

Electronic supplementary information

A Mild, Large-Scale Synthesis of 1,3-Cyclooctanedione: Expanding Access to Difluorinated Cyclooctyne for Copper-free Click Chemistry

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General Information

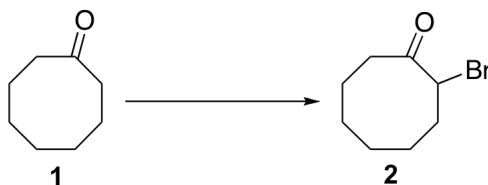
Unless otherwise noted, all reactions were performed under an argon atmosphere in flame- or oven-dried glassware and were stirred with a Teflon-coated magnetic spinbar. Reaction temperature refers to the bath temperature, not the internal temperature of the reaction vessel. Solvents and liquid reagents were transferred via syringe or cannula. All reagents were obtained from commercial suppliers in the highest available purity and used without further purification unless otherwise stated. Solvents were removed by rotary evaporation (rotovap).

All nuclear magnetic resonance (NMR) spectra were run in deuteriochloroform (CDCl_3) obtained from Cambridge Isotope Laboratories. ^1H NMR spectra were recorded on a Varian INOVA 500 MHz instrument. $^{13}\text{C}\{^1\text{H}\}$ and 2D-COSY experiments were recorded on a Bruker Avance-III 300 MHz instrument. Chemical shifts are reported in parts per million (δ) from TMS and multiplicities are denoted using standard abbreviations. The residual CHCl_3 peak was used as an internal reference standard (7.26 ppm for ^1H and 77.16 ppm for ^{13}C). J values are reported in Hz.

High-resolution mass spectra (HRMS) were obtained on an electrostray ionization instrument (ESI) at the University of Colorado-Boulder Central Analytical Laboratory.

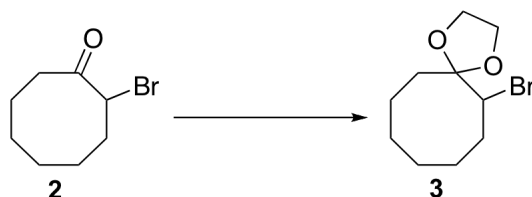
Flash chromatography was performed on silica gel, standard grade, 60 $^\circ\text{A}$, 18-32 μm obtained from Sorbtech following the general procedure by Still.¹ Reaction mixtures and chromatography fractions were analyzed by thin layer chromatography (TLC) on silica gel 60 F_{254} plates from EM Separatory Technologies. TLC plates were developed in the solvent system indicated and compounds were revealed by staining with ceric ammonium molybdate (CAM), or by visualizing with UV light at 254 nm.

2-Bromocyclooctanone (2)



Cyclooctanone (65.75 g, 521 mmol, 1.0 equiv.) and ethanol (700 mL) were added to a 2-L round-bottom flask and stirred until dissolution was complete. 180 mL of 1 N HCl was added and the solution was cooled to 0 °C while purging with argon. Bromine (125 g, 782 mmol, 1.5 equiv.) was then added in a slow, steady stream and the solution was stirred at 0 °C for 72 hr. The reaction was quenched with sat. Na₂SO₃ (150 mL) and most of the ethanol was removed by rotovap. The cloudy, heterogeneous solution was extracted with diethyl ether (4 x 500 mL) and the combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated to give a pale yellow liquid (95.95 g, 468 mmol, 90%) that was used without further purification; ¹H NMR (500 MHz, CDCl₃) δ = 4.27 (dd, *J* = 4.0, 11.4, 1H), 2.87 (td, *J* = 3.7, 12.1, 1H), 2.42 – 2.36 (m, 2H), 2.36 – 2.28 (m, 1H), 1.97 – 1.89 (m, 1H), 1.82 – 1.64 (m, 3H), 1.61 – 1.51 (m, 2H), 1.46 – 1.34 (m, 1H), 1.22 – 1.12 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 208.80, 54.49, 36.30, 32.79, 28.84, 26.66, 25.52, 24.06; HRMS (ESI⁺): calcd for [(C₈H₁₃BrO)+H]⁺ 205.0223; found 205.0215.

6-Bromo-1,4-dioxaspiro[4.7]dodecane (3)



To a 2-L round-bottom flask containing benzene (500 mL) were added 2-bromocyclooctanone (2, 86.77 g, 423 mmol, 1.0 equiv.), 1,2-ethanediol (235 mL, 4.230 mol, 10 equiv.), and *p*-toluenesulfonic acid (8.05 g, 42.3 mmol, 10 mol%). The flask was fitted with a Dean-Stark condenser and refluxed (104

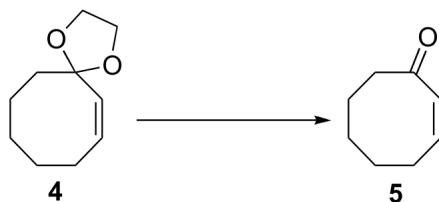
°C) until no additional water accumulated in the trap (24 hr), making periodic draw-offs of water as necessary to avoid overflow. The two-phase solution was cooled to rt, washed with water (2 x 400 mL). The water washes were extracted once with benzene (400 mL) and the combined organics were washed with brine (300 mL), dried over MgSO₄, filtered, and concentrated to yield a pale yellow liquid (69.96 g, 416 mmol, 97%) that was used without further purification; ¹H NMR (500 MHz, CDCl₃) δ 4.56 – 4.47 (m, 1H), 4.19 – 4.10 (m, 2H), 4.01 – 3.92 (m, 2H), 2.34 – 2.25 (m, 2H), 2.05 – 1.95 (m, 1H), 1.89 – 1.82 (m, 1H), 1.73 – 1.46 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 111.06, 66.16, 65.24, 59.70, 34.35, 33.89, 27.56, 26.82, 25.07, 22.35; HRMS (ESI+): calcd for [(C₁₀H₁₇BrO₂)+⁷Li]⁺ 255.0566; found 255.0576.

(Z)-1,4-dioxaspiro[4.7]dodec-6-ene (4)



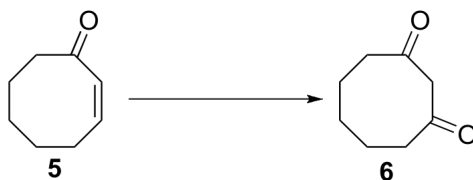
Bromoketal **3** (104.64 g, 420 mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 300 mL) were added to a 1-L round-bottom flask and heated at 160 °C for 3 hr. During cooling a rapid precipitation event occurred, causing most of the solution to crystallize. The solidified reaction mixture was dissolved in water (1 L) and extracted with diethyl ether (3 x 600 mL). The combined organics were washed with brine (300 mL), dried over MgSO₄, filtered, and concentrated to give a pale yellow liquid (69.95 g, 416 mmol, 99%) that was used without further purification; ¹H NMR (500 MHz, CDCl₃) δ 5.67 – 5.54 (m, 2H), 3.91 (s, 4H), 2.43 – 2.34 (m, 2H), 1.86 – 1.82 (m, 2H), 1.69 – 1.42 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 133.49, 131.53, 109.91, 64.05, 39.33, 27.91, 24.61, 24.01, 21.78; HRMS (ESI+): calcd for [(C₁₀H₁₆O₂)+⁷Li]⁺ 175.1305; found 175.1303.

(Z)-Cyclooct-2-enone (5)



To a solution of acetone/water (95:5, 164.8 mL) in a 500-mL round-bottom flask was added ketal-ene **4** (27.72 g, 164.8 mmol) and pyridinium *p*-toluenesulfonate (4.14 g, 16.5 mmol, 10 mol%). The solution was refluxed (70 °C) overnight then most of the acetone was removed via rotovap. Sat. NaHCO₃ (250 ml) was added to the reaction mixture, which was then extracted with diethyl ether (3 x 200 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude reaction product was purified by flash chromatography (15:1 hexanes/ethyl acetate) to yield a pale yellow liquid (18.46 g, 148.7 mmol, 90%). R_f = 0.28 (10:1 hexanes/ethyl acetate, visualized with CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 6.34 (dt, *J* = 7.1, 12.5, 1H), 6.00 (d, *J* = 12.5, 1H), 2.68 – 2.61 (m, 2H), 2.55 – 2.46 (m, 2H), 1.85 – 1.78 (m, 2H), 1.67 – 1.52 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 206.08, 141.70, 132.45, 42.78, 28.62, 25.18, 23.15, 22.64; HRMS (ESI⁺): calcd for [(C₈H₁₂O)+H]⁺ 125.0961; found 125.0965.

Cyclooctane-1,3-dione (6)

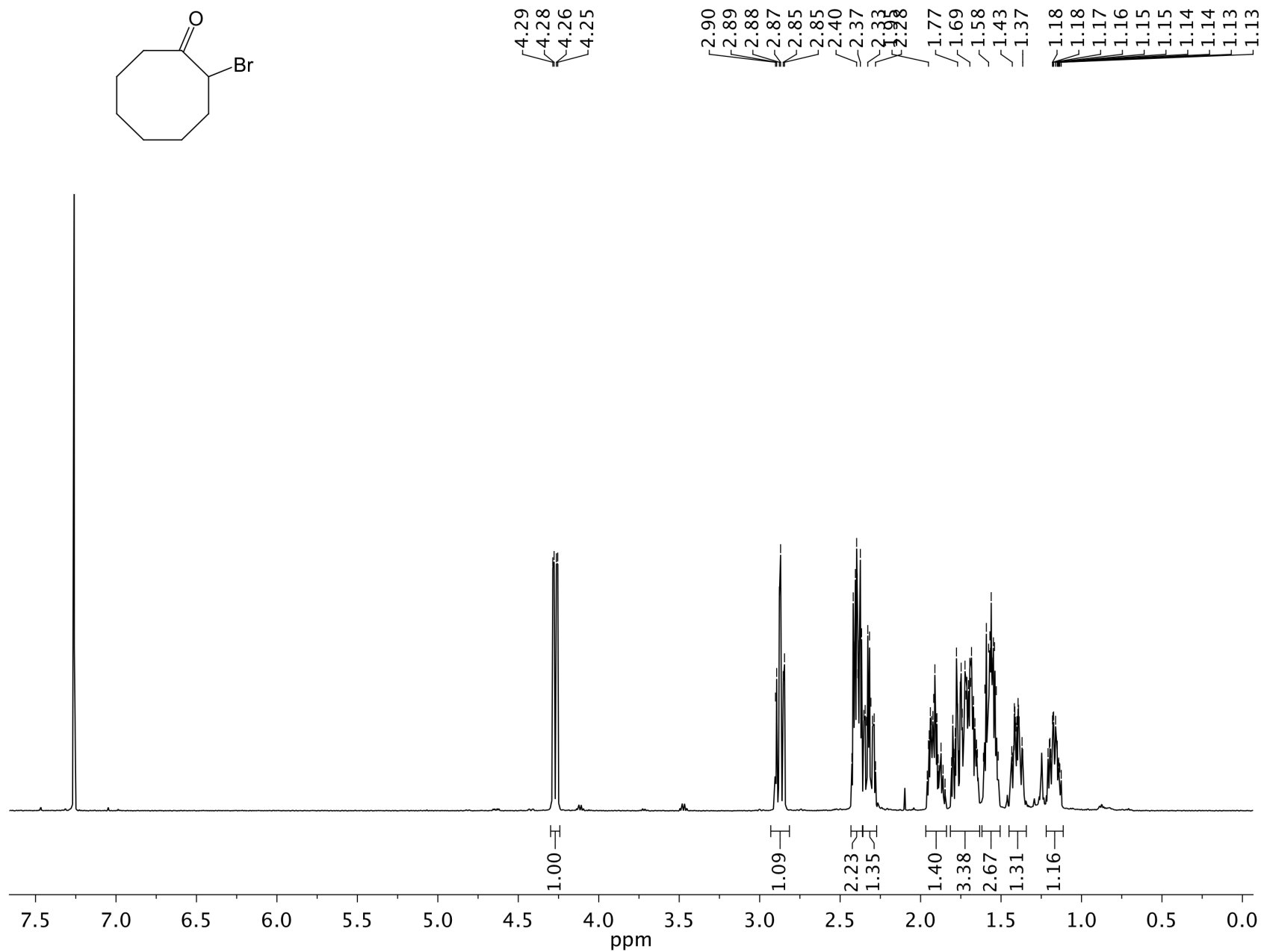
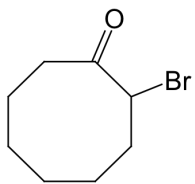


To a solution of 2-propanol and water (50:50, 300 mL) were added enone **5** (37.4 g, 301.4 mmol), *tert*-butylhydroperoxide (129 mL of a 70% aqueous solution, 904 mmol, 3 equiv.), and Na₂PdCl₄ (8.86 g, 30.1 mmol, 10 mol%). The reaction mixture was stirred and heated at 50 °C overnight then diluted with cold water (300 mL) and extracted with dichloromethane (3 x 300 mL). The combined organics were washed with 1 N HCl (500 mL) and brine (300

mL), dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (10:1 hexanes/ethyl acetate) to yield a pale yellow liquid (15.5 g, 110.6 mmol, 37%). R_f = 0.24 (4:1 hexanes/ethyl acetate, visualized with CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 3.50 (s, 2H), 2.51 – 2.46 (m, 4H), 1.83 – 1.77 (m, 4H), 1.66 – 1.60 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 206.33, 59.03, 44.08, 27.43, 24.21; HRMS (ESI+): calcd for [(C₈H₁₂O₂)+H]⁺ 141.0910; found 141.0915.

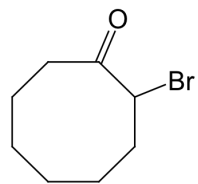
References

1. Still, W. C.; Kahn, M.; Mitra, A., Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, (14), 2923-2925.



Compound 2 ¹H NMR.

—208.80



—54.49

—36.30

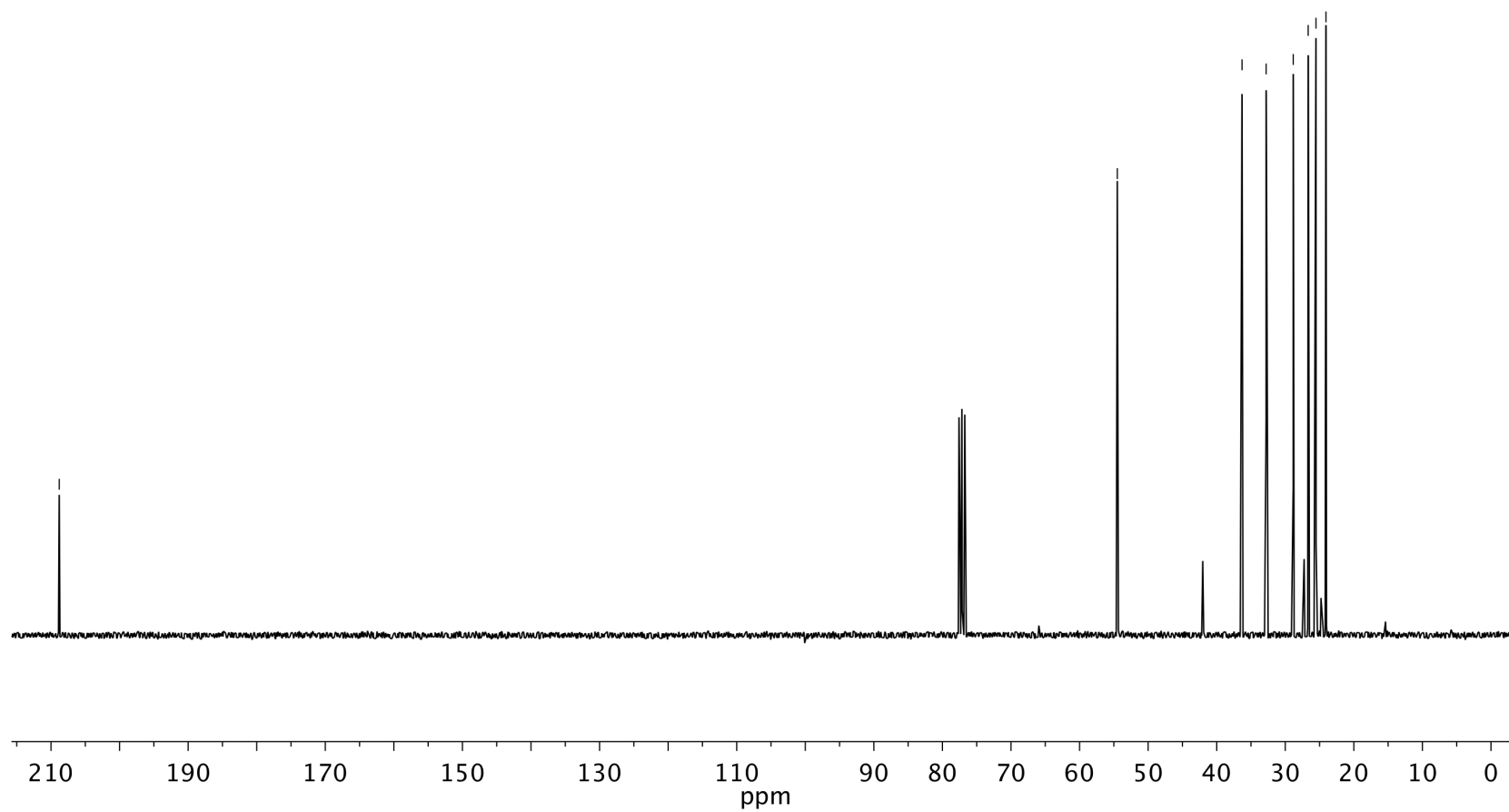
—32.79

—28.84

—26.66

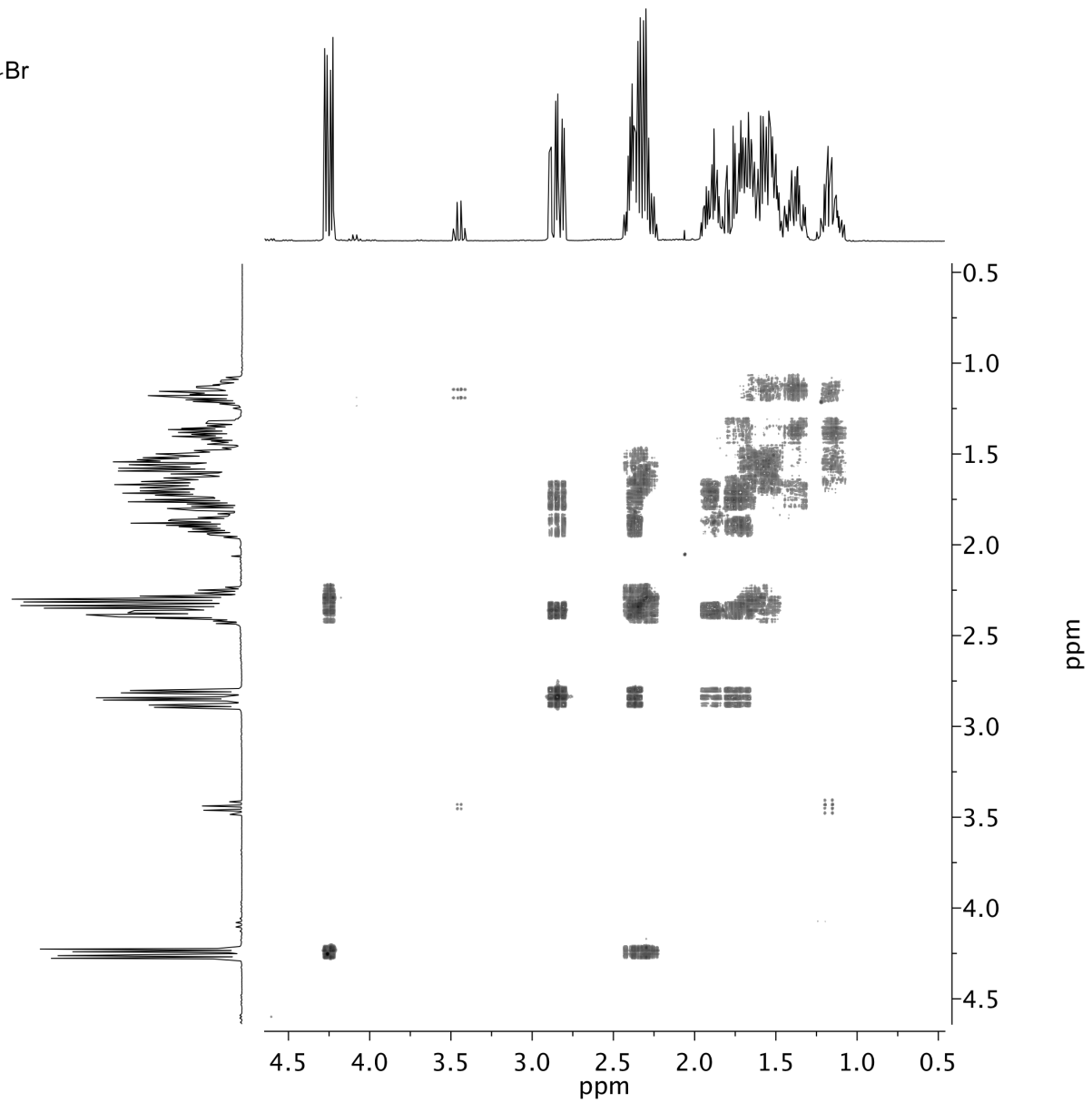
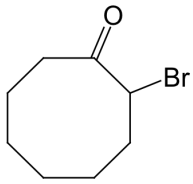
—25.52

—24.06

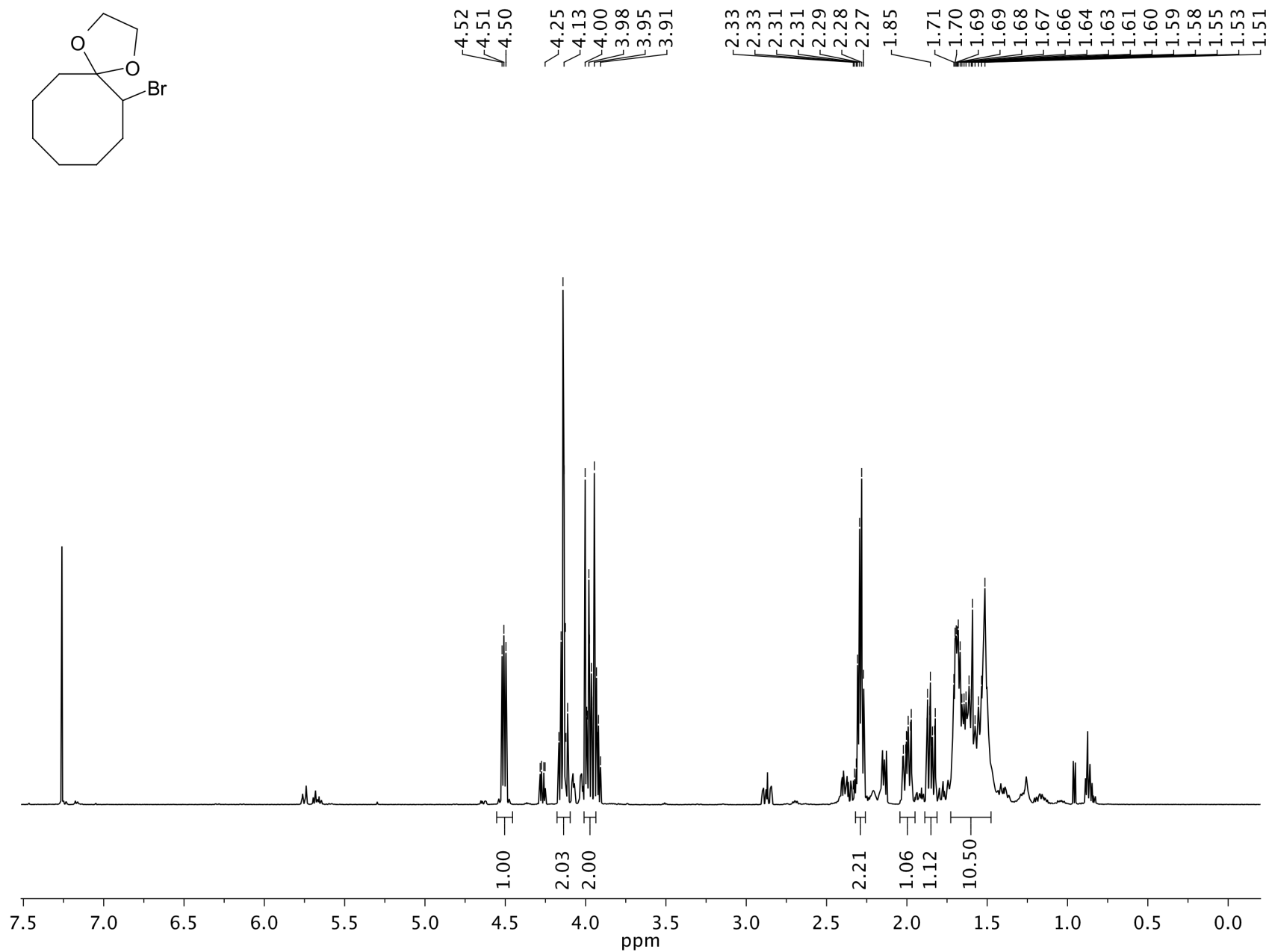
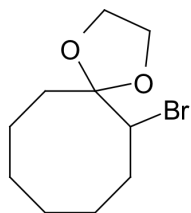


Compound **2** ¹³C NMR.

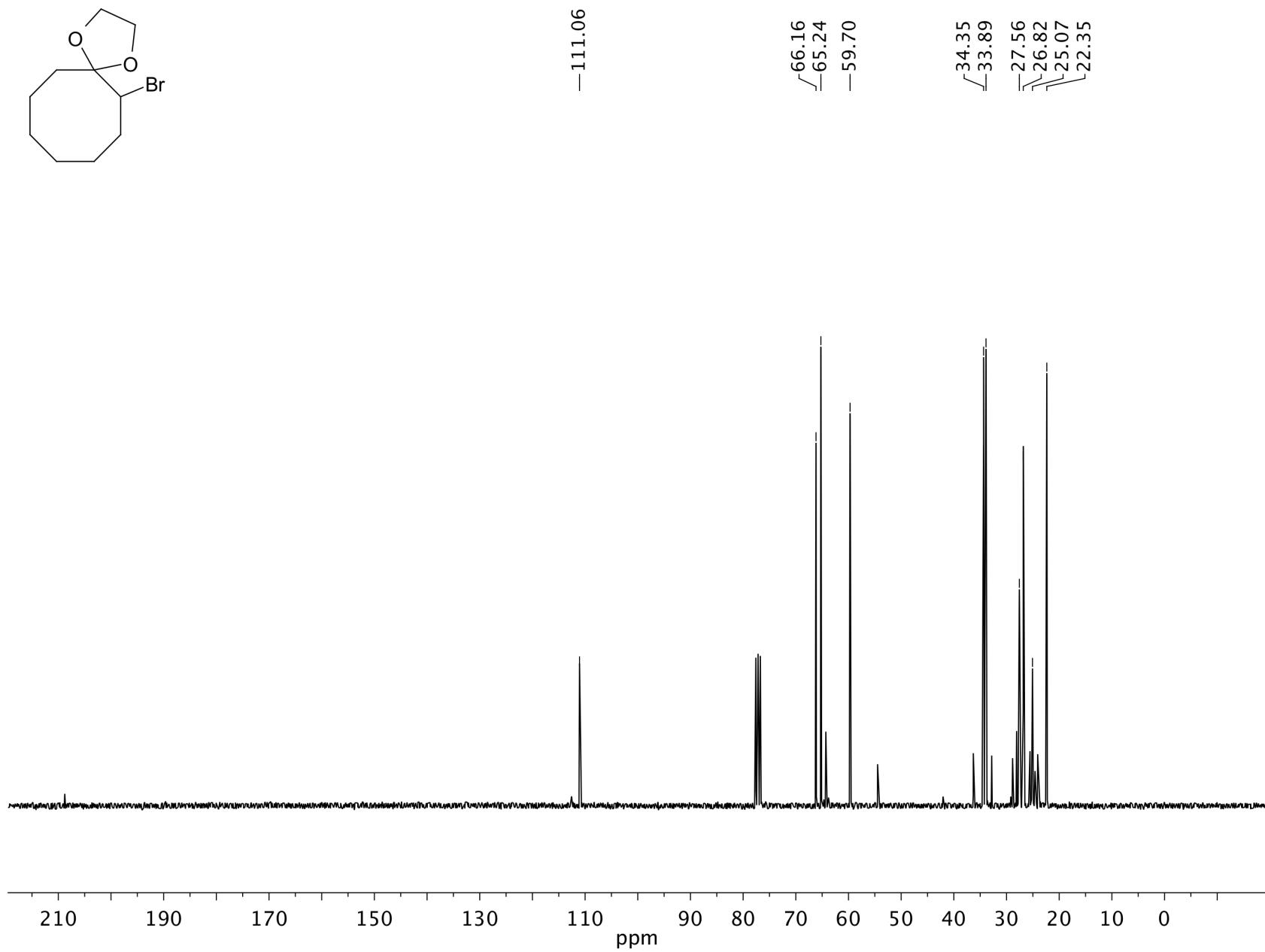
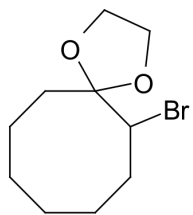
S8



Compound 2 2D-COSY
S9

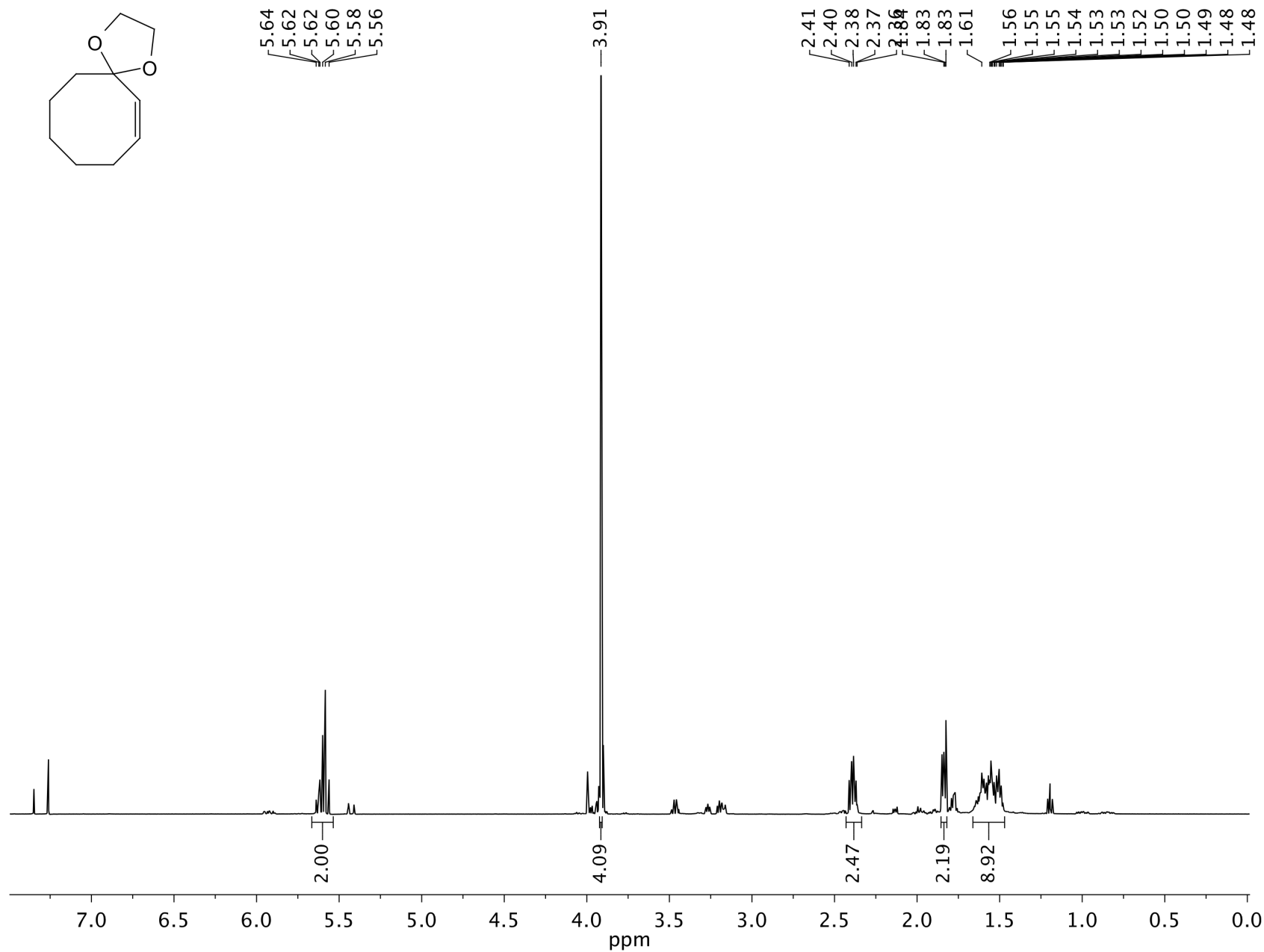
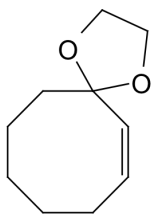


Compound 3 ¹H NMR.

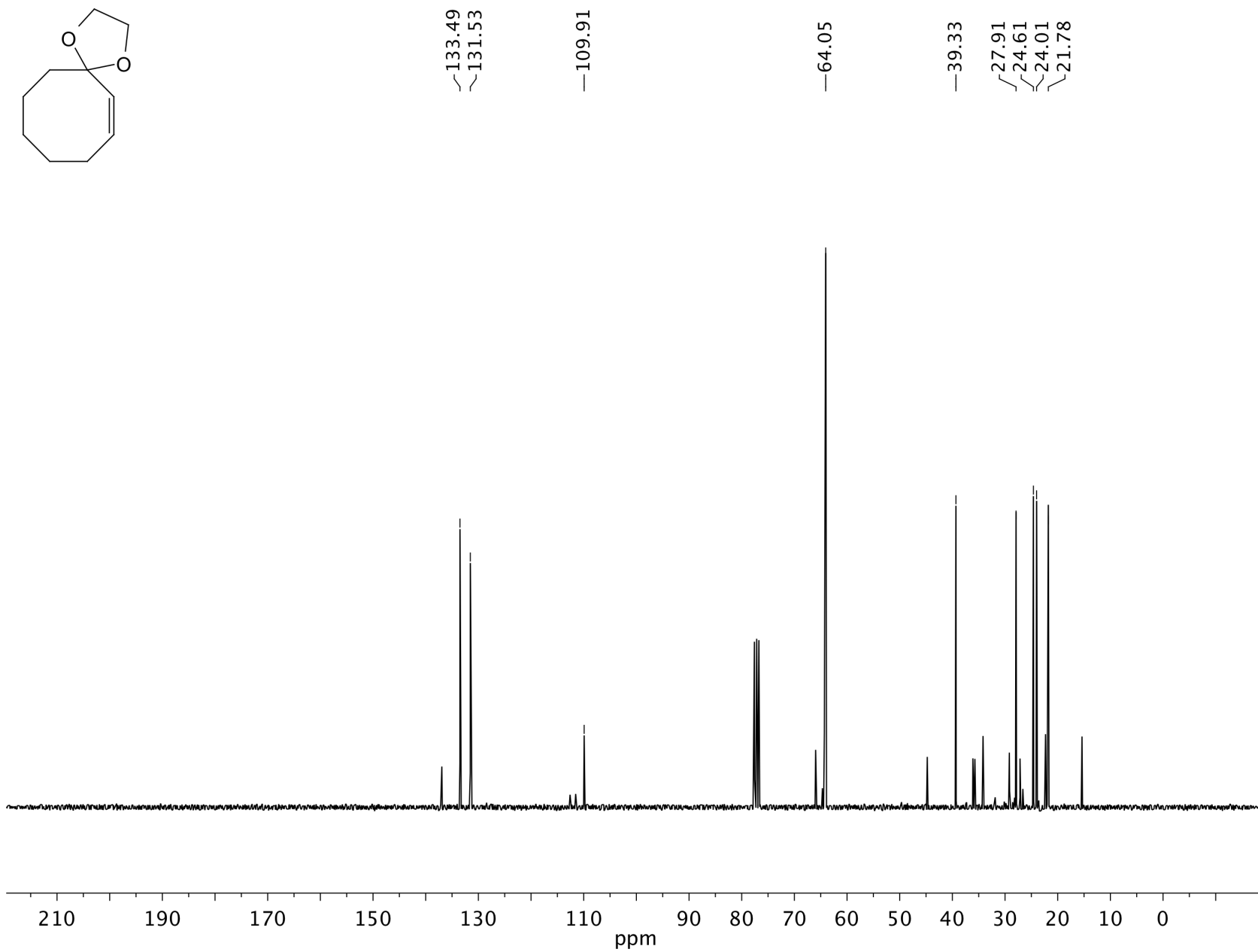
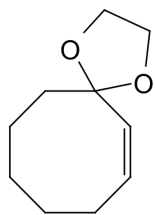


Compound 3 ¹³C NMR.

S11

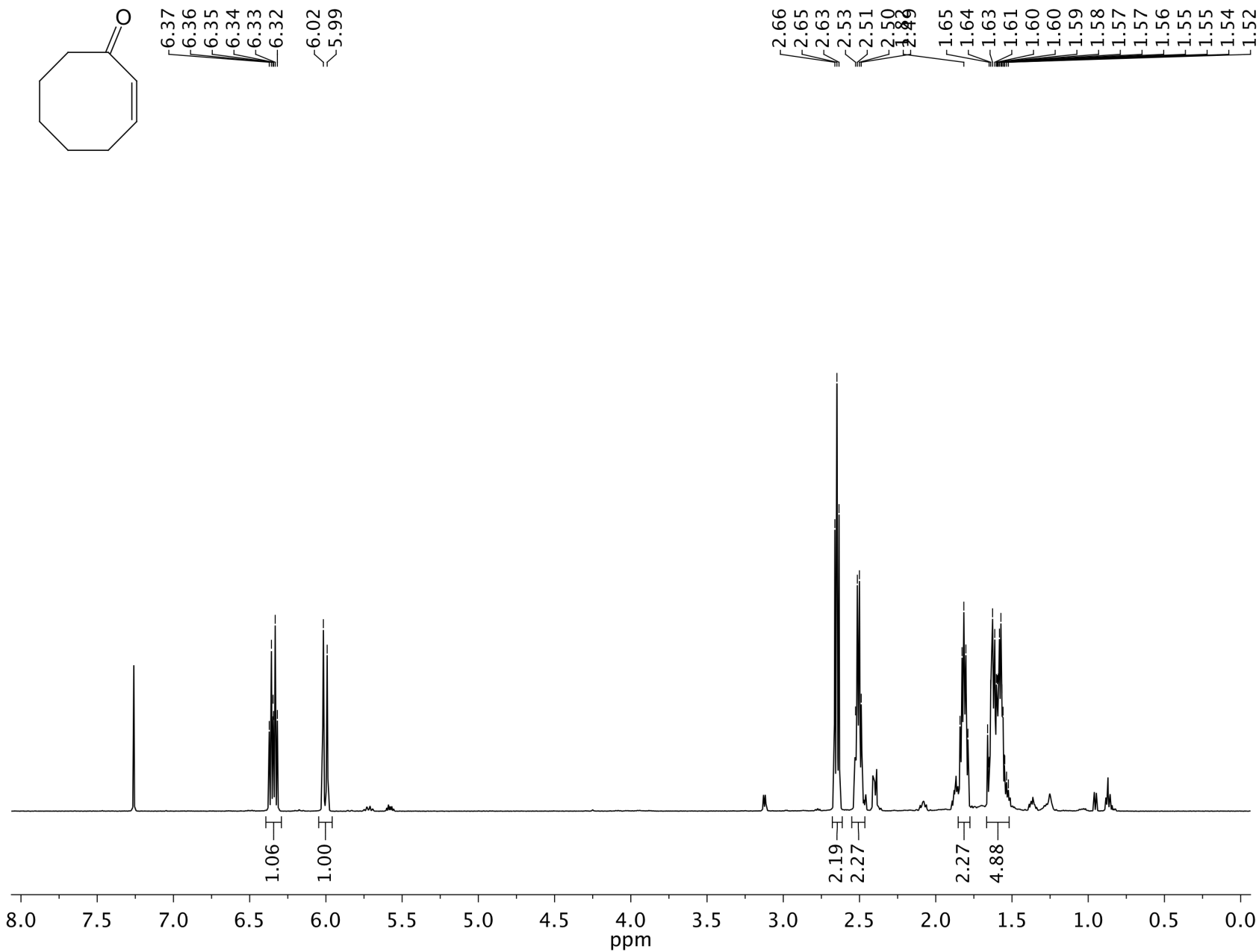


Compound 4 ¹H NMR.

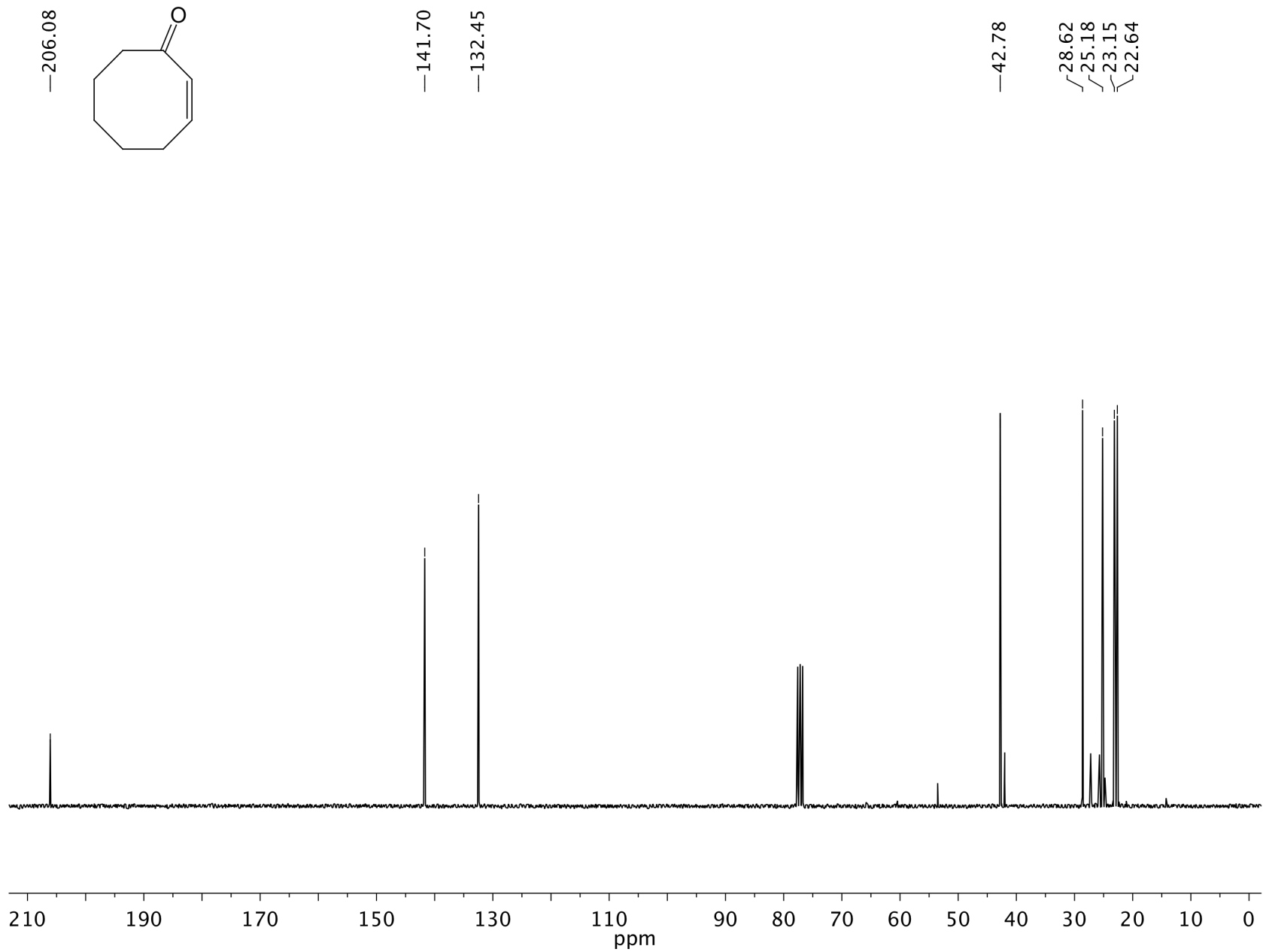


Compound 4 ¹³C NMR.

S13

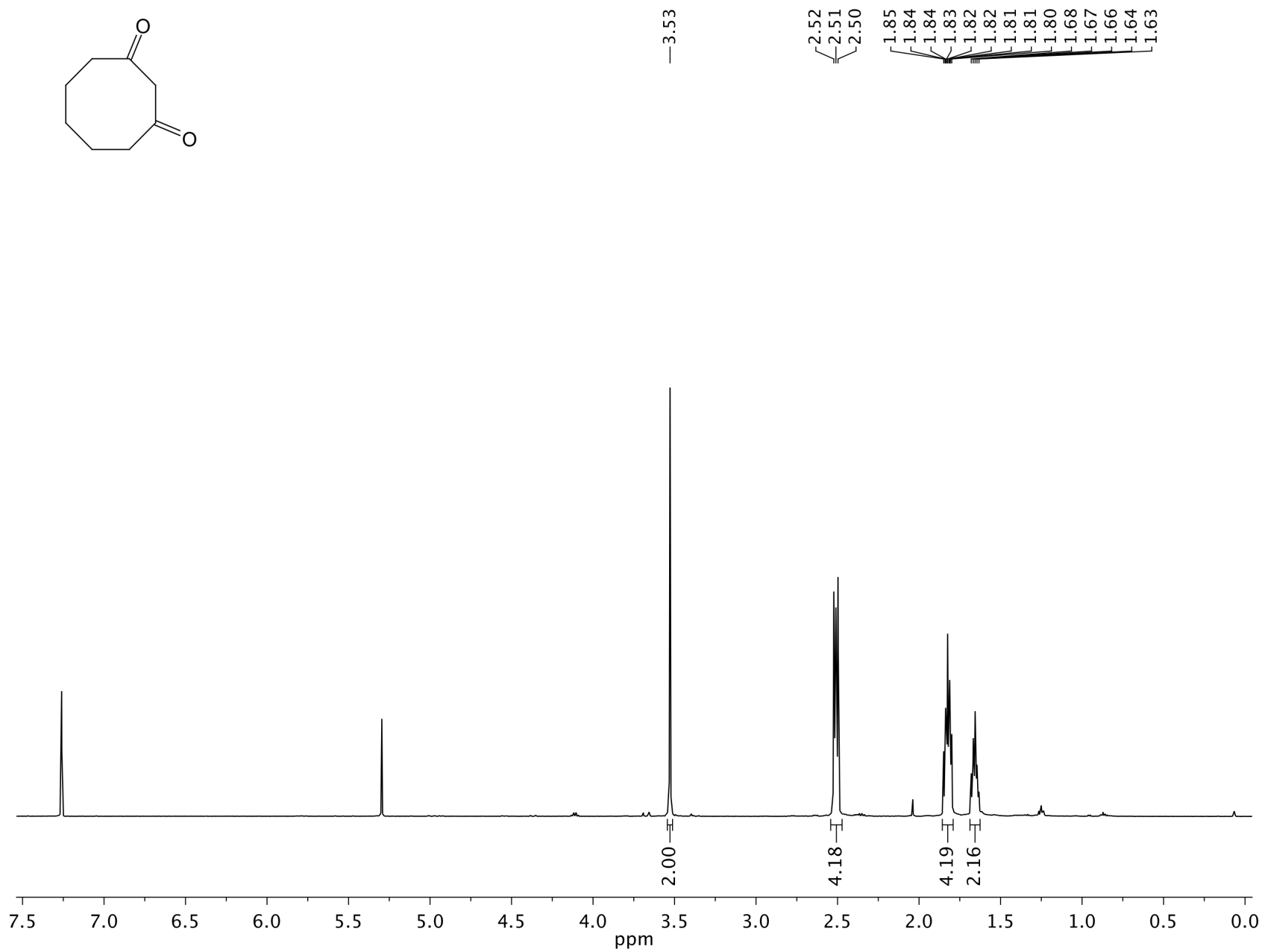
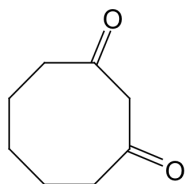


Compound 5 ¹H NMR.



Compound 5 ^{13}C NMR.

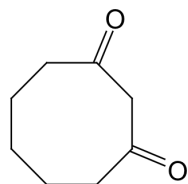
S15



Compound **6** ^1H NMR.

S16

—206.33

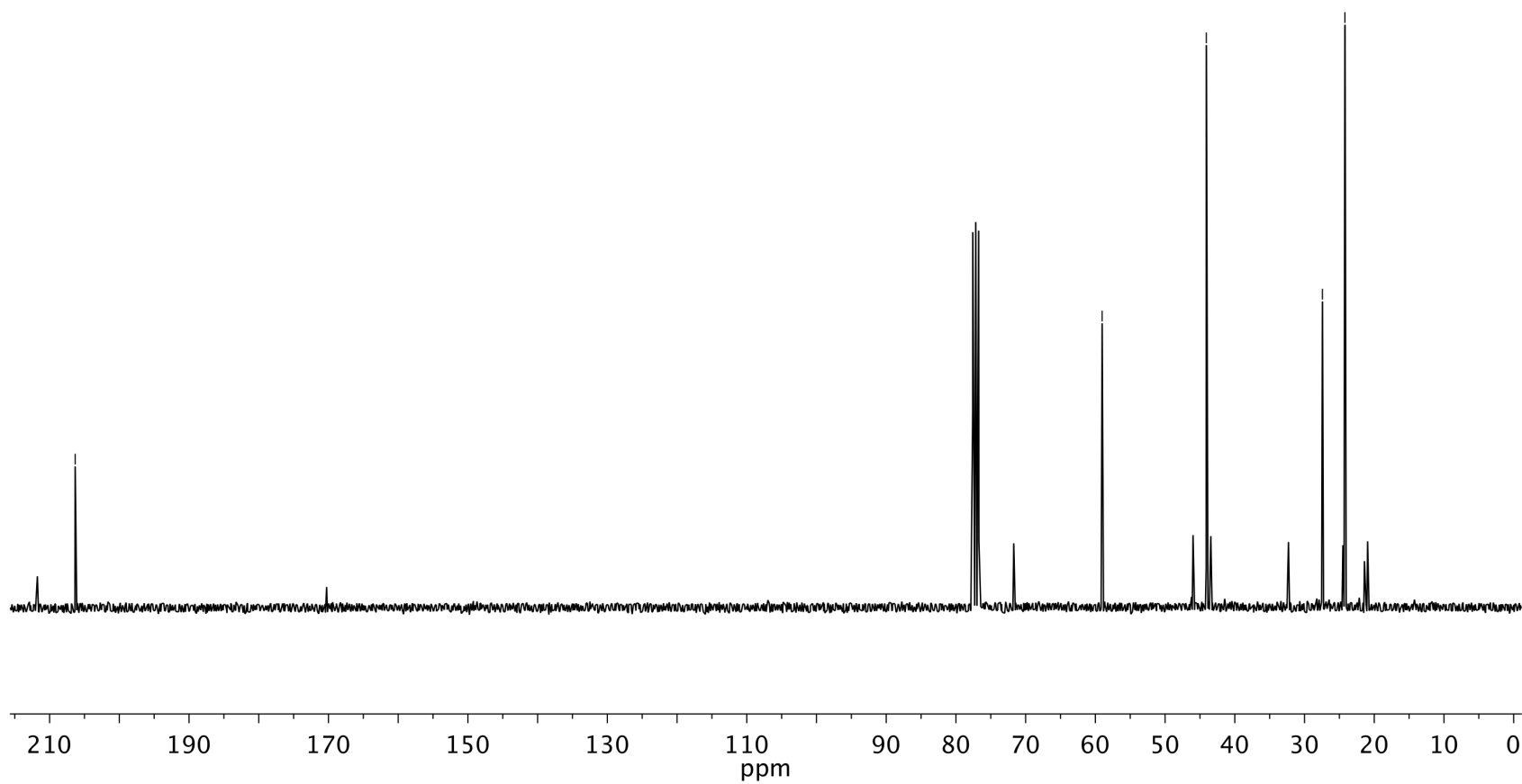


—59.03

—44.08

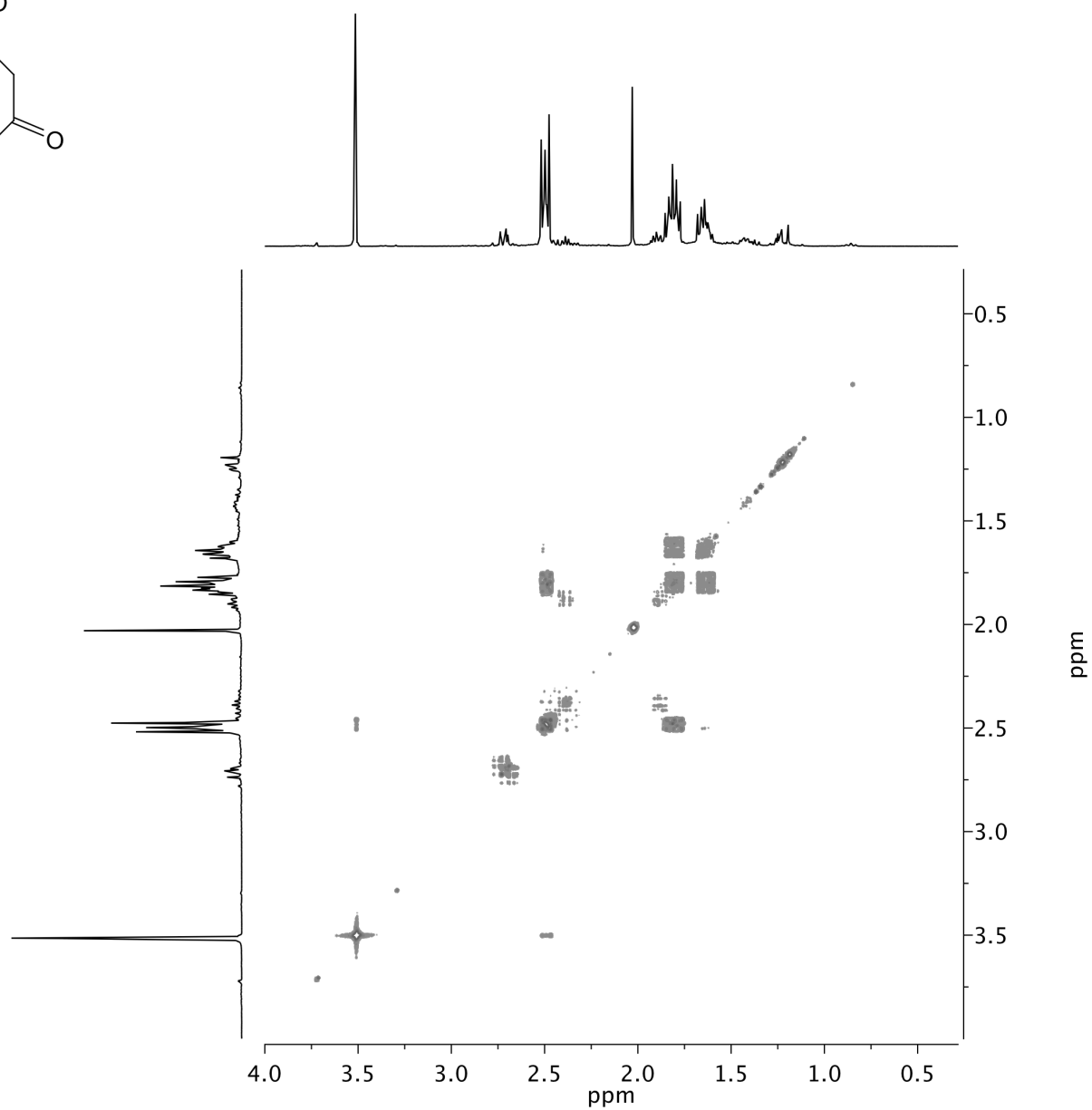
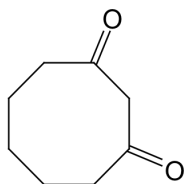
—27.43

—24.21



Compound **6** ¹³C NMR.

S17



Compound 6 2D-COSY.

S18