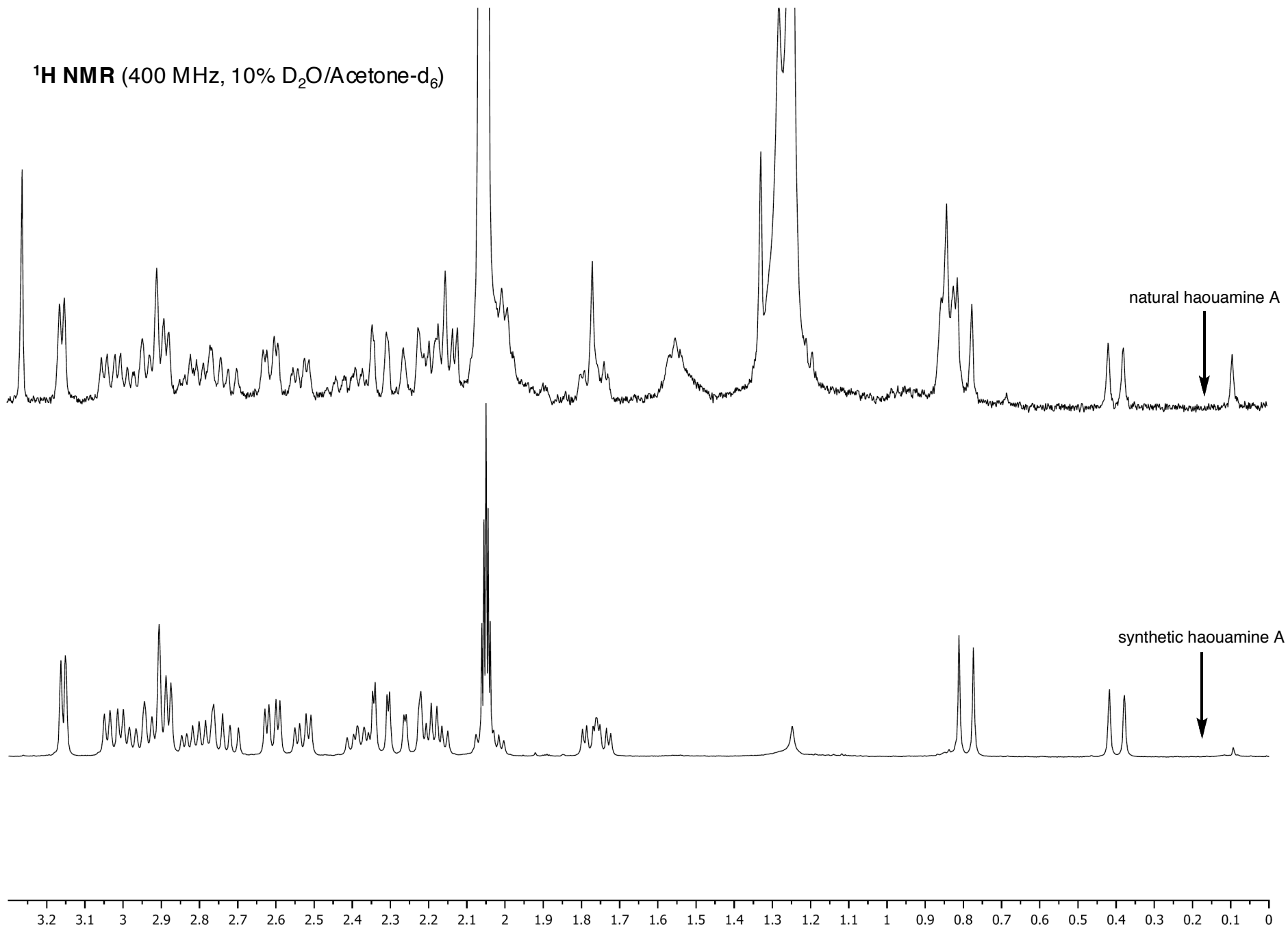
$^1\text{H NMR}$  (400 MHz, 10%  $\text{D}_2\text{O}/\text{Acetone-d}_6$ )



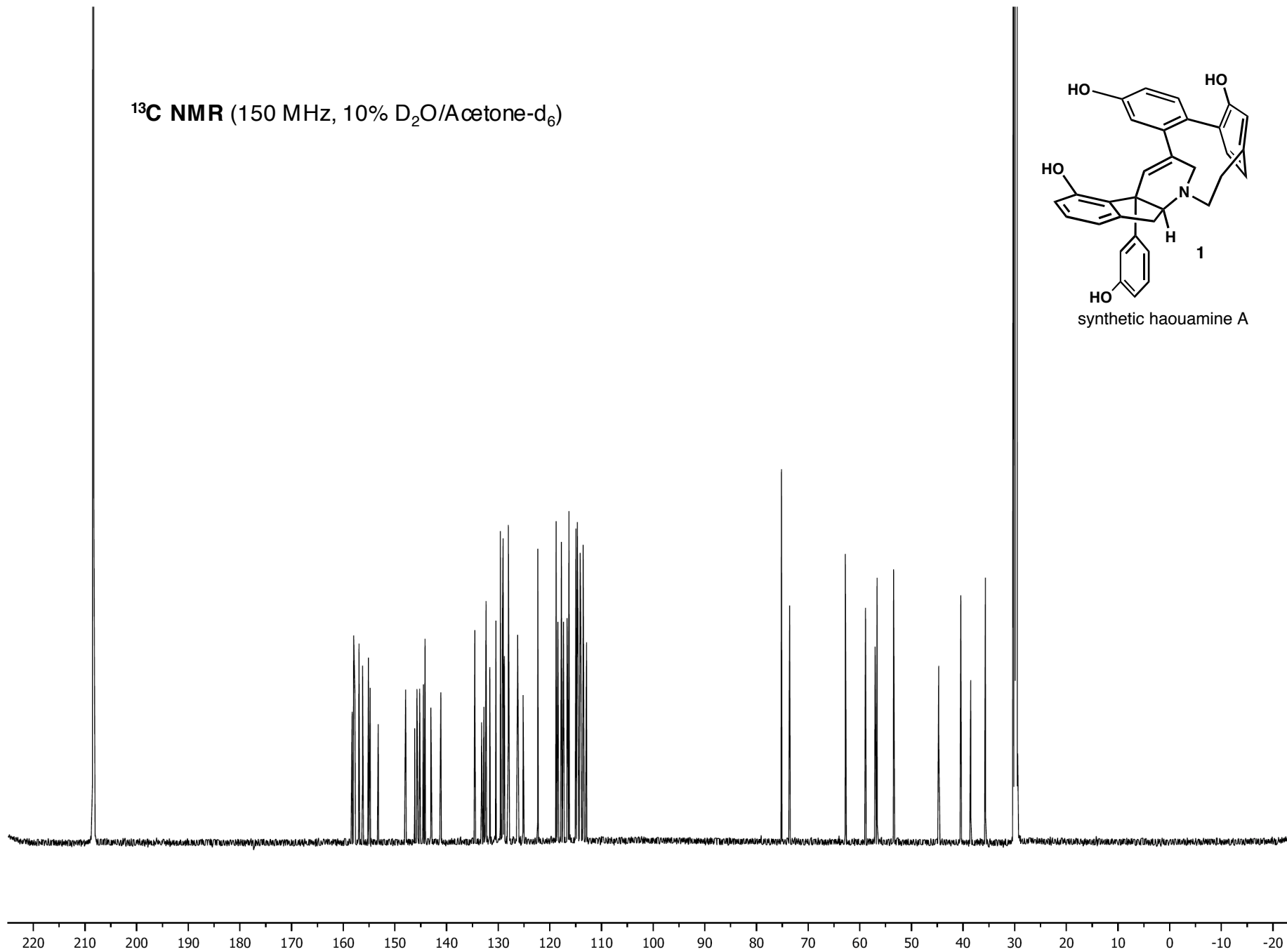
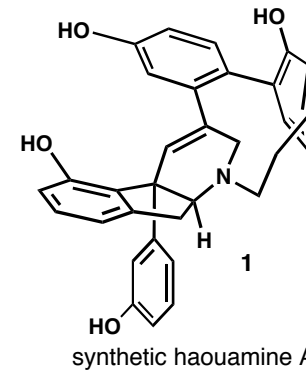
$^1\text{H}$  NMR (400 MHz, 10%  $\text{D}_2\text{O}/\text{Acetone-d}_6$ )

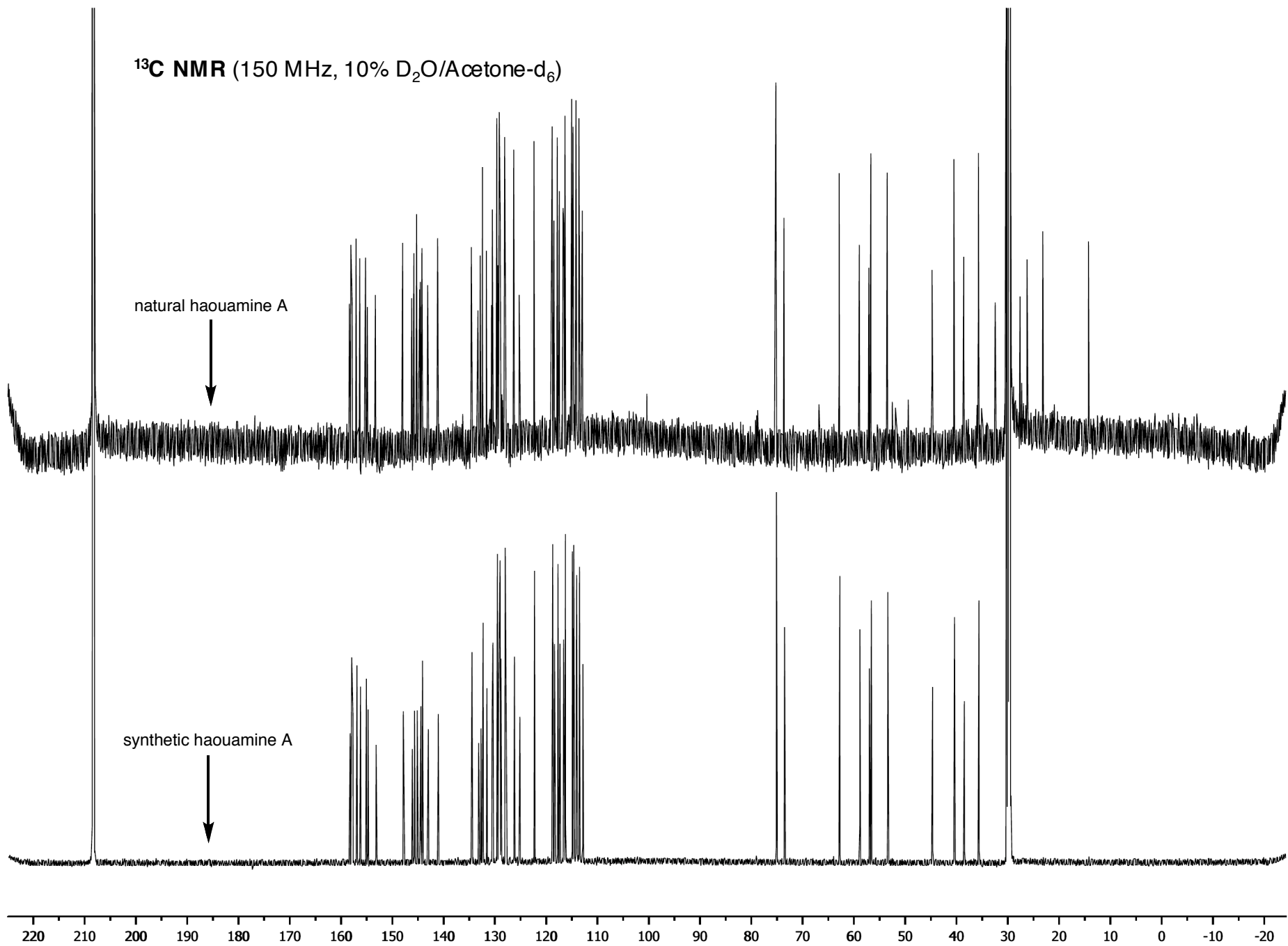


**<sup>1</sup>H NMR (400 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)**



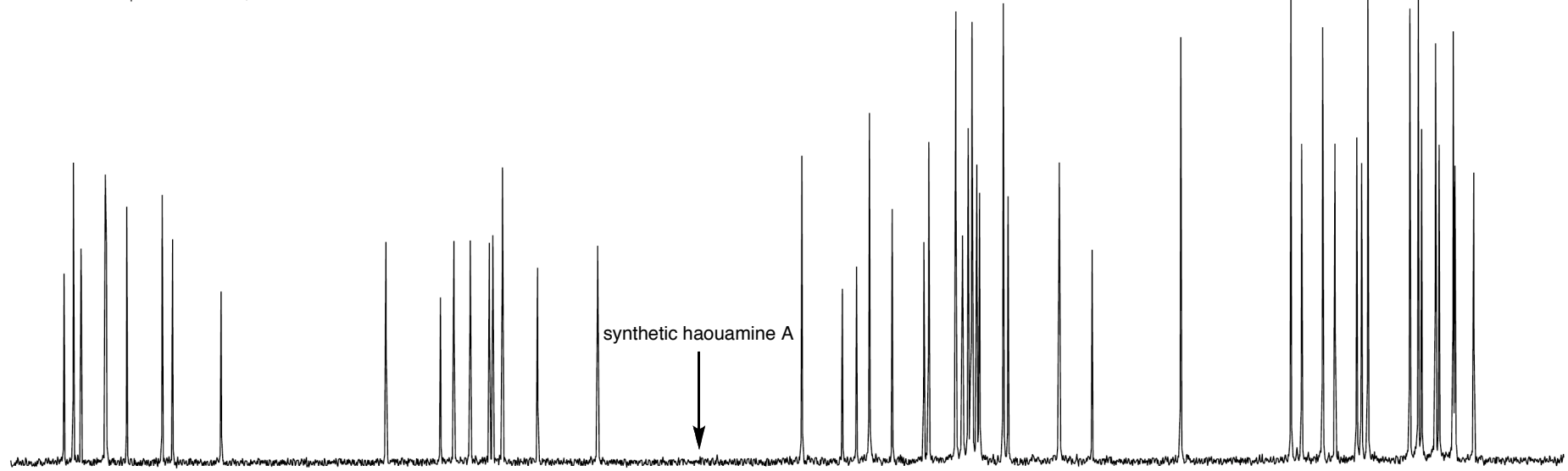
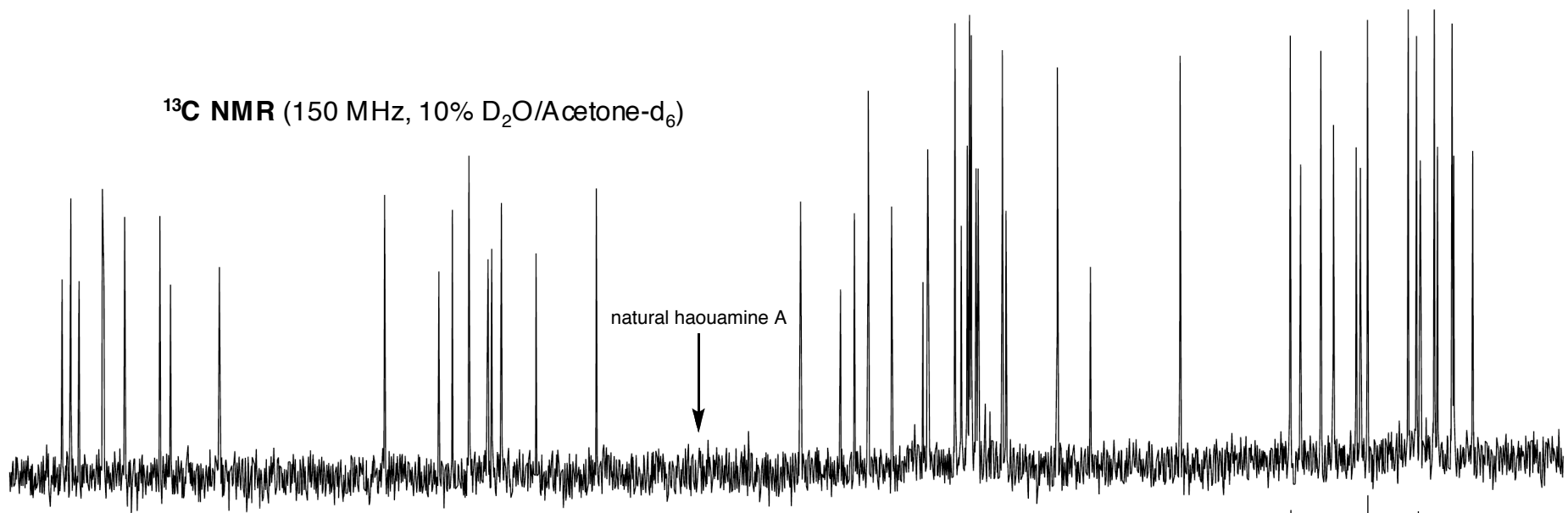
**<sup>13</sup>C NMR** (150 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)





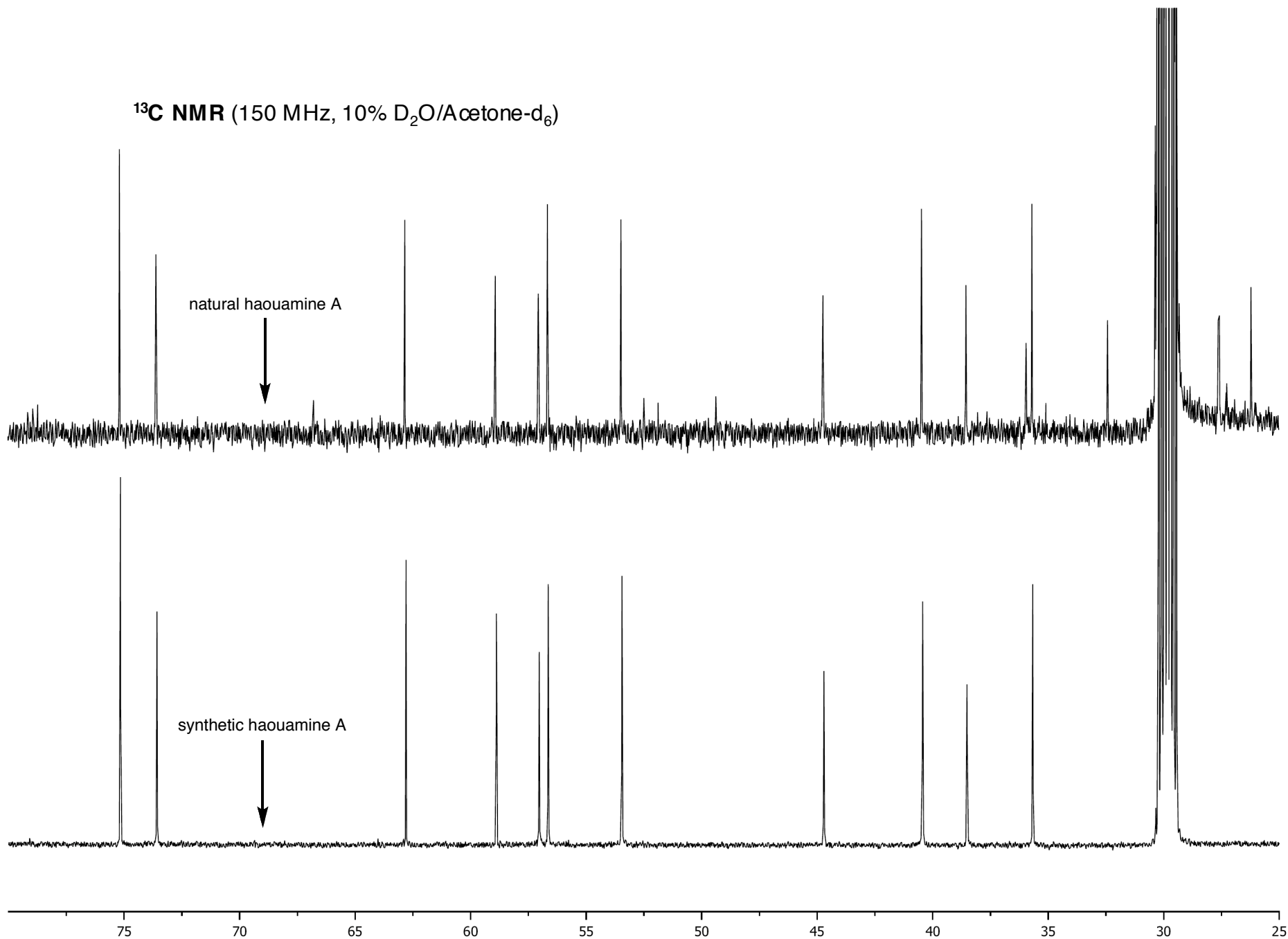


**<sup>13</sup>C NMR (150 MHz, 10% D<sub>2</sub>O/Ac<sub>2</sub>O-d<sub>6</sub>)**

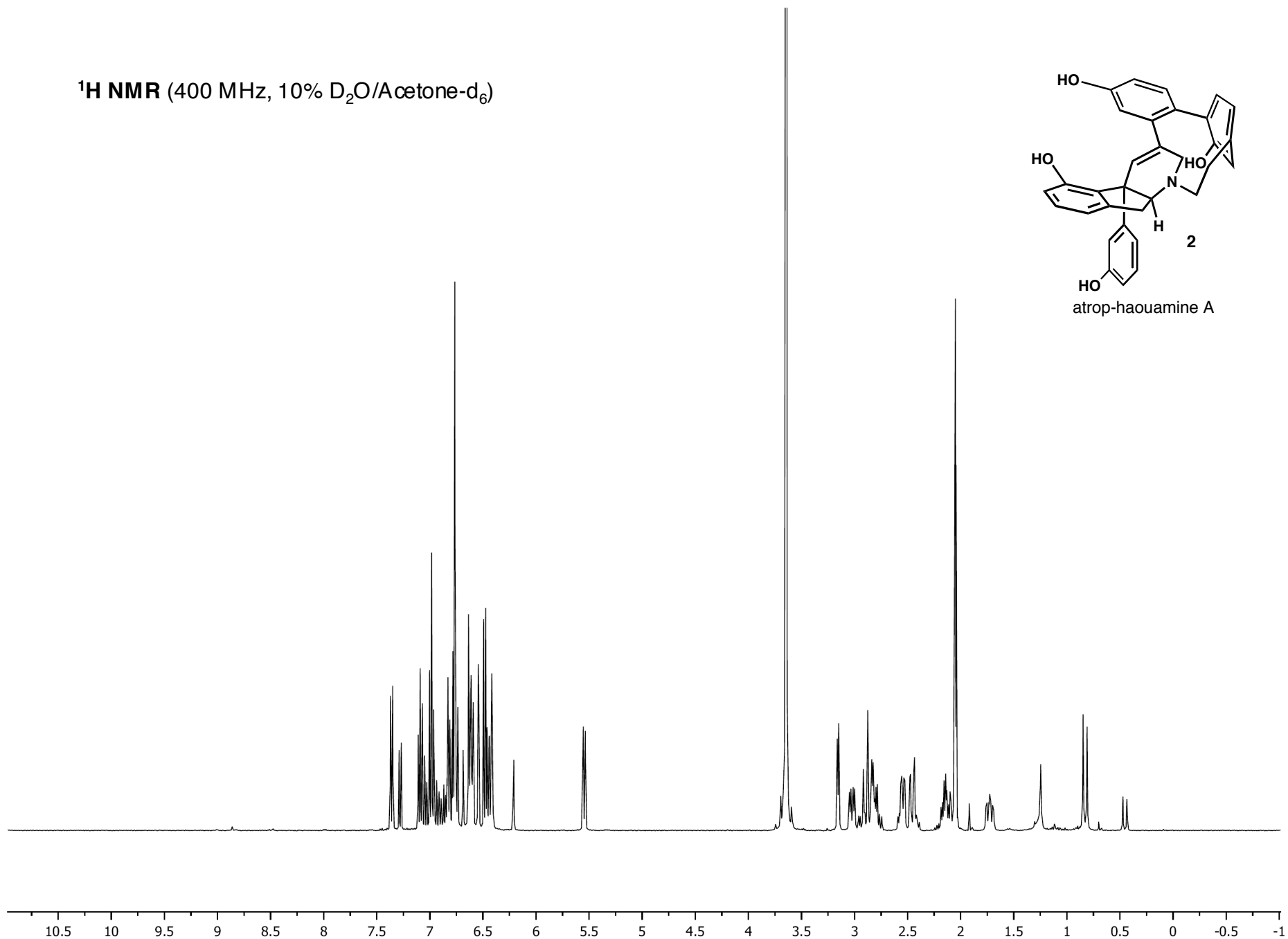
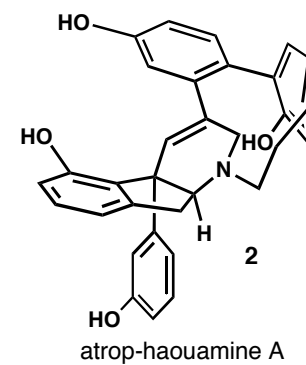


160 155 150 145 140 135 130 125 120 115 110

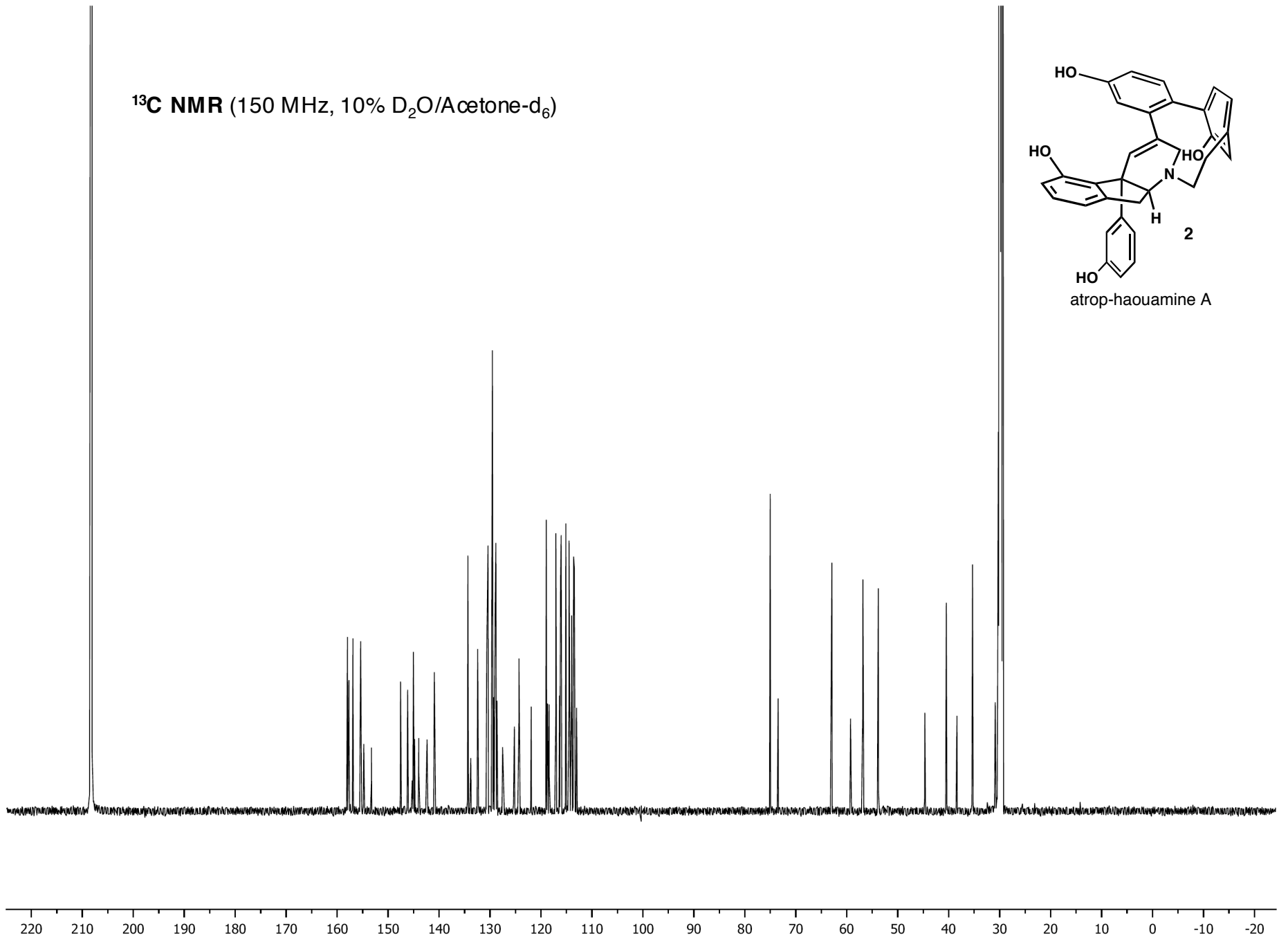
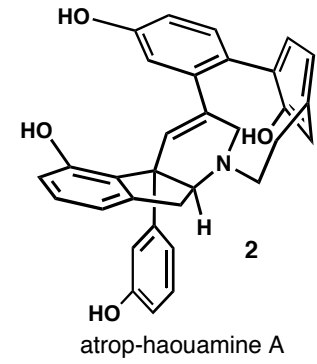
<sup>13</sup>C NMR (150 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)



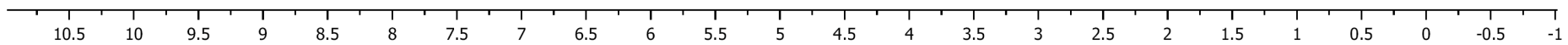
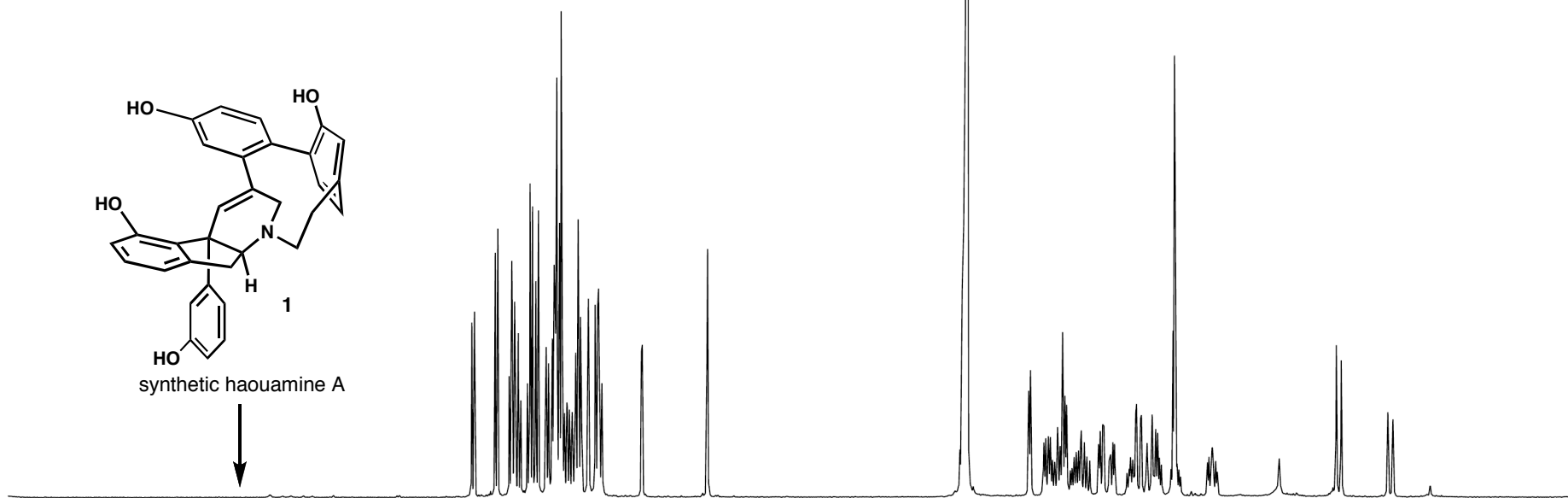
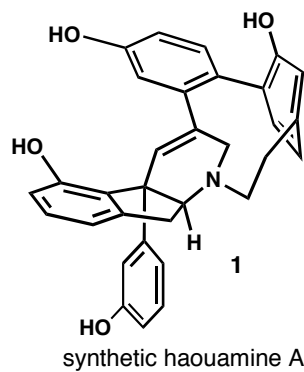
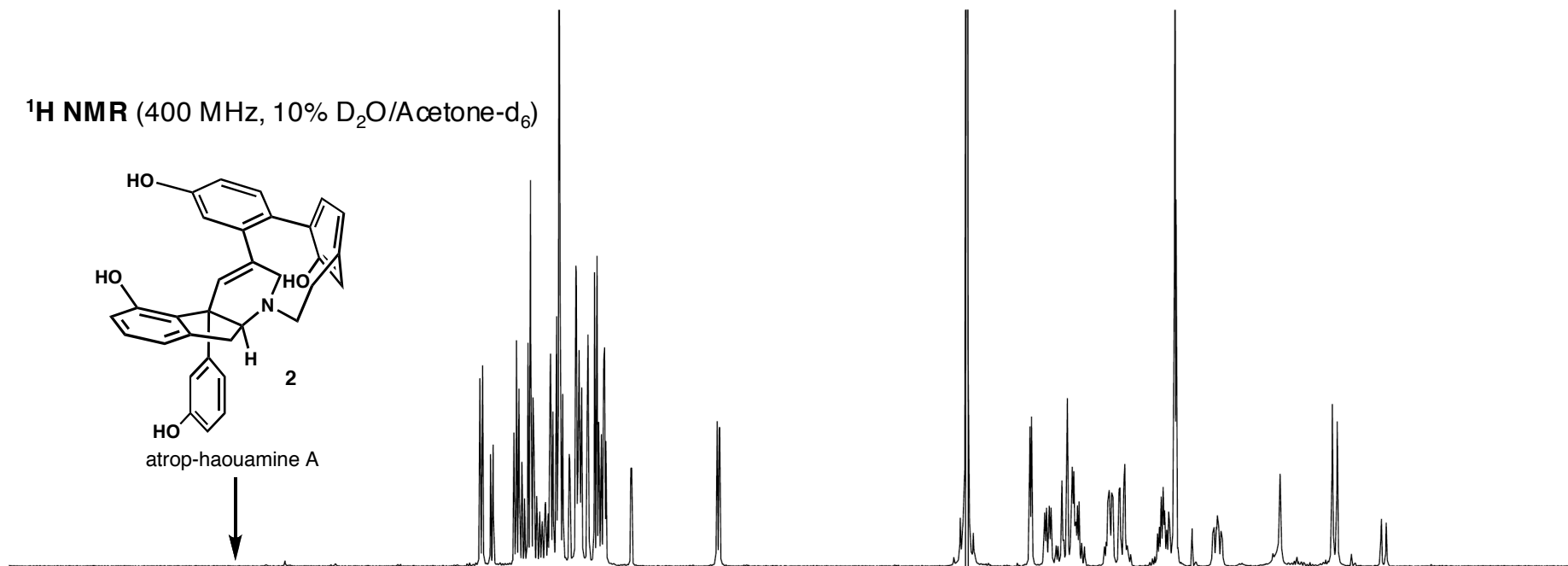
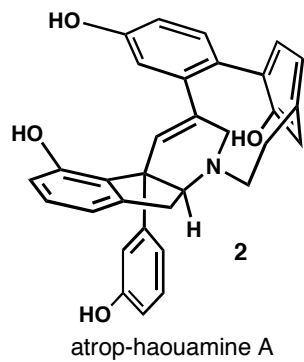
<sup>1</sup>H NMR (400 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)



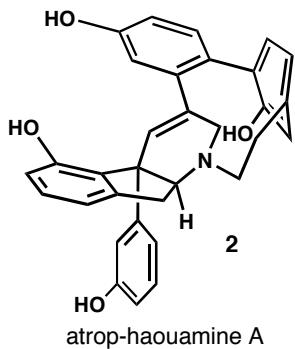
**<sup>13</sup>C NMR (150 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)**



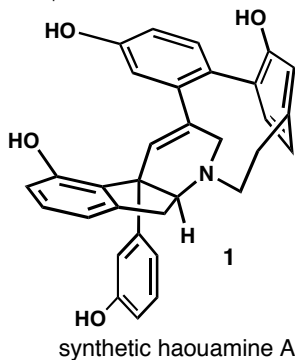
$^1\text{H}$  NMR (400 MHz, 10%  $\text{D}_2\text{O}/\text{Acetone-d}_6$ )



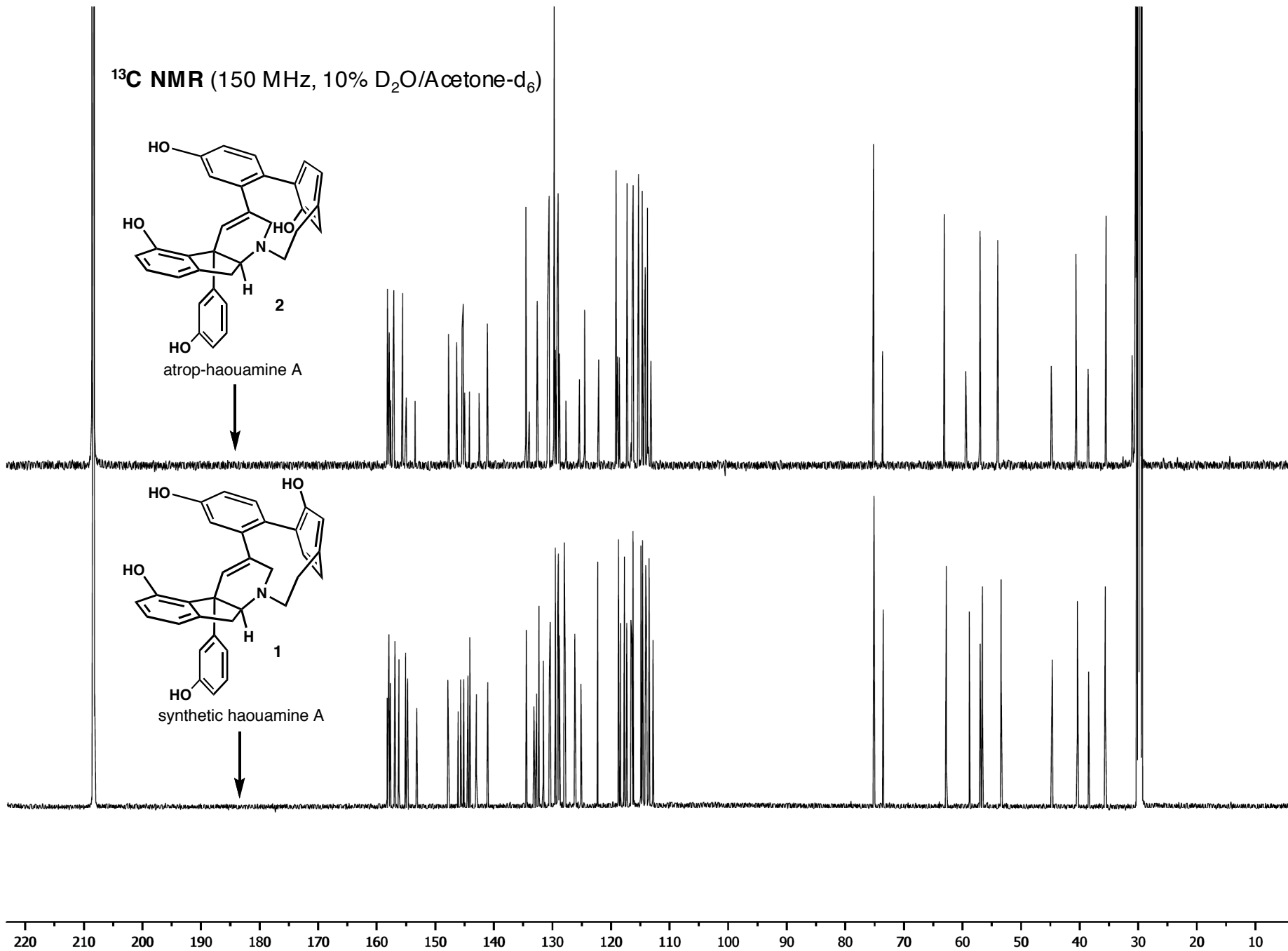
<sup>13</sup>C NMR (150 MHz, 10% D<sub>2</sub>O/Acetone-d<sub>6</sub>)



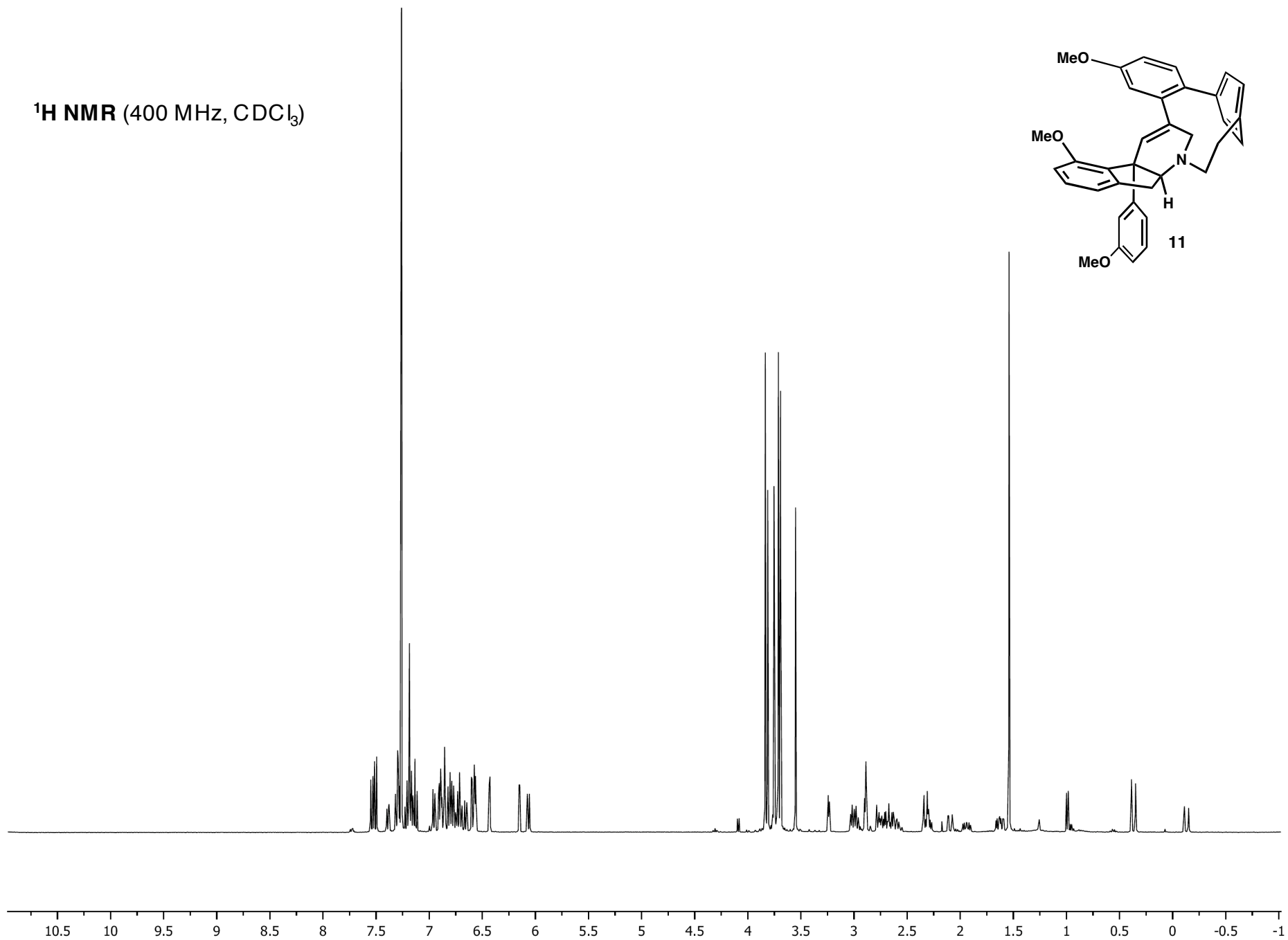
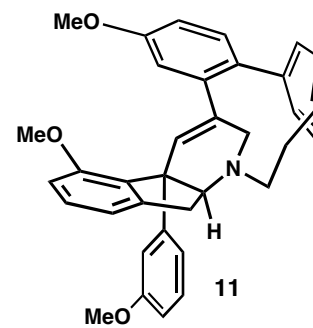
atrop-haouamine A



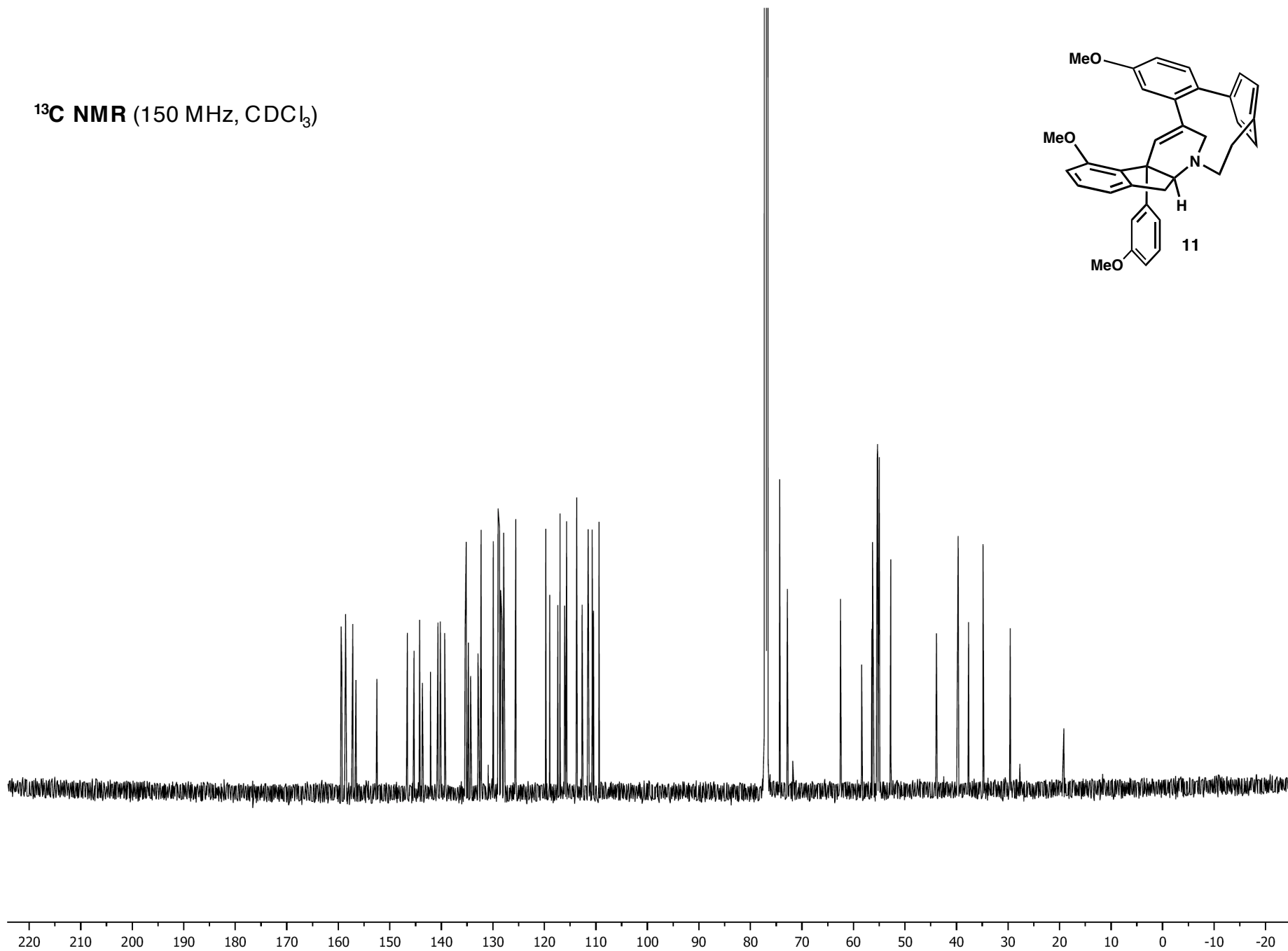
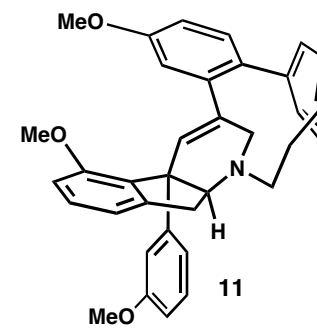
synthetic haouamine A



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )**





$^{13}\text{C}$ -APT NMR (150 MHz,  $\text{CDCl}_3$ )

