Enantioselective Formal Synthesis of (−)-Englerin A via a Rh-catalyzed [4+3] Cycloaddition Reaction

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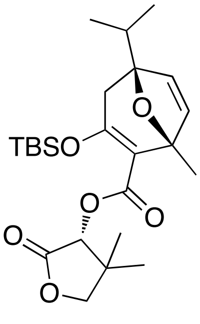
SUPPORTING INFORMATION

General Procedures

All reactions were carried out under argon atmosphere. Solvents were dried as follows: THF over sodium-benzophenone, toluene over Na, dichloromethane and MeOH over CaH_2. NEt_3, diisopropylamine and propanaldehyde were dry distilled from flamed dried 4Å powdered molecular sieves. Dry hexanes was purchased from Sigma Aldrich and used directly. Chromatography: Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using Hexane-EtOAc (H-E) mixtures of increasing polarity. ^{13}C NMR and ^{1}H NMR spectra: These were recorded on 400 MHz and 500 MHz Varian instruments and 500 MHz JOEL instrument. $CDCl_3$ was treated with flamed dried K_2CO_3, chemical shifts (δH) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak ($CHCl_3$), with the abbreviations s, br s, d, t, q, and m denoting singlet, broad singlet, doublet, triplet, and multiplet respectively. *J* = coupling constants given in Hertz (Hz) were analyzed by MestReNova software. Mass spectra**:** HRMS were recorded on a trisector WG AutoSpecQ spectrometer. Optical Rotation: $[\alpha]_D$ measurments were collected on a Jasco P-1010 polarimeter using HPLC grade $CHCl_3$ (dried over molecular sieves). Microwave reactor: Microwave experiments were carried out in Biotage (model:Initiator) microwave reactor using high pressure vessels.

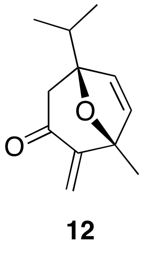
(1*R*,5*S*)-(*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl3-[(*tert*-butyldimethylsilyl)oxy]-5-isopropyl-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (5).



5

A solution of **7** (11.2 g, 31.6 mmol) in dry hexanes (750 mL) was added dropwise over 5.5 hours to a refluxing solution of **6** (7.85 g, 8.8 mL) and Rhodium(II) octanoate dimer (492 mg) in dry hexanes (750 mL). The reaction mixture was stirred an additional 30 minutes, at which time TLC showed no starting material remaining. The reaction mixture was then allowed to cooled down to room temperature, filtered and concentrated. Crude product purification using flash column chromatography (hexanes to 10%, very slow gradient, EtOAc/hexanes) afforded 8.1 g of bicyclic ester **5** as colorless thick oil (68%).
$[\alpha]_D^{23}$ = + 36.40 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.38 (dd, *J* = 5.7, 0.5 Hz, 1H), 5.72 (d, *J* = 5.7 Hz, 1H), 5.40 (s, 1H), 4.04 (q, *J* = 8.9 Hz, 2H), 2.41 (d, *J* = 17.4 Hz, 1H), 1.95 - 1.83 (m, 2H), 1.62 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 164.2, 157.2, 141.6, 126.8, 117.9, 88.6, 82.8, 76.3, 75.0, 40.2, 37.1, 34.3, 25.8, 23.4, 21.5, 20.6, 18.4, 17.2, 17.1, -3.4, -3.5. HRMS (FAB) *m/z*: cacld for $C_{24}H_{38}O_6SiNa$ (M+Na$^+$) 473.2330, found: 473.2331.

(1*R*,5*S*)-5-isopropyl-1-methyl-2-methylene-8-oxabicyclo[3.2.1]oct-6-en-3-one (12).

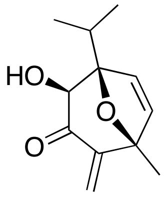


12

To a solution of **5** (20.7 g, 45.9 mmol) in dry dichloromethane (459 mL) was added quickly dropwise via addition funnel a 1.0 M solution of DIBAL in heptanes (344.3 mmol, 344.3 mL) at -78 °C. After completion of addition, the reaction was stirred for 15 min at which time TLC showed no starting material. The reaction mixture was quenched with saturated potassium sodium tartrate solution (300 mL), was allowed to reach room temperature and was stirred for 1 hour. The reaction mixture was filtered through celite and washed with DCM until TLC showed no more crude product remaining in the filter cake. The filtered mixture was separated, extracted (2 x 150 mL), washed with brine (300 mL) dried over Na_2SO_4, filtered, and concentrated under vacuum to 500 mL of DCM. This solution was flushed with Argon and treated directly with $BF_3{\cdot}Et_2O$ (68.9 mmol, 8.7mL) dropwise at -30 °C. 5 min after addition TLC showed no starting material. The reaction mixture was further diluted with DCM (250 mL), quenched with saturated $NaHCO_3$ solution (350 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Crude product purification using flash column chromatography (1% to 10%, EtOAc/Hexanes) afforded 5.2 g of ketone **12** as a yellow oil (59%).

$[\alpha]_D^{23}$ = + 103.01 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.05 (d, *J* = 5.8 Hz, 1H), 5.96 (d, *J* = 0.5 Hz, 1H), 5.92 (d, *J* = 5.7 Hz, 1H), 5.24 (s, 1H), 2.56 (d, *J* = 17.7 Hz, 1H), 2.46 (d, *J* = 17.7 Hz, 1H) 2.00 - 1.89 (m, 1H), 1.61 (s, 3H), 0.99 (d, *J* = 4.9 Hz, 3H), 0.98 (d, *J* = 4.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 147.3, 136.2, 133.4, 115.2, 89.7, 84.8, 45.8, 33.6, 19.8, 17.3. HRMS (FAB) *m/z*: cacld for $C_{12}H_{17}O_2$ ($M+H^+$) 193.1223, found: 193.1224.

(1*S*,2*S*,5*R*)-2-hydroxy-1-isopropyl-5-methyl-4-methylene-8-oxabicyclo[3.2.1]oct-6-en-3-one



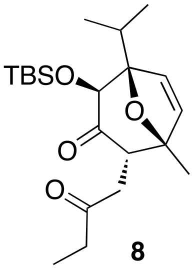
13

n-Butyllithium (77.6 mL, 124.2 mmol) was added dropwise to a solution of dry diisopropylamine (19 mL, 135.0 mmol) in dry THF (800 mL) at -78 °C. The reaction mixture was stirred for 15 minutes, and then a solution of **12** (5.2 g, 27.0 mmol) in dry THF (500 mL) was added quickly dropwise to the reaction mixture. The reaction mixture temperature was raised from -78 °C to 0 °C over 45 minutes and stirred 1 hour at 0 °C. The reaction mixture was cooled down to -78 °C and TMSCl (15.8 mL, 124.2 mmol) was added dropwise. The reaction mixture temperature was raised from -78 °C to 0 °C over 45 minutes and stirred for 1 hour at 0 °C at which time TLC showed no starting material. The reaction mixture was diluted in hexanes (650 mL) quenched with 5% $NaHCO_3$ solution (500 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. To a solution of the crude enol ether product in DCM (250 mL) a solution of $NaHCO_3$ (250 mL, 10%) was added all at once at 0 °C. Then a solution of *m*CPBA (5.2 g, 30.0 mmol) in DCM (60 mL) was added slowly while vigorous stirring of the reaction mixture. The reaction was closely monitored by TLC. When traces of enol ether (> 5%) was observed the reaction was further diluted in DCM (200 mL), quenched with saturated $NaHSO_3$ solution (300 mL), allowed to reach room temperature, extracted with DCM (2 x 200 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to approximately 250 mL. To this solution of crude epoxide product was added a solution of $(COOH)_2$ (15.6 g, 124.2 mmol) in MeOH (150 mL). After 30 min of stirring at room temperature TLC showed no epoxide product remaining. The reaction mixture was slowly quenched with saturated K_2CO_3 solution until neutral pH was achieved and extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Crude product purification using flash column chromatography (1% to 20%, EtOAc/Hexanes) afforded **12** (2.7 g) and 2.2 g of α-hydroxy ketone **13** as a crystalline solid (83% b.r.s.m). Recrystallization from hexanes afforded high purity crystals for X-Ray characterization.

$[\alpha]_D^{23}$ = + 101.00 (c 1.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 6.08 (dd, *J* = 5.8, 0.9 Hz, 1H), 6.00 (d, *J* = 5.9 Hz, 1H), 5.97 (s, 1H), 5.28 (s, 1H), 3.81 (d, *J* = 6.4 Hz, 1H), 2.37 - 2.28 (m, 1H), 1.62 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ: 199.0, 146.9, 140.2, 130.1, 116.5, 93.4, 85.5, 73.3, 28.5, 19.4, 17.7, 17.0. HRMS (ESI) *m/z*: cacld for $C_{12}H_{16}O_3Na$ ($M+Na^+$) 231.0992, found: 231.0993.

(1*S*,2*S*,4*S*,5*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-isopropyl-5-methyl-4-(2-oxobutyl)-8-oxabicyclo [3.2.1]oct-6-en-3-one (8)

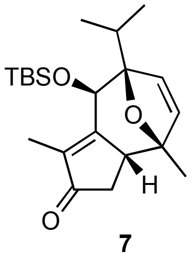


8

To a solution of **13 (**1.30 g, 6.2 mmol) in DCM (62 mL) at 0 °C was added NEt_3 (4.3 mL, 31.0 mmol). Then TBSOTf (2.9 mL, 12.4 mmol) was added dropwise to the reaction mixture. The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h at which time TLC showed no starting material. The reaction mixture was diluted in hexanes (150 mL), quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with hexanes (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Crude product purification using flash column chromatography (10:1, hexanes: EtOAc) afforded 1.96 g of corresponding TBS ether (98%) as a yellow solid. Propanaldehyde (1.7 mL, 24.4 mmol), TBS-ether (1.96 g, 6.1 mmol), catalyst **14** (329 mg, 1.2 mmol) and NEt_3 (1.0 mL, 7.3 mmol) were heated to 85 °C in a dry conical flask under argon atmosphere for 5 h. At this time TLC showed no starting material. The reaction mixture was diluted in EtOAc (150 mL), quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Crude product purification using flash column chromatography (1% to 15%, slow gradient, EtOAc/hexanes) afforded 1.78 g of diketone **8** (77%) as a yellow oil.

$[\alpha]_D^{23}$ = + 32.3 (c 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.05 (dd, *J* = 5.9, 0.6 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 3.78 (s, 1H), 3.57 (dd, *J* = 9.5, 3.8 Hz, 1H), 2.69 - 2.55 (m, 2H), 2.52 - 2.42 (m, 1H), 2.37 - 2.29 (m, 1H), 2.10 (dd, *J* = 16.5, 3.8 Hz, 1H), 1.44 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 6H), 0.90 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.6, 206.8, 138.9, 131.1, 93.7, 86.6, 74.9, 74.9, 54.6, 37.6, 36.4, 27.4, 25.9, 21.4, 18.3, 17.5, 17.3, 8.0, -4.8, -5.2. HRMS (ESI) *m/z*: cacld for $C_{12}H_{16}O_3Na$ ($M+Na^+$) 403.2275, found: 403.2278.

(3a*R*,4*R*,7*S*,8*R*)-8-((*tert*-butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyl-3a,4,7,8-tetrahydro-4,7-epoxyazulen-2(3*H*)-one (7).

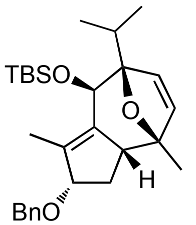


7

NaHMDS (1.0 M in THF, 11.7 ml, 5 eq.) was added dropwise to a stirred solution of **8** (890 mg, 2.34 mmol) in dry THF (3.6 ml) at 0 °C. This reaction was stirred for 2 hours at this temperature before quenched with saturated NH_4Cl solution. Then the mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (2% to 25% EtOAc/hexanes) gave 400 mg of aldol product (70% b.r.s.m.) and 250 mg recovered **8**. This aldol product was dissolved in anhydrous methanol (8 mL), and sodium methoxide (75 mg, 1.3 eq.) was quickly added in one portion. The flask was immersed in an oil bath which has pre-heated to 65 °C and stirred for 10 minutes, at which time TLC showed no starting material. This reaction was cooled to 0 °C and quenched with saturated NH_4Cl solution. Then this mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (2% to

25% EtOAc/hexanes) gave 303 mg of **7** (43% b.r.s.m. over 2 steps) as an oil.
$[\alpha]_D^{23}$ = + 188.5 (c 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.90 (d, *J* = 5.7 Hz, 1H), 5.84 (d, *J* = 5.7 Hz, 1H), 4.50 (s, 1H), 3.05 (m, 1H), 2.49 (dd, *J* = 18.9 Hz, *J* = 6.9 Hz, 1H), 2.34 (hept, *J* = 6.9 Hz, 1H), 1.71 (dd, *J* = 18.9 Hz, *J* = 3.5 Hz, 1H), 1.71 (m, 4H), 1.44 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.12 (s, 3H), -0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 208.9, 171.0, 138.0, 135.7, 132.1, 94.4, 87.2, 64.9, 45.5, 36.2, 27.8, 25.7, 21.7, 21.0, 18.3, 17.5, 17.4, 8.6, -4.5, -4.7. HRMS (ESI) *m/z*: calcd for $C_{21}H_{34}O_3SiNa$ (M+Na$^+$) 385.2169, found: 385.2173.

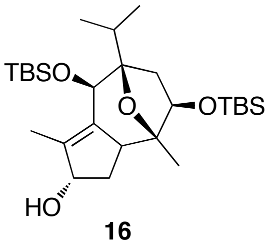
(((2*S*,3a*R*,4*R*,7*S*,8*R*)-2-(benzyloxy)-7-isopropyl-1,4-dimethyl-2,3,3a,4,7,8-hexahydro-4,7-epoxy-azulen-8-yl)oxy)(*tert*-butyl)dimethylsilane (15).



15

$NaBH_4$ (160 mg, 5 eq.) was added portionwise to a stirred solution of **7** (303 mg, 0.84 mmol) in anhydrous methanol (4 mL) at 0 °C. The ice bath was removed and this reaction was stirred for 15 min at room temperature before carefully quenched with saturated NH_4Cl solution. This mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated and dried under high vacuum to give the corresponding allylic alcohol, which was clean enough to be used directly in next step. The allylic alcohol was dissolved in anhydrous DMF (8 mL), and sodium hydride (134 mg, 4 eq., 60% in mineral oil) was added in one portion at 0 °C. The reaction was stirred at 0 °C for 5 min before benzyl bromide was added dropwise (800 µL, 8 eq.). This reaction was then heated to 60 °C for 20 minutes, at which time TLC showed no starting material. This reaction was cooled to 0 °C and quenched with saturated NH_4Cl solution. Then this mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (hexanes to 5% EtOAc/hexanes) gave about 350 mg of the product (contaminated with dibenzylether, contains 271 mg of **15**, 71% over 2 steps based on ^{1}H NMR analysis) as a colorless oil. $[\alpha]_D^{25}$ = + 58.2 (c 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.32 - 7.27 (m, 5H), 5.90 (d, *J* = 6.0 Hz, 1H), 5.87 (d, *J* = 6.0 Hz, 1H), 4.55 - 4.44 (m, 2H), 4.40 (t, *J* = 7.2 Hz, 1H), 4.25 (s, 1H), 2.74 (t, *J* = 8.1 Hz, 1H), 2.35 (dt, *J* = 12.5, 7.4 Hz, 1H), 2.27 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.36 (s, 4H), 0.98 (d, *J* = 6.9 Hz, 5H), 0.88 (d, *J* = 6.9 Hz, 6H), 0.86 (s, 9H), 0.06 (s, 3H), -0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 138.8, 138.4, 138.3, 137.2, 136.7, 131.6, 127.6, 94.2, 87.3, 86.2, 71.2, 64.3, 49.0, 32.4, 28.2, 25.9, 21.4, 18.4, 17.6, 17.5, 11.7, 1.12, -4.3, -4.4. HRMS (ESI) *m/z*: calcd for $C_{28}H_{42}O_3SiNa$ (M+Na$^+$) 477.2795, found: 477.2794.

(2*S*,4*S*,5*R*,7*R*,8*R*)-5,8-bis((*tert*-butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulen-2-ol(16).

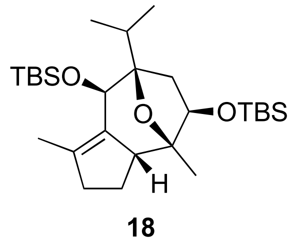


16

To a solution of **15** (150 mg, 0.33 mmol) in dry THF was added borane-THF complex (1 mL, 1.0 M in THF, 3 eq.) dropwise at 0 °C. The reaction was then stirred at room temperature for 1.5 h, at which time TLC showed no starting material. The reaction was cooled to 0°C, then was carefully added a pre-mixed solution of 3N NaOH and 30% H_2O_2 (3 mL, 1 : 1), the ice bath was removed and the reaction was stirred at ambient temperature for 1 h, at which time TLC showed no starting material. The reaction was quenched with saturated NH_4Cl solution, then this mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (5% to 40% EtOAc/hexanes) gave 94 mg (60%) of the desired C-9 β-alcohol. The C-9 β-alcohol (0.20 mmol) and triethylamine (110 µL, 4 eq.) was then dissolved in dry dichloromethane (2 mL), then TBS-triflate (92 µL, 2 eq.) was added dropwise at 0 °C. This reaction was then stirred at room temperature for 1 h before quenched with saturated $NaHCO_3$ solution. The mixture was extracted with hexanes (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give 114 mg of crude product which was used directly in the next step. The crude product (114 mg, 0.194 mmol) was dissolved in methanol (2 mL) and $Pd(OH)_2$ (11 mg, 10%) was added. After hydrogenation at atmospheric pressure for 1 h, the mixture was filtered through Celite and the solvent was removed in *vacuo*. The residue was purified by column chromatography on silica gel (2% to 10% EtOAc/hexanes) to give alcohol **16** (97 mg, 100%) as a colorless oil.

$[\alpha]_D^{23} = -2.52$ (c 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.71 - 4.64 (m, 1H), 4.06 (s, 1H), 3.98 (d, J = 2.0 Hz, 1H), 2.83 (t, J = 5.6 Hz, 1H), 2.44 - 2.37 (m, 1H), 1.75 (dd, J = 2.3, 1.0 Hz, 1H), 1.56 (dd, J = 13.5, 2.0 Hz, 1H), 1.49 - 1.44 (m, 1H), 1.19 - 1.13 (m, 1H), 0.97 (d, J = 6.8 Hz, 1H), 0.88 (s, 2H), 0.86 (s, 2H), 0.82 (d, J = 7.0 Hz, 1H), 0.06 (s, 1H), 0.03 (d, J = 3.0 Hz, 2H), -0.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 137.5, 135.8, 88.1, 87.3, 79.9, 72.4, 67.4, 50.4, 39.0, 34.3, 28.1, 25.9, 25.9, 26.1, 19.5, 18.4, 18.1, 17.8, 16.2, 11.3, -4.4, -4.4, -4.5, -4.8. HRMS (ESI) *m/z*: calcd for $C_{27}H_{52}O_4Si_2Na$ (M+Na$^+$) 519.3296, found: 519.3294.

(((3a*R*,4*S*,5*R*,7*R*,8*R*)-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (18).

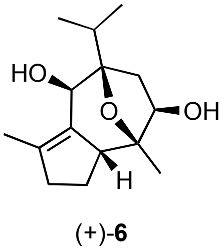


18

16 (97 mg, 0.194 mmol) was dissolved in anhydrous toluene (2 mL) and Burgess reagent (233 mg, 5 eq.) was added. This reaction was heated to 80 °C for 30 min, at which time TLC showed no starting material. Then this reaction was cooled and quenched with water, extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was dissolved directly in methanol (2 mL) and Pd/C (9 mg, 10%) was added. After hydrogenation at atmospheric pressure for 1 h, the mixture was filtered through Celite and the solvent was removed in *vacuo*. The residue was purified by column chromatography on silica gel (hexanes to 5% EtOAc/hexanes) to give **18** (84 mg, 90% over 2 steps) as a colorless oil.

$[\alpha]_D^{23}$ = + 3.98 (c 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.03 (s, 1H), 3.76 (dd, *J* = 7.2, 2.0 Hz, 1H), 3.01 - 2.87 (m, 1H), 2.47 - 2.36 (m, 1H), 2.31 (m, 1H), 2.25 - 2.17 (m, 1H), 1.93 (m, 1H), 1.73 - 1.66 (m, 3H), 1.58 (s, 3H), 1.49 (dd, *J* = 13.4, 2.1 Hz, 1H), 1.38 (dd, *J* = 13.4, 7.2 Hz, 1H), 1.15 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 8H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.03 (s, 2H), 0.00 (s, 2H), -0.00 (s, 2H), -0.05 (s, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 134.2, 134.1, 88.1, 87.7, 72.6, 67.6, 52.7, 39.2, 37.8, 29.9, 28.1, 26.0, 25.9, 22.9, 18.4, 18.2, 17.8, 16.4, 14.3, -4.5, -4.5, -4.6, -4.9 HRMS (ESI) *m/z*: calcd for $C_{29}H_{36}O_4Na$ (M+Na$^+$) 503.3347, found: 503.3350.

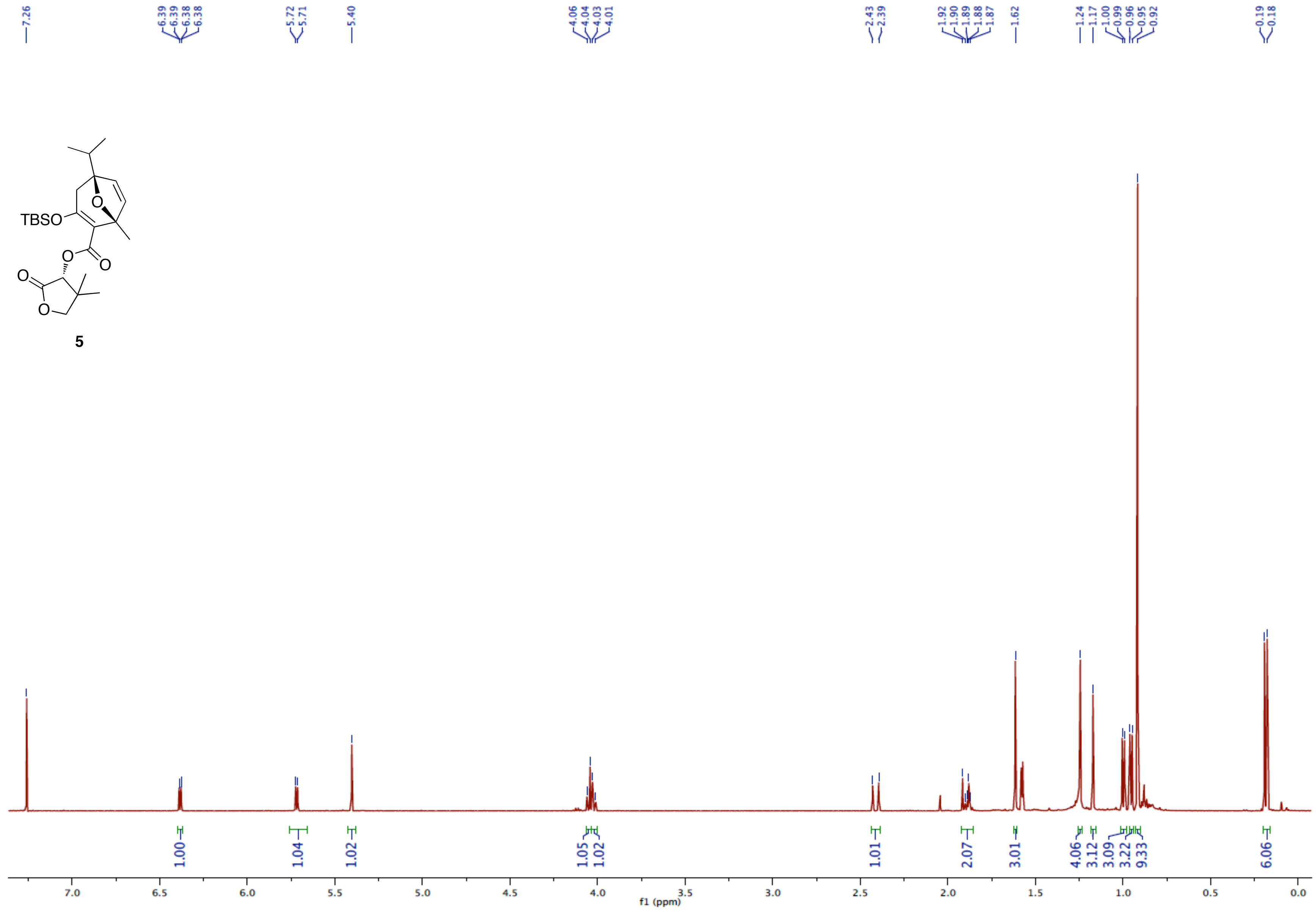
(3a*R*,4*S*,5*R*,7*R*,8*R*)-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulene-5,8-diol ((+)-6).



(+)-**6**

18 (48.1 mg, 0.1 mmol) and TBAF (1.0 M in THF, 0.3 mL, 3 eq.) was dissolved in dry THF (2 mL) in a sealed tube. This tube was then microwaved at 80 °C for 45 minutes. The reaction was then cooled to ambient temperature, quenched with pH = 7.0 buffer, Then this mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (5% to 50% EtOAc/hexanes) to give 23 mg of **(+)-6** (93%) as a colorless oil.

$[\alpha]_D^{23}$ = + 17.5 (c 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.06 (s, 1H), 3.89 (dd, *J* = 7.4 Hz, *J* = 1.5 Hz, 1H), 2.96 (m, 1H), 2.43 - 2.36 (m, 2H), 2.27 - 2.21 (m, 1H), 2.08 (br, 1H), 2.01 - 1.95 (m, 1H), 1.71 (br, s, 1H), 1.68 - 1.57 (m, 2H), 1.40 - 1.32 (m, 1H), 1.26 (m, 1H), 1.24 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ: 136.8, 132.7, 88.3, 87.3, 72.5, 66.9, 52.1, 39.0, 37.5, 28.3, 23.5, 19.2, 17.8, 16.3, 13.6. HRMS (ESI) *m/z*: calcd for $C_{15}H_{24}O_3Na$ ($M+Na^+$) 275.1618, found: 275.1619.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6.38
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5.40
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4.04
4.03
4.01
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2.39
1.92
1.90
1.89
1.88
1.87
1.62
1.24
1.17
1.00
0.99
0.96
0.95
0.92
0.19
0.18
TBSO
O
O
O
O
O
5
1.00
1.04
1.02
1.05
1.02
1.01
2.07
3.01
4.06
3.12
3.09
3.22
9.33
6.06
7.0
6.5
6.0
5.5
5.0
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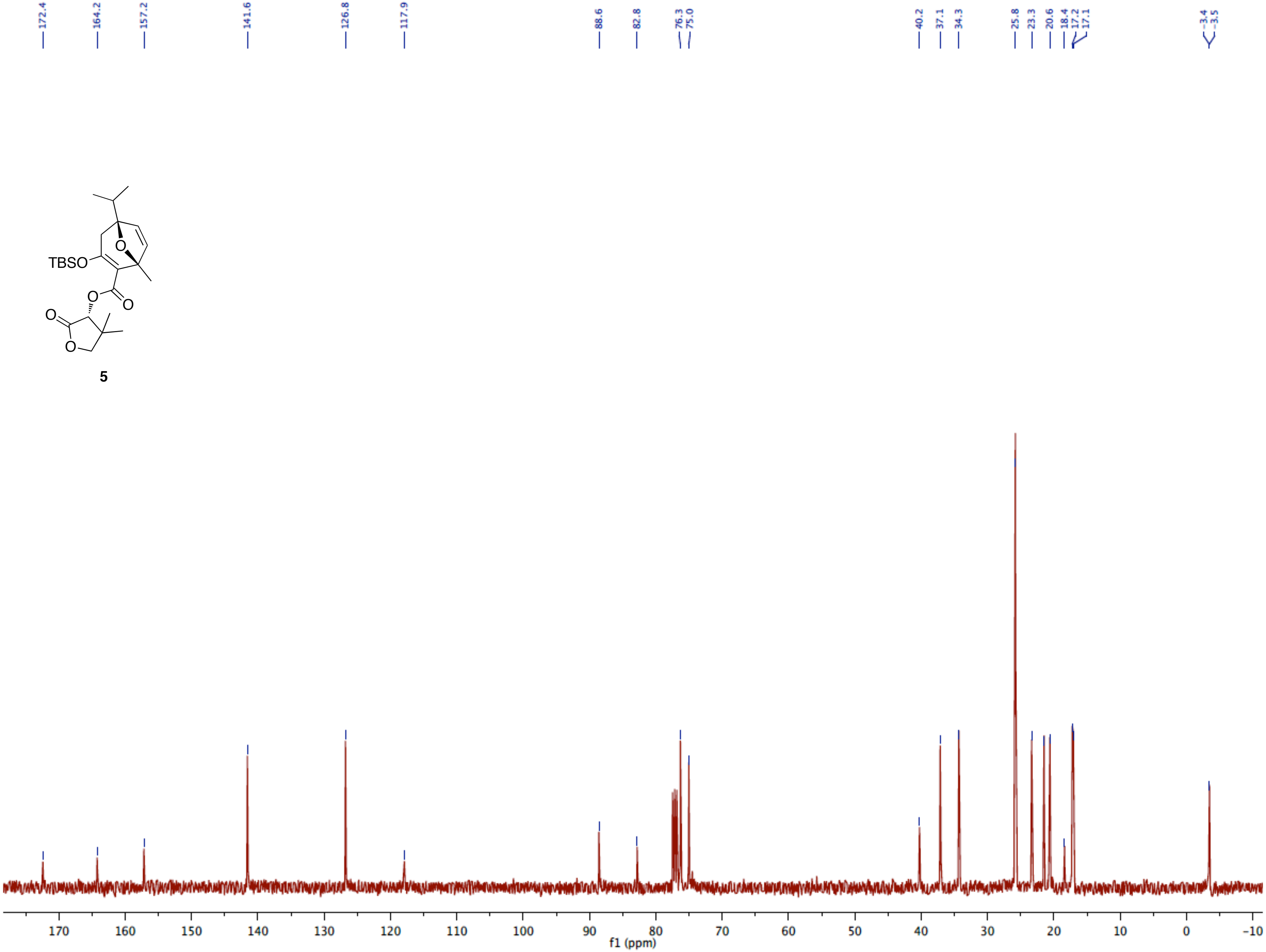
0.0
f1 (ppm)

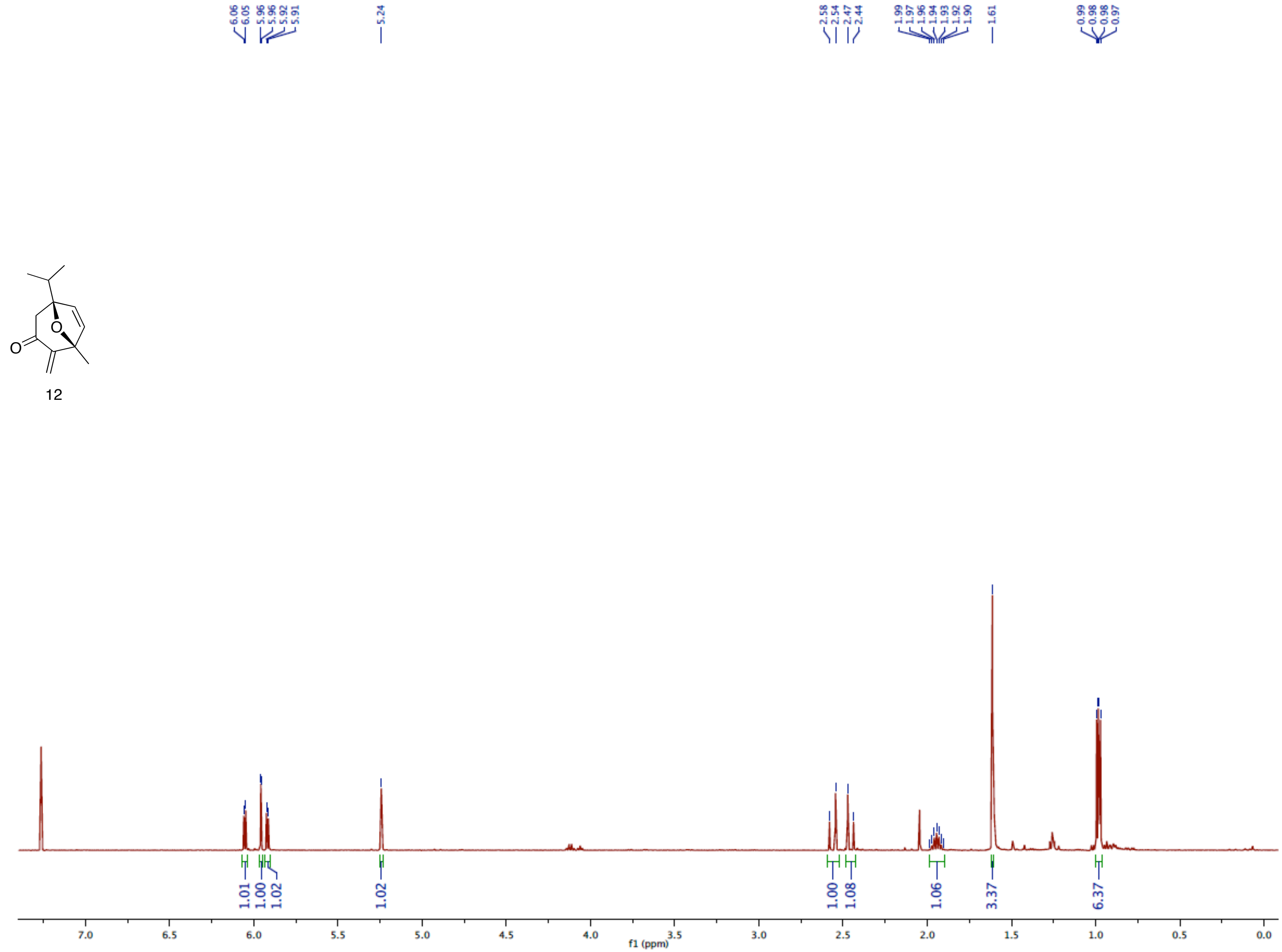

TBSO
O
O
O
O
O

5

172.4
164.2
157.2
141.6
126.8
117.9
88.6
82.8
76.3
75.0
40.2
37.1
34.3
25.8
23.3
20.6
18.4
17.2
17.1
-3.4
-3.5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

O
O

12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5.24
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1.97
1.96
1.94
1.93
1.92
1.90
1.61
0.99
0.98
0.98
0.97
1.01
1.00
1.02
1.02
1.00
1.08
1.06
3.37
6.37
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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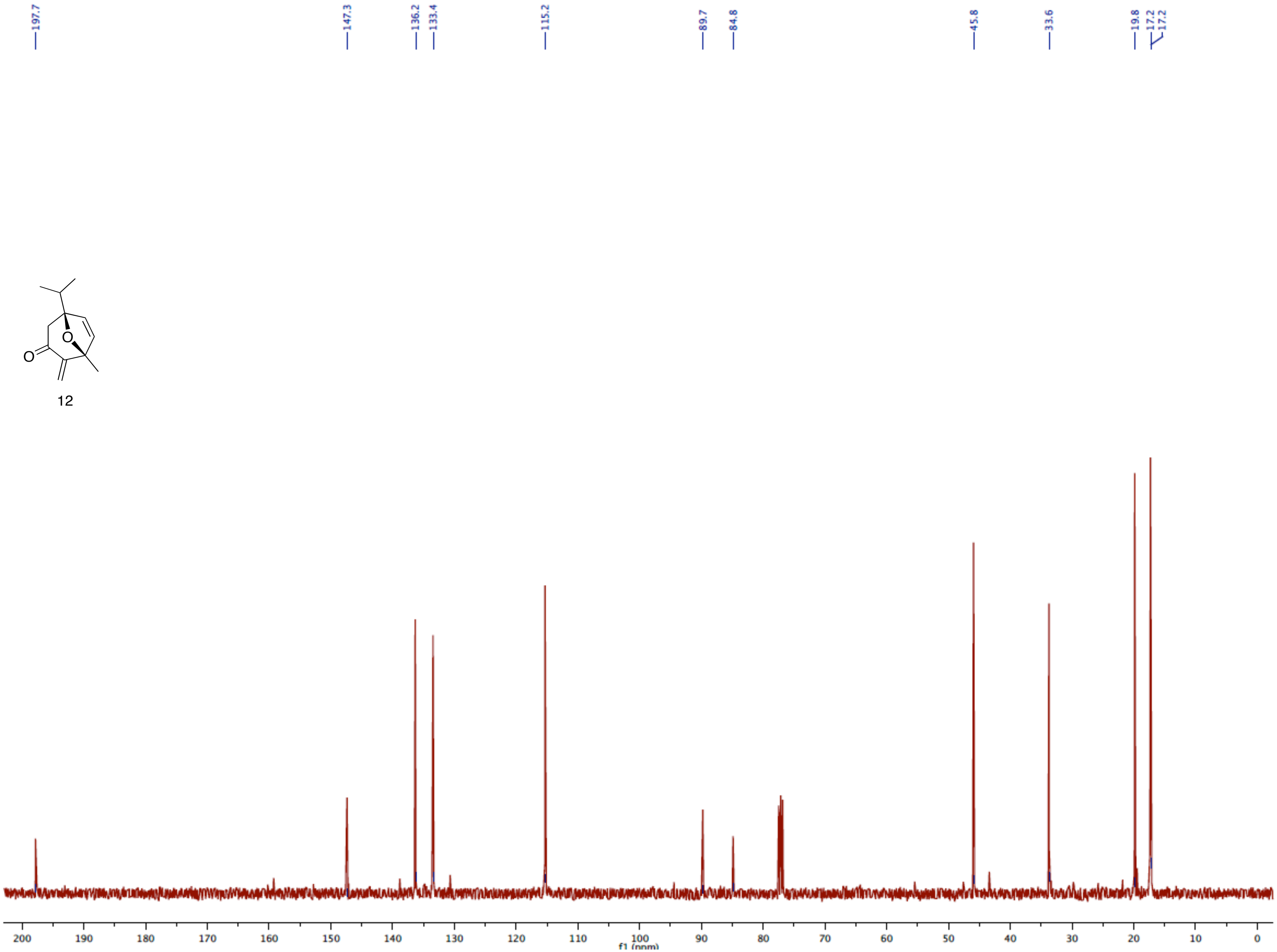
0.0
f1 (ppm)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147.3
136.2
133.4
115.2
89.7
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45.8
33.6
19.8
17.2
17.2
O
O
12
200
190
180
170
160
150
140
130
120
110
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90
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50
40
30
20
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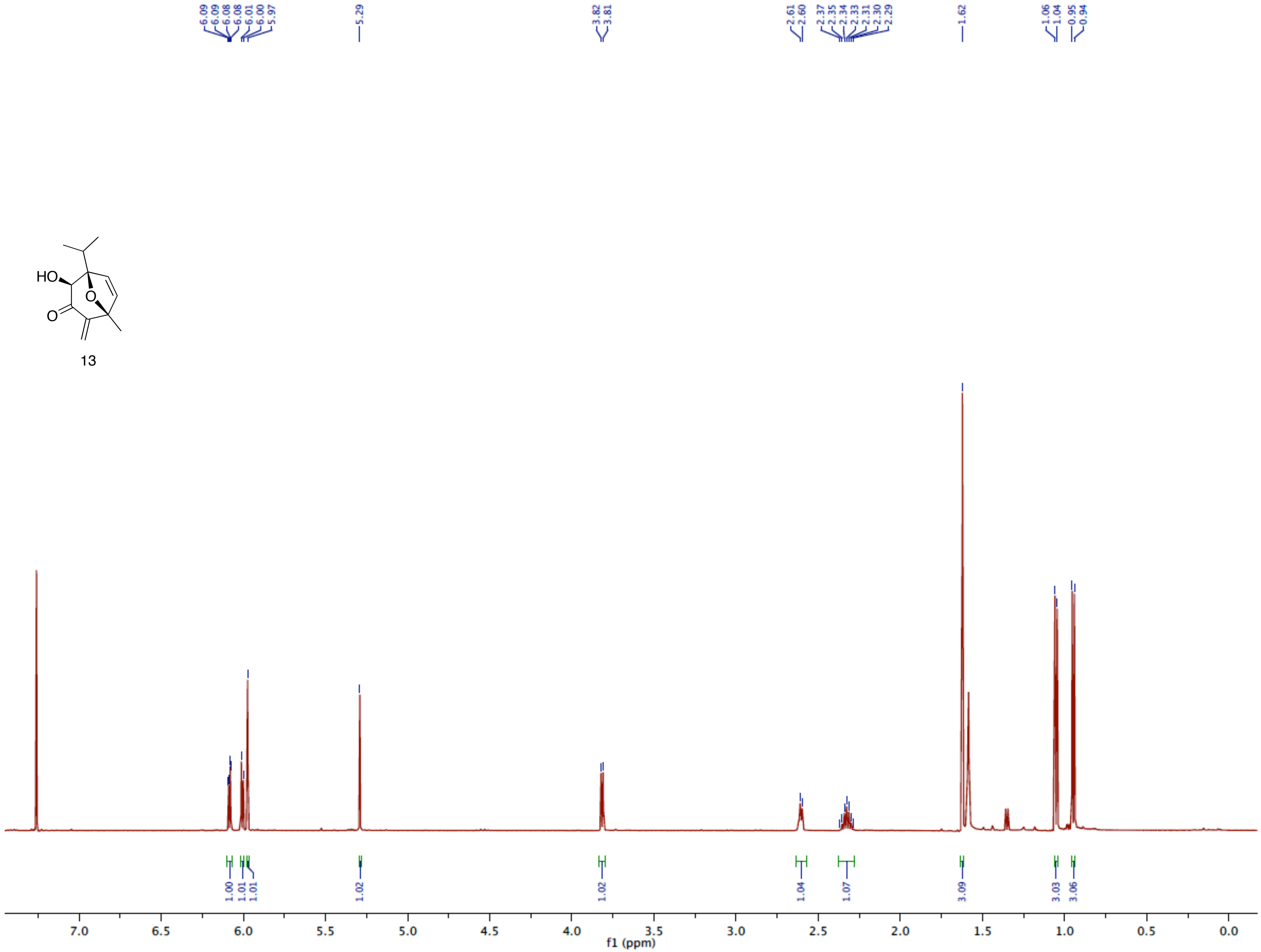
0
f1 (ppm)


13

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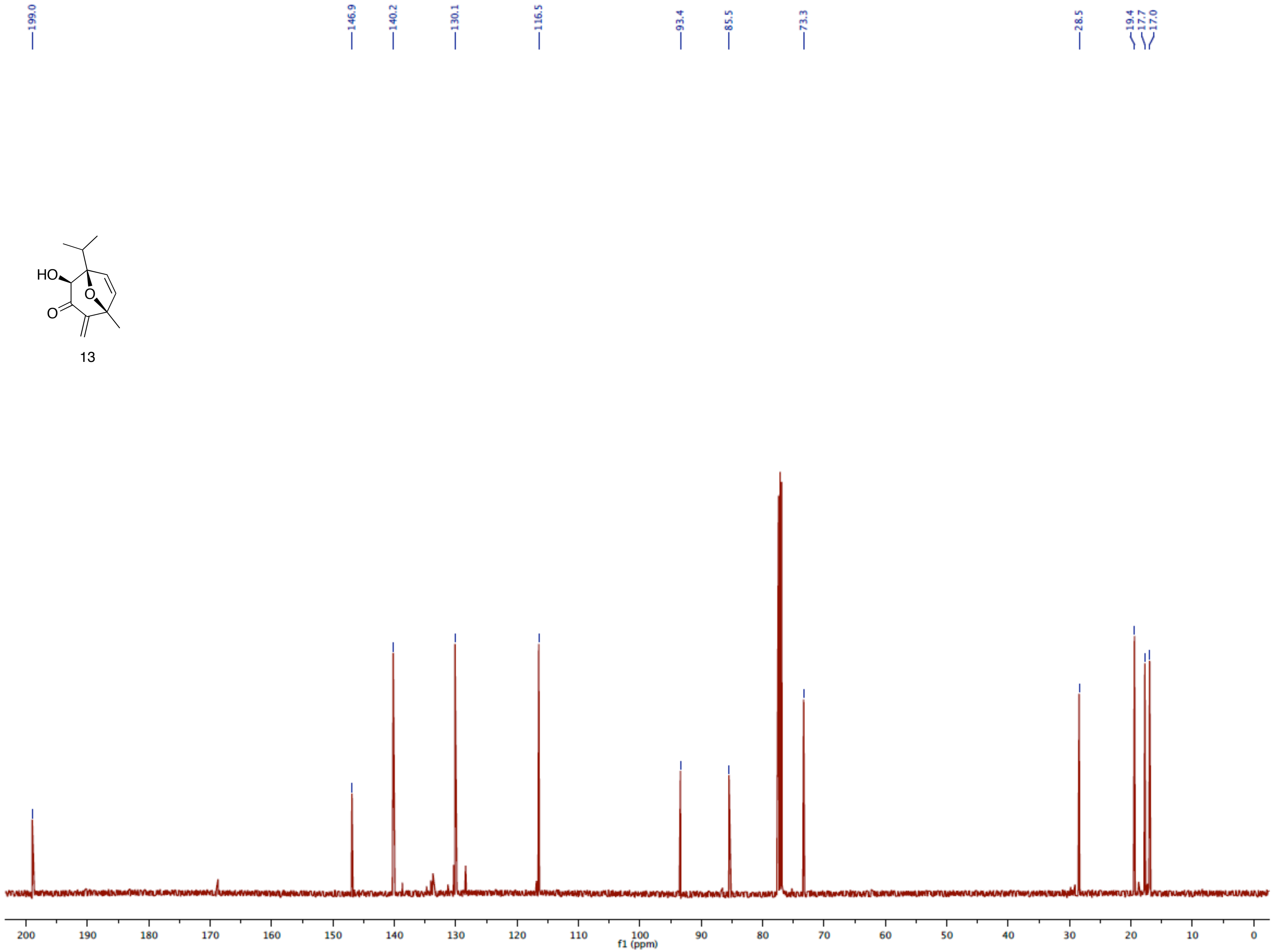
6.09
6.08
6.08
6.01
6.00
5.97
5.29
3.82
3.81
2.61
2.60
2.37
2.35
2.34
2.33
2.31
2.30
2.29
1.62
1.06
1.04
0.95
0.94
HO
O
O
1.00
1.01
1.01
1.02
1.02
1.04
1.07
3.09
3.03
3.06
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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93.4
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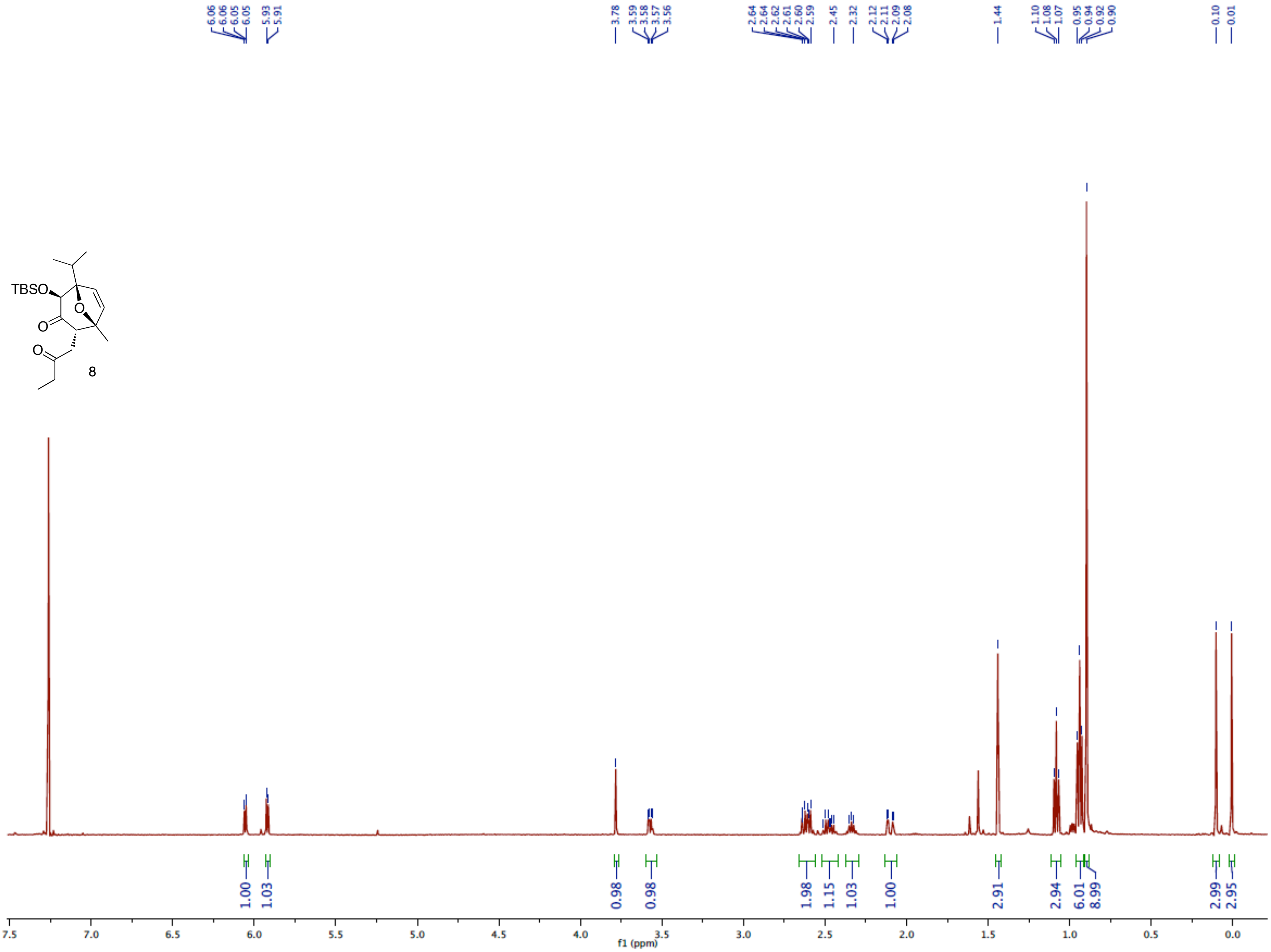
73.3
28.5
19.4
17.7
17.0
HO
O
O
13
200
190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10
0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2.60
2.59
2.45
2.32
2.12
2.11
2.09
2.08
1.44
1.10
1.08
1.07
0.95
0.94
0.92
0.90
0.10
0.01
TBSO
O
O
O
1.00
1.03
0.98
0.98
1.98
1.15
1.03
1.00
2.91
2.94
6.01
8.99
2.99
2.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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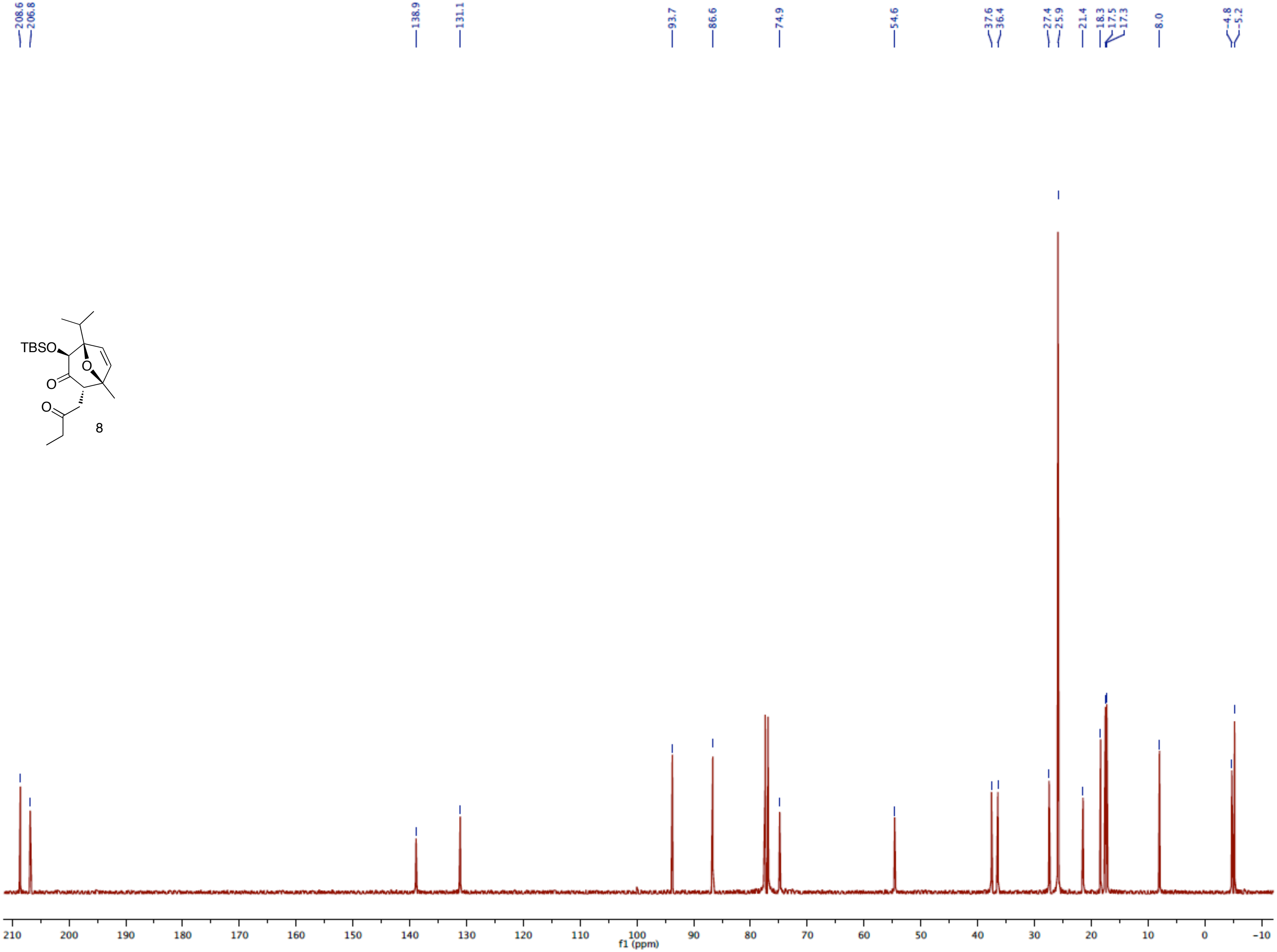
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

8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138.9
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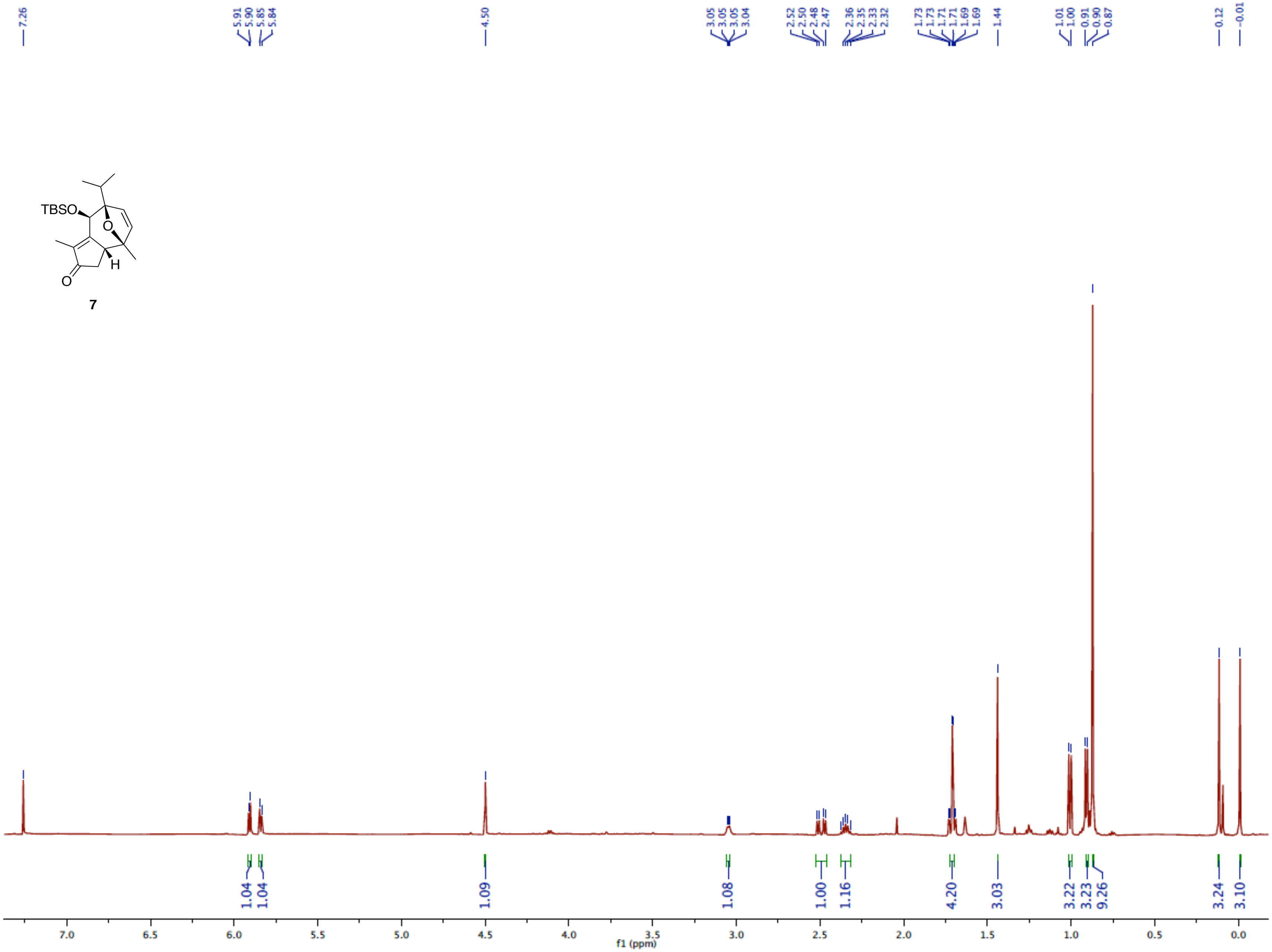
86.6
74.9
54.6
37.6
36.4
27.4
25.9
21.4
18.3
17.5
17.3
8.0
-4.8
-5.2
TBSO
O
O
O
8
210
200
190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10
0
-10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3.05
3.05
3.04
2.52
2.50
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2.47
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2.35
2.33
2.32
1.73
1.73
1.71
1.71
1.69
1.69
1.44
1.01
1.00
0.91
0.90
0.87
0.12
-0.01
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O
H
O
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1.04
1.09
1.08
1.00
1.16
4.20
3.03
3.22
3.23
9.26
3.24
3.10
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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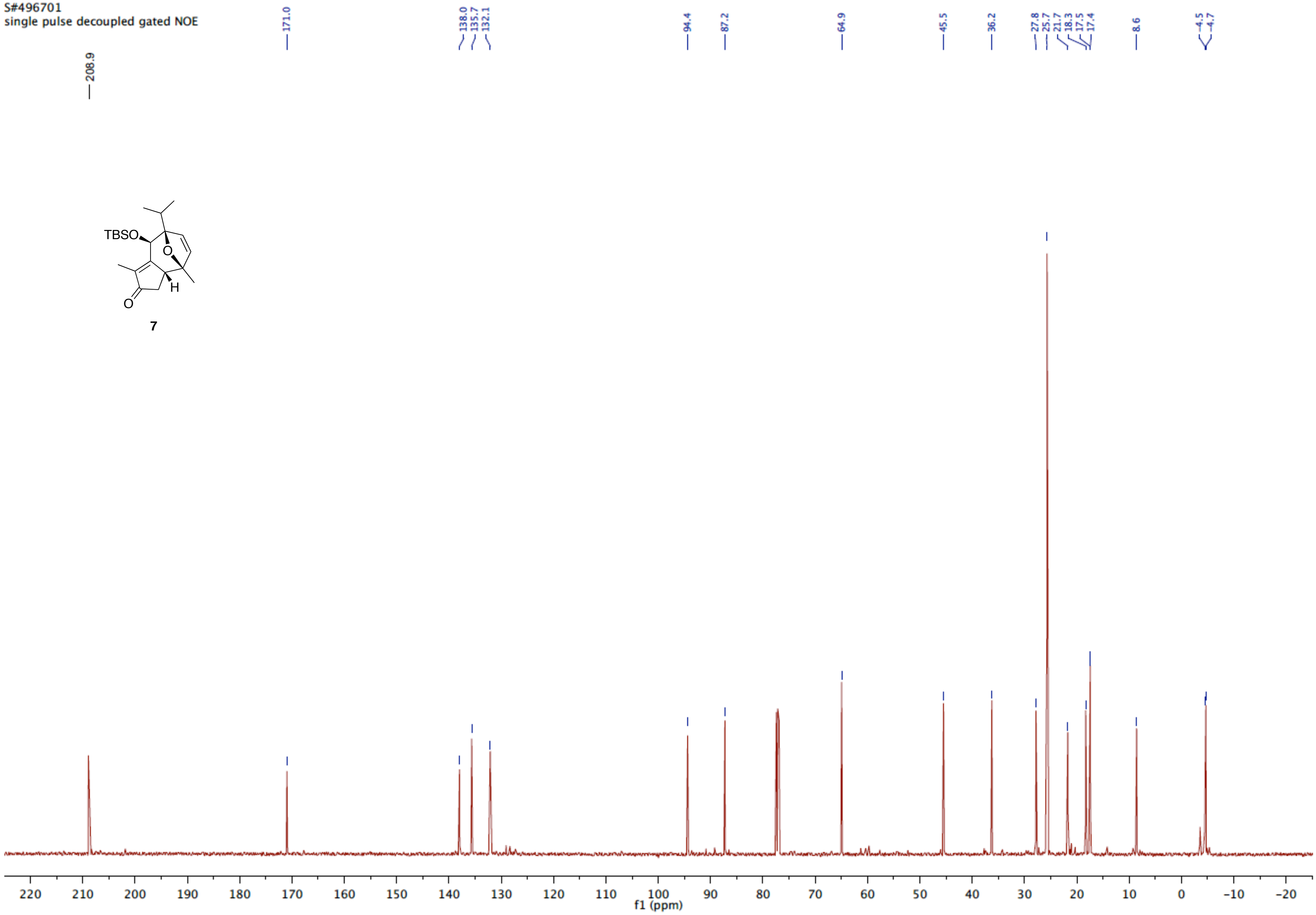
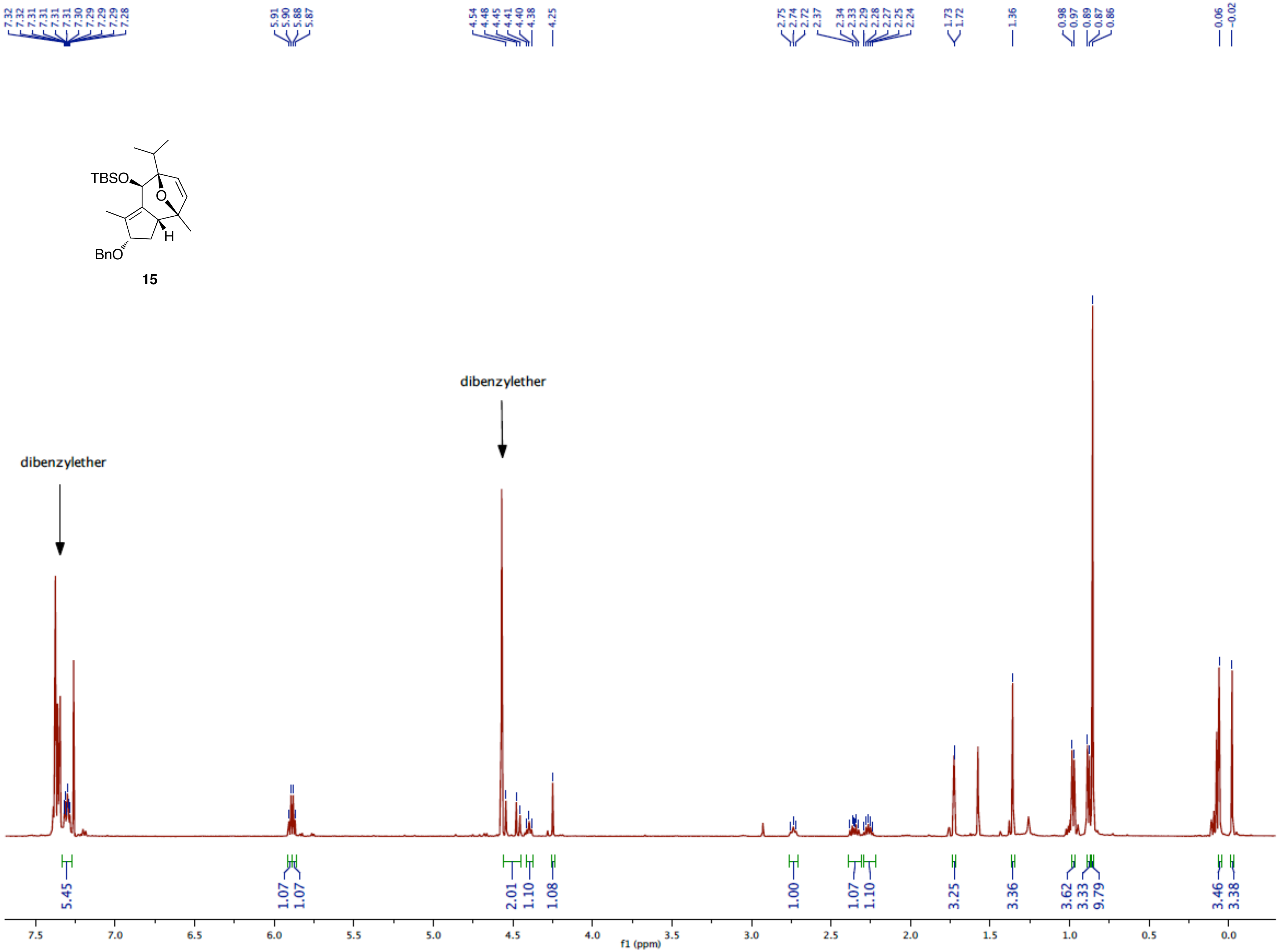
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

7

S#496701
single pulse decoupled gated NOE

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7.29
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5.90
5.88
5.87
4.54
4.48
4.45
4.41
4.40
4.38
4.25
2.75
2.74
2.72
2.37
2.34
2.33
2.29
2.28
2.27
2.25
2.24
1.73
1.72
1.36
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0.97
0.89
0.87
0.86
0.06
-0.02
TBSO
O
H
BnO
15
dibenzylether
dibenzylether
5.45
1.07
1.07
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1.10
1.08
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1.07
1.10
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3.38
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6.5
6.0
5.5
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f1 (ppm)
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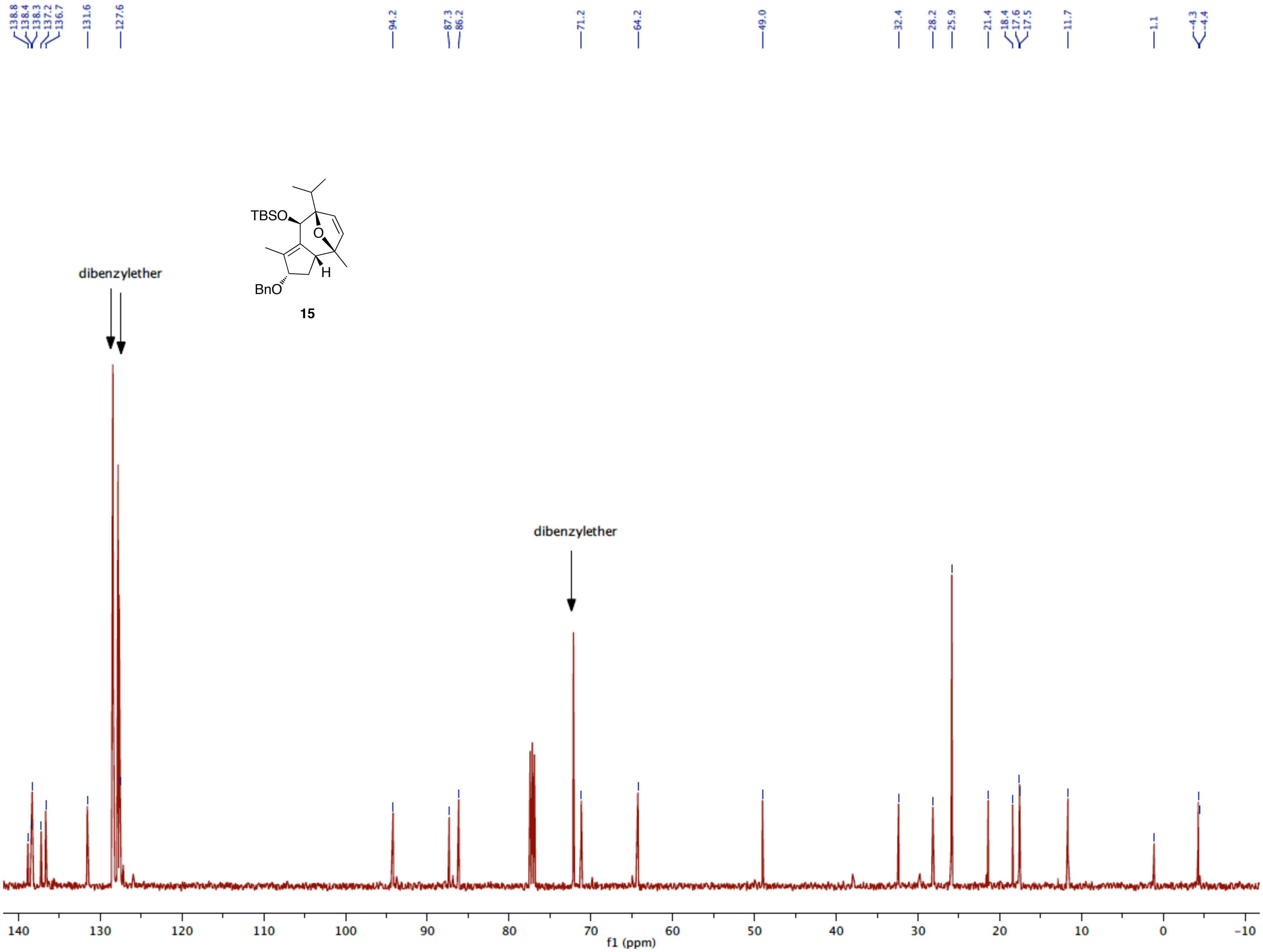
2.5
2.0
1.5
1.0
0.5
0.0



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138.3
137.2
136.7
131.6
127.6
94.2
87.3
86.2
71.2
64.2
49.0
32.4
28.2
25.9
21.4
18.4
17.6
17.5
11.7
1.1
-4.3
-4.4
TBSO
O
H
BnO
15
dibenzylether
dibenzylether
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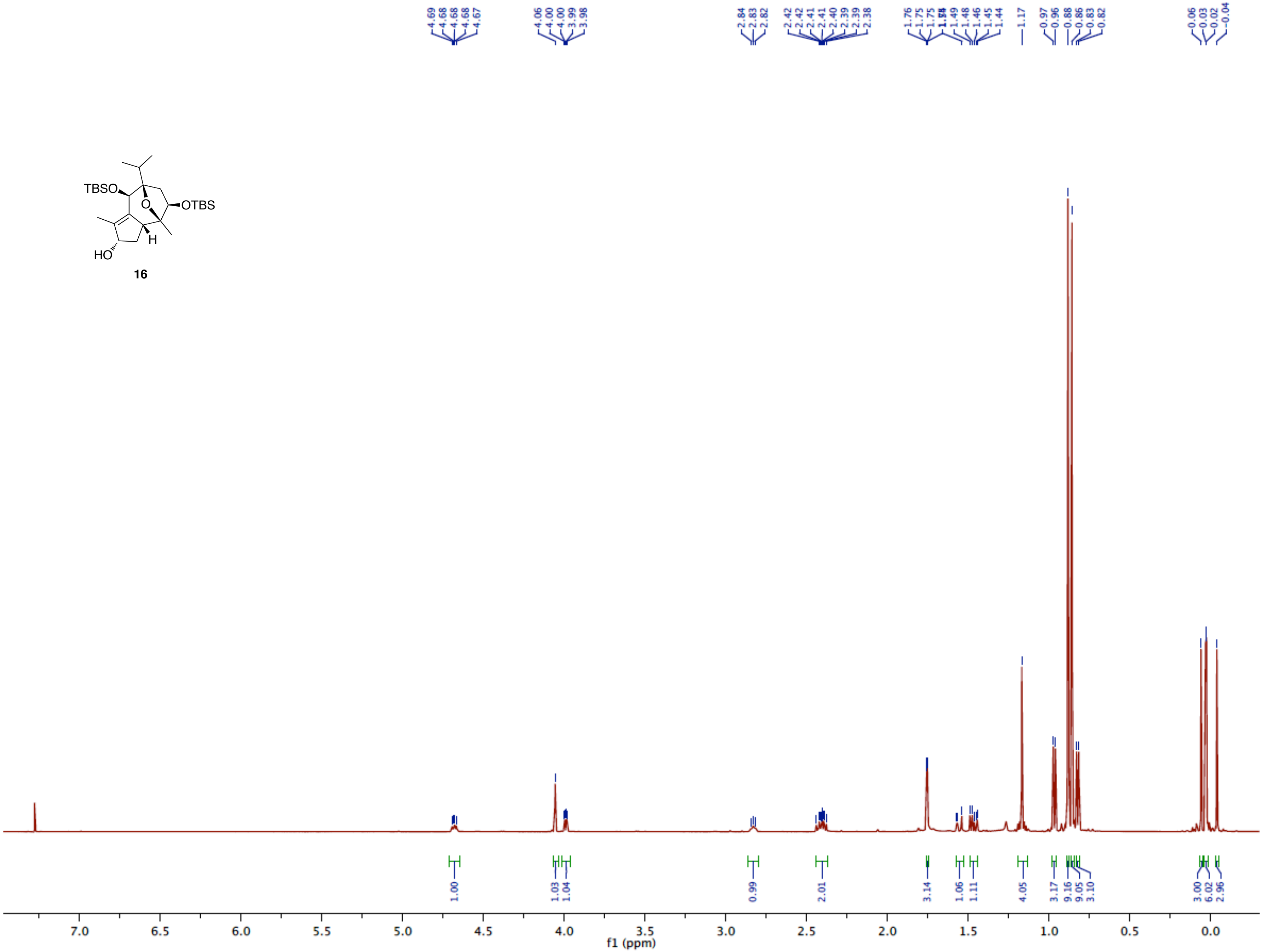
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

16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4.00
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2.82
2.42
2.42
2.41
2.41
2.40
2.39
2.39
2.38
1.76
1.75
1.75
1.54
1.49
1.48
1.46
1.45
1.44
1.17
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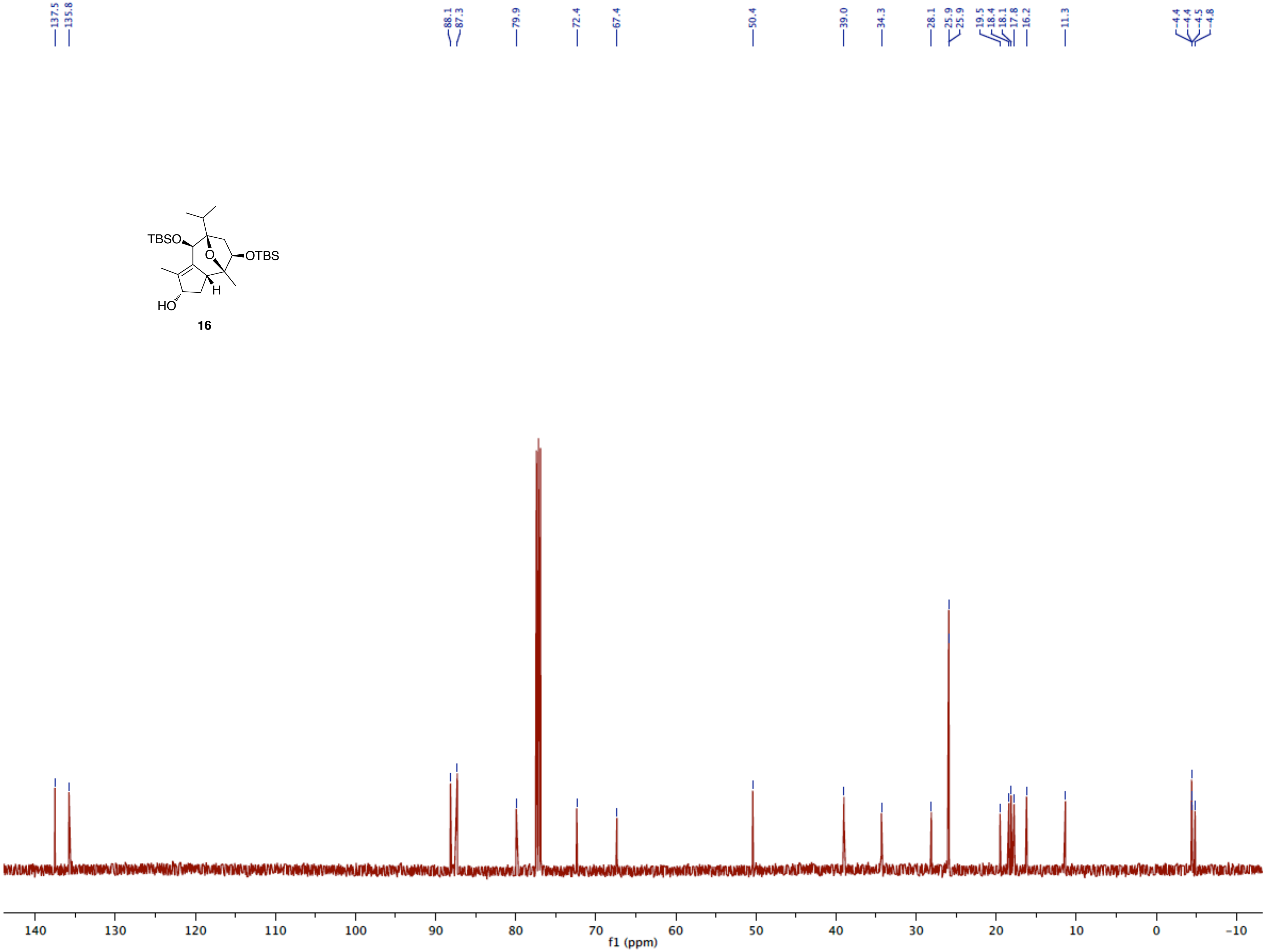
0.96
0.88
0.86
0.83
0.82
0.06
0.03
0.02
-0.04
1.00
1.03
1.04
0.99
2.01
3.14
1.06
1.11
4.05
3.17
9.16
9.05
3.10
3.00
6.02
2.96
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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72.4
67.4
50.4
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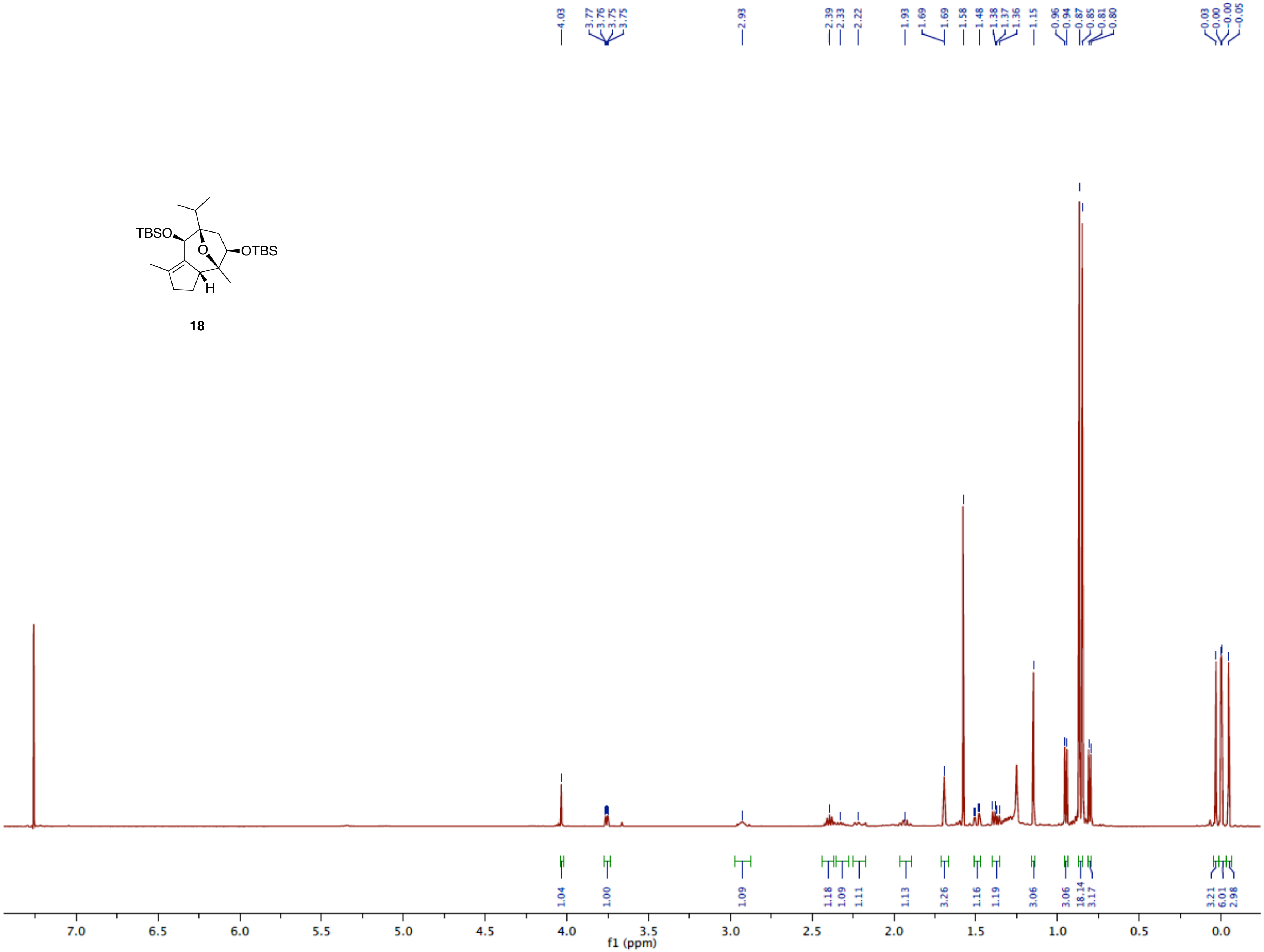
34.3
28.1
25.9
25.9
19.5
18.4
18.1
17.8
16.2
11.3
-4.4
-4.4
-4.5
-4.8
TBSO
OTBS
O
H
HO
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

16

TBSO
O
OTBS
H

18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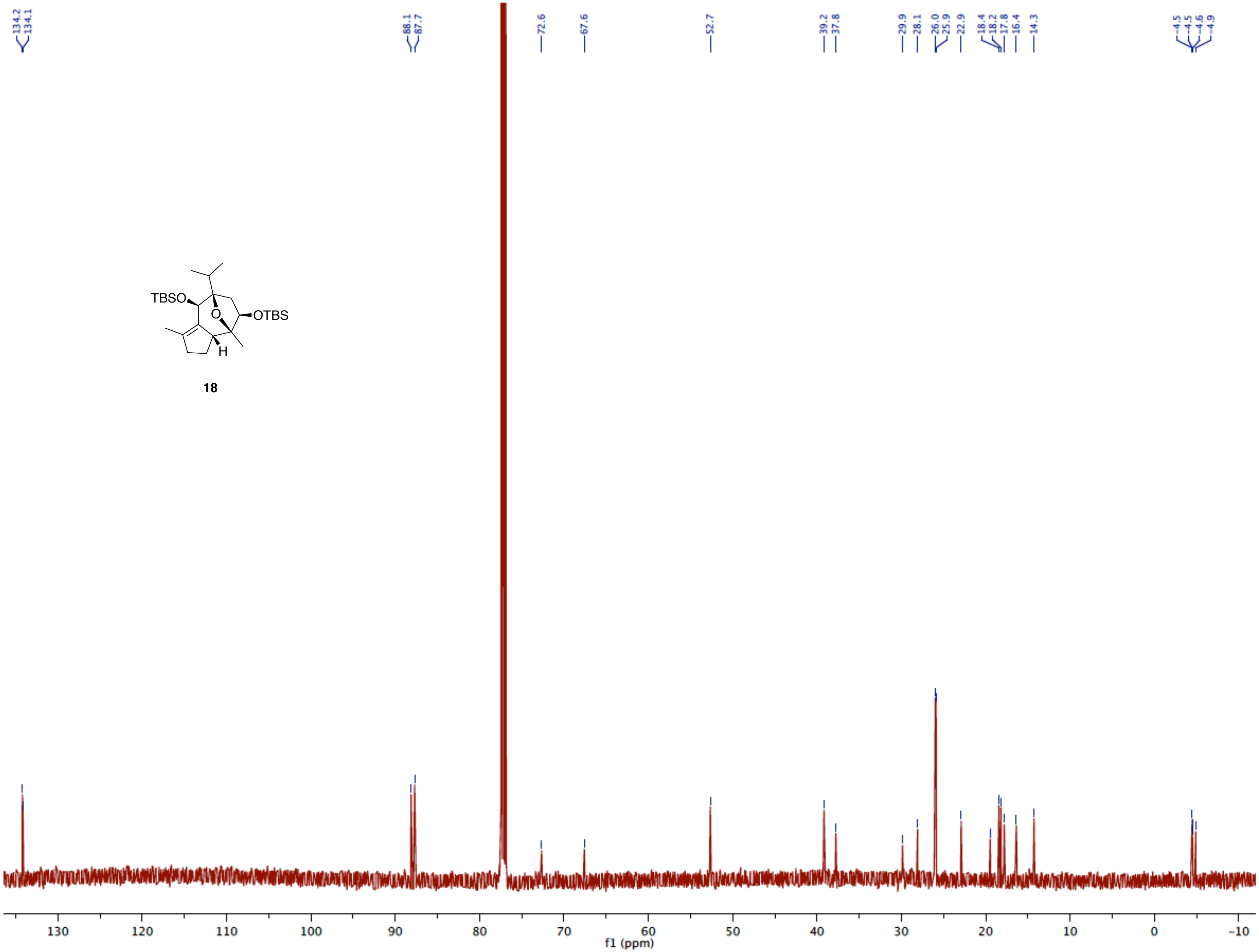
2.33
2.22
1.93
1.69
1.69
1.58
1.48
1.38
1.37
1.36
1.15
0.96
0.94
0.87
0.85
0.81
0.80
0.03
0.00
-0.00
-0.05
1.04
1.00
1.09
1.18
1.09
1.11
1.13
3.26
1.16
1.19
3.06
3.06
18.14
3.17
3.21
6.01
2.98
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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87.7
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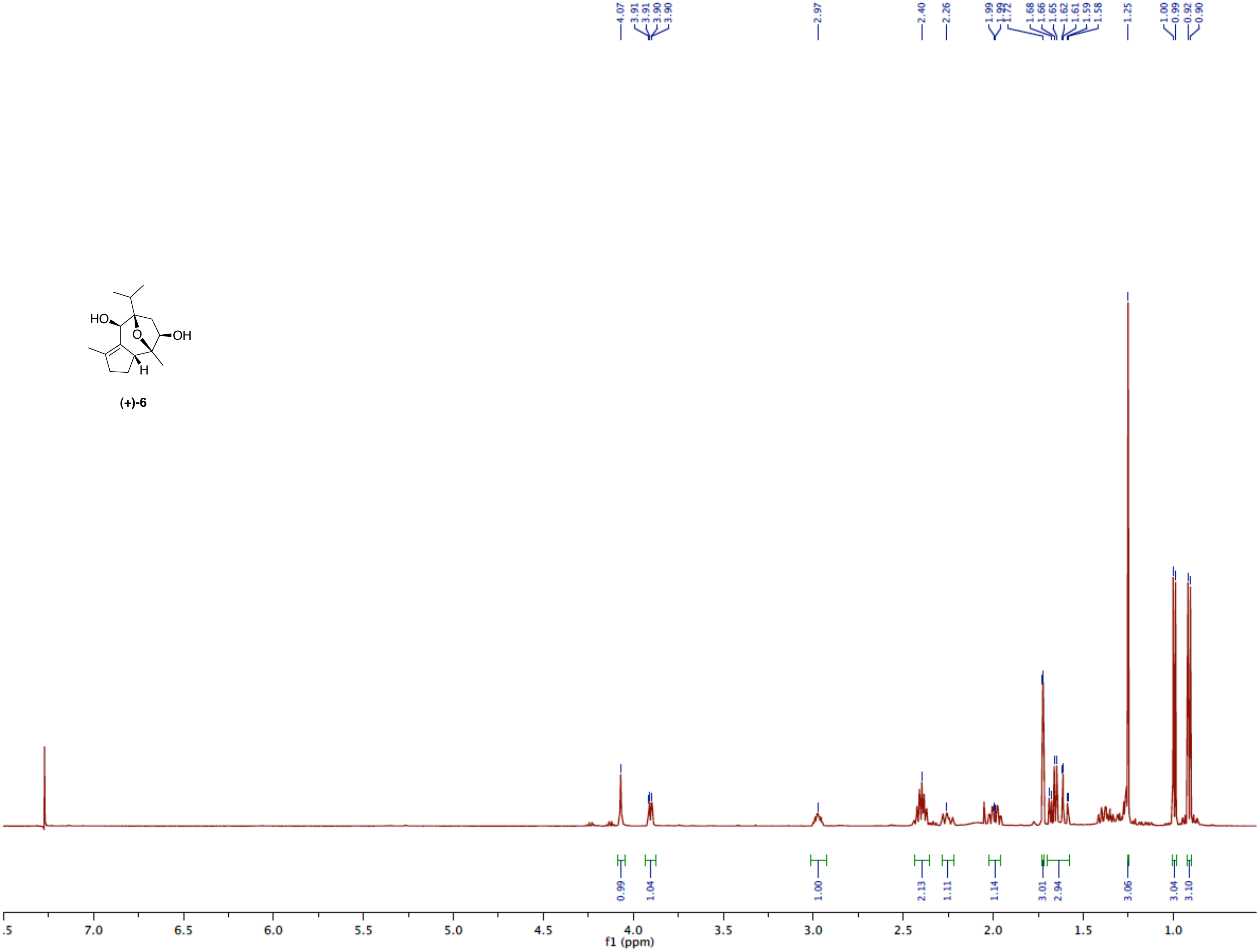
67.6
52.7
39.2
37.8
29.9
28.1
26.0
25.9
22.9
18.4
18.2
17.8
16.4
14.3
-4.5
-4.5
-4.6
-4.9
TBSO
O
OTBS
H
18
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


(+)-6
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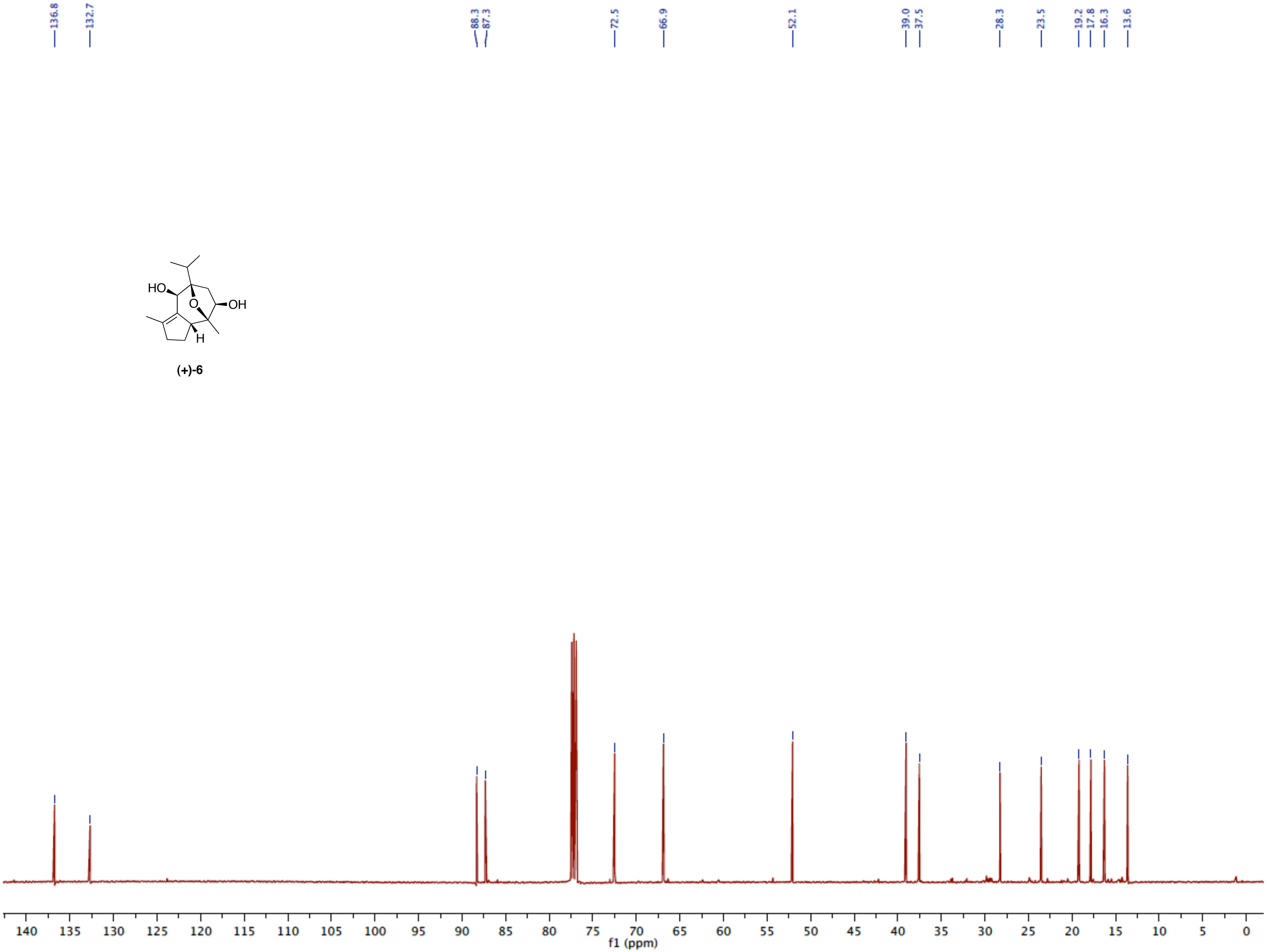
3.91
3.90
3.90
2.97
2.40
2.26
1.99
1.99
1.72
1.68
1.66
1.65
1.62
1.61
1.59
1.58
1.25
1.00
0.99
0.92
0.90
HO
O
OH
H
0.99
1.04
1.00
2.13
1.11
1.14
3.01
2.94
3.06
3.04
3.10
.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


136.8
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72.5
66.9
52.1
39.0
37.5
28.3
23.5
19.2
17.8
16.3
13.6
HO
O
OH
H
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

(+)-6

Table 1. Crystal data and structure refinement for Compound **13**.

Identification code	Compound **13**	
Empirical formula	C12 H16 O3	
Formula weight	208.25	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.8430(5) Å	α= 90°
	b = 10.1285(7) Å	β= 90°
	c = 17.0834(12) Å	γ = 90°
Volume	1184.04(15) Å^3	
Z	4	
Density (calculated)	1.168 g/cm^3	
Absorption coefficient	0.676 mm^{-1}	
F(000)	448	
Crystal size	0.33 x 0.22 x 0.11 mm^3	
Theta range for data collection	5.08 to 62.57°	
Index ranges	-7<=h<=7, -11<=k<=11, -19<=l<=18	
Reflections collected	3417	
Independent reflections	1500 [R(int) = 0.0364]	
Completeness to theta = 55.00°	95.1 %	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	1500 / 0 / 136
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0393, wR2 = 0.0967
R indices (all data)	R1 = 0.0446, wR2 = 0.0993
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.130 and -0.183 e Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for Compound **13**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7673(2)	4447(2)	9449(1)	22(1)
O(2)	5174(2)	2432(2)	9972(1)	26(1)
O(3)	3774(3)	2274(2)	8288(1)	38(1)
C(1)	4514(3)	3447(2)	9461(1)	21(1)
C(2)	5664(4)	4716(2)	9649(1)	21(1)
C(3)	5117(4)	5748(2)	9043(1)	26(1)
C(4)	6328(4)	5655(2)	8446(1)	26(1)
C(5)	7772(4)	4559(2)	8606(1)	23(1)
C(6)	6920(4)	3274(2)	8288(1)	23(1)
C(7)	4958(4)	2961(2)	8630(1)	24(1)
C(8)	5562(4)	5116(2)	10508(1)	29(1)
C(9)	6812(5)	6338(3)	10659(2)	46(1)
C(10)	3455(5)	5354(3)	10771(2)	36(1)
C(11)	9864(4)	4832(3)	8369(2)	33(1)
C(12)	7758(4)	2465(3)	7790(2)	34(1)

Table 3. Bond lengths [Å] and angles [°] for Compound **13**.

O(1)-C(5)	1.446(3)
O(1)-C(2)	1.442(3)
O(2)-C(1)	1.423(3)
O(3)-C(7)	1.217(3)
C(1)-C(7)	1.533(3)
C(1)-C(2)	1.540(3)
C(2)-C(8)	1.524(3)
C(2)-C(3)	1.518(3)
C(3)-C(4)	1.318(4)
C(4)-C(5)	1.511(3)
C(5)-C(11)	1.514(4)
C(5)-C(6)	1.526(3)
C(6)-C(12)	1.314(4)
C(6)-C(7)	1.498(4)
C(8)-C(10)	1.529(4)
C(8)-C(9)	1.527(4)
C(5)-O(1)-C(2)	105.34(17)
O(2)-C(1)-C(7)	105.86(17)
O(2)-C(1)-C(2)	108.21(17)
C(7)-C(1)-C(2)	111.07(19)
O(1)-C(2)-C(8)	108.72(19)

O(1)-C(2)-C(3)	101.78(18)
C(8)-C(2)-C(3)	117.53(19)
O(1)-C(2)-C(1)	106.28(17)
C(8)-C(2)-C(1)	113.51(19)
C(3)-C(2)-C(1)	107.84(18)
C(4)-C(3)-C(2)	108.9(2)
C(3)-C(4)-C(5)	108.8(2)
O(1)-C(5)-C(4)	102.02(18)
O(1)-C(5)-C(11)	109.0(2)
C(4)-C(5)-C(11)	115.8(2)
O(1)-C(5)-C(6)	105.65(18)
C(4)-C(5)-C(6)	108.2(2)
C(11)-C(5)-C(6)	114.9(2)
C(12)-C(6)-C(7)	120.8(2)
C(12)-C(6)-C(5)	126.6(2)
C(7)-C(6)-C(5)	112.6(2)
O(3)-C(7)-C(6)	122.1(2)
O(3)-C(7)-C(1)	119.7(2)
C(6)-C(7)-C(1)	118.1(2)
C(2)-C(8)-C(10)	111.6(2)
C(2)-C(8)-C(9)	110.6(2)
C(10)-C(8)-C(9)	110.5(2)

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for Compound **13**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	18(1)	25(1)	4(1)	-3(1)	-1(1)
O(2)	26(1)	17(1)	34(1)	8(1)	-2(1)	-3(1)
O(3)	31(1)	41(1)	41(1)	-16(1)	3(1)	-10(1)
C(1)	22(1)	16(1)	24(1)	2(1)	-1(1)	-1(1)
C(2)	24(1)	13(1)	27(1)	1(1)	0(1)	-2(1)
C(3)	28(1)	16(1)	33(1)	2(1)	-3(1)	2(1)
C(4)	30(1)	16(1)	32(1)	9(1)	-4(1)	2(1)
C(5)	23(1)	19(1)	26(1)	6(1)	-1(1)	1(1)
C(6)	27(1)	20(1)	23(1)	2(1)	-2(1)	4(1)
C(7)	29(1)	17(1)	27(1)	0(1)	-3(1)	-1(1)
C(8)	40(2)	18(1)	29(1)	0(1)	-1(1)	-5(1)
C(9)	61(2)	35(2)	42(2)	-14(1)	3(1)	-17(1)
C(10)	48(2)	28(1)	33(1)	-4(1)	9(1)	3(1)
C(11)	30(1)	32(1)	38(1)	8(1)	3(1)	-2(1)
C(12)	35(1)	32(1)	35(1)	-1(1)	6(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10 ^{3}) for Compound **13**.

	x	y	z	U(eq)
H(2A)	4230	1942	10093	39
H(1A)	3079	3598	9528	25
H(3A)	4072	6361	9087	31
H(4A)	6299	6189	7989	31
H(8A)	6105	4374	10827	34
H(9A)	8154	6170	10484	69
H(9B)	6812	6539	11220	69
H(9C)	6274	7089	10368	69
H(10A)	2674	4561	10669	55
H(10B)	2908	6101	10479	55
H(10C)	3435	5552	11332	55
H(11A)	10290	5672	8598	50
H(11B)	9950	4884	7797	50
H(11C)	10707	4118	8559	50
H(12A)	7120	1670	7642	41
H(12B)	9003	2675	7577	41