

# Highly Substituted Oxabicyclic Derivatives From Furan:

## Synthesis of (±)-Platensimycin

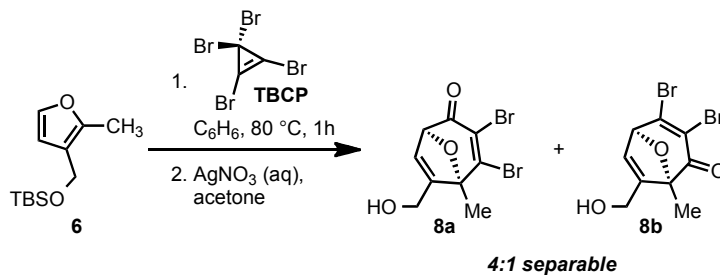
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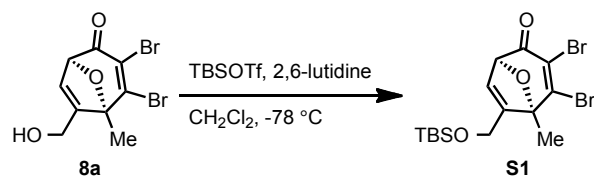
### SUPPORTING INFORMATION

**General procedures.** All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Commercial grade reagents and solvents were used without further purification except as indicated below. Hexanes, tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), and dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) were used directly from a Baker cycle-tainer system. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR) homogenous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on Whatman silica gel 60 Å precoated plates using UV light as the visualizing agent and an acidic mixture of anisaldehyde or basic aqueous potassium permanganate (KMnO<sub>4</sub>) and heat as developing agents. Flash chromatography was performed using Baker silica gel (60 Å particle size). NMR spectra were recorded on Bruker-500 and 400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl<sub>3</sub> at δ 7.26 ppm <sup>1</sup>H NMR, δ 77.0 ppm <sup>13</sup>C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR Spectra were recorded on Shimadzu FT-IR 8400 spectrometer. Melting points (m.p.) are uncorrected and were recorded on a Mel-Temp digital melting point apparatus. High resolution mass spectra (HRMS) were obtained from the Notre Dame Mass Spectral Facility by electrospray ionization of flight reflectron experiments.

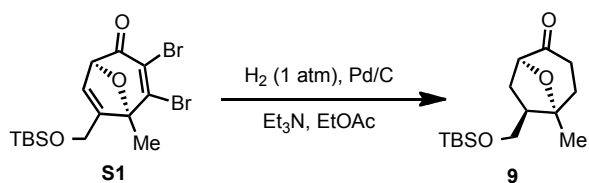


**Dibromoenone 8a:** To a flame dried pressure tube was added furan **6**<sup>1</sup> (3.75 g, 16.6 mmol) and benzene (5 mL, 3.0 M) under argon. The solution was treated with freshly distilled tetrabromocyclopropene<sup>2</sup> (5.89 g, 16.6 mmol) at room temperature and the tube was sealed. The sealed tube was placed in an oil bath at room temperature then gradually heated to 90 °C for 2 h. Upon cooling, all volatiles were removed *in vacuo* to give the crude tetrabromide as an inconsequential mixture of regioisomers (1.4 : 1, <sup>1</sup>H NMR).

The crude mixture (16.6 mmol) was dissolved in acetone-H<sub>2</sub>O (2:1, 90 mL) and treated portionwise with AgNO<sub>3</sub> (5.6 g, 33.2 mmol) over a 30 min period. The reaction mixture was allowed to stir at room temperature for 2 h before being poured over solid NaHCO<sub>3</sub> (7 g). The solids were filtered through a pad of Celite and washed with acetone (250 mL). The acetone was removed under reduced pressure and the resulting aqueous layer was extracted with EtOAc (5 x 100 mL). The combined organics were washed with NaHCO<sub>3</sub> (100 mL), H<sub>2</sub>O (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the crude dibromoenone as a mixture of regioisomers (4:1, <sup>1</sup>H NMR). The crude material was purified by flash chromatography (SiO<sub>2</sub>, 200 g, 25% EtOAc in hexanes) to provide 1.90 g of mixed regioisomers (**8a+8b**) and **8a** (3.2 g, 94 % overall) as a pale yellow oil: R<sub>f</sub> = 0.24 (25% EtOAc in hexanes); IR (KBr):  $\nu$ : 3470, 1704, 1539, 1049 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.27 (dd, *J* = 4.0, 2.0 Hz, 1H), 5.12 (dt, *J* = 2.4, 1.2 Hz, 1H), 4.45 (dt, *J* = 15.8, 1.7 Hz, 1H), 4.39 (ddd, *J* = 15.9, 1.9, 1.1 Hz, 1H), 1.81 (bs, 1H), 1.78 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  183.7, 156.4, 153.2, 123.9, 121.2, 91.3, 85.9, 58.6, 21.5; HRMS (ESI) calcd for C<sub>9</sub>H<sub>8</sub>Br<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 344.8738; found: 344.8732.

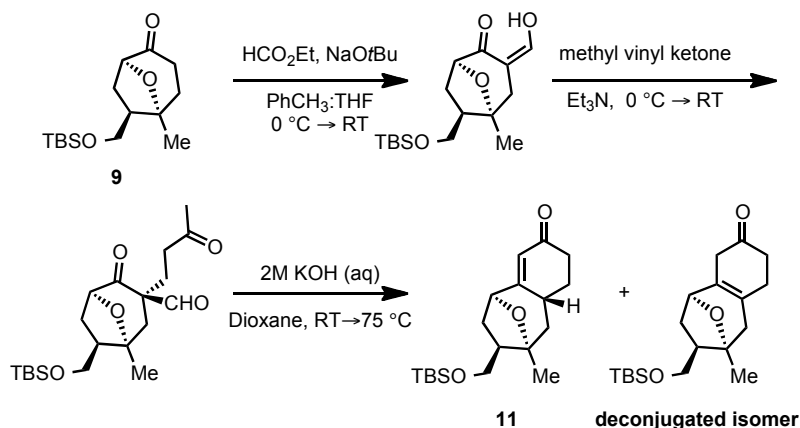


**Dibromo-enone S1:** Alcohol **8a** (3.00 g, 9.26 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL), cooled to  $-78\text{ }^\circ\text{C}$ , and treated with 2,6-lutidine (1.62 mL, 13.89 mmol). To the cooled solution was added TBSOTf (2.34 mL, 10.19 mmol) and stirring was continued for 1 h. Upon completion, the reaction was quenched by addition of  $\text{H}_2\text{O}$  and the biphasic mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude material was purified by flash chromatography ( $\text{SiO}_2$ , 50 g, 10% EtOAc in Hexanes) to afford **S1** (3.97 g, 98%) as a pale yellow oil:  $R_f = 0.68$  (15% EtOAc in Hexanes); IR (KBr):  $\nu$ : 2953, 2929, 1710, 1541, 1072, 839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.19 (q,  $J = 1.9$  Hz, 1H), 5.10 (dt,  $J = 2.4, 1.3$  Hz, 1H), 4.40 (dt,  $J = 15.8, 1.8$  Hz, 1H), 4.35 (ddd,  $J = 15.8, 2.0, 1.0$  Hz, 1H), 1.75 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  183.8, 156.7, 153.1, 123.4, 121.1, 91.2, 85.9, 59.1, 25.6, 21.6, 18.3, -5.4, -5.5; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{23}\text{Br}_2\text{O}_3\text{Si}$   $[\text{M}+\text{H}]^+$ : 436.9783; found: 436.9778.



**Ketone 9:** Dibromo-enone **S1** (3.5 g, 7.99 mmol) was dissolved in EtOAc (20 mL) and treated with  $\text{Et}_3\text{N}$  (7.8 mL, 55.9 mmol). To the solution was added 10% Pd/C (1.7 g) and the flask was evacuated and backfilled with  $\text{H}_2$  (3 cycles). The reaction mixture was stirred under an atmosphere of  $\text{H}_2$  (balloon) for 4 h before being filtered through a pad of  $\text{SiO}_2$  eluting with EtOAc (100 mL). The solvent was removed under vacuum and the residue was purified by flash chromatography ( $\text{SiO}_2$ , 50g, 10% EtOAc in hexanes) to give ketone **9** (2.21 g, 96 %) as a clear oil;  $R_f = 0.61$  (25% EtOAc in hexanes); IR (KBr):  $\nu$ : 2955, 2930, 1732, 1095, 1078, 838  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.22 (d,  $J =$

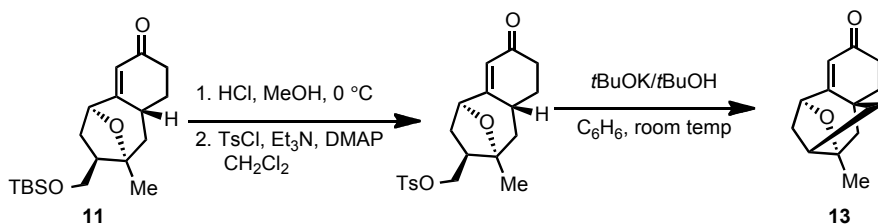
8.8 Hz, 1H), 3.80 (dd,  $J = 10.6, 5.5$  Hz, 1H), 3.72 – 3.66 (m, 1H), 2.54 – 2.33 (m, 3H), 2.27 – 2.19 (m, 1H), 2.15 – 2.08 (m, 1H), 2.02 – 1.94 (m, 1H), 1.56 – 1.50 (m, 1H), 1.43 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  208.2, 81.7, 80.8, 62.8, 48.9, 32.5, 32.1, 31.7, 26.7, 25.8, 18.2, -5.5, -5.6; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{29}\text{O}_3\text{Si}$   $[\text{M}+\text{H}]^+$ : 285.1886; found: 285.1880.



**Tricyclic enone 11:** A 100 mL two-necked flask fit with a pressure equalizing addition funnel was charged with sodium *tert*-butoxide (1.35 g, 14.04 mmol) and toluene (9 mL). The suspension was cooled to 0 °C and ethyl formate (3.95 mL, 49.14 mmol) was added. The suspension was stirred at this temperature for 15 min before ketone **9** (1.00 g, 3.51 mmol) in THF (9 mL) was added via addition funnel over a 10 min period. Upon complete addition, the funnel was washed with 2 mL THF, stirred at 0 °C for 30 min, and then warmed to room temperature. After 1 h at room temperature, the reaction was again cooled to 0 °C and acidified to pH 2 with 2N HCl. The aqueous layer extracted with EtOAc (3 x 25 mL) and the combined organics were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give the crude vinylogous acid as a yellow oil.

To the vinylogous acid (3.51 mmol) obtained above was added methyl vinyl ketone (1.00 mL, 12.29 mmol) and the mixture cooled to 0 °C. The solution was treated with  $\text{Et}_3\text{N}$  (3.11 mL, 22.46 mmol) and stirred at 0 °C for 1 h before being warmed to room temperature. After 4 h at room temperature, the volatiles were removed under reduced pressure to give the crude diketoaldehyde. The resulting oil was redissolved in dioxane (7.5 mL) and a solution of KOH (927 mg, 14.0 mmol, 85%) in  $\text{H}_2\text{O}$  (7.5 mL) was added.

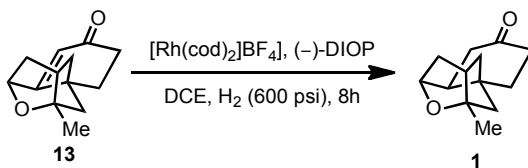
The mixture was stirred at room temperature for 30 min (disappearance of starting diketoaldehyde by TLC) and then heated to 75 °C. After stirring at this temperature for 1 h, the reaction mixture was diluted with H<sub>2</sub>O (10 mL), saturated with NaCl, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (7 x 25 mL). The combined organics were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO<sub>2</sub>, 30 g, 10% EtOAc in hexanes) to afford enone **11** and its deconjugated isomer (850 mg, 72%, 5:1 mixture, 3 steps) as a clear oil [Note: The isomers were inseparable and ultimately inconsequential; no attempts were made to isomerize the deconjugated isomer to **11**]: R<sub>f</sub> = 0.24 (10% EtOAc in hexanes); mp = 80–82 °C; IR (KBr):  $\nu$ : 2954, 2929, 1676, 1252, 1088, 1070, 838 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.74 (t, *J* = 5.1 Hz, 1H), 4.53 (d, *J* = 7.9 Hz, 1H), 3.81 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.73 (dd, *J* = 10.5, 8.2 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.48 – 2.38 (m, 2H), 2.30 – 2.25 (m, 1H), 2.24 – 2.15 (m, 2H), 2.08 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.65 (dddd, *J* = 15.1, 13.2, 11.2, 4.1 Hz, 1H), 1.48 (ddd, *J* = 13.2, 6.9, 1.4 Hz, 1H), 1.44 – 1.38 (m, 2H), 1.34 (s, 3H), 0.88 (d, *J* = 2.9 Hz, 9H), 0.06 (s, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  199.8, 163.8, 121.6, 81.7, 78.1, 62.6, 49.2, 41.1, 37.7, 33.8, 31.0, 30.6, 26.5, 25.8, 18.2, -5.5, -5.6; HRMS (ESI) calcd for C<sub>19</sub>H<sub>33</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 337.2199; found: 337.2193.



**Enone 13:** To a cooled solution (0 °C) of silyl ether **11** (461 mg, 1.37 mmol) in MeOH (45 mL, 0.03 M) was slowly added conc. HCl (0.50 mL). The solution was stirred at 0 °C for 1.5 h before being quenched with sat. aq. NaHCO<sub>3</sub> (20 mL). The MeOH was removed under reduced pressure and the remaining aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL). The combined organics were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give the crude alcohol as a clear oil: [R<sub>f</sub> = 0.13 (75% EtOAc in hexanes)].

The crude alcohol (1.37 mmol) obtained above was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) and treated sequentially with Et<sub>3</sub>N (0.38 mL, 2.74 mmol), DMAP (335 mg, 2.74 mmol), and *p*-toluenesulfonylchloride (518 mg, 2.74 mmol). The mixture was stirred at room temperature for 2 h before it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and poured into H<sub>2</sub>O (15 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL) and the combined organics were washed with H<sub>2</sub>O (20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give the crude tosylate as a yellow oil: [R<sub>f</sub> = 0.48 (75% EtOAc in hexanes)].

To a solution of the crude tosylate (1.37 mmol) obtained above in dry benzene (27 mL, 0.05 M) was slowly added a 1.0 M solution of *t*BuOK in *t*BuOH (6.85 mL) at room temperature. The alkaline solution was stirred for an additional 20 min before the addition of sat. aq. NaHCO<sub>3</sub> (25 mL). The benzene and *t*BuOH were removed under reduced pressure and the remaining aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO<sub>2</sub>, 10 g, 15% EtOAc in hexanes) to afford enone **13** (182 mg, 65%, 3 steps) as a clear oil: R<sub>f</sub> = 0.55 (50% EtOAc in hexanes); IR (KBr):  $\nu$ : 2961, 2360, 1678, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.75 (s, 1H), 4.59 (d, *J* = 4.5 Hz, 1H), 2.49 (t, *J* = 6.2 Hz, 1H), 2.39 – 2.34 (m, 2H), 2.17 (dddd, *J* = 11.0, 6.3, 4.6, 2.7 Hz, 1H), 2.02 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.87 – 1.82 (m, 1H), 1.82 – 1.78 (m, 1H), 1.77 – 1.71 (m, 2H), 1.66 (d, *J* = 11.3 Hz, 1H), 1.45 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  199.6, 164.0, 120.7, 86.8, 80.5, 54.5, 47.9, 46.8, 45.1, 43.6, 35.3, 30.1, 22.7; HRMS (ESI) calcd for C<sub>13</sub>H<sub>17</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 205.1229; found: 205.1223.

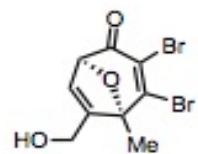


**Ketone 1:** Prepared by a modified procedure reported by Corey<sup>3</sup>: Enone **13** (106 mg, 0.519 mmol), [Rh(cod)<sub>2</sub>]BF<sub>4</sub> (42 mg, 0.20 equiv, 0.104 mmol), (4*R*,5*R*)-DIOP (52 mg, 0.20 equiv, 0.104 mmol) were placed in a dry glass vial and dissolved in 1,2-dichloroethane (10 mL, 0.05 M). The vial was placed in a hydrogenation apparatus and

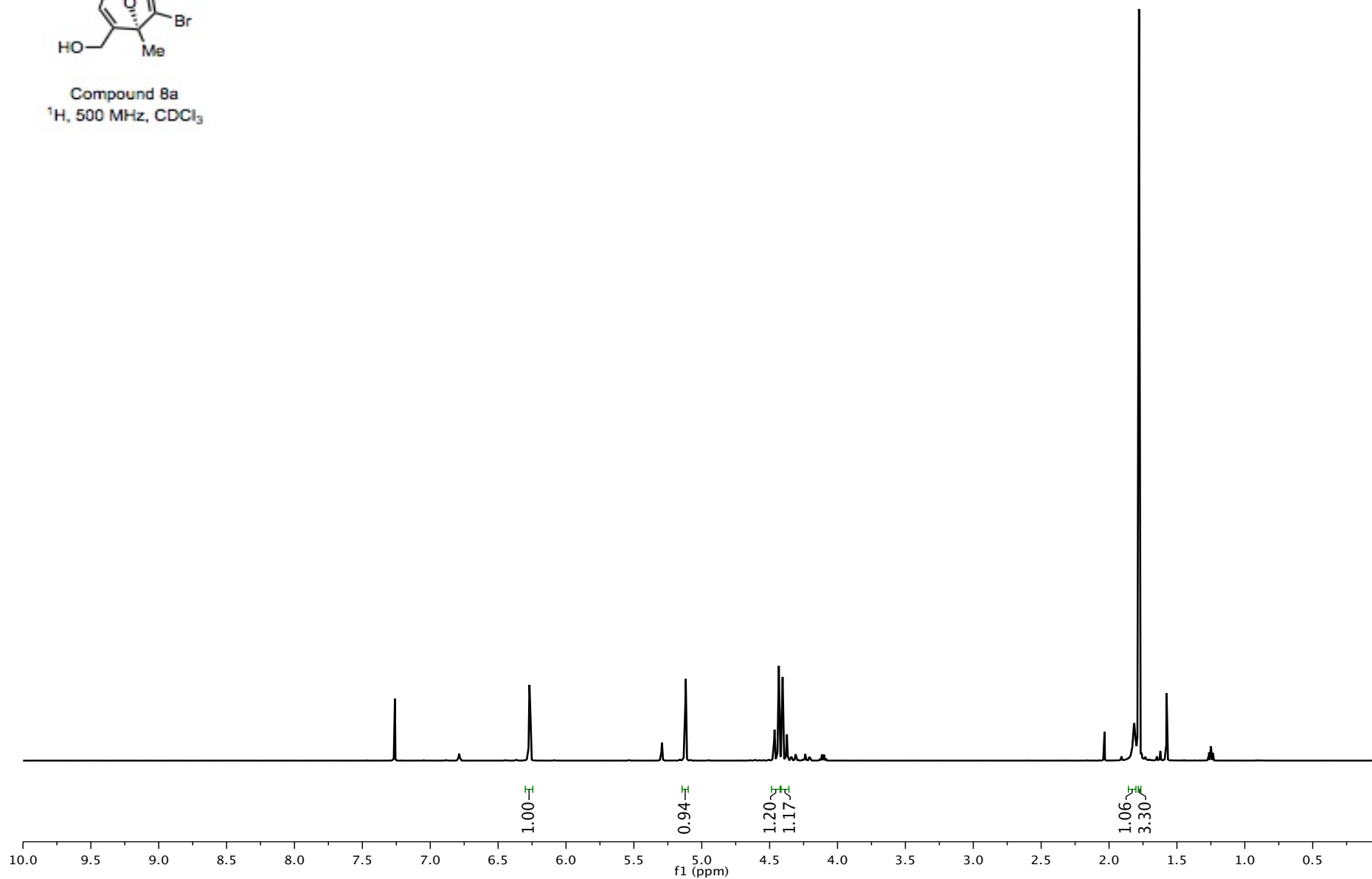
purged three times ( $\text{H}_2$ ) prior to pressurizing the reaction vessel with  $\text{H}_2$  (600 psi). The reaction mixture was allowed to stand (no stirring) for 8 h before carefully releasing the pressure. Because TLC revealed a large amount of an over-reduced by-product ( $R_f = 0.27$ , 50% EtOAc in hexanes), the solution was placed under an atmosphere of argon and solid  $\text{NaHCO}_3$  (436 mg, 5.19 mmol) and Dess-Martin periodinane (440 mg, 1.04 mmol) were added [Note: Similar over-reduction was seen in the Corey synthesis of this intermediate].<sup>3</sup> The mixture was stirred at room temperature for 1 h before addition of sat. aq.  $\text{Na}_2\text{S}_2\text{O}_4$  (10 mL). The biphasic mixture was stirred for an additional 1 h before diluting the reaction with  $\text{CH}_2\text{Cl}_2$  (15 mL). The layers were separated and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organics were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography ( $\text{SiO}_2$ , 30 g, 10% EtOAc in hexanes) to afford ketone **1** and its C9 diastereomer (101 mg, 94%, 5:1 mixture) as a clear oil:  $R_f = 0.54$  (50% EtOAc in hexanes); IR (KBr):  $\nu$ : 2944, 2359, 1042  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.08 (s, 1H), 2.33 (td,  $J = 12.9, 5.9$  Hz, 3H), 2.27 – 2.23 (m, 2H), 2.09 (dd,  $J = 10.9, 4.7$  Hz, 1H), 2.04 (dd,  $J = 11.7, 3.5$  Hz, 1H), 1.90 – 1.85 (m, 2H), 1.81 (td,  $J = 13.3, 6.1$  Hz, 1H), 1.69 (dd,  $J = 11.4, 3.5$  Hz, 1H), 1.62 (ddd,  $J = 13.1, 5.5, 2.7$  Hz, 1H), 1.55 – 1.51 (m, 1H), 1.45 – 1.41 (m, 1H), 1.41 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  210.6, 86.1, 79.3, 52.7, 45.2, 45.0, 44.4, 41.6, 40.0, 39.2, 37.1, 35.1, 23.1; HRMS (ESI) calcd for  $\text{C}_{13}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 207.1385; found: 207.1380

## References:

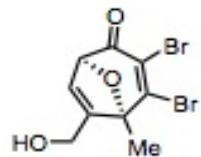
- (1) Paterson, I.; Mark, G.; Banks, B.J. *Tetrahedron* **1989**, 45, 5283-5292
- (2) Tobey, S.W.; West, R.; *J. Am. Chem. Soc.* **1966**, 88, 2481-2488.
- (3) Lalic, G.; Corey, E.J.; *Org. Lett.* **2007**, 9, 4921-4923



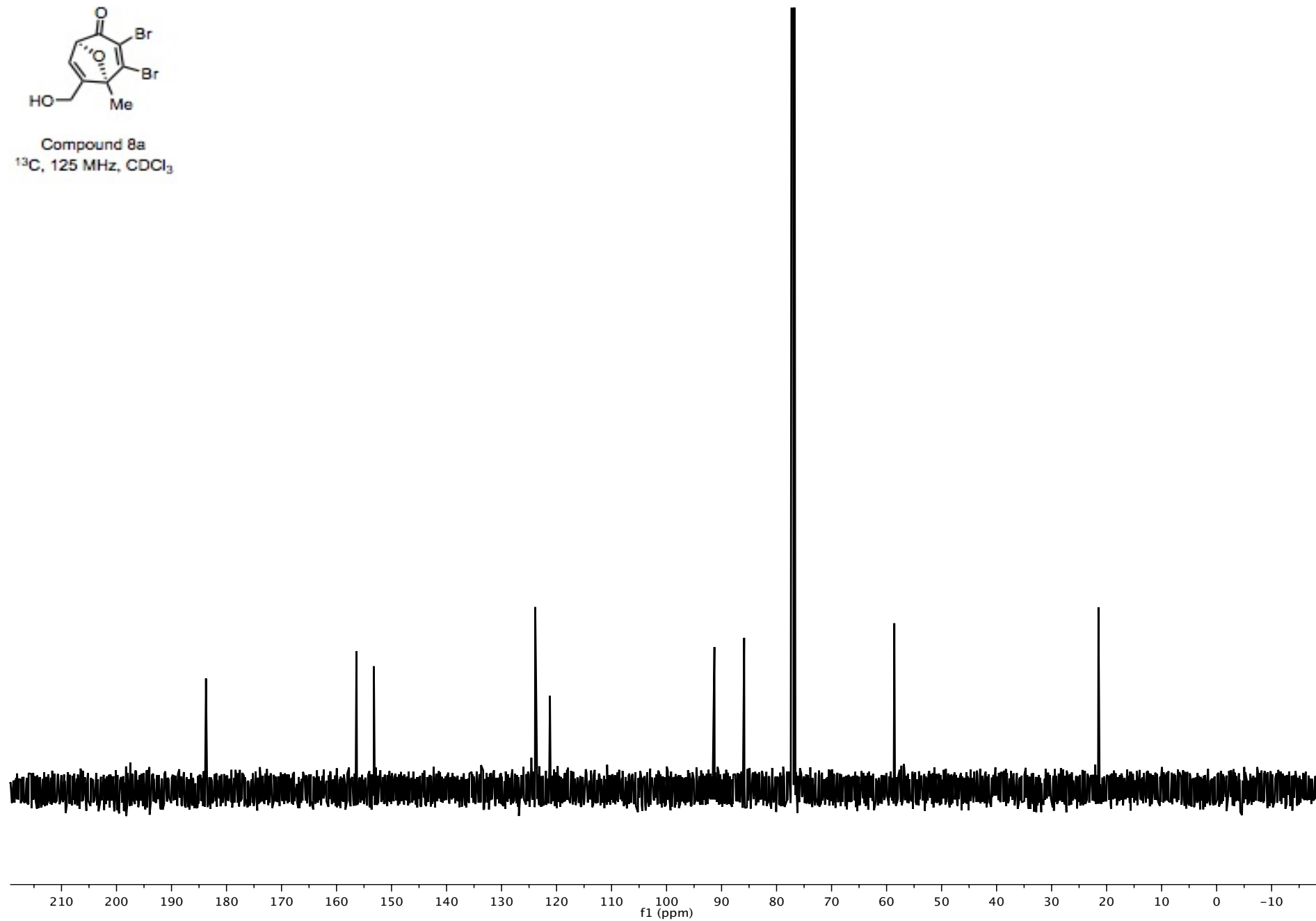
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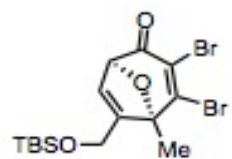




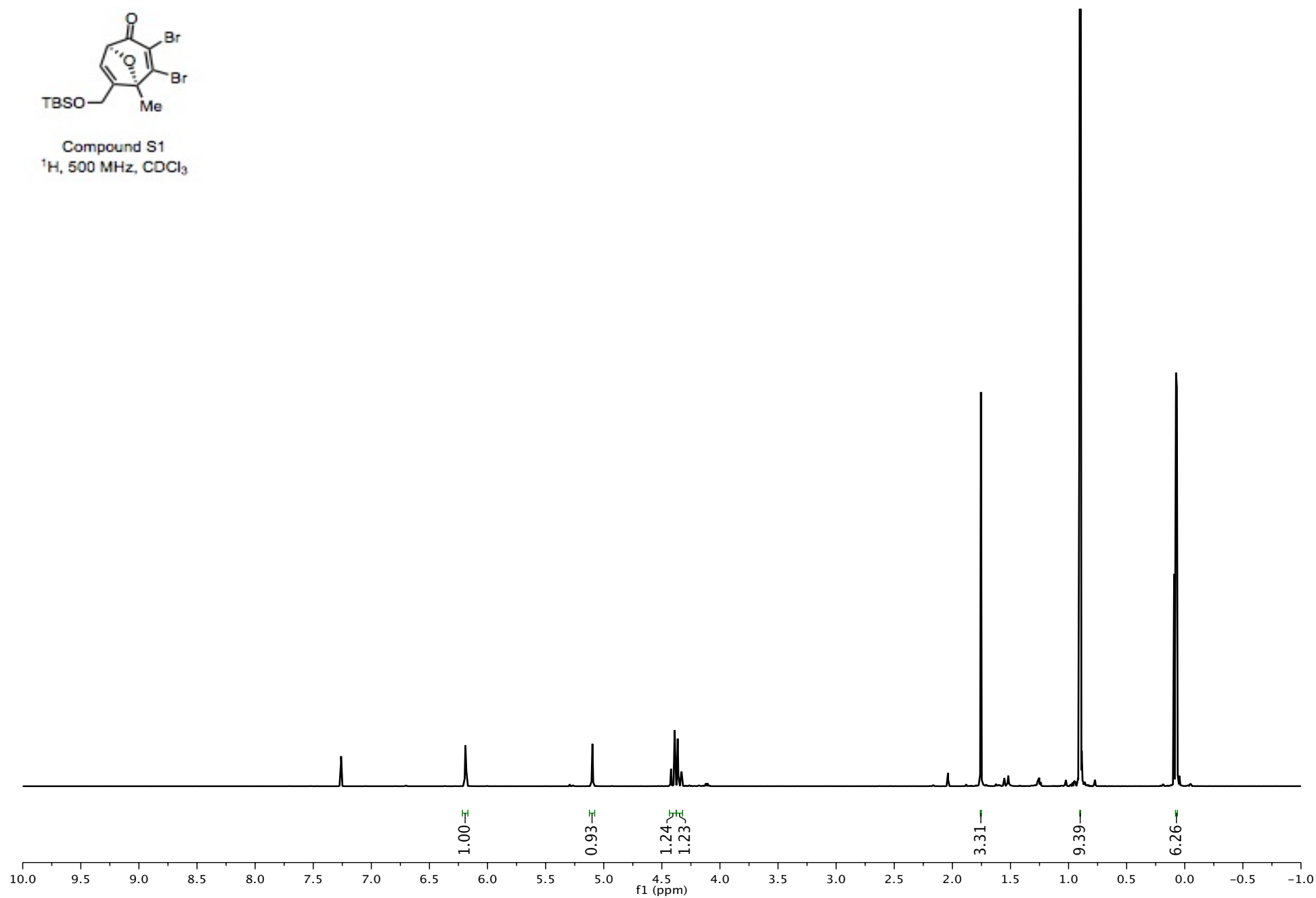


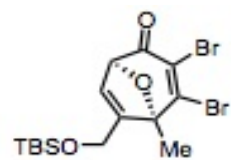
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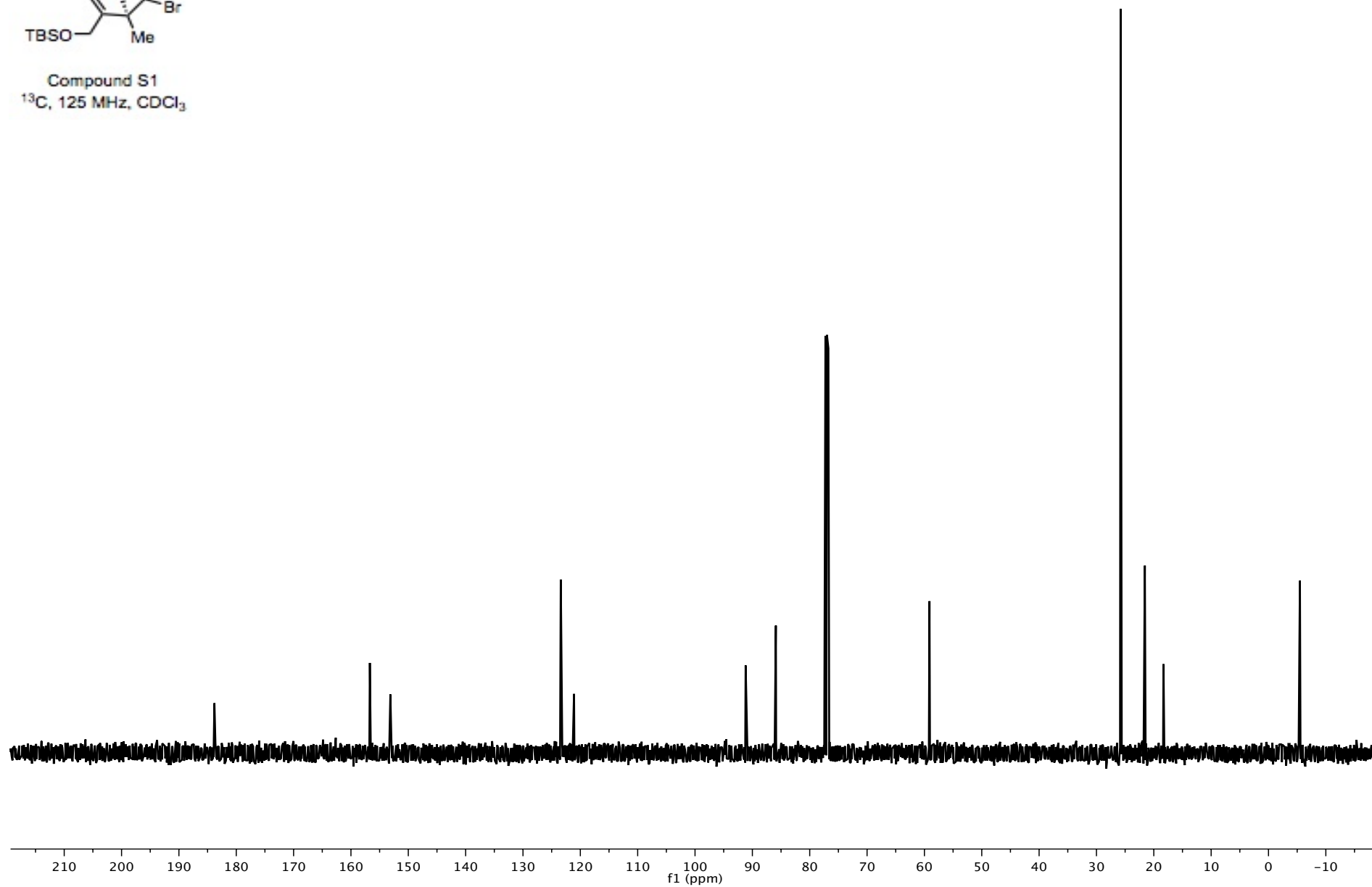


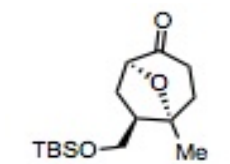
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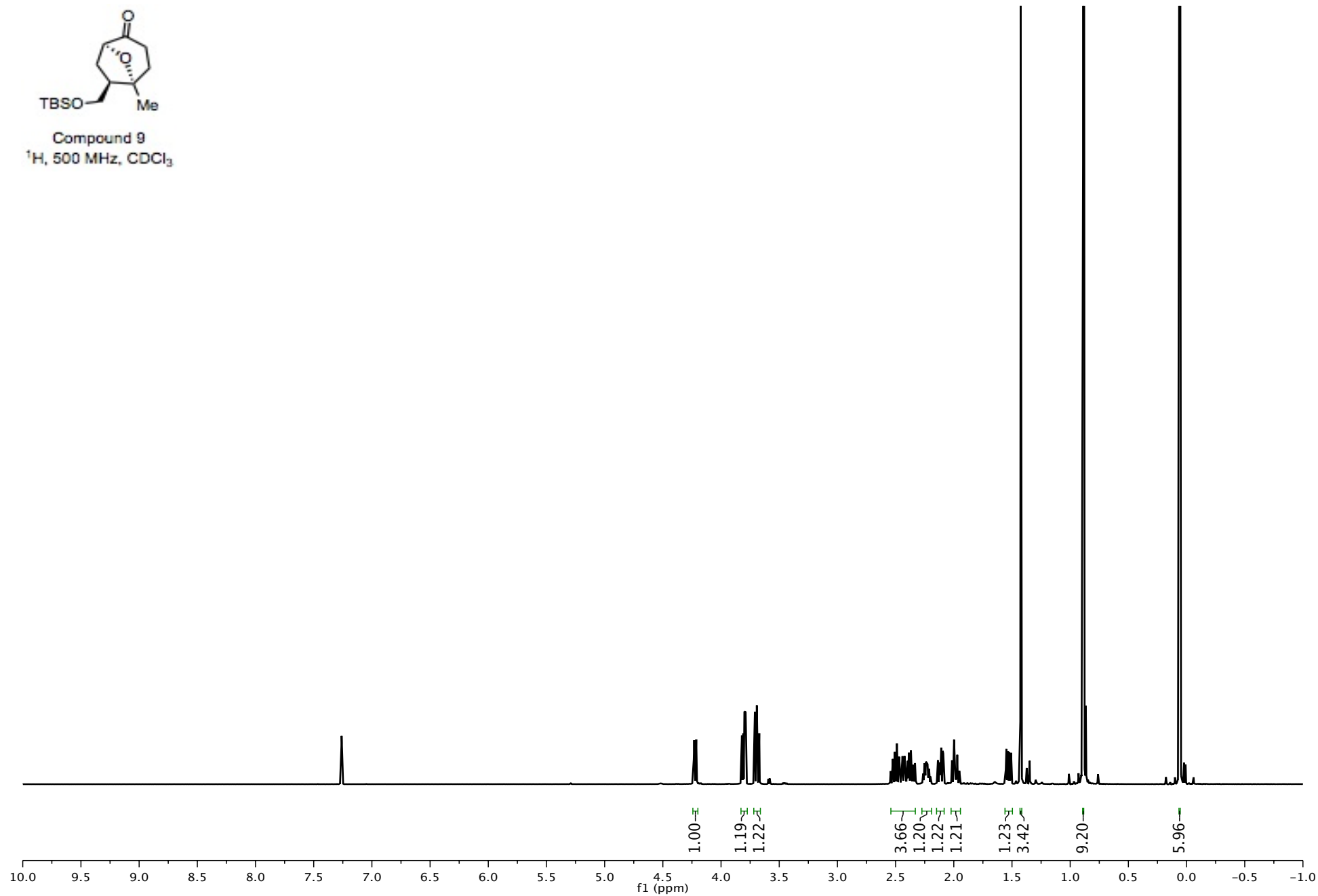


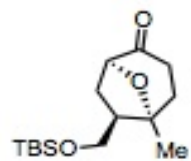
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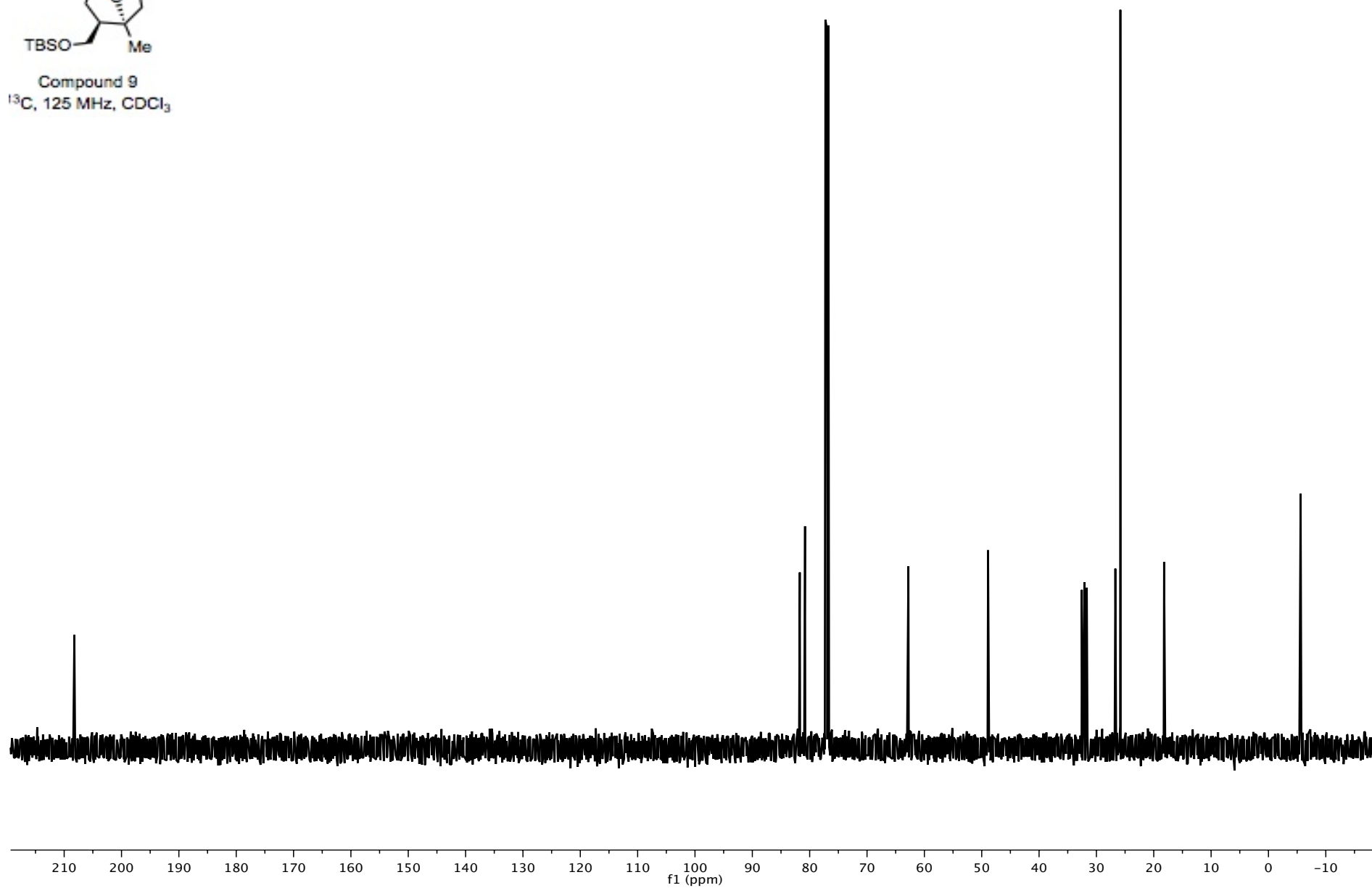


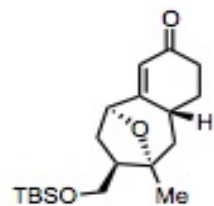
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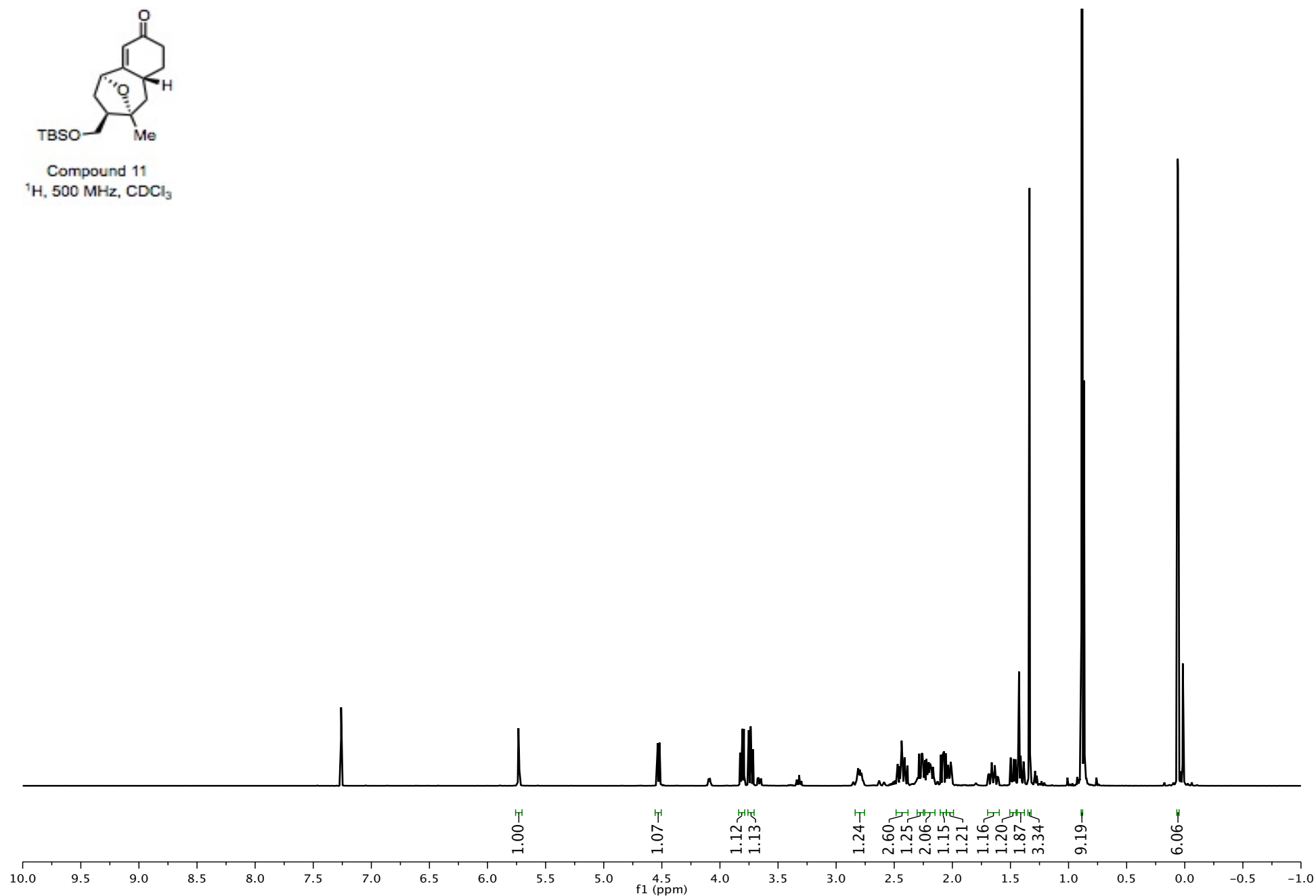


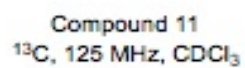
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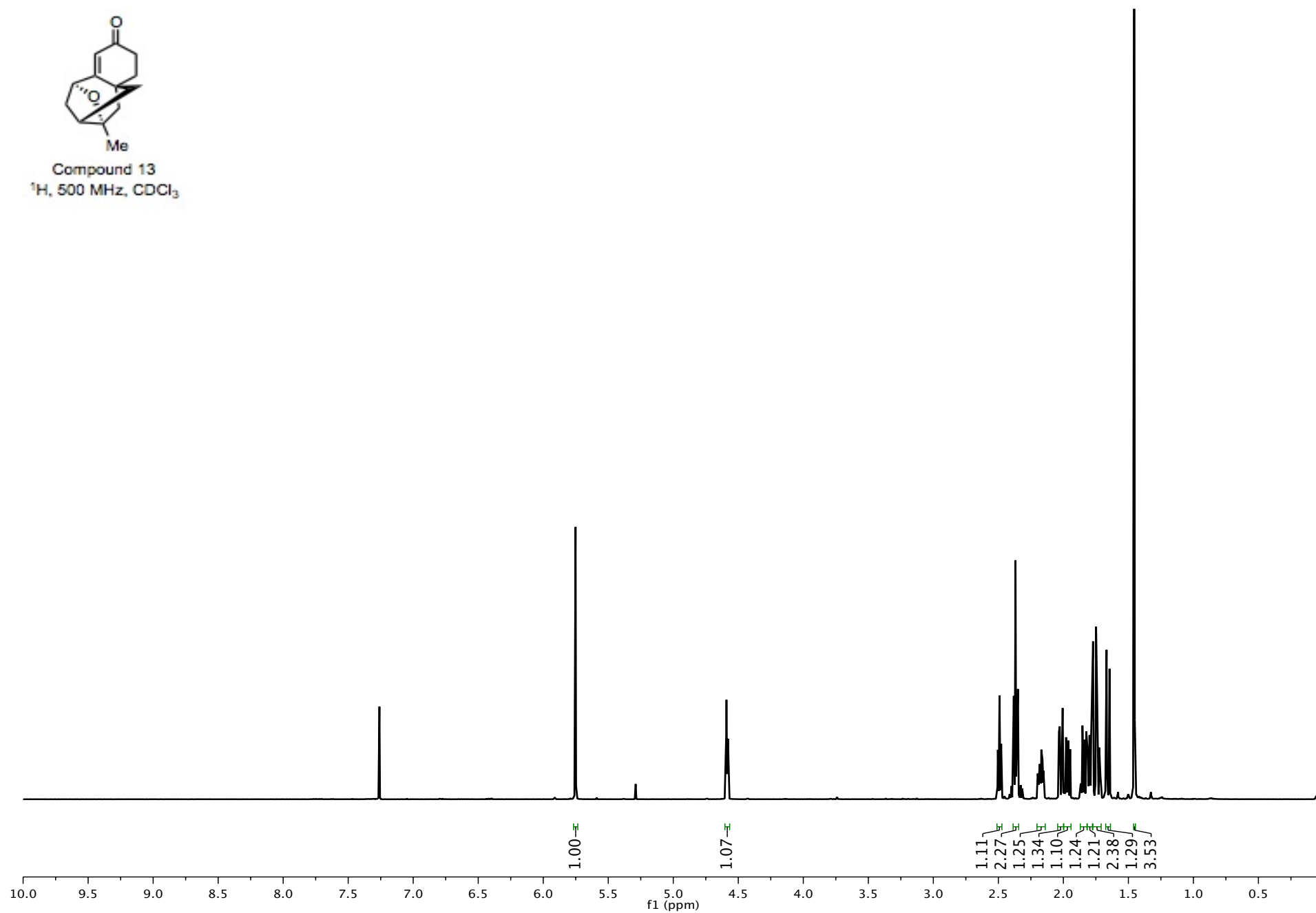
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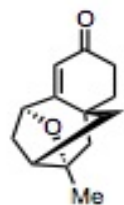




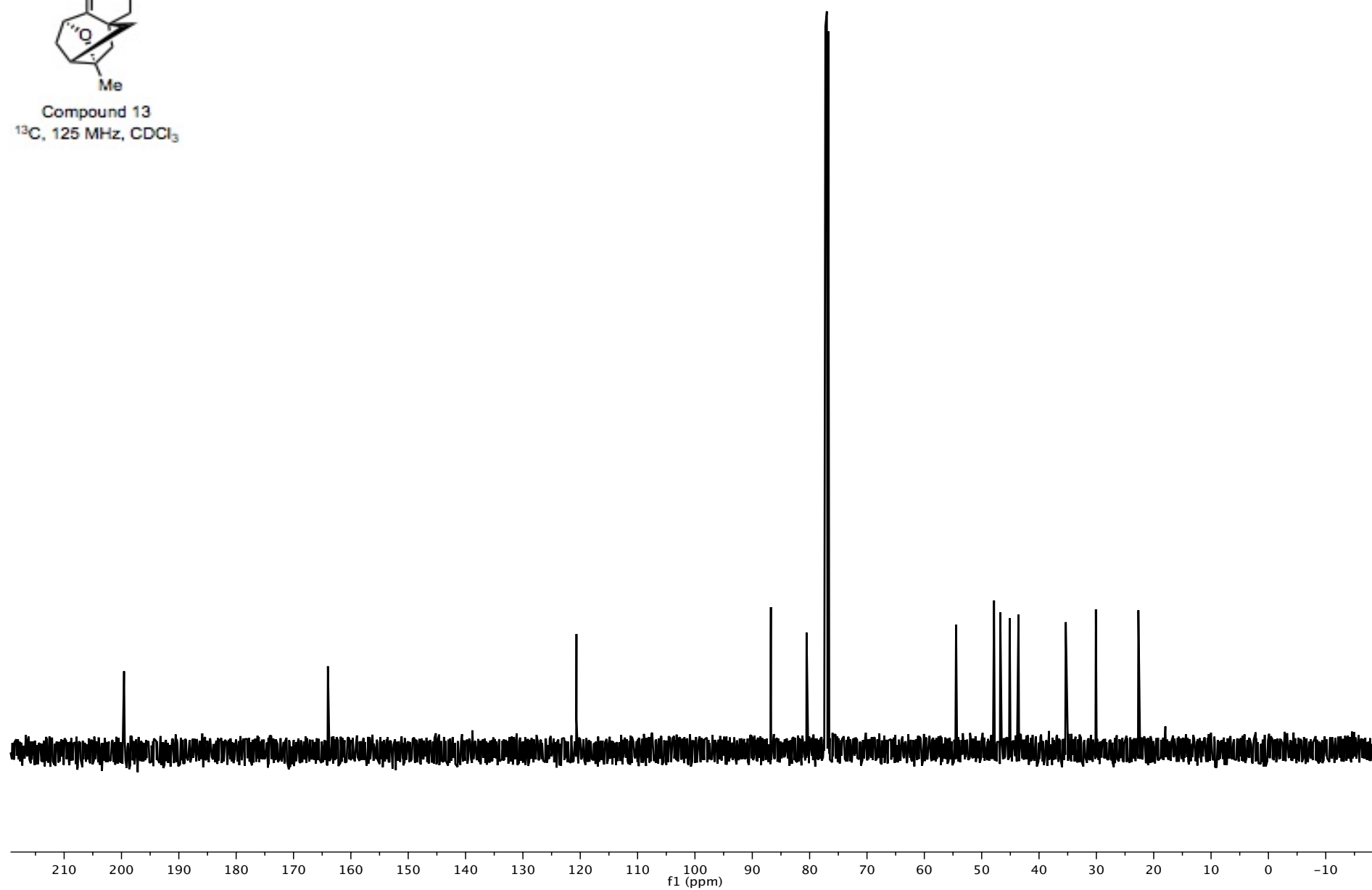
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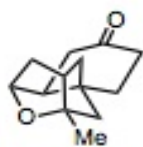




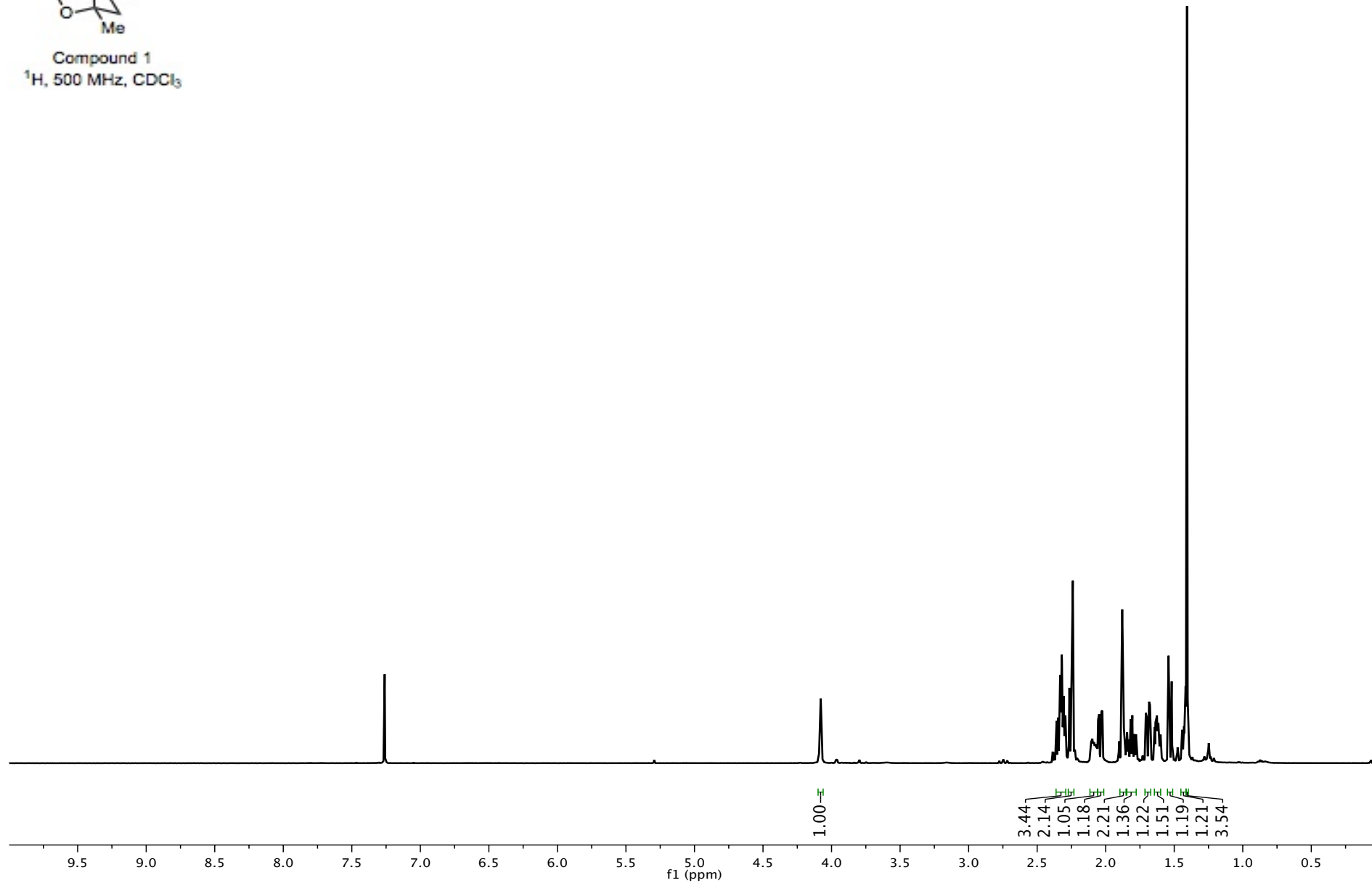


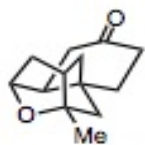
Compound 13  
 $^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$





Compound 1  
 $^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$





Compound 1  
 $^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$

