Supporting Information for

Chemical synthesis and self-assembly of a ladderane phospholipid

Jaron A. M. Mercer, Carolyn M. Cohen, Steven R. Shuken, Anna M. Wagner, Myles W. Smith, Frank R. Moss III, Matthew D. Smith, Riku Vahala, Alejandro Gonzalez-Martinez,* Steven G. Boxer,* and Noah Z. Burns*

*correspondence to: alejandro.gonzalezmartinez@aalto.fi, sboxer@stanford.edu, nburns@stanford.edu

Table of Contents

1. General Information.....S3

2. Chemical Synthesis Schemes.....S4

3. Chemical Synthesis Experimental Procedures.....S6

4. Anammox Biomass Production and Lipid Isolation.....S44

5. Biophysical Characterization of Ladderane Phospholipid **1**.....S47

6. ^{1}H and ^{13}C NMR Spectra.....S50

7. Chiral HPLC Spectra.....S83

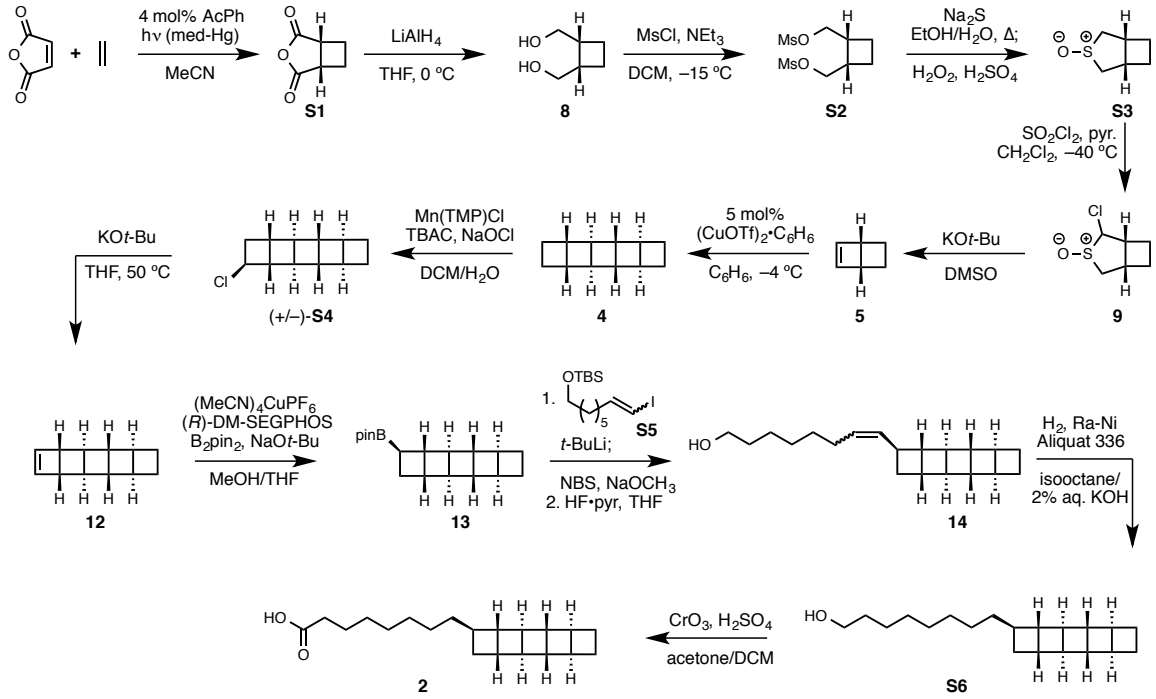
8. X-Ray Crystallographic Information.....S92

9. References.....S104

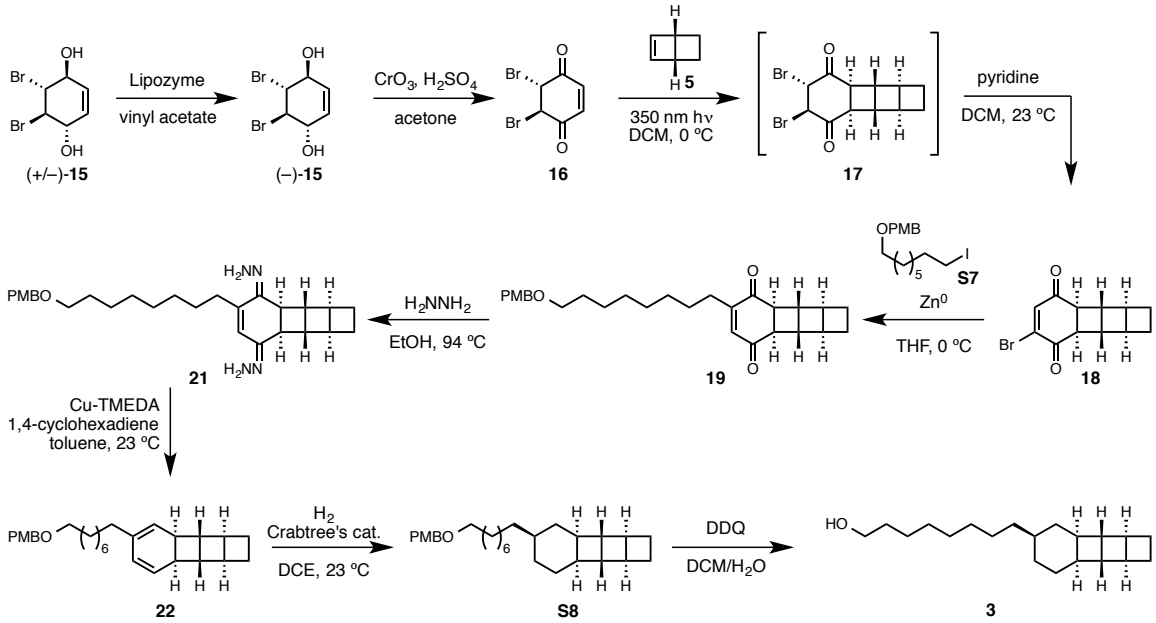
1. General Information

All reactions were conducted in oven- or flame-dried glassware under an atmosphere of nitrogen or argon unless otherwise noted. Commercial reagents and solvents were used as received unless otherwise noted with the exception of the following: hexanes (ACS grade, 4.2% various methylpentanes), toluene, tetrahydrofuran, acetonitrile, methanol, benzene, and dichloromethane were dried by passing through a bed of activated alumina in a JC Meyer Solvent System. Mn(TMP)Cl was purchased from Frontier Scientific and used as received. (*R*)-DM-SEGPHOS was purchased from TICI and used as received. $Rh(COD)_2OTf$ and (–)-DIOP were purchased from Strem Chemicals and used as received. $(MeCN)_4CuPF_6$, Aliquat 336, Lipozyme®, and Cu-TMEDA were purchased from Aldrich and used as received. Flash column chromatography was performed using F60 silica gel (40-63 μm, 230-400 mesh, 60Å) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was carried out on 250 μm 60-F254 silica gel plates purchased from EMD Millipore, and visualization was effected by observation of fluorescence-quenching with ultraviolet light and staining with either p-anisaldehyde or phosphomolybdic acid with cerium sulfate (Seebach's stain) as a developing agent. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Inova 600, Varian Inova 500, Varian Mercury 400, or Varian Inova 300 spectrometers operating respectively at 600, 500, 400, and 300 MHz for ^{1}H and at 150, 125, 100, and 75 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm) with respect to residual protonated solvent for ^{1}H ($CHCl_3$ = δ 7.26) and with respect to carbon resonances of the solvent for ^{13}C ($CDCl_3$ = δ 77.0). Peak multiplicities are annotated as follows: app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet. Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR spectrometer. LC-MS (ESI) data were collected on a Waters Micromass ZQ or a Waters Micromass LCT Premier mass spectrometer. GC-MS (CI) data were collected on a Waters Micromass GCT Premier or a VG Micromass 7070 mass spectrometer. Isotopic abundance patterns observed alongside each major ion reported matched calculated ratios. Optical rotations were measured using a JASCO P-2000 polarimeter. Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260 with commercial ChiralPak 4.6 x 250 mm columns. HPLC trace integration was performed by the Agilent OpenLab processing suite. Uncorrected melting point data were collected using a Thomas Hoover Uni-Melt apparatus.

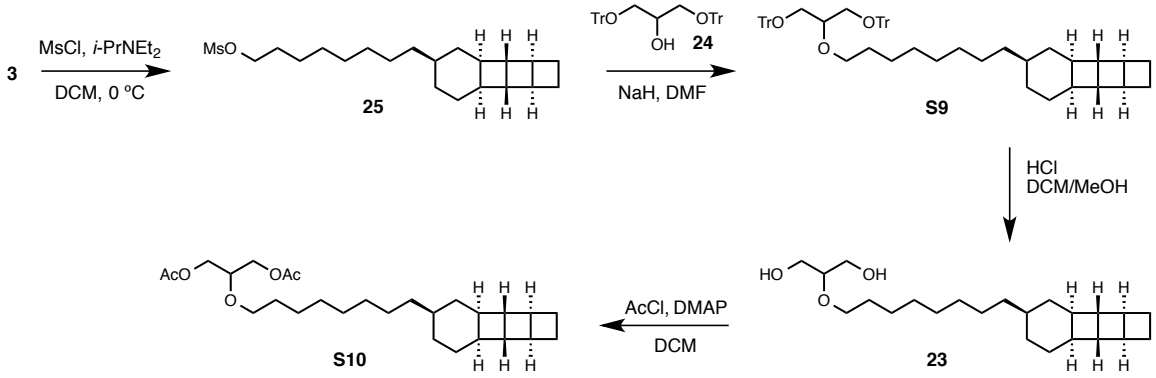
2. Chemical Synthesis Schemes



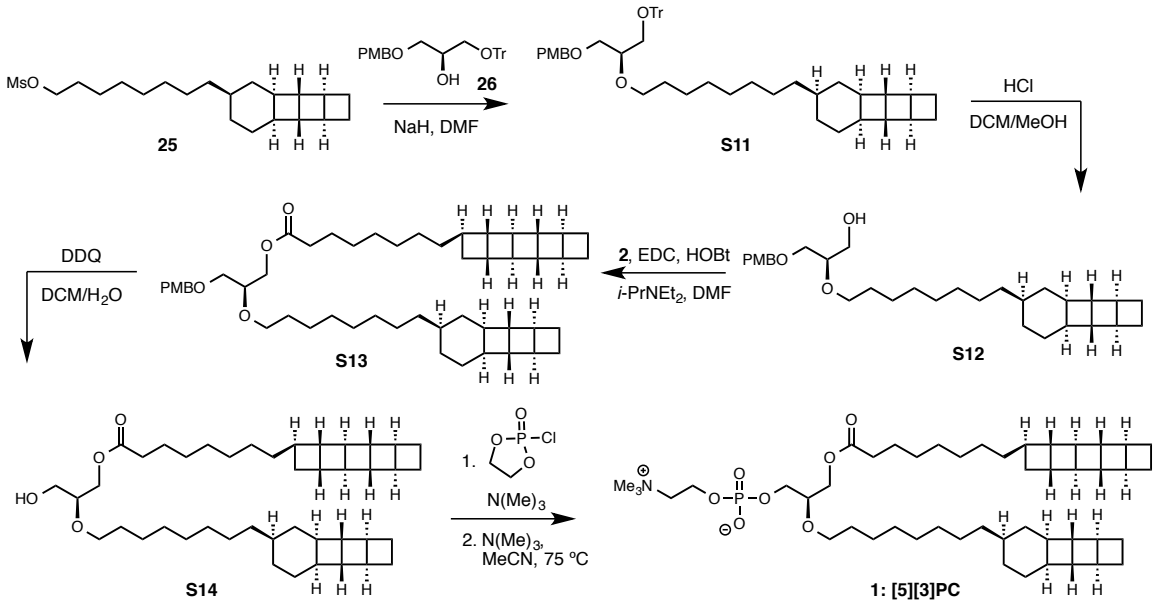
Scheme S1. Outline of the synthesis of [5]-ladderanoic acid **2**.



Scheme S2. Outline of the synthesis of [3]-ladderanol **3**.

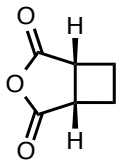


Scheme S3. Outline of the synthesis of [3]-ladderane diol **23** and diacetate **S10**.



Scheme S4. Outline of the synthesis of **[5][3]PC 1**.

3. Chemical Synthesis Experimental Procedures



Anhydride S1:

The following was adapted from a reported procedure.[1] A 1-L photochemical reaction vessel (Ace) equipped with a pyrex immersion well and a stir bar was charged with maleic anhydride (68.0 g, 693 mmol, 1.0 equiv). The solid was taken up in acetonitrile (900 mL, 0.77 M). To the resulting solution was added acetophenone (3.24 mL, 27.7 mmol, 4 mol%) by syringe. Ethylene was introduced via a sparger tube and allowed to bubble through the solution for 20 minutes with stirring. A medium-pressure mercury lamp (450 watt, 13 cm arc length) was lowered into the immersion well. A benchtop chiller (PolyScience) was employed to circulate a 1:1 mixture of ethylene glycol:water through the immersion well, cooling the lamp. The reaction mixture was irradiated for 7 days while maintaining a constant, slow introduction of ethylene. The circulant in the chiller reached an equilibrium temperature of 37 ºC with the lamp on. Reaction progress was monitored by ^{1}H NMR. Once beyond 80% conversion, the reaction vessel was disassembled and the reaction mixture concentrated *in vacuo*. Unreacted maleic anhydride was removed by sublimation under strong vacuum (<0.5 torr) over two days. This provided 64.2 g of **S1** (73% crude yield) that was carried forward without further purification.

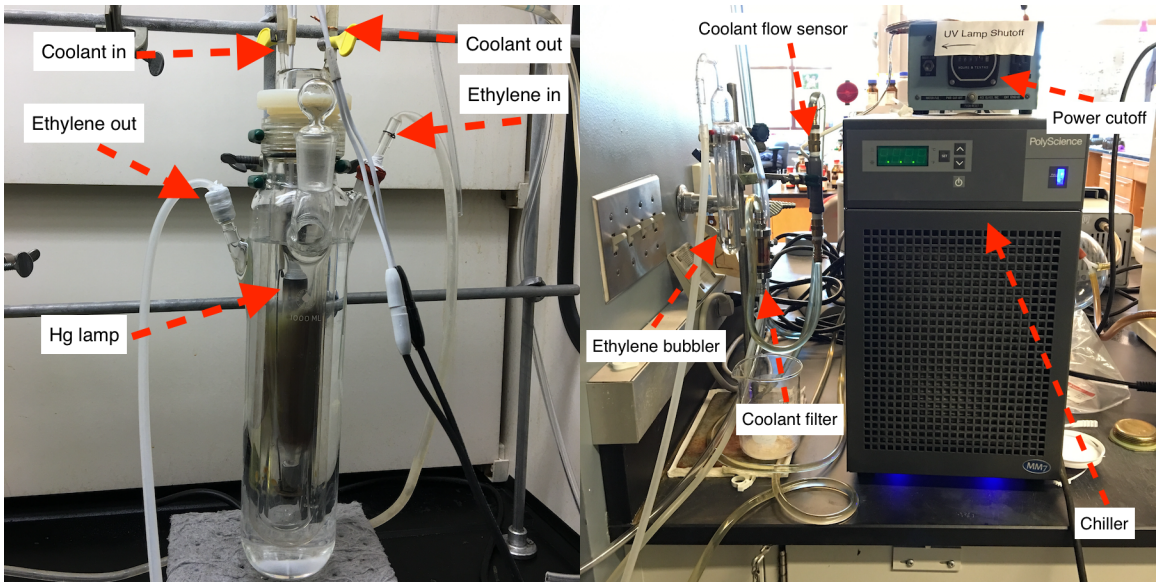
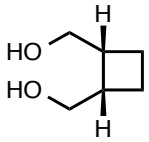


Figure S1. Experimental setup for the preparation of **S1**.
Left: Photochemical reaction vessel. Inlets and outlets for coolant (circulated through immersion well) and ethylene (bubbled through reaction mixture) are indicated. Frequent use causes a residue to build up on the inner walls of the immersion well that needs to be cleaned periodically with dilute (0.1 N) HCl. **Right:** Benchtop chiller, coolant flow

sensor, ethylene bubbler. Power to the lamp is cut if the coolant stops circulating. All components of this setup are commercially available from Ace.

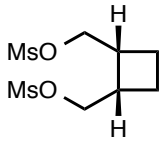


Diol 8:

Anhydride **S1** from the previous step was split into two roughly equal portions; both halves of the material were subjected to $LiAlH_4$ reduction simultaneously and recombined after workup. We found it operationally simpler to maintain stirring and control exotherms on this scale.

$LiAlH_4$ (Batch 1: 11.6 g, 291 mmol, 1.1 equiv; Batch 2: 10.7 g, 261 mmol, 1.1 equiv) was added to vigorously stirring THF (Batch 1: 900 mL; Batch 2: 820 mL) at 0 ºC in small portions (ca. 3 g) with extreme caution. A slurry of anhydride **S1** (Batch 1: 33.4 g, 265 mmol, 1.0 equiv; Batch 2: 30.8 g, 244 mmol, 1.0 equiv) in THF (Batch 1: 425 mL; Batch 2: 400 mL) was poured cautiously into the solution of $LiAlH_4$ in small portions over 15 min. Once addition was complete, the reaction mixtures were allowed to stir vigorously for 1 hour at 0 ºC. The reaction mixtures were quenched according to the Fieser protocol: water (Batch 1: 11.6 mL; Batch 2: 10.7 mL), then 15% aq. NaOH (Batch 1: 11.6 mL; Batch 2: 10.7 mL), then water again (Batch 1: 34.8 mL; Batch 2: 32.1 mL) were added sequentially by pipet with extreme caution. The quenched reaction mixtures were allowed to stir for 8 hours, during which time a fine off-white precipitate formed. The two mixtures were filtered through a pad of celite into the same flask. The precipitate was collected from the filter cake and suspended in warm (40 ºC) THF. This mixture was allowed to stir vigorously for two hours and then filtered through celite. The combined filtrate was concentrated and purified by flash column chromatography on silica gel (40 to 60% EtOAc/hexanes), providing diol **8** (23.2 g, 29% over two steps) as a colorless liquid.

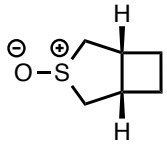
Spectroscopic data matched those reported in the literature.[2]



Dimesylate S2:

To a solution of diol **8** (16.2 g, 139.5 mmol, 1.0 equiv) in anhydrous DCM (700 mL, 0.2 M) at –15 ºC (ice/acetone bath) under nitrogen was added mesyl chloride (22.2 mL, 285.9 mmol, 2.05 equiv) poured quickly from a graduated cylinder. Triethylamine (40.8 mL, 292.9 mmol, 2.1 equiv) was added slowly by syringe. The reaction mixture was allowed to warm to room temperature over an hour. After this time, the reaction mixture was quenched by the addition of 1 N HCl (380 mL). The organic layer was removed, and the aqueous layer was extracted twice with 30% *i*-PrOH/$CHCl_3$ (2 x 230 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (30 to 80% EtOAc/hexanes) to provide dimesylate **S2** (35.6 g, 94%) as a colorless oil that solidified on cooling.

Physical properties: white solid, mp = 36–38 ºC;
R_f = 0.40 (silica gel, 1:1 EtOAc/hexanes run twice, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3019, 2940, 1340, 1329, 1172 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 – 4.25 (m, 4H), 3.04 (s, 6H), 2.96 – 2.84 (m, 2H), 2.23 – 2.09 (m, 2H), 1.91 – 1.77 (m, 2H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 69.34, 37.33, 35.12, 20.94;
HRMS (ESI) calcd. for $C_8H_{16}O_6S_2$ $[M + Na]^+$ 295.0286, found 295.0289.

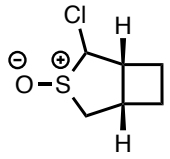


Sulfoxide S3:

To a solution of dimesylate **S2** (37.7 g, 138 mmol, 1.0 equiv) in EtOH (197 mL) and H_2O (79 mL) was added solid sodium sulfide nonahydrate (39.9 g, 166 mmol, 1.2 equiv) at room temperature. The mixture was brought to reflux for 12 hours, then cooled to 0 ºC (ice bath). In a well-ventilated fume hood, sulfuric acid was added as a 0.35 M solution in *i*-PrOH (158 mL, 55.2 mmol, 0.4 equiv) slowly from a graduated cylinder. Hydrogen peroxide (35.2 mL, 345 mmol, 2.5 equiv) was added from a graduated cylinder and the reaction mixture was allowed to warm to room temperature. After 16 hours the reaction mixture was returned to 0 ºC for the careful addition of sat. aq. $NaHCO_3$ (184 mL) and 1.5 M Na_2SO_3 (184 mL). Chloroform (400 mL) was added and the layers were separated. The aqueous layer was extracted twice with 30% *i*-PrOH/$CHCl_3$ (2 x 400 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5 to 10% MeOH/EtOAc) to provide sulfoxide **S3** (16.8 g, 93%) as a colorless oil.

S3 is isolated as a 5:1 mixture of diastereomers that are separable chromatographically. The mixture is inconsequential: both diastereomers perform the same in the following reaction.

Physical properties: colorless oil;
R_f = 0.44 (silica gel, 10% MeOH/EtOAc, visualized with Seebach's stain);
IR (film) ν_{max} = 2939, 2862, 1111, 1089, 1053, 1014 cm^{-1};
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (s, 2H), 3.23 (minor diast, d, *J* = 14.5 Hz, 2H), 3.19 – 3.08 (major diast, m, 2H), 2.92 (major diast, dd, *J* = 13.4, 3.8 Hz, 2H), 2.82 (minor diast, dd, *J* = 14.6, 6.9 Hz, 2H), 2.45 – 2.31 (m, 2H), 1.73 – 1.61 (major diast, m, 2H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 60.07, 59.56, 41.64, 39.10, 24.60, 23.93;
HRMS (CI) calcd. for $C_6H_{10}OS$ $[M + NH_4]^+$ 148.0796, found 148.0800.



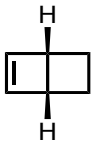
α-Chlorosulfoxide (9):

To a solution of sulfoxide **S3** (27.4 g, 210 mmol 1.0 equiv) in anhydrous DCM (500 mL) at –40 ° C (dry ice/acetonitrile bath) under nitrogen was added pyridine (33.8 mL, 420 mmol, 2.0 equiv) A solution of sulfuryl chloride (17.0 mL, 210 mmol, 1.0 equiv) in DCM (200 mL) was added dropwise by cannula over 10 minutes. The reaction mixture was allowed to stir at –40 ºC for 1 hour. After this time, 1 N HCl (700 mL) was added and the cooling bath was removed. The layers were separated, and the aqueous layer was extracted with 30% *i*-PrOH/$CHCl_3$ (2 x 500 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (40 to 75% EtOAc/hexanes), providing α-chlorosulfoxide **9** (30.7 g, 89%) as a colorless oil that solidified on cooling.

9 is isolated as an inseparable mixture of chloride epimers that were carried together into the subsequent reaction.

9 was observed to decompose spontaneously if stored at room temperature for too long (>12 hours). No decomposition has been observed over a year of storage under nitrogen at –20 ºC.

Physical properties: white solid, mp = 38–41 ˚C;
R_f = 0.19 (silica gel, 1:1 EtOAc/hexanes, visualized with Seebach's stain);
IR (film) ν_{max} = 2979, 2949, 2926, 2858, 1403, 1091, 1053, 1029 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.01 (major diast, s, 1H), 4.85 (minor diast, d, *J* = 8.8 Hz, 1H), 3.52 – 3.33 (m, 1H), 3.34 – 3.12 (m, 2H), 3.12 – 2.96 (m, 1H), 2.78 – 2.63 (minor diast, m, 1H), 2.43 – 2.19 (m, 2H), 2.19 – 2.08 (minor diast, m, 1H), 1.83 – 1.67 (major diast, m, 1H), 1.68 – 1.55 (major diast, m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 76.38, 56.69, 55.10, 44.06, 38.76, 34.75, 24.72, 23.80, 22.35, 19.72;
HRMS (CI) calcd. for C_6H_9ClOS $[M + NH_4]^+$ 182.0406, found 182.0402.

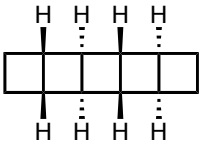


Bicyclohexene 5:

A 2-L round bottom flask equipped with a large magnetic stir bar was flame dried under vacuum. Once cool, the flask was flushed with nitrogen and charged with potassium *tert*-butoxide (62.8 g, 559 mmol, 3.0 equiv). The solid was taken up in DMSO (833 mL) and the resulting solution was allowed to stir vigorously. A solution of α-chlorosulfoxide **9** (30.7 g, 186 mmol, 1.0 equiv) in DMSO (200 mL) was added by cannula over 3 hours; the reaction mixture darkened immediately to red/brown and eventually to black. The reaction mixture was allowed to stir for 12 hours at room temperature under nitrogen. After this time, the flask was connected to a vacuum distillation apparatus consisting of an angled glass tube leading to a cold finger. A Schlenk tube was connected to the bottom of the cold finger and to a vacuum pump equipped with a manometer. Both the cold finger and Schlenk tube were cooled to –78 ºC (dry ice/acetone). The pressure was reduced cautiously to 250 mbar; gas evolution was observed but no liquid condensed. The reaction mixture was heated to 90 ºC (oil bath). The pressure was reduced slowly in 10 mbar increments over 4 hours. At pressures below 150 mbar neat **5** could be observed condensing on the cold finger and dripping into the Schlenk tube. At pressures below 50 mbar large amounts of *tert*-butanol could be observed solidifying on the cold finger. The vacuum was disconnected at this point, and the entire apparatus was backfilled with nitrogen. The Schlenk tube was capped with a glass stopper and allowed to warm to room temperature under a nitrogen balloon. Once warm, the distillate (ca. 9 mL) was washed with small portions of brine (3 x 3 mL) and water (3 x 3 mL) to remove *tert*-butanol and DMSO. The washed product was dried with sodium sulfate and filtered through cotton into a scintillation vial for storage. 7.3 g (49%) of neat **5** was obtained as a colorless liquid.

Alternatively, this procedure can be conducted directly on crude **9** from the preceding reaction without affecting purity or overall yield of **5**. Chlorination of 57.8 g of sulfoxide **S3** (444 mmol) provided 71.0 g **9** (97% crude yield) without chromatographic purification. Subjecting this material to the Ramberg–Bäcklund and distillation procedure gave 15.3 g **5** (43% over two steps).

Physical properties: colorless liquid, bp = 66–67 ºC, density = 0.819 g/mL;
IR (neat) ν_{max} = 3099, 3031, 2975, 2938, 2849, 1548, 1302, 753, 719 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 2H), 3.27 (d, *J* = 7.0 Hz, 2H), 2.26 – 2.10 (m, 2H), 1.64 – 1.56 (m, 2H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 141.71, 44.13, 20.79.



[5]-Ladderane 4:

$(CuOTf)_2 \bullet C_6H_6$ was prepared as reported by Salomon and Kochi[3] and stored in a nitrogen glove box. Six oven-dried quartz tubes (15 cm height, 13 cm outer diameter, 11 cm inner diameter) were capped with rubber septa and flushed with nitrogen. The tubes were cooled to –78 ºC in a hexanes/dry ice bath under nitrogen. A solution of bicyclohexene **5** (112 mg, 1.4 mmol, 1.0 equiv) in dry, degassed benzene (3.36 mL) and a separate solution of $(CuOTf)_2 \bullet C_6H_6$ (17.6 mg, 35 μmol, 5 mol%) in dry, degassed benzene (3.5 mL) were added simultaneously via syringes in fine streams to each tube. The mixture froze to a white solid within 30 seconds of addition.

Irradiation took place in a Rayonet photoreactor equipped with 254 nm low-pressure mercury lamps, a stir plate, and a quartz beaker (20 cm height, 15 cm diameter) filled with 1.8 L 1:1 ethylene glycol:water. The temperature of the bath was maintained at –4 ºC with a cryocool. The quartz tubes containing the solid reaction mixture were placed in the bath along the rim of the beaker and irradiated for 60 hours. Every 12 hours, the tubes were briefly returned to –78 ºC in a hexanes/dry ice bath while any ice that had formed on the outside of the beaker was removed.

The tubes were allowed to warm to room temperature, causing the reaction mixtures to thaw. The contents of all six tubes were combined and partitioned between pentane (70 mL) and 30% aq. NH_4OH (100 mL). The layers were separated, and the organic layer was washed with 30% aq. NH_4OH (3 x 100 mL) and sat. aq. NaCl (1 x 100 mL). The washed organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo* (>80 torr). The residue was purified by flash column chromatography on silica gel (pentane) to provide [5]-ladderane **4** (280 mg, 42%) as a white crystalline solid.

Product **4** was contaminated with <5% of what appears to be a stereoisomer by NMR. The two co-elute on silica gel. While we rely on visualization of a high-R_f TLC spot to guide isolation, we suspect that this staining spot corresponds to the minor stereoisomer; diastereomerically pure samples of the major isomer do not stain. Derivatives of the minor isomer were not observed in future steps. The structure of **4** was confirmed by X-ray crystallography (see Section 8).

Physical properties: white crystalline solid, mp = 75–78 ºC;
R_f = 0.93 (silica gel, hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2958, 2920, 2908, 2845 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.78 – 2.70 (m, 4H), 2.63 (s, 4H), 2.60 – 2.51 (m, 4H), 2.08 – 1.99 (m, 4H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 49.39, 41.79, 26.50;
HRMS (CI) calcd. for $C_{12}H_{16}$ $[M + H]^+$ 161.1330, found 161.1329.

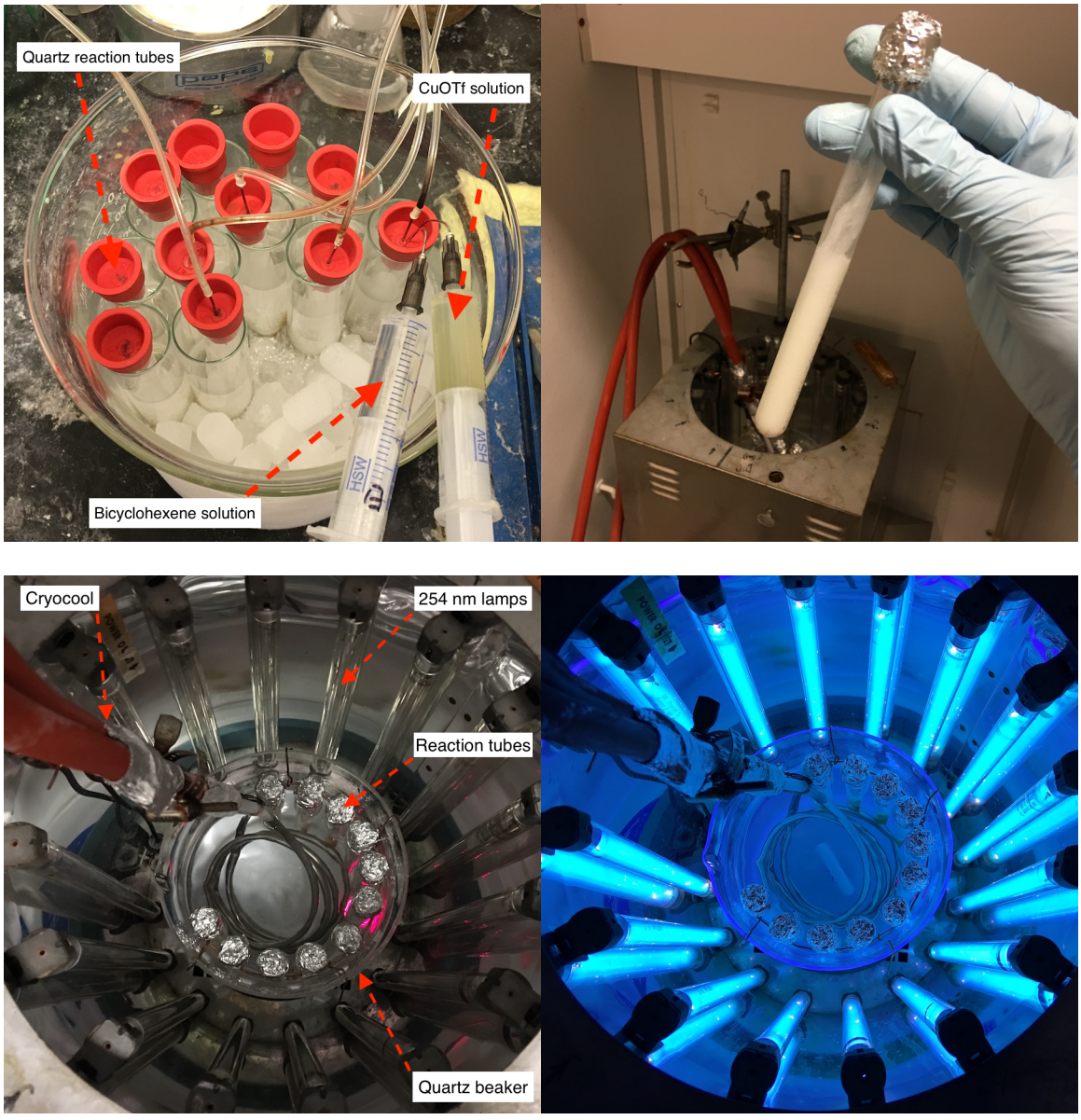
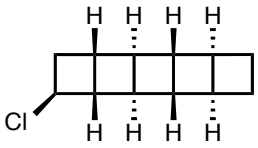


Figure S2. Experimental setup for the preparation of **4**.
Top left: Simultaneous addition of bicyclohexene and CuOTf solutions. **Top right:** Quartz tube containing frozen reaction mixture. **Bottom left:** Rayonet photoreactor setup. **Bottom right:** Photoreactor setup during irradiation.

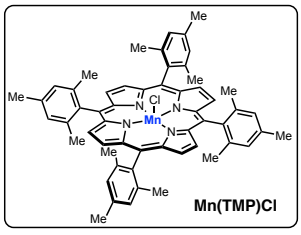


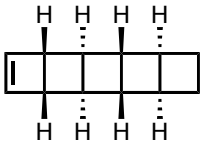
(+/–)

Ladderane chloride S4:

To a 25 mL round-bottom flask containing ladderane **4** (317 mg, 1.98 mmol, 1.0 equiv) and manganese(III) meso-tetra(2,4,6-trimethylphenyl)porphine chloride (**Mn(TMP)Cl**, 86 mg, 0.098 mol, 0.05 equiv) under argon was added dichloromethane (7.0 mL) and a solution of tetra-*n*-butylammonium chloride (66 mg, 0.237 mmol, 0.12 equiv) in water (3.5 mL). The resulting dark green biphasic mixture was allowed to stir rapidly (1300 rpm) and 12.5% aqueous NaOCl (3.5 mL, 7.09 mmol, 3.6 equiv) was added dropwise (the reaction mixture became orange-brown). After 2.25 h of stirring at room temperature, the color had returned to dark green, and additional Mn(TMP)Cl (86 mg, 0.098 mol, 0.05 equiv) and 12.5% aqueous NaOCl (3.5 mL, 7.09 mmol, 3.6 equiv) were added. After a further 1.75 h at room temperature, the reaction mixture was diluted with dichloromethane (25 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted further with dichloromethane (2 x 30 mL). The combined organic layers were washed with brine (30 mL) and the brine layer was back-extracted with dichloromethane (15 mL). The combined dichloromethane extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. In order to remove the Mn catalyst, the dark green crude material was filtered through a plug of silica gel, eluting with 10% diethyl ether in pentane directly into a round bottom flask and concentrated *in vacuo*. The resulting light orange material was then purified by flash column chromatography (pentane, silica gel) to afford chloride **S4** as a clear, colorless oil which solidified on storage (153 mg, 40% yield), along with recovered ladderane **4** (57 mg, 18%) and dichlorinated ladderanes (27 mg, 6%).

Physical properties: colorless solid, mp = 31–33 ˚C;
R_f = 0.63 (silica gel, hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2920, 2850, 1429, 1232, 1166, 946, 841, 710, 638 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 (t, *J* = 5.7 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.93 – 2.87 (m, 1H), 2.88 – 2.76 (m, 2H), 2.72 (d, *J* = 4.0 Hz, 2H), 2.67 (s, 3H), 2.64 – 2.51 (m, 3H), 2.13 – 1.97 (m, 2H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 58.62, 53.16, 48.92, 48.65, 48.18, 46.63, 41.67, 40.55, 38.30, 26.39;
HRMS (APCI) calcd. for $C_{12}H_{15}Cl$ $[M + H]^+$ 195.0935, found 195.0933.

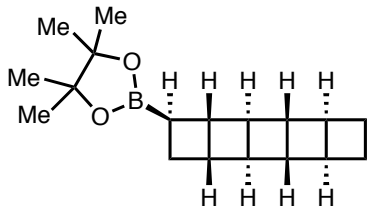




[5]-Ladderene 12:

To a solution of ladderane chloride **S4** (442 mg, 2.27 mmol, 1.0 equiv) in THF (15.9 mL) at 0 ºC was added KO*t*-Bu as a 1.0 M solution in THF (6.81 mL, 6.81 mmol, 3 equiv). The mixture was heated to 50 ºC (oil bath) for 10 hours, then cooled to 0 ºC (ice bath). The reaction mixture was quenched by the dropwise addition of sat. aq. NH_4Cl (2 mL). The mixture was partitioned between pentane (100 mL) and sat. aq. NaCl (100 mL). The layers were separated, and the organic layer was washed with sat. aq. NaCl (2 x 100 mL) and with water (2 x 100 mL). The washed organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (pentane) to provide [5]-ladderene **12** (328 mg, 91%) as a white crystalline solid.

Physical properties: white crystalline solid, mp = 52–55 ºC;
R_f = 0.88 (silica gel, hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3097, 3027, 2925, 2911, 2847, 1297, 1160, 735 cm^{-1};
1H NMR (500 MHz, $CDCl_3$): δ 6.35 – 6.29 (m, 2H), 3.21 (s, 2H), 2.77 – 2.68 (m, 2H), 2.63 – 2.50 (m, 4H), 2.38 (s, 2H), 2.13 – 1.99 (m, 2H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 140.13, 50.13, 48.18, 44.75, 41.97, 26.21;
HRMS (APCI) calcd. for $C_{12}H_{14}$ $[M + H]^+$ 159.1168, found 159.1169.



[5]-Pinacolboronic ester 13:

Initially, we developed conditions for an enantioseletive rhodium-catalyzed hydroboration of **12** based loosely on a procedure developed by Burgess (method 1).[4] During the preparation of this manuscript, Tortosa and coworkers reported a copper-catalyzed hydroboration of cyclobutenes that provided substatially better results (method 2).[5] The material carried forward to [5]-ladderanoic acid **2** and ladderane phospholipid **1** was 80% ee, prepared by method 1.

Method 1: Rhodium-catalyzed hydroboration

The anhydrous toluene used in this reaction was sparged with argon for 20 minutes while sonicating. Great care was taken to exclude oxygen at all times. In a nitrogen glove box, a 25-mL round bottom flask equipped with a magnetic stir bar was charged with $Rh(COD)_2OTf$ (50.0 mg) and capped with a rubber septum. Once removed from the box, the flask was maintained under a balloon of argon. Toluene (10.7 mL) was added.

A separate flame-dried 25-mL round bottom flask was charged with (–)-DIOP (83.4 mg). The flask was evacuated and refillled with argon sequentially three times. The ligand was taken up in toluene (11.15 mL). 10.7 mL of this solution was added dropwise over 30 seconds to the vigorously stirring suspension of $Rh(COD)_2OTf$. Stirring was allowed to continue at 23 ºC for 45 minutes while the mixture became orange with a faint precipitate.

A separate flame-dried 100-mL flask equipped with a magnetic stir bar was purged with argon and charged with [5]-ladderene **12** (300 mg, 1.86 mmol, 1.0 equiv). The solid was taken up in toluene (9.48 mL). 18.96 mL of the Rh•DIOP solution (corresponding to 44.4 mg, 94.8 µmol, 5 mol% $Rh(COD)_2OTf$ and 70.9 mg, 142.2 µmol, 7.5 mol% (–)-DIOP) was added in a fine stream at 23 ºC. The resulting mixture was cooled to –20 ºC in a cryogenic bath. A solution of catecholborane (285 µL, 2.84 mmol, 1.5 equiv) in toluene (9.20 mL) was added dropwise by syringe over 5 minutes. After 10.5 hours, EOH (1.11 mL, 18.96 mmol, 10 equiv) was added dropwise by syringe. The resulting mixture was allowed to warm to 0 ºC (ice bath). A solution of pinacol (672 mg, 5.69 mmol, 3.0 equiv) in toluene (9.38 mL) was added in a fine stream by cannula; transfer was completed by rinsing forward into the receiving flask with two 1-mL portions of toluene. The mixture was allowed to stir at 0 ºC for 6 hours. After this time, the reaction mixture was partitioned between EtOAc (80 mL) and sat. aq. NaCl (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (1.5 to 3% EtOAc/hexanes) to provide boronic ester **13** (383 mg, 71%, –80% ee) as a colorless oil.

The same procedure on 116 mg **12** (733 μmol) but employing (+)–DIOP provided 138 mg (66% yield) **13** in 84% ee.

The enantiomeric excess was determined by chiral HPLC after derivatization (see Section 7).

Physical properties: colorless oil;
R_f = 0.39 (silica gel, 5% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2919, 2853, 1370, 1313, 1143, 968, 851 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (s, 4H), 2.68 (d, *J* = 5.8 Hz, 2H), 2.63 (d, *J* = 7.9 Hz, 2H), 2.60 – 2.47 (m, 3H), 2.21 – 2.12 (m, 1H), 2.08 – 1.95 (m, 3H), 1.27 (s, 12H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 82.94, 50.92, 49.38, 49.25, 49.20, 42.58, 41.75, 41.72, 41.31, 27.61, 26.47, 26.46, 24.72, 24.71, 14.17;
HRMS (APCI) calcd. for $C_{18}H_{27}BO_2$ $[M + H]^+$ 287.2177, found 287.2180;
$[\alpha]_D^{23}$ = –15.5 (c = 1.0, $CHCl_3$) (80% ee).

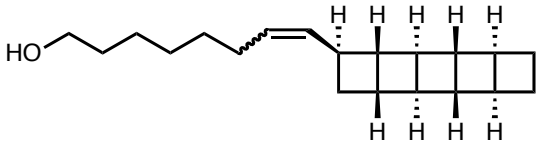
Method 2: Copper-catalyzed hydroboration

The anhydrous THF and methanol used in this procedure was sparged with argon for 20 minutes while sonicating.

A flame-dried 25 mL roud-bottom flask was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (35.3 mg, 94.8 μmol, 10 mol%) and (*R*)-DM-SEGPHOS (75.4 mg, 104 μmol, 11 mol%). The flask was evacuated and backfilled with argon three times. The solids were taken up in THF (3.27 mL), and the resulting solution was allowed to stir at room temperature. After 15 minutes, the solvent was removed by high vac with continued stirring. A separate flame-dried flask was charged with bis(pinacolato)diboron (481 mg, 1.90 mmol, 2.0 equiv.) and the white solid was taken up in THF (2.24 mL). The flask containing the copper catalyst was back-filled with argon, and the solution of bis(pinacolato)diboron was transferred to this flask by cannula; transfer was completed by rinsing forward into the receiving flask with THF (1 mL). The resulting solution was allowed to stir for 10 minutes, turning orange over time. An 0.2 M solution of sodium tert-butoxide in THF (2.37 mL, 474 μmol, 0.5 equiv.) was added dropwise by syringe. The resulting solution was allowed to stir for 10 minutes at room temerpature, turning brown over time, then cooled to –78 ºC (dry ice/actone).

A separate flame-dired flask was charged with [5]-ladderene **12** (150 mg, 948 μmol, 1.0 equiv.) and purged with argon. The substrate was taken up in THF (500 μL) and transferred to the cooled flask by syringe; transfer was completed by rinsing with THF (2 x 500 μL). Methanol (77 μL, 1.90 mmol, 2.0 equiv.) was added dropwise by syringe. The reaction flask was transferred to a cryogenic bath maintained at –20 ºC by a cryocool and allowed to stir at this temperature for 12 hours. After this time, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (1.5 to 3% EtOAc/hexanes) to provide boronic ester **13** (259 mg, 95%, –90% ee) as a colorless oil.

$[\alpha]_D^{23}$ = –15.5 (c = 1.0, $CHCl_3$) (90% ee)



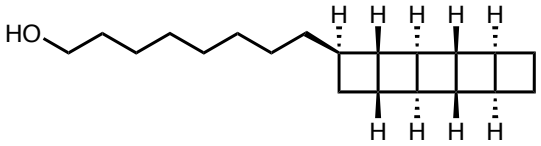
[5]-Ladderenol 14:

To 8.28 mL of stirring anhydrous Et_2O at –78 ºC was added a freshly-titrated solution of *t*-BuLi (881 µL, 1.33 mmol, 4.0 equiv, 1.51 M). A solution of iodide **S5** (256 mg, 664 µmol, 2.0 equiv) in Et_2O (3 mL) was added dropwise by cannula; transfer was completed by rinsing forward into the receiving flask with two 1-mL portions of Et_2O. After 10 minutes, a solution of pinacol boronic ester **13** (95.0 mg, 332 µmol, 1.0 equiv) in THF (2.32 mL) was added dropwise by cannula; transfer was completed by rinsing forward into the receivig flask with two 0.5-mL portions of THF. The resulting mixture was allowed to stir for 15 minutes at –78 ºC, allowed to warm to 0 ºC (ice bath) over 15 minutes, and then returned to –78 ºC. A solution of NBS (118.2 mg, 664 µmol, 2.0 equiv) in THF (2.32 mL) was added dropwise by syringe; transfer was completed by rinsing with two 0.5-mL portions of THF. The resulting orange slurry was allowed to stir for 30 minutes at –78 ºC. A slurry of NaOMe (1.33 mmol, 4.0 equiv) in MeOH (2.66 mL, 0.5 M) was added dropwise by syringe, and the resulting mixture was allowed to warm to room temperature over an hour. Excess oxidant was quenched by the addition of sat. aq. $Na_2S_2O_3$ (ca. 3 mL), resulting in a homogeneous light yellow solution. The solution was concentrated *in vacuo*, and the residue was partitioned between EtOAc (50 mL) and sat. aq. NaCl (50 mL). The layers were separated, and the aqueous layer was extracted three more times with EtOAc (5 x 50 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*.

The crude residue was transferred to a plastic reaction tube in anhydrous THF (5.98 mL). The solution was cooled to 0 ºC and anhydrous pyridine (665 uL) was added by syringe. HF•pyr (347 µL, ca. 13.28 mmol, 20 equiv) was added by micropipet. The reaction mixture was allowed to stir for 8 hours at 0 ºC. Excess HF was quenched by the cautious dropwise addition of sat. aq. $NaHCO_3$ (ca. 10 mL). The biphasic mixture was partitioned between EtOAc (40 mL) and sat. aq. $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 x 50 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (7% EtOAc/hexanes) to provide [5]-ladderenol **14** (84.0 mg, 88%, 2:1 *cis*/*trans*) as a white solid.

Physical properties: white solid, mp = 50–52 ˚C;
R_f = 0.39 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3334 (br), 2922, 2908, 2852, 1463, 1431, 1059 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.68 – 5.57 (m, 1H), 5.35 (minor diast, dt, *J* = 15.9, 6.7 Hz, 1H), 5.23 (major diast, dtd, *J* = 8.7, 7.3, 1.3 Hz, 1H), 3.67 – 3.56 (m, 2H), 3.20 (major diast, dd, *J* = 8.2, 7.3 Hz, 1H), 2.89 (minor diast, dd, *J* = 7.5, 7.0 Hz, 1H), 2.73 (s, 2H), 2.66 (s, 2H), 2.63 (s, 3H), 2.59 – 2.49 (m, 2H), 2.48 (major diast, s, 1H), 2.39 – 2.31 (major diast, m, 1H), 2.31 – 2.22 (m, 1H), 2.10 – 1.91 (m, 4H), 1.59 – 1.49 (m, 2H), 1.42 – 1.23 (m, 7H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.01, 135.19, 127.55, 127.53, 62.94, 62.91, 49.43, 49.41, 49.16, 49.14, 49.11, 49.09, 48.59, 48.53, 48.45, 47.53, 42.29, 41.76, 41.74, 41.73, 38.41, 38.13, 37.57, 34.51, 33.34, 32.69, 32.37, 29.61, 29.54, 28.92, 28.90, 27.44, 26.47, 26.44, 26.42, 25.57, 25.55;
HRMS (APCI) calcd. for $C_{20}H_{30}O$ $[M + H]^+$ 287.2369, found 287.2374.

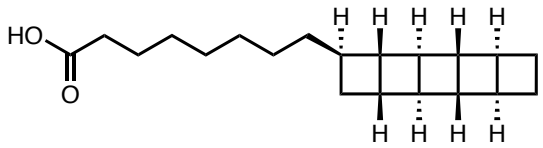


[5]-Ladderanol S6

To a vigorously stirred slurry of [5]-ladderanol alkene **14** (176.0 mg, 614 μmol) in isooctane (15.4 mL, 0.04 M) and 2% aq. KOH (8.8 mL, 0.07M) was added a 0.11 M solution of Aliquat 336 in isooctane (1.95 mL, 214 μmol, 35 mol%). Ra-Ni was added as a slurry in water by pipet (15 drops, ca. 375 mg dry weight). Hydrogen gas was bubbled through the mixture from a balloon for 15 minutes. The reaction mixture was allowed to stir vigorously under a balloon of hydrogen for 24 hours. After this time, nitrogen gas was bubbled through the mixture from a balloon for 15 minutes, and then 10% MeOH/EtOAc (ca. 20 mL) was added by pipet with vigorous stirring until the organic layer became transparent. The biphasic mixture was filtered through a pad of celite to remove Ra-Ni. The filer cake was washed extensively with 10% MeOH/EtOAc (100 mL). The filtrate was concentrated *in vacuo*, and the residue was partitioned between 10% *i*-PrOH/$CHCl_3$ (100 mL). and sat. aq. NaCl (100 mL). The layers were separated, and the aqueous layer was extracted with 10% *i*-PrOH/$CHCl_3$ (2 x 100 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes), providing **S6** (181 mg, quant.) as a white crystalline solid.

The absolute stereochemistry of **S6** was determined by X-ray crystallography (see Section 8).

Physical properties: white crystalline solid, mp = 99–101 ºC;
R_f = 0.41 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3388, 2919, 2850, 1463, 1055 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.59 (t, *J* = 6.7 Hz, 2H), 2.70 (bd, *J* = 6.8 Hz, 2H), 2.60 (bs, 2H), 2.60 (m, 1H), 2.57 (s, 1H), 2.55 (bd, *J* = 2.2 Hz, 1H), 2.54 – 2.50 (m, 2H), 2.33 (s, 1H), 2.21 – 2.10 (m, 2H), 2.05 – 1.95 (m, 3H), 1.75 (s, 1H), 1.57 – 1.50 (m, 2H), 1.50 – 1.36 (m, 2H), 1.34 – 1.22 (m, 8H), 1.22 – 1.14 (m, 2H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 62.81, 49.42, 49.33, 49.16, 48.29, 47.25, 41.79 (2C), 39.89, 38.47, 37.33, 33.23, 32.64, 29.59, 29.57, 29.37, 26.47, 26.44 (2C), 25.69;
HRMS (APCI) calcd. for $C_{20}H_{32}O$ $[M + H]^+$ 289.2529, found 289.2526;
$[\alpha]_D^{24}$ = –13.0 (c = 0.5, $CHCl_3$) (80% ee).



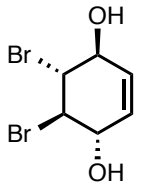
[5]-Ladderanoic acid (2):

To a stirred solution of chromium trioxide (1.0 g, 10.0 mmol) in water (3 mL) at 0 ºC was added conc. H_2SO_4 (1 mL). The resulting orange-red solution of Jones' reagent was maintained at 0 ºC and used immediately.

In a separate flask, a solution of [5]-ladderanol **S6** (181 mg, 628 μmol, 1.0 equiv) in DCM (0.05 M, 12.6 mL) and acetone (0.05 M, 12.6 mL) was cooled to 0 ºC (ice bath). To this mixture was added1.88 mL of Jones reagent (ca. 7.5 equiv CrO_3). Temperature was maintained at 0 ºC while the reaction mixture was allowed to stir for 3 hours. After this time, isopropanol (ca. 2 mL) was added dropwise by pipet, causing the formation of a blue precipitate. The resulting mixture was partitioned between $CHCl_3$ (80 mL) and sat. aq. NaCl (100 mL). The layers were separated, and the aqueous layer was extracted twice more with 10% *i*-PrOH/$CHCl_3$ (2 x 25 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10 to 25% EtOAc/hexanes), providing **2** (159 mg, 86% from **14**) as a fine white solid.

Spectroscopic data of **2** were in agreement with those reported by Corey (see Section 6).[6]

Physical properties: fine white solid, mp = 108–109 ºC;
R_f = 0.27 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2919, 2849, 1697, 681 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.73 (bd, *J* = 6.7 Hz, 2H), 2.63 (bs, 2H), 2.63 (m, 2H), 2.60 (s, 1H), 2.57 (d, *J* = 2.9 Hz, 1H), 2.57 – 2.52 (m, 2H), 2.35 (app. t, *J* = 7.5 Hz, 3H), 2.26 – 2.11 (m, 2H), 2.09 – 1.97 (m, 3H), 1.63 (app. p, *J* = 7.4 Hz, 2H), 1.52 – 1.38 (m, 2H), 1.37 – 1.24 (m, 6H), 1.24 – 1.18 (m, 2H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 179.79, 49.42, 49.33, 49.17, 48.29, 47.23, 41.80 (2C), 39.87, 38.47, 37.32, 33.97, 33.26, 29.44, 29.26, 29.02, 26.51, 26.47, 26.41, 24.65;
MS (CI) calcd. for $C_{20}H_{30}O_2$ $[M - H]^-$ 301.2, found 301.1;
$[\alpha]_D^{25}$ = –15.4 (c = 0.5, $CHCl_3$) (80% ee).

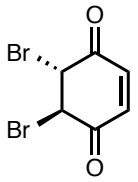


Dibromodiol (−)-15:

Resolution of **15** was conducted according to a literature procedure.[7]

To a mixture of racemic dibromodiol **15** (1.0 g, 4.4 mmol, 1.0 equiv) and Lipozyme (1.5 g, 1.5 equiv by mass) in *tert*-butyl methyl ether (100 mL, 10 mg/mL) was added vinyl acetate (2.0 mL, 22 mmol, 5.0 equiv). The mixture was heated to 45 °C for 12 hours, then allowed to cool to room temperature. The solid Lipozyme was removed by vacuum filtration, and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (40% to 70% EtOAc in hexanes) to give pure diol (−)-**13** (445 mg, 45%) as a white solid.

The enantiomeric excess of (−)-**15** was determined to be 99% by HPLC analysis (see Section 7).



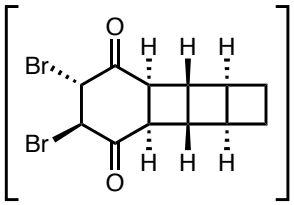
Benzoquinone dibromide 16:

To a stirred solution of chromium trioxide (1.0 g, 10.0 mmol) in water (3 mL) at 0 ºC was added conc. H_2SO_4 (1 mL). The resulting orange-red solution of Jones' reagent was maintained at 0 ºC and used immediately.

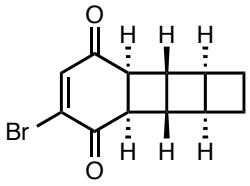
In a separate flask, a solution of dibromodiol **15** (312 mg, 1.37 mmol, 1.0 equiv) in acetone (27.4 mL, 0.05M) was cooled to 0 °C. To this mixture was added 2.74 mL Jones reagent (6.86 mmol, 5.0 equiv). The reaction was allowed to stir at 0 °C for 20 minutes, after which time isopropanol (0.5 mL) was added dropwise by pipet, causing the formation of a blue precipitate. The mixture was diluted with H_2O (15 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with a saturated solution of NaCl (4 x 20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Recrystallization from hot hexanes gave **16** (251 mg, 82%) as a flaky yellow solid.

The enantiomeric excess of **16** was determined to be 99% by HPLC analysis (see Section 7).

Physical properties: flaky yellow solid;
R_f = 0.79 (silica gel, 40% EtOAc/hexanes, visualized with $KMnO_4$ stain);
IR (film) ν_{max} = 1697, 1601, 1371, 1282, 1215, 1107, 1011, 848, 642, 498 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (s, 2H), 4.79 (s, 2H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 187.21, 136.42, 44.92;
MS (ESI) calcd. for $C_6H_4Br_2O_2$ $[M + OCH_3]^-$ 298.9, found 298.6;
$[\alpha]_D^{23}$ = –121.88 (c = 0.5, $CHCl_3$) (74% ee).



17



18

[3]-Ladderane bromide 18:

A solution of **16** (689 mg, 2.57 mmol, 1.0 equiv) in dry DCM (10 mL) was sparged with nitrogen while sonicating for 15 minutes. To the degassed solution was added bicyclohexene (503 μL, 5.14 mmol, 2.0 equiv) by syringe. The solution was transferred by syringe into three 13 x 100 mm Pyrex test tubes (approximately equal volumes) equipped with flat stir bars and capped with rubber septa. Irradiation took place in a Luzchem photoreactor equipped with 350 nm low-pressure mercury lamps, a stir plate, and an ice bath (0 ºC) in a pyrex dish. The tubes were placed in the ice bath and irradiated for 6.5 hours. The ice bath needed to be periodically refreshed (ca. every 2 hours). The reaction mixtures were combined and filtered through a small pad of silica gel, eluting with DCM (20 mL). The filtrate was concentrated to provide crude dibromide **17** (833 mg, 93% crude yield) as an oil.

Dibromide **17** was taken up immediately in anhydrous DCM (24 mL, 0.1 M), and pyridine (213 μL, 2.63 mmol, 1.1 equiv) was added by syringe at 23 ºC. After 1 hour, the reaction was quenched by the addition of 1M HCl (5 mL); the layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes), giving **18** (504 mg, 73% over two steps) as a yellow solid.

This reaction sequence can be performed as a one-pot procedure by adding pyridine directly to the [2+2] adduct upon completion of irradiation, followed by workup as described above, giving comparable yields of bromide **18**.

The enantiomeric excess of **18** was determined to be 89% by HPLC analysis (see Section 7). The structure of the major isomer was confirmed by X-ray crystallography (see Section 8).

Physical properties: light yellow solid, mp = 77–78 ˚C;
R_f = 0.55 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2936, 1686, 1669, 1583, 1250, 1121, 975, 896 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 0.9 Hz, 1H), 3.57 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.46 (ddd, *J* = 7.5, 2.3, 0.9 Hz, 1H), 3.03 – 2.96 (m, 2H), 2.94 (dt, *J* = 4.0, 1.9 Hz, 1H), 2.90 (dt, *J* = 3.8, 1.9 Hz, 1H), 2.59 – 2.51 (m, 2H), 2.01 – 1.92 (m, 2H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 194.50, 189.93, 144.32, 144.02, 48.88, 48.46, 47.82, 47.24, 43.48, 43.41, 25.44, 25.42;
MS (ESI) calcd. for $C_{12}H_{11}BrO_2$ $[M + H + MeCN]^+$ 308.03, found 308.1;
$[\alpha]_D^{23}$ = –32.1 (c = 0.5, $CHCl_3$) (89% ee).

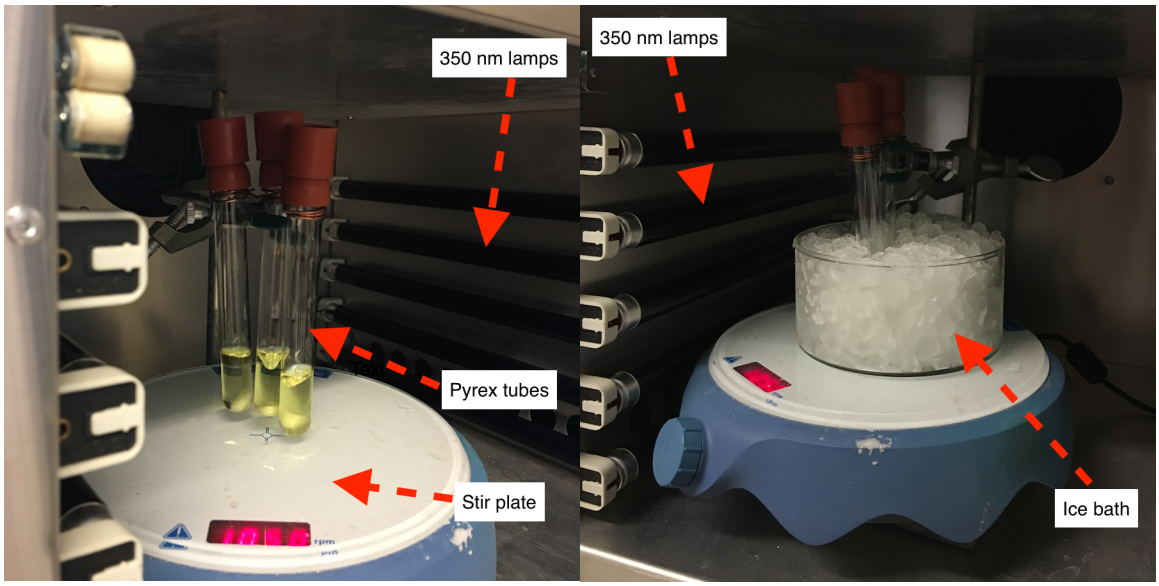
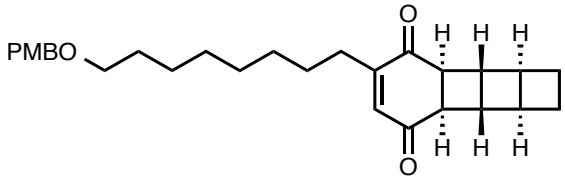


Figure S3. Experimental setup for the preparation of **17**.
Left: Luzchem photochemical reactor and pyrex reaction tubes before cooling. **Right:** Tubes cooled in an ice bath.



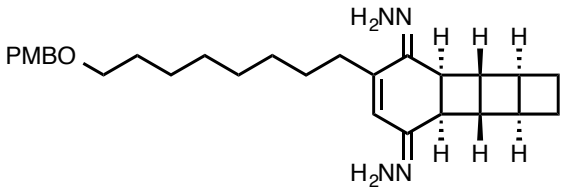
Enedione 19:

The alkylzinc iodide reagent was prepared according to literature procedure.[8] An oven-dried flask purged with nitrogen was charged with zinc powder (510 mg, 7.8 mmol, 1.5 equiv) and solid iodine (66 mg, 0.26 mmol, 0.05 equiv). Distilled DMA (4 mL) was added, and the resulting mixture was allowed to stir vigorously until the yellow color of iodine disappeared (5 min). A solution of iodide **S7** (1.96 g, 5.2 mmol, 1.0 equiv) in DMA (1.2 mL) was added dropwise by syringe, and the mixture was heated to 80 °C (oil bath) for 1.5 hours. The titre of the resulting alkylzinc iodide reagent was determined to be 0.73 M by ^{1}H NMR analysis.

In a separate flask, a solution of bromide **18** (458 mg, 1.71 mmol, 1.0 equiv) in anhydrous THF (17.1 mL, 1.0 M) was cooled to 0 ºC (ice bath). The solution of alkylzinc iodide (0.73 M, 4.7 mL, 2.0 equiv) was added by syringe. The reaction mixture was allowed to stir at 0 °C for 4.5 hours. After this time, the reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (10 mL). Solids were removed by filtration through celite, washing with Et_2O (15 mL). The biphasic filtrate was partitioned between Et_2O (15 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to give **19** (580 mg, 78%) as a yellow oil which solidified upon storage.

The enantiomeric excess was determined to be 88% by HPLC analysis (see Section 7).

Physical properties: yellow oil;
R_f = 0.41 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2931, 2854, 1666, 1612, 1513, 1247, 1096, 1035, 818 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.68 (s, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.41 – 3.36 (m, 2H), 2.98 (bt, *J* = 3.6 Hz, 2H), 2.86 (s, 2H), 2.59 – 2.51 (m, 2H), 2.49 – 2.33 (m, 2H), 2.01 – 1.92 (m, 2H), 1.59 (app. p, *J* = 6.8 Hz, 2H), 1.47 (app. q, *J* = 7.5 Hz, 2H), 1.40 – 1.24 (m, 8H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 197.99, 197.90, 158.99, 155.62, 138.23, 130.67, 129.16, 113.65, 72.45, 70.07, 55.20, 48.86, 48.37, 47.95, 47.77, 43.37, 43.30, 29.85, 29.68, 29.25, 29.23, 29.21, 27.62, 26.10, 25.50, 25.45;
MS (ESI) calcd. for $C_{28}H_{36}O_4$ $[M + Na]^+$ 459.25, found 459.3;
$[\alpha]_D^{23}$ = −1.48 (c = 0.5, $CHCl_3$) (88% ee).

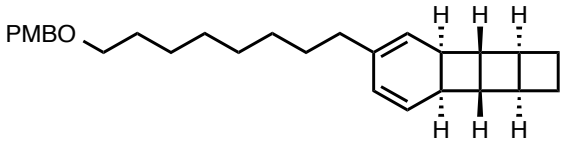


Bis-hydrazone 21:

To a solution of enedione **19** (460 mg, 1.05 mmol, 1.0 equiv) in EtOH (10.5 mL, 0.1 M) was added anhydrous hydrazine (331 μL, 10.5 mmol, 10.0 equiv) by syringe. The reaction mixture was heated to 94 °C for 4 hours, then cooled to room temperature and concentrated *in vacuo* to give **21** as a tan solid (488 mg, quant. crude yield).

21 was carried forward without further purification; an analytically pure sample could be obtained by recrystallization from EtOH (reflux to –15 ºC).

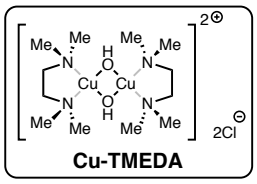
Physical properties: tan solid, mp = 69−72 °C;
R_f = 0.23 (silica gel, 5% MeOH/DCM, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3379 (br), 3208 (br), 2926, 2853, 1612, 1512, 1464, 1247, 1095, 1035, 819, 662, 599 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.20 (s, 1H), 5.08 (bs, 2H), 5.00 (bs, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.51 – 3.44 (m, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 3.04 (bd, *J* = 6.2 Hz, 2H), 2.73 – 2.68 (m, 1H), 2.68 – 2.65 (m, 1H), 2.63 – 2.52 (m, 2H), 2.44 – 2.30 (m, 2H), 2.05 – 1.94 (m, 2H), 1.62 – 1.54 (m, 2H), 1.54 – 1.45 (m, 2H), 1.38 – 1.21 (m, 8H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.97, 148.80, 147.13, 139.16, 130.73, 129.17, 126.09, 113.65, 72.43, 70.19, 55.22, 46.20, 45.80, 42.55, 42.51, 36.24, 36.06, 31.16, 29.71, 29.52, 29.45, 29.38, 28.59, 26.15, 25.67, 25.59;
MS (ESI) calcd. for $C_{28}H_{40}N_4O_2$ $[M + H]^+$ 465.32, found 465.4;
$[\alpha]_D^{24}$ = −2.04 (c = 1.0, $CHCl_3$) (88% ee).



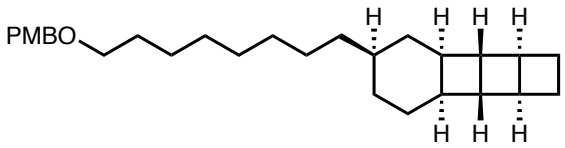
Diene 22:

To a solution of bis-hydrazone **21** (488 mg, 1.05 mmol, 1.0 equiv) in chlorobenzene (5.25 mL, 0.2 M) and 1,4-cyclohexadiene (5.25 mL, 0.2 M) was added Di-μ-hydroxo-bis[(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)copper(II)] chloride (**Cu-TMEDA**, 244 mg, 0.525 mmol, 0.5 equiv) in a single portion. The reaction vessel was left open to air, and the mixture was allowed to stir vigorously at room temperature for 5 hours. After this time, the solids were removed by filtration through celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to provide diene **22** (250 mg, 59%) as a light yellow oil.

Physical properties: light yellow oil;
R_f = 0.51 (silica gel, 10% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2924, 2852, 1613, 1512, 1463, 1301, 1246, 1171, 1097, 1037, 819, 749 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.60 – 5.49 (m, 2H), 5.16 (d, *J* = 4.2 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.09 – 2.98 (m, 2H), 2.88 (bd, *J* = 6.0 Hz, 2H), 2.82 (d, *J* = 5.4 Hz, 2H), 2.53 – 2.40 (m, 2H), 1.98 – 1.88 (m, 4H), 1.67 – 1.54 (m, 2H), 1.42 – 1.32 (m, 4H), 1.32 – 1.23 (m, 6H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.98, 132.11, 130.70, 129.13, 126.65, 124.17, 120.00, 113.63, 72.43, 70.15, 56.32, 56.12, 55.15, 43.99, 43.90, 37.96, 37.64, 36.03, 29.72, 29.40 (2C), 29.07, 27.98, 26.15, 25.83, 25.78;
MS (ESI) calcd. for $C_{28}H_{38}O_2$ $[M + Na]^+$ 429.28, found 429.4;
$[\alpha]_D^{23}$ = +30.98 (c = 1.0, $CHCl_3$) (88% ee).



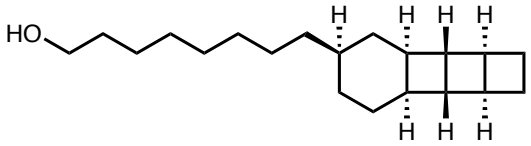
Cu-TMEDA



[3]-Ladderanol PMB ether S8:

To a solution of diene **22** (76.3 mg, 0.188 mmol, 1.0 equiv) in 1,2-dichloroethane (3.75 mL, 0.05 M) was added Crabtree's catalyst (22.7 mg, 0.028 mmol, 0.15 equiv) in a single portion. The reaction vessel was capped with a rubber septum and hydrogen gas was bubbled through the solution from a balloon for 15 minutes. The reaction mixture was allowed to stir under a hydrogen atmosphere for 12 hours, then filtered through a small pad of silica, eluting with 40% EtOAc/hexanes (10 mL). The filtrate was concentrated *in vacuo* to provide **S8** as a colorless oil (77 mg, 99%).

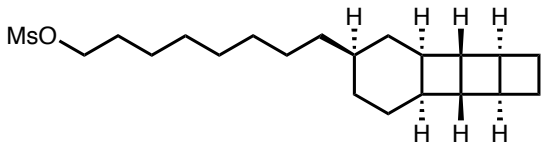
Physical properties: colorless oil;
R_f = 0.46 (silica gel, 10% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2920, 2850, 1613, 1512, 1463, 1360, 1301, 1245, 1171, 1097, 1038, 819 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.25 (m, 2H), 6.91 – 6.86 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.76 – 2.70 (m, 1H), 2.62 (bt, *J* = 4.0 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.45 – 2.36 (m, 2H), 2.30 (d, *J* = 3.5 Hz, 1H), 2.29 – 2.24 (m, 1H), 2.24 – 2.17 (m, 1H), 1.98 – 1.91 (m, 1H), 1.89 – 1.81 (m, 1H), 1.78 – 1.71 (m, 1H), 1.64 – 1.56 (m, 2H), 1.56 – 1.46 (m, 3H), 1.39 – 1.32 (m, 2H), 1.32 – 1.22 (m, 8H), 1.22 – 1.14 (m, 3H), 1.14 – 1.06 (m, 1H), 1.06 – 0.98 (m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.02, 130.75, 129.19, 113.68, 72.47, 70.21, 55.23, 49.34, 47.26, 42.20, 41.47, 38.13, 37.84, 37.64, 34.23, 32.47, 29.90, 29.76, 29.63, 29.48, 28.19, 26.85, 26.19, 26.16, 25.49, 25.46;
MS (ESI) calcd. for $C_{28}H_{42}O_2$ $[M + Na]^+$ 433.31, found 433.4;
$[\alpha]_D^{24}$ = +10.97 (c = 1.0, $CHCl_3$) (88% ee).



[3]-Ladderanol 3:

To a solution of PMB ether **S8** (87.9 mg, 0.214 mmol, 1.0 equiv) in DCM (4.3 mL, 0.05 M) and H_2O (0.43 mL, 0.5 M) at 0 °C (ice bath) was added DDQ (97 mg, 0.428 mmol, 2.0 equiv) in a single portion. The biphasic reaction mixture was allowed to stir vigorously for 2 hours. After this time, solids were removed by filtration through celite, washing with DCM (10 mL). To the filtrate was added a saturated solution of $NaHCO_3$ (4 mL), and the layers were separated. The organic layer was extracted with DCM (3 x 5 mL), and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% Et_2O/toluene), providing **3** (54.9 mg, 89%) as a colorless residue that solidifies on standing.

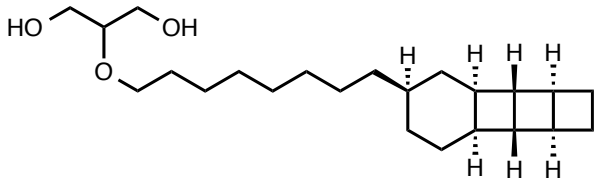
Physical properties: white solid, mp = 40−43 °C;
R_f = 0.39 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3330 (br), 2920, 2850, 1466, 1058 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (t, *J* = 6.7 Hz, 2H), 2.73 (bd, *J* = 6.3 Hz, 1H), 2.62 (bt, *J* = 3.8 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.34 (m, 2H), 2.29 (d, *J* = 3.5 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.23 – 2.16 (m, 1H), 1.98 – 1.90 (m, 1H), 1.88 – 1.80 (m, 1H), 1.78 – 1.70 (m, 1H), 1.60 – 1.53 (m, 2H), 1.53 – 1.45 (m, 3H), 1.37 – 1.22 (m, 10H), 1.22 – 1.13 (m, 3H), 1.13 – 1.06 (m, 1H), 1.06 – 0.97 (m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 70.19, 49.31, 47.23, 42.17, 41.44, 38.06, 37.81, 37.60, 37.29, 34.19, 32.43, 29.77, 29.42, 29.07, 28.99, 28.16, 26.77, 26.13, 25.43, 25.38;
HRMS (APCI) calcd. for $C_{20}H_{34}O$ $[M + H]^+$ 291.2682, found 291.2698;
$[\alpha]_D^{24}$ = +16.3 (c = 1.0, $CHCl_3$) (88% ee).



[3]-Ladderanol mesylate 25:

To a solution of [3]-ladderanol **3** (41.5 mg, 0.143 mmol, 1.0 equiv) in anhydrous DCM (0.72 mL, 0.2 M) at 0 °C was added anhydrous *N,N*-diisopropylethylamine (37 μL, 0.214 mmol, 1.5 equiv) by syringe, followed by mesyl chloride (13 μL, 0.172 mmol, 1.2 equiv) by syringe. The reaction mixture was allowed to stir for 2.5 hours at 0 ºC. After this time, the reaction was quenched by the addition of saturated solution of $NaHCO_3$ (1 mL). The resulting biphasic reaction mixture was partitioned between DCM (2 mL) and water (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/hexanes) to give mesylate **25** (51.2 mg, 97%) as a white solid.

Physical properties: white solid, mp = 35−38 ˚C;
R_f = 0.42 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2919, 2851, 1466, 1352, 1174, 973, 950, 828, 528 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (t, *J* = 6.6 Hz, 2H), 3.00 (s, 3H), 2.72 (bd, *J* = 7.6 Hz, 1H), 2.61 (bt, *J* = 3.8 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.44 – 2.35 (m, 2H), 2.28 (d, *J* = 3.1 Hz, 1H), 2.27 – 2.23 (m, 1H), 2.23 – 2.16 (m, 1H), 1.98 – 1.89 (m, 1H), 1.87 – 1.80 (m, 1H), 1.78 – 1.70 (m, 3H), 1.56 – 1.45 (m, 3H), 1.43 – 1.35 (m, 2H), 1.35 – 1.22 (m, 8H), 1.22 – 1.13 (m, 3H), 1.12 – 1.05 (m, 1H), 1.05 – 0.96 (m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 70.20, 49.30, 47.24, 42.21, 41.50, 38.07, 37.79, 37.63, 37.37, 37.24, 34.18, 32.44, 29.78, 29.43, 29.08, 29.00, 28.16, 26.78, 26.18, 25.47, 25.39;
MS (ESI) calcd. for $C_{21}H_{36}O_3S$ $[M + Na]^+$ 391.23, found 391.3;
$[\alpha]_D^{24}$ = +12.3 (c = 1.0, $CHCl_3$) (88% ee).



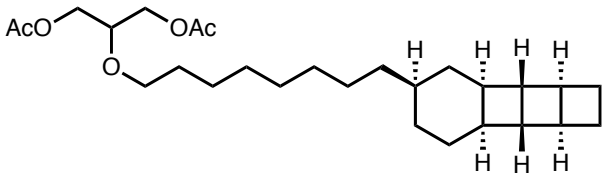
[3]-Ladderane glycerol diol 23:

To a solution of glycerol **24** (88 mg, 0.152 mmol, 2.0 equiv) in anhydrous DMF (190 μL) at 23 °C was added a 2M solution of NaH in DMF (190 μL, 0.38 mmol, 5.0 equiv) dropwise by syringe. After 15 minutes, a solution of mesylate **25** (28 mg, 0.076 mmol, 1.0 equiv) in DMF (380 μL) was added dropwise via syringe. The reaction mixture was allowed to stir vigorously at 70 °C. After 2 hours, the mixture was cooled to 0 ºC and quenched by the dropwise addition of sat. aq. NH_4Cl (1 mL). The resulting biphasic mixture was partitioned between sat. aq. NaCl (1 mL) and Et_2O (3 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 3 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes), providing intermediate **S9** (58.6 mg, 91%).

To a solution of **S9** (54 mg, 0.068 mmol, 1.0 equiv) in a mixture of anhydrous DCM (0.68 mL, 0.1 M) and anhydrous MeOH (0.68 mL, 0.1M) at 0 °C was added acetyl chloride (29 μL, 0.41 mmol, 6.0 equiv). The reaction mixture was allowed to stir at 0 °C for 3 hours, then quenched by the addition of sat. aq. $NaHCO_3$ (1 mL). The reaction mixture was partitioned between H_2O (1 mL) and DCM (3 mL), and the layers were separated. The aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50 to 75% EtOAc/hexanes) to provide **23** (15.6 mg, 71%) as a colorless solid.

23 was found to be spectroscopically identical to natural material isolated from an anammox enrichment culture (Sections 4, 6).

Physical properties: colorless semi-solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3359 (br), 2919, 2851, 1466, 1351, 1226, 1118, 1053, 973, 722, 669 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.81 – 3.72 (m, 2H), 3.72 – 3.64 (m, 2H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.46 (p, *J* = 4.8 Hz, 1H), 2.73 (bd, *J* = 7.5 Hz, 1H), 2.62 (bt, *J* = 3.7 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.45 – 2.37 (m, 2H), 2.29 (d, *J* = 3.6 Hz, 1H), 2.28 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 1.98 – 1.88 (m, 1H + 2OH), 1.88 – 1.81 (m, 1H), 1.78 – 1.71 (m, 1H), 1.64 – 1.57 (m, 2H), 1.55 – 1.46 (m, 3H), 1.41 – 1.22 (m, 10H), 1.22 – 1.12 (m, 3H), 1.12 – 1.06 (m, 1H), 1.06 – 0.98 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 79.49, 70.20, 62.22, 49.39, 47.33, 42.26, 41.54, 38.14, 37.89, 37.67, 34.23, 32.49, 30.06, 29.90, 29.61, 29.46, 28.20, 26.85, 26.18, 26.13, 25.51, 25.50;
MS (ESI) calcd. for $C_{23}H_{40}O_3$ $[M + Na]^+$ 387.29, found 387.3;
$[\alpha]_D^{24}$ = +12.4 (c = 0.5, $CHCl_3$) (88% ee).

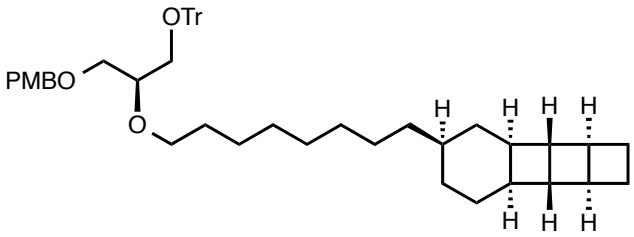


[3]-Ladderane glycerol diacetate S10:

To a solution of [3]-ladderane glycerol **23** (11.6 mg, 0.0318 mmol, 1.0 equiv) and 4-(dimethylamino)pyridine (11.7 mg, 0.0954 mmol, 3.0 equiv) in anhydrous DCM (0.32 mL, 0.1 M) was added acetyl chloride (7 μL, 0.0954 mmol, 3.0 equiv). The reaction was allowed to stir at 23 °C for 3 hours, after which time a 1M aqueous solution of HCl (0.5 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (2 x 1 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by preparatory TLC (silica gel, 30% EtOAc/hexanes) to provide **S10** (10.2 mg, 71%) as a colorless oil.

Spectroscopic data on **S10** was found to be in agreement with isolation literature.[9]

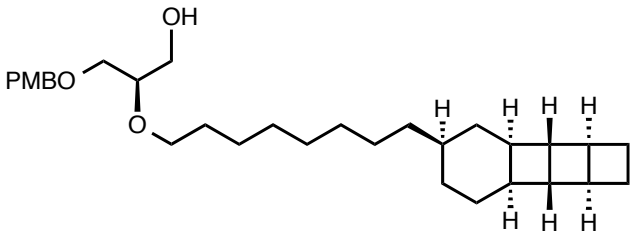
Physical properties: colorless oil;
R_f = 0.64 (silica gel, 30% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film)) ν_{max} = 2922, 2852, 1746, 1455, 1367, 1225, 1127, 1049 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.18 (dd, *J* = 11.6, 5.0 Hz, 2H), 4.13 (dd, *J* = 11.7, 5.4 Hz, 2H), 3.68 (p, *J* = 5.1 Hz, 1H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.72 (bd, *J* = 6.6 Hz, 1H), 2.62 (bt, *J* = 3.6 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.44 – 2.37 (m, 2H), 2.29 (d, *J* = 3.4 Hz, 1H), 2.28 – 2.24 (m, 1H), 2.23 – 2.17 (m, 1H), 2.08 (s, 6H), 1.97 – 1.91 (m, 1H), 1.87 – 1.81 (m, 1H), 1.76 – 1.71 (m, 1H), 1.60 – 1.45 (m, 5H), 1.35 – 1.22 (m, 10H), 1.22 – 1.14 (m, 3H), 1.12 – 1.06 (m, 1H), 1.05 – 0.98 (m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.81, 74.98, 70.69, 63.18, 49.35, 47.27, 42.21, 41.48, 38.13, 37.85, 37.64, 34.24, 32.48, 29.90, 29.84, 29.65, 29.42, 28.19, 26.86, 26.16, 25.96, 25.50, 25.47, 20.87;
MS (ESI) calcd. for $C_{27}H_{44}O_5$ $[M + Na]^+$ 471.31, found 471.4;
$[\alpha]_D^{23}$ = +11.7 (c = 0.5, $CHCl_3$) (88% ee).



[3]-Ladderane glycerol S11:

To a solution of protected glycerol **26** (123.3 mg, 271 μmol, 2.0 equiv) in anhydrous DMF (150 μL) under nitrogen at 23 ºC was added a solution of 2 M NaH in DMF (343 μL, 685 μmol, 5.0 equiv) dropwise by syringe. The mixture was warmed to 75 ºC. After 15 minutes, a solution of [3]-ladderanol mesylate **25** (50.0 mg, 137 μmol, 1.0 equiv) in DMF (578 μL) was added dropwise by syringe. Addition was completed by rinsing with two 150-μL portions of DMF by syringe. The reaction mixture was allowed to stir vigorously at 75 ºC. After 1 hour, the mixture was cooled to 0 ºC and quenched by the dropwise addition of sat. aq. NH_4Cl (1 mL). The resulting mixture was partitioned between EtOAc (10 mL) and sat. aq. NaCl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (2 to 4% EtOAc/hexanes), providing **S11** (60.0 mg, 60%) as a colorless oil.

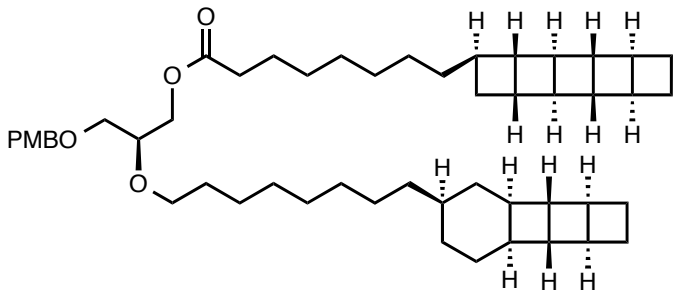
Physical properties: colorless oil;
R_f = 0.63 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2922, 2852, 1613, 1513, 1247, 1093, 705 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 6.9 Hz, 6H), 7.30 – 7.18 (m, 9H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.42 (dd, *J* = 15.8, 11.7 Hz, 2H), 3.78 (s, 3H), 3.62 – 3.45 (m, 5H), 3.18 (d, *J* = 4.5 Hz, 2H), 2.71 (bd, *J* = 7.2 Hz, 1H), 2.61 (bt, *J* = 4.0 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.45 – 2.32 (m, 2H), 2.28 (d, *J* = 3.5 Hz, 1H), 2.27 – 2.22 (m, 1H), 2.22 – 2.14 (m, 1H), 1.98 – 1.87 (m, 1H), 1.87 – 1.77 (m, 1H), 1.77 – 1.67 (m, 1H), 1.60 – 1.54 (m, 2H), 1.52 – 1.43 (m, 3H), 1.36 – 1.20 (m, 10H), 1.20 – 1.12 (m, 3H), 1.13 – 1.05 (m, 1H), 1.05 – 0.94 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.03, 144.12, 130.53, 129.12, 128.74, 127.70, 126.86, 113.65, 86.51, 78.31, 72.89, 70.68, 70.16, 63.50, 55.24, 49.39, 47.32, 42.25, 41.53, 38.16, 37.88, 37.68, 34.23, 32.49, 30.14, 29.94, 29.68, 29.54, 28.20, 26.88, 26.18, 26.17, 25.51, 25.50;
MS (ESI) calcd. for $C_{50}H_{62}O_4$ $[M + Na]^+$ 749.45, found 749.6;
$[\alpha]_D^{24}$ = +2.5 (c = 0.7, $CHCl_3$).



[3]-Ladderane glycerol S12:

To a solution of **S11** (60.0 mg, 82.5 μmol, 1.0 equiv) in anhydrous DCM (825 μL, 0.1 M) and anhydrous MeOH (825 μL, 0.1 M) under nitrogen at 0 ºC (ice bath) was added acetyl chloride (17.7 μL, 248 μmol, 3.0 equiv). After 6 hours, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The mixture was partitioned between DCM (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10 to 20% EtOAc/hexanes), providing **S12** (34.4 mg, 86%) as a colorless oil.

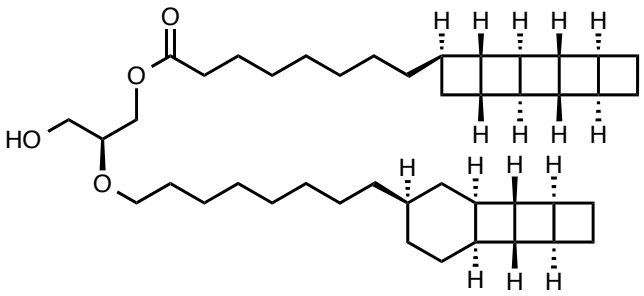
Physical properties: colorless oil;
R_f = 0.21 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3452 (br), 2920, 2852, 1613, 1513, 1247, 1094, 1038, 820 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.47 (dd, *J* = 14.3, 11.7 Hz, 2H), 3.80 (s, 3H), 3.77 – 3.67 (m, 1H), 3.62 – 3.46 (m, 6H), 2.72 (bd, *J* = 7.5 Hz, 1H), 2.62 (bt, *J* = 3.7 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.34 (m, 2H), 2.29 (d, *J* = 3.5 Hz, 1H), 2.28 – 2.24 (m, 1H), 2.23 – 2.16 (m, 1H), 2.14 (bs, 1H), 1.98 – 1.88 (m, 1H), 1.88 – 1.78 (m, 1H), 1.78 – 1.71 (m, 1H), 1.60 – 1.55 (m, 2H), 1.54 – 1.45 (m, 3H), 1.37 – 1.22 (m, 10H), 1.22 – 1.13 (m, 3H), 1.13 – 1.05 (m, 1H), 1.05 – 0.97 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 159.24, 130.07, 129.26, 113.79, 78.38, 73.16, 70.38, 69.68, 62.93, 55.25, 49.38, 47.32, 42.24, 41.53, 38.14, 37.88, 37.67, 34.22, 32.48, 30.06, 29.90, 29.62, 29.46, 28.19, 26.86, 26.17, 26.10, 25.50, 25.49;
MS (ESI) calcd. for $C_{31}H_{48}O_4$ $[M + Na]^+$ 507.35, found 507.4;
$[\alpha]_D^{24}$ = +13.8 (c = 0.45, $CHCl_3$).



[5][3]PMB ether S13:

[5]-ladderanoic acid **2** (21.5 mg, 71.0 μmol, 1.0 equiv) and [3]-ladderanyl glycerol **S12** (34.4 mg, 71.0 μmol, 1.0 equiv) were concentrated from ca. 3 mL benzene in a 10-mL round bottom flask. The flask was equipped with a magnetic stir bar, flushed with nitrogen, and capped with a rubber septum under nitrogen. The solids were taken up in anhydrous DMF (710 μL, 0.1M) and the resulting mixture was cooled to 0 ºC (ice bath). Hünig's base (24.6 μL, 142 μmol, 2.0 equiv) was added by syringe and the mixture was allowed to warm to room temperature. EDC•HCl (27.2 mg, 142 μmol, 2.0 equiv), HOBt•H_2O (21.7 mg, 142 μmol, 2.0 equiv), and DMAP (1 chip, ca. 1 mg) were added in a single portion. The rubber septum was replaced with a plastic yellow cap and the reaction mixture was allowed to stir for 26 hours. After this time, the reaction mixture was partitioned between 1N HCl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (2 to 4 to 6% EtOAc/hexanes), providing **S13** (40.2 mg, 74%) as a colorless oil.

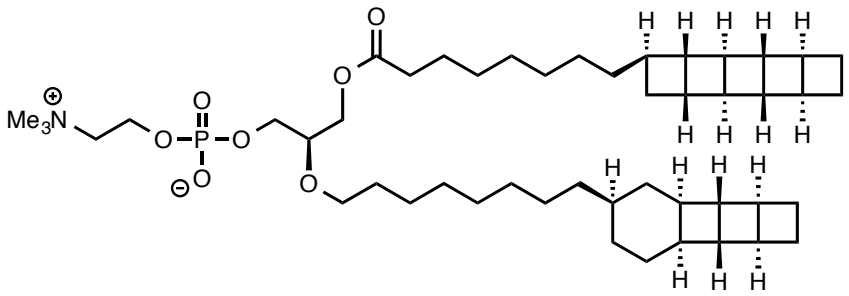
Physical properties: colorless oil;
R_f = 0.59 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2919, 2852, 1739, 1613, 1513, 1248, 1102, 820 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.47 (s, 2H), 4.23 (dd, *J* = 11.6, 4.1 Hz, 1H), 4.11 (dd, *J* = 11.6, 5.8 Hz, 1H), 3.80 (s, 3H), 3.66 – 3.61 (m, 1H), 3.54 (t, *J* = 6.7 Hz, 2H), 3.50 (dd, *J* = 5.4, 2.7 Hz, 2H), 2.72 (bd, *J* = 6.2 Hz, 3H), 2.65 – 2.60 (m, 4H), 2.59 (s, 1H), 2.57 (bs, 1H), 2.56 – 2.52 (m, 2H), 2.52 – 2.44 (m, 1H), 2.44 – 2.36 (m, 2H), 2.34 (s, 1H), 2.32 – 2.23 (m, 4H), 2.23 – 2.12 (m, 3H), 2.07 – 2.01 (m, 2H), 2.01 – 1.97 (m, 1H), 1.97 – 1.90 (m, 1H), 1.87 – 1.80 (m, 1H), 1.77 – 1.71 (m, 1H), 1.62 – 1.57 (m, 2H), 1.56 – 1.52 (m, 2H), 1.52 – 1.46 (m, 3H), 1.46 – 1.37 (m, 2H), 1.33 – 1.22 (m, 16H), 1.22 – 1.12 (m, 5H), 1.12 – 1.05 (m, 1H), 1.05 – 0.95 (m, 1H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.67, 159.15, 130.11, 129.25, 113.71, 76.49, 73.05, 70.59, 69.14, 63.69, 55.25, 49.40, 49.34, 49.16, 48.27, 47.26, 47.22, 42.20, 41.77, 41.46, 39.86, 38.46, 38.14, 37.84, 37.63, 37.34, 34.24, 33.25, 32.48, 29.98, 29.94, 29.68, 29.51, 29.48, 29.32, 29.12, 28.19, 26.89, 26.49, 26.44, 26.16, 26.05, 25.48, 24.93;
MS (ESI) calcd. for $C_{51}H_{76}O_5$ $[M + Na]^+$ 791.56, found 791.6;
$[\alpha]_D^{24}$ = +2.7 (c = 0.35, $CHCl_3$).



[5],[3]-Glycerol alcohol S14:

To a solution of **S13** (40 mg, 52.0 µmol, 1.0 equiv) in DCM (1.04 mL, 0.05M) and water (104 µL, 0.5M) at 0 ºC was added DDQ (23.6 mg, 104 µmol, 2.0 equiv) in a single portion. The reaction mixture was allowed to stir vigorously at 0 ºC for 8 hours, then filtered through a pad of celite, washing thoroughly with DCM (10 mL total). To the filtrate was added sat. aq. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The organic layers were combined, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (0.5 to 2% MeOH/DCM), providing **S14** (30.1 mg, 89%) as a colorless wax.

Physical properties: colorless wax;
R_f = 0.41 (silica gel, 20% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3436 (br), 2917, 2851, 1739, 1465, 1167, 1117, 1076 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 – 4.13 (m, 2H), 3.68 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.61 (dq, *J* = 8.0, 5.7, 4.7 Hz, 3H), 3.50 (dt, *J* = 9.3, 6.6 Hz, 1H), 2.72 (bd, *J* = 6.5 Hz, 3H), 2.65 – 2.60 (m, 4H), 2.59 (s, 1H), 2.57 – 2.56 (m, 1H), 2.56 – 2.52 (m, 2H), 2.52 – 2.44 (m, 1H), 2.44 – 2.35 (m, 2H), 2.35 – 2.30 (m, 3H), 2.28 (d, *J* = 3.4 Hz, 1H), 2.27 – 2.23 (m, 1H), 2.23 – 2.12 (m, 3H), 2.10 (d, *J* = 6.0 Hz, 1H), 2.03 (d, *J* = 6.5 Hz, 2H), 2.01 – 1.96 (m, 1H), 1.96 – 1.90 (m, 1H), 1.87 – 1.80 (m, 1H), 1.77 – 1.69 (m, 1H), 1.61 (t, *J* = 7.2 Hz, 2H), 1.59 – 1.54 (m, 2H), 1.54 – 1.46 (m, 3H), 1.46 – 1.37 (m, 2H), 1.35 – 1.22 (m, 16H), 1.22 – 1.13 (m, 5H), 1.12 – 1.05 (m, 1H), 1.05 – 0.97 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.80, 77.59, 70.51, 62.65, 62.01, 49.41, 49.35, 49.32, 49.16, 48.28, 47.28, 47.23, 42.21, 41.79, 41.49, 39.87, 38.47, 38.13, 37.85, 37.64, 37.32, 34.23, 34.20, 33.25, 32.48, 29.98, 29.91, 29.64, 29.48, 29.46, 29.29, 29.10, 28.19, 26.87, 26.50, 26.46, 26.43, 26.16, 26.06, 25.49, 25.47, 24.92;
MS (ESI) calcd. for $C_{43}H_{68}O_4$ $[M + Na]^+$ 671.50, found 671.6;
$[\alpha]_D^{24}$ = –7.7 (c = 0.07, $CHCl_3$).



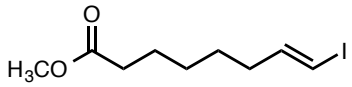
[5],[3]-Phosphatidyl choline 1:

[5],[3]-glycerol alcohol **S14** (30 mg, 46.2 umol, 1.0 equiv) was concentrated from toluene (ca. 1 mL) in a 5-mL pointed microwave vial. The vial was equipped with a triangular magnetic stir bar, capped with a rubber septum, and flushed with nitrogen. The residue was taken up in anhydrous toluene (462 µL, 0.1M) and the resulting solution was cooled to 0 ºC under nitrogen. Neat trimethylamine from a pressurized cylinder was introduced via a needle and ca. 250 µl was allowed to condense in the microwave vial. Freshly distilled 2-chloro-1,3,2-dioxaphospholane 2-oxide (12.7 µL, 139 µmol, 3.0 equiv) was added by syringe. The resulting mixture was allowed to stir at 0 ºC for 1 hour. Reaction progress was monitored by ^{1}H NMR analysis of small aliquots.

When the reaction was complete, the flask was allowed to warm to room temperature and a stream of nitrogen was introduced to remove trimethylamine. The resulting suspension was filtered through pad of celite to remove trimethylamine hydrochloride, rinsing thoroughly with toluene (ca. 5 mL). The filtrate was concentrated in a 15-mL screw-cap pressure tube. The tube was equipped with a magnetic stir bar, capped with a rubber septum, and flushed with nitrogen. The residue was taken up in anhydrous MeCN (462 µL, 0.1M), and the resulting solution was cooled to –78 ºC. Neat trimethylamine was introduced as before and ca. 1.5 mL was allowed to condense. The rubber septum was replaced quickly with a screw cap, and the reaction vessel was allowed to warm first to room temperature and then to 75 ºC in an oil bath. After 18 hours, the reaction vessel was returned to –78 ºC briefly while the screw cap was removed, then allowed to warm slowly to room temperature as excess trimethylamine evaporated. The resulting slurry was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (65:15:2 DCM:MeOH:H_2O). Fractions containing the desired product were combined and concentrated. The residue was taken up in chloroform and the resulting solution was dried with sodium sulfate, filtered, and concentrated to provide [5],[3]-phosphatidyl choline **1** (18.9 mg, 50%) as a colorless wax.

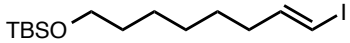
Physical properties: colorless wax;
R_f = 0.21 (silica gel, 65:15:2 DCM:MeOH:H_2O, visualized with Seebach's stain);
IR (film) ν_{max} = 2918, 2850, 1729, 1467, 1236, 1089, 969 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.39 – 4.30 (m, 2H), 4.28 (dd, *J* = 11.7, 3.2 Hz, 1H), 4.08 (dd, *J* = 11.7, 7.1 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.89 – 3.78 (m, 3H), 3.68 – 3.62 (m, 1H), 3.60 – 3.54 (m, 1H), 3.52 – 3.46 (m, 1H), 3.37 (s, 9H), 2.73 (bd, *J* = 6.5 Hz, 3H), 2.65 – 2.60 (m, 4H), 2.60 (bs, 1H), 2.58 – 2.57 (m, 1H), 2.57 – 2.53 (m, 2H), 2.52 – 2.44 (m, 1H), 2.44 – 2.36 (m, 2H), 2.36 – 2.33 (m, 1H), 2.31 – 2.28 (m, 3H), 2.28 – 2.25 (m, 1H), 2.22 – 2.14 (m, 3H), 2.07 – 2.02 (m, 2H), 2.02 – 1.97 (m, 1H), 1.97 – 1.90 (m, 1H), 1.88

– 1.81 (m, 1H), 1.77 – 1.71 (m, 1H), 1.64 – 1.56 (m, 2H), 1.55 – 1.47 (m, 5H), 1.47 – 1.38 (m, 2H), 1.31 – 1.23 (m, 16H), 1.22 – 1.13 (m, 5H), 1.13 – 1.06 (m, 1H), 1.06 – 0.98 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.80, 70.50, 66.32, 64.41, 63.90, 59.19, 54.42, 49.40, 49.33, 49.31, 49.15, 48.26, 47.27, 47.23, 42.20, 41.78, 41.48, 39.88, 38.47, 38.19, 37.84, 37.63, 37.37, 34.29, 34.24, 33.26, 32.50, 30.08, 30.03, 29.79, 29.60, 29.40, 29.22, 28.19, 26.96, 26.50, 26.46, 26.16, 26.07, 25.48, 25.46, 24.98;
^{31}P NMR (162 MHz, $CDCl_3$) δ –0.69;
MS (ESI) calcd. for $C_{48}H_{80}NO_7P$ $[M + H]^+$ 814.58, found 814.7;
$[\alpha]_D^{24}$ = +9.0 (c = 0.38, $CHCl_3$).



S15

S16



S5

Vinyl iodide **S5** was prepared according to the following sequence:

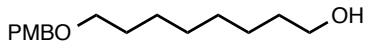
To a rapidly stirring suspension of chromium(II) chloride (10.0 g, 81.4 mmol, 6.0 equiv) in THF (136 mL) at 0 ºC (ice bath) was added a solution of methyl 7-oxoheptanoate (2.15 g, 13.6 mmol, 1.0 equiv) and iodoform (10.7 g, 27.2 mmol, 2 equiv) in THF (68 mL). The reaction mixture was allowed to stir for 3 hours at 0 ºC. After this time, the mixture was partitioned between sat. aq. NaCl (300 mL) and diethyl ether (300 mL). The layers were separated, and the organic layer was washed with sat. aq. NaCl (200 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (0 to 2% ethyl acetate/hexanes), providing vinyl iodide **S15** (1.84 g, 48%) as a 3:1 mixture of *trans*:*cis* olefin isomers.

To a solution of **S15** (1.79 g, 6.34 mmol, 1.0 equiv) in THF (63.4 mL) at –78 ºC was added a 1.0 M solution of diisobutylaluminum hydride (14.0 mL, 14.0 mmol, 2.2 equiv) by syringe in a fine stream. After 1 hour, the reaction mixture was quenched by the careful addition of EtOAc (2 mL) by pipet. The cooling bath was removed, and sat. aq. potassium sodium tartrate (100 mL) and ethyl acetate (100 mL) were added. The resulting biphasic mixture was allowed to stir vigorously for 12 hours. The layers were separated, and the organic layer was washed with sat. aq. NaCl (100 ml). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10 to 20% EtOAc/hexanes), providing alcohol **S16** (1.50 g, 93%).

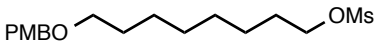
To a solution of **S16** (789 mg, 3.10 mmol, 1.0 equiv) and imidazole (507 mg, 7.44 mmol, 2.4 equiv.) in anhydrous DCM (15.5 M, 0.2 M) at 0 ºC (ice bath) was added *tert*-butyldimethylsilyl chloride (562 mg, 3.73 mmol, 1.2 equiv) in a single portion. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for three hours. After this time, 1N HCl (30 mL) and DCM (15 mL) were added. The layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (0 to 2% EtOAc/hexanes), providing **S5** (1.085 g, 91%) as a 3:1 mixture of *trans*:*cis* olefin isomers.

Physical properties: colorless oil;
R_f = 0.56 (silica gel, 5% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 2927, 2855, 1462, 1253, 1097, 940, 823, 773, 660 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (dt, *J* = 14.3, 7.2 Hz, 1H, major diast), 6.23 – 6.12 (m, 2H, minor diast), 5.97 (dt, *J* = 14.3, 1.5 Hz, 1H, major diast), 3.65 – 3.51 (m, 2H), 2.18 – 2.09 (m, 2H, minor diast), 2.09 – 1.98 (m, 2H, major diast), 1.54 – 1.45 (m, 2H), 1.45 – 1.23 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H);

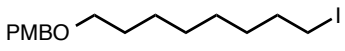
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.56, 141.26, 82.22, 74.36, 63.14, 63.07, 35.95, 34.59, 32.71, 32.67, 28.85, 28.65, 28.30, 27.91, 25.96, 25.94, 25.61, 25.51, 18.32, 18.31, -5.27, -5.28;
HRMS (APCI) calcd. for $C_{12}H_{29}IOSi$ $[M + H]^+$ 369.1105, found 369.1106.



S17



S18



S7

Alkyl iodide **S7** was prepared according to the following sequence:

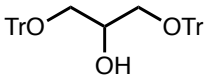
To a solution of octane diol (21.8 g, 149 mmol, 1.0 equiv) in DCM (750 mL, 0.2 M) in a 2-liter round-bottom flask was added Amberlyst-15 (2.18g, 10% w/w) in a single portion. To the resulting suspension was added anisyl alcohol (20.4 mL, 164 mmol, 1.1 equiv). The flask was fitted with a relux condenser and the mixture was heated to reflux (41 °C) for 4h. The reaction mixture was cooled to room temperature and solid Amberlyst-15 was removed via vacuum filtration, washing with DCM (100 mL). The solvent was removed *in vacuo* to provide a crude residue, which was purified by flash column chromatography (40% to 60% EtOAc/hexanes) to give alcohol **S17** (22.8 g, 58% yield) as a 1.4 : 1 mixture with anisyl alcohol.

A solution of alcohol **S17** (3.65 g, 15.4 mmol, 1.0 equiv; as a 1.4 : 1 mixture with anisyl alcohol) in DCM (106 mL, 0.2 M) was cooled to –15 °C (wet ice/acetone). To this solution was added triethylamine (3.86 mL, 27.7 mmol, 1.1 equiv) and MsCl (2.05 mL, 26.4 mmol, 1.05 equiv). The reaction was allowed to stir at –15 °C for 2 hours, after which time it was quenched by the addition 1 M aq. HCl (20 mL) and H_2O (30 mL). The mixture was transferred to a separatory funnel and the DCM layer was removed. The aqueous layer was extracted with 3 : 1 $CHCl_3$:*i*-PrOH (2 x 30 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% to 40% EtOAc/hexanes) to give mesylate **S18** (4.5 g, 85%) as a colorless oil.

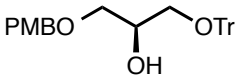
To a solution of **S18** (2.58 g, 7.5 mmol, 1.0 equiv) in acetone (10 mL) at 0 °C was added a solution of sodium iodide (5.6 g, 37.4 mmol, 5.0 equiv) in acetone (27.5 mL) slowly via pipette. This cloudy mixture was allowed to warm to room temperature, then heated to 50 °C for 1.5 hours. After this time, the reaction was allowed to cool to room temperature and filtered through celite, washing with Et_2O (10 mL). The filtrate was transferred to a separatory funnel and washed with sat. aq. $Na_2S_2O_3$ (10 mL) and brine (10 mL). The washed organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc/hexanes) to provide iodide **S7** (2.64 g, 94%) as a colorless oil.

Physical properties: colorless oil;
R_f = 0.47 (silica gel, 10% EtOAc/hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} = 2928, 2853, 1612, 1568, 1512, 1463, 1361, 1301, 1246, 1171, 1097, 1036, 820, 513 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.83 (s, 3H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 1.84 (dd, *J* = 99.7, 7.1 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.44 – 1.30 (m, 8H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 158.96, 130.63, 129.12, 113.62, 72.42, 70.00, 55.19, 55.16, 33.41, 30.34, 29.62, 29.15, 28.39, 26.02, 7.29;
HRMS (APCI) calcd. for $C_{16}H_{25}IO_2$ $[M + Na]^+$ 399.0791, found 399.0788.



24



26

Protected glycerol derivatives **24**[10] and **26**[11] were prepared according to literature procedures.

4. Anammox Biomass Production and Lipid Extraction

Four identical 2-L laboratory scale bioreactors employing CANON (Completely Autotrophic Nitrogen removal) technology were operated simultaneously according to procedures described previously for a period of 4 months.[12] Each bioreactor was charged with inoculum obtained from a stable laboratory scale CANON bioreactor operating at 33 ºC.[12a] Each reactor was operated under a hydraulic retention time of 4 h, a pH range of 7.30–7.65, and a temperature of 33 °C. The bioreactors were continuously aerated, maintaining dissolved oxygen concentrations in the range of 0.80–1.30 mg/L.[12c] Additionally, bioreactors were supplied with $(NH_4)_2SO_4$ (2.35 g/L), $NaHCO_3$ (3.25 g/L), $CaCl_2$ (0.30 g/L), KH_2PO_4 (0.07 g/L), $MgSO_4$ (0.02 g/L), $FeSO_4 \cdot 7H_2O$ (0.009 g/L), and H_2SO_4 (0.005 g/L). The total nitrogen removal performance achieved in the CANON bioreactor was around 85% during the stabilized period.[12a]

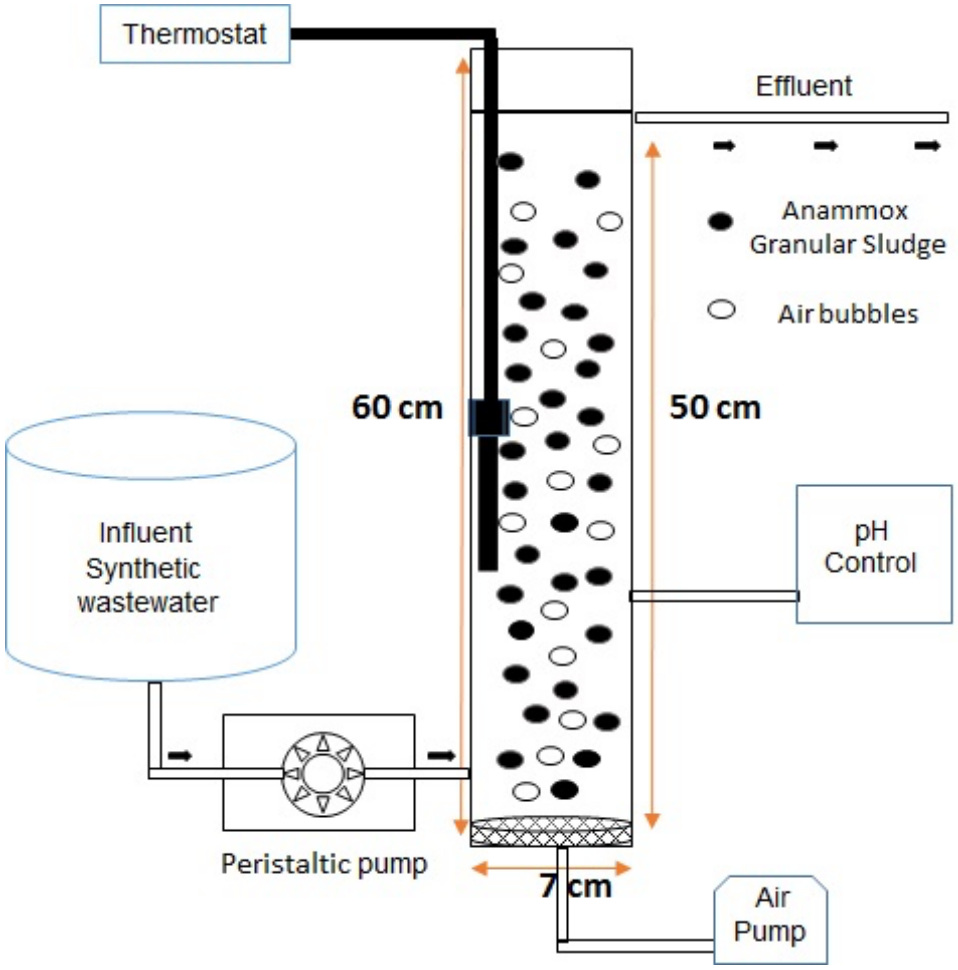


Figure S4. Schematic representation of an anammox bioreactor employing CANON technology. The mixture of inorganics described above is formulated to mimic the ammonia-rich wastewater where anammox bacteria thrive and is frequently referred to as synthetic wastewater.

Figure S5. Experimental setup of four laboratory scale CANON bioreactors.

Lipid Extraction

Granular biomass (80g dry weight) was extracted using a modified Bligh-Dyer procedure.[13] DCM (450 ml), methanol (900 ml) and water (360 ml) were added to the biomass and the resulting slurry was allowed to stir vigorously for 3 h. The mixture was sonicated for 30 minutes and then filtered. DCM (450 ml) and water (450 ml) were added to the filtrate. The layers were separated, and the aqueous layer was extracted with DCM (3x 200 ml), adding methanol where necessary to disrupt emulsions. The solid collected from filtration was extracted using this method twice more. The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo* to yield the total lipid extract (868 mg) as an orange-brown oil.

Global reduction and isolation of diol 23

To a 500 ml round-bottom flask containing the total lipid extract (868 mg) was added 80 ml dry THF. While stirring, lithium aluminum hydride (580 mg) was added portionwise at 0 °C (ice bath). After 1.5 h, the brown heterogeneous suspension was allowed to warm to room temperature. After 4.5 h, the green-gray suspension was cooled to 0 °C and EtOAc was added cautiously by pipet until bubbling ceased, then diluted to 250 mL volume. An additional 350 mL of potassium sodium tartrate (1M in water) was added and the resulting mixture was allowed to stir vigorously for 14 hours. Water (500 ml), EtOAc (100 ml), and diethyl ether (300 ml) were then added and the mixture was allowed to stir an additional 24 hours, at which point separation of layers was observed. The layers were separated and the aqueous layer was extracted with EtOAc (4x 300 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the reduced lipid extract (672 mg) as a caramel-colored oil. Flash column chromatography using a slow solvent gradient (0 to 100% EtOAc/hexanes) yielded diol **23** (20 mg) as a colorless solid.

Physical properties: colorless solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} = 3363 (br), 2919, 2850, 1466, 1261, 1048, 1053, 802 cm^{-1};
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.80 – 3.73 (m, 2H), 3.72 – 3.64 (m, 2H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.46 (p, *J* = 4.8 Hz, 1H), 2.73 (d, *J* = 6.1 Hz, 1H), 2.62 (t, *J* = 3.9 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.45 – 2.37 (m, 2H), 2.29 (d, *J* = 3.5 Hz, 1H), 2.28 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 2.00 – 1.89 (m, 3H), 1.89 – 1.79 (m, 1H), 1.78 – 1.70 (m, 1H), 1.65 – 1.59 (m, 2H), 1.56 – 1.45 (m, 3H), 1.40 – 1.22 (m, 10H), 1.22 – 1.13 (m, 3H), 1.13 – 1.06 (m, 1H), 1.06 – 0.97 (m, 1H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 79.45, 70.19, 62.18, 49.36, 47.28, 42.22, 41.49, 38.12, 37.85, 37.64, 34.24, 32.48, 30.04, 29.89, 29.61, 29.46, 28.20, 26.85, 26.17, 26.12, 25.50, 25.47;
MS (ESI) calcd. for $C_{23}H_{40}O_3$ $[M + Na]^+$ 387.29, found 387.3;
$[\alpha]_D^{24}$ = +14.1 (c = 0.5, $CHCl_3$).

5. Biophysical Characterization of Ladderane Phospholipid 1

General Information

Texas Red 1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine (Texas Red DHPE) and Oregon Green 488 1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine (Oregon Green DHPE) were purchased from Thermo Fisher Scientific. Solvents were ACS grade and used as used as supplied. All water used was from a Millipore (Billerica, MA) MilliQ system with a resistivity of ~ 18.2 MΩ·cm. The concentration of ladderane lipid stock solutions was determined by performing LC-MS with a quantitative PC standard (12:0-13:0 PC) from Avanti.

Differential Scanning Calorimetry

A film of ladderane phospholipid **1** was prepared by concentrating a solution of 1.5 mg **1** in 0.3 mL chloroform in a glass microvial under house vacuum for 3 hours. A multilamellar lipid dispersion was prepared by adding 40 μL of 1:1 ethylene glycol : buffer (240 mM NaCl + 10 mM NaH_2PO_4) to the film and then subjecting the resulting mixture to bath sonication at 69 °C for 5 minutes. 25 μL of the resulting suspension was loaded into a 40-μL T-Zero aluminum pan (TA Instruments, New Castle, DE) and hermetically sealed. Calorimetric scans were performed in a TA Instruments Q2000 DSC using an empty T-Zero aluminum pan as a reference at a scan rate of 10 °C/min. A scan from –20 °C to 80 °C was performed to locate the major transition which was readily apparent near 9 °C. Four scans ranging from –6 °C to 24 °C were performed. Data were analyzed in Excel using the =MIN function to locate T_m, which was found to be 9.32 ± 0.07 °C.

Giant Unilamellar Vesicle Formation and Fluorescence Microscopy

Giant unilamellar vesicles (GUVs) were formed by the gentle hydration method.[14] A solution of 100 nmol of **1** in chloroform was mixed with 0.1 mol% Texas Red DHPE in a glass vial. A thin lipid film was prepared by evaporating the chloroform under a gentle stream of argon while rotating the vial. Residual solvent was removed by placing the vial under house vacuum for at least 4 hours. 1 mL of 500 mM sucrose at 37°C was gently added, and the resulting mixture was incubated at 37°C overnight. After incubation vials were cooled to room temperature. 10 μL of vesicle solution was gently pipetted into a well containing 200 μL of 500 mM glucose in a PDMS gasket bonded to a #1.5 glass microscope coverslip. After allowing the giant vesicles to sink for at least 10 minutes, they were imaged with a Nikon Ti-U inverted epifluorescence microscope with a 100X oil immersion objective (Nikon Instruments, Melville, NY; NA-1.49) equipped with an Andor iXon 897 camera (Andor Technology, Belfast, United Kingdom). Standard emission and excitation filters for Texas Red were used. Metamorph (Molecular Devices, Sunnyvale, CA) was used to acquire images, and images were processed with ImageJ (National Institutes of Health, USA).

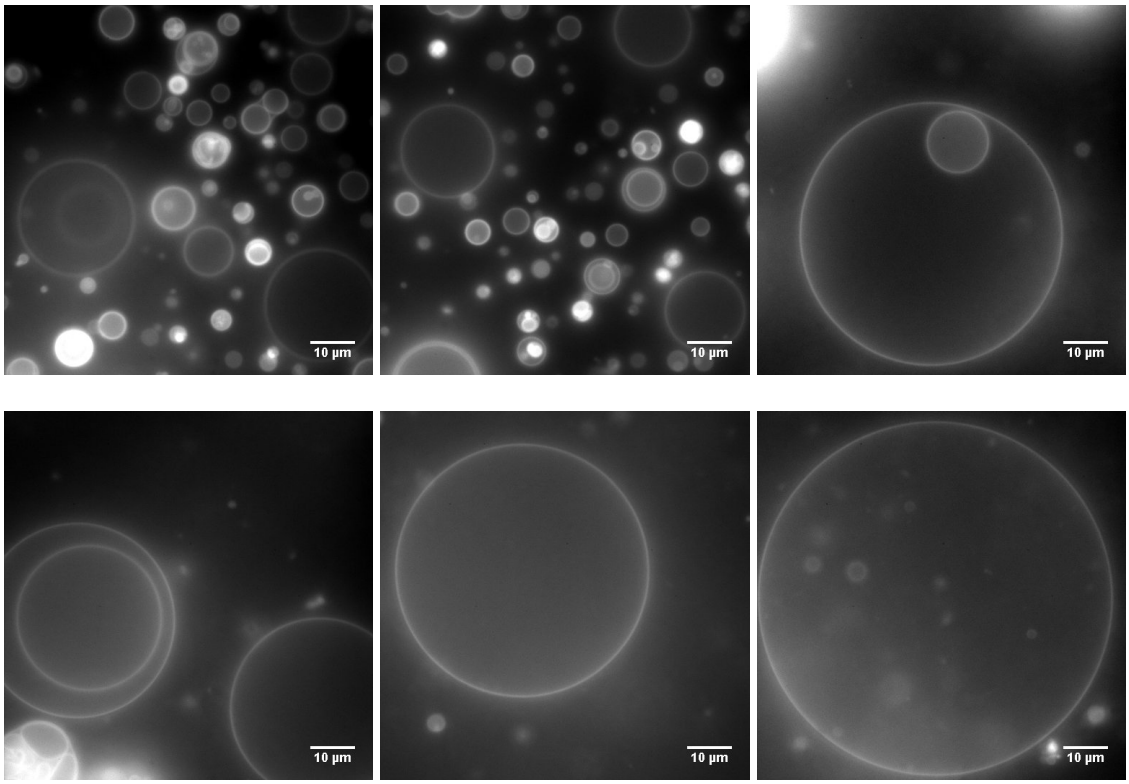


Figure S6. Giant unilamellar vesicles formed by gentle hydration of **1**. As is typical in gentle hydration procedures, some heterogeneity with respect to lamellarity and vesicle size is obseved.

Fluorescence Recovery after Photobleaching

Supported lipid bilayers (SLBs) for fluorescence recovery after photobleaching (FRAP) experiments were formed by fusion of GUVs to clean glass. A film of 100 nmol of **1** with 0.1 mol% Oregon Green DHPE was prepared in a glass vial by the same procedure as preparing lipid films for gentle hydration. GUVs were formed by gentle hydration as described in the previous section. A PDMS gasket with holes punched in it was bonded to plasma-cleaned #1.5 glass coverslip. The gasket was charged with 200 µL of a 1:1 mixture of the solution of GUVs and a hydration buffer (240 mM NaCl, 10 mM NaH_2PO_4, pH=7.4). After 10 minutes, the gasket was rinsed thoroughly with water to remove excess vesicles. FRAP was performed on the same inverted microscope that was used to visualize GUVs. An aperture was used to rapidly bleach an approximately 20-µm spot on the SLB. Fluorescence recovery was monitored by acquiring an image every 10 seconds, 30 seconds, or 1 minute until fully recovered (see Figure S6).

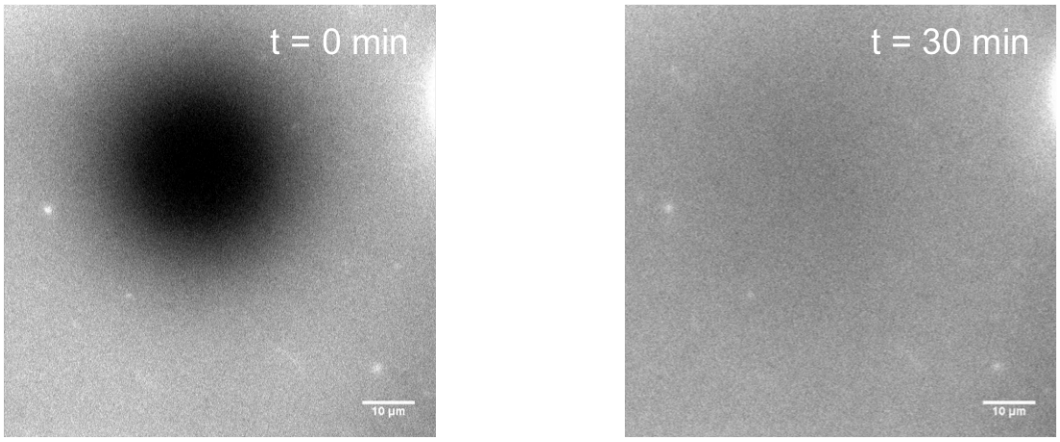
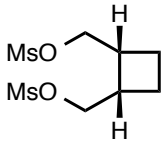


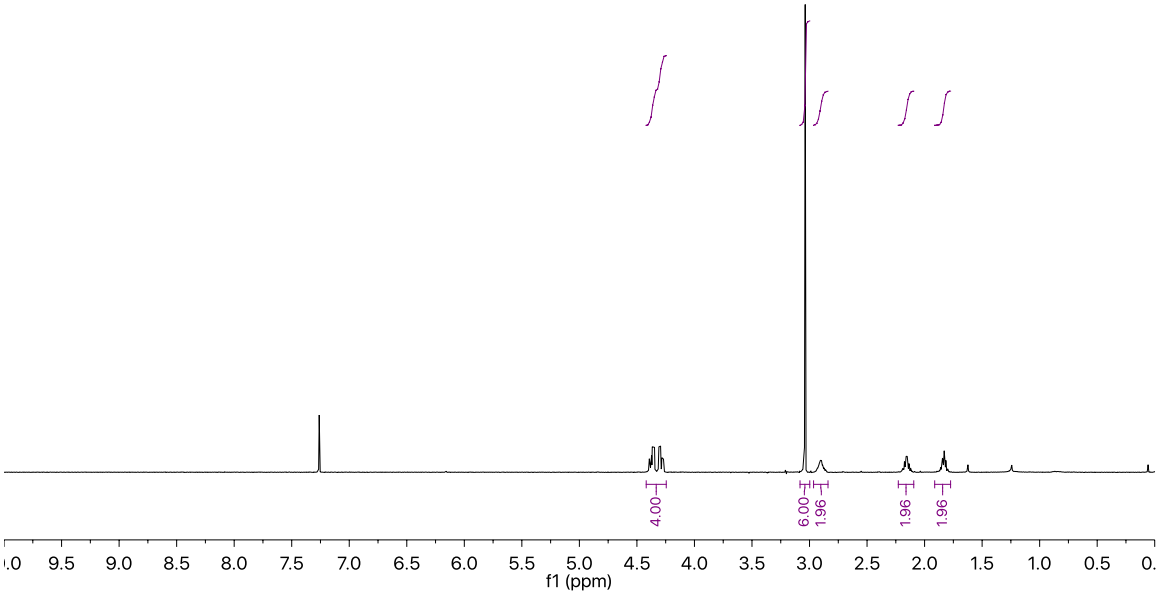
Figure S7. Fluorescence recovery after photobleaching a supported bilayer of **1**.

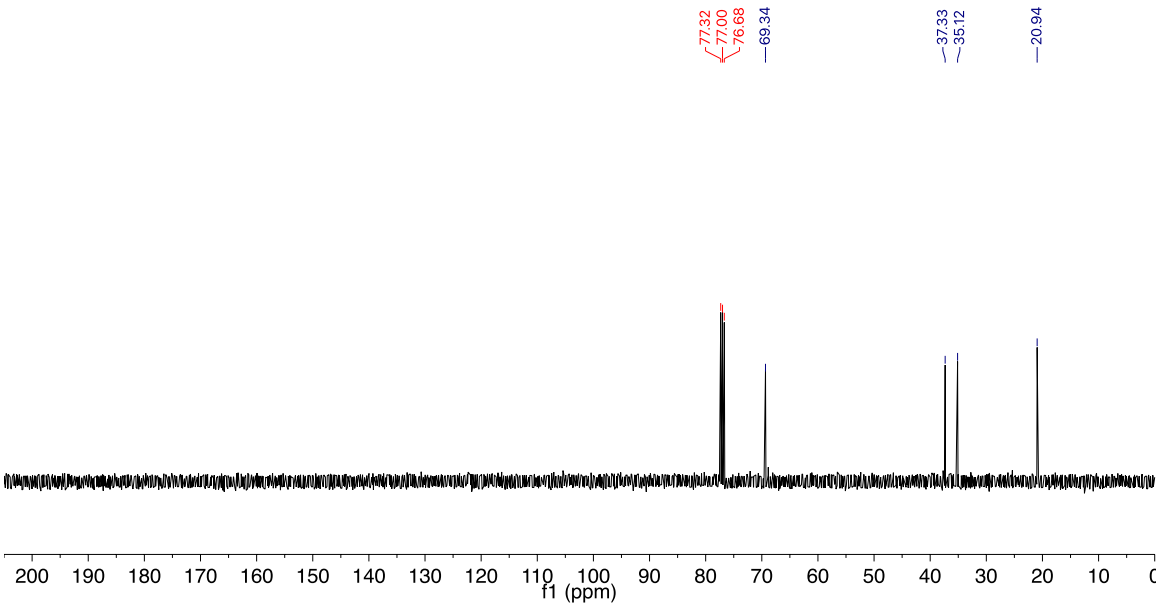
6. ^{1}H and ^{13}C NMR Spectra

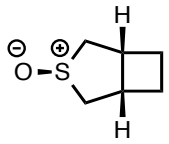
Top: ^{1}H NMR; bottom: ^{13}C NMR.



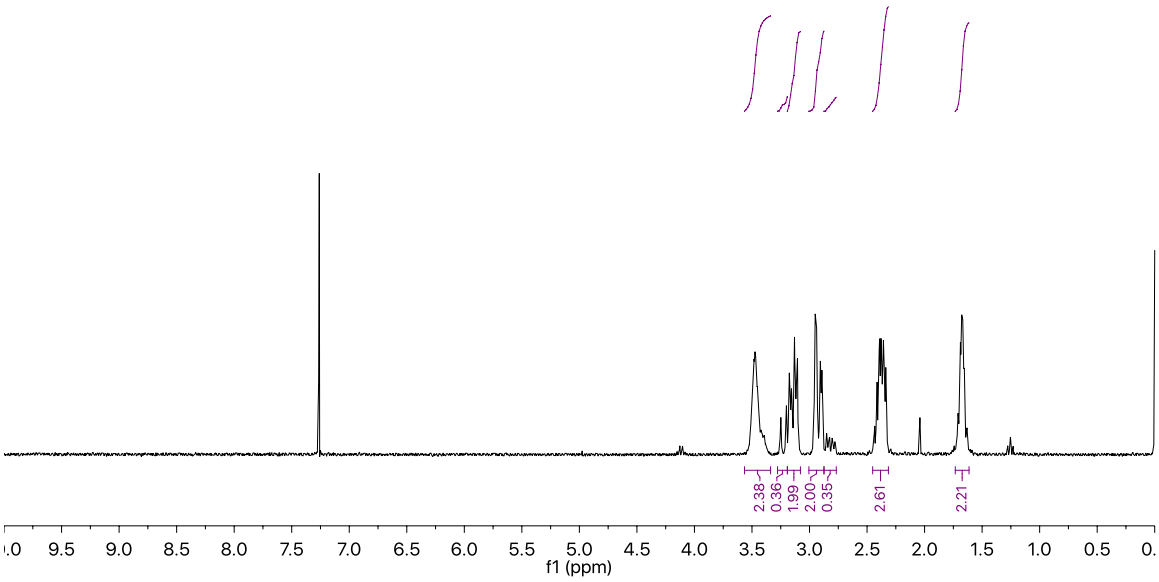
S2

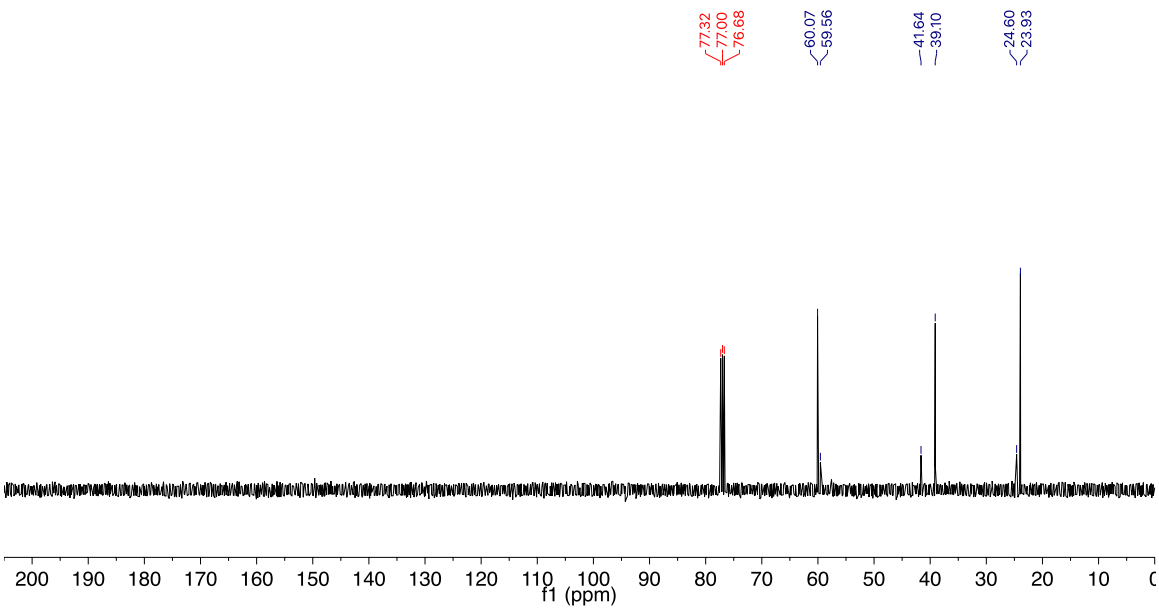


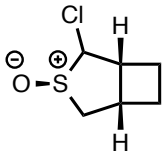




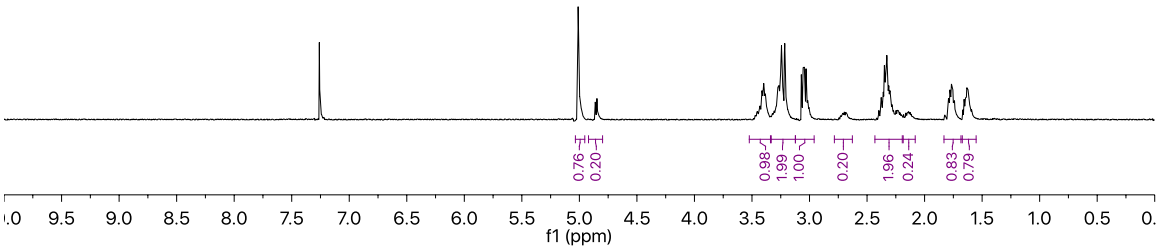
S3

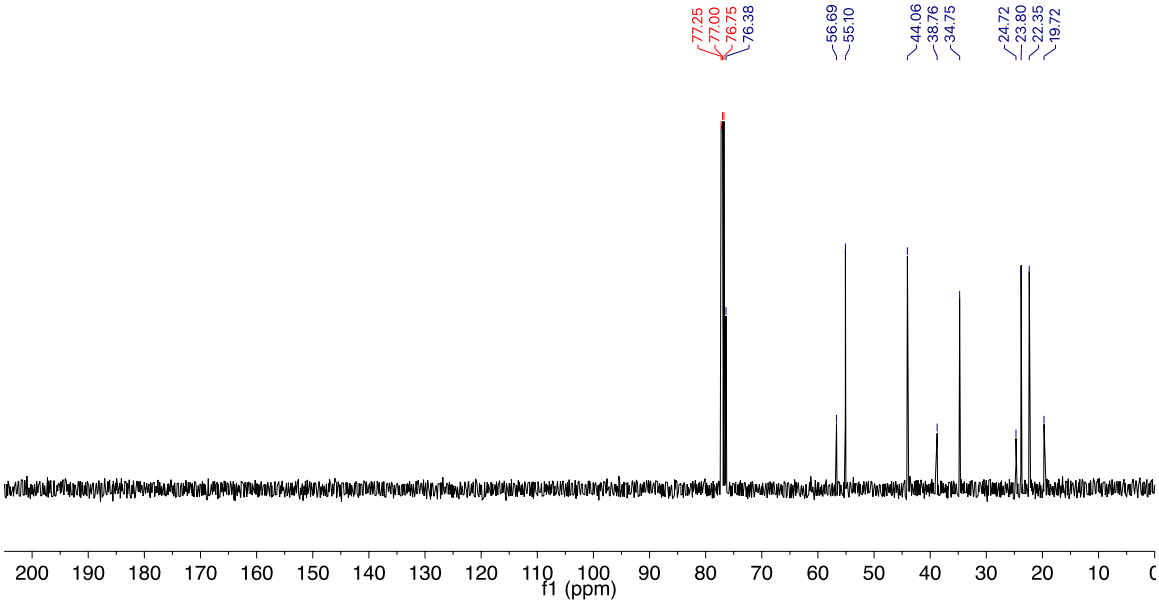

2.38
0.36
1.99
2.00
0.35
2.61
2.21
f1 (ppm)

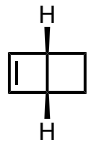

77.32
77.00
76.68
60.07
59.56
41.64
39.10
24.60
23.93
f1 (ppm)


Cl
H
O
S
H

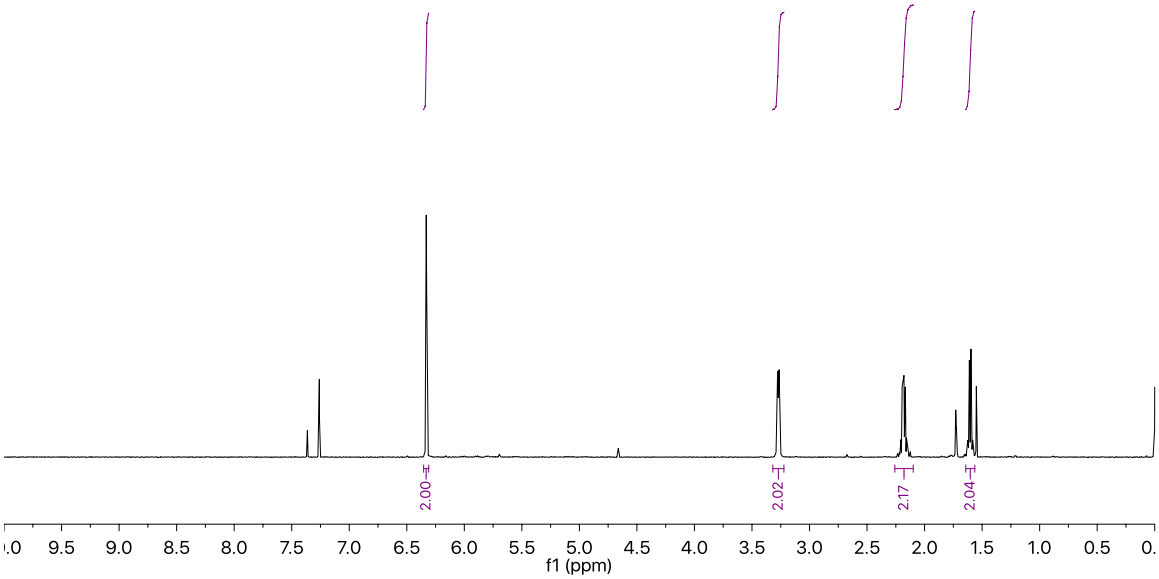
9

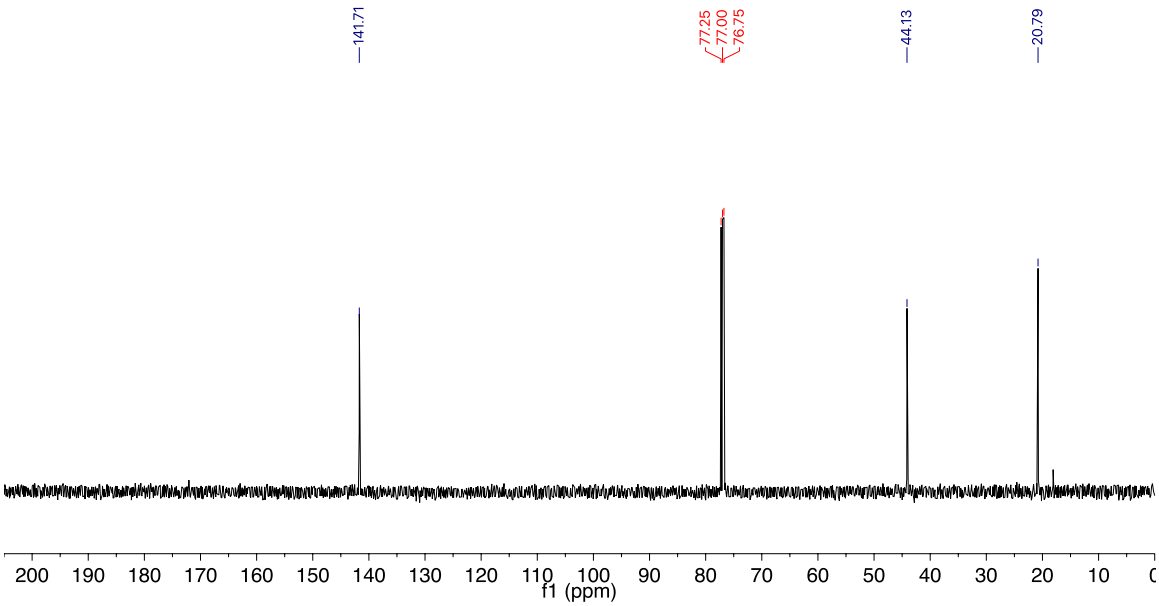

0.76
0.20
0.98
1.99
1.00
0.20
1.96
0.24
0.83
0.79
f1 (ppm)

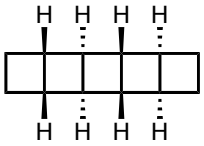

77.25
77.00
76.75
76.38
56.69
55.10
44.06
38.76
34.75
24.72
23.80
22.35
19.72
f1 (ppm)



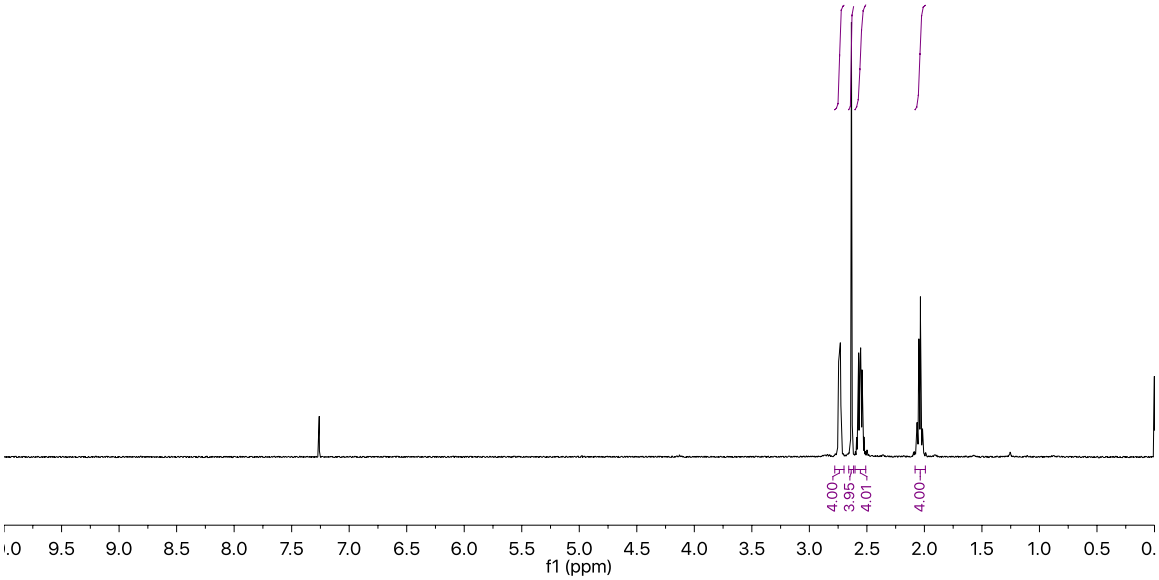
5

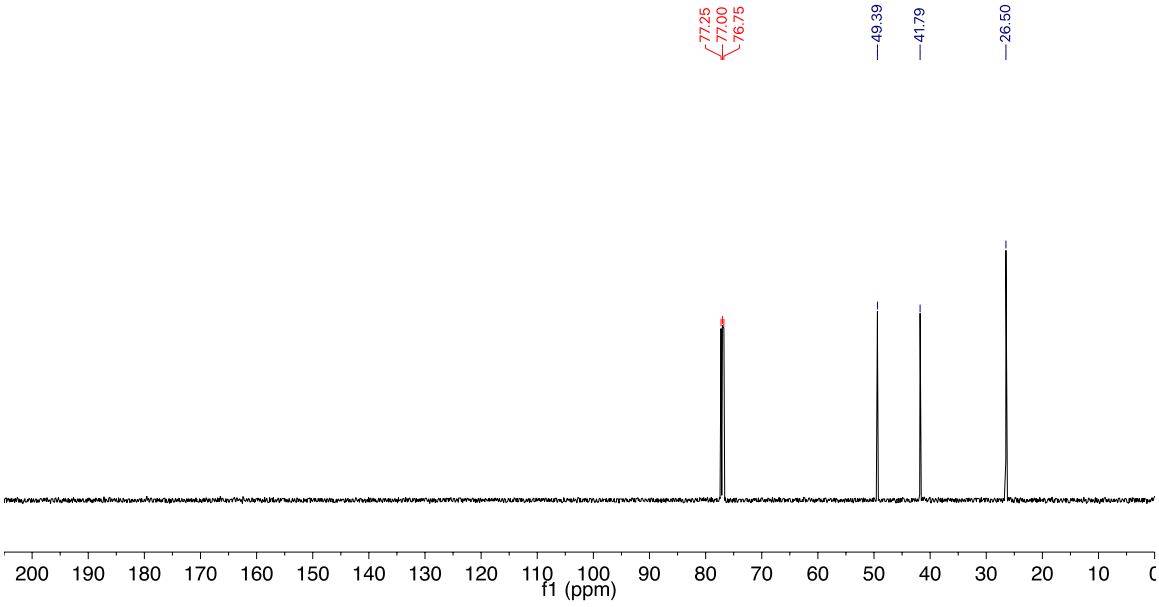


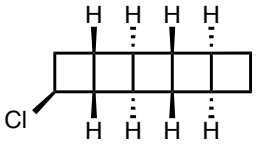



H H H H
H H H H

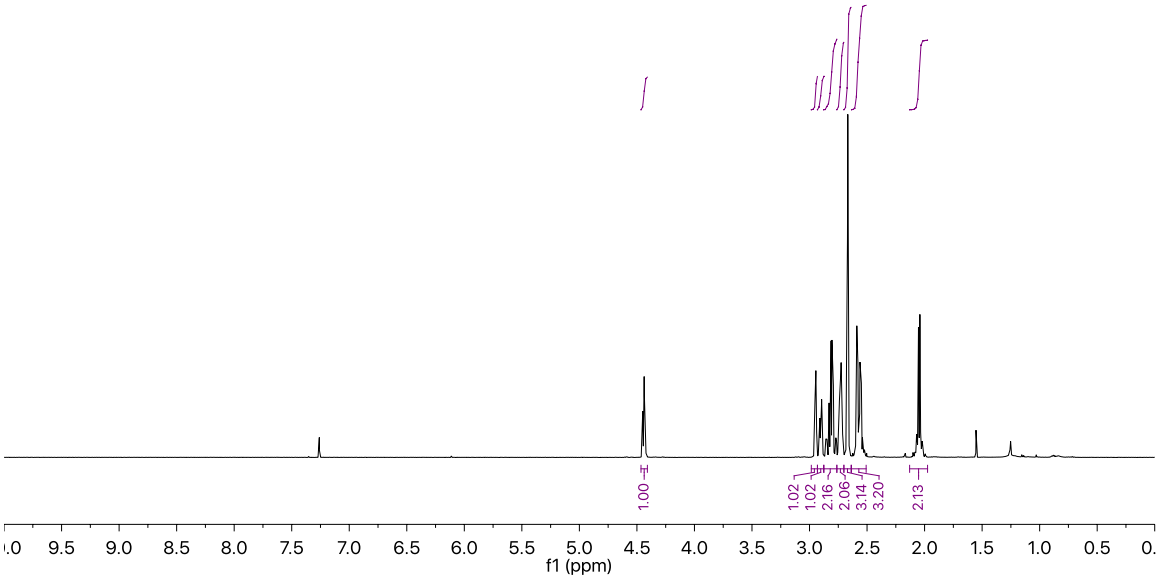
4

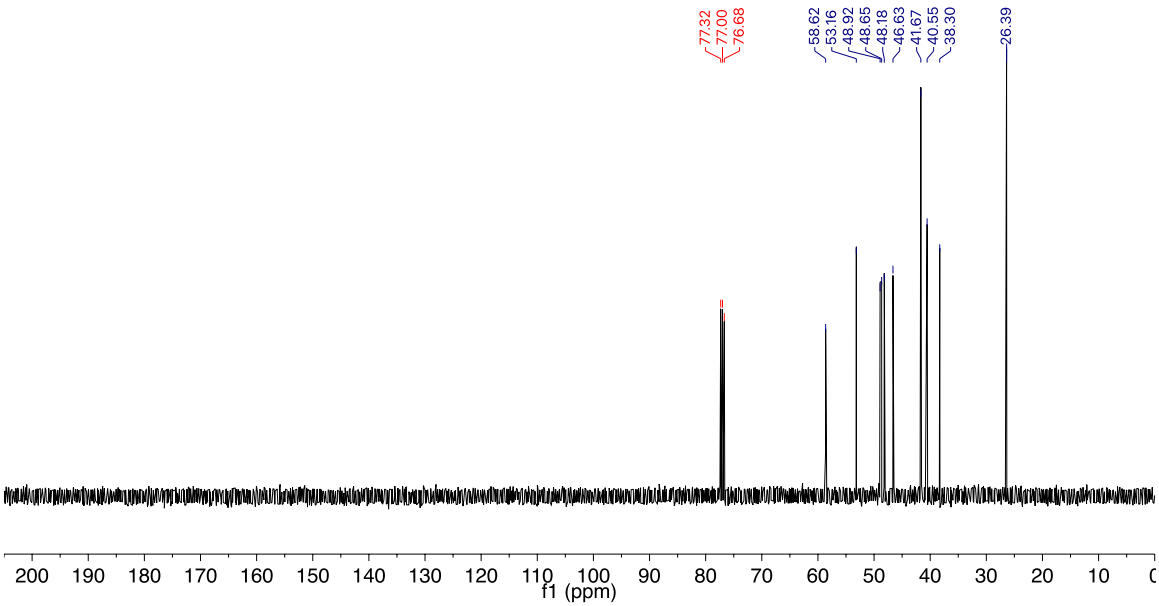

4.00
3.95
4.01
4.00
f1 (ppm)

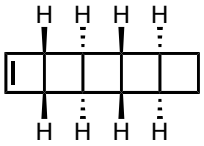

77.25
77.00
76.75
49.39
41.79
26.50
f1 (ppm)


H H H H
Cl
H H H H

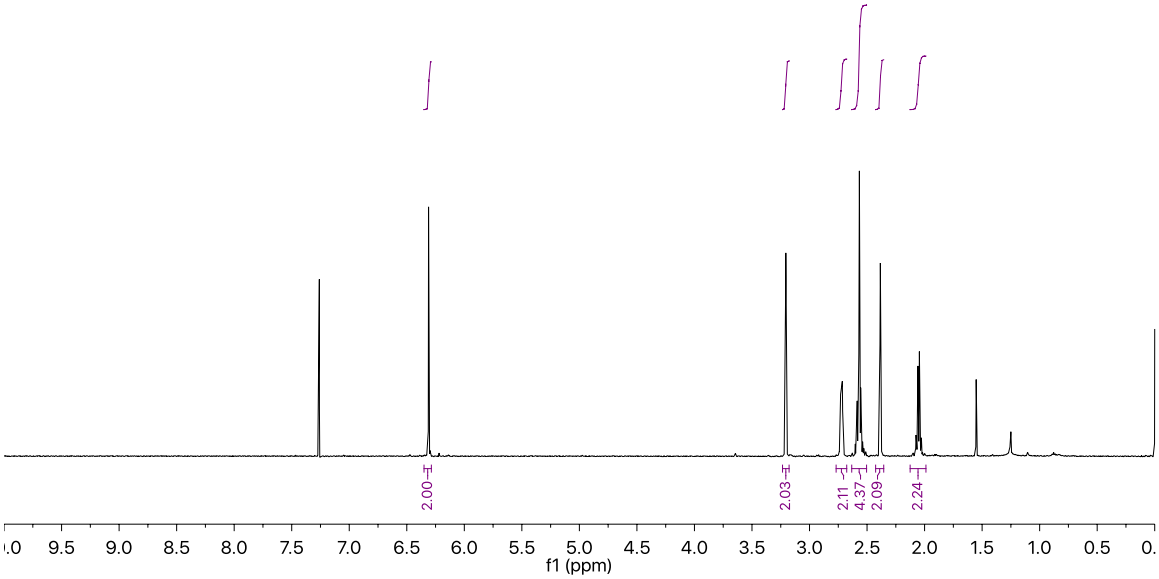
(+/–)-**S4**

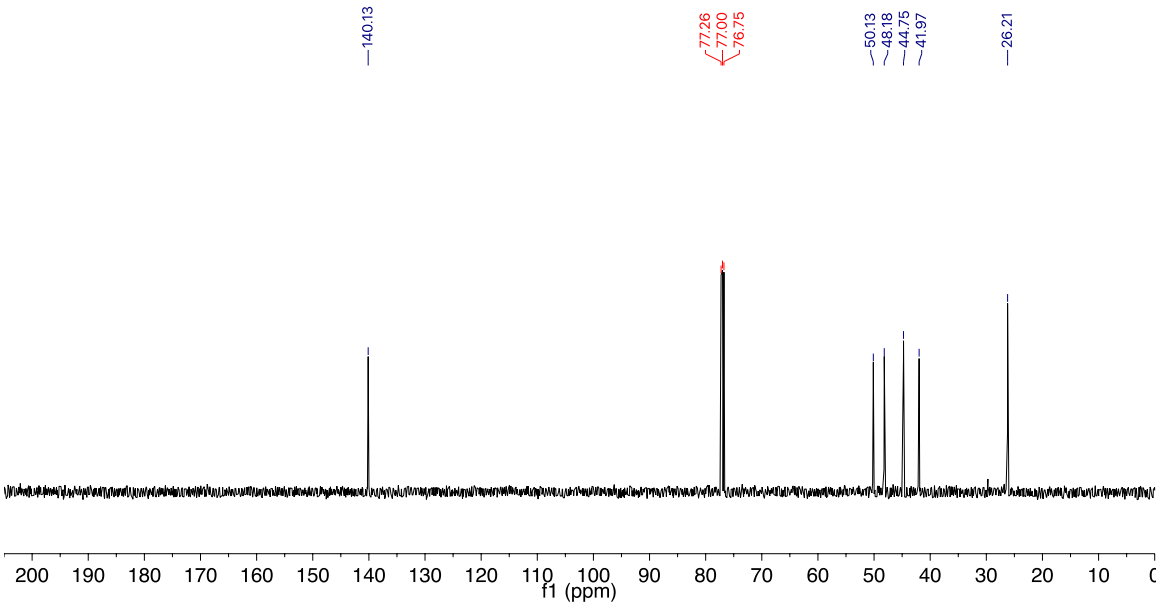

1.00
1.02
1.02
2.16
2.06
3.14
3.20
2.13
f1 (ppm)

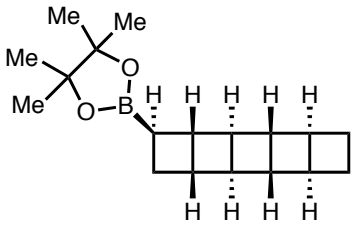

77.32
77.00
76.68
58.62
53.16
48.92
48.65
48.18
46.63
41.67
40.55
38.30
26.39
f1 (ppm)



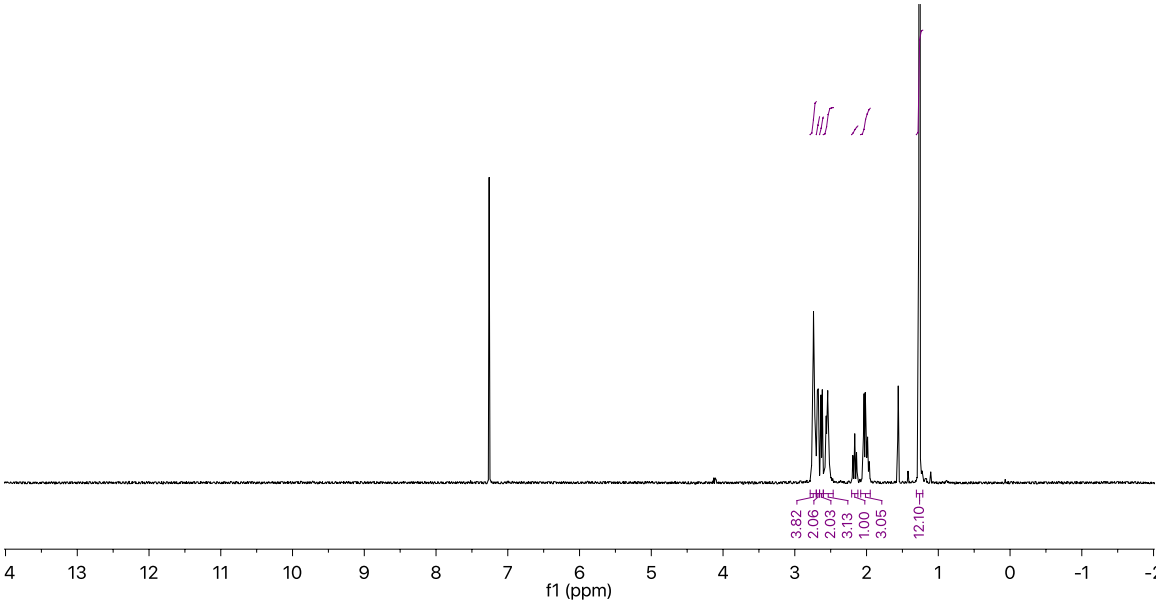
12

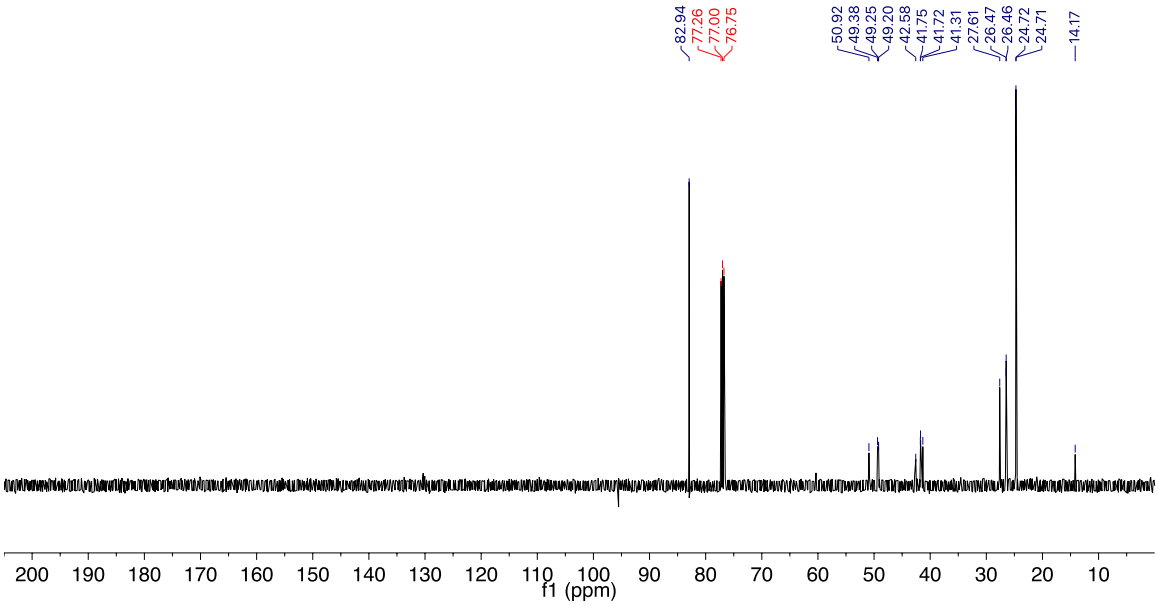

2.00
2.03
2.11
4.37
2.09
2.24
f1 (ppm)

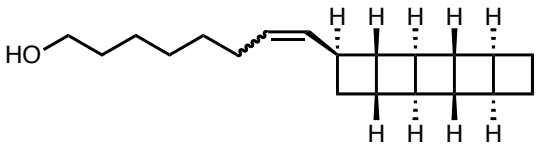

140.13
77.26
77.00
76.75
50.13
48.18
44.75
41.97
26.21
f1 (ppm)


Me
Me
Me
Me
O
O
B
H
H
H
H
H
H
H
H
H

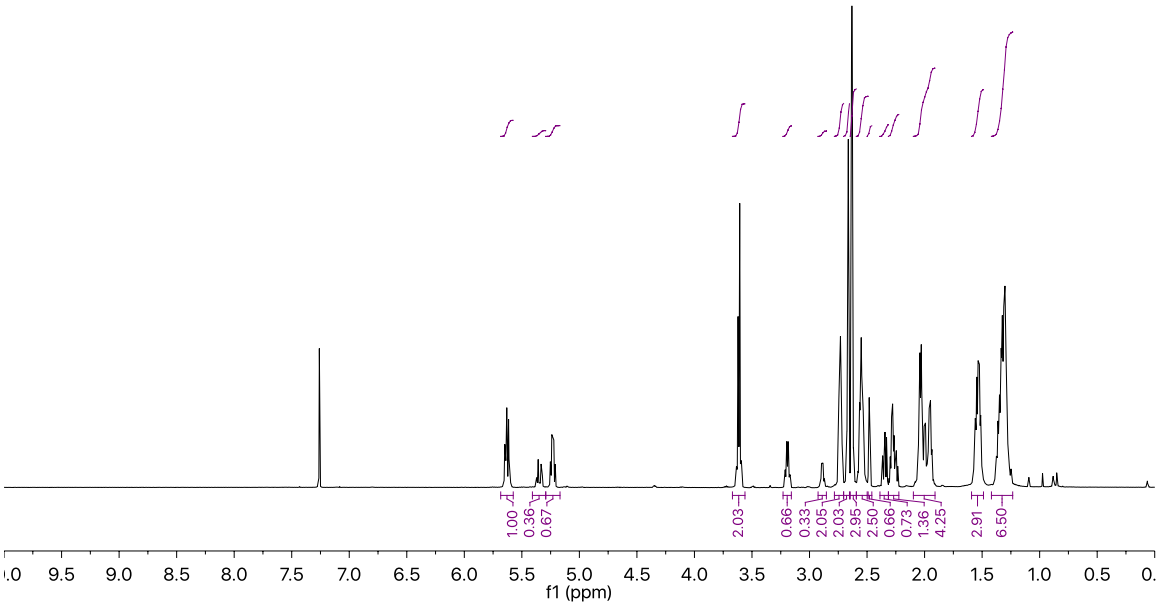
13

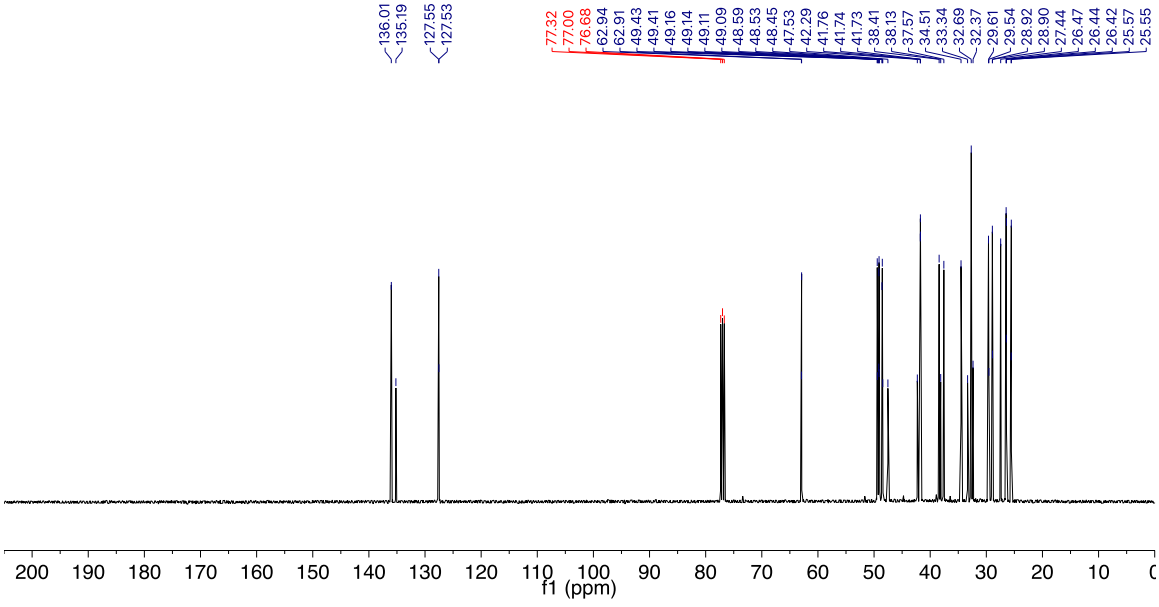

3.82
2.06
2.03
3.13
1.00
3.05
12.10
f1 (ppm)

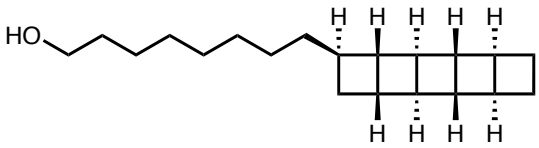

82.94
77.26
77.00
76.75
50.92
49.38
49.25
49.20
42.58
41.75
41.72
41.31
27.61
26.47
26.46
24.72
24.71
14.17
f1 (ppm)


HO
H H H H H
H H H H

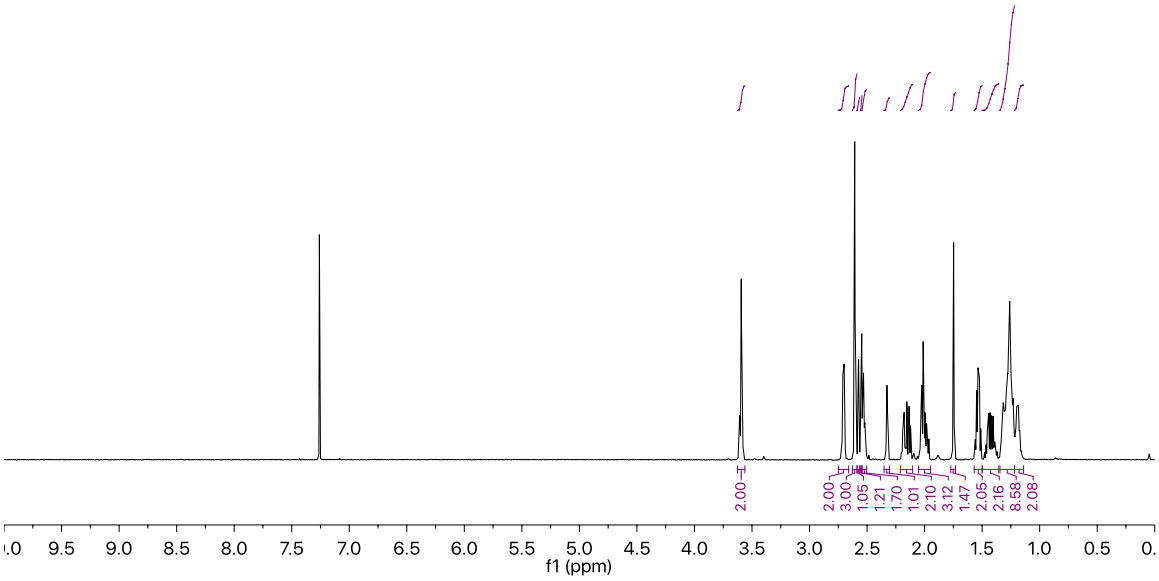
14

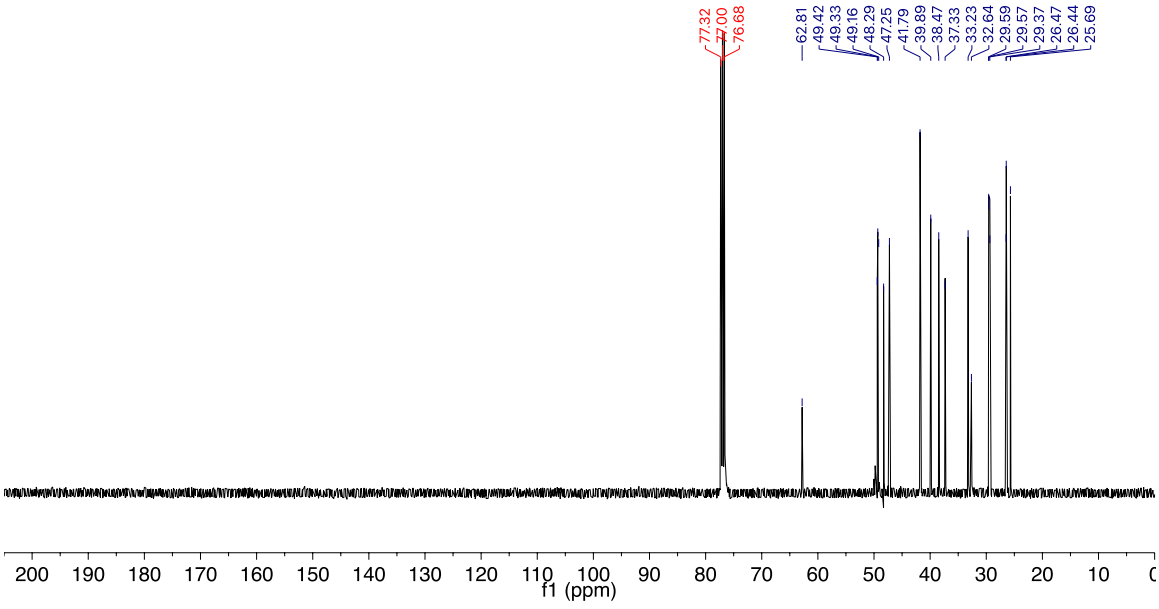

1.00
0.36
0.67
2.03
0.66
0.33
2.05
2.03
2.95
2.50
0.66
0.73
1.36
4.25
2.91
6.50
f1 (ppm)

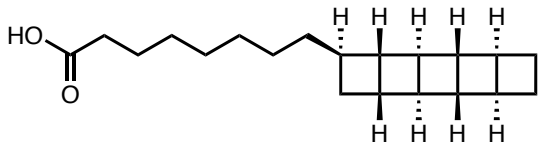

136.01
135.19
127.55
127.53
77.32
77.00
76.68
62.94
62.91
49.43
49.41
49.16
49.14
49.11
49.09
48.59
48.53
48.45
47.53
42.29
41.76
41.74
41.73
38.41
38.13
37.57
34.51
33.34
32.69
32.37
29.61
29.54
28.92
28.90
27.44
26.47
26.44
26.42
25.57
25.55
f1 (ppm)


HO
H H H H H
H H H H

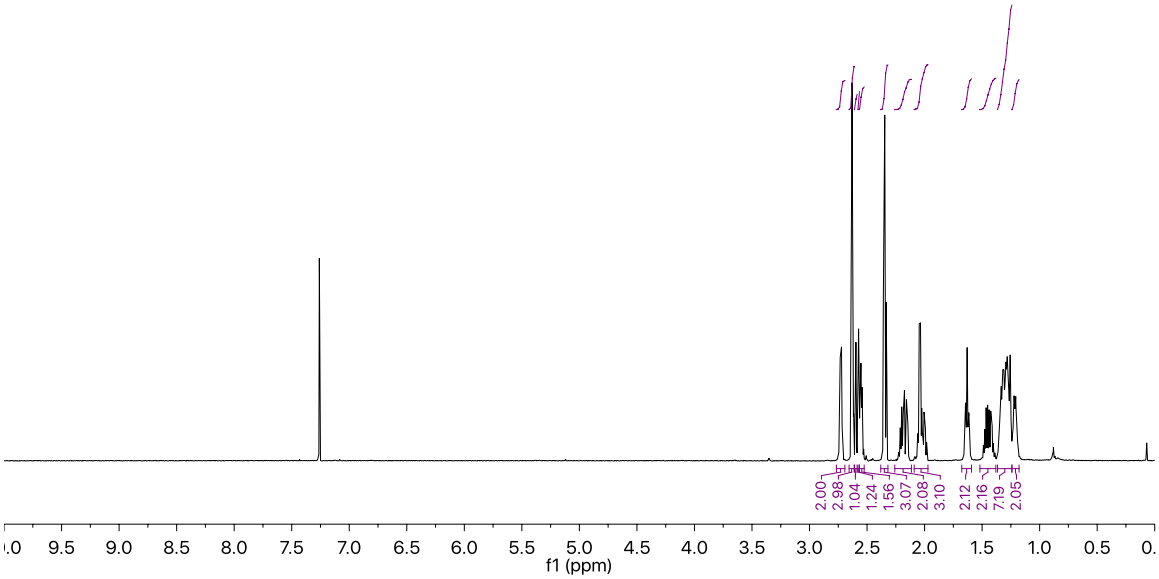
S6

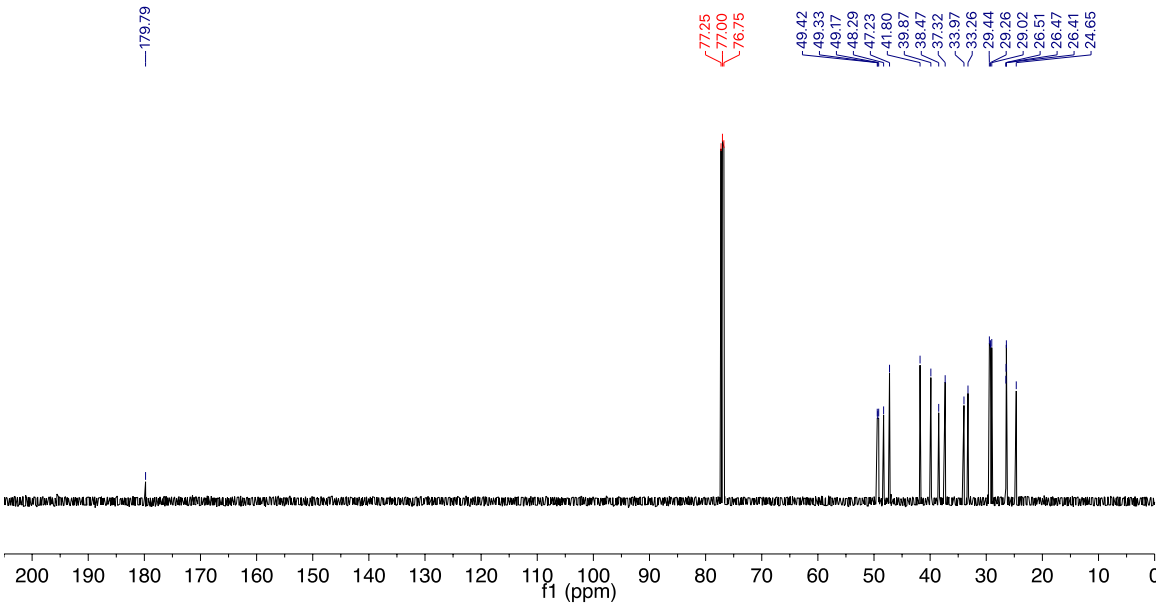

2.00
2.00
3.00
1.05
1.21
1.70
1.01
2.10
3.12
1.47
2.05
2.16
8.58
2.08
f1 (ppm)

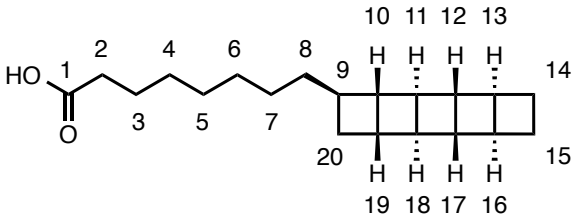

77.32
77.00
76.68
62.81
49.42
49.33
49.16
48.29
47.25
41.79
39.89
38.47
37.33
33.23
32.64
29.59
29.57
29.37
26.47
26.44
25.69
f1 (ppm)


HO
O
H H H H H
H H H H

2


2.00
2.98
1.04
1.24
1.56
3.07
2.08
3.10
2.12
2.16
7.19
2.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

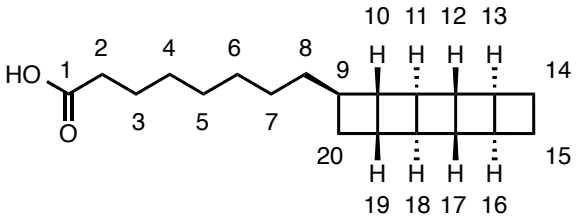

179.79
77.25
77.00
76.75
49.42
49.33
49.17
48.29
47.23
41.80
39.87
38.47
37.32
33.97
33.26
29.44
29.26
29.02
26.51
26.47
26.41
24.65
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)



2

Signal	This work	Corey
13, 16	2.73 (bd, J = 6.7 Hz, 2H)	2.73 (bd, 2H)
12, 17	2.63 (bs, 2H)	2.62 (bs, 2H)
19	2.63 (m, 1H)	2.62 (m, 1H)
18	2.60 (s, 1H)	2.59 (bs, 1H)
11	2.57 (d, J = 2.9 Hz, 1H)	2.57 (bs, 1H)
14α, 15α	2.57 – 2.52 (m, 2H)	2.58 – 2.52 (m, 2H)
2, 10	2.35 (app. t, J = 7.5 Hz, 3H)	2.35 (app. bt, J = 7.3 Hz, 3H)
20α	2.26 – 2.11 (m, 2H)	2.20 (m, 1H)
9		2.18 (m, 1H)
14β, 15β	2.09 – 1.97 (m, 3H)	2.04 (m, 2H)
20β		2.00 (m, 1H)
3	1.63 (app. p, J = 7.4 Hz, 2H)	1.63 (app. p, J = 7.4 Hz, 2H)
8	1.52 – 1.38 (m, 2H)	1.50 – 1.38 (m, 2H)
4, 5, 6	1.37 – 1.24 (m, 6H)	1.36 – 1.26 (6H)
7	1.24 – 1.18 (m, 2H)	1.22 (m 2H)

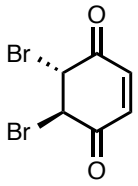
Table S1. ^{1}H NMR comparison of **2** from this work (600 MHz, $CDCl_3$) and as reported (500 MHz, $CDCl_3$) by Corey;[6] signals as assigned by Sinninghe Damsté.[9]



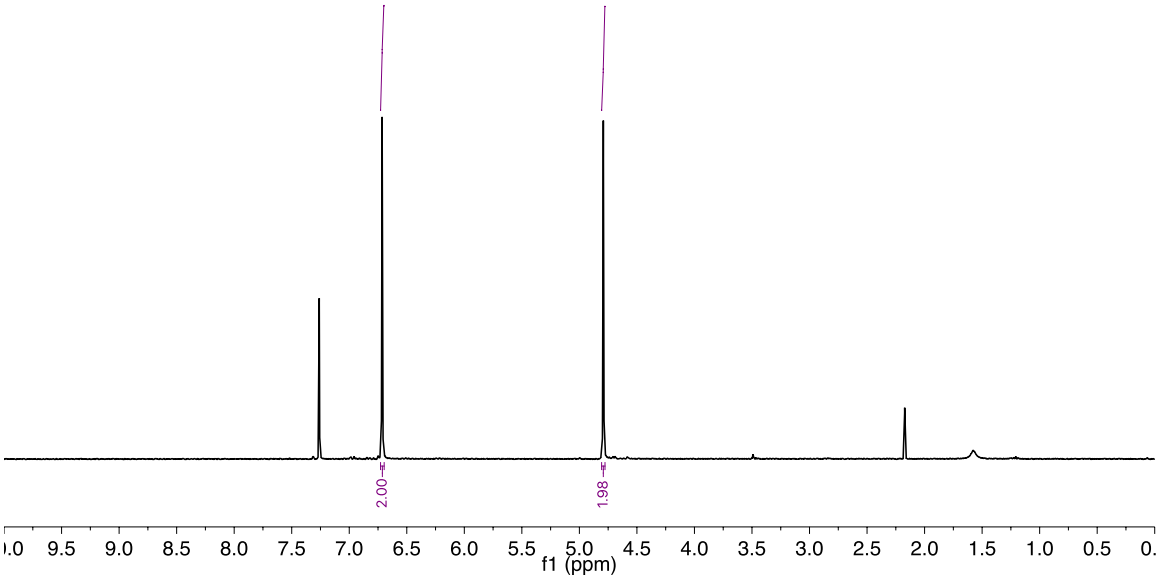
2

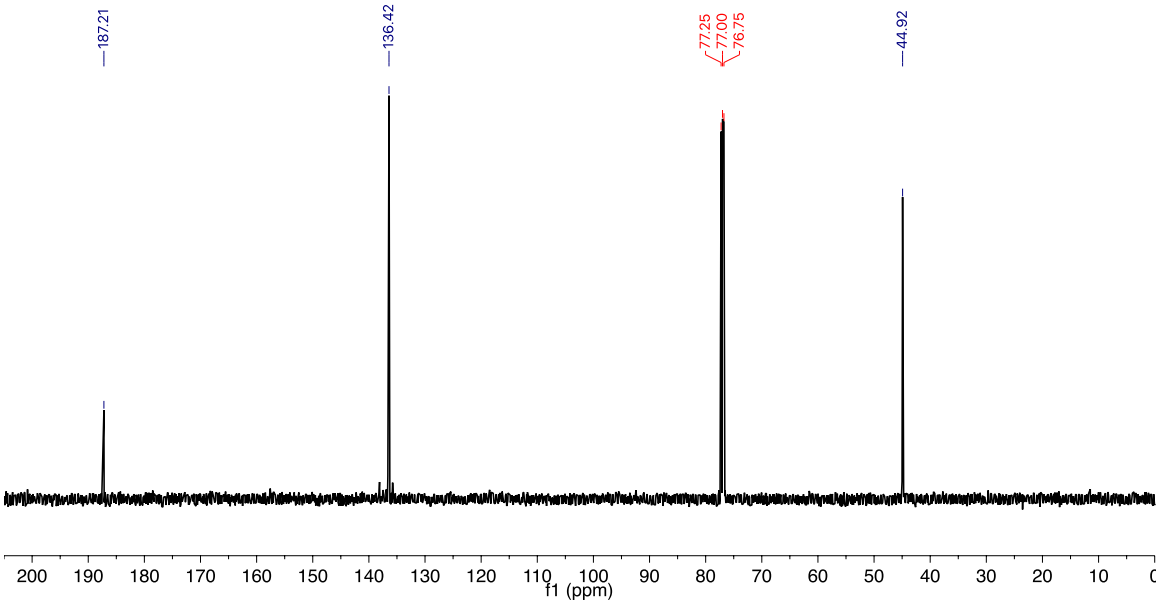
Signal	This work	Corey
1	179.79	179.7
12/17	49.42	49.4
12/17	49.33	49.3
18	49.17	49.2
11	48.29	48.3
10	47.23	47.3
16, 13	41.80	41.8
9	39.87	39.9
19	38.47	38.5
8	37.32	37.3
2	33.97	34.0
20	33.26	33.3
4/5/6	29.44	29.4
4/5/6	29.26	29.3
4/5/6	29.02	29.0
14/15	26.51	26.5
14/15	26.47	26.5
7	26.41	26.4
3	24.65	24.7

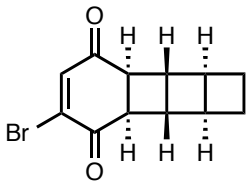
Table S2. ^{13}C NMR comparison of **2** from this work (600 MHz, $CDCl_3$) and as reported (500 MHz, $CDCl_3$) by Corey;[6] signals as assigned by Sinninghe Damsté.[9]



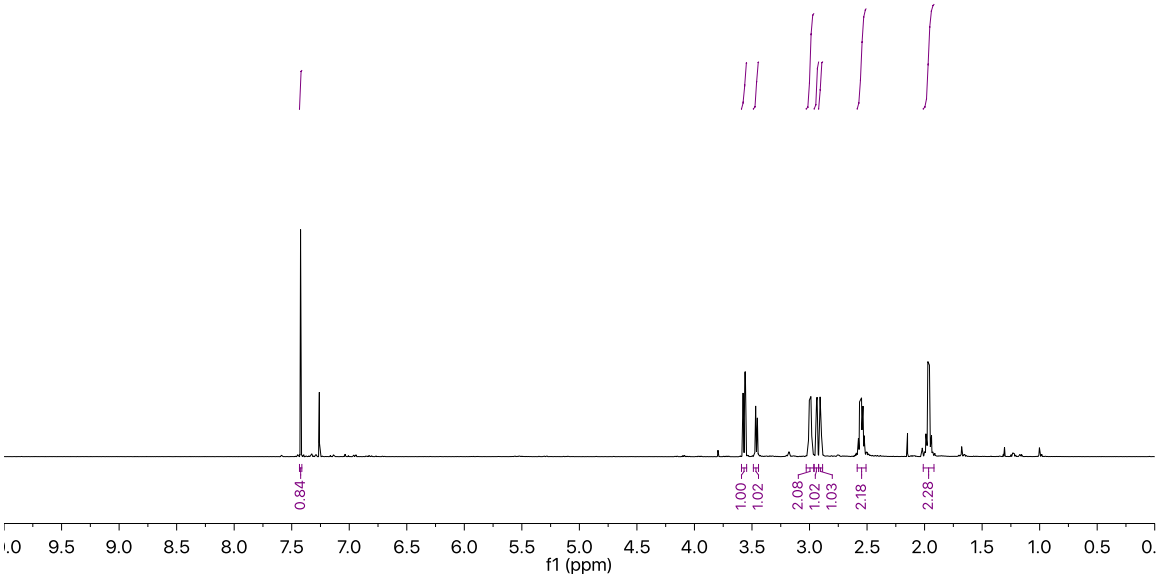
16

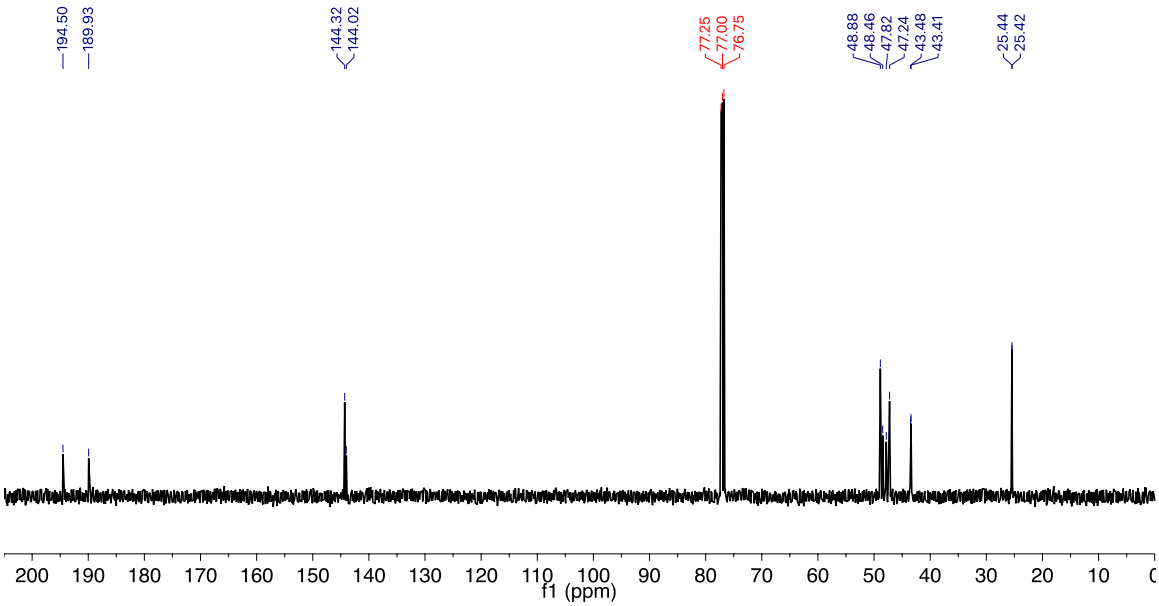


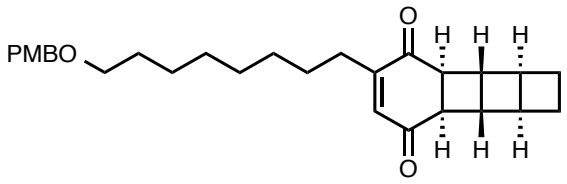



O
H
H
H
Br
H
H
H
O

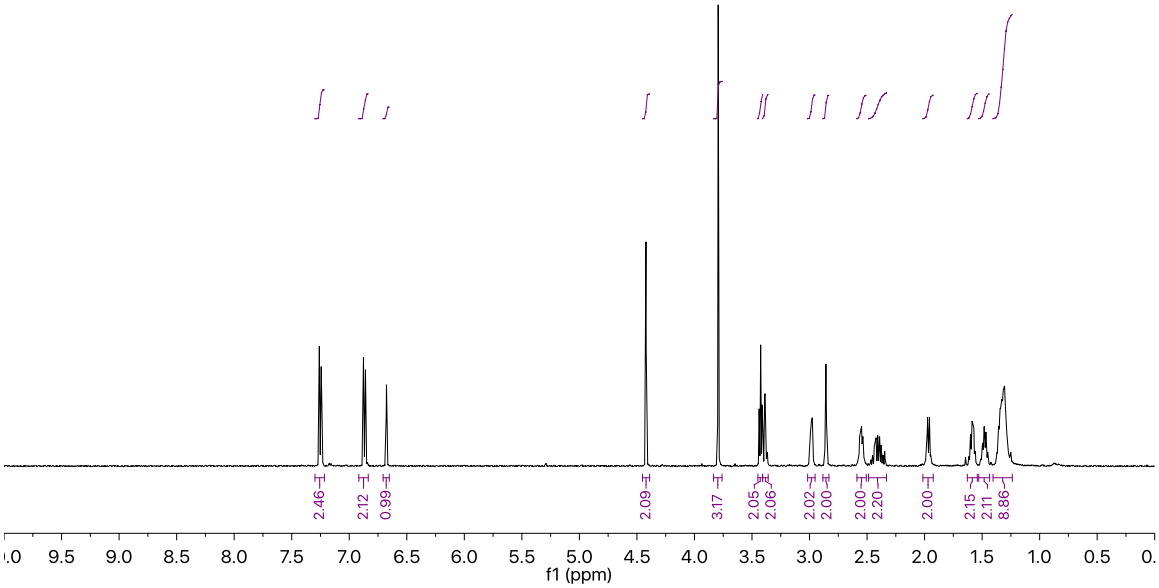
18

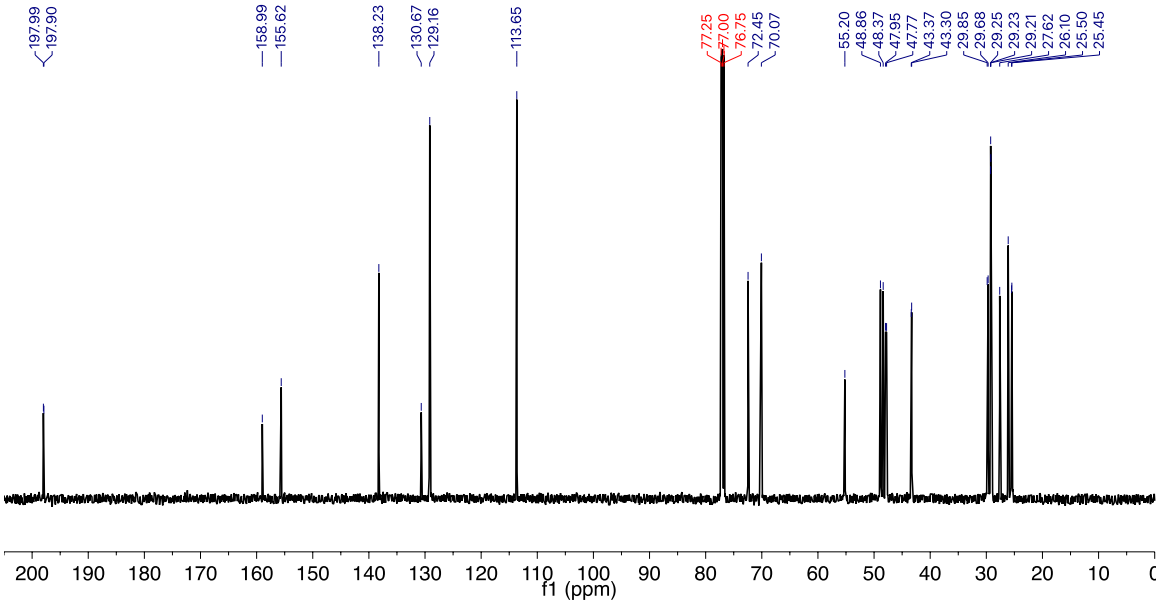

0.84
1.00
1.02
2.08
1.02
1.03
2.18
2.28
f1 (ppm)

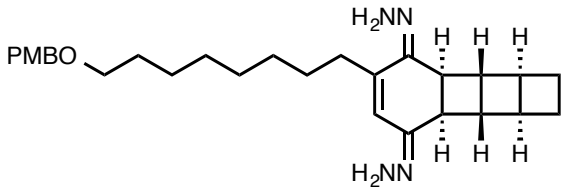

194.50
189.93
144.32
144.02
77.25
77.00
76.75
48.88
48.46
47.82
47.24
43.48
43.41
25.44
25.42
f1 (ppm)


PMBO
O
H
H
H
H
H
H
O

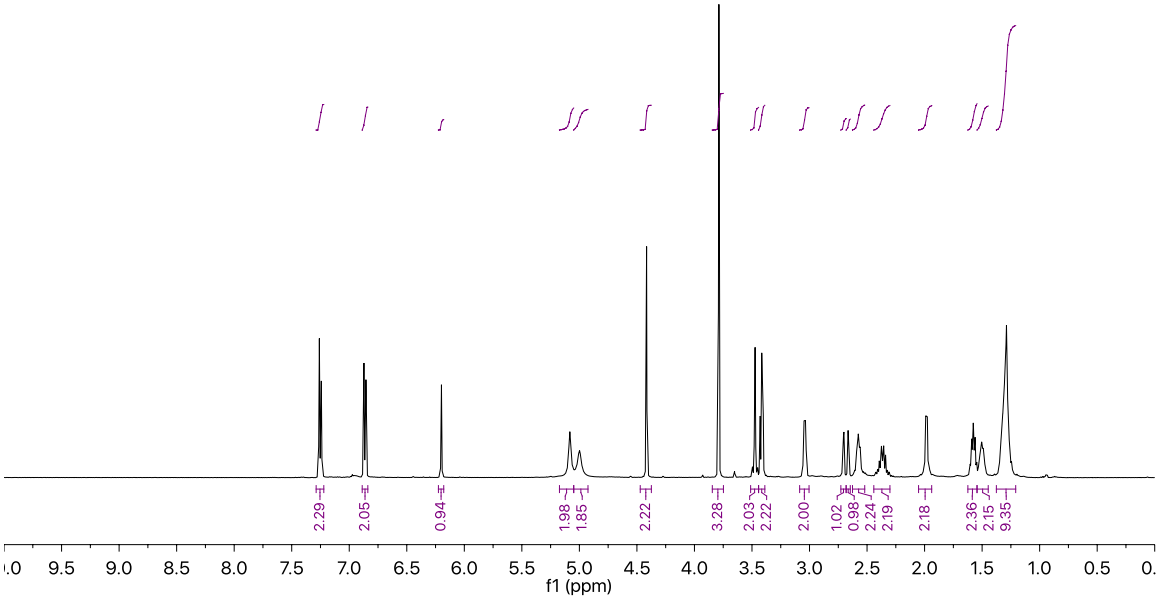
19

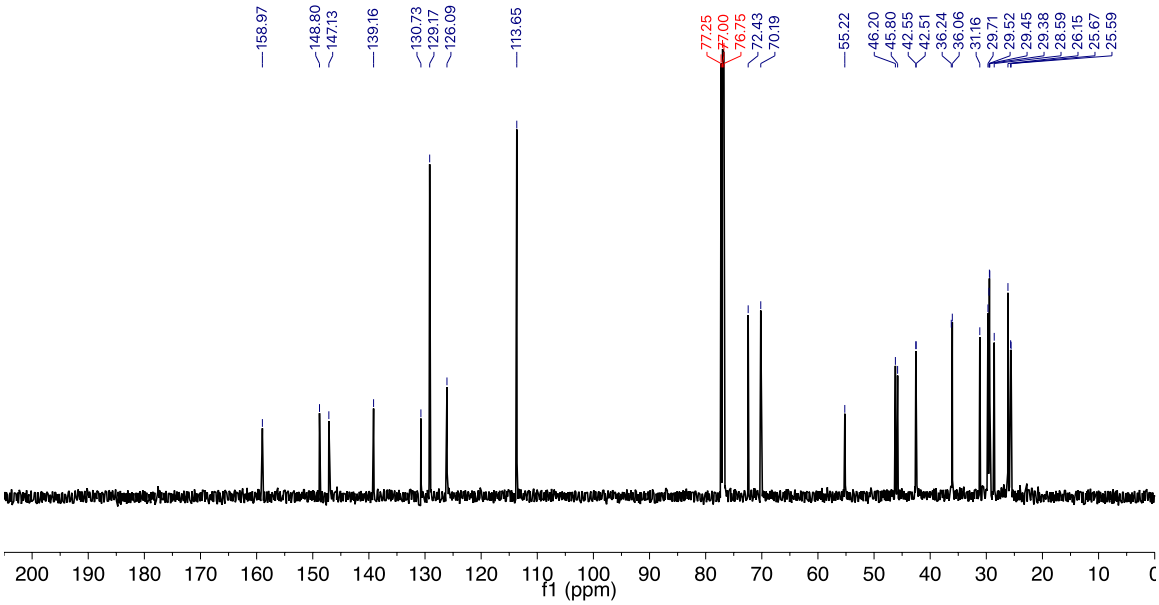

2.46
2.12
0.99
2.09
3.17
2.05
2.06
2.02
2.00
2.00
2.20
2.00
2.15
2.11
8.86
f1 (ppm)

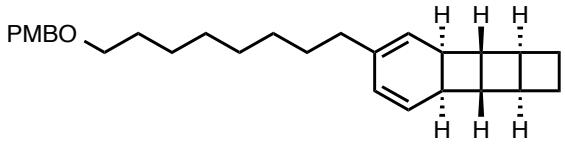

197.99
197.90
158.99
155.62
138.23
130.67
129.16
113.65
77.25
77.00
76.75
72.45
70.07
55.20
48.86
48.37
47.95
47.77
43.37
43.30
29.85
29.68
29.25
29.23
29.21
27.62
26.10
25.50
25.45
f1 (ppm)


PMBO
H2NN
H2NN
H
H
H
H
H
H

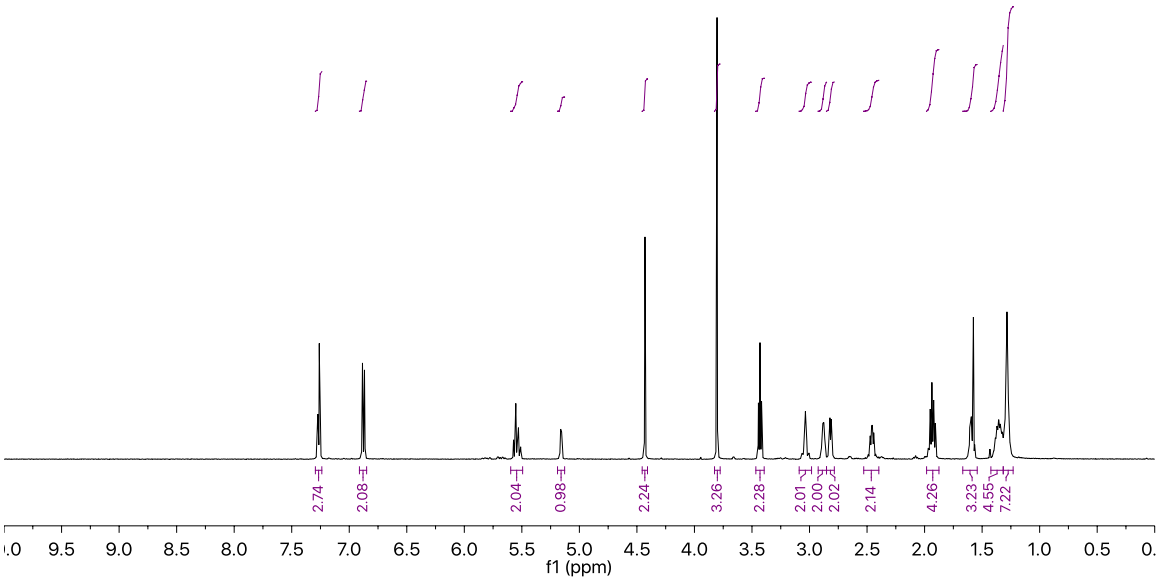
21

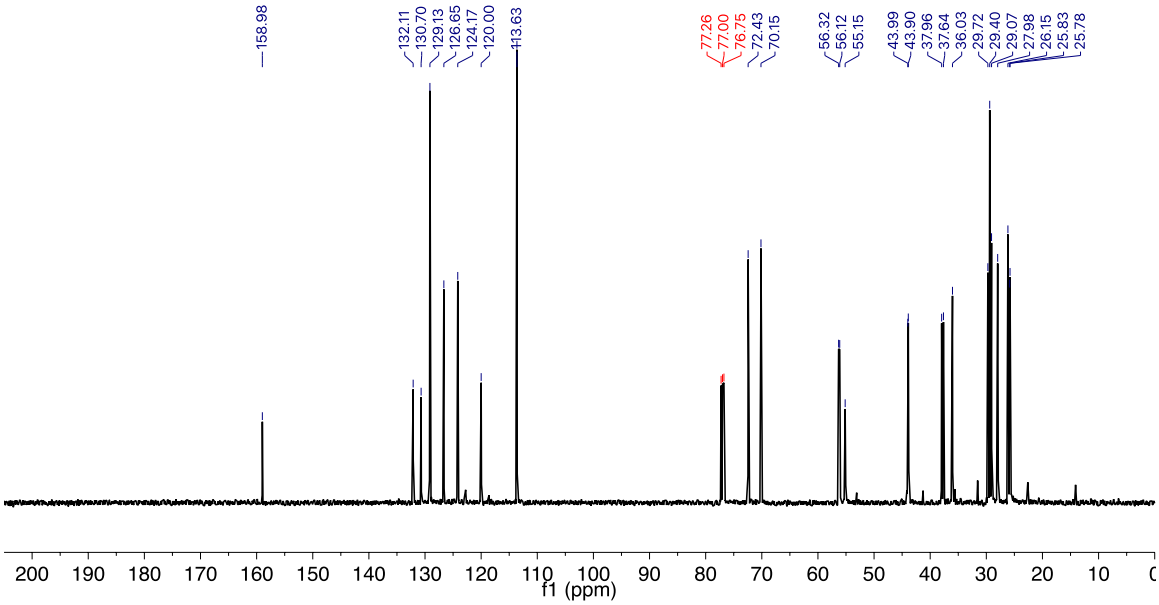

2.29
2.05
0.94
1.98
1.85
2.22
3.28
2.03
2.22
2.00
1.02
0.98
2.24
2.19
2.18
2.36
2.15
9.35
f1 (ppm)

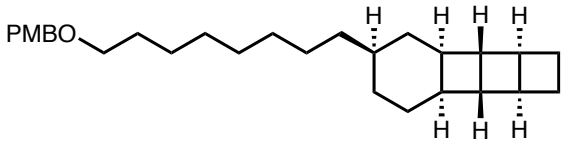

158.97
148.80
147.13
139.16
130.73
129.17
126.09
113.65
77.25
77.00
76.75
72.43
70.19
55.22
46.20
45.80
42.55
42.51
36.24
36.06
31.16
29.71
29.52
29.45
29.38
28.59
26.15
25.67
25.59
f1 (ppm)


PMBO
H
H
H
H
H
H

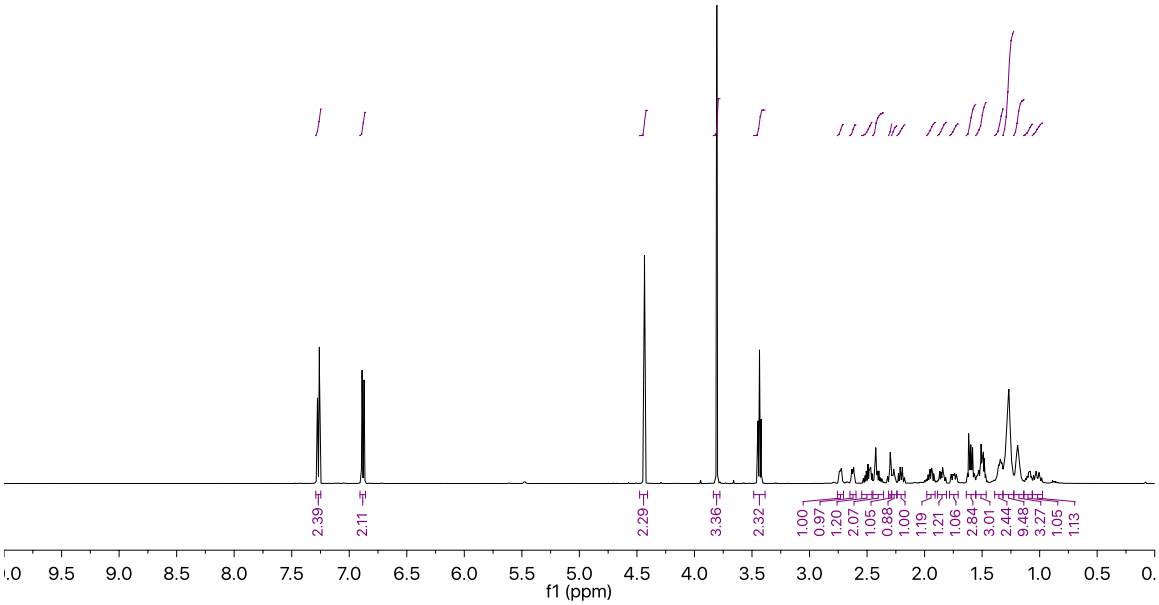
22

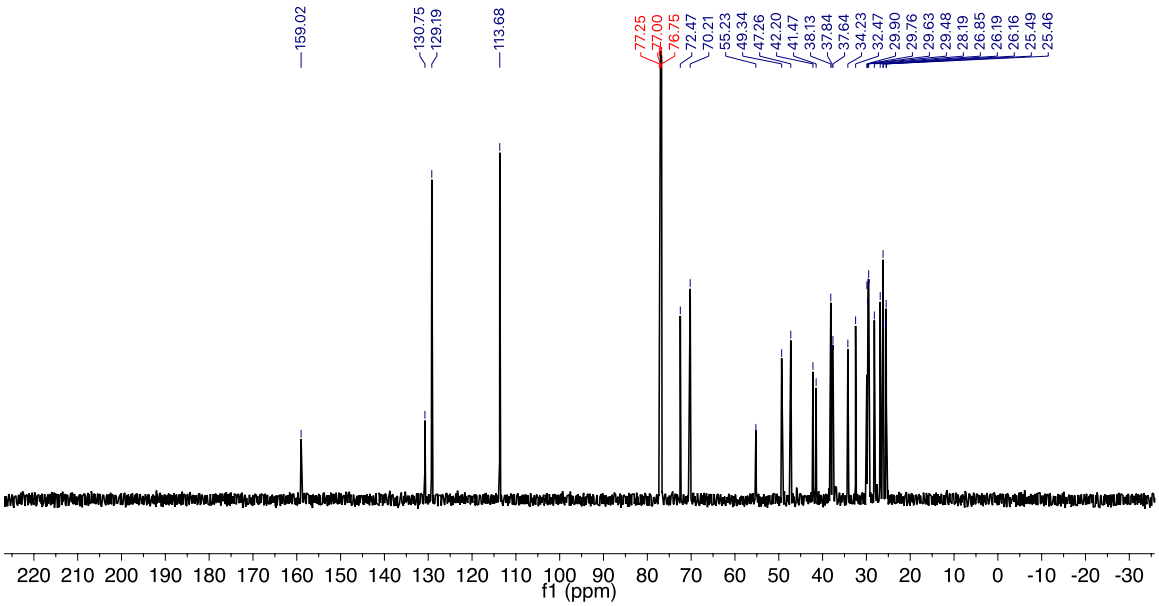

2.74
2.08
2.04
0.98
2.24
3.26
2.28
2.01
2.00
2.02
2.14
4.26
3.23
4.55
7.22
f1 (ppm)

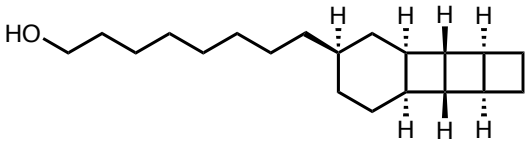

158.98
132.11
130.70
129.13
126.65
124.17
120.00
113.63
77.26
77.00
76.75
72.43
70.15
56.32
56.12
55.15
43.99
43.90
37.96
37.64
36.03
29.72
29.40
29.07
27.98
26.15
25.83
25.78
f1 (ppm)


PMBO
H
H
H
H
H
H
H

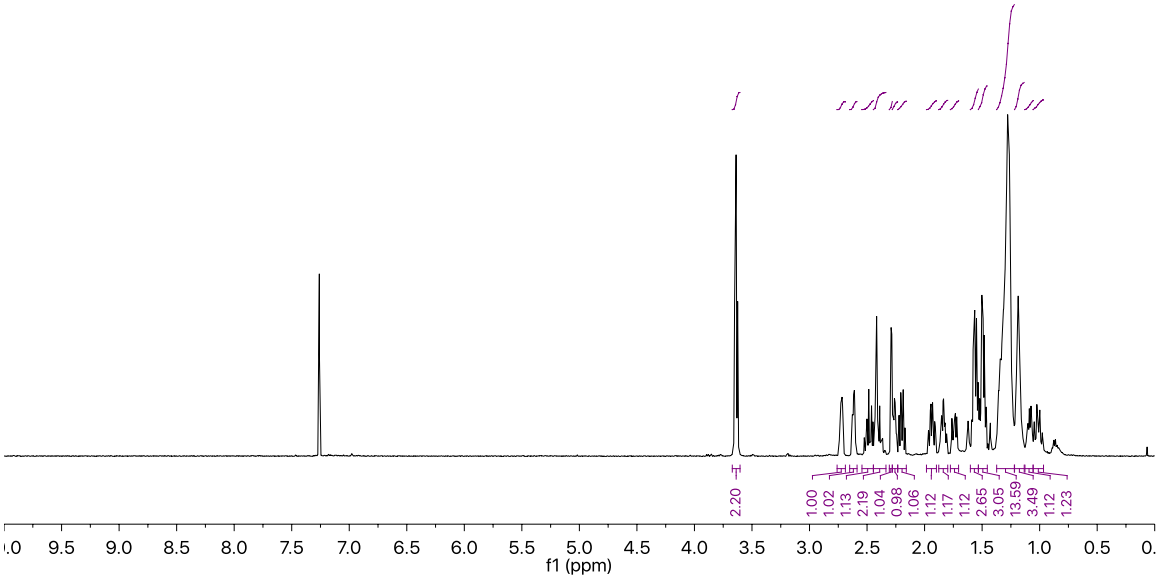
S8

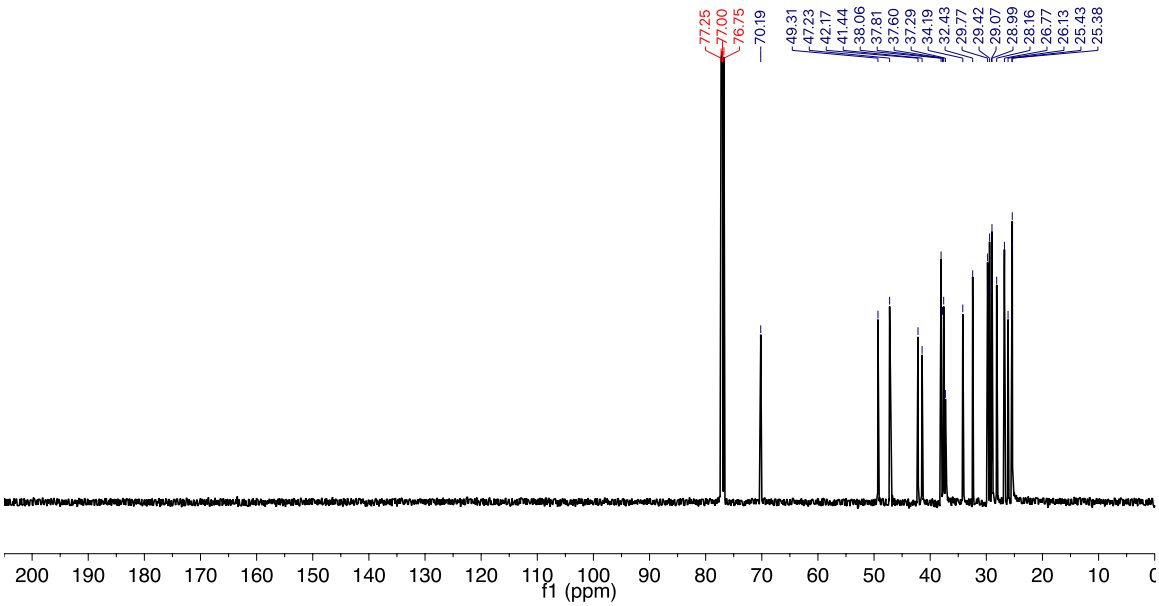

2.39
2.11
2.29
3.36
2.32
1.00
0.97
1.20
2.07
1.05
0.88
1.00
1.19
1.21
1.06
2.84
3.01
2.44
9.48
3.27
1.05
1.13
f1 (ppm)

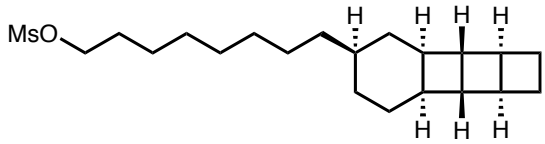

159.02
130.75
129.19
113.68
77.25
77.00
76.75
72.47
70.21
55.23
49.34
47.26
42.20
41.47
38.13
37.84
37.64
34.23
32.47
29.90
29.76
29.63
29.48
28.19
26.85
26.19
26.16
25.49
25.46
f1 (ppm)


HO
H
H
H
H
H
H
H

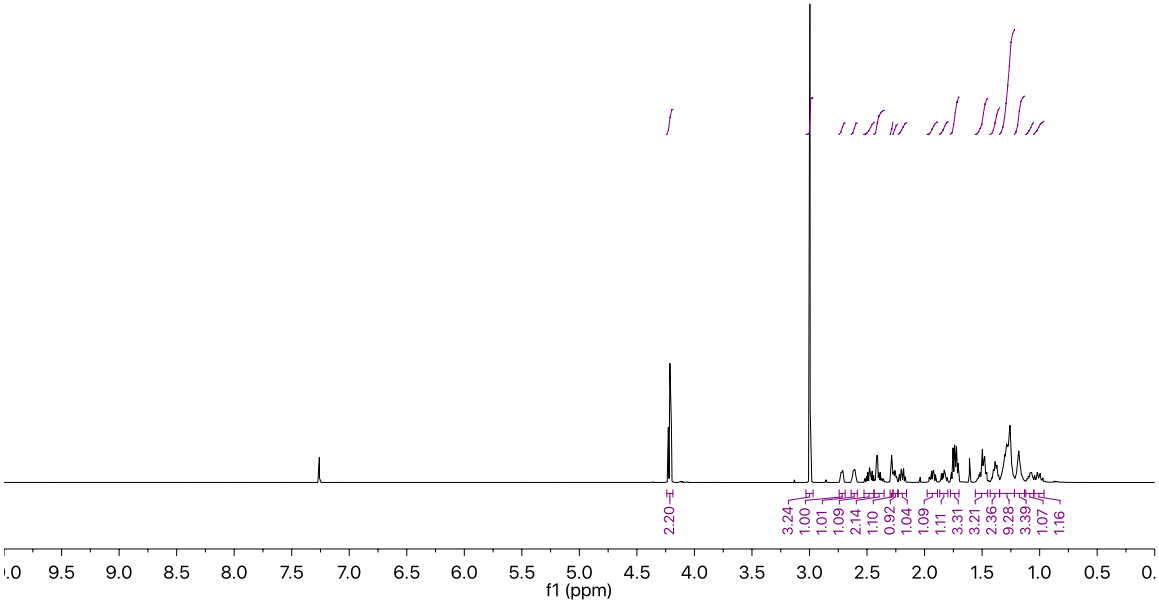
3

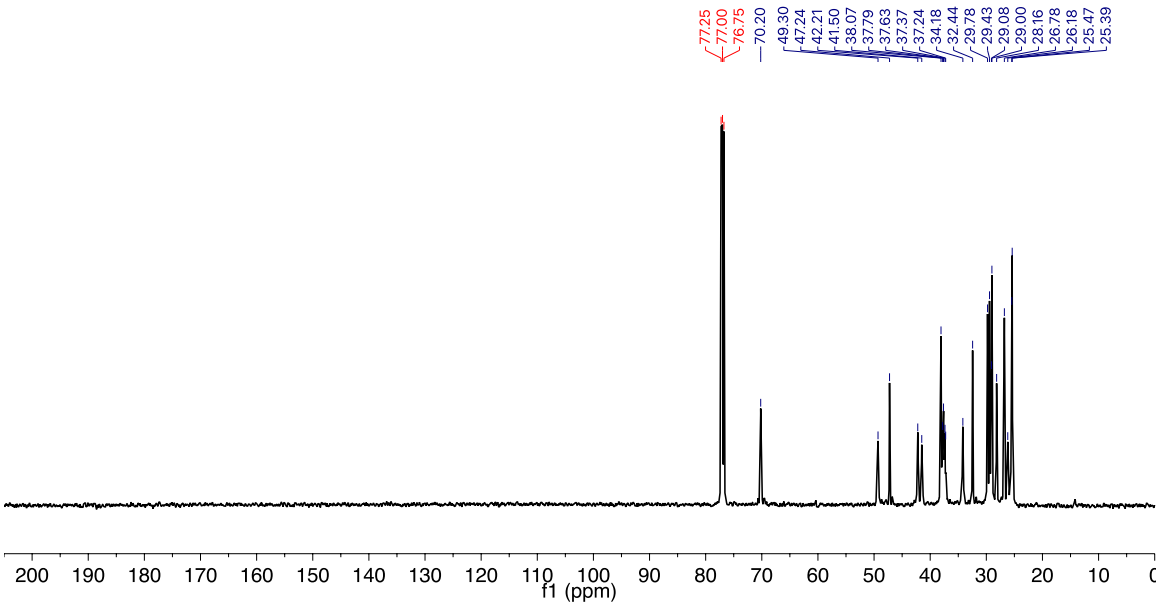

2.20
1.00
1.02
1.13
2.19
1.04
0.98
1.06
1.12
1.17
1.12
2.65
3.05
13.59
3.49
1.12
1.23
f1 (ppm)

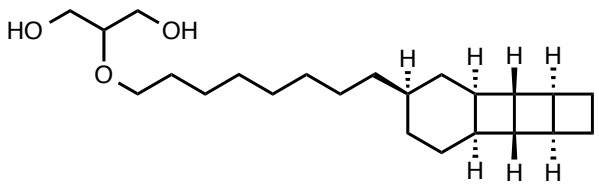

77.25
77.00
76.75
70.19
49.31
47.23
42.17
41.44
38.06
37.81
37.60
37.29
34.19
32.43
29.77
29.42
29.07
28.99
28.16
26.77
26.13
25.43
25.38
f1 (ppm)


MsO
H
H
H
H
H
H
H

25

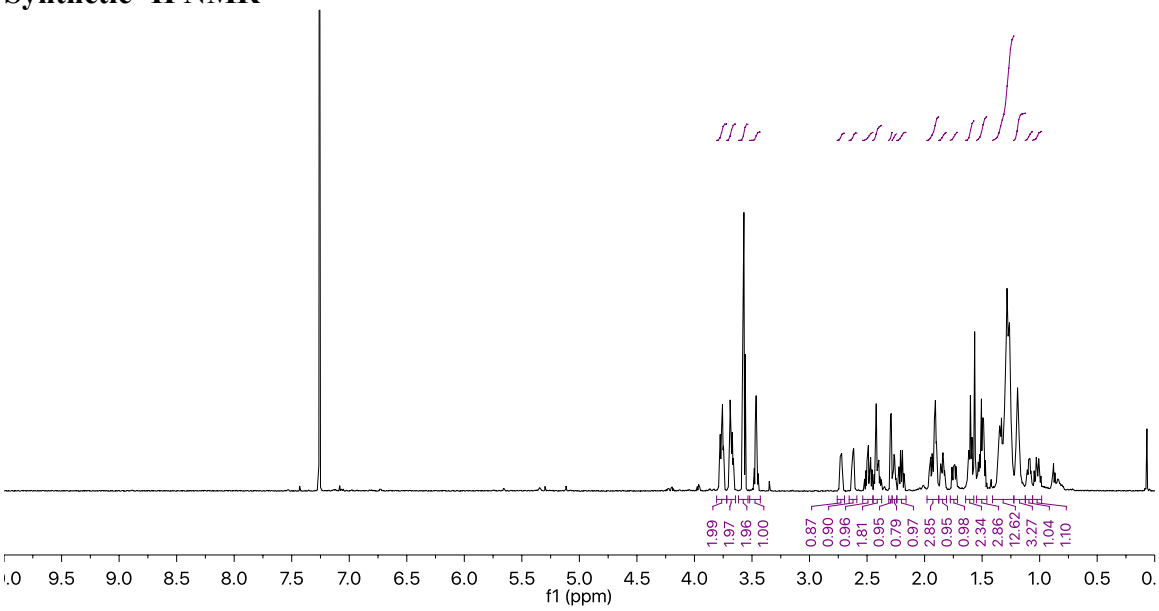

2.20
3.24
1.00
1.01
1.09
2.14
1.10
0.92
1.04
1.09
1.11
3.31
3.21
2.36
9.28
3.39
1.07
1.16
f1 (ppm)


77.25
77.00
76.75
70.20
49.30
47.24
42.21
41.50
38.07
37.79
37.63
37.37
37.24
34.18
32.44
29.78
29.43
29.08
29.00
28.16
26.78
26.18
25.47
25.39
f1 (ppm)

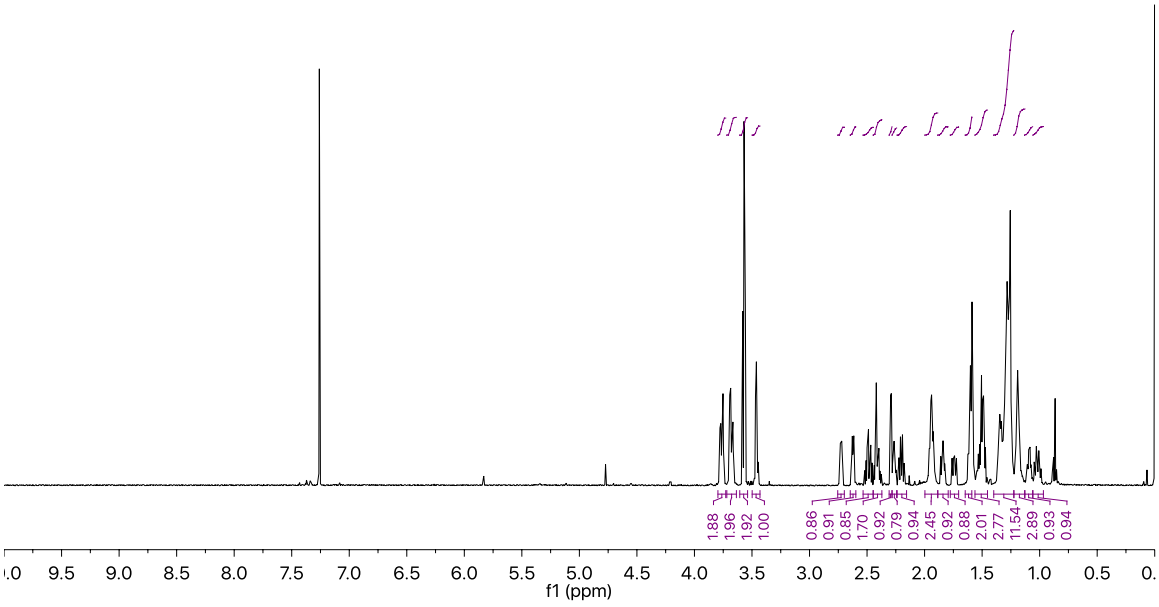


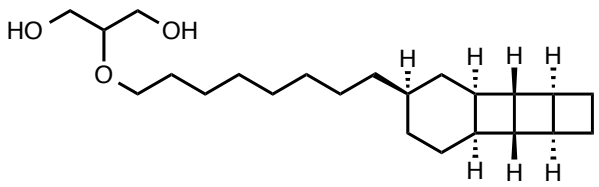
23

Synthetic ^{1}H NMR



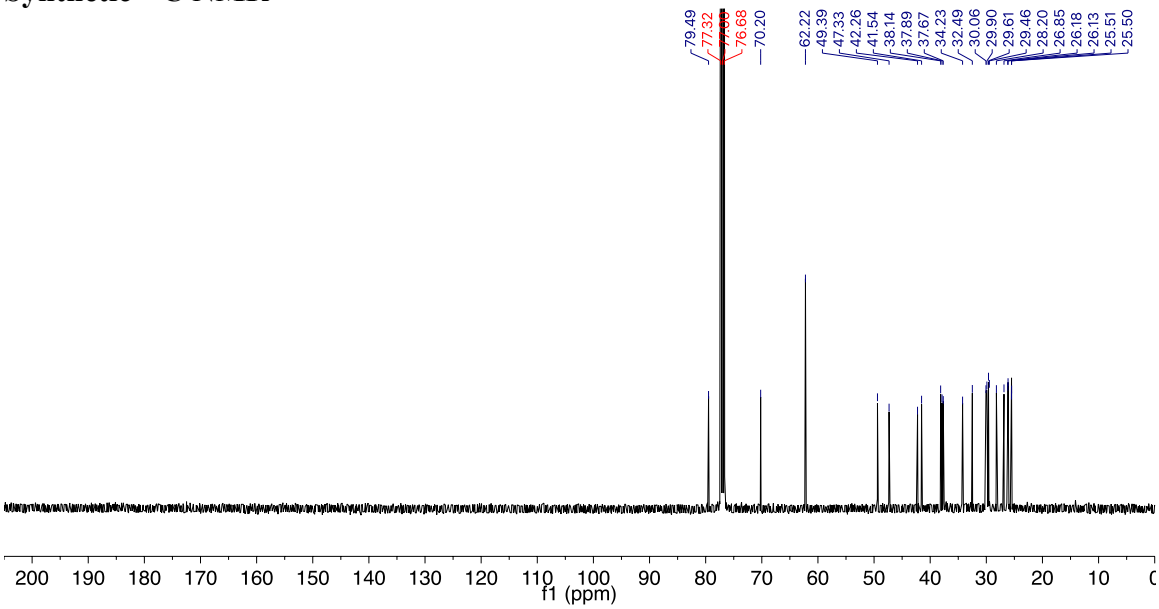
Natural ^{1}H NMR



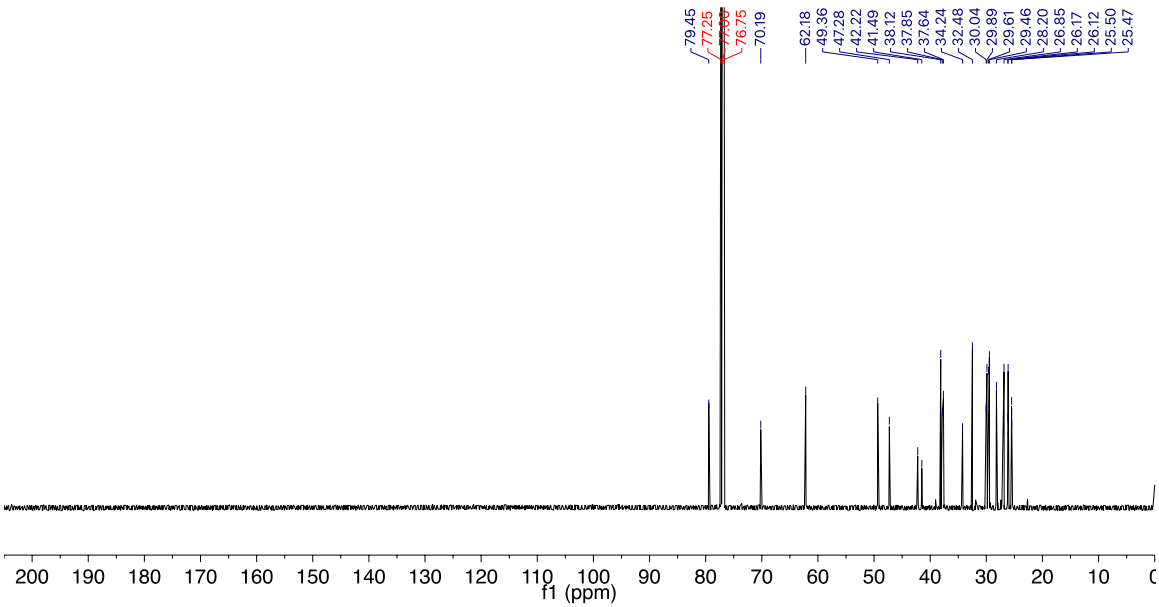


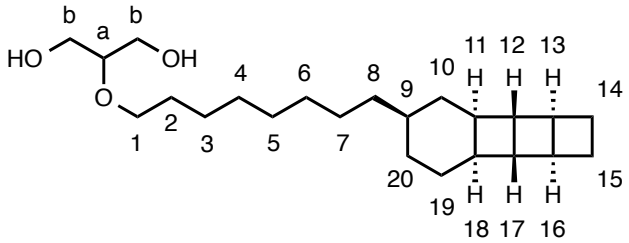
23

Synthetic ^{13}C NMR



Natural ^{13}C NMR

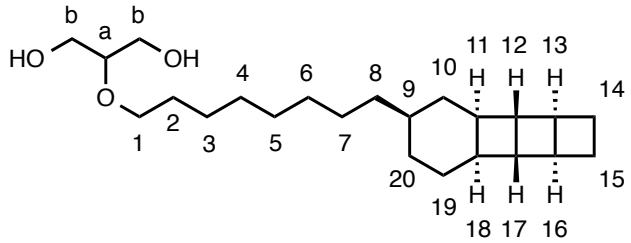




23

Signal	Synthetic	Natural
b	3.81 – 3.72 (m, 2H)	3.80 – 3.73 (m, 2H)
b	3.72 – 3.64 (m, 2H)	3.72 – 3.64 (m, 2H)
1	3.57 (t, *J* = 6.7 Hz, 2H)	3.57 (t, *J* = 6.7 Hz, 2H)
a	3.46 (p, *J* = 4.8 Hz, 1H)	3.46 (p, *J* = 4.8 Hz, 1H)
13	2.73 (bd, *J* = 7.5 Hz, 1H)	2.73 (bd, *J* = 6.1 Hz, 1H)
16	2.62 (bt, *J* = 3.7 Hz, 1H)	2.62 (bt, *J* = 3.9 Hz, 1H)
14α	2.54 – 2.45 (m, 1H)	2.53 – 2.45 (m, 1H)
17, 15α	2.45 – 2.37 (m, 2H)	2.45 – 2.37 (m, 2H)
12	2.29 (d, *J* = 3.6 Hz, 1H)	2.29 (d, *J* = 3.5 Hz, 1H)
18	2.28 – 2.24 (m, 1H)	2.28 – 2.24 (m, 1H)
11	2.24 – 2.16 (m, 1H)	2.24 – 2.16 (m, 1H)
15β, 2OH	1.98 – 1.88 (m, 1H + 2OH)	2.00 – 1.89 (m, 1H + 2OH)
14β	1.88 – 1.81 (m, 1H)	1.89 – 1.79 (m, 1H)
10α	1.78 – 1.71 (m, 1H)	1.78 – 1.70 (m, 1H)
2	1.64 – 1.57 (m, 2H)	1.65 – 1.59 (m, 2H)
19α, 19β, 20α	1.55 – 1.46 (m, 3H)	1.56 – 1.45 (m, 3H)
3, 4, 5, 6, 7	1.41 – 1.22 (m, 10H)	1.40 – 1.22 (m, 10H)
8, 9	1.22 – 1.12 (m, 3H)	1.22 – 1.13 (m, 3H)
20β	1.12 – 1.06 (m, 1H)	1.13 – 1.06 (m, 1H)
10β	1.06 – 0.98 (m, 1H)	1.06 – 0.97 (m, 1H)

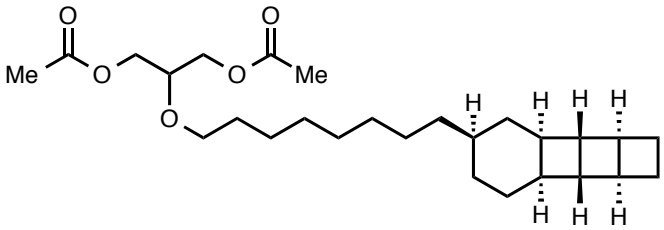
Table S3. ^{1}H NMR comparison of synthetic (600 MHz, $CDCl_3$) and natural (600 MHz, $CDCl_3$) **23**. Signals as assigned by Sinninghe Damsté.[9]



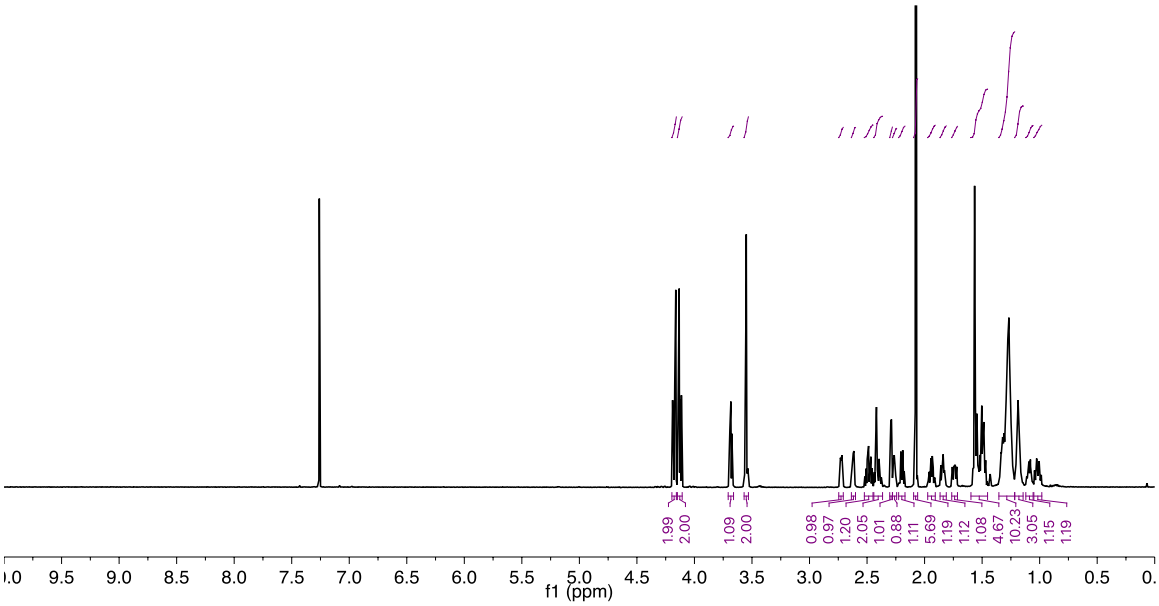
23

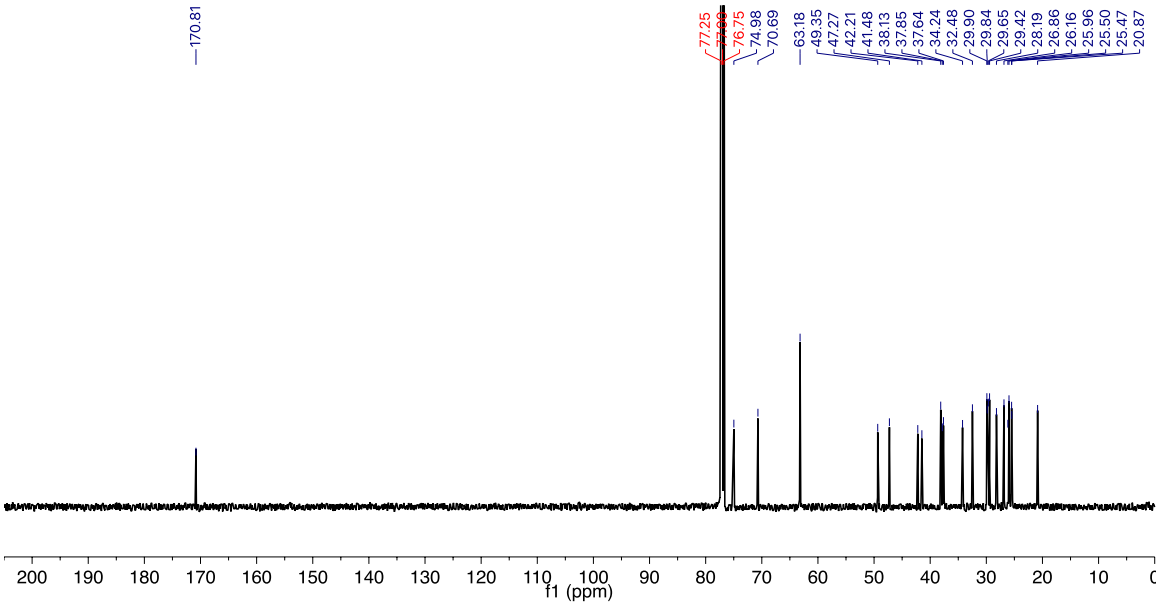
Signal	Synthetic	Natural
a	79.49	79.45
1	70.20	70.19
b	62.22	62.18
12	49.39	49.36
17	47.33	47.28
16	42.26	42.22
13	41.54	41.49
8	38.14	38.12
11	37.89	37.85
18	37.67	37.64
10	34.23	34.24
9	32.49	32.48
4	30.06	30.04
2	29.90	29.89
5	29.61	29.61
7	29.46	29.46
20	28.20	28.20
6	26.85	26.85
14	26.18	26.17
3	26.13	26.12
19	25.51	25.50
15	25.50	25.47

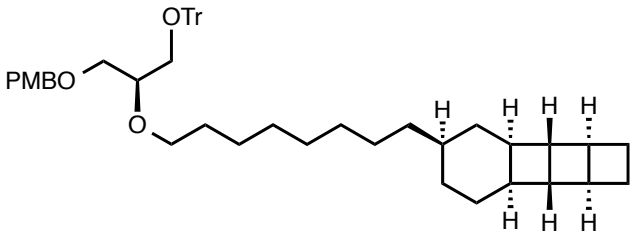
Table S4. ^{13}C NMR comparison of synthetic (101 MHz, $CDCl_3$) and natural (126 MHz, $CDCl_3$) **20**. Signals as assigned by Sinninghe Damsté.[9]


O
O
Me
O
O
Me
O
H
H
H
H
H
H
H

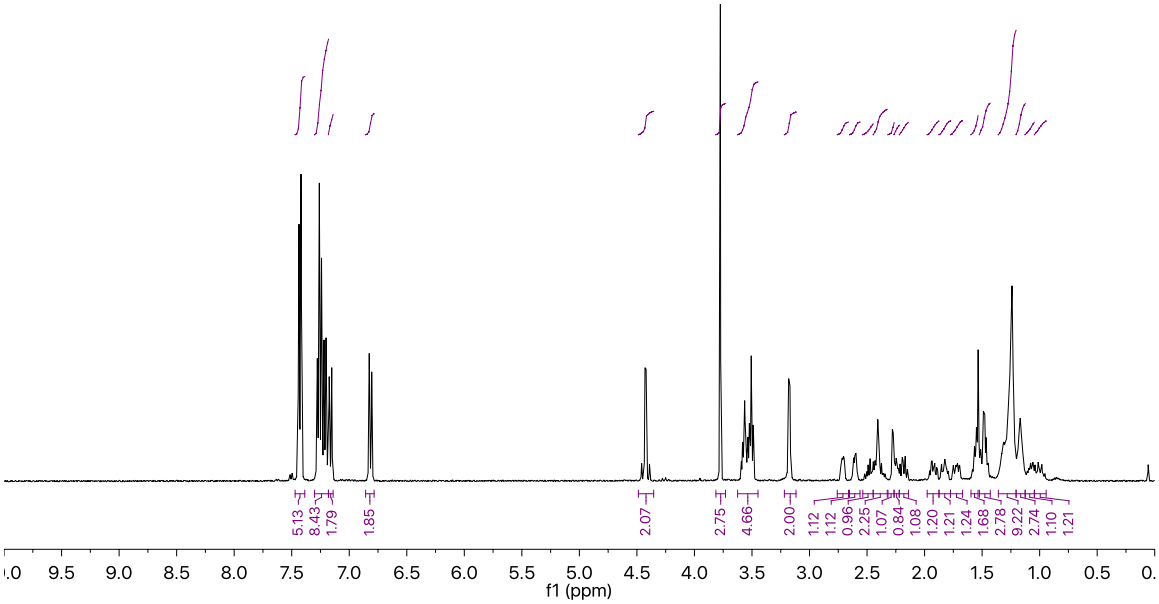
S10

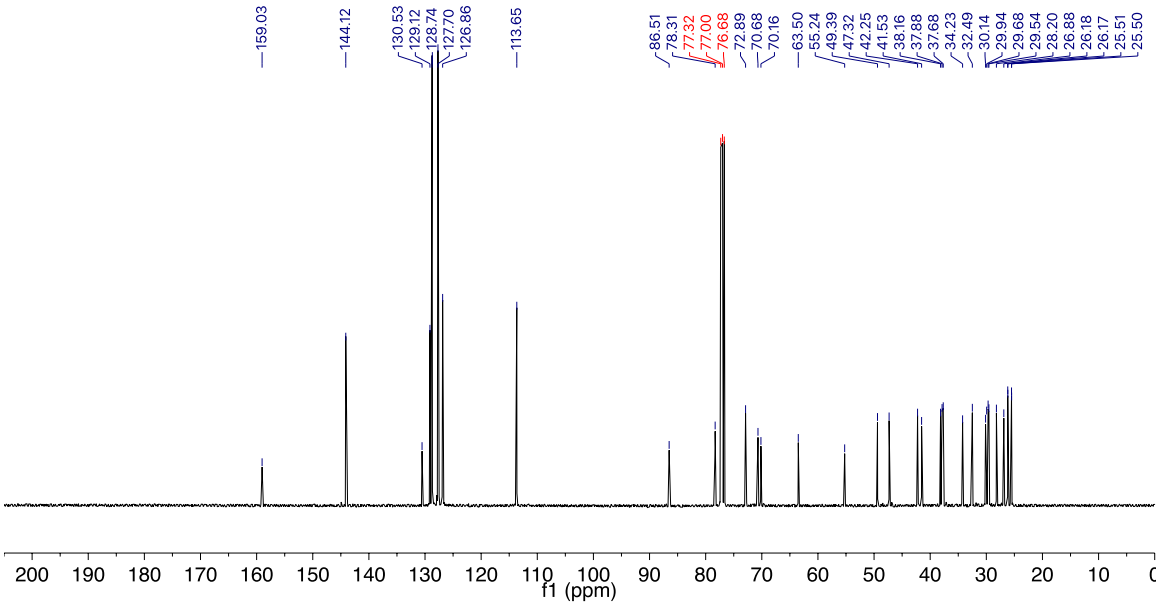

1.99
2.00
1.09
2.00
0.98
0.97
1.20
2.05
1.01
0.88
1.11
5.69
1.19
1.12
1.08
4.67
10.23
3.05
1.15
1.19
f1 (ppm)

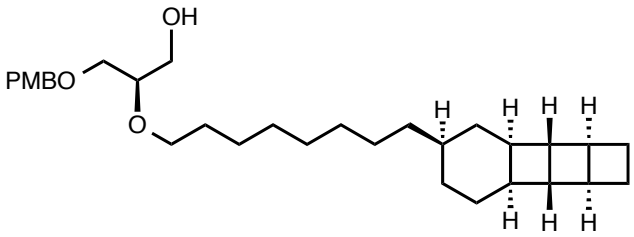

170.81
77.25
76.75
74.98
70.69
63.18
49.35
47.27
42.21
41.48
38.13
37.85
37.64
34.24
32.48
29.90
29.84
29.65
29.42
28.19
26.86
26.16
25.96
25.50
25.47
20.87
f1 (ppm)


OTr
PMBO
O
H
H
H
H
H
H
H

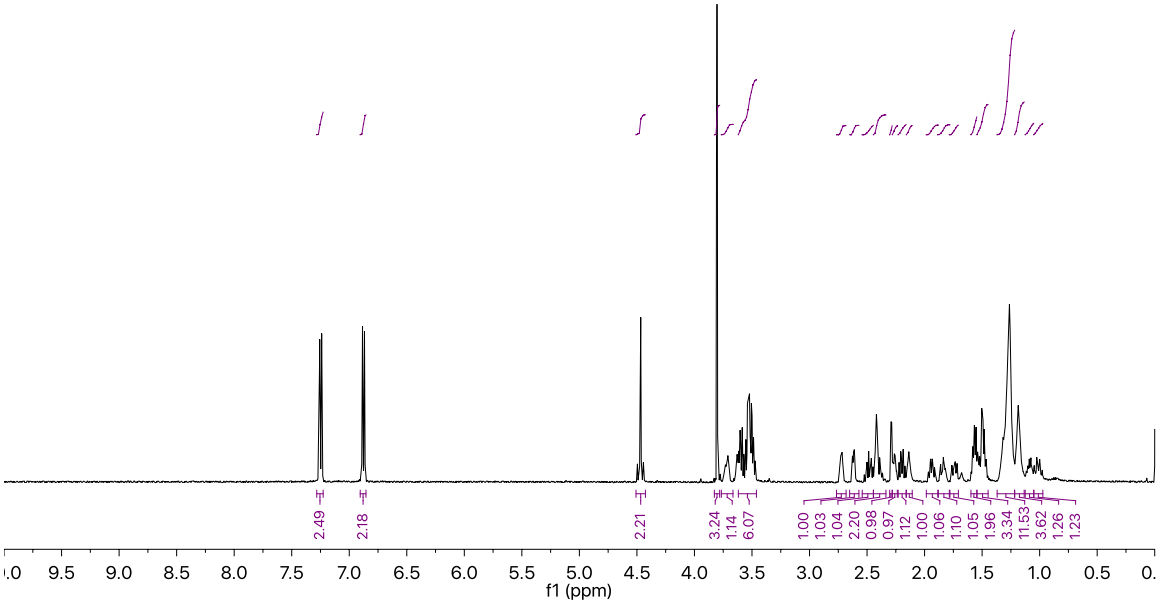
S11

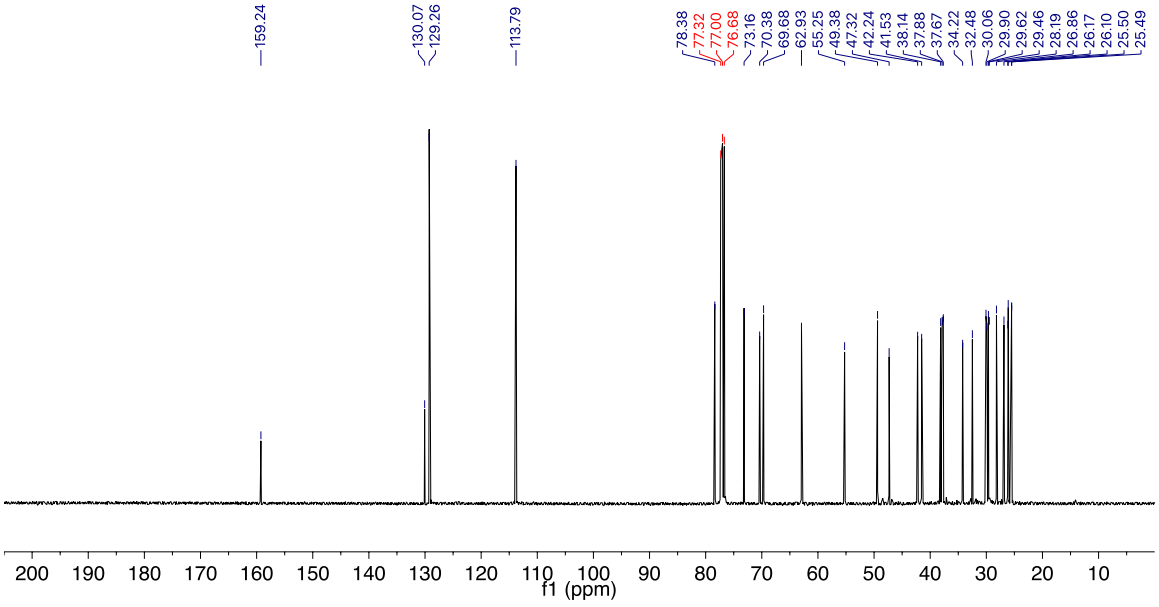

5.13
8.43
1.79
1.85
2.07
2.75
4.66
2.00
1.12
1.12
0.96
2.25
1.07
0.84
1.08
1.20
1.21
1.24
1.68
2.78
9.22
2.74
1.10
1.21
f1 (ppm)

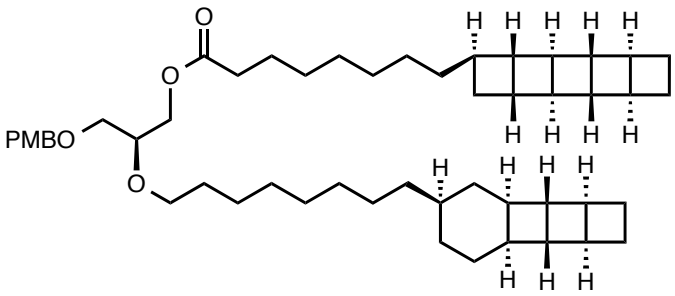

159.03
144.12
130.53
129.12
128.74
127.70
126.86
113.65
86.51
78.31
77.32
77.00
76.68
72.89
70.68
70.16
63.50
55.24
49.39
47.32
42.25
41.53
38.16
37.88
37.68
34.23
32.49
30.14
29.94
29.68
29.54
28.20
26.88
26.18
26.17
25.51
25.50
f1 (ppm)


OH
PMBO
O
H
H
H
H
H
H
H

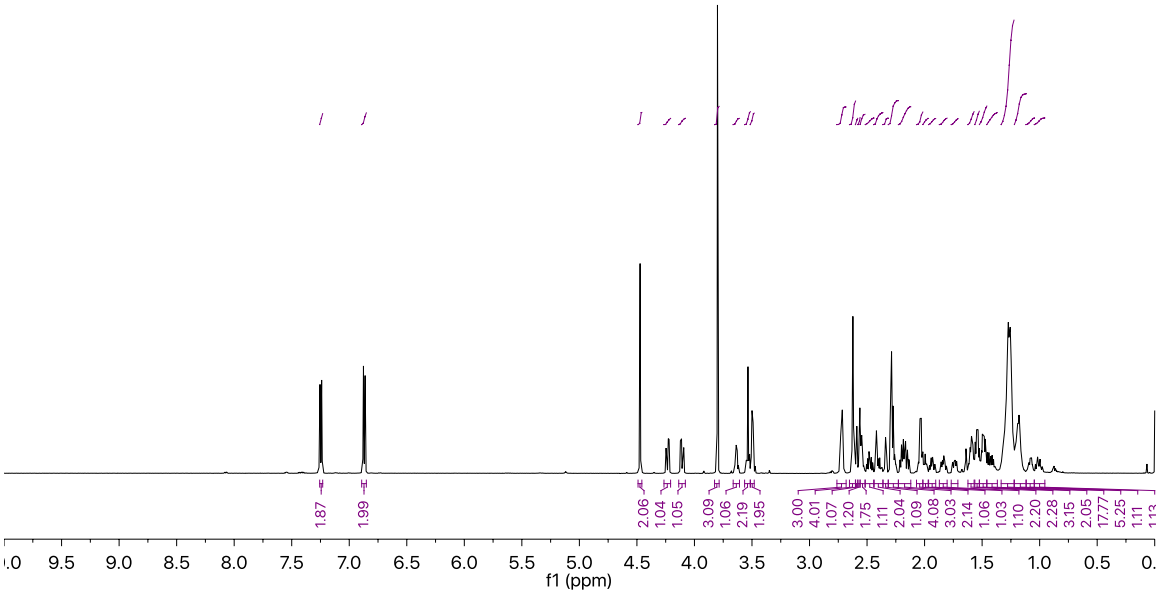
S12

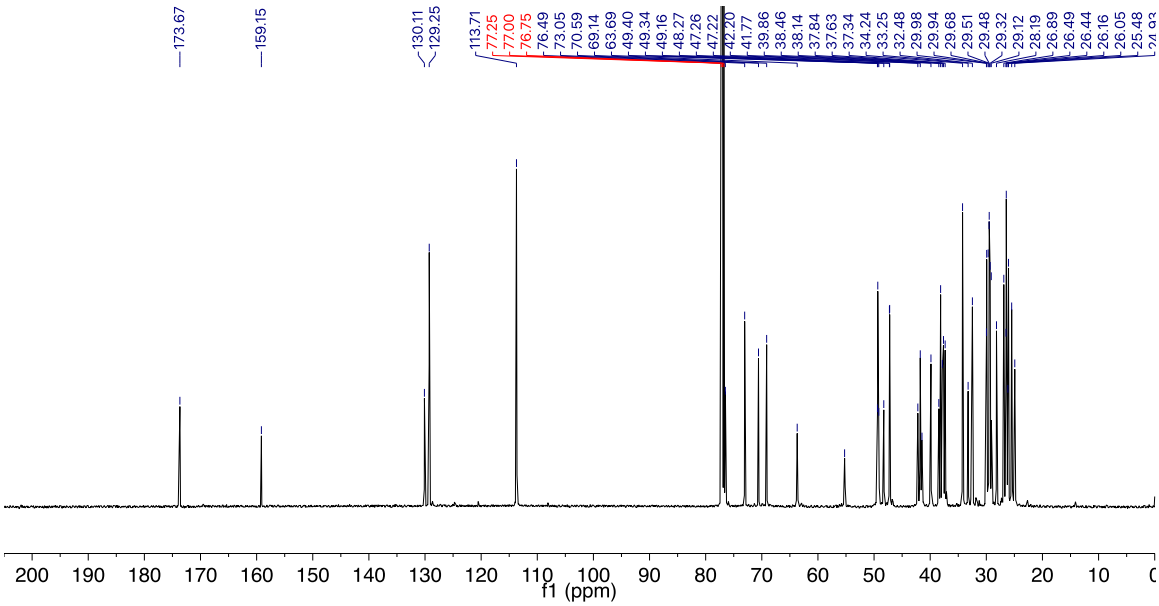

2.49
2.18
2.21
3.24
1.14
6.07
1.00
1.03
1.04
2.20
0.98
0.97
1.12
1.00
1.06
1.10
1.05
1.96
3.34
11.53
3.62
1.26
1.23
f1 (ppm)

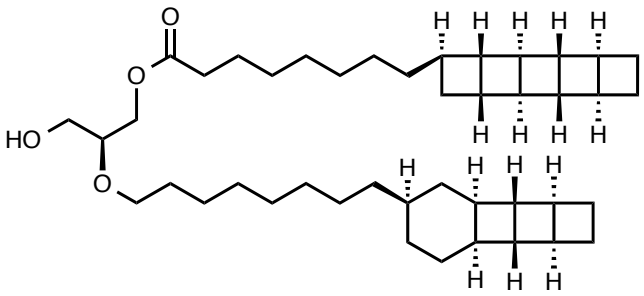

159.24
130.07
129.26
113.79
78.38
77.32
77.00
76.68
73.16
70.38
69.68
62.93
55.25
49.38
47.32
42.24
41.53
38.14
37.88
37.67
34.22
32.48
30.06
29.90
29.62
29.46
28.19
26.86
26.17
26.10
25.50
25.49
f1 (ppm)


O
O
PMBO
O
H H H H H
H H H H
H
H H H
H H H

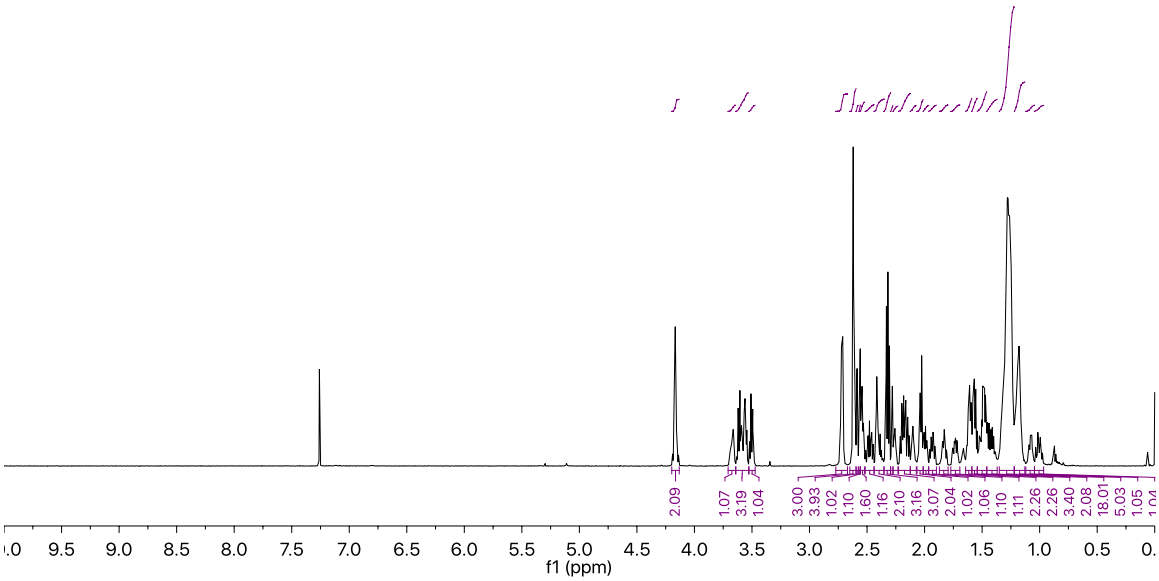
S13

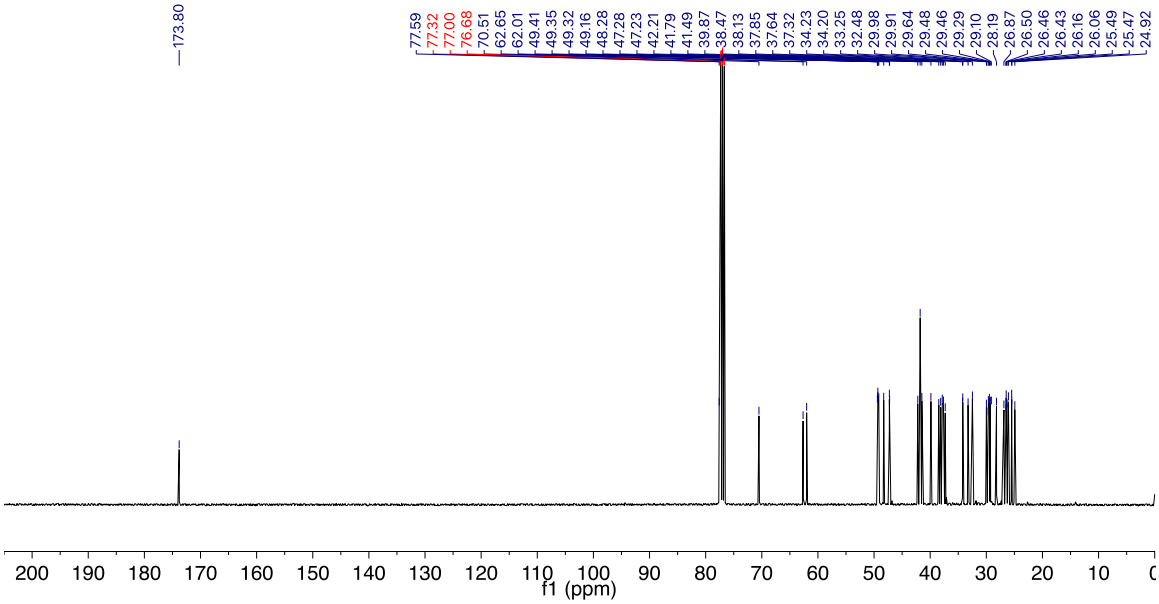

1.87
1.99
2.06
1.04
1.05
3.09
1.06
2.19
1.95
3.00
4.01
1.07
1.20
1.75
1.11
2.04
1.09
4.08
3.03
2.14
1.06
1.03
1.10
2.20
2.28
3.15
2.05
17.77
5.25
1.11
f1 (ppm)

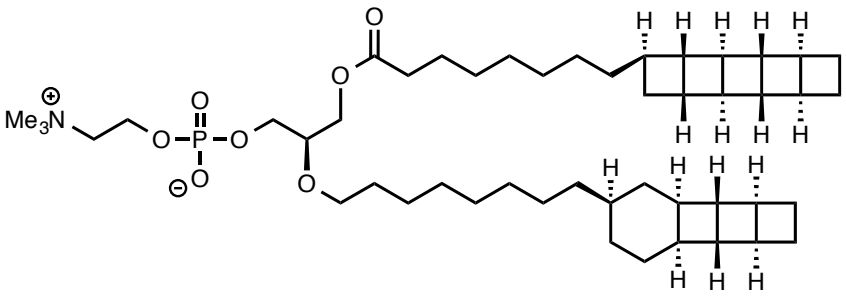

173.67
159.15
130.11
129.25
113.71
77.25
77.00
76.75
76.49
73.05
70.59
69.14
63.69
49.40
49.34
49.16
48.27
47.26
47.22
42.20
41.77
39.86
38.46
38.14
37.84
37.63
37.34
34.24
33.25
32.48
29.98
29.94
29.68
29.51
29.48
29.32
29.12
28.19
26.89
26.49
26.44
26.16
26.05
25.48
f1 (ppm)


O
O
HO
O
H H H H H
H H H H
H H H H
H H H

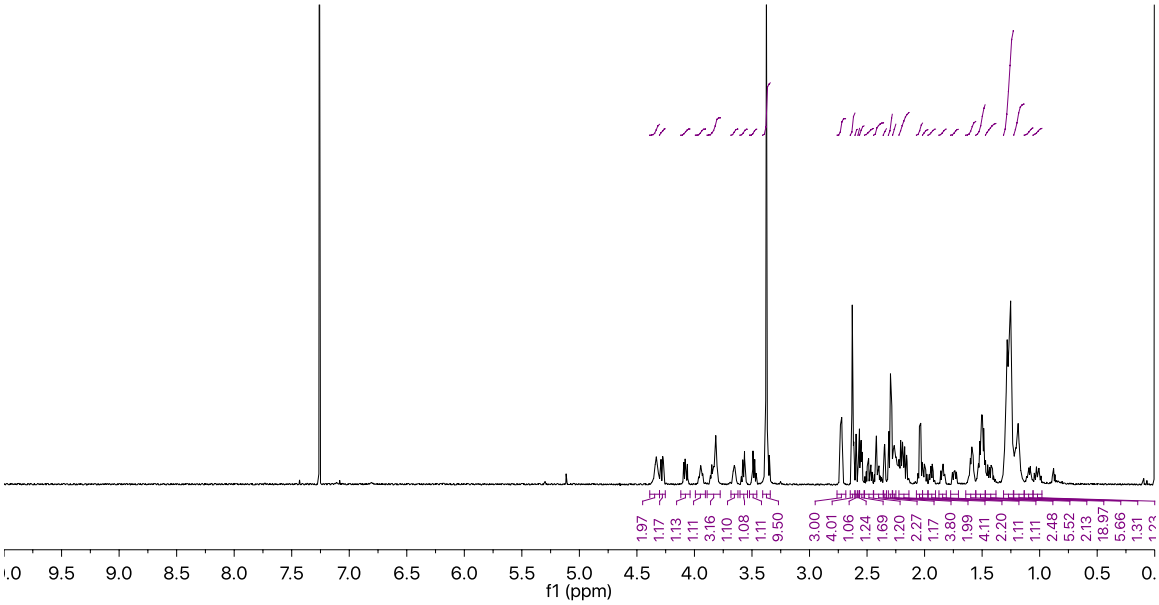
S14

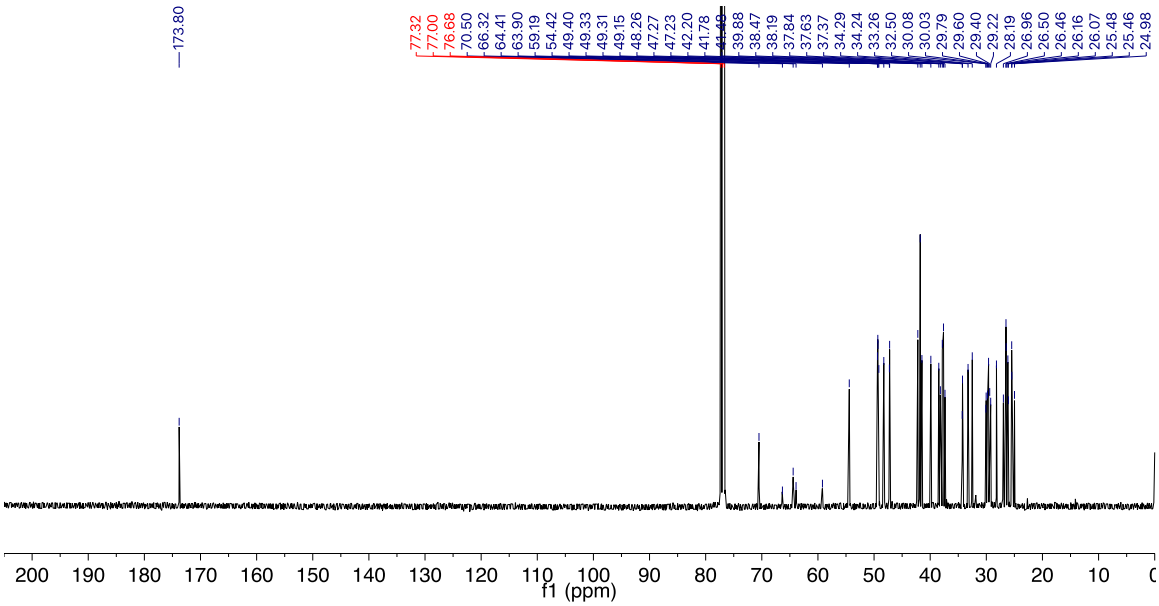

2.09
1.07
3.19
1.04
3.00
3.93
1.02
1.10
1.60
1.16
2.10
3.16
3.07
2.04
1.02
1.06
1.10
1.11
2.26
2.26
3.40
2.08
18.01
5.03
1.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

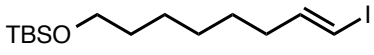

173.80
77.59
77.32
77.00
76.68
70.51
62.65
62.01
49.41
49.35
49.32
49.16
48.28
47.28
47.23
42.21
41.79
41.49
39.87
38.47
38.13
37.85
37.64
37.32
34.23
34.20
33.25
32.48
29.98
29.91
29.64
29.48
29.46
29.29
29.10
28.19
26.87
26.50
26.46
26.43
26.16
26.06
25.49
25.47
24.92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)



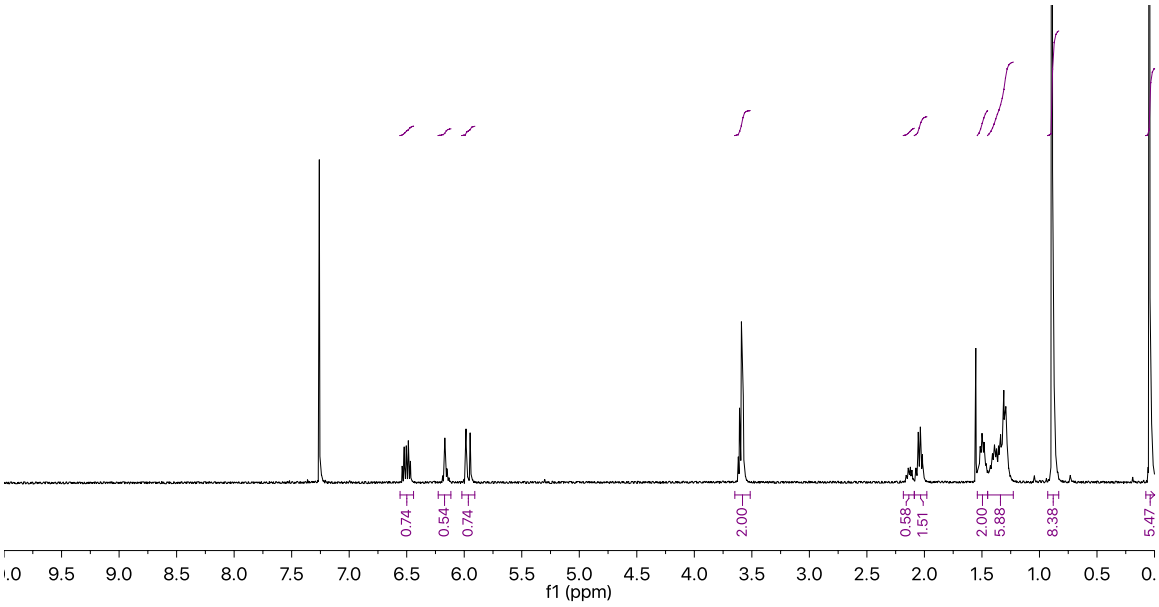
1

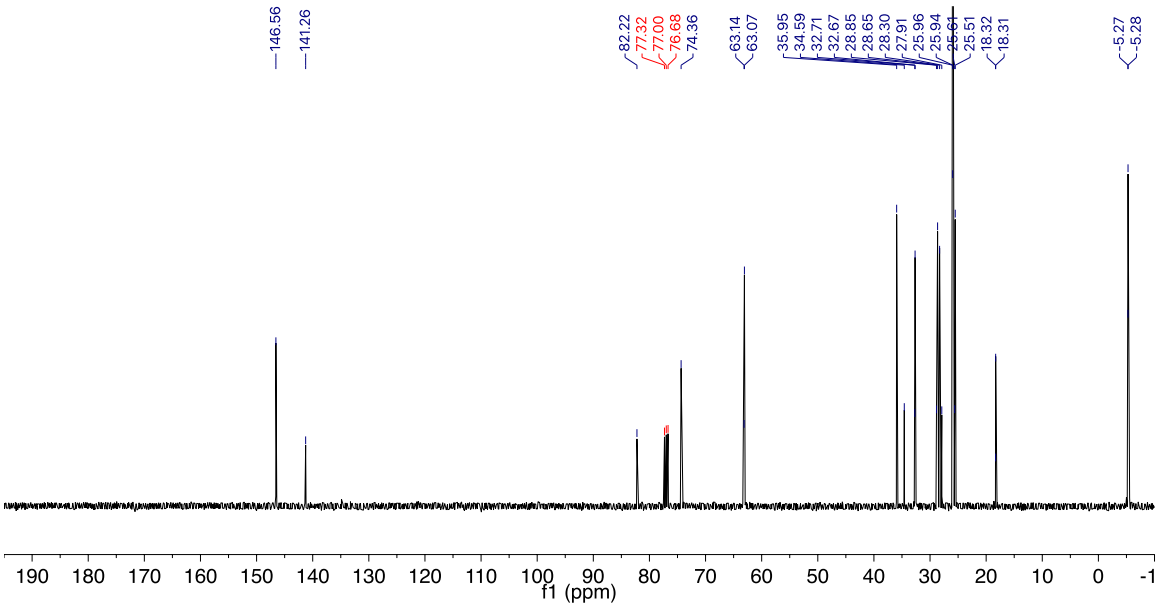

1.97
1.17
1.13
1.11
3.16
1.10
1.08
1.11
9.50
3.00
4.01
1.06
1.24
1.69
1.20
2.27
1.17
3.80
1.99
4.11
2.20
1.11
1.11
2.48
5.52
2.13
18.97
5.66
1.31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

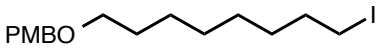

173.80
77.32
77.00
76.68
70.50
66.32
64.41
63.90
59.19
54.42
49.40
49.33
49.31
49.15
48.26
47.27
47.23
42.20
41.78
39.88
38.47
38.19
37.84
37.63
37.37
34.29
34.24
33.26
32.50
30.08
30.03
29.79
29.60
29.40
29.22
28.19
26.96
26.50
26.46
26.16
26.07
25.48
25.46
24.98
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TBSO
I

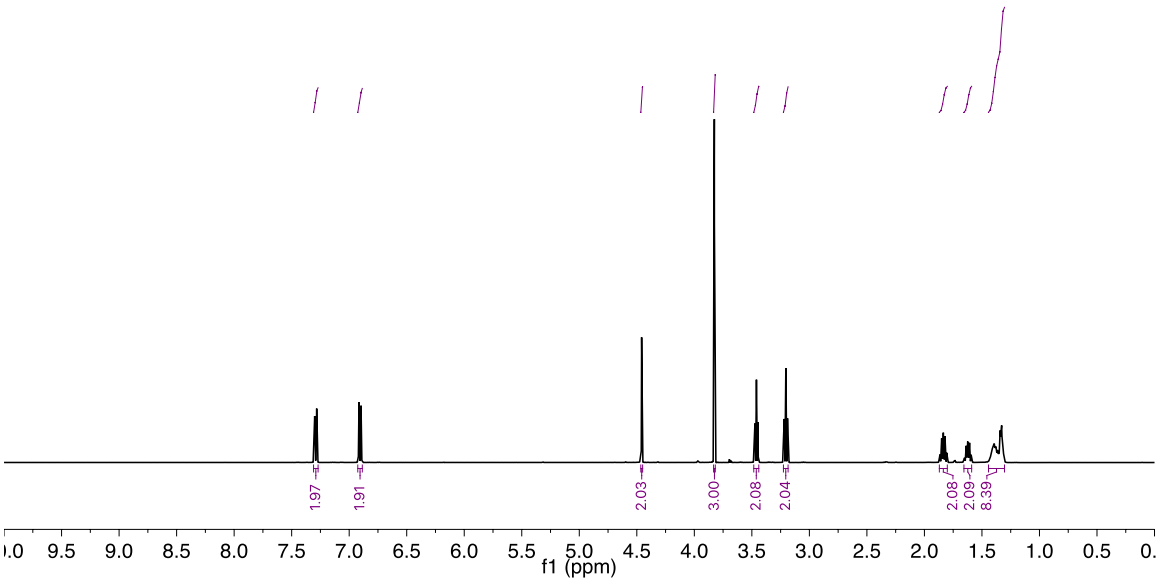
S5

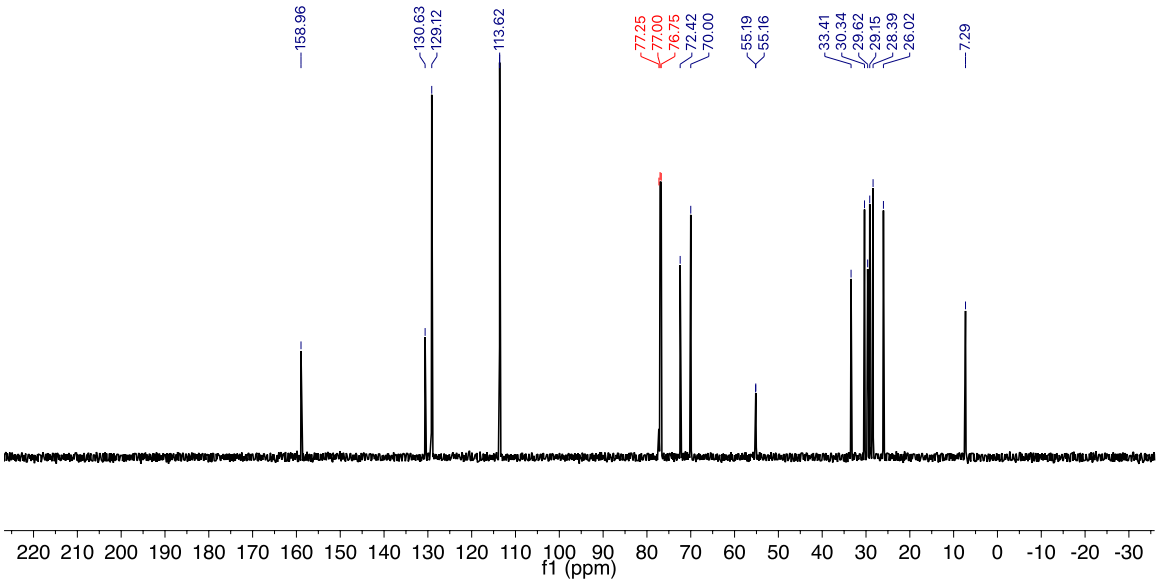

0.74
0.54
0.74
2.00
0.58
1.51
2.00
5.88
8.38
5.47
f1 (ppm)


146.56
141.26
82.22
77.32
77.00
76.68
74.36
63.14
63.07
35.95
34.59
32.71
32.67
28.85
28.65
28.30
27.91
25.96
25.94
25.61
25.51
18.32
18.31
-5.27
-5.28
f1 (ppm)

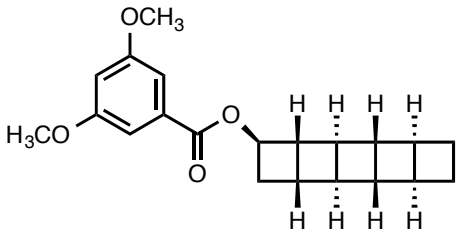

PMBO
I

S7


1.97
1.91
2.03
3.00
2.08
2.04
2.08
2.09
8.39
f1 (ppm)


158.96
130.63
129.12
113.62
77.25
77.00
76.75
72.42
70.00
55.19
55.16
33.41
30.34
29.62
29.15
28.39
26.02
7.29
f1 (ppm)

7. Chiral HPLC Spectra



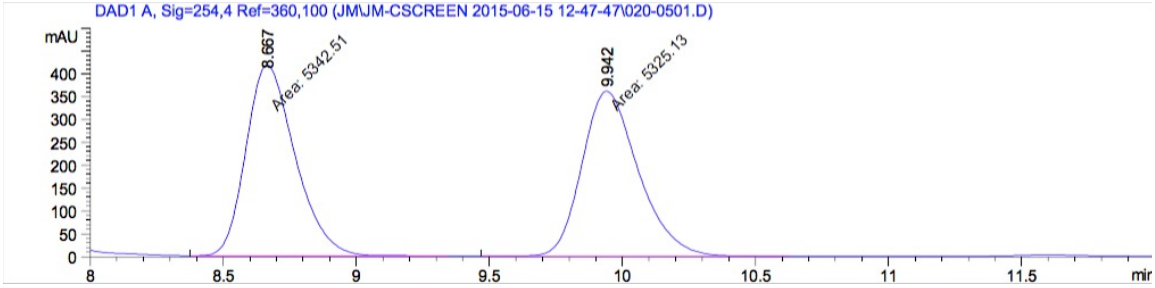
S19

Boronic ester **13** was converted to ester **S19** for HPLC analysis:

A small sample of **13** (ca. 2 mg, 7 µmol, 1.0 equiv) was taken up in THF (300 µL) and EtOH (300 µL). An aqueous solution of 15% NaOH (300 µL) was added dropwise by pipet, followed by an aqueous solution of H_2O_2 (300 µL, 30% wt/wt). The reaction mixture was allowed to stir vigorously at 23 ºC for 6 hours. After this time, the mixture was partitioned between EtOAc (3 mL) and sat. aq. NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated.

The resulting residue was taken up in anhydrous DCM (1 mL). 4-(Dimethylamino)pyridine (7 mg, 56 µmol, 8.0 equiv) was added in a single portion. 3,5-Dimethoxybenzoyl chloride was added as a 0.2 M solution in 1,2-dichloroethane (140 µL, 28 µmol, 4. equiv) dropwise by syringe. The resulting mixture was allowed to stir at 23 ºC for 3 hours, then quenched by the addition of 1N HCl (1 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 1 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated. The residue was purified by preparatory TLC (15% EtOAc/hexanes, run twice) to provide **S19** (ca. 1 mg).

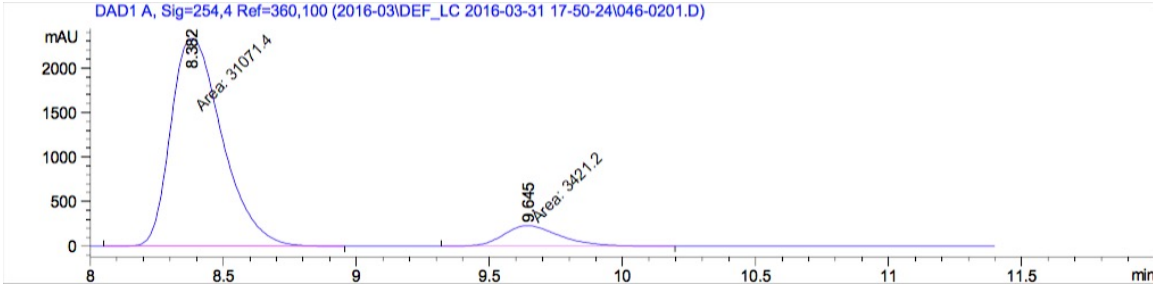
Racemic sample: Chiralpak-AD-H column, 3% *i*PrOH in hexanes, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.667	MM	0.2130	5342.50684	417.95569	50.0815
2	9.942	MM	0.2458	5325.12549	361.13205	49.9185
Totals :				1.06676e4	779.08774	

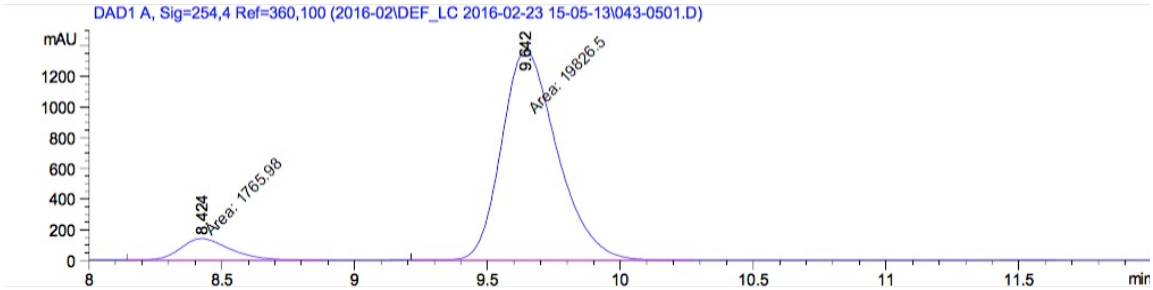
Scalemic sample: Chiralpak-AD-H column, 3% *i*PrOH in hexanes, 1 mL/min, 254 nm
Method 1 with (–)-DIOP



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.382	MM	0.2227	3.10714e4	2325.83008	90.0813
2	9.645	MM	0.2453	3421.20361	232.42558	9.9187
Totals :				3.44926e4	2558.25566	

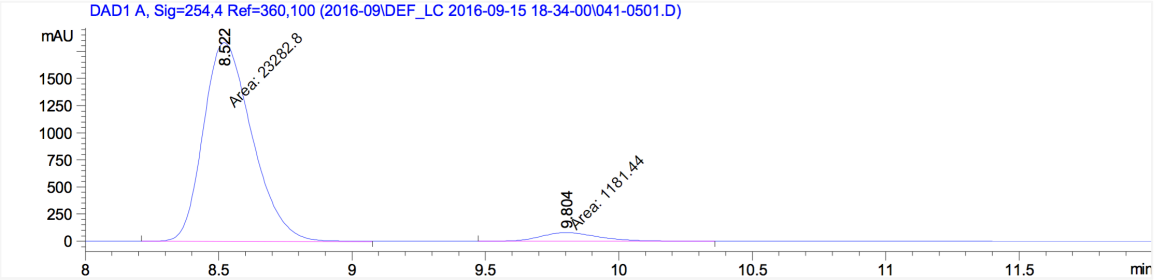
Scalemic sample: Chiralpak-AD-H column, 3% *i*PrOH in hexanes, 1 mL/min, 254 nm
Method 1 with (+)-DIOP



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

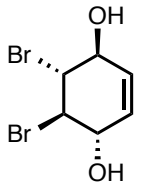
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.424	MM	0.2120	1765.98499	138.81573	8.1787
2	9.642	MM	0.2417	1.98265e4	1367.09900	91.8213
Totals :				2.15925e4	1505.91473	

Scalemic sample: Chiralpak-AD-H column, 3% *i*PrOH in hexanes, 1 mL/min, 254 nm
Method 2 with (*R*)-DM-Segphos



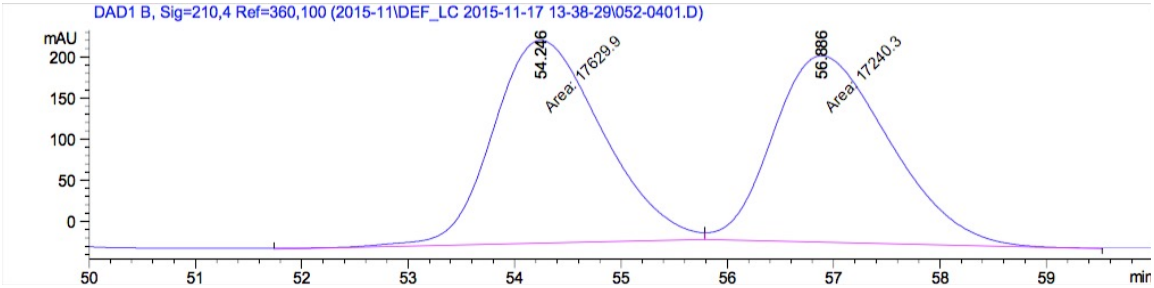
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.522	MM	0.2117	2.32828e4	1833.38330	95.1707
2	9.804	MM	0.2483	1181.44214	79.30681	4.8293
Totals :				2.44643e4	1912.69011	



15

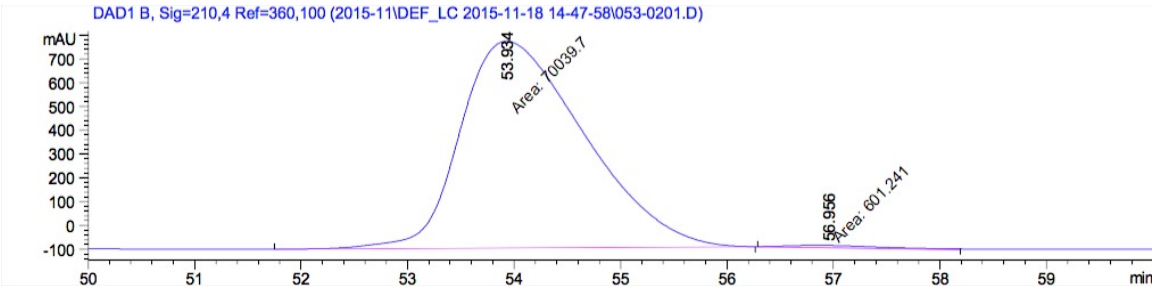
Racemic sample: Chiralpak AS-H column, 5% EtOH in pentane, 0.5 mL/min, 210 nm



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

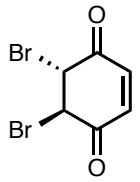
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.246	MM	1.1910	1.76299e4	246.71179	50.5586
2	56.886	MM	1.2685	1.72403e4	226.51775	49.4414
Totals :				3.48702e4	473.22954	

Scalemic sample: Chiralpak AS-H column, 5% EtOH in pentane, 0.5 mL/min, 210 nm



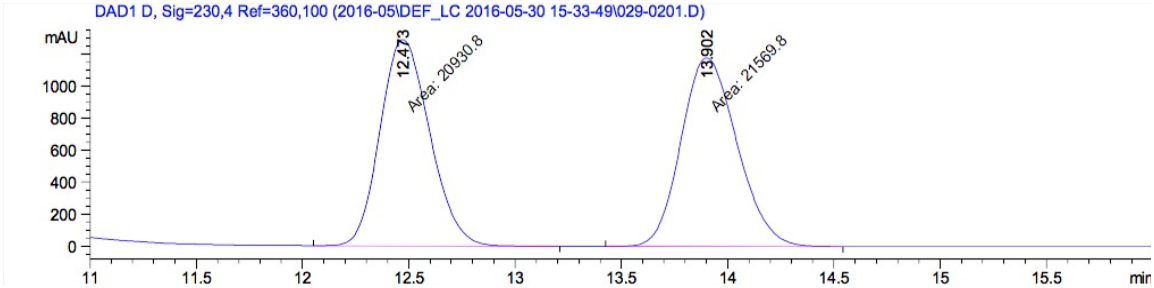
Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.934	MM	1.3449	7.00397e4	867.94055	99.1489
2	56.956	MM	1.0482	601.24097	9.55972	0.8511
Totals :				7.06409e4	877.50027	



16

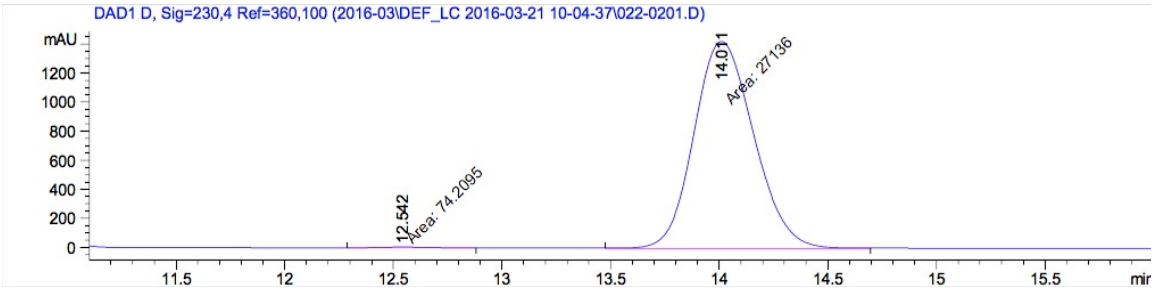
Racemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 230 nm



Signal 3: DAD1 D, Sig=230,4 Ref=360,100

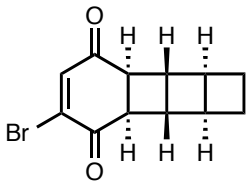
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.473	MM	0.2708	2.09308e4	1288.40710	49.2483
2	13.902	MM	0.3054	2.15698e4	1177.24329	50.7517
Totals :				4.25007e4	2465.65039	

Scalemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 230 nm



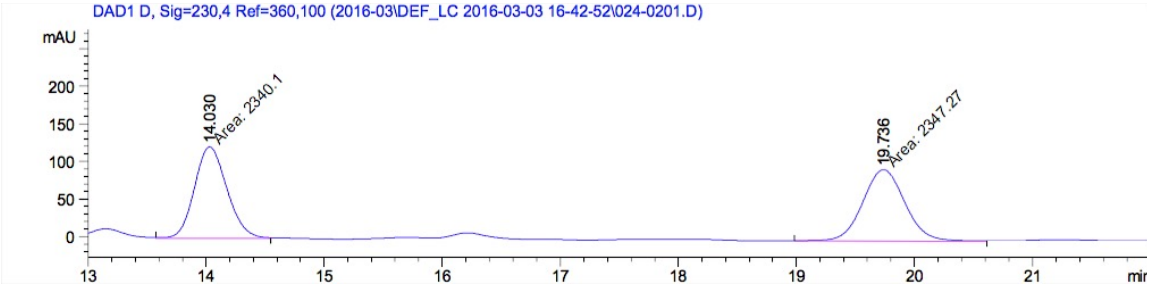
Signal 3: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.542	MM	0.2446	74.20946	5.05652	0.2727
2	14.011	MM	0.3176	2.71360e4	1423.79956	99.7273
Totals :				2.72102e4	1428.85608	



18

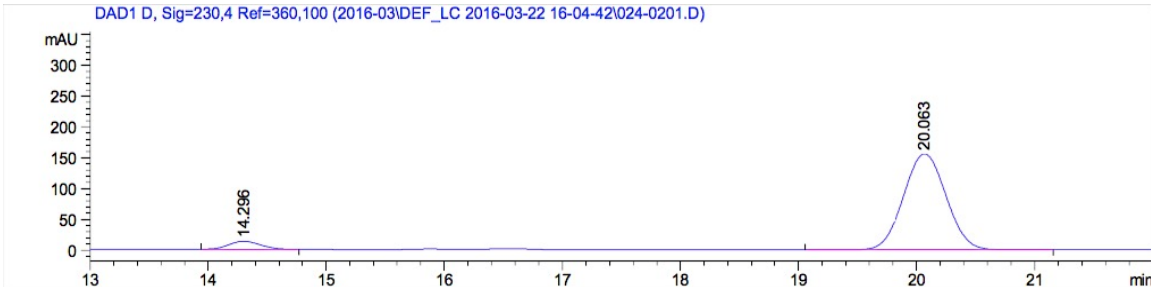
Racemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 230 nm



Signal 3: DAD1 D, Sig=230,4 Ref=360,100

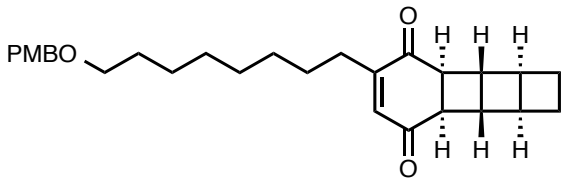
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.030	MM	0.3202	2340.10254	121.81905	49.9236
2	19.736	MM	0.4133	2347.26733	94.65630	50.0764
Totals :				4687.36987	216.47535	

Scalemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 230 nm



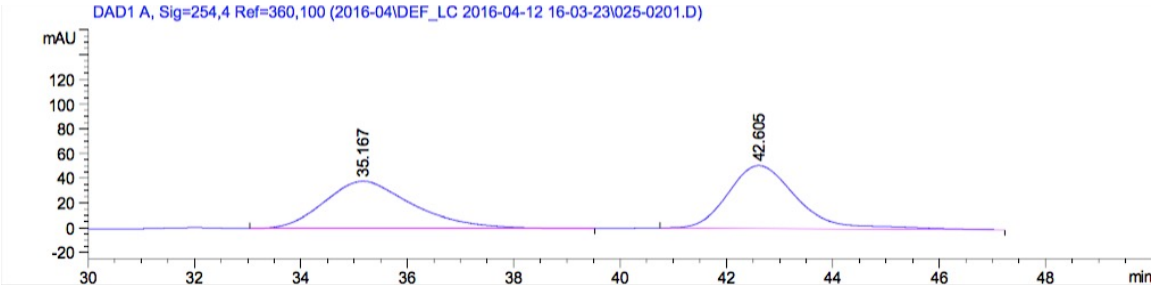
Signal 3: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.296	BB	0.2908	242.03296	13.02499	5.8220
2	20.063	BB	0.3953	3915.20068	155.73296	94.1780
Totals :				4157.23364	168.75795	



(–)-19

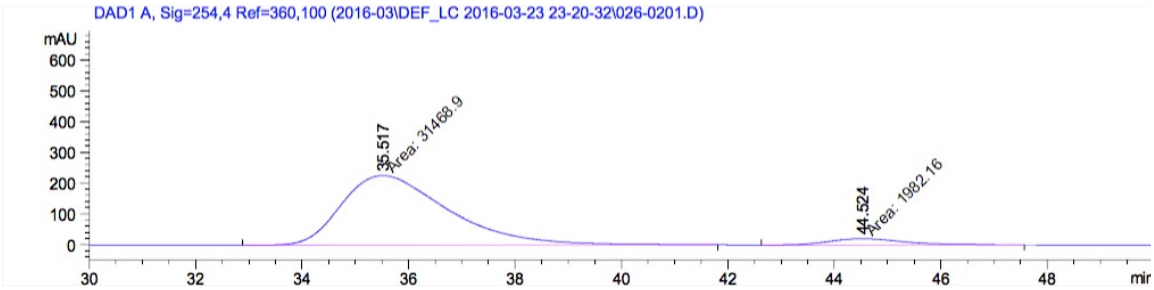
Racemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

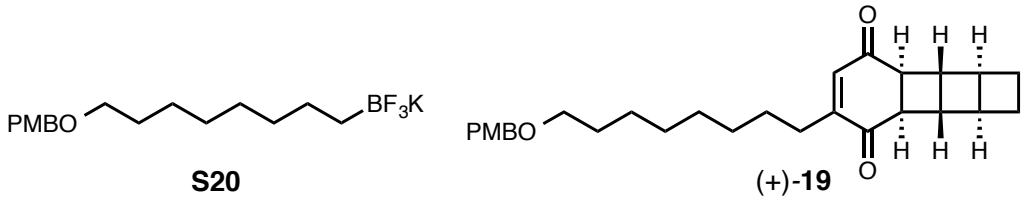
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.167	BB	1.5885	4423.95166	38.16232	49.5012
2	42.605	BB	1.3444	4513.10156	50.61066	50.4988
Totals :				8937.05322	88.77298	

Scalemic sample: Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.517	MM	2.3240	3.14689e4	225.68486	94.0744
2	44.524	MM	1.6331	1982.16479	20.22950	5.9256
Totals :				3.34511e4	245.91436	

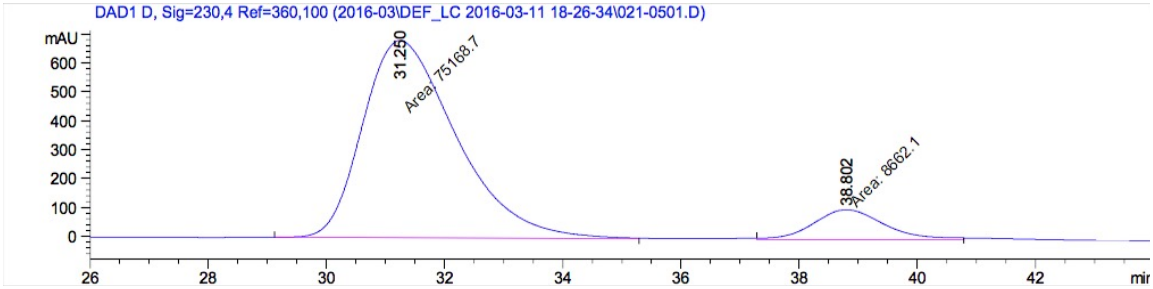


Enedione (+)-19

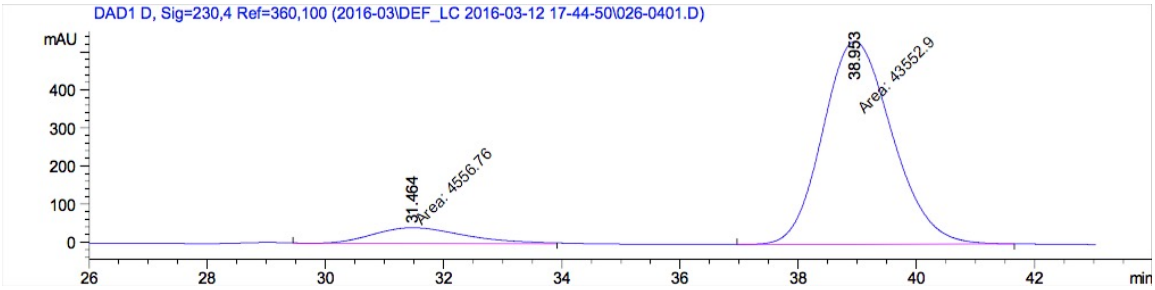
(+)-**19** could be prepared by Suzuki cross-coupling with trifluoroborate salt **S20** following literature procedures.[15] A round-bottom flask was charged with bromide **16** (149 mg, 0.56 mmol, 1.0 equiv, 80% ee), **S20** (218 mg, 0.612 mmol, 1.1 equiv), Cs_2CO_3 (547 mg, 1.68 mmol, 3.0 equiv), and $PdCl_2(dppf)•CH_2Cl_2$ (45.7 mg, 0.056 mmol, 0.1 equiv). The flask was purged with argon, and the solids were taken up in toluene (3.3 mL, 0.17 M, degassed with N_2) and water (1.12 mL, 0.5 M). The resulting mixture was allowed to stir for 3 hours at 80 °C (oil bath). After this time, the reaction mixture was cooled to room temperature and filtered through a small pad of silica gel, eluting with toluene (10 mL). The filtrate was concentrated, and the crude residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to provide *ent*-**17** (167 mg, 68%).

Chiralpak AS-H column, 3% EtOH in hexanes, 1 mL/min, 254 nm

(–)-19 (from 80% ee **18**, via alkylzinc iodide addition):



(+)-19 (from 80% ee **18**, via Suzuki cross-coupling):



(–)-19 (from 80% ee **18**):

Signal 3: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.250	MM	1.8338	7.51687e4	683.18488	89.6672
2	38.802	MM	1.4000	8662.09961	103.12009	10.3328
Totals :				8.38308e4	786.30497	

(+)-19 (from 80% ee **18**):

Signal 3: DAD1 D, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.464	MM	1.8264	4556.75879	41.58326	9.4716
2	38.953	MM	1.3602	4.35529e4	533.63922	90.5284
Totals :				4.81097e4	575.22248	

8. X-Ray Crystallographic Information

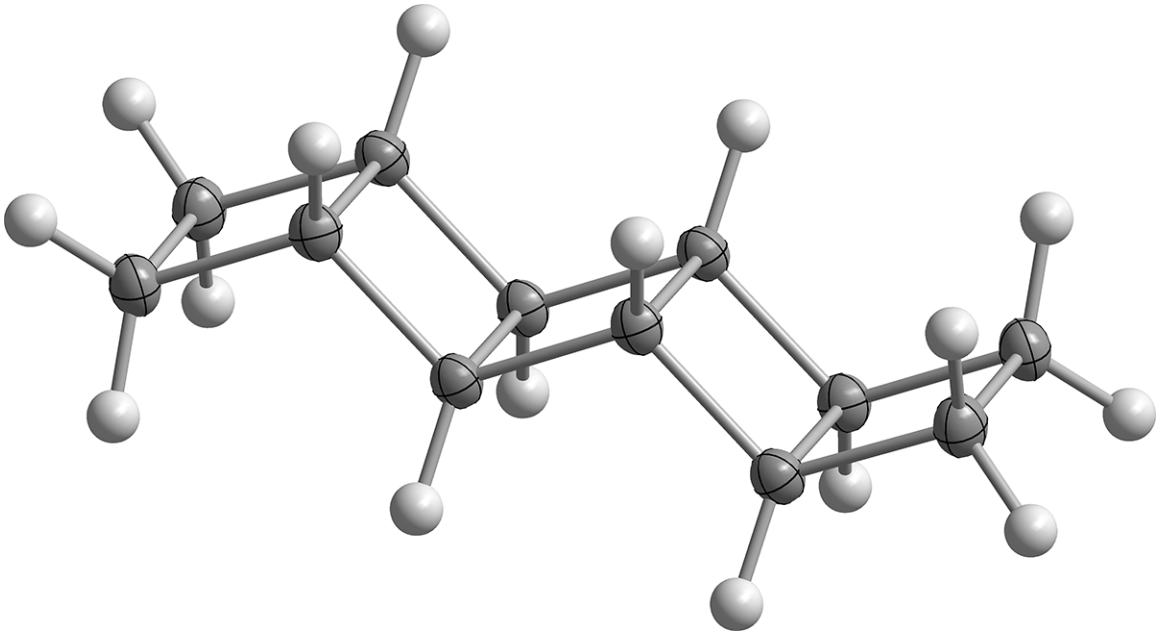


Figure S8. X-ray crystallographic structure for **4** (su1409).

DISCUSSION

The compound crystallizes as colorless plate-like crystals from an ethanol solution. There is one molecule of pentacyclo-dodecane in the unit cell of the primitive, centrosymmetric triclinic space group P-1.

The structure of the compound is as expected (see Figures). The pentacyclo-dodecane adopts a ladder-like conformation. The asymmetric unit consists of only one half of the molecule; it is located about the inversion center at [0.5, 0, 0] and through the inversion symmetry yields the full molecule.

The C4-C5 bond distances are slightly longer than normal (a typical C-C single bond is 1.54 Å). Due to the constrained nature of five fused cyclobutane rings, the C-C-C angles are significantly distorted from an ideal tetrahedral angle of 109.75° (see Table of Bond Distances and Angles).

CRYSTAL SUMMARY

Crystal data for $C_{12}H_{16}$; M_r = 160.25; Triclinic; space group P-1; *a* = 5.1984(9) Å; *b* = 5.3854(10) Å; *c* = 8.0893(14) Å; α = 84.468(5)°; β = 72.840(5)°; γ = 88.402(5)°; V = 215.37(7) $Å^3$; Z = 1; T = 120(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 0.069 mm^{-1}; d_{calc} = 1.236g.cm^{-3}; 5855 reflections collected; 1066 unique (R_{int} = 0.0287); giving R_1 = 0.0488, wR_2 = 0.1381 for 739 data with [I>2σ(I)] and R_1 = 0.0711, wR_2 = 0.1535 for all 1066 data. Residual electron density ($e^-.Å^{-3}$) max/min: 0.305/-0.176.

An arbitrary sphere of data were collected on a colorless plate-like crystal, having approximate dimensions of 0.205 × 0.191 × 0.026 mm, on a Bruker Kappa X8-APEX-II

diffractometer using a combination of ω- and φ-scans of 0.5°.[16] Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by intrinsic phasing methods and expanded routinely.[17,18] The model was refined by full-matrix least-squares analysis of F^2 against all reflections.[19] All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Thermal parameters for the hydrogens were tied to the isotropic thermal parameter of the atom to which they are bonded (1.5 × for methyl, 1.2 × for all others).

Table S5. Crystallographic data for su1409.

	4
Empirical formula	$C_{12}H_{16}$
Formula weight	160.25
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 5.1984(9) Å
	b = 5.3854(10) Å
	c = 8.0893(14) Å
Volume	215.37(7) $Å^3$
Z	1
Density (calculated)	1.236 $g.cm^{-3}$
Absorption coefficient (μ)	0.069 mm^{-1}
F(000)	88
Crystal color, habit	colorless, plate
Crystal size	0.205 × 0.191 × 0.026 mm^3
θ range for data collection	2.647 to 28.266°
Index ranges	$-6 \le h \le 6$, $-7 \le k \le 7$, $-10 \le l \le 10$
Reflections collected	5855
Independent reflections	1066 [R_{int} = 0.0287]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6753
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1066 / 0 / 55
Goodness-of-fit on F^2	1.095
Final R indices [$I>2\sigma(I)$][b]	R_1 = 0.0488, wR_2 = 0.1381
R indices (all data)	R_1 = 0.0711, wR_2 = 0.1535
Extinction coefficient	n/a
Largest diff. peak and hole	0.305 and -0.176 $e^-.Å^{-3}$

[b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(F_o^2)^2]^{1/2}$

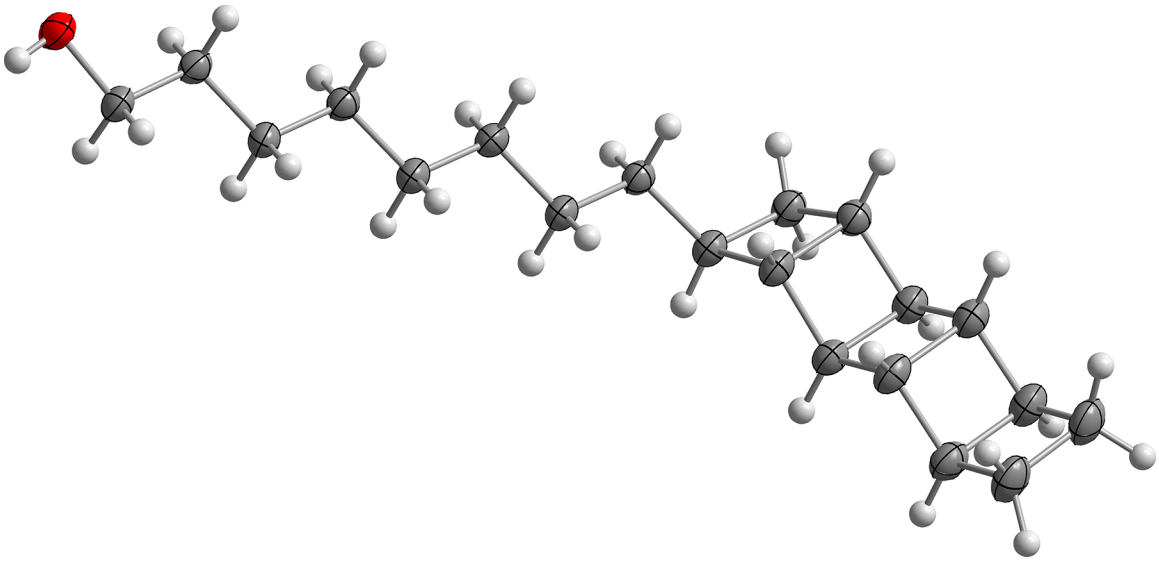


Figure S9. X-ray crystallographic structure for **S6** (stan005).

DISCUSSION

The compound crystallizes as colorless needle-like crystals from a hexanes / ethanol solution. There are four molecules of the compound in the unit cell of the primitive, acentric, orthorhombic space group $P2_12_12_1$.

The correct enantiomorph of the space group and absolute stereochemistry were confirmed from the known chirality of the molecule and by comparison of intensities of Friedel pairs of reflections. The Flack *x* parameter (0.1(3)) and Hooft *y* parameter (0.0(3)) support the assertion that the correct stereochemistry is shown in the Figures.[20,21]

The structure of the compound is as expected. The hydroxyl hydrogen atom was located from a difference Fourier map and forms a hydrogen bond to the hydroxyl oxygen on a neighboring molecule resulting in a one-dimensional chain of H-bonded molecules that are parallel to the a axis.

Bond distances and angles within the fused penta-cyclobutane portion of the molecule reflect the strain imposed by the unusual bonding within this chain. For example, typical C-C single bonds are 1.54 Å, several are longer than this. A typical tetrahedral bond angle is 109.5° (see Tables of Bond Distances and Angles). The long chain moiety has typical, normal bond distances and angles.

CRYSTAL SUMMARY

Crystal data for $C_{20}H_{32}O$; M_r = 288.45; Orthorhombic; space group $P2_12_12_1$; *a* = 4.8399(4) Å; *b* = 5.2806(4) Å; *c* = 65.006(5) Å; α = 90°; β = 90°; γ = 90°; V = 1661.4(2) $Å^3$; Z = 4; T = 150(2) K; λ(synchrotron) = 1.2399 Å; μ(synchrotron) = 0.261 mm^{-1}; d_{calc} = 1.153g.cm^{-3}; 18352 reflections collected; 3365 unique (R_{int} = 0.0840); giving R_1 = 0.0567, wR_2 = 0.1455 for 3097 data with [I>2σ(I)] and R_1 = 0.0605, wR_2 = 0.1483 for all 3365 data. Residual electron density ($e^-.Å^{-3}$) max/min: 0.239/-0.282.

An arbitrary sphere of data were collected on a colorless needle-like crystal,

having approximate dimensions of 0.290 × 0.030 × 0.015 mm, on a Bruker PHOTON-100 CMOS diffractometer using a combination of ω- and φ-scans of 0.5°.[16] Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by vecmap methods and expanded routinely.[17,18] The model was refined by full-matrix least-squares analysis of F^2 against all reflections.[19] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

ACKNOWLEDGMENT

Samples for synchrotron crystallographic analysis were submitted through the SCrALS (Service Crystallography at Advanced Light Source) program. Crystallographic data were collected at Beamline 11.3.1 at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory. The ALS is supported by the U.S. Dept. of Energy, Office of Energy Sciences, under contract DE-AC02-05CH11231.

Table S6. Crystallographic data for stan005.

	S6
Empirical formula	$C_{20}H_{32}O$
Formula weight	288.45
Temperature	150(2) K
Wavelength	1.2399 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 4.8399(4) Å
	b = 5.2806(4) Å
	c = 65.006(5) Å
Volume	1661.4(2) Å^3
Z	4
Density (calculated)	1.153 g.cm^{-3}
Absorption coefficient (μ)	0.261 mm^{-1}
F(000)	640
Crystal color, habit	colorless, needle
Crystal size	0.290 × 0.030 × 0.015 mm^3
θ range for data collection	2.186 to 50.881°
Index ranges	$-5 \le h \le 6$, $-6 \le k \le 6$, $-81 \le l \le 81$
Reflections collected	18352
Independent reflections	3365 [R_{int} = 0.0840]
Completeness to θ = 48.068°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9285 and 0.6739
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3365 / 0 / 191
Goodness-of-fit on F^2	1.043
Final R indices [$I>2\sigma(I)$][b]	R_1 = 0.0567, wR_2 = 0.1455
R indices (all data)	R_1 = 0.0605, wR_2 = 0.1483
Absolute structure parameter	0.1(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.239 and -0.282 e$^-$.Å^{-3}

[b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(F_o^2)^2]^{1/2}$

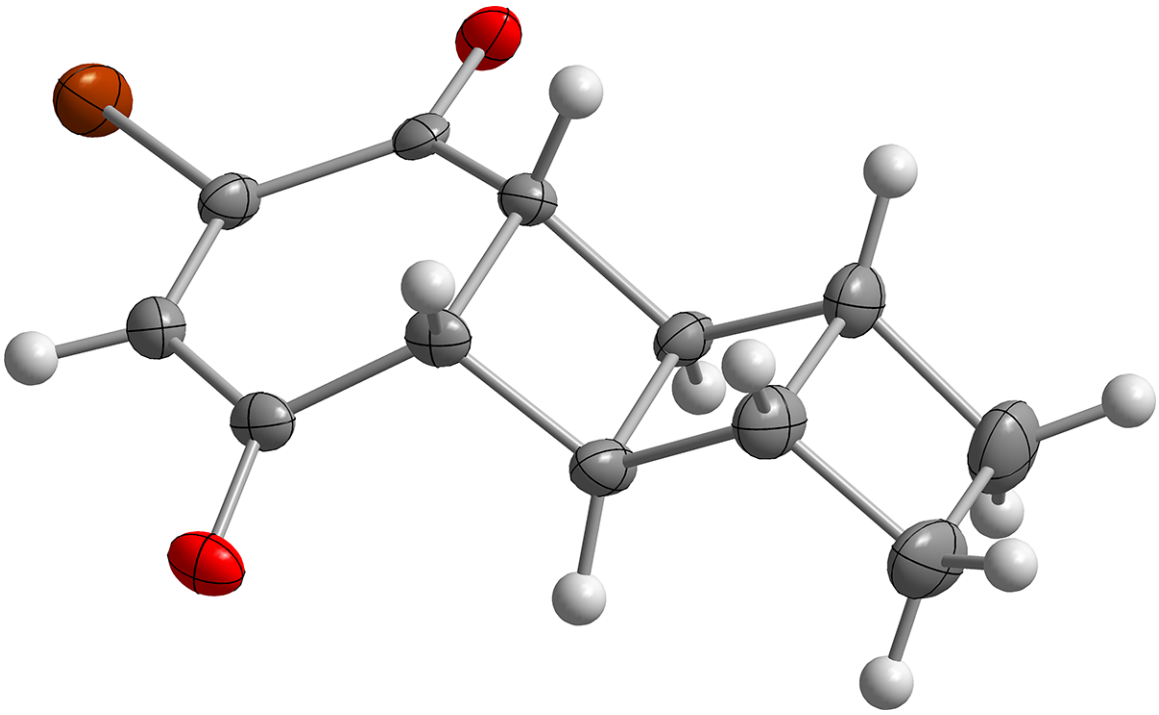


Figure S10. X-ray crystallographic structure for **18** (su1601).

DISCUSSION

The compound crystallizes as colorless tablet-like crystals from a hexanes solution. There are two crystallographically independent, yet chemically identical, molecules of the compound in the asymmetric unit of the primitive, acentric orthorhombic space group $P2_12_12_1$. The correct absolute stereochemistry of both molecules was determined both by comparison with the known handedness and by comparison of Friedel pairs of reflections. Two independent Friedel pair analyses yielded a Flack *x* parameter = 0.014(10)[20] and a Hooft *y* parameter = 0.000(7).[21] Both of these support the correct absolute stereochemistry that is shown in the Figures.

Both of the molecules present in the structure have the expected geometry and connectivity. The C-O distances reflect the double character of these bonds (see Table of Bond Distances) and the presence of a localized double bond at C1-C12 / C13-C24 is also supported by these bond distances. Bond angles along the fused cyclobutane rings are necessarily constrained and distorted from an ideal tetrahedral geometry. The C4-C9, C5-C8, C16-C21 and C17-C20 bond distances are also elongated compared with a typical C-C single bond (around 1.54 Å).

CRYSTAL SUMMARY

Crystal data for $C_{12}H_{11}BrO_2$; M_r = 267.12; Orthorhombic; space group $P2_12_12_1$; *a* = 5.7396(5) Å; *b* = 8.7298(7) Å; *c* = 42.762(3) Å; α = 90°; β = 90°; γ = 90°; V = 2142.6(3) $Å^3$; Z = 8; T = 120(2) K; λ(Cu-Kα) = 1.54184 Å; μ(Cu-Kα) = 5.038 mm^{-1}; d_{calc} = 1.656g.cm^{-3}; 38770 reflections collected; 4162 unique (R_{int} = 0.0478); giving R_1 = 0.0373, wR_2 = 0.0914 for 4146 data with [I>2σ(I)] and R_1 = 0.0374, wR_2 = 0.0915 for all

4162 data. Residual electron density ($e^{-}.Å^{-3}$) max/min: 0.345/-0.574.

An arbitrary sphere of data were collected on a colorless plate-like crystal, having approximate dimensions of 0.337 × 0.206 × 0.050 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5°.[16] Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by intrinsic phasing methods and expanded routinely.[17,18] The model was refined by full-matrix least-squares analysis of F^2 against all reflections.[19] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

Table S7. Crystallographic data for su1601.

	18
Empirical formula	$C_{12}H_{11}BrO_2$
Formula weight	267.12
Temperature	120(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.7396(5) Å
	b = 8.7298(7) Å
	c = 42.762(3) Å
Volume	2142.6(3) $Å^3$
Z	8
Density (calculated)	1.656 $g.cm^{-3}$
Absorption coefficient (μ)	5.038 mm^{-1}
F(000)	1072
Crystal color, habit	colorless, plate
Crystal size	0.337 × 0.206 × 0.050 mm^3
θ range for data collection	2.066 to 72.349°
Index ranges	$-7 \le h \le 6$, $-10 \le k \le 10$, $-52 \le l \le 52$
Reflections collected	38770
Independent reflections	4162 [R_{int} = 0.0478]
Completeness to θ = 67.679°	98.9 %
Absorption correction	Numerical
Max. and min. transmission	0.9526 and 0.2975
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4162 / 0 / 271
Goodness-of-fit on F^2	1.246
Final R indices [I>2σ(I)][b]	R_1 = 0.0373, wR_2 = 0.0914
R indices (all data)	R_1 = 0.0374, wR_2 = 0.0915
Absolute structure parameter	0.014(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.345 and -0.574 $e^-.Å^{-3}$

[b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(F_o^2)^2]^{1/2}$

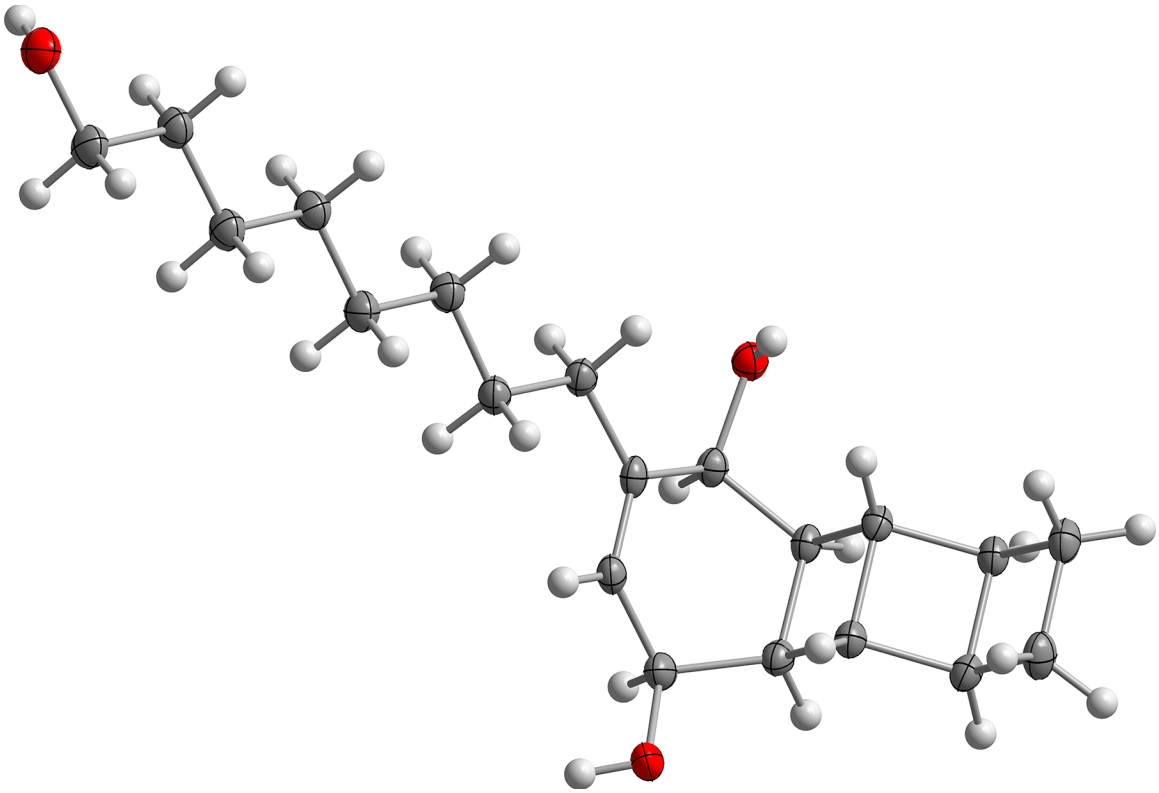
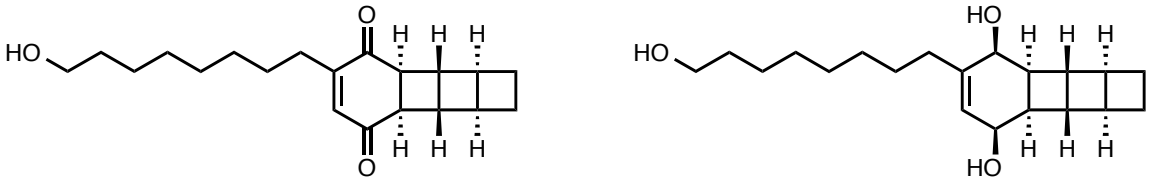


Figure S11. X-ray crystallographic structure for **20** (suRBG).



S21 **20**

[3]-ladderane triol (20):

To a solution of (–)-**19** (80 mg, 0.183 mmol, 1.0 equiv) in DCM (3.7 mL, 0.05 M) and H_2O (0.37 mL, 0.5 M) at 0 ºC (ice bath) was added DDQ (83 mg, 0.366 mmol, 2.0 equiv) in a single portion. The reaction mixture was allowed to stir vigorously for 3 hours, then filtered through celite, eluting with DCM (5 mL). The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (40% EtOAc/hexanes) to yield the intermediate **S21** (50.8 mg, 88%) as a light yellow oil.

S22 (32 mg, 0.101 mmol, 1.0 equiv) was taken up in dry THF (1.0 mL, 0.1 M), and the resulting solution was cooled to –78 °C (dry ice/acetone bath). A 1.0 M solution of DIBAL-H in hexanes (506 µL, 0.506 mmol, 5.0 equiv) was added by syringe, and the resulting solution was allowed to stir at –78 °C for 1 hour, then warmed to 0 °C (ice

bath). After 3 hours at 0 °C, the reaction was quenched by the careful addition of a sat. aq. solution of Rochelle's salt (1 mL), and allowed to stir vigorously for 30 min. The mixture was diluted with Et_2O (3 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 3 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (60% to 100% EtOAc/hexanes) to provide triol **20** (12.6 mg, 39%) as a white solid.

DISCUSSION

The compound crystallizes as colorless needles grown from a $MeOH/H_2O$ solution of 88% *ee* **20**. Within the unit cell, there is only one crystallographically independent molecule within the space group $P2_1$, which is primitive, monoclinic, and acentric.

The correct enantiomorph of the space group and molecular chirality was determined by the known stereochemistry and comparison of intensities of Friedel pairs of reflections. The Flack *x* parameter is given a value of 0.06(7).[20]

ACKNOWLEDGEMENT

Single-crystal X-ray diffraction experiments were performed at the Stanford Nanocharacterization Laboratory (SNL) and at Beamline 11.3.1 at the Advanced Light Source (ALS). The ALS is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under contract no. DE-AC02-05CH11231.

Table S8. Crystallographic data for ccals1.

Empirical formula	C20 H32 O3	
Formula weight	320.45	
Temperature	100(2) K	
Wavelength	1.5498 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.8081(7) Å	a= 90°.
	b = 5.2469(3) Å	b= 113.302(2)°.
	c = 14.5094(8) Å	g = 90°.
Volume	895.54(9) $Å^3$	
Z	2	
Density (calculated)	1.188 Mg/m^3	
Absorption coefficient	0.594 mm^{-1}	
F(000)	352	
Crystal size	0.300 x 0.070 x 0.060 mm^3	
Theta range for data collection	3.334 to 66.524°.	
Index ranges	-15<=h<=15, -5<=k<=5, -17<=l<=17	
Reflections collected	30874	
Independent reflections	2939 [R(int) = 0.0500]	
Completeness to theta = 66.524°	98.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.965 and 0.830	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2939 / 1 / 220	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1100	
R indices (all data)	R1 = 0.0406, wR2 = 0.1103	
Absolute structure parameter	0.06(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.296 and -0.170 $e.Å^{-3}$	

9. References

1. Bloomfield, J. J.; Owsley, D. C. *J. Org. Chem.* **1971**, *36*, 3768–3773.
2. Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821–1824.
3. Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889–1897.
4. Burgess, K.; Ohlmeyer, M. J.; Whitemire, K. H. *Organometallics* **1992**, *11*, 3588–3600.
5. Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M *Angew. Chem. Int. Ed.* **2016**, *55*, 6969–6972.
6. (a) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 15664–15665. (b) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118–3119.
7. Sanfilippo, C.; Patti, A.; Nicolosi, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1043–1045.
8. Huo, S. *Org. Lett.* **2003**, *5*, 423–425.
9. Sinninghe Damsté, J. S.; Strous, M.; Rijpstra, W. I. C.; Hopmans, E. C.; Geevebasen, J. A. J.; van Duin, A. C. T.; van Niftrik, L. A.; Jetten, M. S. M. *Nature* **2002**, *419*, 708–712.
10. Constantinou-Kokotou, V.; Magrioti, V.; Verger R. *Chem. Eur. J.* **2004**, *10*, 1133–1140.
11. Johns, M. K.; Yin, M.-X.; Conway, S. J.; Robinson, D. E. J. E.; Wong, L. S.-M.; Bamert, R.; Wettenhall, R. E. H.; Holmes, A. B. *Org. Biomol. Chem.* **2009**, *7*, 3691–3697.
12. (a) Gonzalez-Martinez, A.; Rodriguez-Sanchez, A.; Garcia-Ruiz, M. J.; Muñoz-Palazon, B.; Cortes-Lorenzo, C.; Osorio, F. *Chem. Eng. J.* **2016**, *287*, 557–567. (b) Gonzalez-Martinez, A.; Rodriguez-Sanchez, A.; Martinez-Toledo, M. V.; Garcia-Ruiz, M.-J.; Hontoria, E.; Osorio-Robles, F.; Gonzalez-Lopez, J. *Sci. Total Environ.* **2014**, *476–477*, 276–287. (c) Hao, X., Heijnen, J. J.; van Loosdrecht, M. C. M. *Biotech. Bioeng.* **2002**, *77*, 266–277.
13. Bligh, E. G.; Dyer, W. J. *Can. J. Biochem. Physiol.* **1959**, *37*, 911–917.
14. Reeves, J. P.; Dowben, R. M. *J. Cell. Physio.* **1969**, *73*, 49–60.
15. (a) Manchoju, A.; Thorat, R. G.; Pansare, S. V. *Eur. J. Org. Chem.* **2015**, 5939–5943. (b) Molander, G. A.; Ham, J.; Seapy, D. G.; *Tetrahedron* **2007**, *63*, 768−775. (c) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.
16. Bruker AXS. *APEX-2*. Bruker-Nonius AXS. Madison, Wisconsin, 2014.
17. Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112–122.
18. Sheldrick, G. M. *Acta Cryst.* **2015**, *A71*, 3–8.
19. Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3–8.
20. Parsons, S.; Flack, H. D.; Wagner, T. *Acta Cryst*. **2013**, *B69*, 249–259.
21. Hooft, R. W. W., Straver, L. H. & Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96–103.
22. Sheldrick, G. M. *SHELXL-97, a program for crystal structure refinement*. Göttingen, 1997.
23. Muller, P.; Herbst-Irmer, R.; Spek, A. L.; Schneider, T. R.; Sawaya, M. R. *Crystal Structure Refinement: A Crystallographer's Guide to SHELXL*. Oxford University Press, New York, 2006.
24. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.