

**Toward a more step-economical and scalable synthesis of spongistatin 1 to  
facilitate cancer drug development efforts**

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*SUPPLEMENTARY INFORMATION*

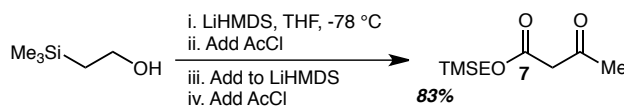
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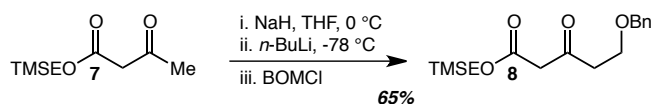
## 1. General Information

Unless otherwise stated, all chemical compounds were purchased from common commercial sources, and all reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring unless otherwise indicated. The syntheses of aldehydes **23** and **25** and isoprenylsilane (*R,R*)-**19** have been previously described.<sup>1</sup> “Buffered silica gel” was prepared by adding 10% pH 7 buffer (by mass) to a round bottom flask half filled with silica gel. The resulting mixture was rotated on a rotary evaporator for >12 h (at atmospheric pressure) and then stored for future use. Degassed solvents were purified by passage through an activated alumina column. Thin-layer chromatography (TLC) was carried out on glass backed silica gel TLC plates (250  $\mu$ m) from Silicycle; visualization by UV light, phosphomolybdic acid (PMA), *p*-Anisaldehyde (*p*-Anis) or potassium permanganate (KMnO<sub>4</sub>) stain. Gas chromatographic analyses were performed on a Hewlett-Packard 6890 Series Gas Chromatograph equipped with a capillary split-splitless inlet and flame ionization detector with electronic pneumatics control using either a Supelco  $\beta$ -Dex 120 (30 m x 0.25 mm) or Supelco  $\beta$ -Dex 325 (30 m x 0.25 mm) capillary GLC column. HPLC analysis was carried out on an Agilent 1200 Series using either a Chiralpak AD-H (250 x 4.5 mm ID) column or Chiralcel OD (250 x 4.5 mm ID) column. <sup>1</sup>H NMR spectra were recorded on a Bruker DPX-300 (300 MHz), Bruker DRX-300 (300 MHz), Bruker AVIII nano bay-400 (400 MHz), Bruker AVIII single bay-400 (400 MHz), Avance III 500 (500 MHz) or a Avance III 500 Ascend magnet (500 MHz) spectrometer and are reported in ppm from CDCl<sub>3</sub> internal standard (7.26 ppm). Data are reported as follows: (bs= broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, h = hexet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets; coupling constant(s) in Hz; integration). Proton decoupled <sup>13</sup>C NMR spectra were recorded on a Bruker DRX-300 (300 MHz), Bruker AVIII single bay-400 (400 MHz), Bruker AVIII nano bay-400 (400 MHz), Avance III 500 (500 MHz) or a Avance III 500 Ascend magnet (500 MHz) spectrometer and are reported in ppm from CDCl<sub>3</sub> internal standard (77.0 ppm). Infrared spectra were recorded on a Nicolet Avatar 370DTGS FT-IR. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. (APCI)-MS was conducted on a JMS-LCmate LCMS (JEOL).

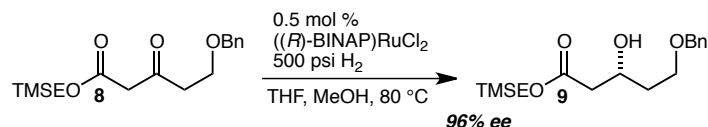
## 2. Experimental Procedures and Characterization Data



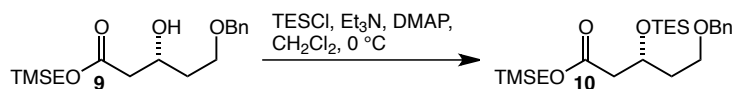
A 500 mL round bottom flask was charged with lithium bis(trimethylsilyl)amide (LiHMDS) (185 mL, 185 mmol, 1 M in THF). The solution was cooled to -78 °C, and 2-(trimethylsilyl)ethanol (26.5 mL, 21.9 g, 185 mmol) was added over 5 min (**Caution!** the 2-(trimethylsilyl)ethanol should be added slowly to avoid the generation of excess heat) during which time a precipitate formed. After 5 min acetyl chloride (13.2 mL, 185 mmol) was added to the mixture over 5 min (**Caution!** the acetyl chloride should be added slowly to avoid the generation of excess heat) during which time the reaction mixture became homogeneous. A separate 1 L round bottom flask was charged with LiHMDS (370 mL, 370 mmol, 1 M in THF) and cooled to -78 °C. 10 Min after the completion of the acetyl chloride addition, the contents of the 500 mL flask were added to the 1 L flask by cannula (the addition should be carried out slowly enough to avoid the generation of excess heat) with 2 x 20 mL THF rinses. Acetyl chloride (13.2 mL, 185 mmol) was added to the reaction mixture over 1 h via syringe pump. After 15 min the reaction was quenched by the addition of 300 mL of 1 M HCl. The mixture was allowed to warm to room temperature over ~1 h and then poured into a 2 L separatory funnel and diluted with EtOAc (600 mL). The layers were mixed well and then separated, and the organic phase was washed with a mixture of 1 M HCl (200 mL) and Brine (100 mL) mixture followed by brine (100 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated. Distillation (b.p. ~113 °C at ~15 mm Hg) of the residue afforded  $\beta$ -keto ester **7** (31 g, 153 mmol, 83% yield) as a colorless oil which exists as a ~10:1 mixture of the keto and enol tautomers by as revealed by <sup>1</sup>H NMR spectroscopy. *R*<sub>f</sub> = 0.5 (15% EtOAc/Hexanes, *p*-anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) keto form:  $\delta$  4.24 (m, 2H), 3.43 (s, 2H), 2.27 (s, 3H), 1.02 (m, 2H), 0.05 (s, 9H); enol form:  $\delta$  12.14 (s, 1H), 4.96 (s, 1H), 4.23 (m, 2H), 1.95 (s, 3H), 1.00 (m, 2H), 0.04 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) keto form:  $\delta$  200.8, 167.4, 63.9, 50.5, 30.3, 17.5, -1.4; enol form:  $\delta$  90.1, 62.3, 21.4, 17.5, -1.5; IR (NaCl neat) 2956, 2900, 1742, 1720, 1650, 1414, 1361, 1317, 1251 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>9</sub>H<sub>18</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup> 225.31, found 226.16.



This procedure was adapted from the procedure of Cooper.<sup>2</sup> To a cooled (0 °C) solution/suspension of NaH (60% suspension in mineral oil, 6.17 g, 154 mmol in THF (300 mL) was added  $\beta$ -keto ester **7** (30 g, 147 mmol, 1.0 equiv) dropwise over 15 min (**Caution!** this addition must be carried out slowly to avoid excess pressure build-up as H<sub>2</sub> gas is evolved; to help avoid the build-up of excess pressure, the reaction mixture was vented with two 16 G needles placed in the septum during the addition). After ~20 min the gas evolution subsided and the reaction mixture was cooled to -78 °C. *n*-Buli (70 mL, 160 mmol, 2.3 M in hexanes) was added over 20 min (**Caution!** the addition must be carried out slowly to avoid the generation of excess heat). After 30 min benzyl chloromethyl ether (BOM-Cl)<sup>3</sup> (20.4 mL, 147 mmol) was added over 10 min. After 10 min, the dry ice/acetone bath was replaced with an ice/water bath. After 30 min, the reaction was quenched by the slow addition of 300 mL of 1 M HCl. After 5 min, the mixture was allowed to warm to room temperature, transferred to a 2 L separatory funnel and diluted with EtOAc (600 mL). The layers were mixed well and separated, and the organic phase was washed with brine (300 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated. First benzyl alcohol and then recovered starting material **7** were removed from the mixture by distillation under reduced pressure to provide **7** (8 g, 39 mmol, 26% recovered, b.p. ~113 °C at ~15 mm Hg). The residue was purified by flash chromatography on silica gel (gradient 10% to 15% EtOAc/Hexanes) to afford benzyl ether **8** (31 g, 96 mmol, 65% yield) as a pale yellow oil, which exists as a ~9:1 mixture of keto and enol tautomers by <sup>1</sup>H NMR spectroscopy. R<sub>f</sub> = 0.4 (15% EtOAc/Hexanes, *p*-anisaldehyde stain); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) keto form:  $\delta$  7.40-7.17 (m, 5H), 4.52 (s, 2H), 4.22 (m, 2H), 3.76 (t, *J* = 6.2 Hz, 2H), 3.48 (s, 2H), 2.84 (t, *J* = 6.2 Hz, 2H) 1.01 (m, 2H), 0.05 (s, 9H); enol form:  $\delta$  12.18 (s, 1H), 7.40-7.17 (m, 5H), 5.05 (s, 1H), 4.54 (s, 2H), 4.24 (m, 2H), 3.71 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 1.03 (m, 2H), 0.06 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) keto form:  $\delta$  201.6, 167.4, 138.2, 128.6, 127.9, 73.5, 65.2, 63.9, 50.2, 43.3 36.0, 17.5, -1.3; IR (NaCl neat) 3436, 3065, 3032, 2955, 2899, 1742, 1717, 1648, 1496, 1454, 1409, 1367, 1311, 1251 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>17</sub>H<sub>25</sub>O<sub>4</sub>Si [M-H]<sup>+</sup> 321.16, found 321.04.

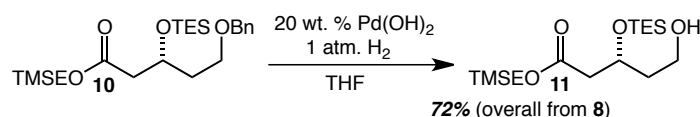


A 300 mL capacity glass liner for a Parr bomb was charged with a solution of  $\beta$ -keto ester **8** (34 g, 105 mmol) in THF (52 mL) and MeOH (52 mL). (*R*)-(BINAP)RuCl<sub>2</sub> (420 mg, 0.53 mmol, 0.0050 equiv) was added and the resulting mixture was stirred for 1 min. The glass liner was inserted into the Parr bomb (which was equipped with a gas inlet and release valve and a pressure gauge), and the bomb was sealed. The bomb was charged to 500 psi with H<sub>2</sub> and vented to ~100 psi and this process was repeated twice. The bomb was charged to 500 psi with H<sub>2</sub> and then placed in an oil bath (80 °C, external temperature). After 2 h, the oil bath was removed and the bomb and its contents were allowed to cool to room temperature over the course of 1 h. The bomb was vented, and the reaction mixture was diluted with a solution of 25% EtOAc/Hexanes (300 mL). The solution was filtered through a pad of silica gel with 4 x 250 mL 25% EtOAc/Hexanes rinses. The filtrate was concentrated and the residue (a dark brown oil) was used in the next step without further purification. A small portion of this material was purified by silica gel chromatography (15% EtOAc/Hexanes) to afford a pure sample of **9** for characterization. The enantiomeric excess of **9** was determined to be 96% by chiral HPLC (see HPLC trace below).  $[\alpha]_D^{23} = +12^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f = 0.4$  (20% EtOAc/Hexanes, PMA stain); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.47-7.17 (m, 5H), 4.53 (s, 2H), 4.34-4.13 (m, 3H), 3.84-3.54 (m, 2H), 3.39 (d, *J* = 3.4 Hz, 1H), 2.49 (d, *J* = 6.3 Hz, 2H), 1.94-1.73 (m, 2H), 1.10-0.92 (m, 2H), 0.05 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.8, 138.3, 128.6, 127.9, 127.8, 73.5, 68.1, 67.1, 63.1, 41.9, 36.3, 17.5, -1.3; IR (cast film) 3506, 2953, 1730, 1454, 1250, 1168, 1100 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>17</sub>H<sub>29</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 325.60, found 325.32.



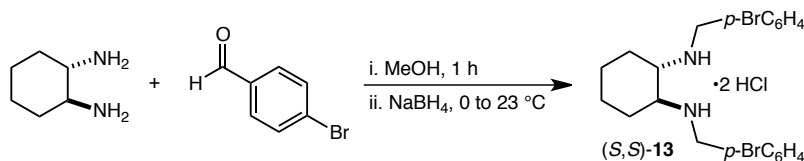
The brown oil (alcohol **9**) from the previous step (ca. 34g, 105 mmol, 1.0 equiv) was diluted with benzene (350 mL) and the resulting solution was concentrated. The resulting azeotropically dried residue was treated with CH<sub>2</sub>Cl<sub>2</sub> (350 mL) and then Et<sub>3</sub>N (17.6 mL, 126 mmol). The resulting mixture was cooled to 0 °C and triethylsilyl chloride (TESCl) (17.6 mL, 105 mmol) was added over 5 min (**Caution!** the TES-Cl must be added slowly to avoid the generation of excess heat). 4-Dimethylaminopyridine (DMAP) (642 mg, 5.25 mmol) was then

added and after 5 min the ice/water bath was removed and the mixture was allowed to warm to room temperature (Note: the reaction quickly became thick with Et<sub>3</sub>N•HCl salts). After 30 min, the reaction was quenched by the addition of MeOH (8.5 mL). The mixture was concentrated and the resulting brown sludge was treated with a solution of 15% EtOAc/Hexanes (500 mL). The mixture was filtered through a pad of silica gel with 4 x 250 mL 15% EtOAc/Hexanes rinses. The filtrate was concentrated and the dark amber oil residue was used in the next step without further purification. A small portion of this material was purified by silica gel chromatography (15% EtOAc/Hexanes) to afford a sample of **10** for characterization.  $[\alpha]_D^{23} = -5^\circ$  (*c* 1.7, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.8 (15% EtOAc/Hexanes, PMA stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.40-7.21 (m, 5H), 4.55-4.45 (m, 2H), 4.33 (dt, *J* = 11.8, 6.2 Hz, 1H), 4.21-4.11 (m, 2H), 3.56 (td, *J* = 6.4, 1.6 Hz, 2H), 2.48 (d, *J* = 6.3 Hz, 2H), 1.91-1.76 (m, 2H), 1.03- 0.97 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 10H), 0.60 (q, *J* = 8.1 Hz, 6H), 0.05 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.9, 138.7, 128.5, 127.8, 127.6, 73.1, 67.1, 66.8, 62.7, 43.5, 37.7, 17.5, 7.0, 5.2, -1.3; IR (cast film) 2953, 2876, 1733, 1453, 1414, 1384, 1249, 1164, 1098 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>23</sub>H<sub>43</sub>O<sub>4</sub>Si<sub>2</sub> [M+H]<sup>+</sup> 439.76, found 439.43.



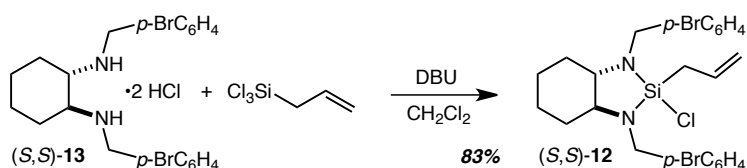
A 1 L round bottom flask was charged with Pearlman's catalyst (20 wt. % Pd(OH)<sub>2</sub> on carbon) (3.69 g, 5.25 mmol) and the flask was evacuated and back-filled with N<sub>2</sub>. THF (100 mL) was added resulting in a black slurry, and a solution of the unpurified benzyl ether **10** from the previous step (ca. 46g, 105 mmol, 1.0 equiv) in THF (600 mL) was added. The flask was fitted with a ~1 L balloon filled with H<sub>2</sub> gas and then vented with a needle to ensure the head-space was filled with H<sub>2</sub>. The flask was then fitted with a full 1 L balloon of H<sub>2</sub>. After 2 h (**NOTE**: it is important to monitor the reaction progress by TLC as cleavage of the TES ether occurs at longer reaction times. This TES ether cleavage begins before the benzyl group hydrogenation is complete, so it is recommended that the reaction be worked up as soon as it gets near to completion. This time varied depending on the batch of Pearlman's catalyst and was anywhere from 1.5 to 6 h.) the balloon was removed, the flask was vented and the mixture was filtered through a pad of celite with EtOAc washes. The filtrate was concentrated and the residue was purified by silica gel chromatography (gradient 10% to 15% to 20% EtOAc/Hexanes) to afford

alcohol **11** (26.4 g, 75.6 mmol, 72% yield from **8**) as a pale yellow oil.  $[\alpha]_D^{23} = -3^\circ$  ( $c$  2.8,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.25$  (15% EtOAc/Hexanes,  $\text{KMnO}_4$  stain);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.48-4.30 (m, 1H), 4.23-4.10 (m, 2H), 3.90-3.67 (m, 2H), 2.55 (qd,  $J = 15.1, 6.5$  Hz, 2H), 2.26 (t,  $J = 5.4$  Hz, 1H), 1.88 (ddt,  $J = 14.4, 7.9, 4.7$  Hz, 1H), 1.05-0.95 (m, 2H), 0.98 (d,  $J = 8.0$  Hz, 9H), 0.63 (q,  $J = 8.1$  Hz, 6H), 0.05 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.6, 68.5, 62.9, 60.0, 42.8, 39.0, 17.5, 6.9, 6.9, 5.0, -1.3. IR (cast film) 3453, 2954, 2878, 1733, 1459, 1415, 1385, 1310, 1250, 1162, 1090  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{16}\text{H}_{37}\text{O}_4\text{Si}_2$   $[\text{M}+\text{H}]^+$  349.64, found 349.30.



(Note: this is a modified version of our previously reported procedure<sup>4</sup> that employed the diamine as its tartrate salt. In this case the diamine was purchased and employed as the free base.) A 5 L, 2-neck roundbottom flask was charged with (S,S)-(+)-1,2-diaminocyclohexane (60g, 525 mmol, 1.0 equiv). Methanol (1.3 L) was added and the flask was equipped with an overhead mechanical stirrer. p-Bromobenzaldehyde (195 g, 1.05 mol) was added with vigorous stirring. After ~20 min, the bis-imine precipitated out of the reaction solvent, and after an additional 40 min the mixture was cooled to 0 °C. NaBH<sub>4</sub> (43.7 g, 1.155 mol) was added in 5g portions every 5 min until the addition was complete (**Caution!** the reaction bubbled vigorously during the NaBH<sub>4</sub> addition, it must be added slowly to avoid excess heat and pressure evolution). The mixture was stirred overnight (~14 h) during which time the ice/water bath was allowed to melt/warm to room temperature. The reaction mixture was recooled to 0 °C and quenched by the **SLOW** addition of deionized H<sub>2</sub>O (200 mL). The resulting mixture was transferred to a 2 L round bottom flask and concentrated. The resulting viscous, yellow slurry was treated with Et<sub>2</sub>O (800 mL) and H<sub>2</sub>O (600 mL), and the flask was equipped with a mechanical stirrer and cooled to 0 °C. Conc. HCl (300 mL of a 12.1 M solution) was added slowly in 50 mL portions (**Caution!** The HCl must be added slowly to avoid excess heat generation). The resulting heterogeneous mixture was vigorously stirred for 1 h and then filtered through a 2 L vacuum filter frit with a 2 L wash with 1 M HCl and then 3 x 1 L washes with Et<sub>2</sub>O. The white solid was then washed with 1 M HCl (2 L) solution and then Et<sub>2</sub>O (3 L) (Note: purified Et<sub>2</sub>O was used for this wash as a

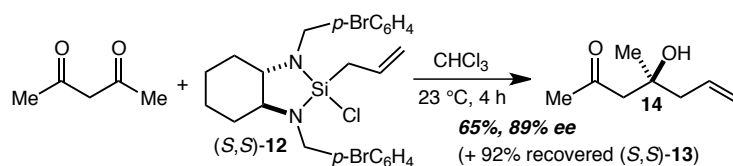
mixture of products was observed when Et<sub>2</sub>O stabilized with EtOH was employed). The resulting wet solid was dried by aspiration open to the air (with occasional stirring) for 24 h (this is to ensure complete removal of the Et<sub>2</sub>O), and was then transferred to a large crystallizing dish and dried in an oven at 85 °C for 16 h (**Caution!!! the solid must be free of residual Et<sub>2</sub>O before being placed in the oven**) to afford (*S,S*)-**13** (273 g, 520 mmol, 99% yield) as a fluffy white powder. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.20 (bs, 2H), 9.95 (bs, 2H), 8.02-7.50 (m, 8H), 4.25 (dd, *J* = 80.1, 13.2 Hz, 5H), 3.91-3.53 (m, 2H), 2.38-2.23 (m, 2H), 2.21-1.70 (m, 5H), 1.22 (d, *J* = 10.5 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 133.16, 131.90, 131.42, 122.87, 56.56, 47.29, 26.05, 22.65.



(Note: this is a modified version of our previously reported procedure<sup>4</sup> that employed the diamine **13** as its free base.) A 1 L 2-neck round bottom flask was charged with (*S,S*)-**13** (52.5 g, 100 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (330 mL). The resulting slurry was cooled to 0 °C and allyltrimethylsilane (16 mL, 110 mmol) was added followed by DBU (64 mL, 430) over 10 min (Note: as the DBU was added, the white salts solvated and the solution took on an amber hue). After 5 min, the ice/water bath was removed and the mixture was allowed to warm to room temperature. After 1 h, <sup>1</sup>H NMR spectroscopic analysis of a reaction aliquot revealed that the reaction was complete. The solvent was removed by placing the flask in a room temperature water bath, connecting it to an adjacent -78 °C cold-finger, and carefully reducing the pressure with a manometer partitioned through the pump manifold. Pentane (330 mL) was then added to the residue at room temperature, and the solution was shaken vigorously for ~10 min until the DBU•HCl salts powdered out into a fine white precipitate. This heterogeneous solution was stirred vigorously for an additional 1 h. The tinted yellow supernatant was transferred by cannulation using Teflon tubing (3/16 i.d.) equipped with a glass microfiber filter (Grade GF/D) into a dry 1 L, 2-neck roundbottom flask. Pentane (100 mL) was added to the remaining DBU•HCl salts and the flask was shaken vigorously. The supernatant was again cannulated into the new 1L, 2-Neck roundbottom flask as before. This process was repeated with a final pentane wash (50 mL). The solvent was again removed by placing the flask in a room temperature water

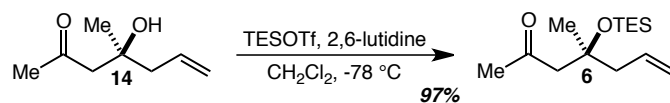


bath, connecting it to an adjacent  $-78\text{ }^{\circ}\text{C}$  cold-finger, and carefully reducing the pressure with a manometer partitioned through the pump manifold until the resulting oil became opaque and foamy. This product oil was retaken in boiling pentane (50 mL, 2.0 M) and a seed crystal of previously purified prepared (*S,S*)-**12** was added to the flask. The flask was placed in a  $-20\text{ }^{\circ}\text{C}$  freezer for  $\geq 12\text{ h}$  to fully crystallize the product. While the flask was still cold, the supernatant pentane was rotated away from the solid product and allowed to warm to room temperature. The pentane was removed from the flask via syringe and residual solvent was pumped off under vacuum. The desired solid was transferred to a dry, tared flask to afford allylsilane (*S,S*)-**12** (46 g, 83 mmol, 83% yield) as a white, crystalline solid. Full spectral characterization of this compound has been previously published.<sup>4</sup>

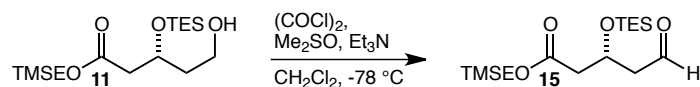


(Note: the following is a slightly modified version of the previously reported<sup>5</sup> procedure that is appropriate for larger scale reactions.) A 2 L round bottom flask was charged with a solution of (*S,S*)-**12** (66.6 g, 120 mmol) in  $\text{CHCl}_3$  (1 L) and the flask was placed in a room temperature water bath (Note: the external water bath serves to prevent a significant temperature increase resulting from the exothermic nature of the reaction). Acetylacetone (12 mL, 10.0 g, 100 mmol, 1.0 equiv) was added by syringe with vigorous stirring (Note: the solution becomes bright yellow at first and goes on to turn a dark red with fine white salts floating in the solution as the reaction continues). After 4 h, the mixture was cooled to  $0\text{ }^{\circ}\text{C}$  and  $\text{TBAF}\cdot 3\text{H}_2\text{O}$  (37.9 g, 120 mmol) was added. The resulting mixture was allowed to warm to room temperature over the course of 1 h and was then concentrated (Note: concentration by rotary evaporation must be done at  $0\text{--}10\text{ }^{\circ}\text{C}$  to avoid excessive evaporation of the desired, volatile product). The resulting thick, red oil was treated with  $\text{Et}_2\text{O}$  (500 mL) and the mixture was shaken vigorously which caused a precipitate to begin forming. 1 M HCl (500 mL) was then added and the flask was shaken for 10 min to fully form and precipitate out (*S,S*)-**13**. This heterogeneous mixture was filtered through a large, coarse filter frit with  $\text{Et}_2\text{O}$  washes (3 x 300 mL). The filtrate was set aside and the red/white solids in the frit were washed with 1 M HCl (1 L) until the solids were completely white. These white solids were then washed with  $\text{Et}_2\text{O}$  (1 L), aspirated open to air for  $\geq 2\text{ h}$ , and baked in the oven at  $85\text{ }^{\circ}\text{C}$  (**Caution! ALL of the  $\text{Et}_2\text{O}$  must be removed before the solid**

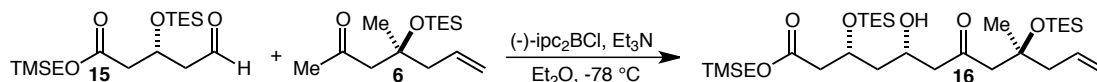
material is placed in the oven.) for 16 h to afford recovered (*S,S*)-**13** (58 g, 110 mmol, 92% recovered) as a fluffy white powder. The filtrate from above was concentrated (Note: concentration by rotary evaporation must be done at 0-10 °C to avoid excessive evaporation of the desired, volatile product). The residue (a red, wet oil) was purified by silica gel chromatography (gradient 20% to 30% to 50% to 60% Et<sub>2</sub>O/Pentane, combined product fractions concentrated at 0-10 °C) to afford **14** (9.3 g, 65 mmol, 65% yield) as a pale orange oil. The enantiomeric excess of **14** was determined to be 89% by chiral GC (see GC trace below). Full spectral characterization of **14** has been previously published.<sup>5</sup>



A flame-dried 1 L roundbottom flask was charged with CH<sub>2</sub>Cl<sub>2</sub> (650 mL, 0.1 M). Tertiary alcohol **14** (9.3g, 65.4 mmol, 1.0 equiv) was added to the flask, followed by 2,6-lutidine (9.2 mL, 78.5 mmol, 1.2 equiv). The roundbottom flask was equipped with a flame-dried 60 mL addition funnel and cooled to -78 °C. TESOTf (16.3 mL, 72.0 mmol, 1.1 equiv) was carefully added to the addition funnel via syringe and dripped into the cold reaction mixture at a rate of ~1 drop/sec. The addition was complete in ca. 25 min, at which time TLC analysis confirmed full conversion to the desired product. The reaction was quenched at -78 °C with MeOH (3.5 mL, 85.0 mmol, 1.3 equiv) followed by sat. NH<sub>4</sub>Cl (250 mL). The resulting mixture was allowed to warm to room temperature for 1 h. The organic phase was separated, leaving behind the lutidine salts observed at the aqueous layer interface. The organic phase was washed with 1 M AcOH (250 mL), then sat. NaHCO<sub>3</sub> (250 mL) before being concentrated to a yellow oil. This oil was retaken in 8% EtOAc/Hex and filtered over a pad of SiO<sub>2</sub> gel (rinsed with four bed-lengths worth of 8% EtOAc/Hexanes – approximately 1.2 L of solvent). The resulting solution was concentrated to afford tertiary silyl-ether **6** (16.3 g, 63.6 mmol, 97% yield) as a pale yellow oil.  $[\alpha]_D^{23} = +41^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.8 (10% EtOAc/Hexanes, PMA stain); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.83 (dddd, *J* = 17.0, 10.4, 8.0, 6.6 Hz, 1H), 5.14-4.98 (m, 2H), 2.58 (d, *J* = 13.5 Hz, 1H), 2.46 (d, *J* = 13.5 Hz, 1H), 2.37 (ddt, *J* = 13.6, 6.5, 1.3 Hz, 1H), 2.27 (ddt, *J* = 13.6, 6.5, 1.3 Hz, 1H), 2.17 (s, 3H), 1.31 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 208.6, 134.6, 118.2, 75.1, 54.7, 47.7, 32.8, 28.0, 7.3, 7.0; IR (cast film) 2956, 2912, 2877, 1711, 1640, 1457, 1356, 1239, 1139, 1080, 1030, 1005 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>14</sub>H<sub>29</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 357.47, found 357.39.

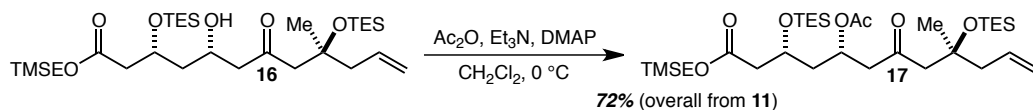


A 1 L 2-neck round bottom flask was charged with CH<sub>2</sub>Cl<sub>2</sub> (350 mL) and equipped with a flame-dried 60 mL addition funnel. Oxalyl chloride (5.5 mL, 64.2 mmol) was added and the resulting solution was cooled to -78 °C. DMSO (6.8 ml, 96.4 mmol) was rapidly added (Note: the vigorous gas evolution that accompanies the addition of the DMSO was vented with two 16 G needles in the septum on the reaction flask). After 20 min, a solution of alcohol **11** (11.2 g, 32.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was transferred to the addition funnel and then added at a rate of ~1 drop/sec to the reaction mixture. After 30 min Et<sub>3</sub>N (16.3 g, 22.5 mL, 161 mmol) was added to the reaction mixture via the addition funnel over ~15 min. The resulting thick white slurry was stirred vigorously at -78 °C for an additional 15 min, and the dry ice/acetone bath was then removed and the mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated. The residue was treated with 15% EtOAc/Hexanes (300 mL) and the resulting mixture was filtered through a pad of pH 7 buffered SiO<sub>2</sub> gel with 4 x 200 mL 15% EtOAc/Hexanes rinses. The filtrate was concentrated and the pale yellow oil residue was used in the next step without further purification (Note: aldehyde **15** could be stored as a frozen benzene solution, but was typically used within 24 h of its preparation). A small portion of this material was purified by silica gel chromatography (15% EtOAc/Hexanes, pH 7 buffered SiO<sub>2</sub> gel) to afford a pure sample of **15** for spectral characterization.  $[\alpha]_D^{23} = -11^\circ$  (*c* 1.4, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f = 0.6$  (10% EtOAc/Hexanes, *p*-anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.83 (t, *J* = 2.1 Hz, 1H), 4.67 (qd, *J* = 6.4, 5.1 Hz, 1H), 4.27-4.11 (m, 2H), 2.77-2.59 (m, 2H), 2.64-2.49 (m, 2H), 1.05-0.99 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 8.1 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 201.04, 170.90, 64.86, 62.90, 50.97, 42.86, 17.30, 6.76, 4.78, -1.51; IR (cast film) 2955, 2878, 1729, 1459, 1414, 1386, 1250, 1165, 1084, 1007 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>16</sub>H<sub>35</sub>O<sub>4</sub>Si<sub>2</sub> [M+H]<sup>+</sup> 347.61, found 347.36.



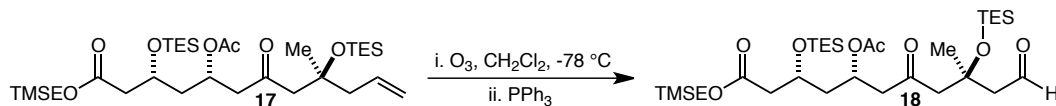
To a cooled (0 °C) solution of (-)-*B*-chlorodiisopinocampheylborane ((-)-DIP-chloride) (13.6 g, 42.5 mmol, 1.3 equiv) in Et<sub>2</sub>O (140 mL) was added Et<sub>3</sub>N (6.85 mL, 49.1 mmol). A solution of ketone **6** (9.34 g, 36.4 mmol, azeotropically dried with benzene just prior to use) in Et<sub>2</sub>O (40 mL) was then added by cannula over ~10 min during which time a precipitate

(Et<sub>3</sub>N•HCl) formed. After 30 min to ensure complete enolate formation, the reaction mixture was cooled to -78 °C, and a solution of aldehyde **15** from the previous procedure (ca. 11.3 g, 32.7 mmol) in Et<sub>2</sub>O (40 mL) was added by cannula over ~10 min. After 3 h, the dry ice/acetone bath was replaced with an ice/water bath. After 15 min the reaction was quenched by the addition of pH 7 buffer (220 mL) and the resulting mixture was allowed to warm to room temperature. The layers were mixed well and separated, and the aqueous phase was extracted with Et<sub>2</sub>O (2 x 150 mL). The combined organic layers were concentrated. The residue was treated with MeOH (220 mL) and pH 7 buffer (220 mL) and the resulting mixture was cooled to 0 °C. Hydrogen peroxide (43 mL, 30 wt. % in water) was then added slowly (**Caution!** the hydrogen peroxide must be added slowly to avoid a vigorous exotherm). After 5 min the ice/water bath was removed and the mixture was allowed to warm to room temperature. After 30 min, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (250 mL). The layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 200 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was partially purified by silica gel chromatography (gradient 1% to 5% to 10% EtOAc/Hexanes) to afford recovered ketone **6** (2.5 g, 9.9 mmol) and a mixture of aldol adduct **16** and isopinocampheylol which was taken on to the next reaction without further purification. The diastereoselectivity of the reaction was determined by <sup>1</sup>H NMR analysis to be 10:1 dr, and a small portion of aldol adduct XX was more rigorously purified for characterization. [α]<sub>D</sub><sup>23</sup> = +20° (c 1.7, CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> = 0.3 (10% EtOAc/Hexanes, *p*-anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.91-5.75 (m, 1H), 5.13-5.00 (m, 2H), 4.39 (p, *J* = 6.2 Hz, 1H), 4.21-4.09 (m, 3H), 3.32 (d, *J* = 2.6 Hz, 1H), 2.70-2.42 (m, 6H), 2.38 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.28 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.71 (ddt, *J* = 12.4, 9.0, 4.5 Hz, 1H), 1.61 (ddd, *J* = 13.9, 6.6, 3.1 Hz, 1H), 1.32 (s, 3H), 0.96 (td, *J* = 7.9, 1.3 Hz, 20H), 0.61 (p, *J* = 8.0 Hz, 12H), 0.05 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 210.9, 171.8, 134.5, 118.4, 75.2, 67.8, 65.5, 62.8, 54.4, 52.3, 47.8, 43.9, 42.9, 28.1, 17.5, 7.3, 7.0, 5.1, -1.3; IR (cast film) 3532, 2964, 2913, 2878, 1734, 1415, 1379, 1250, 1163, 1083, 1006 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>30</sub>H<sub>62</sub>O<sub>6</sub>Si<sub>3</sub> [M]<sup>+</sup> 603.07, found 603.61.



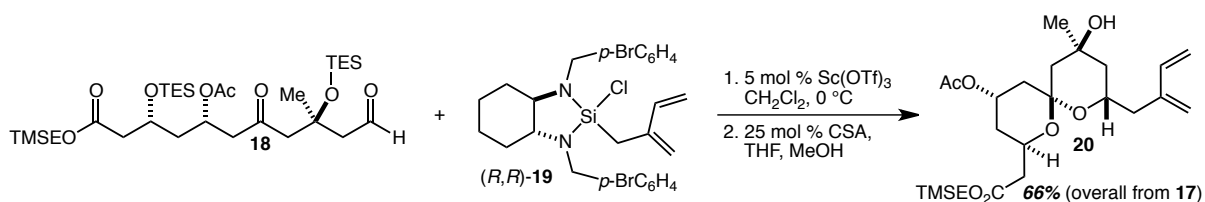
To a cooled (0 °C) solution of the mixture of **16** and isopinocampheylol from the previous procedure in THF (220 mL) was added Et<sub>3</sub>N (13.7 mL, 98.1 mmol), followed by acetic

anhydride (9.3 mL, 98.1 mmol) and DMAP (1.0 g, 8.2 mmol). After 5 min, the ice/water bath was removed and the reaction mixture was allowed to warm to room temperature. After 45 min the reaction was quenched by the addition of MeOH (4 mL). The mixture was concentrated and the resulting cloudy amber oil was treated with 15% EtOAc/Hexanes (300 mL). The mixture was then filtered through a pad of SiO<sub>2</sub> gel with 3 x 250 mL 15% EtOAc/Hexanes rinses. The filtrate was concentrated and the residue was purified by silica gel chromatography (gradient 1% to 6% to 7% to 60% EtOAc/Hexanes) to afford **17** (15.1 g, 23.4 mmol, 72% yield over 3 steps from **11**) as a pale yellow oil.  $[\alpha]_D^{23} = -2^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.5 (10% EtOAc/Hexanes, *p*-anisaldehyde); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.83 (dddd, *J* = 16.9, 10.4, 8.0, 6.5 Hz, 1H), 5.26 (tt, *J* = 7.0, 5.4 Hz, 1H), 5.14-4.98 (m, 2H), 4.27-4.06 (m, 3H), 2.85 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.73 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.65-2.41 (m, 4H), 2.37 (ddt, *J* = 13.5, 6.5, 1.3 Hz, 1H), 2.28 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.01 (s, 3H), 1.92-1.75 (m, 2H), 1.31 (s, 3H), 1.07-0.84 (m, 20H), 0.61 (qd, *J* = 7.9, 2.8 Hz, 12H), 0.05 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 206.6, 171.7, 170.3, 134.6, 118.3, 75.2, 67.5, 66.5, 62.7, 54.2, 49.7, 47.5, 42.2, 42.2, 28.1, 21.2, 17.5, 7.3, 7.0, 7.0, 5.0, -1.3; IR (cast film) 2955, 2878, 1739, 1373, 1239, 1166, 1082, 1042, 1009 cm<sup>-1</sup>; LRMS (FAB<sup>+</sup>) calc'd for C<sub>32</sub>H<sub>64</sub>O<sub>7</sub>Si<sub>3</sub> [*M*]<sup>+</sup> 645.10, found 645.65.



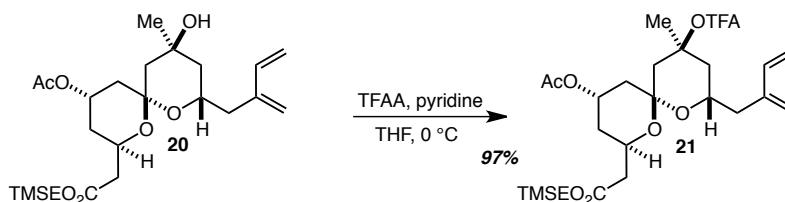
Into a cooled (-78 °C) solution of **17** (19.9 g, 30.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (310 mL) was bubbled oxygen. After 5 min, the ozone generator was initiated, and O<sub>3</sub> was bubbled into solution. After 40 min, the reaction mixture had turned dark blue and TLC analysis confirmed full conversion of the starting material. Oxygen was then bubbled through the solution to purge excess O<sub>3</sub>, and after 20 min of purging with O<sub>2</sub>, the blue color dissipated. Following an additional 20 min of O<sub>2</sub> bubbling, PPh<sub>3</sub> (9.71 g, 37.0 mmol) was added. The dry ice/acetone bath was removed and the mixture was allowed to warm to room temperature. After 15 h, TLC analysis confirmed full conversion of the initial ozonide product to aldehyde **18** (**Caution!** it is imperative to confirm complete reduction of the initial ozonide product as ozonides can be explosive when concentrated) and the mixture was concentrated. The residue was treated with hexanes (310 mL), which resulted in a heterogeneous mixture (the triphenylphosphine oxide is insoluble in hexanes). The heterogeneous mixture was stirred vigorously for 10 min and then

filtered with 2 x 100 mL hexanes washes. The filtrate was concentrated and this trituration process was repeated. The filtrate was concentrated and the residue was employed in the next step without further purification. A small portion of this material was purified by silica gel chromatography (10% EtOAc/Hexanes, pH 7 buffered SiO<sub>2</sub> gel) to afford a sample of aldehyde **18** for characterization.  $[\alpha]_D^{23} = -13^\circ$  ( $c$  2.3, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f = 0.5$  (15% EtOAc/Hexanes, *p*-anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.81 (t,  $J = 2.5$  Hz, 1H), 5.28 (pd,  $J = 7.2, 6.1, 1.8$  Hz, 1H), 4.25-4.08 (m, 3H), 2.85-2.59 (m, 6H), 2.56 (dd,  $J = 15.2, 5.1$  Hz, 1H), 2.45 (dd,  $J = 15.2, 7.3$  Hz, 1H), 2.01 (s, 3H), 1.82 (qdd,  $J = 14.2, 9.9, 4.9$  Hz, 2H), 1.43 (s, 3H), 1.03-0.88 (m, 20H), 0.68-0.53 (m, 12H), 0.04 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  205.6, 202.0, 171.7, 170.3, 73.6, 67.3, 66.5, 62.8, 54.7, 54.6, 49.6, 42.4, 42.0, 29.2, 21.2, 17.5, 7.2, 7.0, 6.9, 5.1, -1.3; IR (cast film) 2955, 2878, 1732, 1274, 1239, 1166, 1100, 1010 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>31</sub>H<sub>62</sub>O<sub>8</sub>Si<sub>3</sub> [M]<sup>+</sup> 647.08, found 647.61.



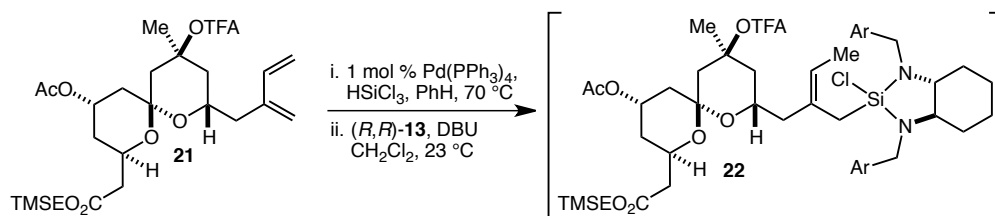
To a cooled (0 °C) solution of aldehyde **18** from the previous procedure (azeotropically dried with toluene immediately prior to use) in CH<sub>2</sub>Cl<sub>2</sub> (310 mL) was added (*R,R*)-**19**<sup>1</sup> (57 mL of a ~0.6 M stock solution in CH<sub>2</sub>Cl<sub>2</sub>, ~34.0 mmol) followed by Sc(OTf)<sub>3</sub> (759 mg, 1.54 mmol). The mixture was vigorously stirred for 2 h at which point TLC analysis revealed complete conversion of aldehyde **18**. The reaction was quenched by the addition of *n*-Bu<sub>4</sub>NF•3H<sub>2</sub>O (10.7 g, 34.0 mmol) and the mixture was stirred overnight and allowed to warm to room temperature as the ice/water bath warmed. The mixture was concentrated and the residue was treated with CH<sub>2</sub>Cl<sub>2</sub> (~10 mL). The mixture was filtered through a pad of silica gel with 4 x 250 mL 10% EtOAc/hexanes washes. The filtrate was concentrated and the residue was treated with 200 mL of 10% EtOAc/hexanes. The solution was filtered through a pad of silica gel with 4 x 250 mL 10% EtOAc/hexanes washes (**Note**: the purpose of these filtrations is the removal of most of the diamine and *n*-Bu<sub>4</sub>NF byproducts. The second filtration was only required on the larger scale of this reaction). The filtrate was concentrated and the residue (a yellow oil) was used in the next step without further purification.

To a solution of the residue from the previous step in THF (77 mL) and MeOH (77 mL) was added 1*S*-(+)-10-camphorsulfonic acid (CSA) (1.79 g, 7.71 mmol). After 1.5 h, TLC analysis confirmed full conversion, and the reaction was quenched by the addition of Et<sub>3</sub>N (3.2 mL, 23.1 mmol). The mixture was concentrated and the residue was purified by silica gel chromatography (gradient 1% to 15% to 25% EtOAc/Hexanes) to afford **20** (9.6 g, 20.5 mmol, 66% yield over 3 steps from **17**).  $[\alpha]_D^{23} = -55^\circ$  (*c* 4.1, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.2 (15% EtOAc/Hexanes, PMA stain); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.41 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.18 (dt, *J* = 23.9, 1.6 Hz, 2H), 5.09 (d, *J* = 10.8 Hz, 1H), 5.04 (dt, *J* = 5.7, 2.8 Hz, 1H), 4.43 (dddd, *J* = 11.1, 8.7, 4.4, 2.1 Hz, 1H), 4.30 (s, 1H), 4.31-4.23 (m, 1H), 4.21-4.10 (m, 2H), 2.55 (ddd, *J* = 14.4, 6.5, 1.0 Hz, 1H), 2.51-2.38 (m, 2H), 2.34 (ddd, *J* = 14.3, 6.4, 1.0 Hz, 1H), 2.05 (s, 3H), 2.02 (d, *J* = 15.0 Hz, 1H), 1.81 (dd, *J* = 14.2, 2.4 Hz, 1H), 1.77-1.67 (m, 2H), 1.62 (dd, *J* = 15.1, 3.9 Hz, 1H), 1.60-1.52 (m, 1H), 1.45 (d, *J* = 13.9 Hz, 1H), 1.24 (dd, *J* = 13.5, 11.7 Hz, 1H), 1.16 (s, 3H), 1.00 (ddd, *J* = 9.2, 8.1, 0.9 Hz, 2H), 0.04 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.1, 171.0, 142.7, 139.2, 118.0, 113.9, 98.4, 68.0, 66.4, 65.0, 63.3, 62.3, 46.1, 43.6, 40.8, 37.9, 37.4, 34.5, 30.2, 21.6, 17.5, -1.3; IR (cast film) 3530, 2953, 1731, 1402, 1366, 1249, 1209, 1174, 1058 cm<sup>-1</sup>; LRMS (FAB<sup>+</sup>) calc'd for C<sub>24</sub>H<sub>41</sub>O<sub>7</sub>Si [M+H]<sup>+</sup> 469.67, found 469.30.



To a cooled (0 °C) solution of **20** (13.7g, 29.2 mmol, azeotropically dried with benzene just prior to use) in THF (300 mL) was added pyridine (3.5 mL, 44.0 mmol), followed by trifluoroacetic anhydride (5.0 mL, 35.2 mmol) over ~10 min. After 1 h, TLC analysis showed complete conversion and the reaction was quenched by the *slow* addition of Et<sub>3</sub>N (5.0 mL, 35.2 mmol). The mixture was stirred vigorously for 5 min and then saturated aqueous NaHCO<sub>3</sub> (400 mL) was added. The mixture was allowed to warm to room temperature and was then diluted with EtOAc (250 mL). The mixture was shaken in a separatory funnel and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 200 mL) and the combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (gradient 1% to 15% to 20% EtOAc/Hexanes) to afford **21** (16.0 g, 28.3 mmol, 97% yield) as a pale yellow oil.  $[\alpha]_D^{23} = -68^\circ$  (*c* 3.9, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.5 (20% EtOAc/Hexanes,

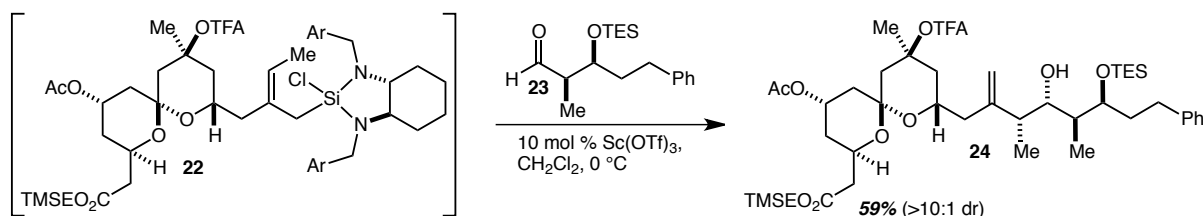
PMA stain);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.42 (dd,  $J = 17.6, 10.9$  Hz, 1H), 5.30 (d,  $J = 17.6$  Hz, 1H), 5.24-5.14 (m, 2H), 5.10 (d,  $J = 10.9$  Hz, 1H), 5.04 (t,  $J = 3.2$  Hz, 1H), 4.42 (dddd,  $J = 13.4, 7.6, 5.7, 1.9$  Hz, 1H), 4.33 (dtd,  $J = 11.4, 6.6, 1.8$  Hz, 1H), 4.23-4.08 (m, 2H), 2.85 (dd,  $J = 15.3, 2.2$  Hz, 1H), 2.58 (dd,  $J = 14.2, 6.6$  Hz, 1H), 2.49 (dd,  $J = 16.2, 5.8$  Hz, 1H), 2.36 (dd,  $J = 14.2, 6.8$  Hz, 1H), 2.27 (dd,  $J = 16.2, 7.6$  Hz, 1H), 2.05 (s, 3H), 2.16 (dt,  $J = 15.0, 2.1$  Hz, 1H), 1.97 (dt,  $J = 15.0, 2.1$  Hz, 1H), 1.87-1.78 (m, 1H), 1.60 (dd,  $J = 15.0, 4.2$  Hz, 1H), 1.57-1.46 (m, 4H), 1.38 (d,  $J = 15.2$  Hz, 1H), 1.28 (dd,  $J = 14.1, 11.4$  Hz, 1H), 0.98 (dd,  $J = 9.4, 7.7$  Hz, 2H), 0.05 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 170.9, 156.5 (q,  $J = 41.1$  Hz), 142.3, 139.1, 118.4, 114.5 (q,  $J = 286.5$  Hz), 113.9, 97.0, 84.3, 66.8, 63.8, 62.7, 61.6, 41.9, 41.0, 40.0, 37.6, 37.5, 33.9, 26.5, 21.6, 17.5, -1.4; IR (cast film) 2953, 1777, 1733, 1377, 1248, 1215, 1151, 1136, 1059  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{26}\text{H}_{40}\text{F}_3\text{O}_8\text{Si}$   $[\text{M}+\text{H}]^+$  565.67, found 565.49.



A 250 mL capacity sealed tube was charged with  $\text{Pd}(\text{PPh}_3)_4$  (18 mg, 0.015 mmol), evacuated, and then back-filled with  $\text{N}_2$ . A solution of diene **21** (847 mg, 1.5 mmol) in benzene (15 mL) was added followed by trichlorosilane (0.30 mL, 3.0 mmol) and the tube was tightly sealed. The sealed tube was placed in an oil bath set at  $70\text{ }^\circ\text{C}$  (**Caution!** although the pressure in this reaction is likely not particularly high, the use of a blast shield for this and all reactions under pressure is strongly recommended). After 11 h the oil bath was removed and the sealed tube was allowed to cool to room temperature. The resulting light brown solution was transferred by cannula into a 100 mL round bottom flask with 2 x 3 mL of benzene rinses. The flask was attached to a vacuum line equipped with a manometer and a  $-78\text{ }^\circ\text{C}$  coldfinger, and then placed in a warm ( $\sim 40\text{ }^\circ\text{C}$ ) water bath. All volatiles (principally benzene and residual trichlorosilane) were carefully removed by application of vacuum until a viscous oil remained. The oil was treated with  $\text{CH}_2\text{Cl}_2$  (15 mL) and  $(R,R)\text{-13}$  (788 mg, 1.5 mmol) was added to the resulting solution. The resulting white slurry was cooled to  $0\text{ }^\circ\text{C}$  and DBU (0.90 mL, 6.0 mmol) was added over 10 min. After 5 min, the mixture was allowed to warm to room temperature. After 2 h, the flask was attached to a vacuum line equipped with a manometer and a  $-78\text{ }^\circ\text{C}$  coldfinger, and then placed in a room temperature water bath. All volatiles were removed by careful

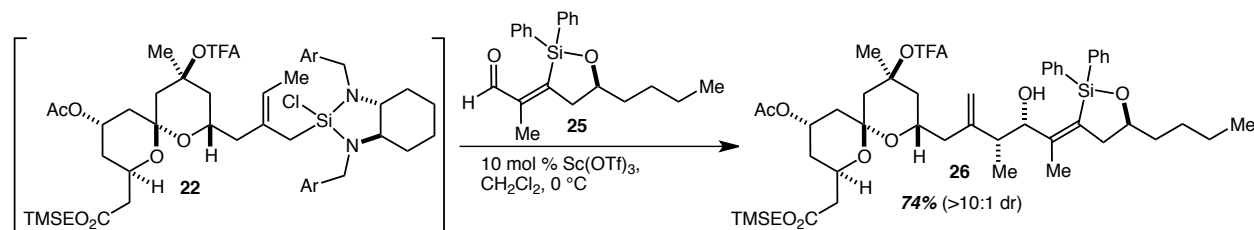


application of vacuum, and the residue was treated with Et<sub>2</sub>O (15 mL). The mixture was shaken vigorously for 10 min during which time the DBU•HCl salts were observed forming as a white precipitate. The heterogeneous mixture was stirred vigorously for an additional 6.5 h during which time the DBU•HCl salts became a very fine white precipitate. The tinted yellow supernatant was cannulated through a flame-dried, air-free filter frit into a 100 mL round bottom flask and the residual DBU•HCl salts were rinsed with Et<sub>2</sub>O (2 x 5 mL) and the resulting supernatants were again cannulated through the frit into the flask. The flask was attached to a vacuum line equipped with a manometer and a -78 °C coldfinger, and then placed in a room temperature water bath. All volatiles were removed by careful application of vacuum until the resulting yellow oil became opaque and foamy. The residue was treated with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and the resulting solution of **22** in CH<sub>2</sub>Cl<sub>2</sub> was split into two equal portions.

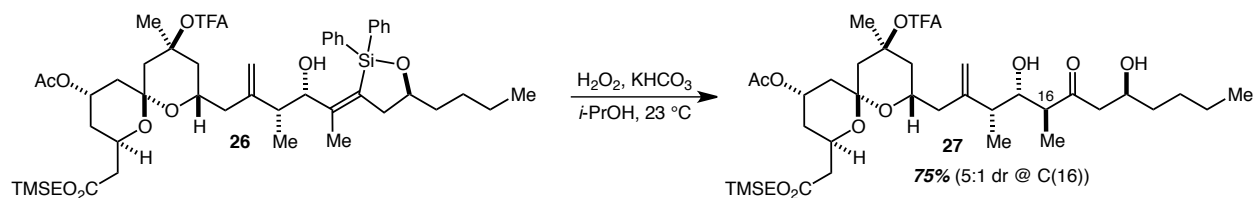


One of the portions of **22** in CH<sub>2</sub>Cl<sub>2</sub> from above was cooled to 0 °C with an ice/water bath, and aldehyde **23**<sup>1</sup> (230 mg, 0.75 mmol) was added followed by Sc(OTf)<sub>3</sub> (37mg, 0.075 mmol). The resulting mixture was vigorously stirred for 2 h and then the reaction was quenched by the addition of *n*-Bu<sub>4</sub>NF•3H<sub>2</sub>O (237 mg, 0.75 mmol). The resulting mixture was stirred for 16 h during which time the ice/water bath was allowed to melt and warm to room temperature. The mixture was concentrated and the residue was purified by silica gel chromatography (gradient, 15% to 20% EtOAc/Hexanes) to afford **24** (383mg, 0.44 mmol, 59% yield from diene **21**) as a pale yellow oil. The diastereoselectivity of the reaction was determined to be ≥10:1 by <sup>1</sup>H NMR analysis. [α]<sub>D</sub><sup>23</sup> = -44° (*c* 2.6, CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> = 0.4 (20% EtOAc/Hexanes, PMA stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32-7.24 (m, 2H), 7.22-7.15 (m, 3H), 5.15 (s, 1H), 5.05-5.00 (m, 2H), 4.38-4.25 (m, 2H), 4.19-4.07 (m, 2H), 4.04 (ddd, *J* = 7.6, 4.8, 2.2 Hz, 1H), 3.66 (dd, *J* = 9.7, 2.2 Hz, 1H), 3.33 (bs, 1H), 2.85 (dd, *J* = 15.2, 2.2 Hz, 1H), 2.78 (ddd, *J* = 13.4, 11.3, 5.3 Hz, 1H), 2.56-2.42 (m, 2H), 2.43-2.34 (m, 2H), 2.29-2.18 (m, 2H), 2.02 (s, 3H), 2.02-1.91 (m, 2H), 1.90-1.75 (m, 3H), 1.60 (dd, *J* = 15.0, 4.3 Hz, 1H), 1.52 (s, 3H), 1.50-1.41 (m, 1H), 1.38 (d, *J* = 15.2 Hz, 1H), 1.32-1.24 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.02-0.92 (m, 11H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.64 (q, *J* = 7.9 Hz, 6H), 0.04 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.1, 170.6, 156.4

(q,  $J = 41.6$  Hz) 148.0, 142.4, 128.5, 128.5, 126.0, 114.5 (q,  $J = 286.9$  Hz), 113.4, 96.8, 84.3, 75.7, 72.4, 66.5, 63.6, 62.6, 61.5, 42.5, 41.3, 41.1, 40.1, 40.0, 37.7, 35.4, 33.8, 33.4, 26.5, 21.6, 17.4, 11.5, 10.6, 7.1, 5.3, -1.4; IR (cast film) 3513, 2957, 2882, 1776, 1735, 1378, 1248, 1215, 1164, 1100, 1060, 1000, 977  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{44}\text{H}_{71}\text{F}_3\text{O}_{10}\text{Si}_2$   $[\text{M}]^+$  873.19, found 873.50.

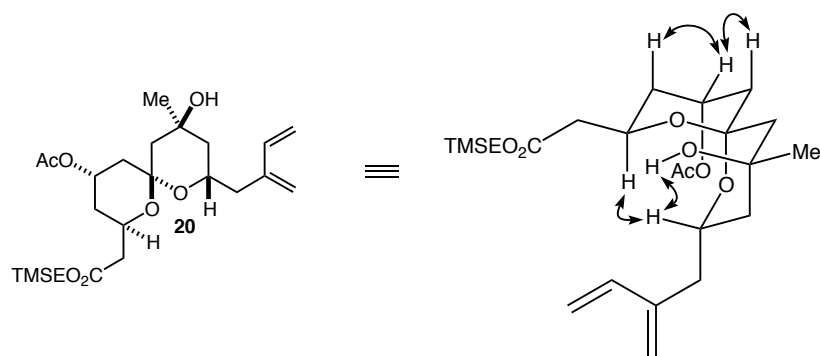


One of the portions of **22** in  $\text{CH}_2\text{Cl}_2$  from above was cooled to  $0\text{ }^\circ\text{C}$  with an ice/water bath, and aldehyde **25**<sup>1</sup> (263 mg, 0.75 mmol) was added followed by  $\text{Sc}(\text{OTf})_3$  (37mg, 0.075 mmol). The resulting mixture was vigorously stirred for 2 h and then the reaction was quenched by the addition of  $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$  (237 mg, 0.75 mmol). The resulting mixture was stirred for 10 h during which time the ice/water bath was allowed to melt and warm to room temperature. The mixture was concentrated and the residue was purified by silica gel chromatography (gradient, 15% to 20% EtOAc/Hexanes with pH 7 buffered silica gel) to afford **26** (508 mg, 0.55 mmol, 74% yield from diene **21**) as a viscous pale yellow oil. The diastereoselectivity of the reaction was determined to be  $\geq 10:1$  by  $^1\text{H}$  NMR analysis.  $[\alpha]_{\text{D}}^{23} = -33^\circ$  ( $c$  3.8,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (20% EtOAc/Hexanes, PMA stain);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75-7.65 (m, 2H), 7.65-7.52 (m, 2H), 7.53-7.31 (m, 5H), 5.11 (dd,  $J = 7.2, 1.5$  Hz, 2H), 5.05 (t,  $J = 3.2$  Hz, 1H), 4.99 (s, 1H), 4.41 (dt,  $J = 13.0, 6.5$  Hz, 2H), 4.23-4.07 (m, 2H), 3.54 (bs, 1H), 2.89 (dd,  $J = 15.2, 2.2$  Hz, 1H), 2.77-2.67 (m, 1H), 2.63-2.38 (m, 5H), 2.30 (dd,  $J = 16.4, 7.3$  Hz, 1H), 2.13 (dt,  $J = 14.5, 2.2$  Hz, 1H), 2.02-1.97 (m, 1H), 2.01 (s, 3H), 1.88 (s, 3H), 1.86-1.77 (m, 1H), 1.62 (dd,  $J = 15.0, 4.1$  Hz, 1H), 1.58-1.50 (m, 1H), 1.56 (s, 3H), 1.42 (d,  $J = 15.2$  Hz, 1H), 1.39-1.08 (m, 9H), 0.98 (t,  $J = 8.5$  Hz, 2H), 0.88-0.78 (m, 6H), 0.06 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 170.5, 156.3 (q,  $J = 41.1$  Hz), 155.9, 147.1, 135.9, 135.1, 135.0, 134.5, 130.1, 130.1, 130.0, 127.8, 127.8, 114.3 (q,  $J = 287.4$  Hz), 112.9, 96.7, 86.4, 84.3, 71.2, 66.5, 63.4, 62.5, 61.3, 42.0, 41.7, 40.9, 40.2, 39.9, 37.5, 37.2, 36.8, 33.7, 27.8, 26.4, 22.5, 21.4, 17.3, 14.0, 13.8, 11.4, -1.5; IR (cast film) 3517, 3075, 2961, 2930, 2862, 1777, 1734, 1372, 1249, 1214, 1163, 1059, 1016, 997  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{48}\text{H}_{67}\text{F}_3\text{O}_{10}\text{Si}_2$   $[\text{M}]^+$  917.21, found 917.51.



To a solution of **26** (440 mg, 0.48 mmol) in isopropanol (5 mL) was added  $\text{KHCO}_3$  (240 mg, 2.40 mmol) and hydrogen peroxide (0.63 mL of a 30 wt. % in water solution). The heterogeneous mixture (the  $\text{KHCO}_3$  did not fully dissolve) was stirred vigorously for 24 h. Brine (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography (40% EtOAc/Hexanes) to afford a 5:1 mixture of **27** and the C(16) diastereomer (271 mg, 0.36 mmol, 75% yield of the 5:1 mixture). Data for the major diastereomer **27**:  $R_f = 0.4$  (40% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.23 (s, 1H), 5.06-4.99 (m, 2H), 4.44-4.27 (m, 2H), 4.19-4.04 (m, 4H), 3.77 (dt,  $J = 9.3, 2.2$  Hz, 1H), 3.22 (bs, 1H), 2.85 (dd,  $J = 15.3, 2.4$  Hz, 1H), 2.82-2.76 (m, 1H), 2.73 (dd,  $J = 16.9, 2.5$  Hz, 1H), 2.64-2.51 (m, 2H), 2.45 (dd,  $J = 16.7, 7.0$  Hz, 1H), 2.35-2.19 (m, 4H), 2.04 (s, 3H), 1.95-1.87 (m, 1H), 1.81-1.72 (m, 1H), 1.65-1.56 (m, 3H), 1.54 (s, 3H), 1.52-1.45 (m, 1H), 1.43-1.24 (m, 7H), 1.15 (dd,  $J = 9.9, 7.0$  Hz, 1H), 1.06 (d,  $J = 4.0$  Hz, 3H), 1.05 (d,  $J = 4.1$  Hz, 3H), 0.95 (dd,  $J = 9.2, 7.9$  Hz, 2H), 0.90 (t,  $J = 6.9$  Hz, 3H), 0.03 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  216.2, 171.0, 170.8, 156.3 (q,  $J = 41.0$  Hz) 147.4, 114.5, 114.3 (q,  $J = 286.7$  Hz), 96.9, 84.2, 73.2, 67.6, 66.5, 63.5, 62.7, 61.4, 50.8, 48.4, 42.6, 41.3, 41.2, 40.2, 40.0, 37.7, 36.3, 33.8, 27.9, 26.5, 22.8, 21.6, 17.4, 14.2, 13.1, 11.0, -1.4; IR (cast film) 3497, 2947, 2933, 1778, 1735, 1378, 1249, 1216, 1165, 1136, 1060, 1000  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{36}\text{H}_{59}\text{F}_3\text{O}_{11}\text{Si}$   $[\text{M}]^+$  753.93, found 753.45.

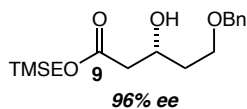
**Stereochemical Determination for 20:** The sense of absolute stereochemical induction of all of the asymmetric reactions employed in the sequence has been rigorously established in numerous examples. To confirm that no unexpected reversals had occurred during the synthesis, spiroketal **20** was subjected to  $^1\text{H}$  COSY and  $^1\text{H}$  NOESY NMR analysis. As illustrated in Supplementary Figure 1, the observed cross-peaks in the NOESY spectrum strongly support the claim that the stereostructure of **20** is as indicated.



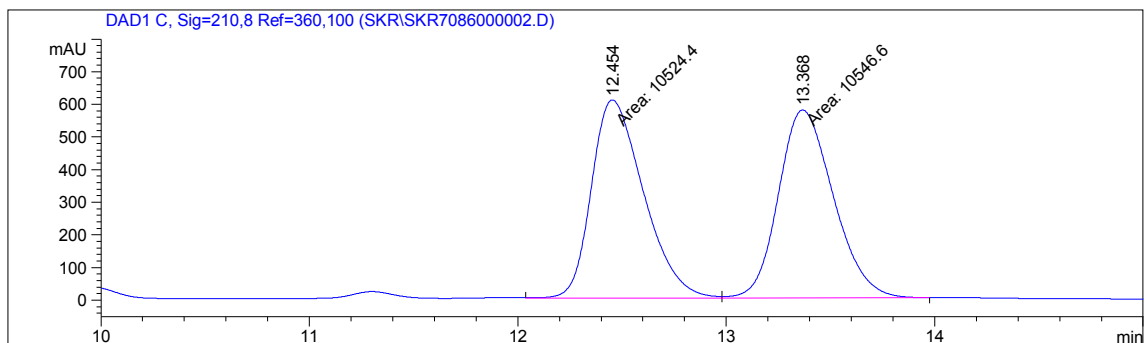
**Supplementary Figure 1:** NOESY analysis of Spiroketal **20**.

**Stereochemical Determination for 24 and 27:** The absolute sense of stereochemical induction in the fragment coupling by crotylation reactions has been rigorously proven,<sup>1</sup> and is assigned here by analogy. The *anti* relative stereochemistry (at C(16) in **27**) in the Tamao oxidation/tautomerization reaction has been rigorously proven,<sup>1</sup> and is assigned here by analogy.

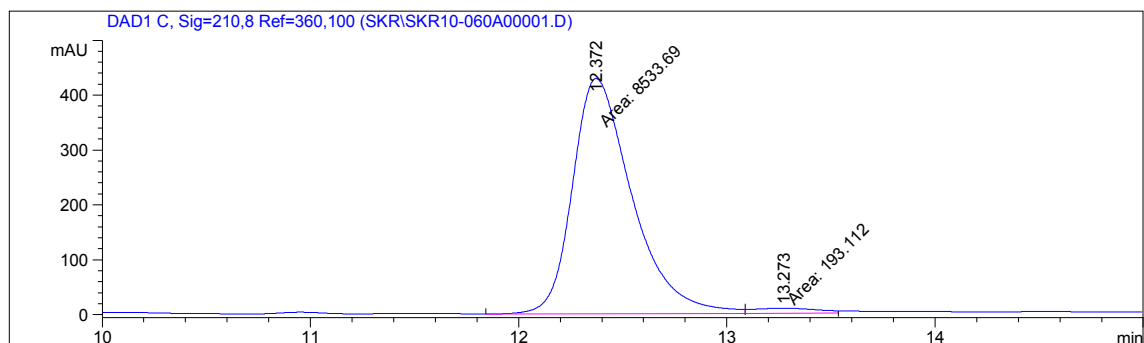
### 3. Determination of Enantiomeric Excesses for 9 and 14



Chiralcel AD-H Column, 2% *i*-PrOH in hexanes, 1 mL/min, 254 nm

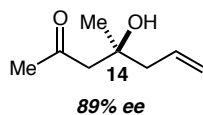


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	12.454	1	MM	1.05244e4	606.62604	49.9473
2	13.368	1	MM	1.05466e4	575.89166	50.0527

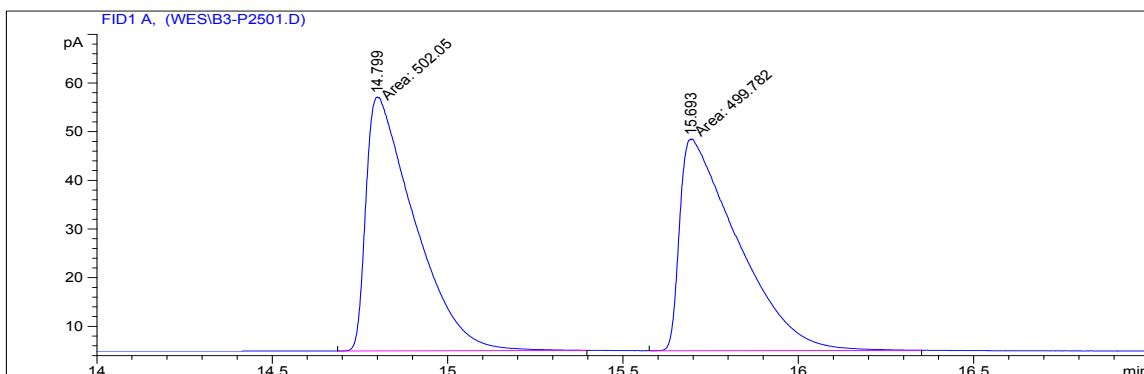


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	12.372	1	MM	8533.68750	428.80310	97.7871
2	13.273	1	MM	193.11183	9.09061	2.2129

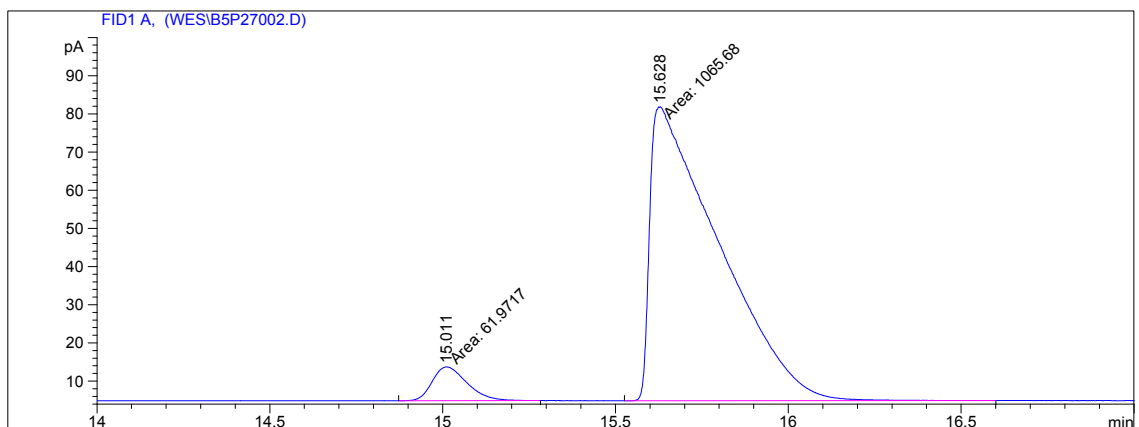
Supplementary Figure 2: Chiral HPLC analysis of compound 9



### Chiral GC Supelco $\beta$ -Dex 125 and 325, 90 °C Isothermal



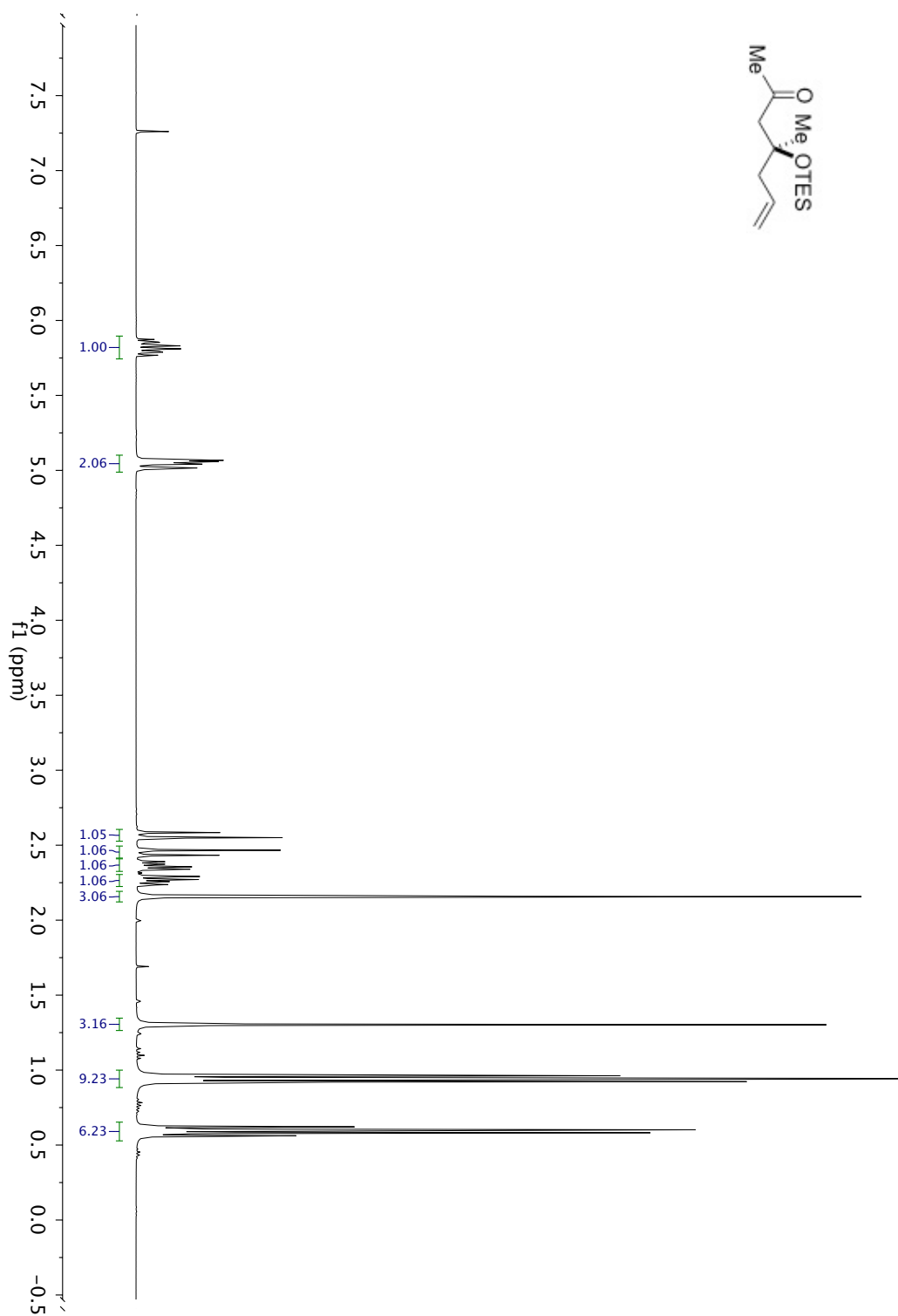
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.799	MM	0.1604	502.05014	52.17256	50.11322
2	15.693	MM	0.1913	499.78159	43.53556	49.88678



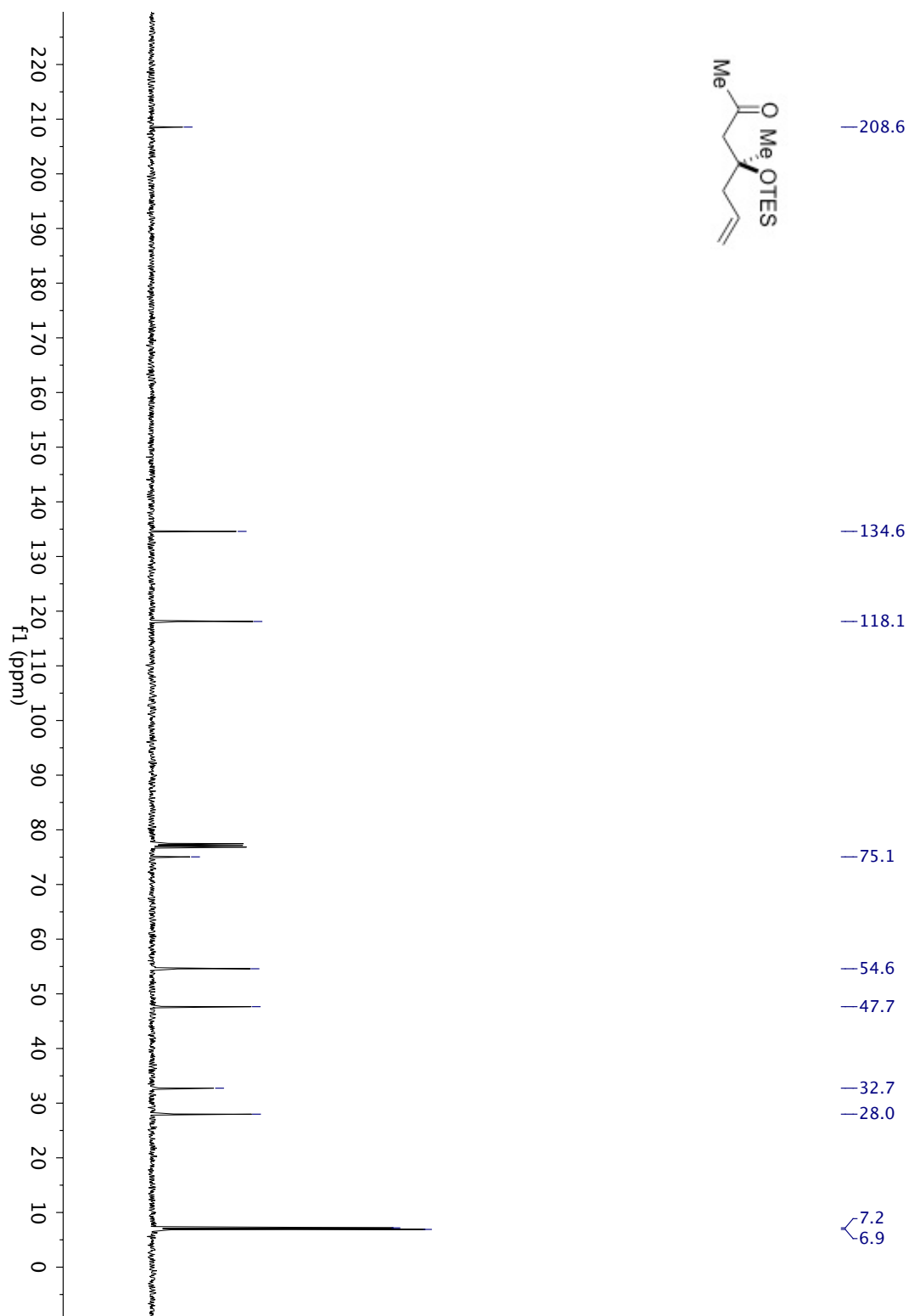
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	15.011	MM	0.1164	61.97166	8.87497	5.49564
2	15.628	MM	0.2308	1065.67969	76.95920	94.50436

### Supplementary Figure 3: Chiral GC analysis of compound 14

#### 4. NMR Spectral Data

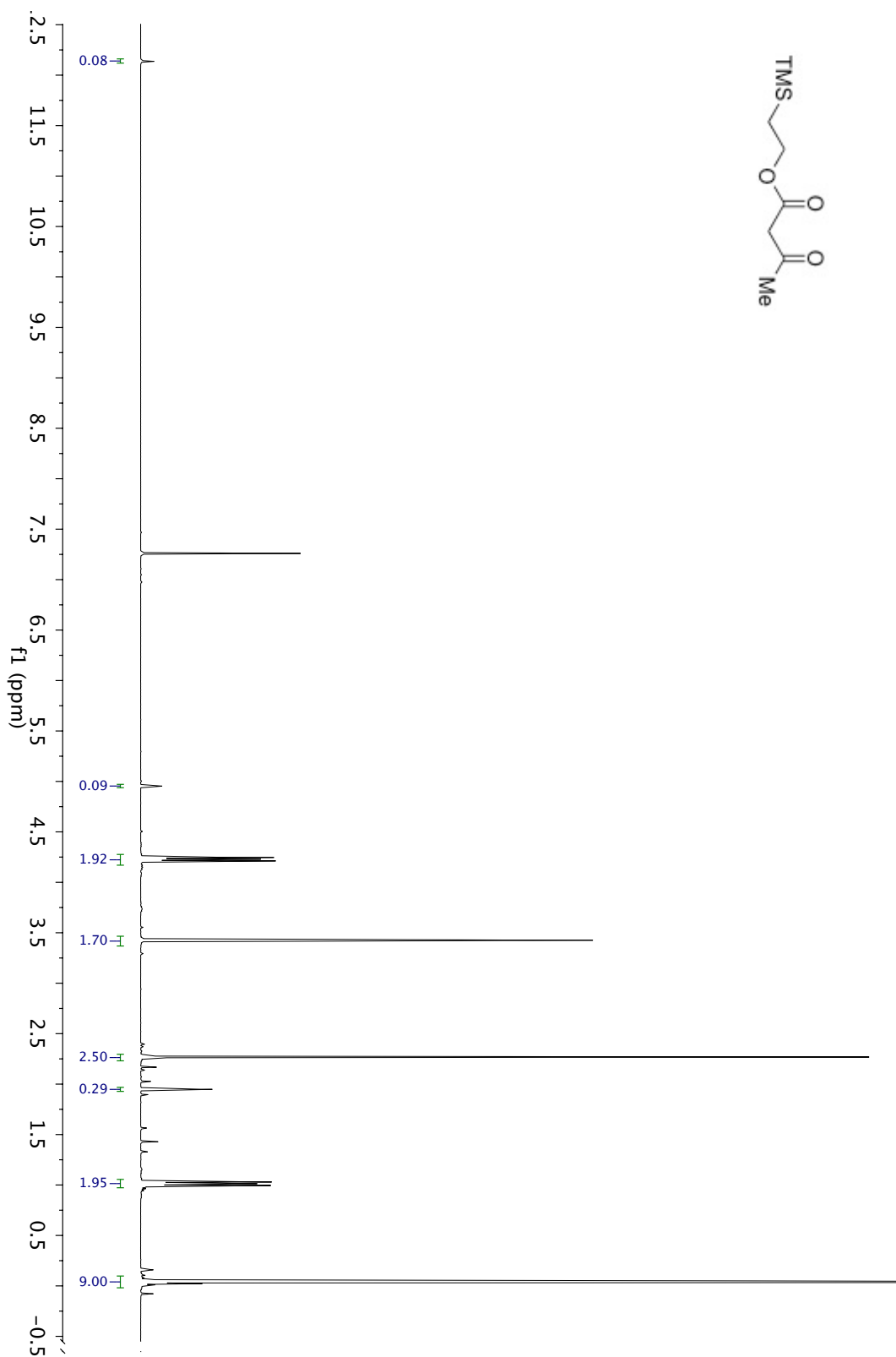


Supplementary Figure 4: <sup>1</sup>H NMR for compound 6

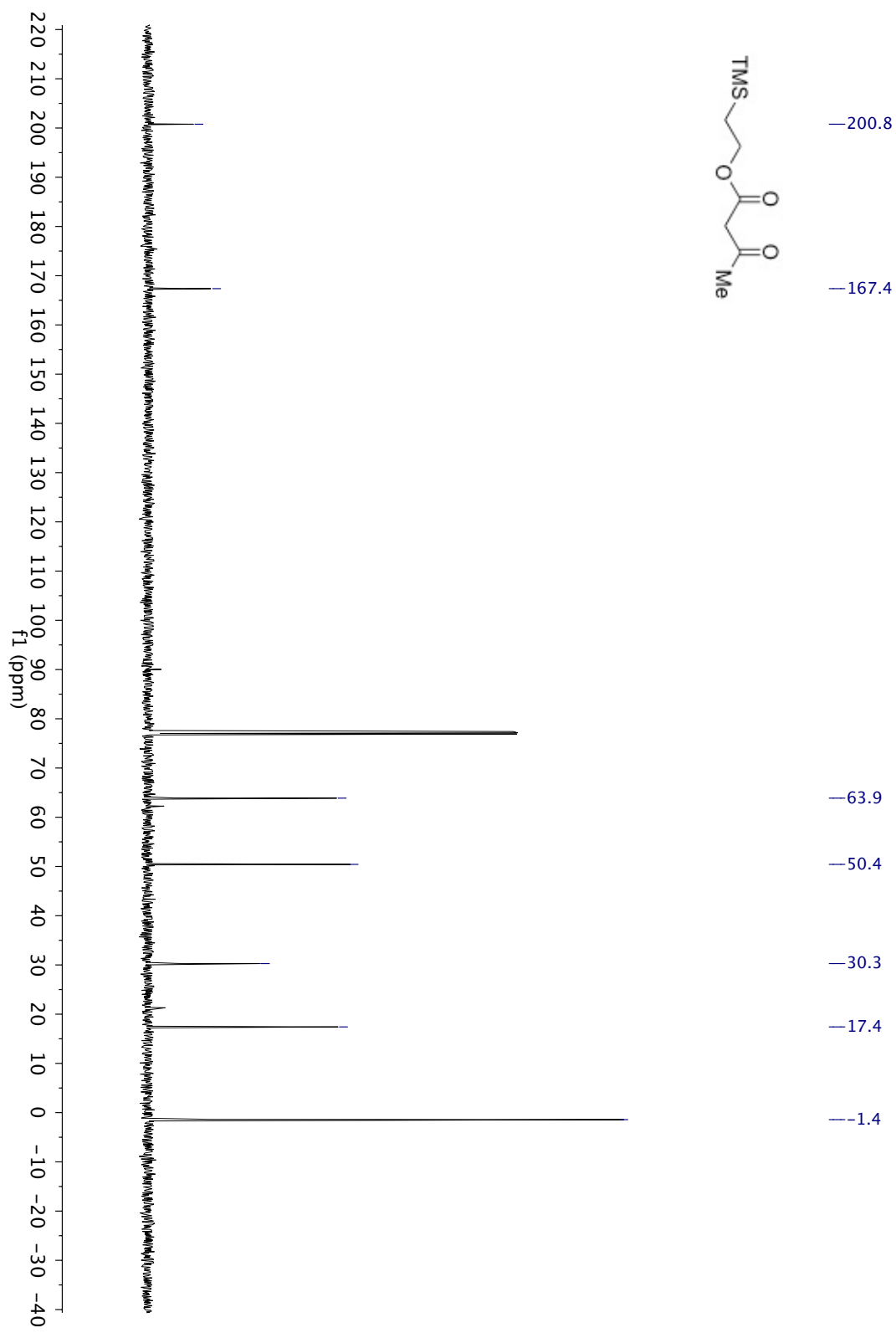


Supplementary Figure 5:  $^{13}\text{C}$  NMR for compound 6

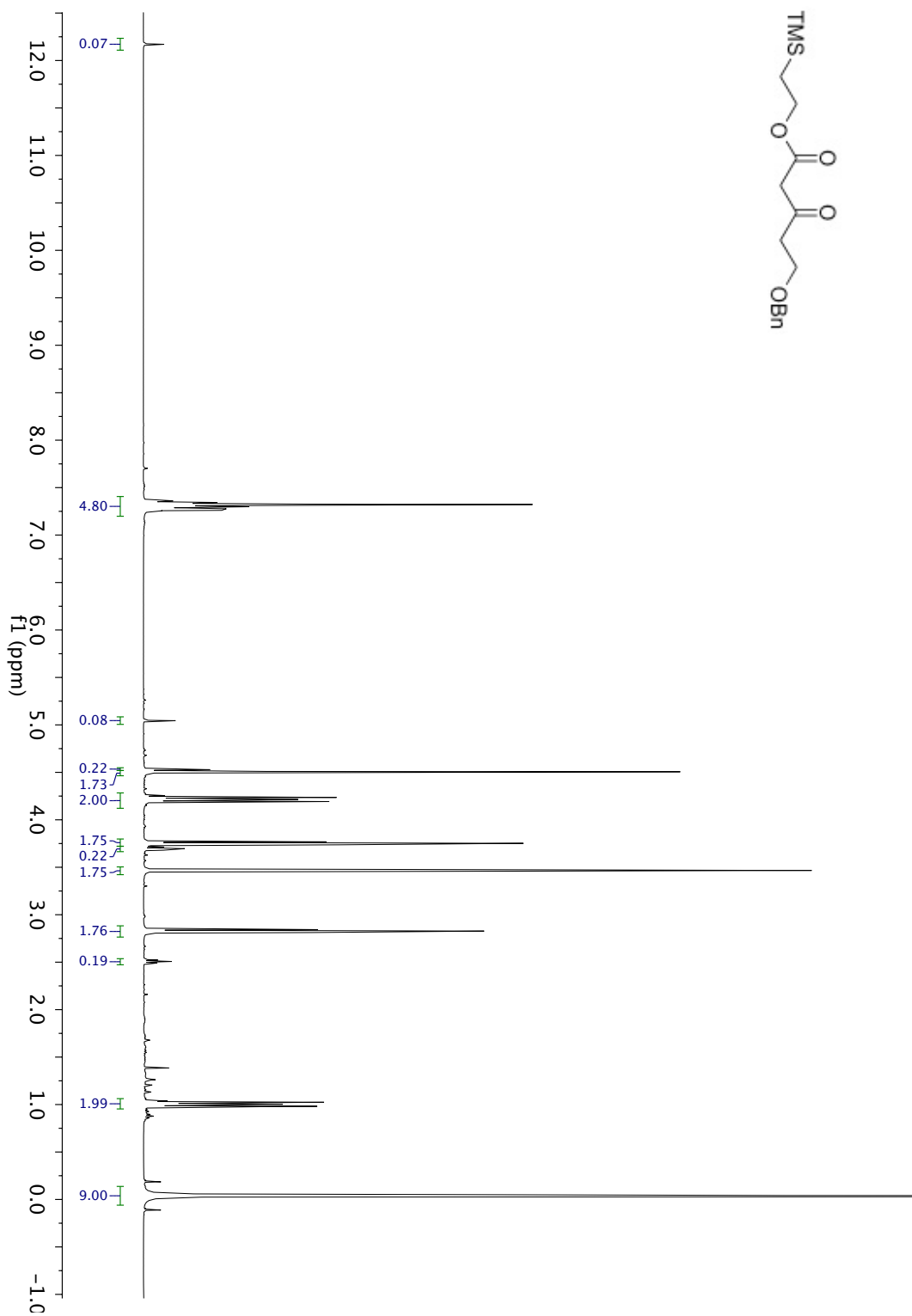


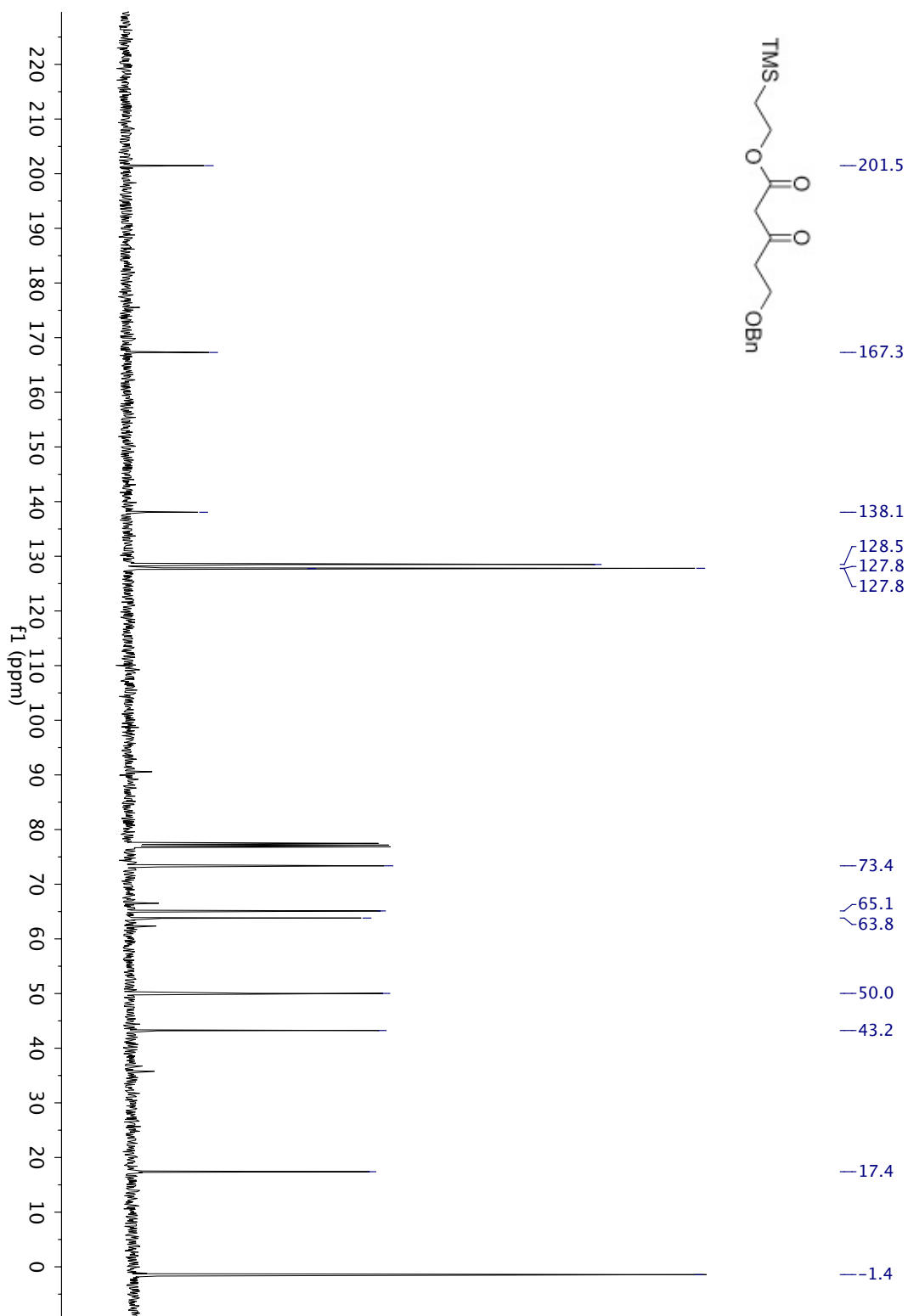


Supplementary Figure 6:  $^1\text{H}$  NMR for compound 7

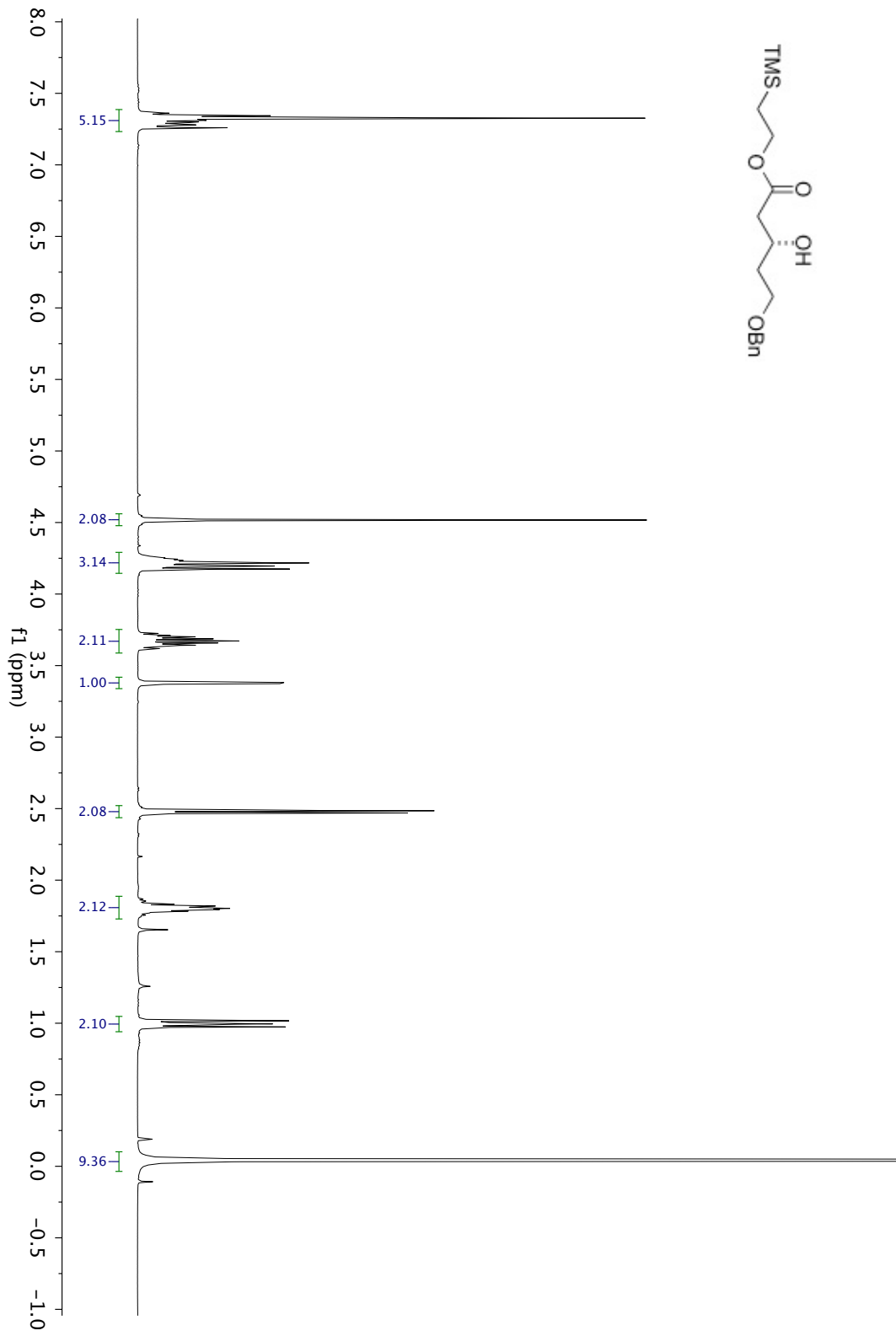


Supplementary Figure 7:  $^{13}\text{C}$  NMR for compound 7

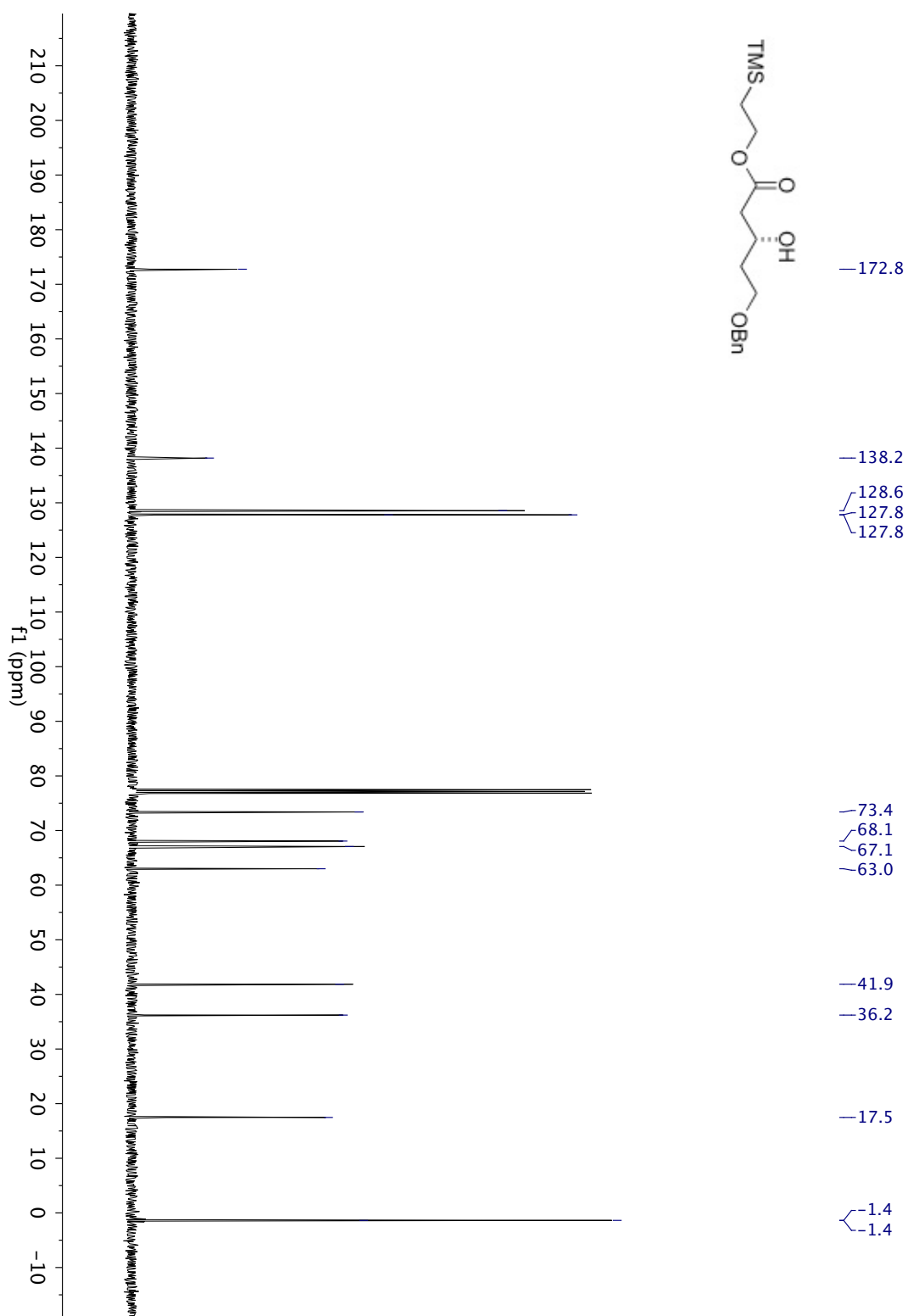




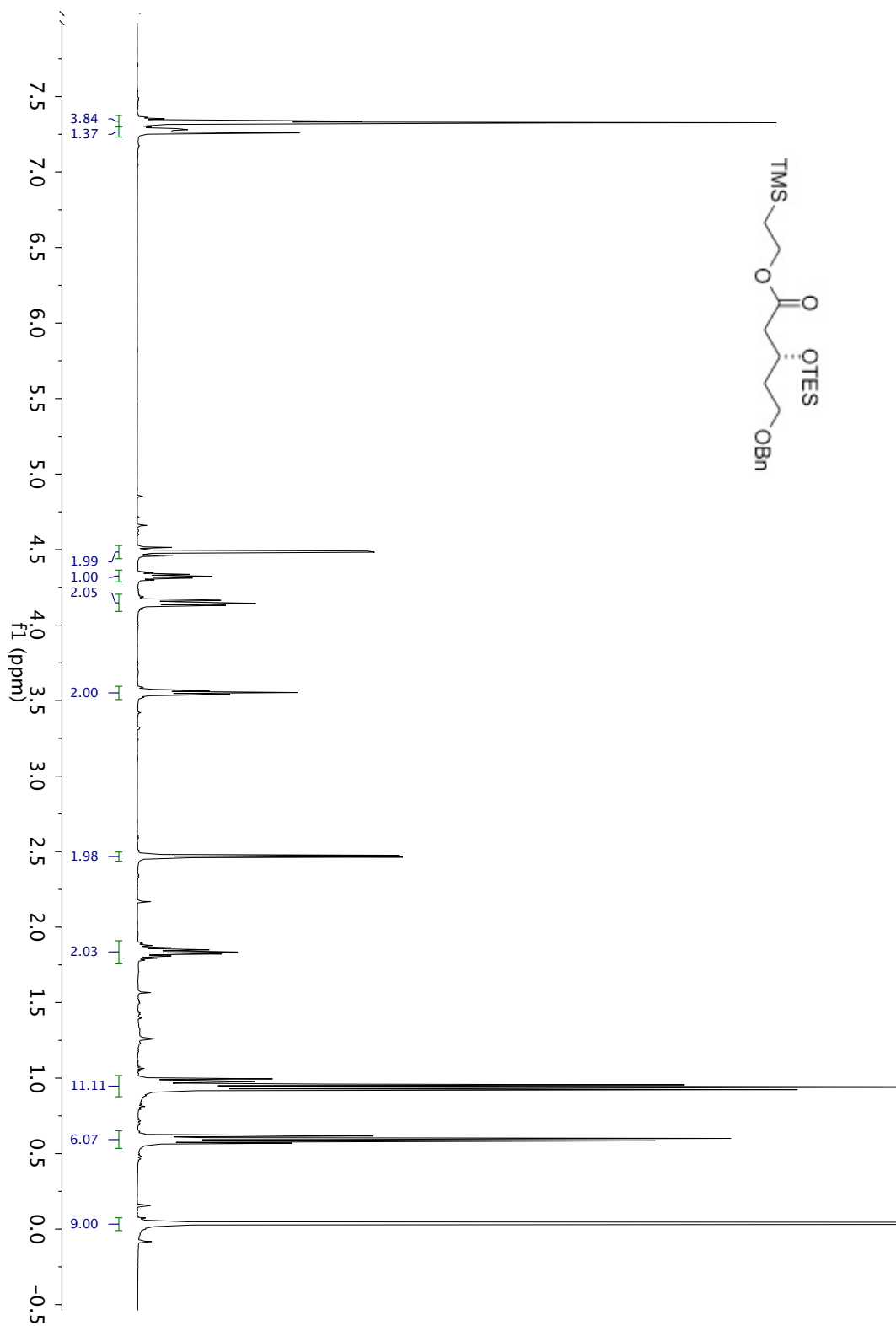
Supplementary Figure 9:  $^{13}\text{C}$  NMR for compound 8



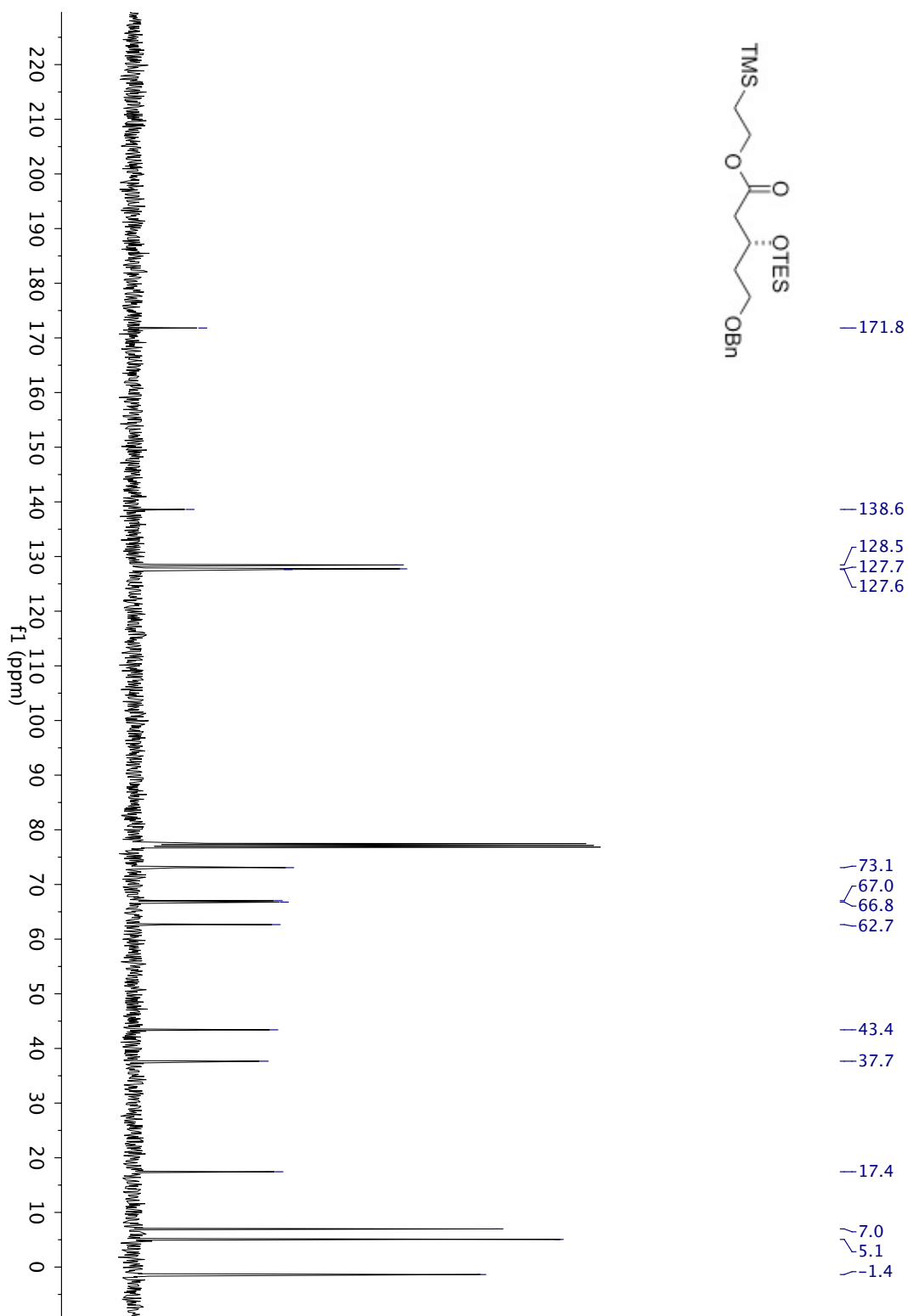
Supplementary Figure 10: <sup>1</sup>H NMR of compound 9



Supplementary Figure 11:  $^{13}\text{C}$  NMR for compound 9

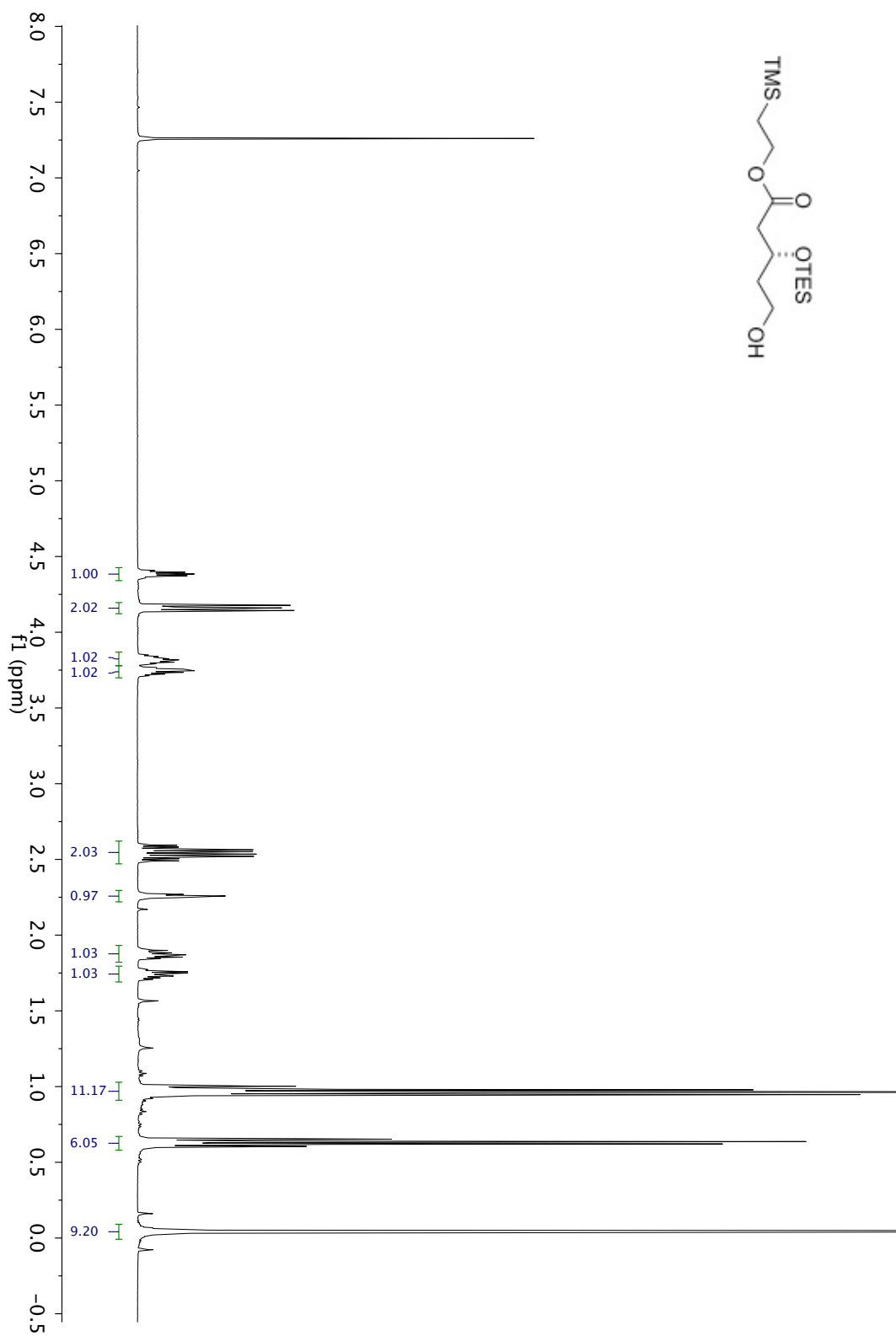


Supplementary Figure 12:  $^1\text{H}$  NMR for compound 10

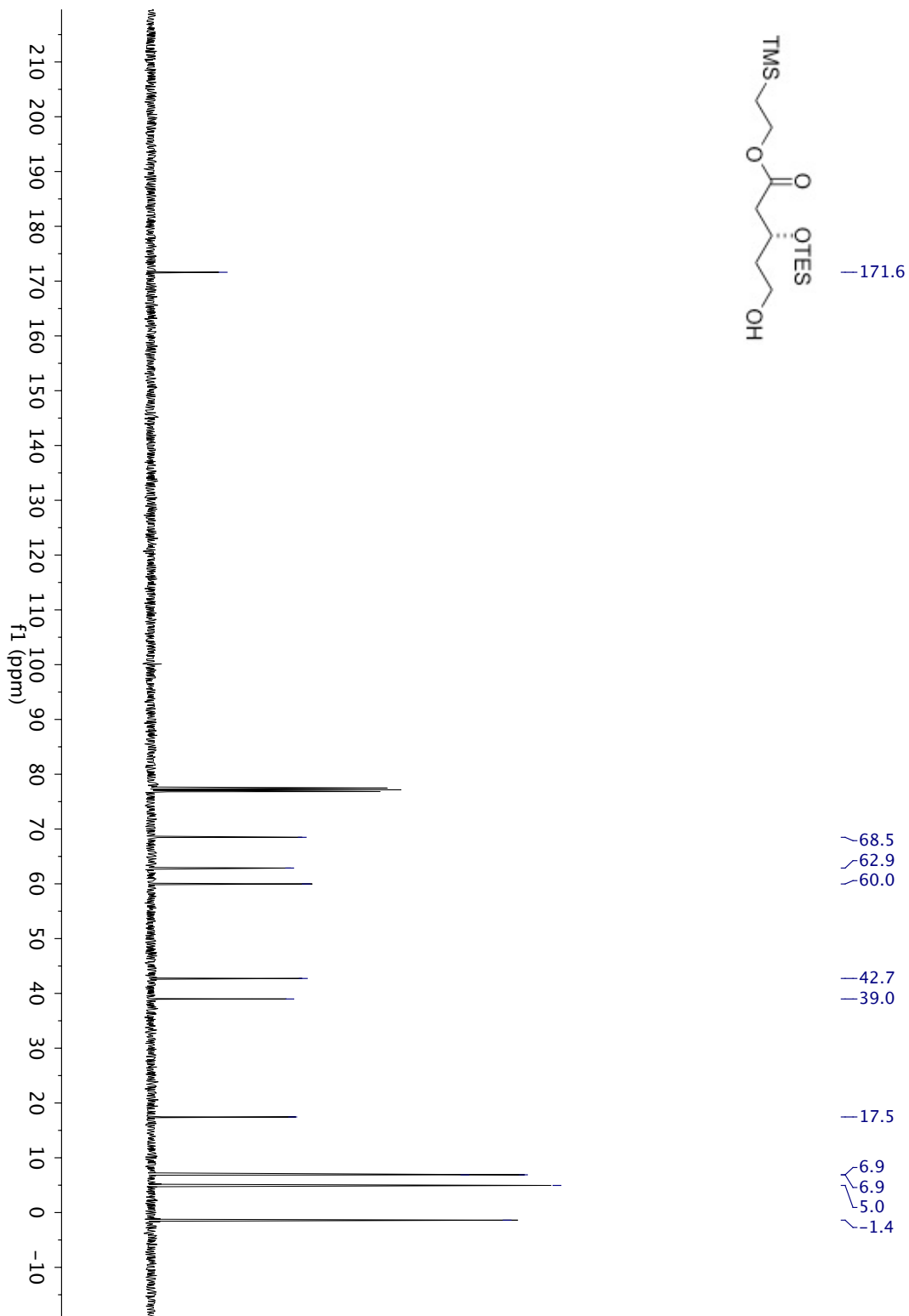


Supplementary Figure 13:  $^{13}\text{C}$  NMR for compound 10

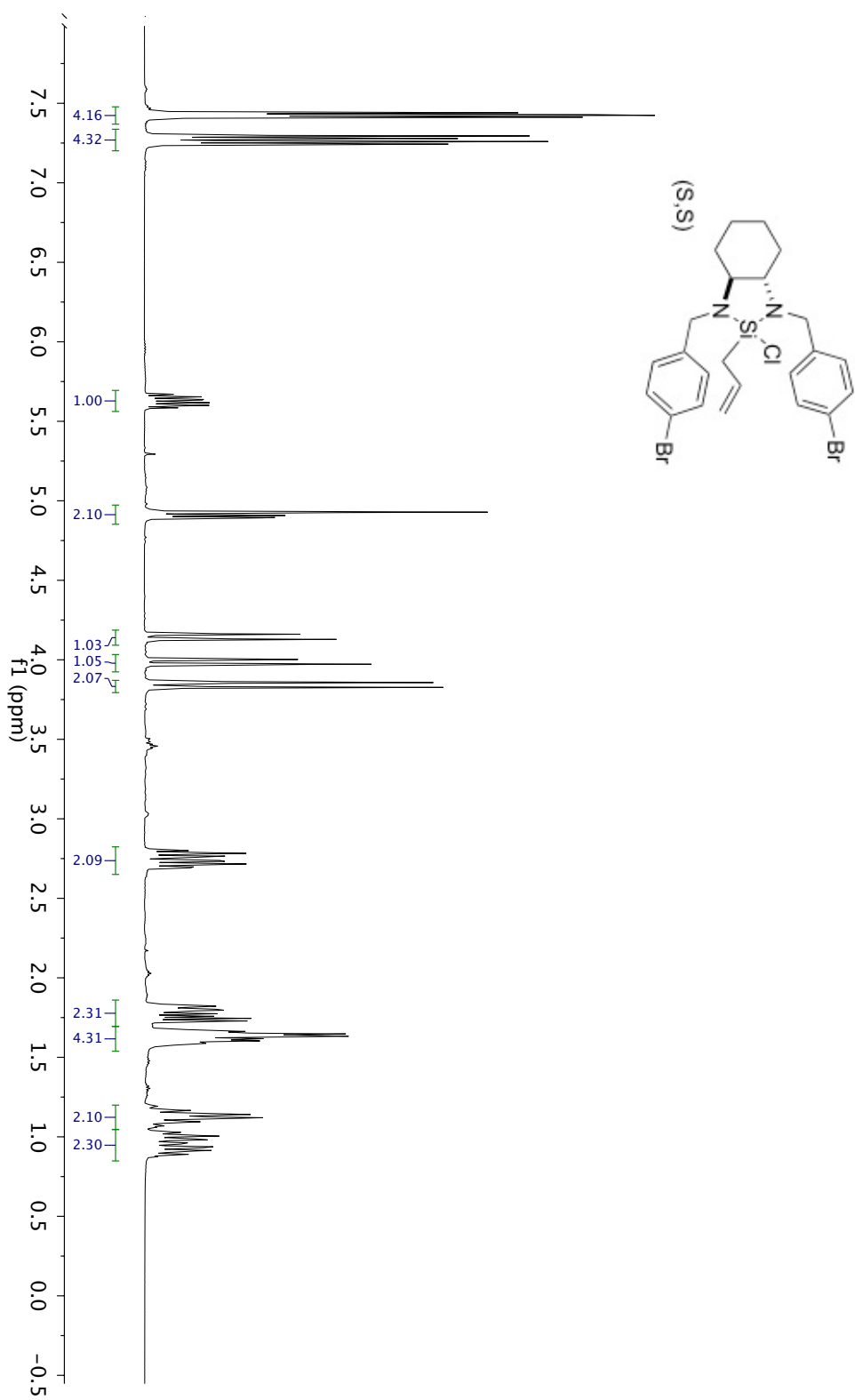




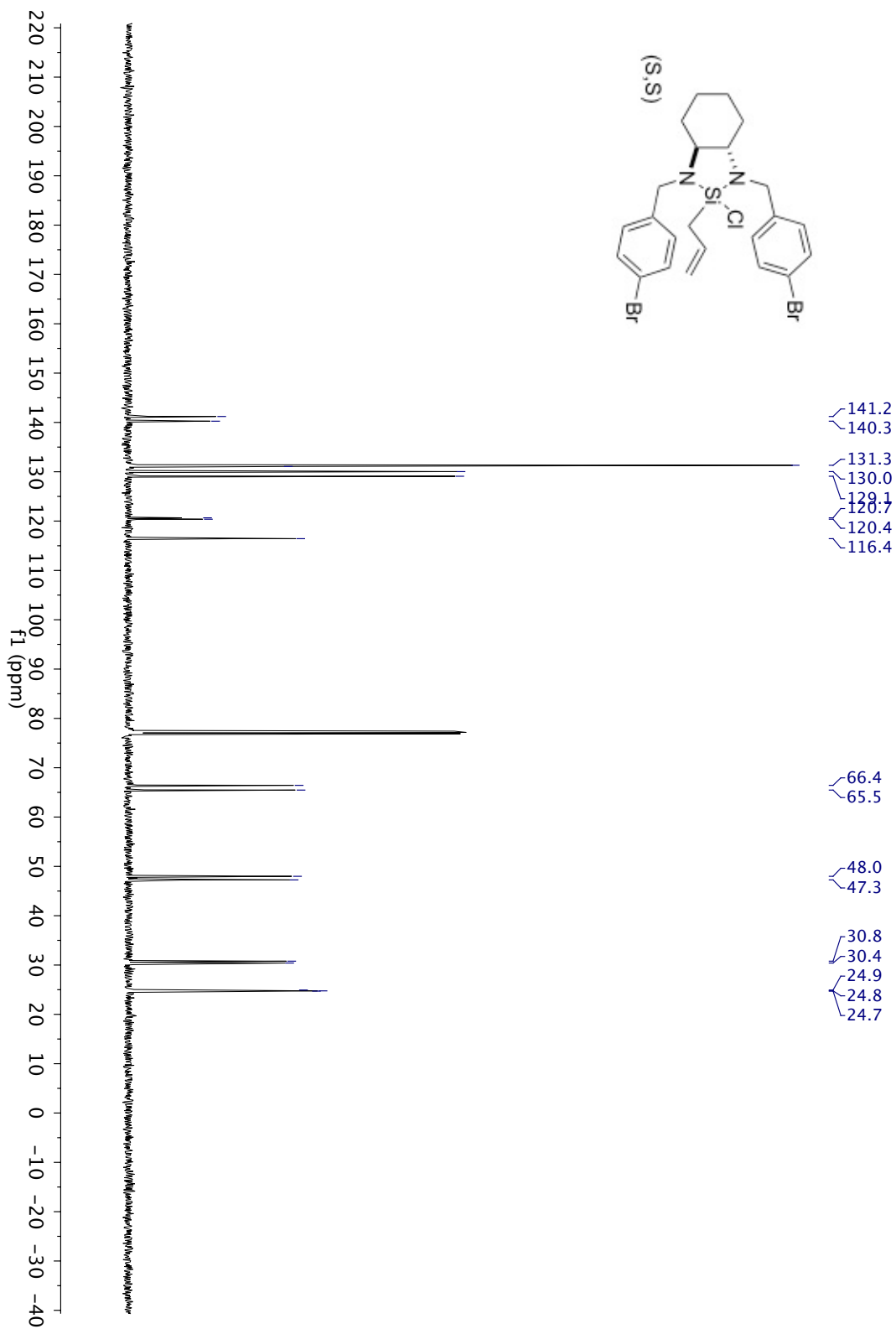
**Supplementary Figure 14:** <sup>1</sup>H NMR for compound 11



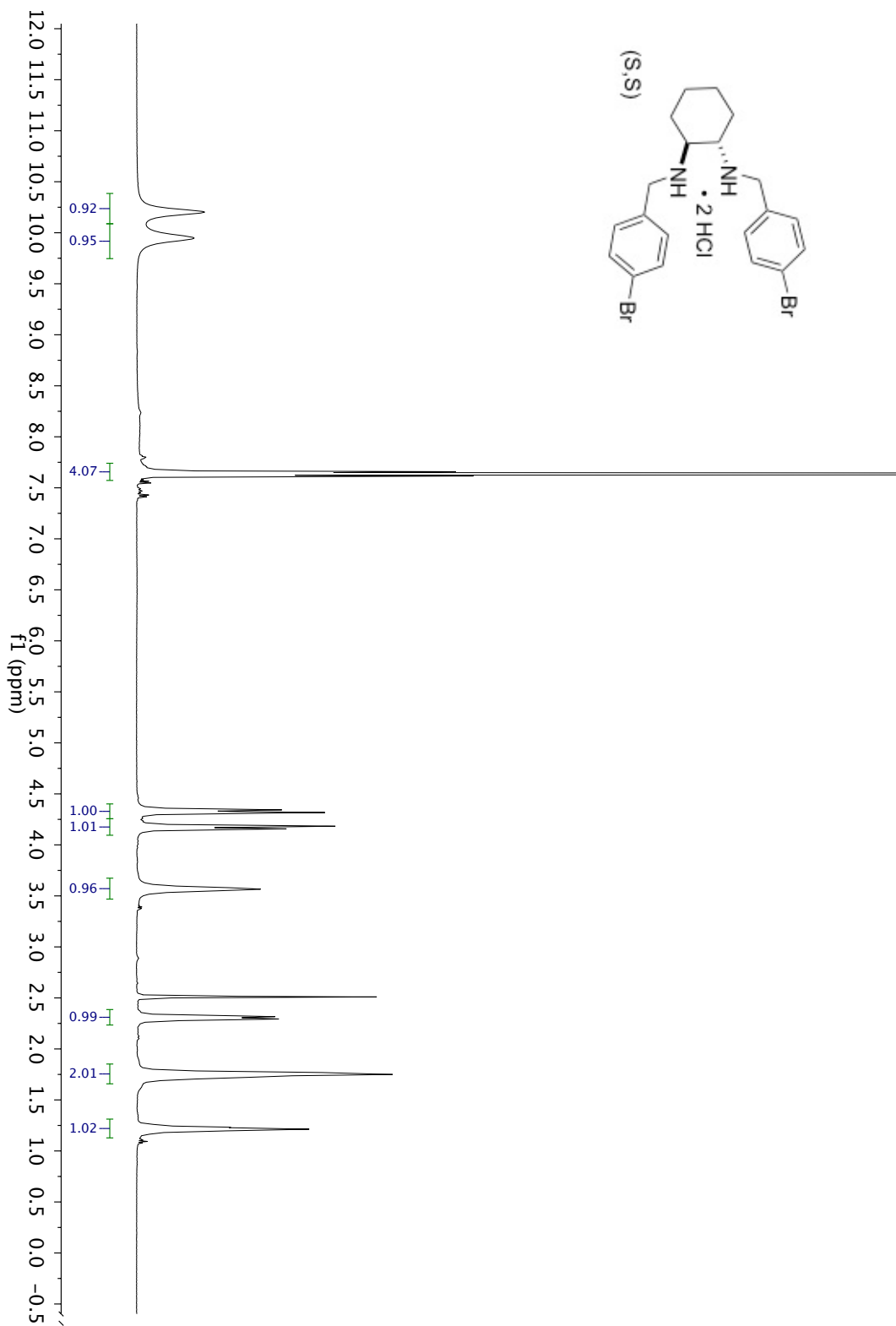
Supplementary Figure 15:  $^{13}\text{C}$  NMR for compound 11



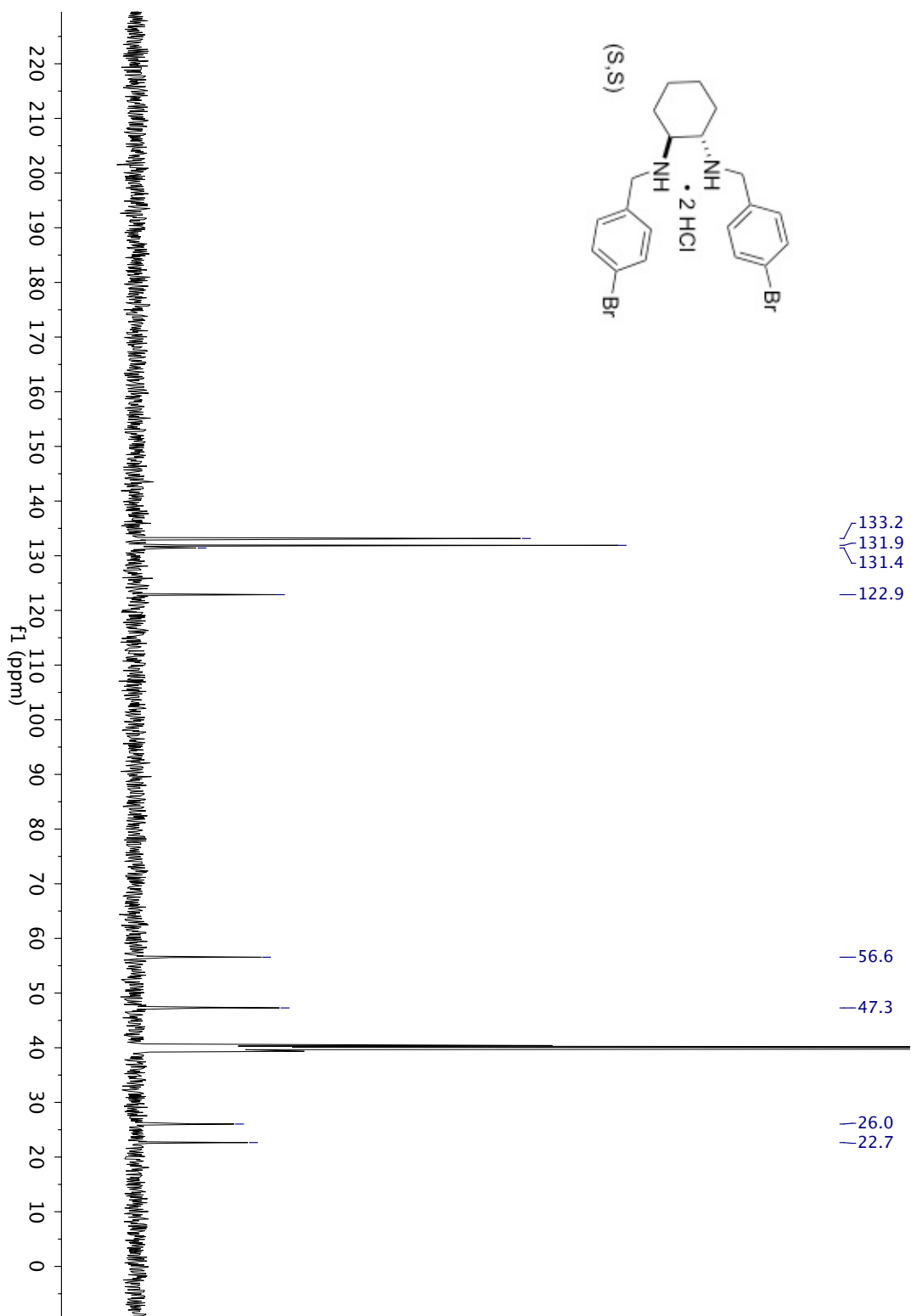
Supplementary Figure 16:  $^1\text{H}$  NMR for compound (S,S)-12



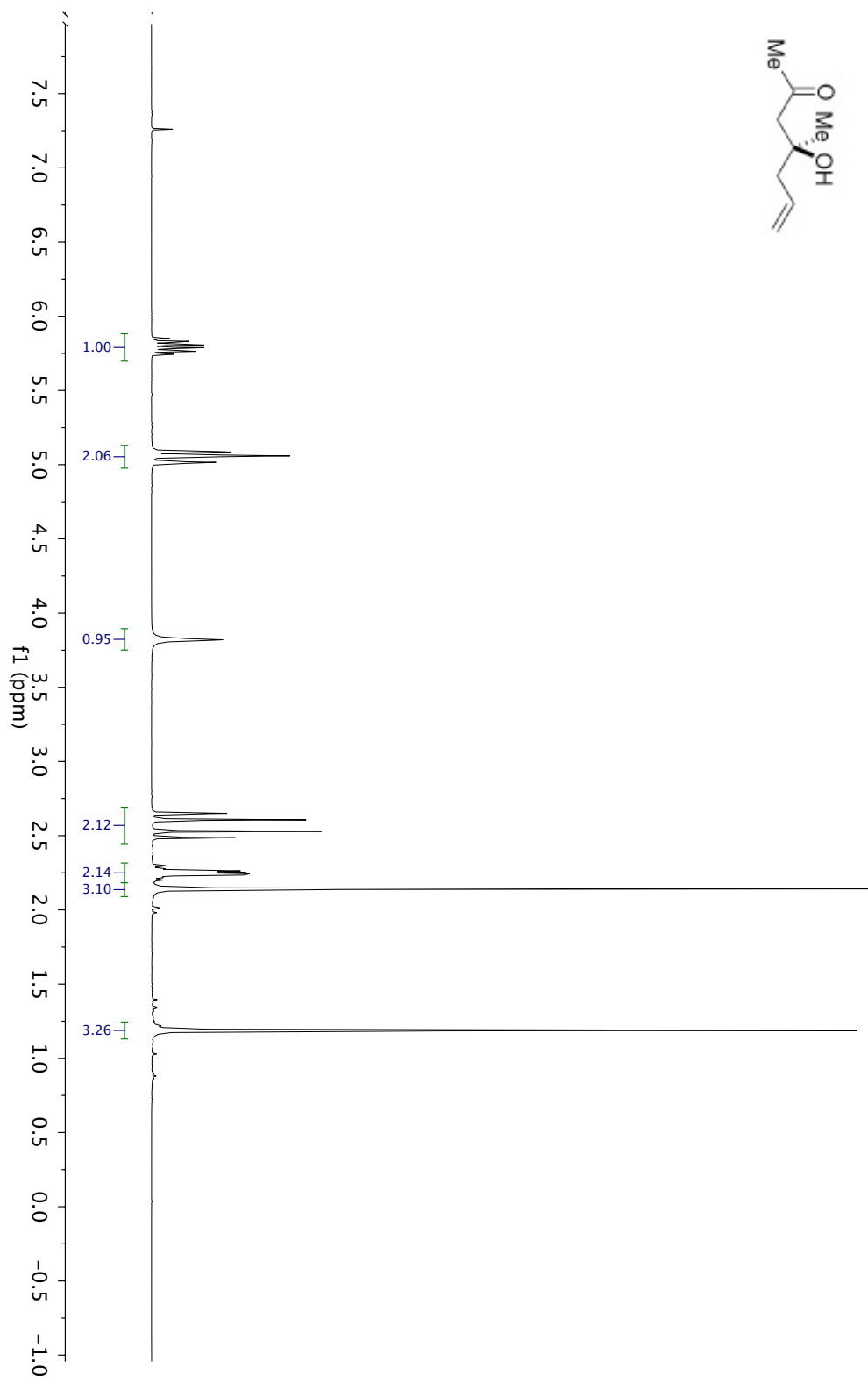
Supplementary Figure 17:  $^{13}\text{C}$  NMR for compound (S,S)-12



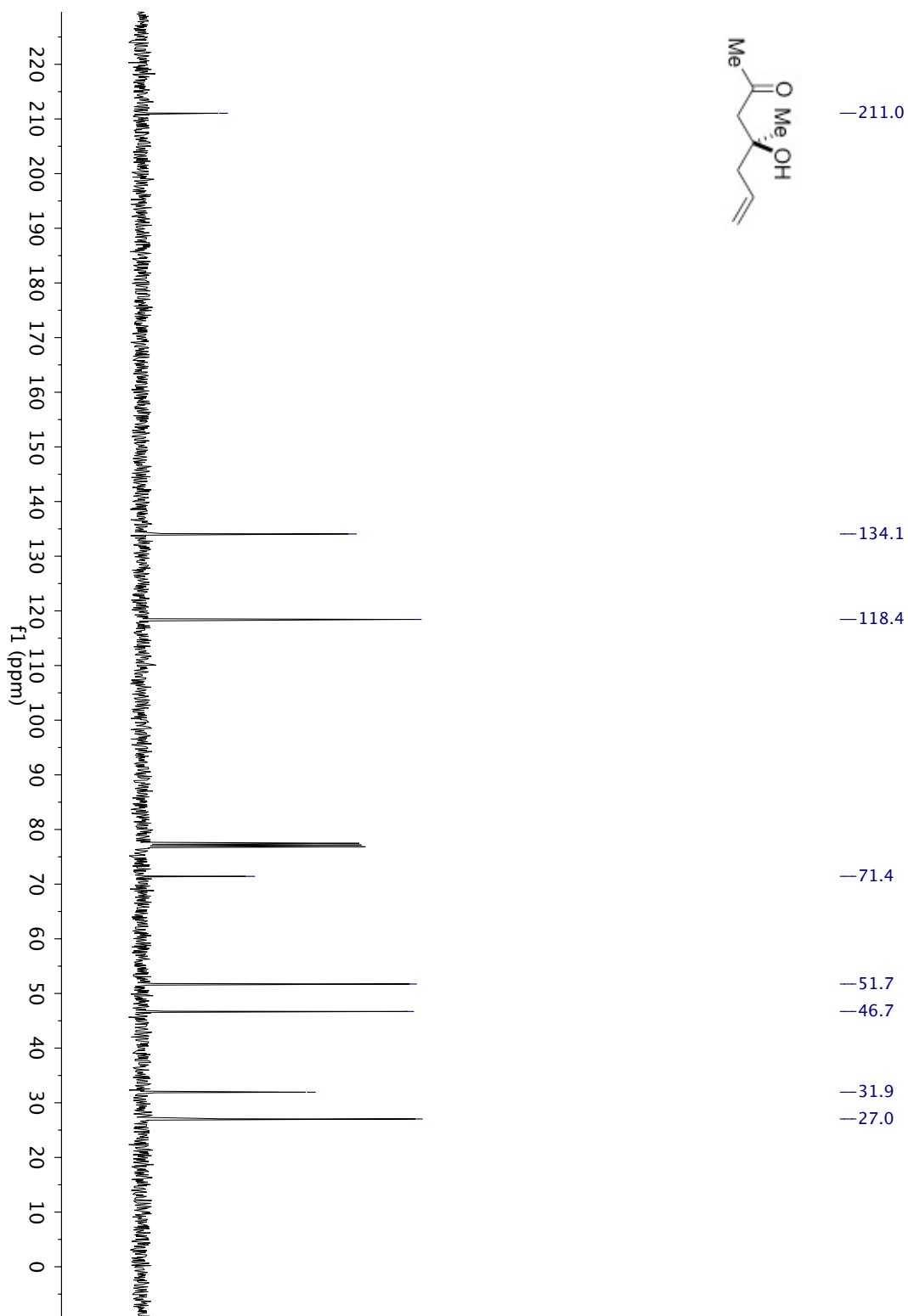
Supplementary Figure 18:  $^1\text{H}$  NMR for compound (*S,S*)-13



Supplementary Figure 19:  $^{13}\text{C}$  NMR for compound (S,S)-13

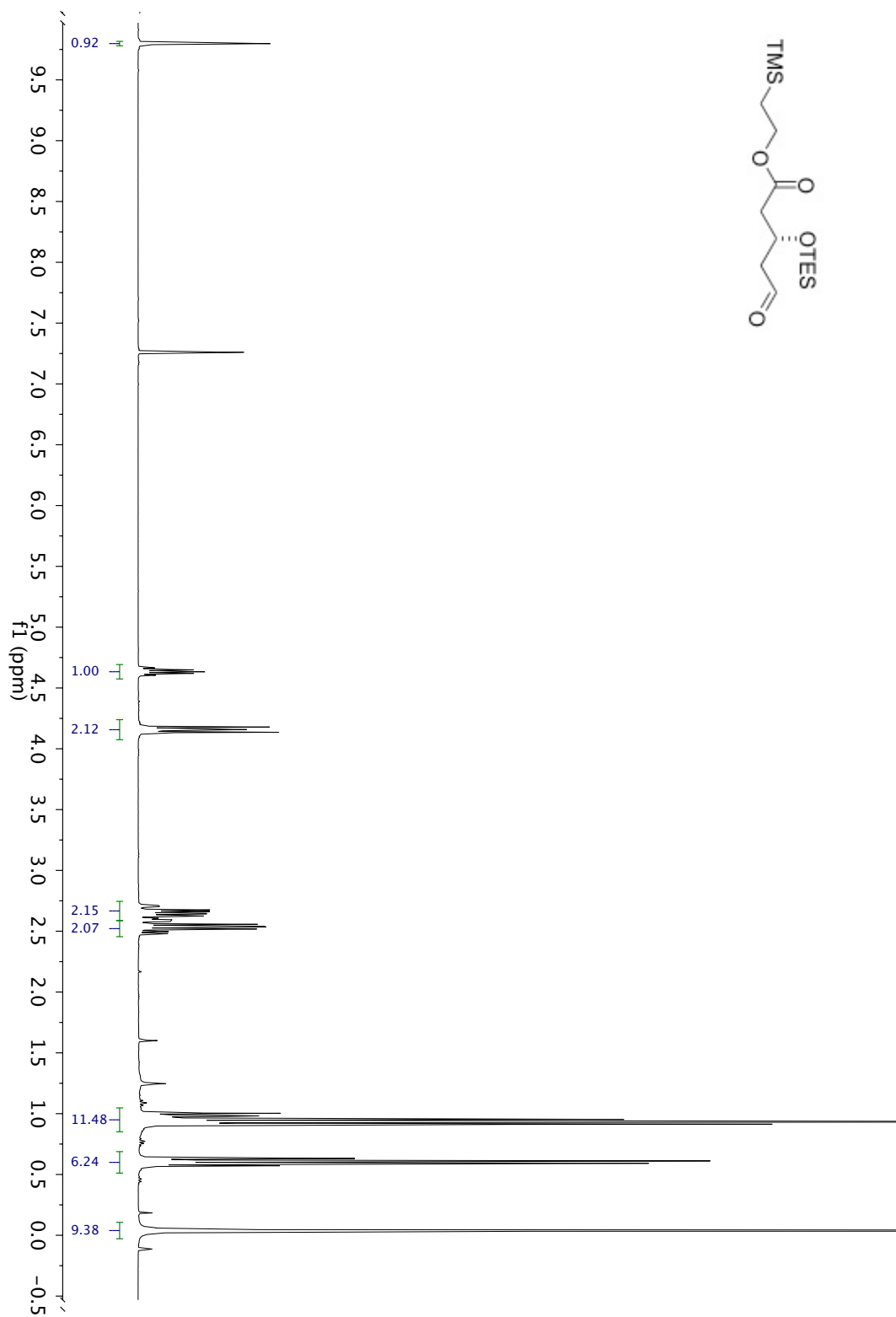


Supplementary Figure 20: <sup>1</sup>H NMR for compound 14

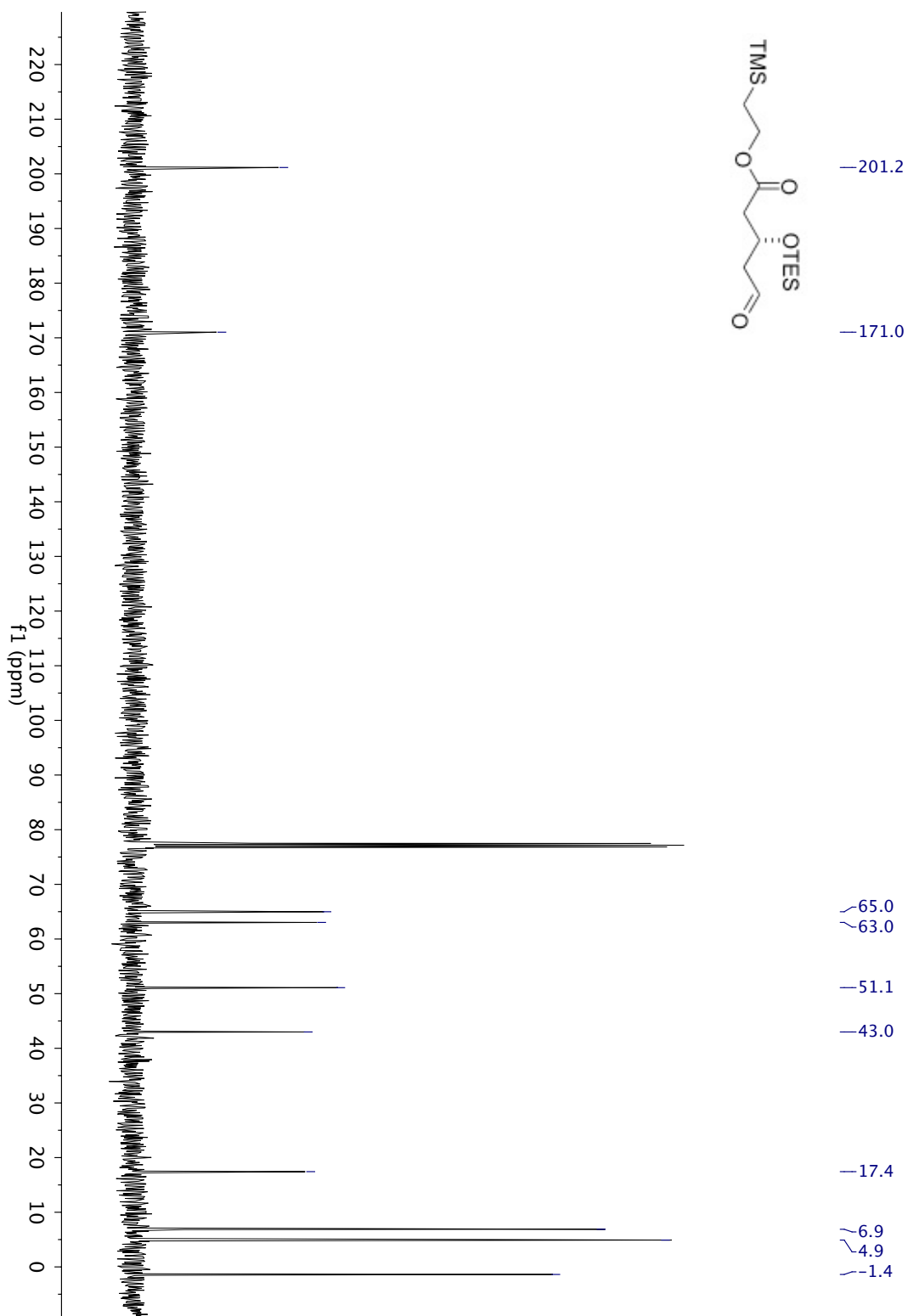


Supplementary Figure 21:  $^{13}\text{C}$  NMR for compound 14

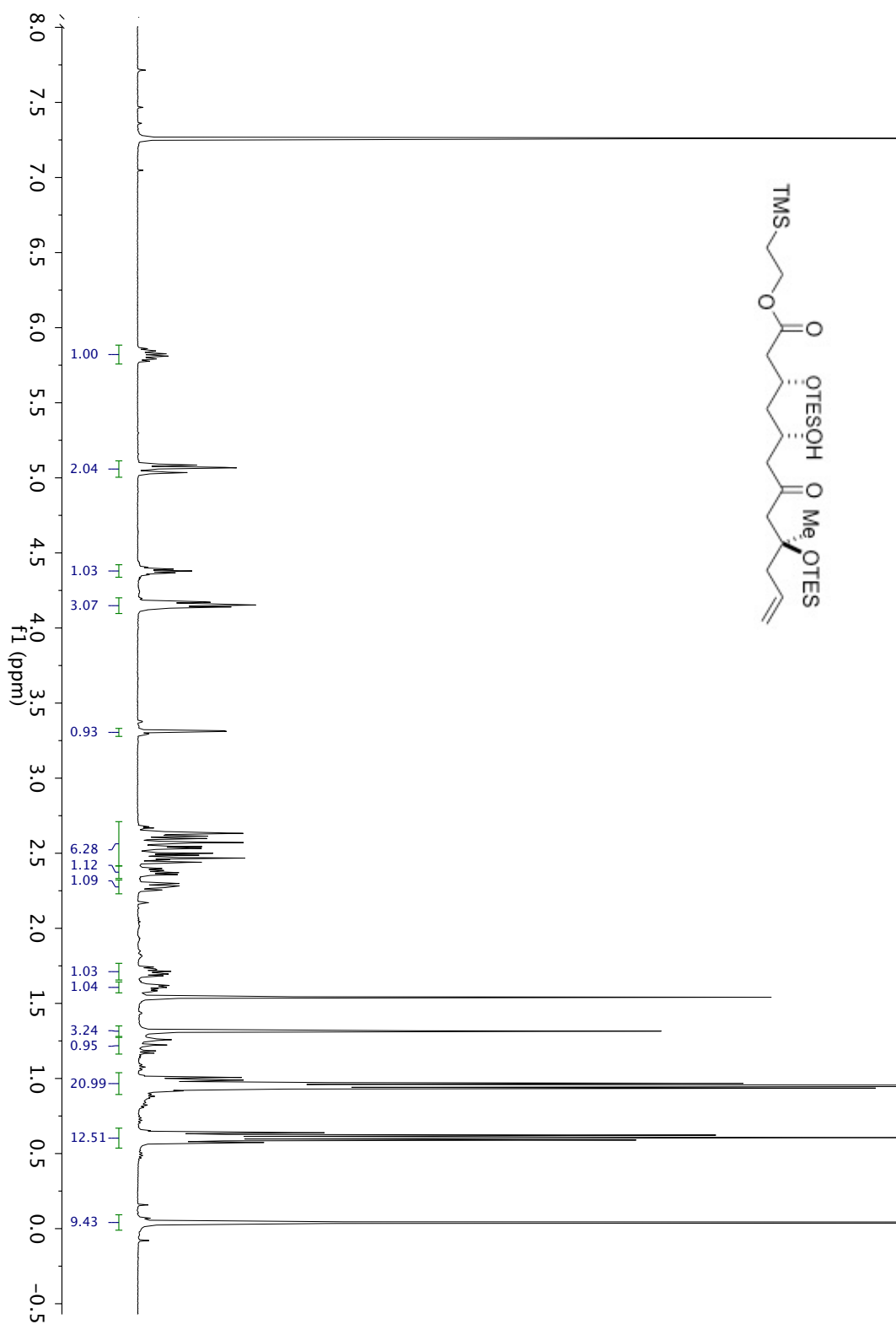




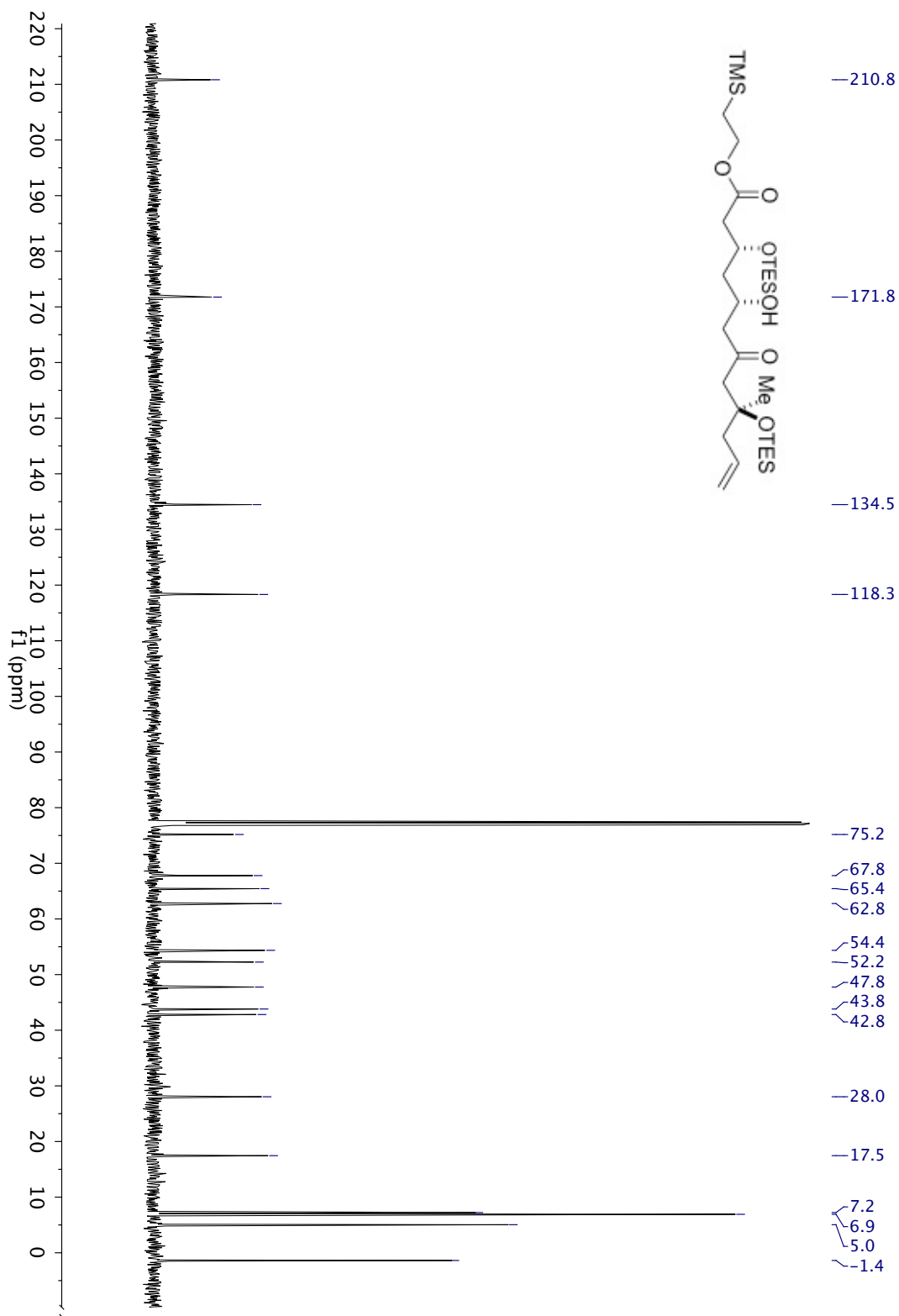
Supplementary Figure 22: <sup>1</sup>H NMR for compound 15



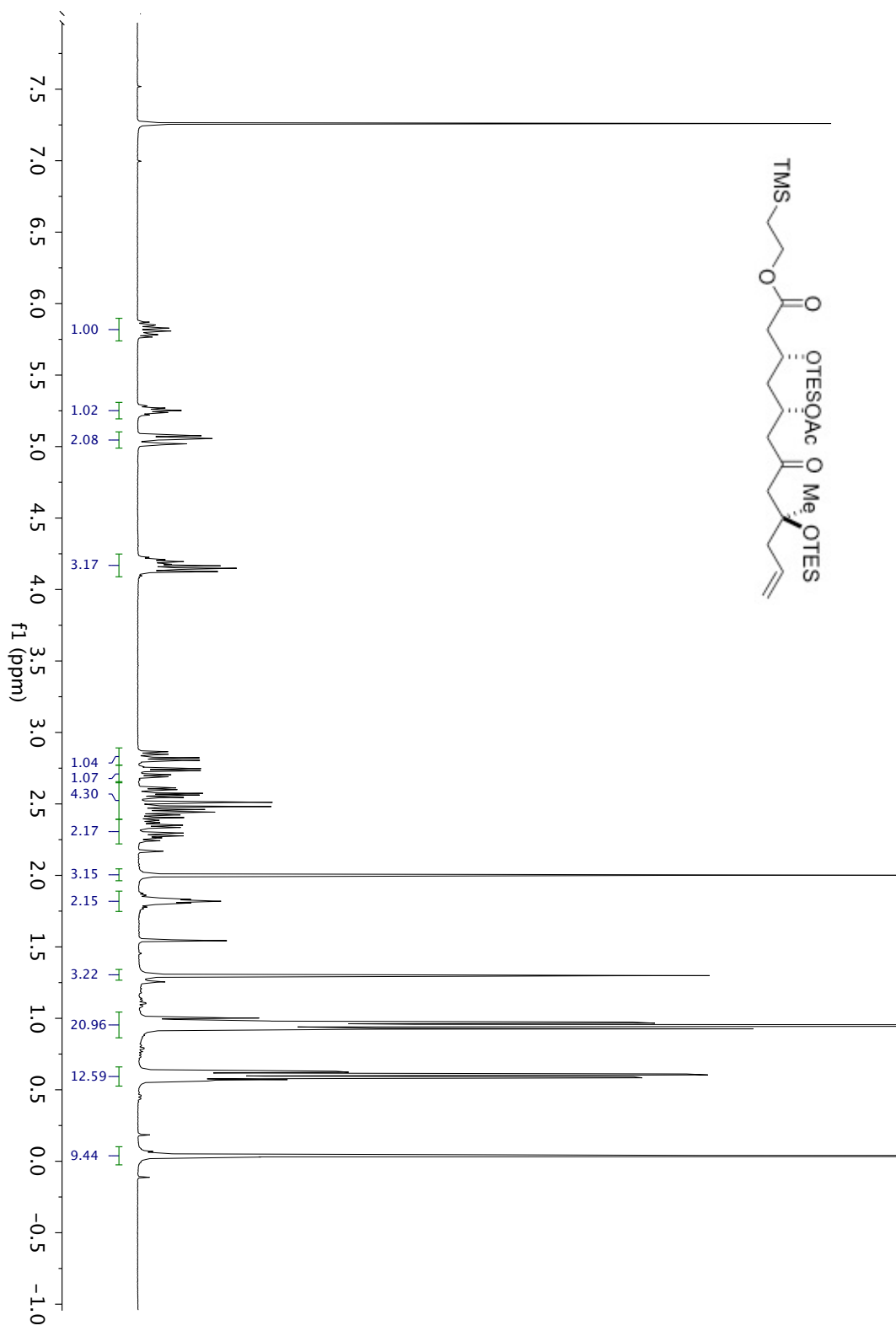
Supplementary Figure 23:  $^{13}\text{C}$  NMR for compound 15



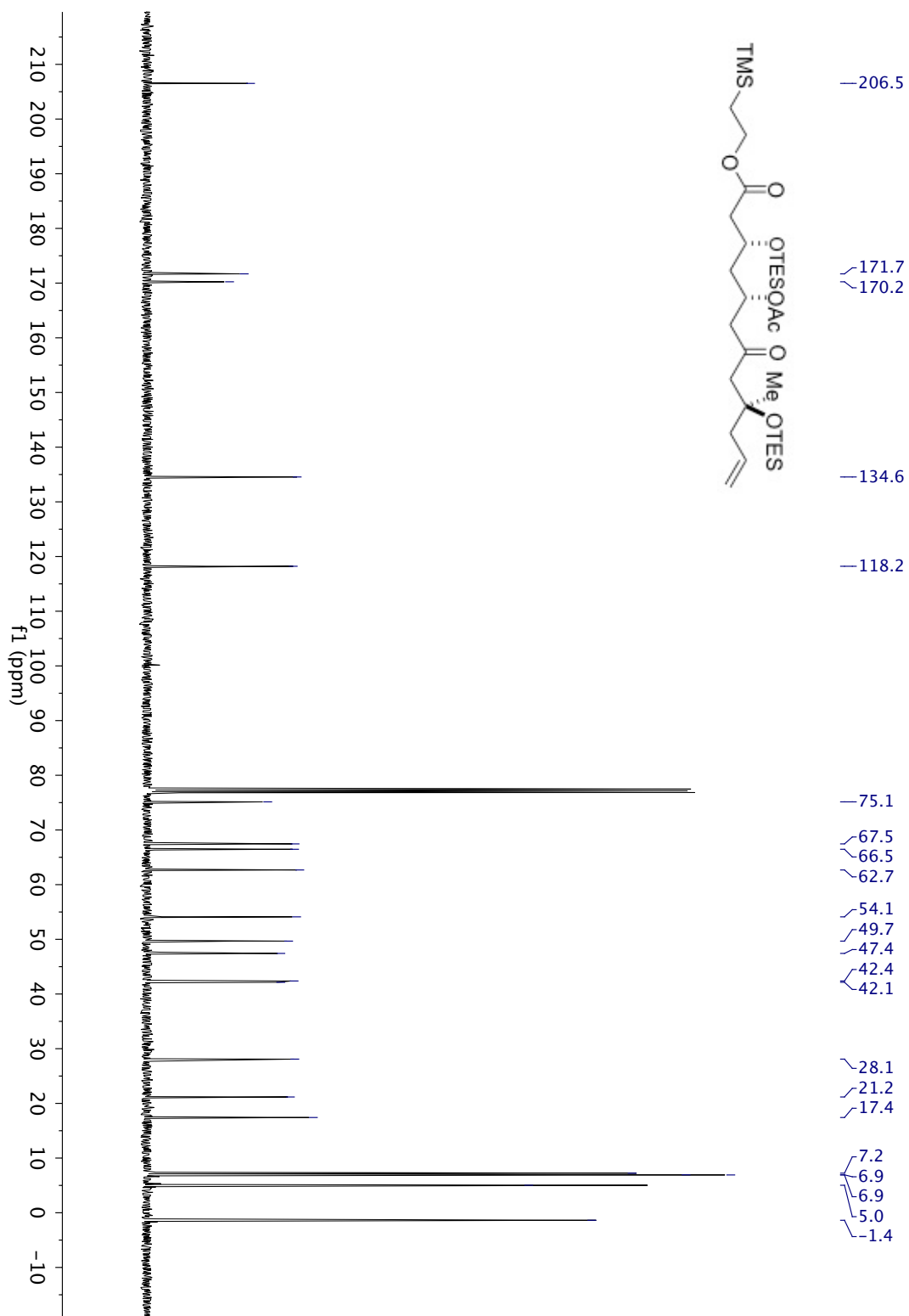
Supplementary Figure 24: <sup>1</sup>H NMR for compound 16



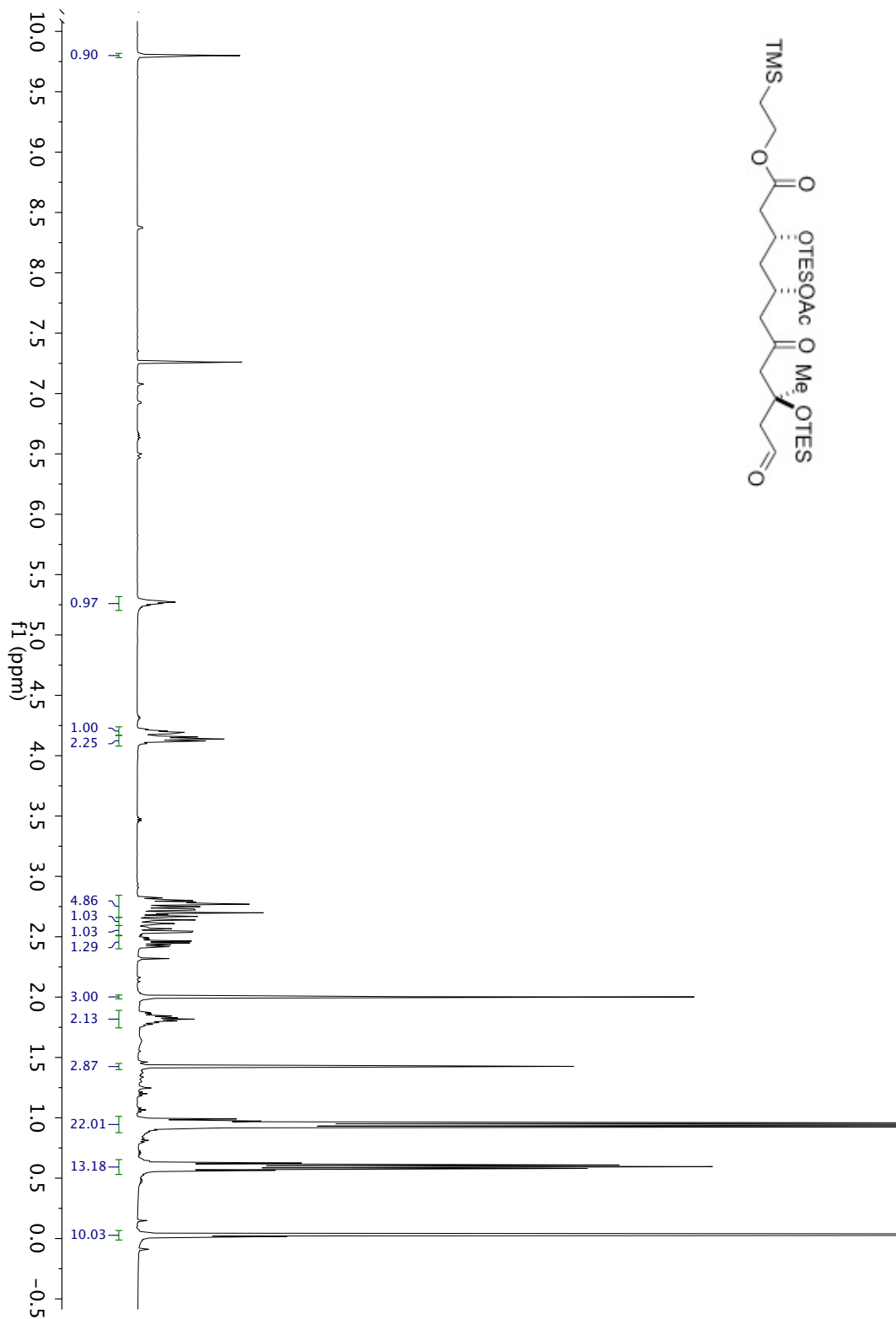
Supplementary Figure 25:  $^{13}\text{C}$  NMR for compound 16



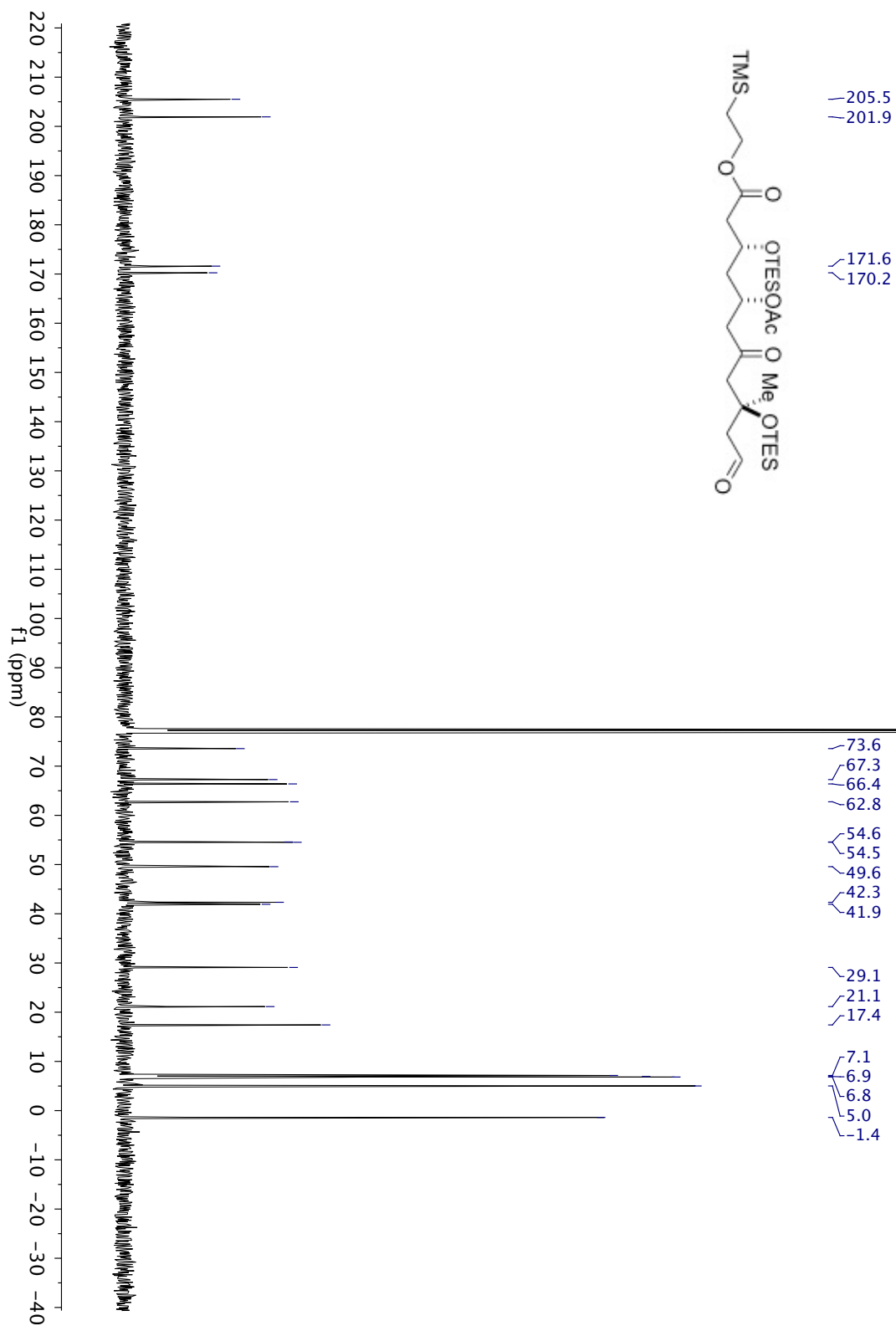
Supplementary Figure 26: <sup>1</sup>H NMR for compound 17



Supplementary Figure 27: <sup>13</sup>C NMR for compound 17

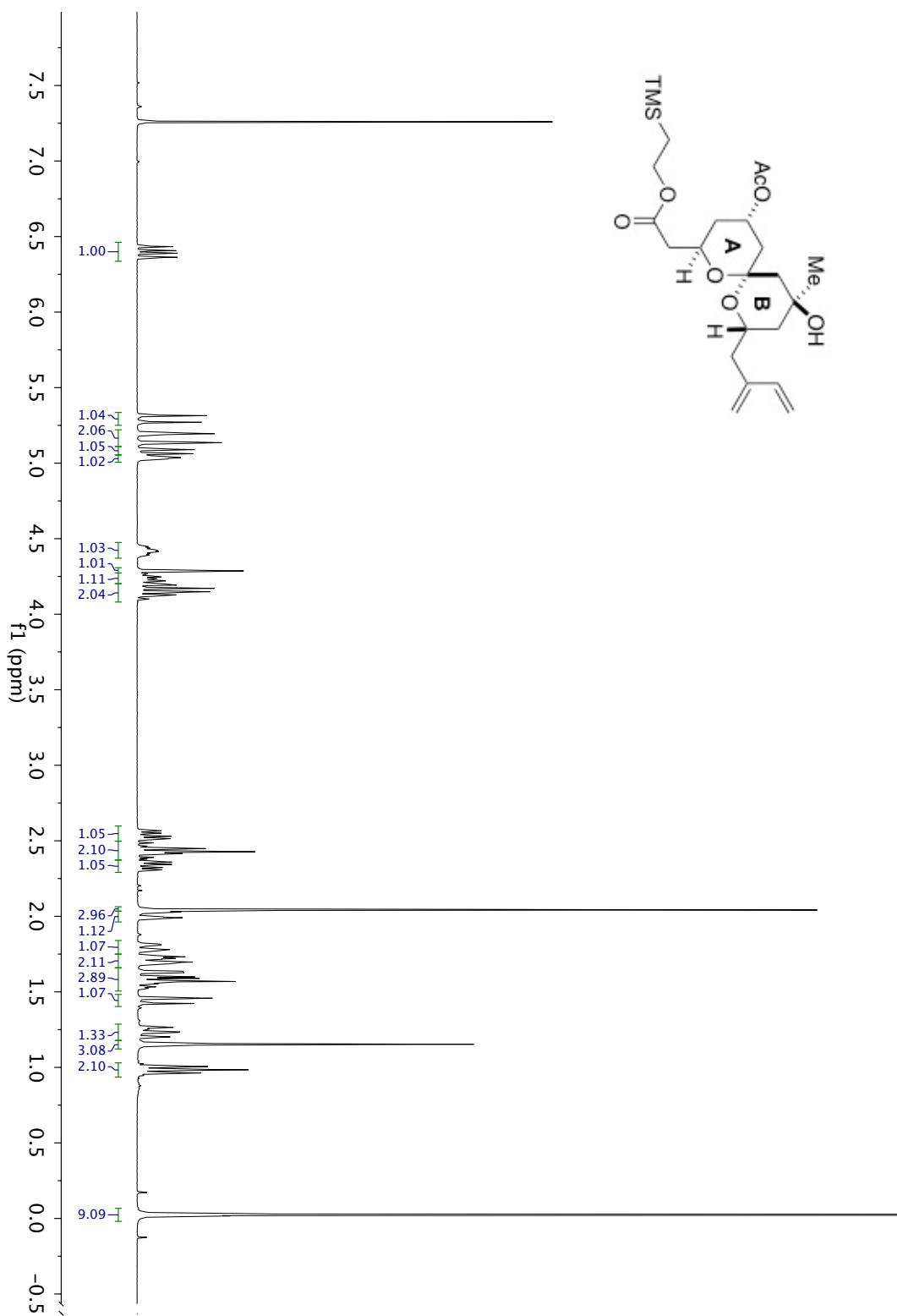


Supplementary Figure 28: <sup>1</sup>H NMR for compound 18

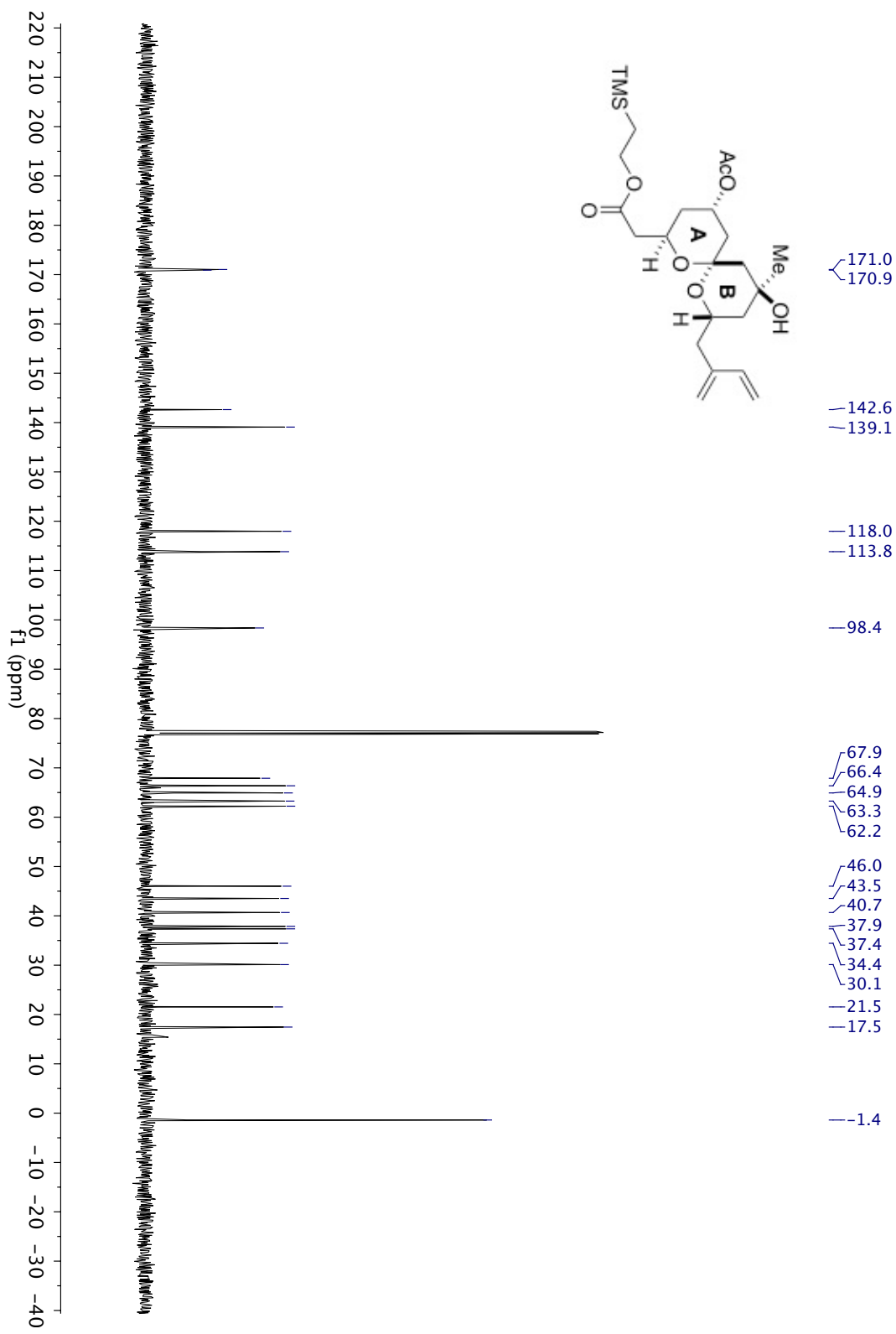


Supplementary Figure 29:  $^{13}\text{C}$  NMR for compound 18

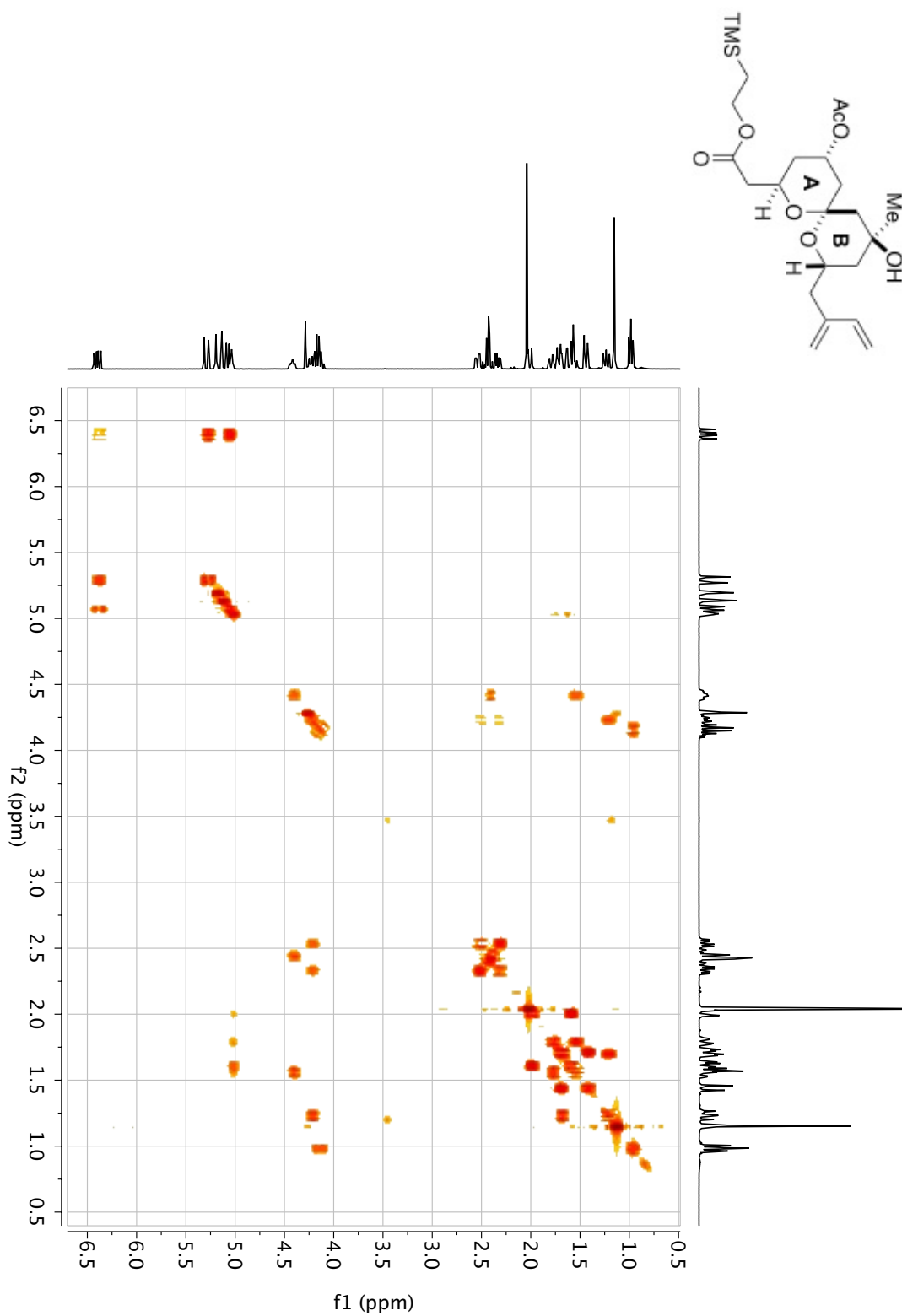




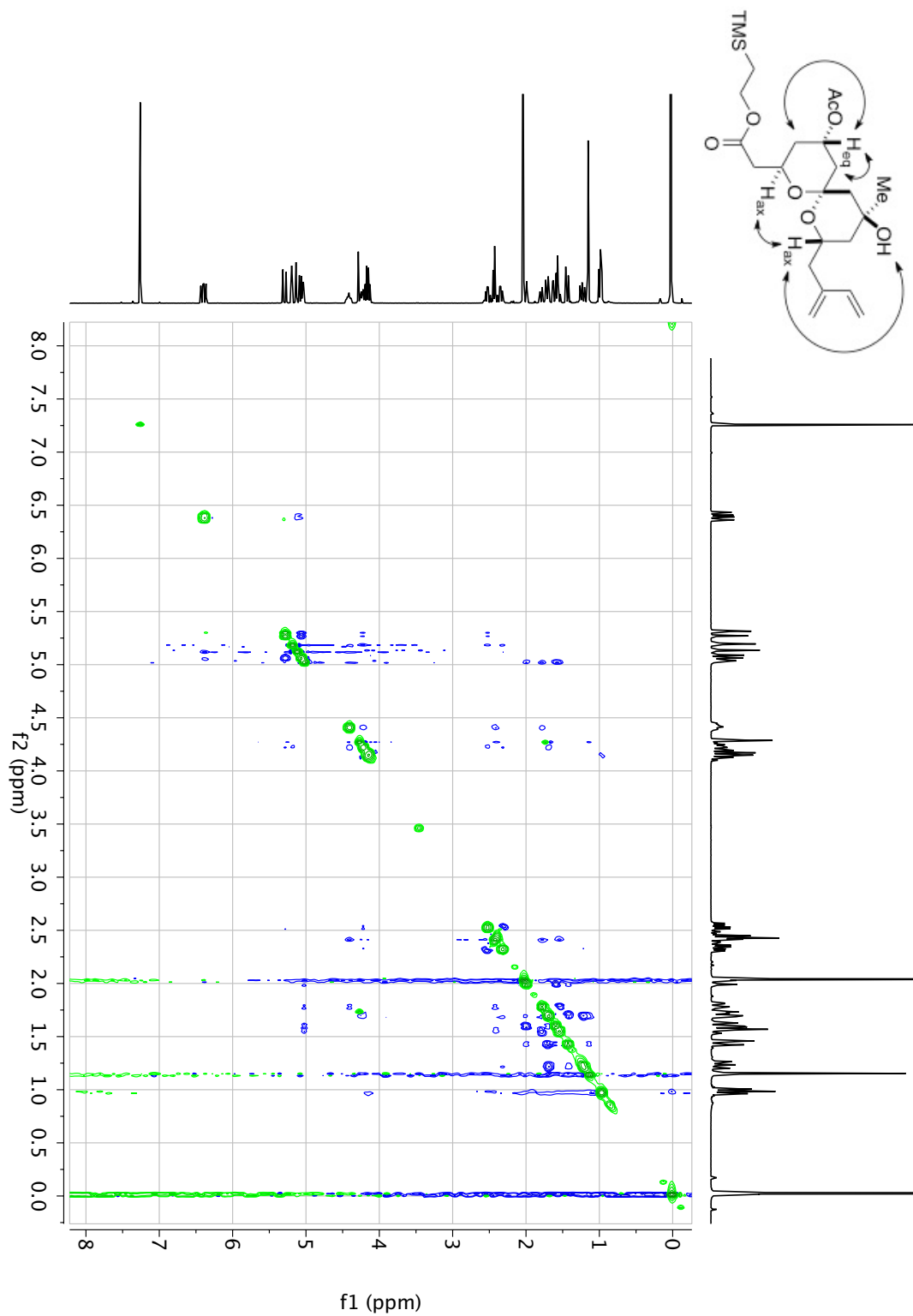
Supplementary Figure 30: <sup>1</sup>H NMR for compound 20



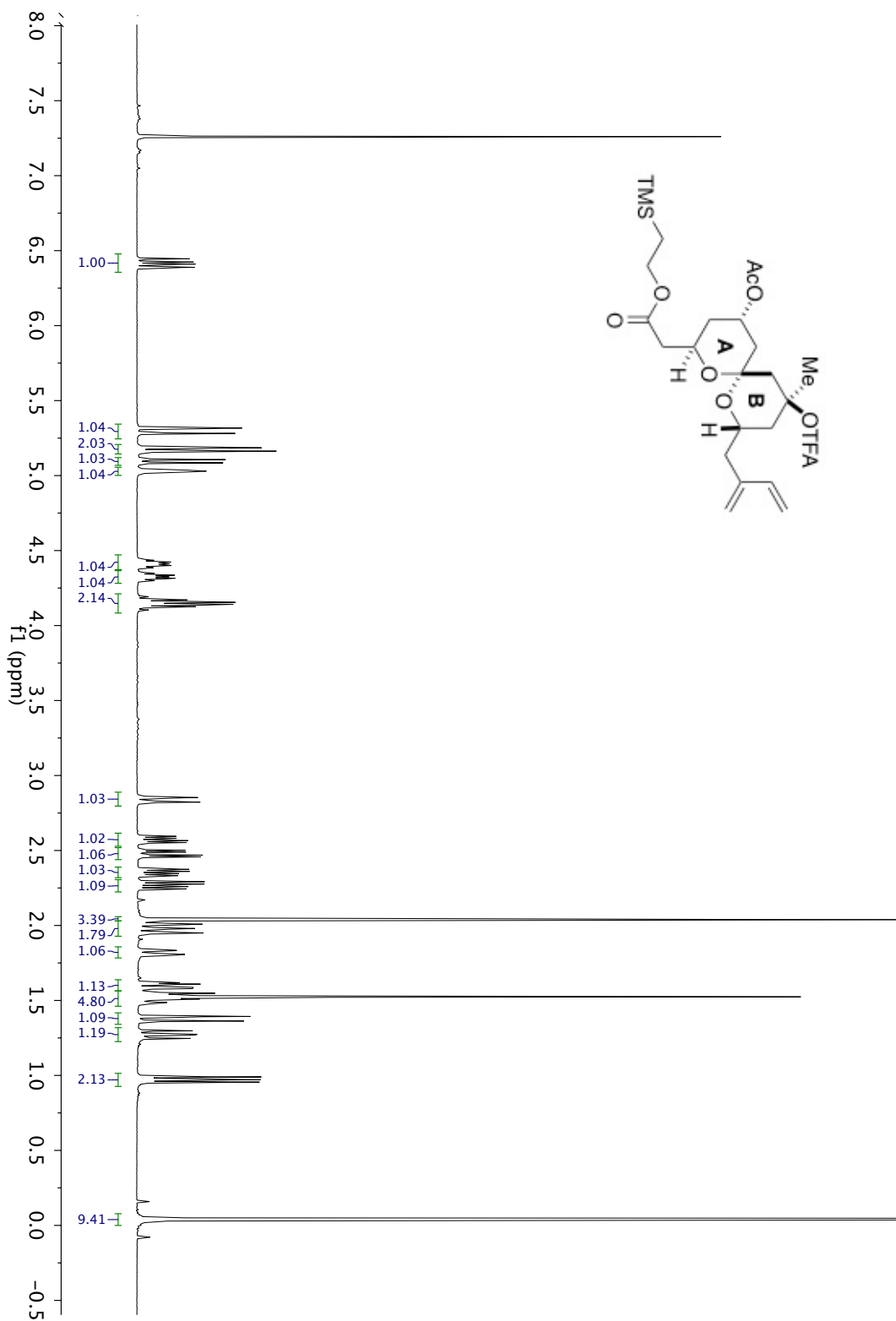
Supplementary Figure 31:  $^{13}\text{C}$  NMR for compound 20



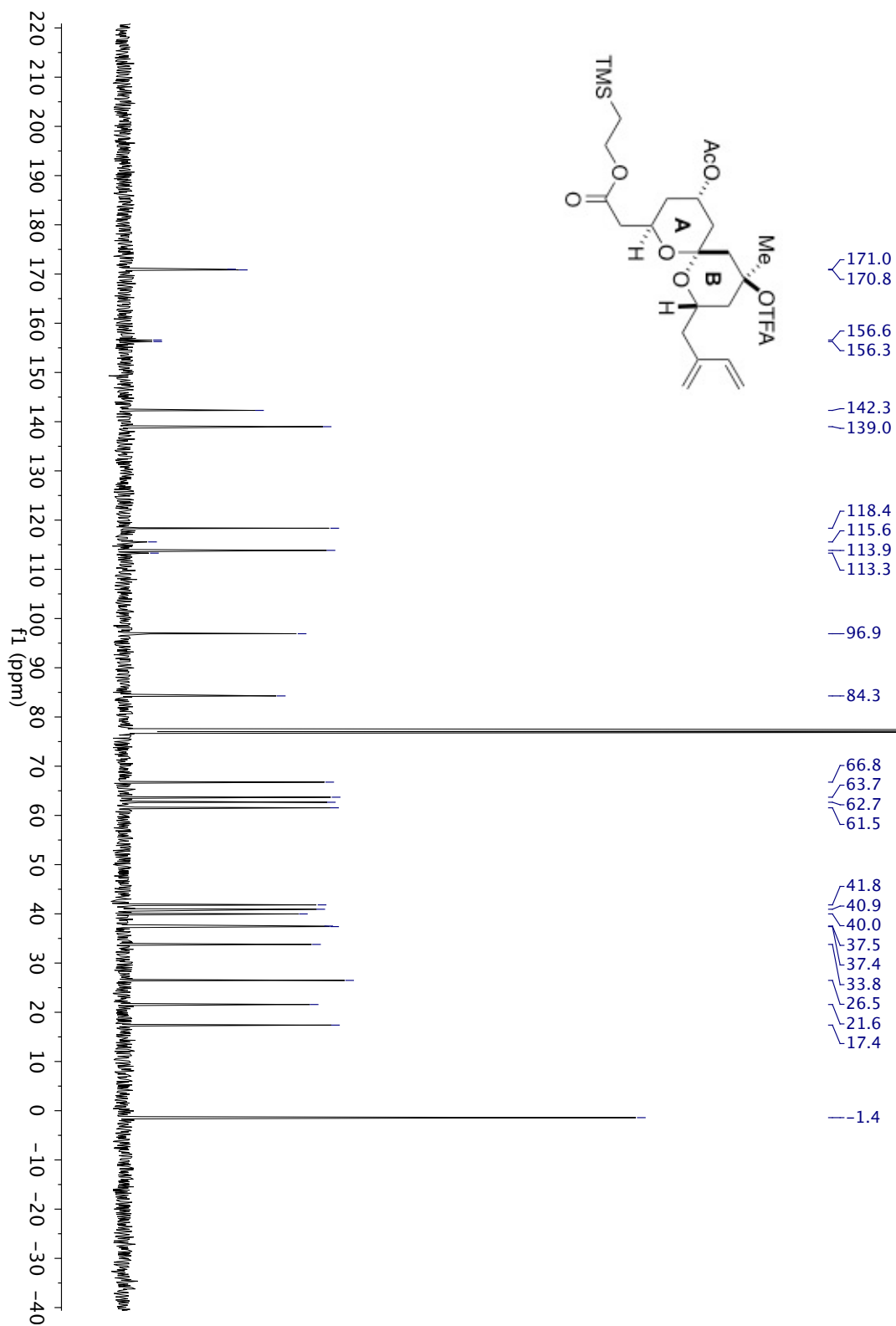
**Supplementary Figure 32: COSY spectrum for compound 20**



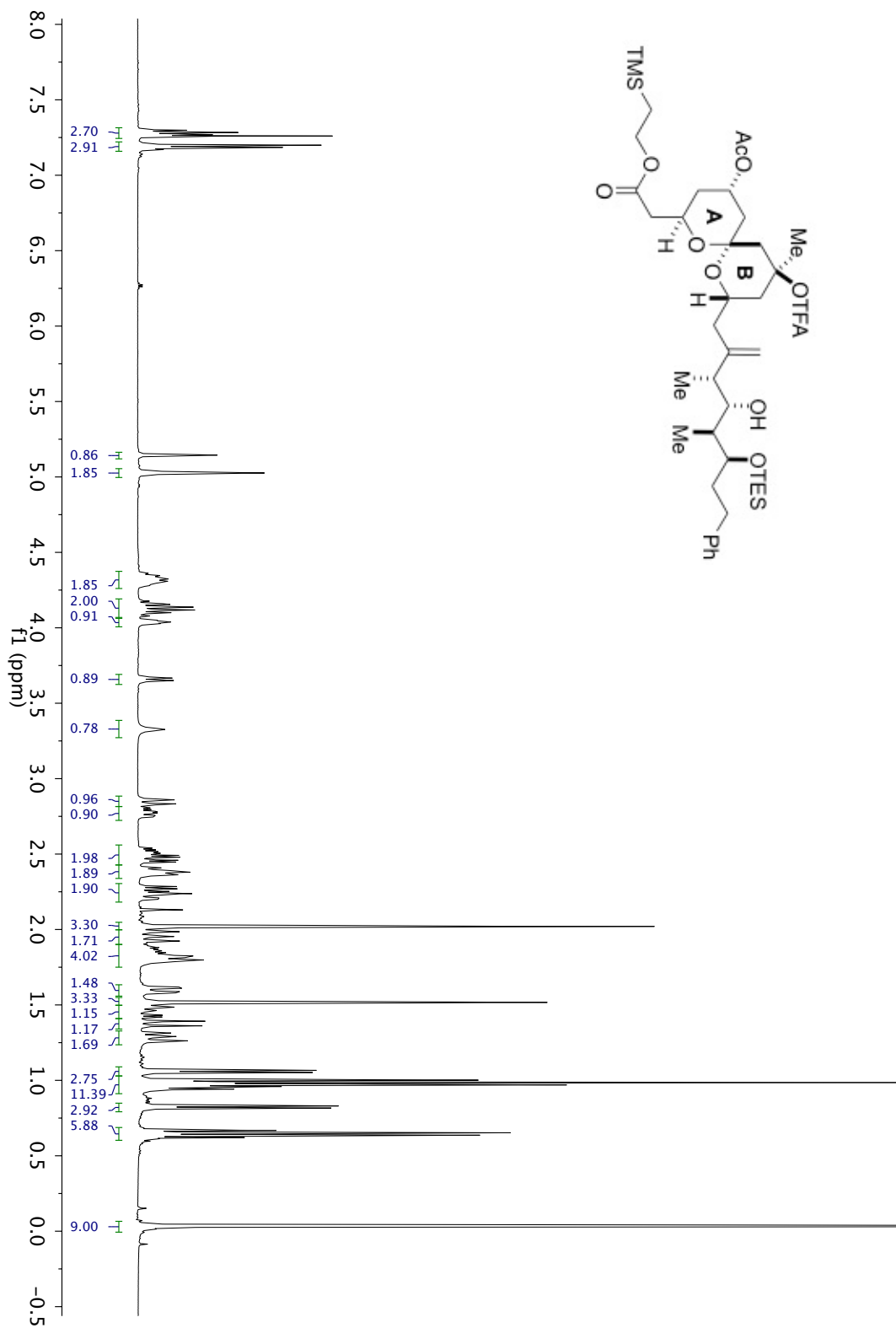
Supplementary Figure 33: NOESY spectrum for compound 20



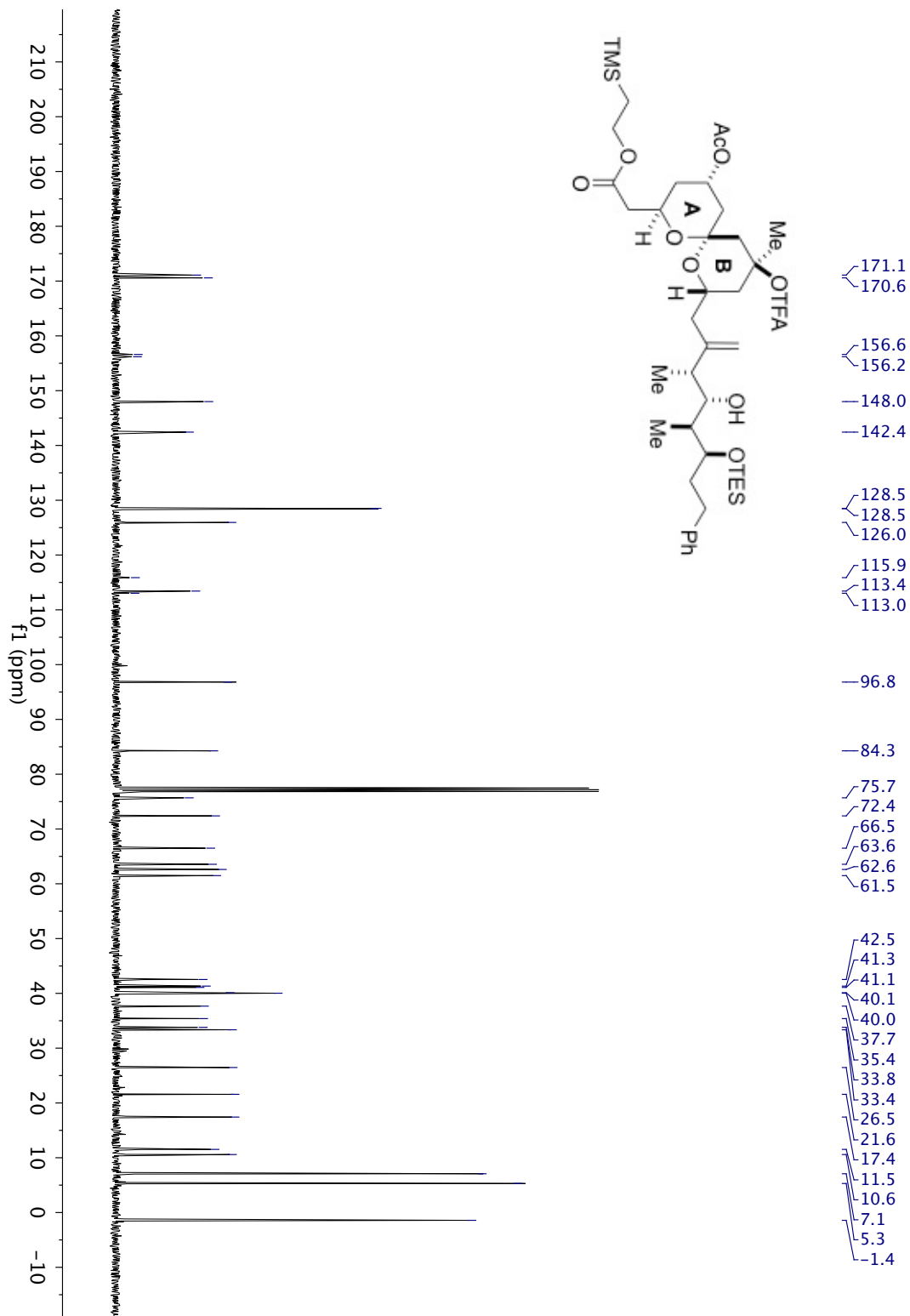
Supplementary Figure 34: <sup>1</sup>H NMR for compound 21



Supplementary Figure 35: <sup>13</sup>C NMR for compound 21

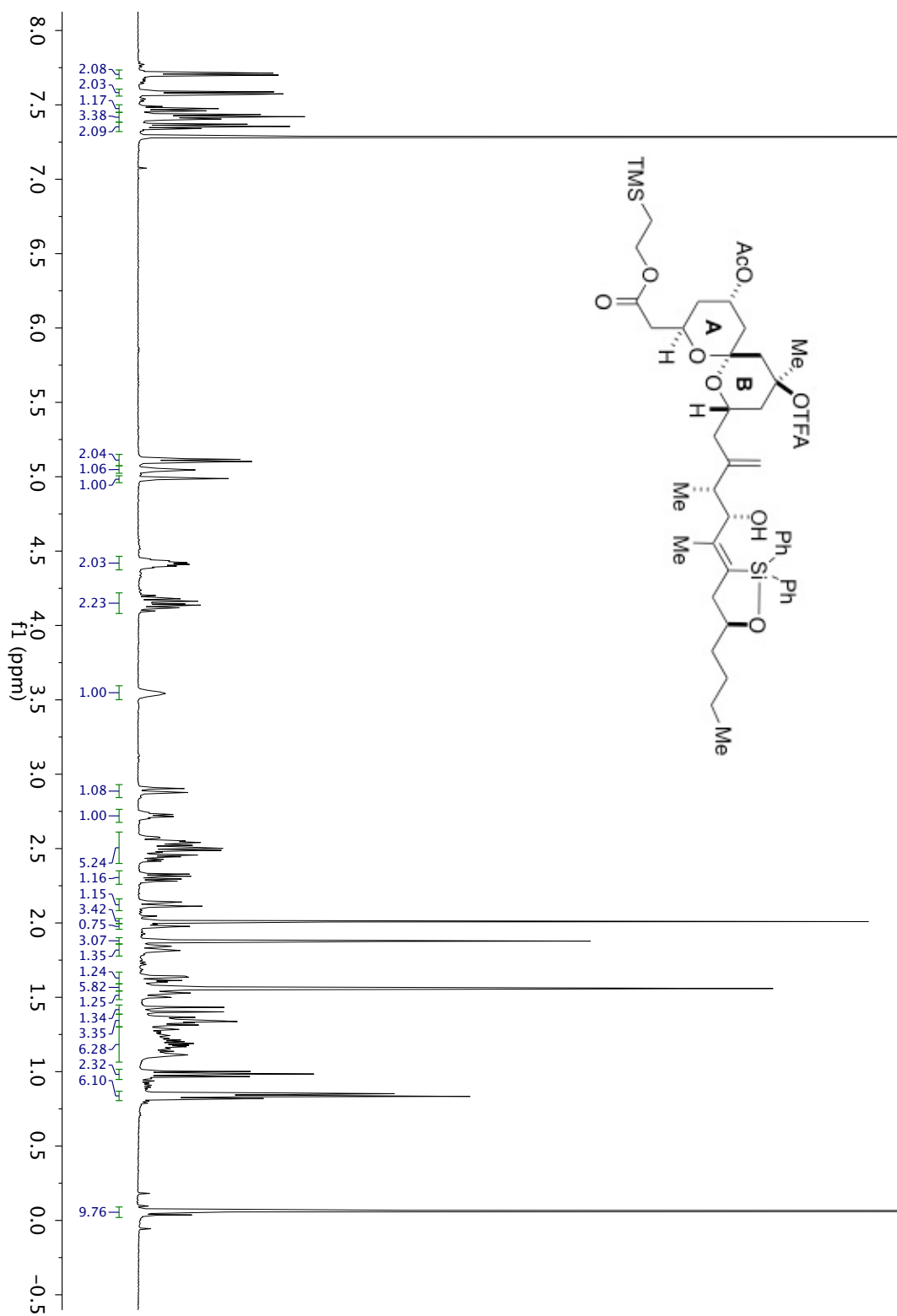


Supplementary Figure 36: <sup>1</sup>H NMR for compound 24

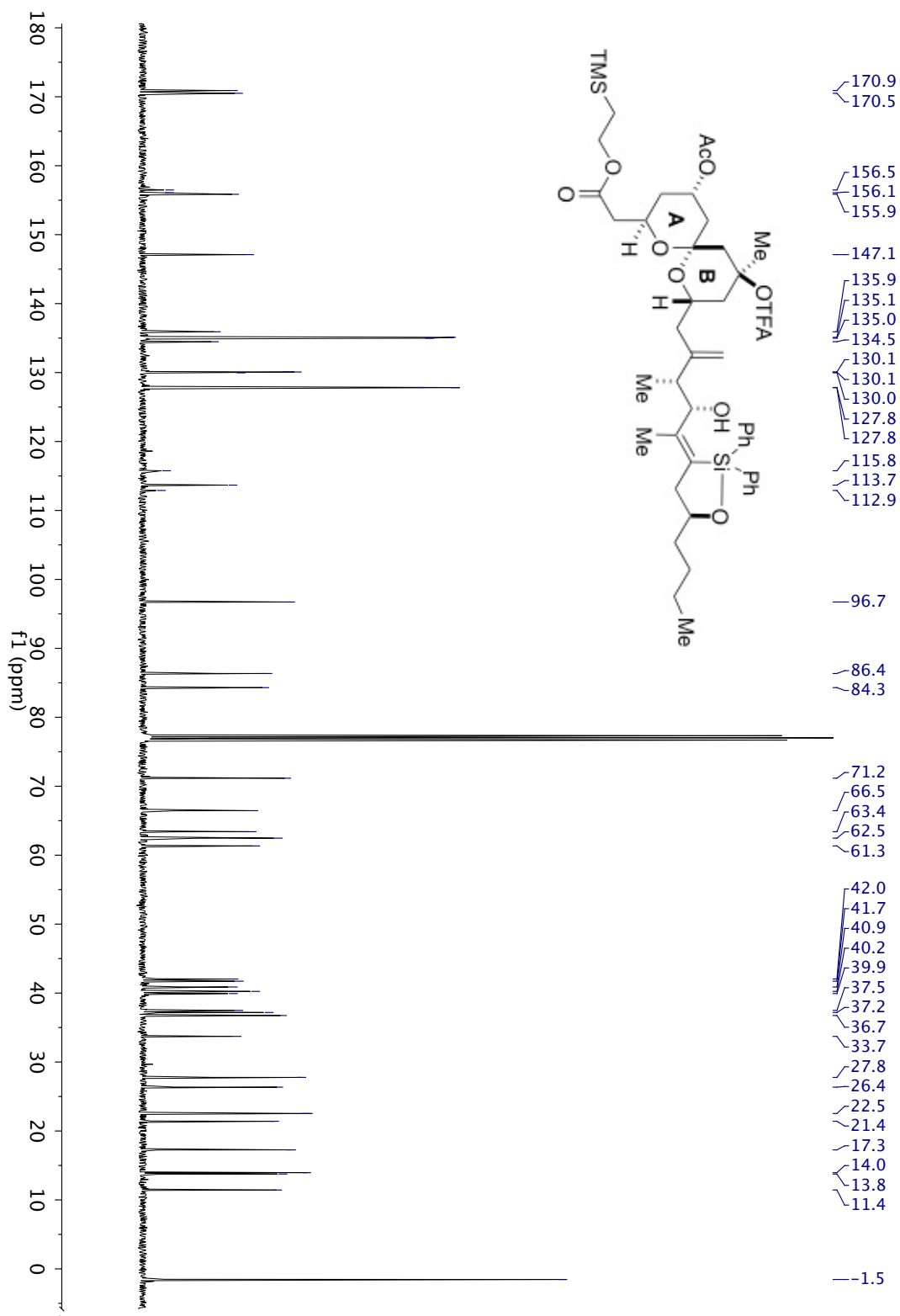


Supplementary Figure 37: <sup>13</sup>C NMR for compound 24

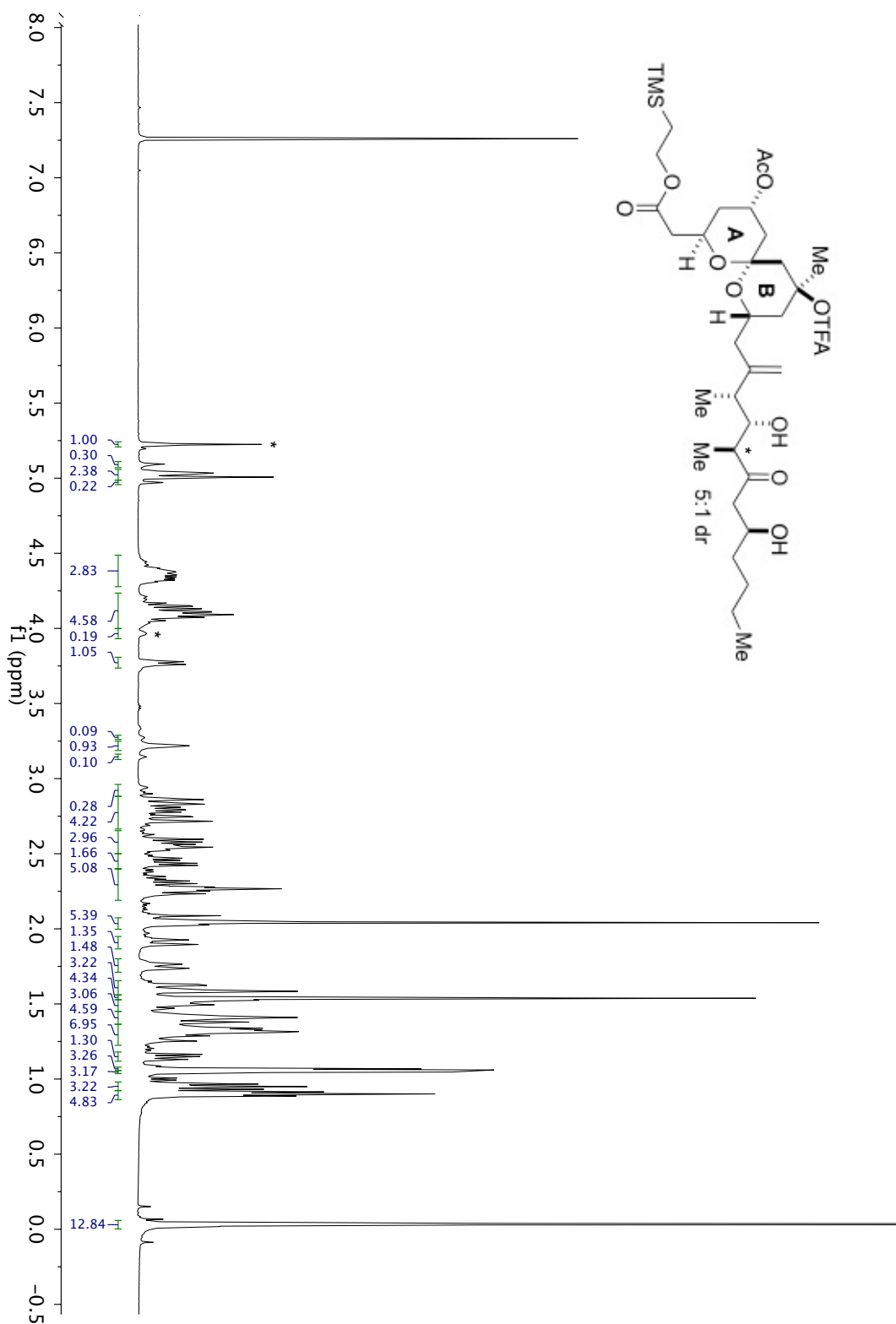




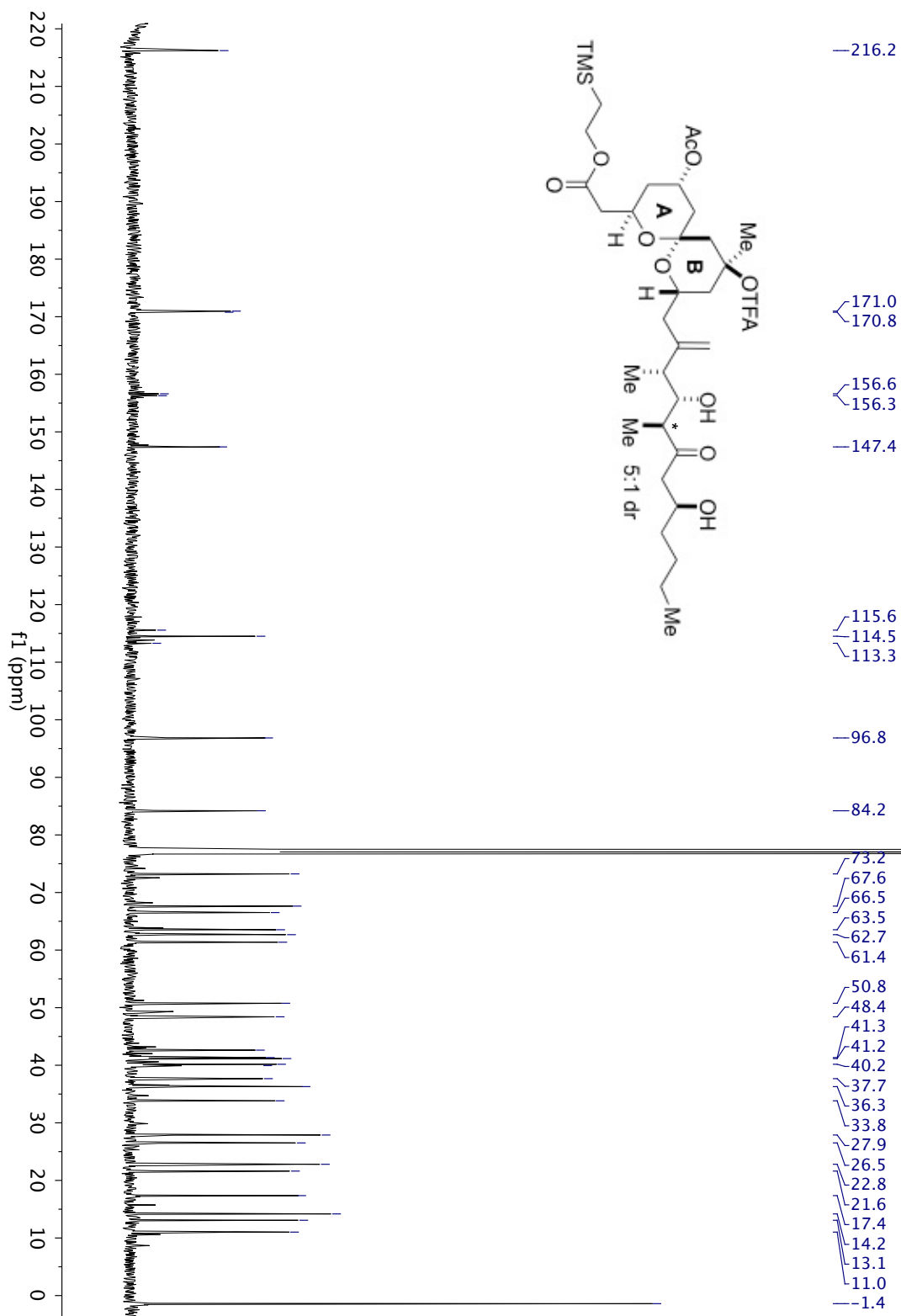
Supplementary Figure 38: <sup>1</sup>H NMR of compound 26



Supplementary Figure 39:  $^{13}\text{C}$  NMR for compound 26



Supplementary Figure 40: <sup>1</sup>H NMR for compound 27



Supplementary Figure 41:  $^{13}\text{C}$  NMR for compound 27

## 5. References

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