

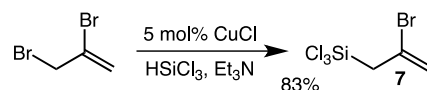
# Complex fragment coupling by crotylation: A powerful tool for polyketide natural product synthesis

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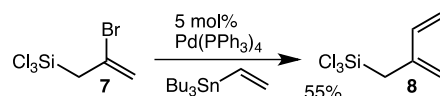
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## Supporting Information

**General Information.** Unless otherwise stated, all chemical compounds were purchased from common commercial sources. All reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring unless otherwise indicated. 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  $\times$  4.5 mm ID) column or Chiralcel OD (250  $\times$  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 = hextet, 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).

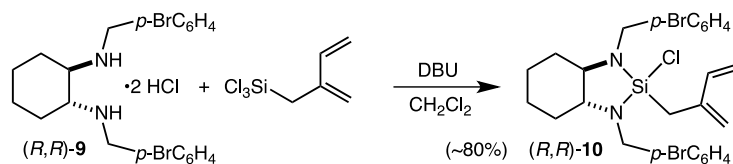


A 2-neck, 500 mL roundbottom flask equipped with a reflux condenser (**Note:** a 24/40 glass adapter joint was attached to the top of the condenser to allow for adequate reaction ventilation and N<sub>2</sub> flow) was charged with anhydrous CuCl (684 mg, 6.91 mmol, 0.05 equiv) and Et<sub>2</sub>O (280 mL), resulting in a green slurry. Triethylamine (23.1 mL, 166 mmol, 1.2 equiv) was added and the mixture took on a green/brown color. The mixture was cooled to 0 °C and 2,3-dibromopropene (13.5 mL, 138 mmol, 1.0 equiv) was added. Trichlorosilane (16.7 mL, 166 mmol, 1.2 equiv) was then *slowly* added to the cooled solution in 4 mL portions every 10 min (**Caution!!** Considerable heat is generated upon addition of the HSiCl<sub>3</sub>, and if it is added too rapidly, we believe there is a significant chance of a vigorous exotherm; it is essential to add the HSiCl<sub>3</sub> slowly and cautiously) (**Note:** the Et<sub>3</sub>N•HCl salts were observed to form immediately upon addition of the HSiCl<sub>3</sub>). After completion of the addition of the HSiCl<sub>3</sub>, the mixture was stirred for an additional 10 min, and then was allowed to warm to room temperature. After 2.5 h, full conversion to product was confirmed by <sup>1</sup>H NMR analysis of a reaction aliquot. The thick reaction mixture was transferred by cannulation to a new 2-neck 1 L round-bottom flask using teflon tubing (3/16 i.d.) equipped with a glass microfiber filter (Grade GF/D). The remaining Et<sub>3</sub>N•HCl salts were washed with Et<sub>2</sub>O (2 x 100 mL) and the Et<sub>2</sub>O washes were transferred by cannulation using teflon tubing (3/16 i.d.) equipped with a glass microfiber filter (Grade GF/D) into the 1 L flask. The volatiles (mostly Et<sub>2</sub>O, and residual HSiCl<sub>3</sub>) were 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 to 100 mm Hg with a manometer partitioned through the pump manifold. Distillation of the residue (b.p. 95 °C at 65 mm Hg) afforded (2-bromoallyl)trichlorosilane **7** (29.2 g, 115 mmol, 83% yield) as a smoky, colorless oil (**Note:** the product is moisture sensitive and fumes if exposed to air). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.74 (dt, *J* = 2.3, 1.1 Hz, 1H), 5.63 (d, *J* = 2.2 Hz, 1H), 2.92 (d, *J* = 1.2 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 121.7, 120.6, 38.8.



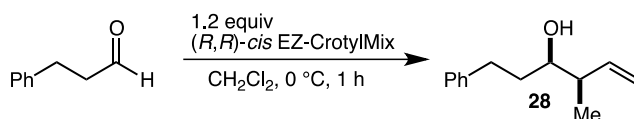
A 500 mL roundbottom flask was charged with Pd(PPh<sub>3</sub>)<sub>4</sub> (9.02 g, 7.8 mmol, 0.05 equiv). The flask was evacuated and back-filled with N<sub>2</sub> before being charged with benzene (165 mL)

resulting in a yellow solution. (2-Bromoallyl)trichlorosilane **7** (39.7 g, 156 mmol, 1.0 equiv) was added to the solution followed by tributyl(vinyl)tin (50.3 mL, 172 mmol, 1.1 equiv). The flask was equipped with a reflux condenser, and the resulting mixture was heated to reflux. After 2 h (during which time the solution was observed to change to a dark red color), nearly full conversion to the desired product was observed by  $^1\text{H}$  NMR analysis of a reaction aliquot. The reflux condenser was replaced with an 8 inch vigreux column and distillation head, and the majority of the benzene was removed by distillation. Distillation of the residue (b.p. 99 °C at 100 mm Hg) afforded trichloro(2-methylenebut-3-en-1-yl)silane **8** (17.3 g, 86 mmol, 55% yield) as a colorless oil (**Note**: the product is moisture sensitive and fumes if exposed to air).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.46 (ddd,  $J = 17.6, 10.8, 0.8$  Hz, 1H), 5.34-5.17 (m, 4H), 2.60 (d,  $J = 1.1$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  137.9, 137.2, 119.5, 115.3, 28.0.



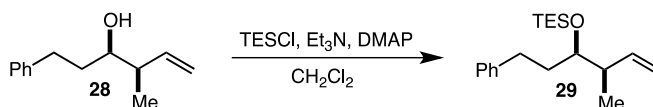
A 3 L, 2-neck roundbottom flask was charged with (*R,R*)-**9** (96.6 g, 184 mmol, 1.0 equiv) and  $\text{CH}_2\text{Cl}_2$  (615 mL, 0.3 M). The resulting slurry was cooled to 0 °C and trichloro(2-methylenebut-3-en-1-yl)silane **8** (37 g, 184 mmol, 1.0 equiv) was added, and DBU (110 mL, 736 mmol, 4.0 equiv) was then added over ~10 min (**Note**: as the DBU was added, the solution became homogeneous and took on an amber hue). After 5 min, the solution was allowed to warm to room temperature, and after 1 h,  $^1\text{H}$  NMR analysis of a reaction aliquot showed full conversion to the desired product. (**Note**: it is important that during the following work-up and purification procedures that exposure to atmospheric moisture is minimized.) The  $\text{CH}_2\text{Cl}_2$  was removed by placing the flask in a room temperature water bath, setting up an adjacent -78 °C cold-finger and carefully reducing the pressure with a manometer partitioned through the pump manifold. Pentane (600 mL) was then added to the residue, and the resulting mixture was shaken vigorously for ~10 min until the  $\text{DBU}\cdot\text{HCl}$  salts powdered out into a fine white precipitate. The mixture 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 (300 mL) was added to the residual  $\text{DBU}\cdot\text{HCl}$  salts and the flask was shaken vigorously. The supernatant was transferred by cannulation using teflon tubing (3/16 i.d.) equipped with a glass microfiber filter (Grade GF/D)

into the 1 L, 2-neck roundbottom flask. This process was repeated with a final pentane wash (150 mL). The pentane was removed by placing the flask in a room temperature water bath, setting up an adjacent -78 °C cold-finger and carefully reducing the pressure with a manometer partitioned through the pump manifold. The residue was treated with 150 mL of CH<sub>2</sub>Cl<sub>2</sub>, and <sup>1</sup>H NMR analysis (integration vs. CH<sub>2</sub>Cl<sub>2</sub> peak) of this solution allowed us to determine that the solution contained ~85 g of isoprenylsilane (*R,R*)-**10** (~147 mmol, ~80% yield) and had a concentration of ~0.60 M. A small aliquot of this stock solution was concentrated for characterization by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.43 (dd, *J* = 8.4, 2.5 Hz, 4H), 7.30 (t, *J* = 8.8 Hz, 4H), 6.38 (dd, *J* = 17.4, 10.4 Hz, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 3H), 4.16 (d, *J* = 16.3 Hz, 1H), 4.03 (d, *J* = 15.2 Hz, 1H), 3.89 (d, *J* = 15.2 Hz, 1H), 3.80 (d, *J* = 16.3 Hz, 1H), 2.81 (ddd, *J* = 11.9, 9.2, 2.9 Hz, 1H), 2.73 (ddd, *J* = 11.9, 9.3, 3.0 Hz, 1H), 1.97 (d, *J* = 15.4 Hz, 1H), 1.88 (d, *J* = 15.5 Hz, 1H), 1.84-1.54 (m, 4H), 1.13 (tt, *J* = 12.7, 10.2 Hz, 2H), 1.01 (qd, *J* = 13.6, 12.7, 4.1 Hz, 1H), 0.91 (tt, *J* = 12.0, 6.4 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 141.5, 140.3, 139.9, 139.5, 131.2, 129.9, 129.0, 120.5, 120.2, 117.2, 114.3, 66.5, 65.2, 48.2, 47.5, 31.0, 30.4, 24.7, 21.3.

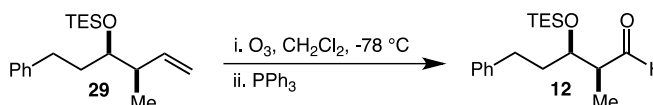


To a cooled (0 °C) solution of hydrocinnamaldehyde (2.63 mL, 20.0 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added (*R,R*)-*cis*-EZ CrotylMix (14.1 g, 24.0 mmol, 1.2 equiv). After 1 h tetrabutylammonium fluoride (TBAF) (60 mL, 60 mmol, 1 M in THF) was added. The resulting mixture was allowed to warm to room temperature and was then concentrated. The residue was purified by silica gel chromatography (gradient 5-15% EtOAc/Hexanes) to afford alkene **28** (3.47 g, 18.2 mmol, 91% yield) as a colorless oil. The diastereoselectivity of the reaction was determined to be >20:1 by <sup>1</sup>H NMR analysis. The enantiomeric excess of **28** was determined to be 97% ee by chiral HPLC analysis (see HPLC trace below). [ $\alpha$ ]<sub>D</sub> = +30° (*c* 5.0, CH<sub>2</sub>Cl<sub>2</sub>); *R*<sub>f</sub> = 0.6 (25% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42-7.30 (m, 2H), 7.30-7.20 (m, 3H), 5.93-5.73 (m, 1H), 5.21-5.08 (m, 2H), 3.58 (ddd, *J* = 8.9, 5.2, 3.2 Hz, 1H), 2.93 (ddd, *J* = 13.7, 10.1, 5.3 Hz, 1H), 2.71 (ddd, *J* = 13.7, 9.8, 6.7 Hz, 1H), 2.44-2.29 (m, 1H), 1.89 (dddd, *J* = 13.5, 10.0, 6.7, 3.2 Hz, 1H), 1.82-1.63 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 142.3, 140.8, 128.5, 128.4, 125.8, 115.5, 74.1, 43.8, 35.9, 32.5, 14.4; IR (cast film)

3384, 2936, 2866, 1496, 1454, 1417, 1373, 1037, 997, 914  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{13}\text{H}_{18}\text{O}$   $[\text{M}]^+$  190.28, found 190.11.



To a solution of **28** (1.90 g, 10.0 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added  $\text{Et}_3\text{N}$  (2.1 mL, 15.0 mmol, 1.5 equiv) followed by TESCl (2.0 mL, 12.0 mmol, 1.2 equiv) and DMAP (367 mg, 0.300 mmol, 0.3 equiv). After 1.5 h, MeOH (0.6 mL) was added and the mixture was concentrated. The residue was treated with hexanes and filtered to remove residual  $\text{Et}_3\text{N}\cdot\text{HCl}$ . The filtrate was concentrated and the residue purified by silica gel chromatography (gradient 0-3% EtOAc/Hexanes) to afford **29** (2.98 g, 9.78 mmol, 98% yield) as a colorless oil.  $[\alpha]_{\text{D}} = +14^\circ$  ( $c$  4.0,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.8$  (5% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (t,  $J = 7.5$  Hz, 2H), 7.25 (d,  $J = 7.4$  Hz, 3H), 5.94 (ddd,  $J = 17.5, 10.5, 7.3$  Hz, 1H), 5.22-5.02 (m, 2H), 3.71 (q,  $J = 5.5$  Hz, 1H), 2.93-2.74 (m, 1H), 2.65 (ddd,  $J = 13.5, 9.8, 6.7$  Hz, 1H), 2.45 (h,  $J = 6.8$  Hz, 1H), 1.81 (dtd,  $J = 9.8, 6.2, 3.5$  Hz, 2H), 1.22-0.97 (m, 12H), 0.72 (q,  $J = 7.9$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  142.8, 141.1, 128.4, 125.7, 114.2, 75.9, 43.3, 36.1, 31.8, 15.5, 7.1, 5.3; IR (cast film) 2955, 2912, 2877, 1456, 1415, 1239, 1074, 1006, 912  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{19}\text{H}_{31}\text{OSi}$   $[\text{M}-\text{H}]^+$  303.53, found 303.31.

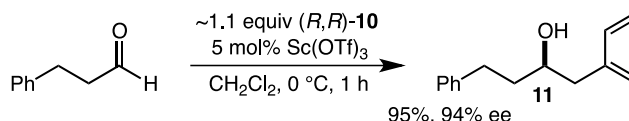


Into a cooled ( $-78^\circ\text{C}$ ) solution of **29** (1.00 g, 3.28 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (33 mL) was bubbled oxygen gas.  $\text{O}_3$  was then bubbled through the solution until it took on a dark blue color ( $\sim 15$  min). The solution was then purged with oxygen until the blue color fully dissipated ( $\sim 10$  min).  $\text{PPh}_3$  (1.12 g, 4.36 mmol, 1.3 equiv) was added and the mixture was allowed to warm to room temperature. After 15 h, the mixture was concentrated. The residue (a yellow oil caked with solids) was treated with hexanes (33 mL) and the mixture was stirred vigorously for 10 min. The resulting white slurry was filtered and the filtrate was concentrated. The trituration process was repeated to provide a pale yellow oil with minimal solids. The residue was purified by silica

gel chromatography (gradient 1-3% EtOAc/Hexanes, pH 7 buffered silica gel<sup>1</sup>) to afford aldehyde **12** (904 mg, 2.95 mmol, 90% yield) as a pale yellow oil.  $[\alpha]_D = +39^\circ$  (*c* 1.5, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f = 0.4$  (5% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.82 (d, *J* = 1.1 Hz, 1H), 7.37-7.26 (m, 2H), 7.26-7.16 (m, 3H), 4.20 (td, *J* = 6.3, 3.8 Hz, 1H), 2.73 (ddd, *J* = 13.7, 10.7, 6.0 Hz, 1H), 2.66-2.58 (m, 1H), 2.58-2.50 (m, 1H), 1.86 (dddd, *J* = 26.1, 13.8, 11.0, 6.4 Hz, 2H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 8.2 Hz, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  205.0, 141.6, 128.5, 128.2, 126.0, 71.9, 51.4, 36.5, 32.2, 8.0, 6.9, 5.2; IR (cast film) 2954, 2913, 2878, 1707, 1645, 1457, 1238, 1103, 1009 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>Si [M]<sup>+</sup> 306.52, found 306.29.

### General Procedure for the Asymmetric Isoprenylation Reactions.

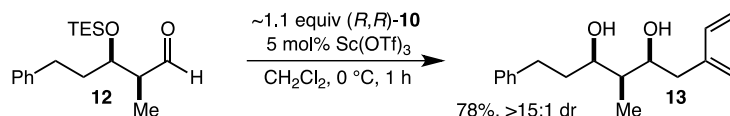
To a cooled (0 °C) solution of aldehyde (1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) is added (*R,R*)-**10** (1.1 equiv of the ~0.60 M stock solution in CH<sub>2</sub>Cl<sub>2</sub> described above) followed by Sc(OTf)<sub>3</sub> (0.050 equiv). The resulting mixture is stirred vigorously until complete consumption of aldehyde is observed by <sup>1</sup>H NMR analysis of a reaction aliquot (1-2 h). Tetrabutylammonium fluoride (4.0 equiv of a 1 M solution in THF) is added, and the mixture is allowed to warm to room temperature. After concentration, the residue is purified by silica gel chromatography to afford the desired products. (**Note:** if the diene products are to be stored for any significant length of time, they should be stored frozen in benzene.)



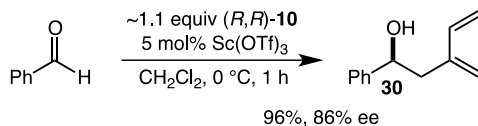
The isoprenylation of hydrocinnamaldehyde (3.8 mL, 28.8 mmol, 1.0 equiv) was carried out according to the general procedure. Purification by silica gel chromatography (gradient 10-25% EtOAc/Hexanes) afforded **11** (5.56 g, 27.5 mmol, 95% yield) as a pale yellow oil. The enantiomeric excess of **11** was determined to be 94% ee by chiral HPLC analysis (see HPLC trace below).  $[\alpha]_D = +21^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f = 0.3$  (15% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37-7.28 (m, 2H), 7.28-7.18 (m, 3H), 6.42 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.25 (d,

(1) pH 7 buffered silica gel was prepared by adding 10% pH 7 buffer (by mass) to a roundbottom flask half filled with SiO<sub>2</sub> gel. The resulting mixture was rotated on a rotary evaporator for >12 h (at atmospheric pressure) and then stored for future use.

$J = 17.6$  Hz, 1H), 5.22-5.09 (m, 3H), 3.82 (dq,  $J = 8.9, 4.7$  Hz, 1H), 2.88 (dt,  $J = 13.9, 8.3$  Hz, 1H), 2.79-2.70 (m, 1H), 2.56 (dd,  $J = 13.9, 3.7$  Hz, 1H), 2.32 (dd,  $J = 13.9, 9.0$  Hz, 1H), 1.94-1.80 (m, 2H), 1.72 (bs, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  143.0, 142.1, 138.4, 128.4, 128.4, 125.8, 118.5, 114.3, 69.1, 40.1, 38.8, 32.1; IR (cast film) 3382, 3027, 2931, 1594, 1496, 1454, 1392, 1083, 993, 900  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{14}\text{H}_{18}\text{O}$   $[\text{M}]^+$  202.29, found 202.28.



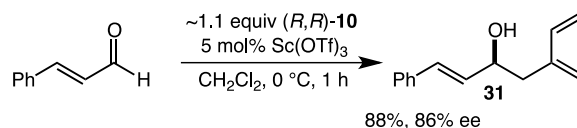
The isoprenylation of aldehyde **12** (904 mg, 2.95 mmol, 1.0 equiv) was carried out according to the general procedure. Purification by silica gel chromatography (25% EtOAc/Hexanes) afforded diol **13** (599 mg, 2.30 mmol, 78% yield) as a pale yellow oil. The diastereoselectivity of the reaction was determined to be >15:1 by  $^1\text{H}$  NMR analysis of the product before chromatography.  $[\alpha]_{\text{D}} = +18^\circ$  ( $c$  3.5,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (25% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.28 (m, 2H), 7.28-7.16 (m, 3H), 6.42 (dd,  $J = 17.6, 10.8$  Hz, 1H), 5.29 (d,  $J = 17.6$  Hz, 1H), 5.22-5.08 (m, 3H), 4.03 (td,  $J = 6.7, 6.1, 1.9$  Hz, 1H), 3.91 (ddd,  $J = 8.7, 4.4, 1.8$  Hz, 1H), 2.98 (bs, 1H), 2.82 (ddd,  $J = 13.8, 10.0, 5.7$  Hz, 1H), 2.68 (ddd,  $J = 13.8, 9.6, 6.4$  Hz, 1H), 2.50-2.36 (m, 3H), 2.03-1.83 (m, 1H), 1.81-1.67 (m, 1H), 1.62 (qt,  $J = 6.9, 2.0$  Hz, 1H), 1.02 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 142.1, 138.3, 128.5, 128.4, 125.8, 118.4, 114.4, 76.1, 74.7, 40.8, 37.7, 37.0, 32.5, 4.7; IR (cast film) 3357, 2943, 1594, 1496, 1454, 1389, 1094, 1030, 973, 901  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{17}\text{H}_{25}\text{O}_2$   $[\text{M}+\text{H}]^+$  261.38, found 261.25.



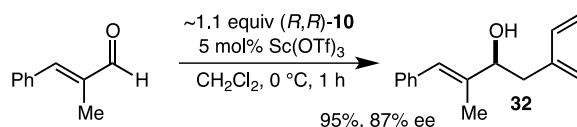
The isoprenylation of benzaldehyde (51  $\mu\text{L}$ , 0.50 mmol, 1.0 equiv) was carried out according to the general procedure. Purification by silica gel chromatography (10% EtOAc/Hexanes) afforded **30** (84 mg, 0.48 mmol, 96% yield) as a pale yellow oil. The enantiomeric excess of **30** was determined to be 86% ee by chiral HPLC analysis (see HPLC trace below).  $[\alpha]_{\text{D}} = -41^\circ$  ( $c$  1.8,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (10% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.17 (m, 5H), 6.33 (dd,  $J = 17.6, 10.8$  Hz, 1H), 5.24 (d,  $J = 17.6$  Hz, 1H), 5.11-4.98 (m, 3H), 4.75 (ddd,  $J = 9.3, 4.0, 2.0$  Hz, 1H), 2.62 (ddd,  $J = 14.1, 4.0, 1.1$  Hz, 1H),



2.47 (ddd,  $J = 14.2, 9.2, 0.8$  Hz, 1H), 1.94 (d,  $J = 2.4$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  144.1, 142.7, 138.3, 128.4, 127.6, 125.8, 118.9, 114.3, 72.2, 42.2; IR (cast film) 3382, 3086, 3032, 2930, 1594, 1454, 1393, 1137, 1083, 1054, 993,  $901\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{12}\text{H}_{14}\text{O}$   $[\text{M}]^+$  174.24, found 174.22.



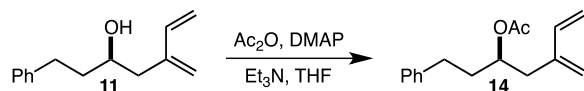
The isoprenylation of *trans*-cinnamaldehyde (63  $\mu\text{L}$ , 0.50 mmol, 1.0 equiv) was carried out according to the general procedure. Purification by silica gel chromatography (15% EtOAc/Hexanes) afforded **31** (88 mg, 0.44 mmol, 88% yield) as a pale yellow oil. The enantiomeric excess of **31** was determined to be 86% ee by chiral HPLC analysis (see HPLC trace below).  $[\alpha]_{\text{D}} = +7^\circ$  ( $c$  0.6,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (15% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46-7.38 (m, 2H), 7.38-7.31 (m, 2H), 7.31-7.23 (m, 1H), 6.65 (dd,  $J = 15.9, 1.1$  Hz, 1H), 6.45 (dd,  $J = 17.6, 11.0$  Hz, 1H), 6.28 (dd,  $J = 15.9, 6.4$  Hz, 1H), 5.35 (d,  $J = 17.6$  Hz, 1H), 5.26-5.14 (m, 3H), 4.50 (dddd,  $J = 7.9, 6.1, 4.5, 3.1, 1.2$  Hz, 1H), 2.65 (ddd,  $J = 14.0, 4.8, 1.0$  Hz, 1H), 2.52 (ddd,  $J = 14.0, 8.4, 0.8$  Hz, 1H), 1.92 (d,  $J = 3.2$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  142.4, 138.5, 136.8, 131.7, 130.2, 128.6, 127.7, 126.5, 119.0, 114.4, 70.8, 40.1; IR (cast film) 3369, 3027, 2929, 1595, 1494, 1449, 1392, 1099, 1026, 992, 966,  $902\text{ cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{14}\text{H}_{16}\text{O}$   $[\text{M}]^+$  200.28, found 200.08.



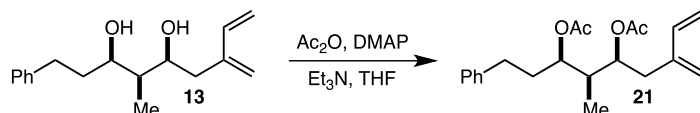
The isoprenylation of  $\alpha$ -methyl-*trans*-cinnamaldehyde (70  $\mu\text{L}$ , 0.50 mmol, 1.0 equiv) was carried out according to the general procedure. Purification by silica gel chromatography (10% EtOAc/Hexanes) afforded **32** (102 mg, 0.475 mmol, 95% yield) as a pale yellow oil. The enantiomeric excess of **32** was determined to be 87% ee by chiral HPLC analysis (see HPLC trace below).  $[\alpha]_{\text{D}} = +18^\circ$  ( $c$  2.4,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (10% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.19 (m, 5H), 6.58 (s, 1H), 6.46 (dd,  $J = 17.6, 11.0$  Hz, 1H), 5.37 (d,  $J = 17.7$  Hz, 1H), 5.26-5.16 (m, 3H), 4.38 (ddd,  $J = 8.9, 4.3, 1.9$  Hz, 1H), 2.70 (ddd,  $J = 14.0, 4.2, 1.1$  Hz, 1H), 2.49 (dd,  $J = 14.0, 8.9$  Hz, 1H), 1.96 (d,  $J = 1.4$  Hz, 2H), 1.88 (d,  $J = 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 139.6, 138.4, 137.6, 129.0, 128.1, 126.5, 125.8, 118.6,



114.3, 75.5, 38.6, 13.6; IR (cast film) 3384, 3086, 2952, 1595, 1492, 1444, 1390, 1335, 1154, 1074, 1010, 994, 900  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{15}\text{H}_{18}\text{O}$   $[\text{M}]^+$  214.30, found 214.03.



To a solution of alcohol **11** (5.56 g, 27.5 mmol, 1.0 equiv) in THF (275 mL) was added  $\text{Et}_3\text{N}$  (5.8 mL, 41.3 mmol, 1.5 equiv),  $\text{Ac}_2\text{O}$  (3.1 mL, 33.0 mmol, 1.2 equiv) and DMAP (1.0 g, 8.25 mmol, 0.3 equiv). After 1.5 h, the mixture was concentrated and the residue was purified by silica gel chromatography (gradient 3-5%  $\text{EtOAc}$ /Hexanes) to afford acetate **14** (6.50 g, 26.6 mmol, 97% yield) as a pale yellow oil.  $[\alpha]_{\text{D}} = -5^\circ$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.8$  (10%  $\text{EtOAc}$ /Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.27 (m, 2H), 7.24-7.16 (m, 3H), 6.38 (dd,  $J = 17.6, 10.7$  Hz, 1H), 5.38 (d,  $J = 17.7$  Hz, 1H), 5.18-5.09 (m, 3H), 5.05 (t,  $J = 1.5$  Hz, 1H), 2.73 (ddd,  $J = 13.9, 10.1, 6.0$  Hz, 1H), 2.68-2.56 (m, 2H), 2.44 (ddd,  $J = 13.9, 6.6, 1.0$  Hz, 1H), 2.05 (s, 3H), 1.99-1.84 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 142.2, 141.6, 138.3, 128.4, 128.3, 125.9, 118.5, 114.2, 72.4, 36.8, 35.6, 31.8, 21.2; IR (cast film) 3028, 2932, 1736, 1596, 1454, 1373, 1239, 1029, 994, 902  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{16}\text{H}_{21}\text{O}_2$   $[\text{M}+\text{H}]^+$  245.34, found 245.23.



To a solution of alcohol **13** (667 mg, 2.56 mmol, 1.0 equiv) in THF (26 mL) was added  $\text{Et}_3\text{N}$  (1.1 mL, 7.68 mmol, 3.0 equiv) followed by  $\text{Ac}_2\text{O}$  (0.61 mL, 6.40 mmol, 2.5 equiv) and DMAP (156 mg, 1.28 mmol, 0.5 equiv). After 2 h, the mixture was concentrated and the residue was purified by silica gel chromatography (15%  $\text{EtOAc}$ /Hexanes) to afford diacetate **21** (630 mg, 1.82 mmol, 72% yield) as a pale yellow oil.  $[\alpha]_{\text{D}} = -3^\circ$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.8$  (30%  $\text{EtOAc}$ /Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.24 (m, 2H), 7.24-7.13 (m, 3H), 6.36 (dd,  $J = 17.6, 10.9$  Hz, 1H), 5.43 (d,  $J = 17.6$  Hz, 1H), 5.20 (td,  $J = 7.1, 3.5$  Hz, 1H), 5.16 (d,  $J = 10.9$  Hz, 1H), 5.13-5.07 (m, 1H), 5.04 (s, 1H), 4.96 (dt,  $J = 7.9, 5.3$  Hz, 1H), 2.69-2.55 (m, 2H), 2.50 (qdd,  $J = 13.8, 7.1, 1.0$  Hz, 2H), 2.06 (s, 3H), 2.01 (s, 3H), 2.01-1.94 (m, 1H), 1.94-1.81 (m, 2H), 1.02 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 170.4, 142.3, 141.4, 138.0, 128.4, 128.3, 125.9, 118.7, 114.5, 74.8, 72.2, 38.4, 34.5, 33.2, 31.8, 21.1, 9.5; IR

(cast film) 2958, 1736, 1455, 1372, 1236, 1023, 903  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{21}\text{H}_{29}\text{O}_4$   $[\text{M}+\text{H}]^+$  345.45, found 345.28.

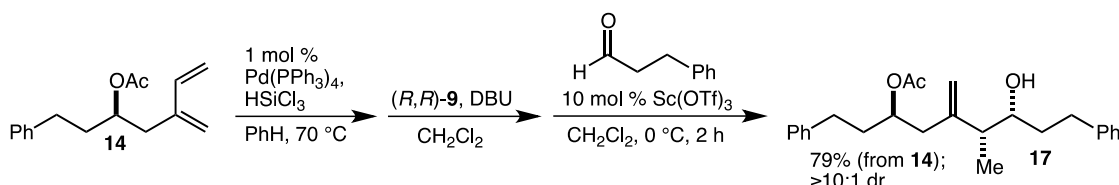
### General Procedure for the Fragment Coupling Crotylation Reactions.

(**Caution/Note:** the following reaction is carried out in a sealed tube. Given that the only reaction component heated above its boiling point is the 2 equiv of  $\text{HSiCl}_3$ , we do not believe that this reaction generates particularly dangerous levels of pressure. Nevertheless, caution is always warranted when using a sealed tube, and we recommend the use of a blast shield.) A flame-dried sealed tube is charged with  $\text{Pd}(\text{PPh}_3)_4$  (0.010 equiv), and then the diene (1.0 equiv) is transferred to the sealed tube as a 0.10 M solution in benzene. Trichlorosilane (2.0 equiv) is then added and the tube is sealed. The reaction vessel is placed in an oil bath heated to 70 °C and the light yellow solution is stirred at 70 °C for 12-16 h. The resulting amber solution is allowed to cool to room temperature, the tube is opened and sealed with a septum, and the mixture is transferred by cannula (with a benzene rinse) into a 2-neck roundbottom flask. The mixture is concentrated by placing the roundbottom flask in a 40 °C water bath, connecting it to an adjacent -78 °C cold-finger and carefully reducing the pressure with a manometer partitioned through the pump manifold. The residue is used in the next step without further purification.

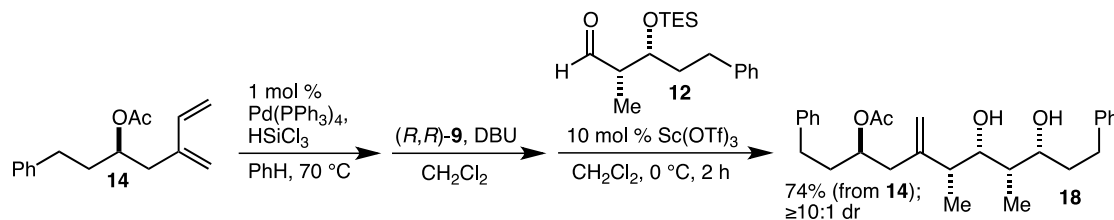
To a solution of the residue in  $\text{CH}_2\text{Cl}_2$  (0.10 M) is added the diamine (*R,R*)-**9** or (*S,S*)-**9** (1.0 equiv). The resulting white slurry is cooled to 0 °C and DBU (4.0 equiv) is added over 10 min. (**Note:** as the DBU is added, the mixture becomes homogeneous and takes on an amber hue.) After 5 min, the mixture is allowed to warm to room temperature. After 2 h, the flask is placed in a room temperature water bath and attached to a vacuum line equipped with a dry ice-acetone cold finger. The mixture is concentrated by careful application of vacuum, and the flask is then back-filled with  $\text{N}_2$ . The resulting oil is dissolved in  $\text{Et}_2\text{O}$  (to a concentration of 0.1 M, based on the amount of diene used in the first step) and the mixture is shaken vigorously for 5-15 min until the  $\text{DBU}\cdot\text{HCl}$  salts form a white precipitate. This heterogeneous mixture is stirred vigorously for an additional 3-5 h until the  $\text{DBU}\cdot\text{HCl}$  salts become a very fine white precipitate. The  $\text{Et}_2\text{O}$  solution is transferred to a new round-bottom flask using teflon tubing (3/16 i.d.) equipped with a glass microfiber filter (Grade GF/D). The residual DBU salts are treated with two additional portions of  $\text{Et}_2\text{O}$  that are then transferred to the new flask the same way. The flask is placed in a room temperature water bath and attached to a vacuum line equipped with a dry

ice-acetone cold finger. The mixture is concentrated by careful application of vacuum to give an oil/foam, which is used in the next step without further purification.

To a cooled (0 °C) solution of the oil/foam in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M, based on the amount of diene used originally) is added the aldehyde (1.0 equiv) followed by Sc(OTf)<sub>3</sub> (0.10 equiv). The reaction mixture is stirred vigorously for 2 h. The reaction is quenched by the addition of 4.0 equiv of TBAF (1 M in THF), and the resulting mixture is allowed to warm to room temperature. The mixture is concentrated, and the residue is purified by silica gel chromatography.

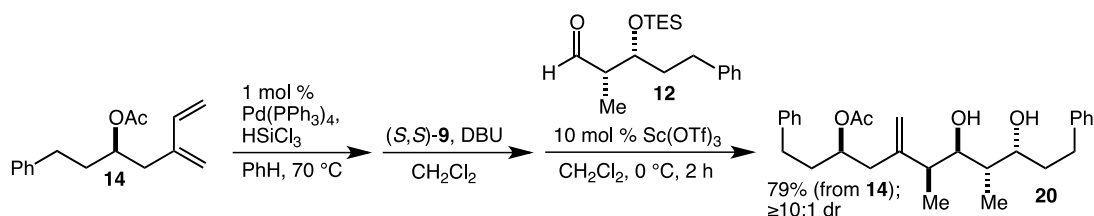


Diene **14** (452 mg, 1.85 mmol) was coupled with hydrocinnamaldehyde (244  $\mu$ L, 1.85 mmol) according to the general procedure using diamine (*R,R*)-**9**. The residue was purified by silica gel chromatography (20% EtOAc/Hexanes) to afford compound **17** (556 mg, 1.46 mmol, 79% yield) as a colorless oil. The diastereoselectivity of the reaction was determined to be  $\geq 10:1$  by <sup>1</sup>H NMR analysis. [ $\alpha$ ]<sub>D</sub> = +46° (*c* 1.9, CH<sub>2</sub>Cl<sub>2</sub>); *R*<sub>f</sub> = 0.3 (15% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37-7.27 (m, 4H), 7.27-7.15 (m, 6H), 5.12 (tt, *J* = 8.5, 4.6 Hz, 1H), 4.98 (d, *J* = 1.3 Hz, 1H), 4.92 (s, 1H), 3.58 (dt, *J* = 8.1, 3.9 Hz, 1H), 2.86 (ddd, *J* = 13.7, 9.7, 5.8 Hz, 1H), 2.77-2.56 (m, 3H), 2.37-2.17 (m, 3H), 2.03 (s, 3H), 1.99-1.70 (m, 4H), 1.58 (bs, 1H), 1.05 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 148.2, 142.1, 141.4, 128.4, 128.4, 128.3, 126.0, 125.8, 113.4, 71.6, 71.1, 43.8, 41.1, 36.1, 32.8, 31.9, 21.1, 12.4; IR (cast film) 3460, 3027, 2930, 1735, 1496, 1454, 1373, 1242, 1030, 901 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>25</sub>H<sub>33</sub>O<sub>3</sub> [M+H]<sup>+</sup> 381.53, found 381.15.

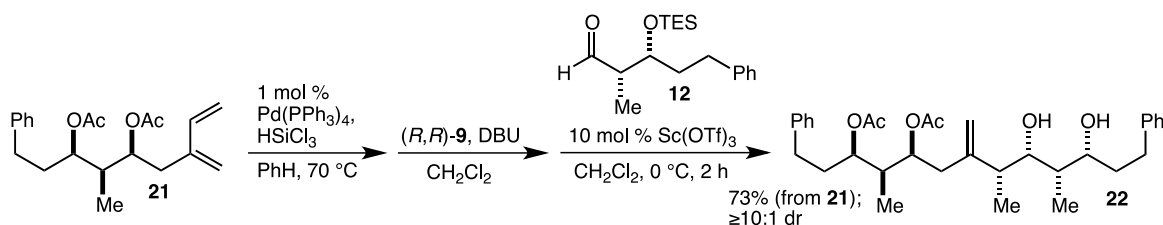


Diene **14** (380 mg, 1.55 mmol) was coupled with aldehyde **12** (475 mg, 1.55 mmol) according to the general procedure using diamine (*R,R*)-**9**. The residue was purified by silica gel chromatography (35% EtOAc/Hexanes) to afford compound **18** (504 mg, 1.15 mmol, 74% yield)

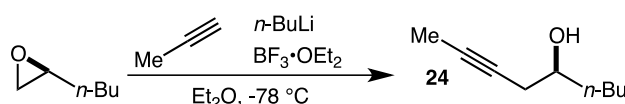
as a colorless oil. The diastereoselectivity of the reaction was determined to be  $\geq 10:1$  by  $^1\text{H}$  NMR analysis.  $[\alpha]_{\text{D}} = +19^\circ$  ( $c$  1.4,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (30% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.25 (m, 4H), 7.25-7.15 (m, 6H), 5.13 (p,  $J = 6.1$  Hz, 1H), 4.90 (d,  $J = 3.9$  Hz, 2H), 3.87-3.74 (m, 1H), 3.66 (dd,  $J = 8.7, 2.5$  Hz, 1H), 2.82-2.58 (m, 5H), 2.53 (bs, 1H), 2.35 (dt,  $J = 14.9, 7.4$  Hz, 2H), 2.20 (dd,  $J = 14.8, 5.3$  Hz, 1H), 2.04 (s, 3H), 1.97-1.81 (m, 3H), 1.78-1.61 (m, 2H), 1.11 (d,  $J = 6.8$  Hz, 3H), 0.95 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 147.9, 141.8, 141.4, 128.4, 128.4, 128.3, 126.0, 125.9, 113.3, 79.1, 76.1, 72.0, 43.2, 39.9, 38.3, 37.0, 35.9, 32.5, 31.9, 21.1, 16.3, 5.4; IR (cast film) 3404, 2932, 1735, 1496, 1457, 1374, 1242, 1090, 1029, 968  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{28}\text{H}_{39}\text{O}_4$   $[\text{M}+\text{H}]^+$  439.61, found 439.40.



Diene **14** (367 mg, 1.50 mmol) was coupled with aldehyde **12** (460 mg, 1.50 mmol) according to the general procedure using diamine (*S,S*)-**9**. The residue was purified by silica gel chromatography (gradient 35-45% EtOAc/Hexanes) to afford compound **20** (520 mg, 1.18 mmol, 79% yield) as a colorless oil. The diastereoselectivity of the reaction was determined to be  $\geq 10:1$  by  $^1\text{H}$  NMR analysis.  $[\alpha]_{\text{D}} = -6^\circ$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.3$  (40% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.12 (m, 10H), 5.05-4.95 (m, 2H), 4.93 (s, 1H), 3.88 (d,  $J = 9.8$  Hz, 1H), 3.60 (dd,  $J = 8.4, 3.6$  Hz, 1H), 3.07-2.88 (m, 2H), 2.80-2.56 (m, 3H), 2.37 (dt,  $J = 12.2, 8.6$  Hz, 3H), 2.23 (dd,  $J = 14.2, 6.9$  Hz, 1H), 2.05 (s, 3H), 1.99-1.79 (m, 2H), 1.73 (dddd,  $J = 13.5, 9.9, 6.5, 3.0$  Hz, 1H), 1.02 (d,  $J = 6.9$  Hz, 3H), 0.89 (d,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 147.9, 142.6, 141.3, 128.5, 128.5, 128.4, 128.3, 126.0, 125.7, 114.1, 74.2, 73.7, 72.6, 41.6, 40.6, 39.3, 35.4, 35.3, 33.0, 31.8, 21.2, 12.1, 11.8; IR (cast film) 3382, 3024, 2932, 1734, 1496, 1459, 1374, 1242, 1030, 970  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{28}\text{H}_{39}\text{O}_4$   $[\text{M}+\text{H}]^+$  439.61, found 439.17.



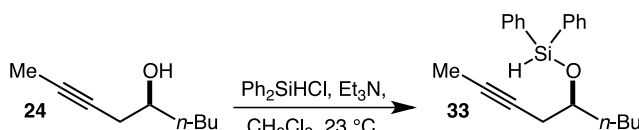
Diene **21** (506 mg, 1.47 mmol) was coupled with aldehyde **12** (450 mg, 1.47 mmol) according to the general procedure using diamine (*R,R*)-**9**. The residue was purified by silica gel chromatography (40% EtOAc/Hexanes) to afford compound **22** (579 mg, 1.07 mmol, 73% yield) as a colorless oil. The diastereoselectivity of the reaction was determined to be  $\geq 10:1$  by  $^1\text{H}$  NMR analysis.  $[\alpha]_{\text{D}} = +23^\circ$  ( $c$  1.3,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.4$  (40% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.26 (m, 4H), 7.26-7.15 (m, 6H), 5.08-4.97 (m, 2H), 4.92 (d,  $J = 6.1$  Hz, 2H), 3.86-3.78 (m, 1H), 3.62 (t,  $J = 5.7$  Hz, 1H), 2.95 (d,  $J = 3.9$  Hz, 1H), 2.81 (ddd,  $J = 13.7, 10.2, 5.6$  Hz, 1H), 2.71-2.54 (m, 3H), 2.41 (ddd,  $J = 18.6, 13.9, 5.3$  Hz, 2H), 2.33 (bs, 1H), 2.16 (dd,  $J = 14.2, 9.3$  Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 2.04-1.95 (m, 1H), 1.90 (dddd,  $J = 14.9, 11.6, 8.3, 4.8$  Hz, 3H), 1.72 (dtd,  $J = 12.6, 5.8, 2.9$  Hz, 1H), 1.63 (tdd,  $J = 7.9, 6.0, 5.3, 3.0$  Hz, 1H), 1.04 (d,  $J = 6.9$  Hz, 3H), 1.00 (d,  $J = 7.1$  Hz, 3H), 0.99 (d,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 170.4, 148.4, 142.1, 141.1, 128.5, 128.4, 128.3, 126.1, 125.8, 113.8, 76.9, 74.1, 74.1, 72.3, 41.8, 40.6, 39.1, 38.2, 37.2, 34.0, 32.7, 32.2, 21.1, 21.0, 14.6, 9.9, 6.7; IR (cast film) 3447, 2936, 1735, 1455, 1373, 1237, 1024, 968  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{33}\text{H}_{47}\text{O}_6$   $[\text{M}+\text{H}]^+$  539.72, found 539.50.



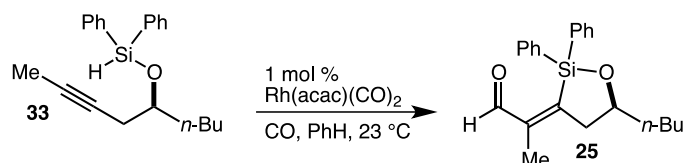
A 500 mL roundbottom flask equipped with an overhead mechanical stirrer was charged with  $\text{Et}_2\text{O}$  (250 mL). The flask was cooled to  $-78^\circ\text{C}$ , and condensed propyne (5 mL, 90.0 mmol, 2.4 equiv) was added by cannula.  $n\text{-BuLi}$  (22.5 mL, 56.3 mmol, 2.5 M in hexanes, 1.5 equiv) was then added by syringe, causing the reaction mixture to become white and thick (**Note**: mechanical stirring of this thick solution was critical for reaction efficiency). After 10 min, (*S*)-1,2-epoxyhexane<sup>2</sup> (4.52 mL 37.5 mmol, 1.0 equiv) was added. After 10 min,  $\text{BF}_3\cdot\text{OEt}_2$  (5.1 mL,

(2) Obtained using the Jacobsen HKR protocol with 1-hexene oxide. See: (a) Tokunaga, M.; Larrow, J.F.; Kakiuchi, F.; Jacobsen, E.N. *Science* **1997**, *277*, 936–938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.;

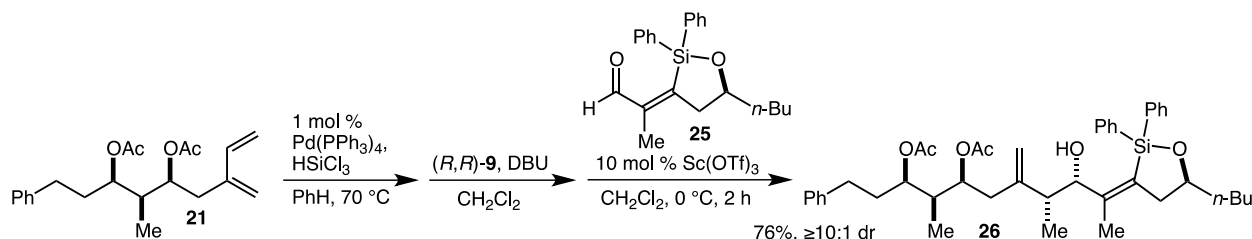
41.3 mmol, 1.1 equiv) was added dropwise over 10 min (**Note:** slow addition of  $\text{BF}_3 \cdot \text{OEt}_2$  was critical for maintaining low reaction temperatures and high regioselectivity of the epoxide opening). After 30 min sat. aq.  $\text{NaHCO}_3$  (75 mL) was added, and the mixture was allowed to warm to room temperature. The layers were mixed well and separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 100 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated (**Note:** during concentration by rotary evaporator, we did not use any heating, due to suspected product volatility) to a yellow oil. Distillation of the residue under reduced pressure (b.p.  $91^\circ\text{C}$  at 12 mm Hg) afforded homopropargylic alcohol **24** (4.62 g, 33.0 mmol, 88% yield) as a colorless oil.  $[\alpha]_D^{25} = +4^\circ$  ( $c$  4.1,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.7$  (25%  $\text{EtOAc}$ /Hexanes,  $p$ -anisaldehyde - stains orange/pink);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.71 (tdd,  $J = 6.9, 5.9, 4.5$  Hz, 1H), 2.41 (ddq,  $J = 16.5, 5.0, 2.5$  Hz, 1H), 2.27 (ddq,  $J = 16.5, 7.3, 2.5$  Hz, 1H), 1.90 (bs, 1H), 1.84 (t,  $J = 2.5$  Hz, 3H), 1.59-1.50 (m, 2H), 1.49-1.26 (m, 4H), 0.94 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  78.3, 75.4, 70.2, 35.9, 27.8, 27.7, 22.6, 14.0, 3.5; IR (cast film) 3374, 2958, 2929, 2861, 1449, 1124, 1081, 1031, 907  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_9\text{H}_{17}\text{O}$   $[\text{M}+\text{H}]^+$  141.23, found 141.15.



To a solution of alcohol **24** (701 mg, 5.0 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added  $\text{Et}_3\text{N}$  (0.91 mL, 6.5 mmol, 1.3 equiv). The resulting mixture was cooled to  $0^\circ\text{C}$  and chlorodiphenylsilane (1.07 mL, 5.5 mmol, 1.1 equiv) was added. The cold bath was removed and the solution was allowed to warm to room temperature. After 30 min, the mixture was concentrated and the residue was treated with hexanes and filtered to remove the  $\text{Et}_3\text{N} \cdot \text{HCl}$  salts. The filtrate was concentrated and the residue (**33**, a brown/orange oil) was used in the next step without further purification.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75-7.62 (m, 4H), 7.51-7.33 (m, 6H), 5.52 (s, 1H), 4.02-3.88 (m, 1H), 2.39 (dtt,  $J = 8.4, 5.3, 2.9$  Hz, 2H), 1.75 (t,  $J = 2.6$  Hz, 3H), 1.71-1.49 (m, 2H), 1.48-1.18 (m, 4H), 0.87 (t,  $J = 6.9$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  134.7, 134.3, 130.2, 127.9, 77.5, 76.2, 73.7, 36.1, 27.5, 27.4, 22.6, 14.0, 3.5.

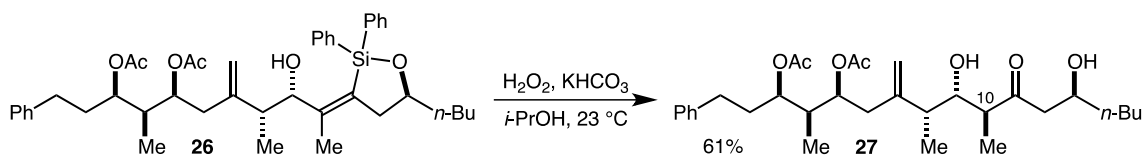


A glass liner for a high pressure Parr bomb was charged with a solution of the unpurified silyl ether **33** from above in  $\text{CH}_2\text{Cl}_2$  (10 mL). The bomb was assembled (with pressure inlet and pressure guage) and charged and vented three times with CO gas (**Note**: the bomb was charged to ~500 psi and vented to 100 psi for each purge). The bomb was charged to ~500 psi of CO and the mixture was stirred (**Note**: the bomb is placed over a stir plate) for 5 min to saturate the solvent with CO. The bomb was then vented and opened and  $\text{Rh}(\text{acac})(\text{CO})_2$  (13 mg, 0.05 mmol, 0.01 equiv) was added. The bomb was reassembled, and then charged and vented three times with CO gas (as above) before being charged with 500 psi CO. After 16 h, the bomb was vented and opened. The resulting brown solution was concentrated and purified by silica gel chromatography (5% EtOAc/Hexanes) to afford aldehyde **25** (1.35 g, 3.85 mmol, 77% yield over 2 steps) as a bright yellow oil. (**Note**: Aldehyde **25** undergoes slow but significant degradation on silica gel. We report the full chromatography procedure here because it leads to analytically pure material. In practice, we simply filtered the unpurified material through a small pad of pH 7 buffered  $\text{SiO}_2$  gel<sup>1</sup> to afford **25** in higher yields (~85-90% over 2 steps) with acceptable purity for use in the fragment coupling by crotylation general procedure.  $[\alpha]_{\text{D}} = -8^\circ$  ( $c$  3.5,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.4$  (5% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.59 (s, 1H), 7.67 (ddt,  $J = 8.3, 6.6, 1.5$  Hz, 4H), 7.52-7.37 (m, 6H), 4.39-4.28 (m, 1H), 3.12 (ddd,  $J = 18.2, 5.5, 1.3$  Hz, 1H), 2.57 (ddq,  $J = 18.2, 8.2, 1.9$  Hz, 1H), 2.00 (t,  $J = 1.5$  Hz, 3H), 1.83 (dddd,  $J = 17.3, 10.1, 7.0, 5.1$  Hz, 1H), 1.70 (ddt,  $J = 13.5, 10.9, 5.5$  Hz, 1H), 1.60-1.32 (m, 3H), 0.94 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  192.7, 163.7, 144.7, 135.2, 135.1, 135.1, 133.2, 132.8, 130.7, 130.6, 128.2, 128.1, 76.1, 41.7, 38.3, 27.8, 22.7, 14.1, 13.3; IR (cast film) 2929, 2858, 1682, 1430, 1263, 1117, 1016, 920  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{22}\text{H}_{27}\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$  351.54, found 351.27.





Diene **21** (506 mg, 1.47 mmol, 1.0 equiv) was coupled with aldehyde **25** (516 mg, 1.47 mmol, 1.0 equiv) according to the general procedure using diamine (*R,R*)-**9**, with one important modification: the crotylation reaction was quenched by the addition of 1.0 equiv of TBAF•(H<sub>2</sub>O)<sub>3</sub> (in lieu of the 4.0 equiv of TBAF described in the general procedure) and the mixture was allowed to warm to room temperature and was stirred for 12 h, before being concentrated. The residue was purified by silica gel chromatography (15% EtOAc/Hexanes, pH 7 buffered SiO<sub>2</sub> gel<sup>1</sup>) to afford compound **26** (783 mg, 1.12 mmol, 76% yield) as a yellow oil. The diastereoselectivity of the reaction was determined to be ≥10:1 by <sup>1</sup>H NMR analysis. [ $\alpha$ ]<sub>D</sub> = +19° (*c* 2.5, CH<sub>2</sub>Cl<sub>2</sub>); *R*<sub>f</sub> = 0.4 (20% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (dt, *J* = 6.7, 1.6 Hz, 2H), 7.59 (dt, *J* = 6.6, 1.5 Hz, 2H), 7.51-7.26 (m, 8H), 7.24-7.20 (m, 1H), 7.17 (dd, *J* = 8.0, 1.4 Hz, 2H), 5.18 (dt, *J* = 9.3, 4.5 Hz, 1H), 5.05 (dt, *J* = 7.6, 5.0 Hz, 1H), 5.01-4.92 (m, 3H), 3.54 (qt, *J* = 6.8, 3.4 Hz, 1H), 2.68-2.41 (m, 6H), 2.31 (dd, *J* = 14.2, 9.4 Hz, 1H), 2.05 (s, 3H), 2.05 (d, *J* = 21.6 Hz, 1H), 2.00 (s, 3H), 1.98-1.82 (m, 2H), 1.87 (s, 3H), 1.44-1.08 (m, 6H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.84 (t, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.7, 170.4, 155.8, 147.2, 141.3, 135.9, 135.1, 134.4, 130.1, 130.1, 130.0, 128.4, 128.3, 127.9, 127.8, 126.0, 114.1, 86.2, 74.3, 72.3, 71.2, 40.5, 40.1, 38.5, 37.2, 36.7, 33.7, 32.1, 27.8, 22.5, 21.1, 21.1, 14.0, 13.9, 11.4, 10.0; IR (cast film) 3464, 2930, 2859, 1735, 1430, 1372, 1238, 1116, 1021, 991 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>43</sub>H<sub>56</sub>O<sub>6</sub>Si [M+H]<sup>+</sup> 698.00, found 697.62.

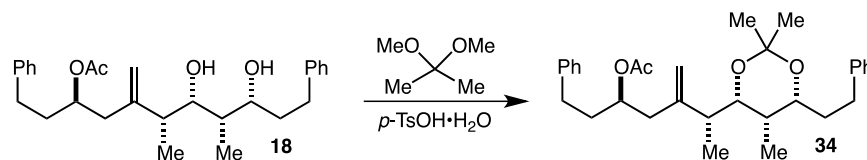


To a solution of silacycle **26** (783 mg, 1.12 mmol, 1.0 equiv) in isopropanol (11 mL) was added KHCO<sub>3</sub> (561 mg, 5.60 mmol, 5.0 equiv) followed by H<sub>2</sub>O<sub>2</sub> as a 30% by weight solution in H<sub>2</sub>O (1.46 mL, 1.3 ml/mmol, ~12 equiv). The mixture was stirred vigorously and reaction progress was monitored by TLC analysis. After 20 h TLC analysis indicated complete consumption of **26**, and brine (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (35% EtOAc/Hexanes) to afford **27** (362 mg, 0.68 mmol, 61% yield) as a colorless oil. (The diastereoselectivity of the reaction at C(10) was determined to be 5:1 by <sup>1</sup>H NMR analysis of the unpurified reaction mixture. Additionally, the

C(10) diastereomer was isolated (72 mg, 0.13 mmol, 12% yield) confirming this ratio.)  $[\alpha]_D = +32^\circ$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.4$  (40% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.26 (m, 2H), 7.26-7.15 (m, 3H), 5.10-4.98 (m, 3H), 4.93 (t,  $J = 1.2$  Hz, 1H), 4.17-4.07 (m, 1H), 3.72 (dt,  $J = 9.2, 2.7$  Hz, 1H), 3.21 (d,  $J = 3.4$  Hz, 1H), 2.83-2.69 (m, 2H), 2.70-2.54 (m, 3H), 2.48-2.35 (m, 2H), 2.21 (dd,  $J = 14.1, 9.9$  Hz, 1H), 2.09 (s, 3H), 2.05 (d,  $J = 2.8$  Hz, 1H), 2.01 (s, 3H), 1.98-1.83 (m, 3H), 1.60-1.26 (m, 6H), 1.07 (d,  $J = 7.0$  Hz, 3H), 1.00 (dd,  $J = 6.9, 2.1$  Hz, 6H), 0.97-0.90 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  215.8, 170.6, 170.3, 147.7, 141.1, 128.4, 128.3, 126.0, 114.6, 73.9, 73.0, 71.9, 67.5, 50.1, 48.4, 40.5, 39.9, 38.9, 36.1, 33.7, 32.1, 27.7, 22.6, 21.0, 20.9, 14.0, 13.1, 11.0, 10.1; IR (cast film) 3457, 2932, 1736, 1456, 1373, 1238, 1024, 975  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{31}\text{H}_{49}\text{O}_7$   $[\text{M}+\text{H}]^+$  533.72, found 533.40.

### Stereochemical Proofs

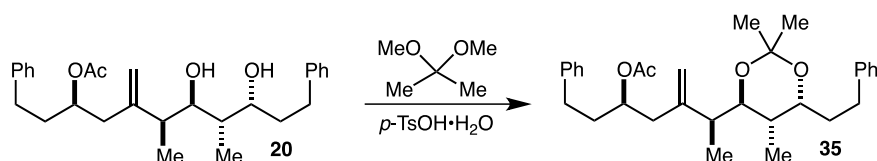
Proofs for **17**, **18**, **20**, and **22**: As described below, compounds **18**, **20**, and **22** were converted to their acetonides **34**, **35**, and **36**.  $^{13}\text{C}$  NMR analysis allowed the determination of whether these acetonides were formed from 1,3-*syn* or 1,3-*anti* diols, according to the method of Rychnovsky.<sup>3</sup> Given that the absolute configuration of **12** is known, this allowed us to confirm that the diamines (*R,R*)-**9** and (*S,S*)-**9** provide the expected sense of stereochemical induction in the fragment coupling by crotylation reactions. The outcome of the reaction that produced **17** was assigned by analogy.



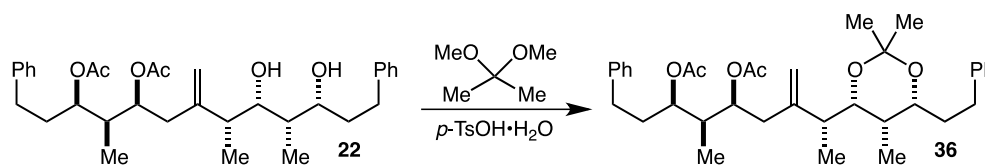
Diol **18** (24 mg, 0.055 mmol, 1.0 equiv) was treated with 2,2-dimethoxypropane (1 mL) and  $p\text{-TsOH}\cdot\text{H}_2\text{O}$  ( $\sim 0.5$  mg). After 20 min, the reaction was quenched by the addition of sat. aq.  $\text{NaHCO}_3$  and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography (7% EtOAc/Hexanes) to afford **34** (23 mg, 0.048 mmol, 87% yield) as a colorless oil. The stereochemistry of the acetonide (1,3-*syn*) was verified by  $^{13}\text{C}$  NMR analysis (see **bolded** peaks below) according to the Rychnovsky method.<sup>3</sup>  $[\alpha]_D = +5^\circ$  ( $c$  2.3,  $\text{CH}_2\text{Cl}_2$ );  $R_f$

(3) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, 58, 3511-3515.

= 0.4 (10% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.26 (m, 4H), 7.21 (ddt,  $J$  = 7.1, 3.1, 2.0 Hz, 6H), 5.17 (tt,  $J$  = 7.5, 5.4 Hz, 1H), 4.96-4.85 (m, 2H), 3.78 (ddd,  $J$  = 8.7, 4.4, 2.1 Hz, 1H), 3.62 (dd,  $J$  = 10.1, 1.9 Hz, 1H), 2.81-2.55 (m, 4H), 2.42-2.27 (m, 2H), 2.24-2.14 (m, 1H), 2.05 (s, 3H), 2.02-1.84 (m, 3H), 1.59 (dddd,  $J$  = 13.7, 9.4, 7.2, 4.5 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.39 (dtd,  $J$  = 6.7, 4.7, 2.3 Hz, 1H), 1.07 (d,  $J$  = 6.7 Hz, 3H), 0.86 (d,  $J$  = 6.7 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 146.7, 142.1, 141.5, 128.5, 128.4, 128.3, 126.0, 125.7, 113.4, **99.1**, 77.2, 72.8, 72.2, 42.1, 39.2, 35.8, 34.5, 33.2, 31.8, 31.7, **30.1**, 21.2, **19.8**, 17.9, 5.3; IR (cast film) 2939, 1736, 1455, 1376, 1240, 1199, 1161, 1110, 1027, 1010  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{31}\text{H}_{43}\text{O}_4$   $[\text{M}+\text{H}]^+$  479.67, found 479.40.

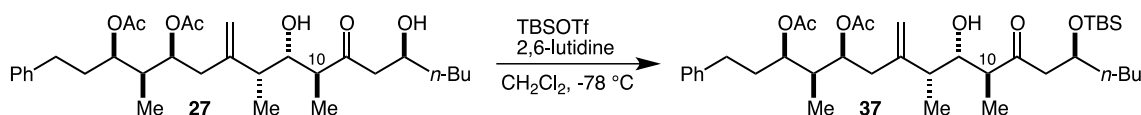


Diol **20** (54 mg, 0.123 mmol, 1.0 equiv) was treated with 2,2-dimethoxypropane (1.2 mL) and  $p\text{-TsOH}\cdot\text{H}_2\text{O}$  (~1 mg). After 30 min, the reaction was quenched by the addition of sat. aq.  $\text{NaHCO}_3$  and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography (7% EtOAc/Hexanes) to afford **35** (48 mg, 0.100 mmol, 82% yield) as a colorless oil. The stereochemistry of the acetonide (1,3-*anti*) was verified by  $^{13}\text{C}$  NMR analysis (see **bolded** peaks below) according to the Rychnovsky method.<sup>3</sup>  $[\alpha]_{\text{D}} = -16^\circ$  ( $c$  1.4,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  = 0.4 (10% EtOAc/Hexanes, PMA);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.26 (m, 4H), 7.22 (ddd,  $J$  = 14.9, 6.9, 1.7 Hz, 6H), 5.11 (qd,  $J$  = 7.2, 4.8 Hz, 1H), 4.98 (s, 1H), 4.85 (d,  $J$  = 1.5 Hz, 1H), 3.79 (dt,  $J$  = 9.2, 4.2 Hz, 1H), 3.30 (dd,  $J$  = 7.4, 3.7 Hz, 1H), 2.82 (ddd,  $J$  = 14.7, 10.0, 5.2 Hz, 1H), 2.77-2.51 (m, 3H), 2.38 (dd,  $J$  = 14.6, 7.4 Hz, 1H), 2.30 (dd,  $J$  = 14.6, 6.1 Hz, 1H), 2.19 (qd,  $J$  = 6.7, 3.5 Hz, 1H), 2.04 (s, 3H), 1.91 (dq,  $J$  = 10.4, 7.7, 4.0 Hz, 2H), 1.81 (dp,  $J$  = 14.2, 4.9 Hz, 1H), 1.76-1.68 (m, 1H), 1.63 (dtd,  $J$  = 13.3, 6.4, 3.2 Hz, 1H), 1.35 (d,  $J$  = 1.3 Hz, 6H), 1.05 (d,  $J$  = 6.9 Hz, 3H), 0.86 (d,  $J$  = 6.8 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 148.1, 142.3, 141.6, 128.4, 128.4, 128.3, 125.9, 125.7, 112.8, **100.3**, 76.9, 72.2, 68.9, 42.6, 40.3, 37.8, 35.8, 32.6, 32.4, 31.8, **25.4**, **23.8**, 21.2, 14.1, 12.3; IR (cast film) 2936, 1736, 1496, 1455, 1378, 1239, 1166, 1140, 1023  $\text{cm}^{-1}$ ; LRMS (FAB+) calc'd for  $\text{C}_{31}\text{H}_{43}\text{O}_4$   $[\text{M}+\text{H}]^+$  479.67, found 479.37.



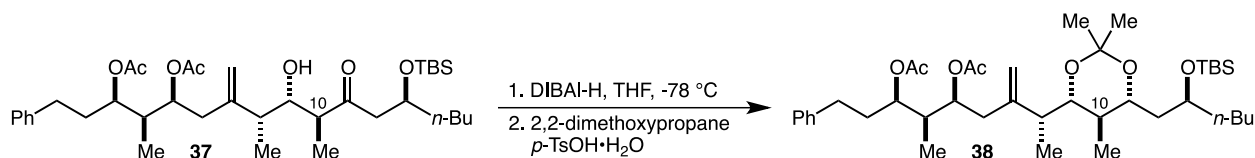
Diol **22** (29 mg, 0.054 mmol, 1.0 equiv) was treated with 2,2-dimethoxypropane (1 mL) and *p*-TsOH·H<sub>2</sub>O (~0.5 mg). After 15 min, the reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to afford **36** (48 mg, 0.100 mmol, 82% yield) as a colorless oil. The stereochemistry of the acetonide (1,3-*syn*) was verified by <sup>13</sup>C NMR analysis (see **bolded** peaks below) according to the Rychnovsky method.<sup>3</sup> [ $\alpha$ ]<sub>D</sub> = +6° (*c* 2.9, CH<sub>2</sub>Cl<sub>2</sub>); *R*<sub>f</sub> = 0.3 (10% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.25 (m, 4H), 7.25-7.15 (m, 6H), 5.16 (tt, *J* = 6.7, 2.9 Hz, 1H), 4.99 (q, *J* = 5.9 Hz, 1H), 4.91 (d, *J* = 17.8 Hz, 2H), 3.78 (ddd, *J* = 8.4, 4.3, 2.0 Hz, 1H), 3.60 (dd, *J* = 10.1, 1.8 Hz, 1H), 2.75 (ddd, *J* = 14.2, 9.2, 5.3 Hz, 1H), 2.69-2.54 (m, 3H), 2.30 (dt, *J* = 13.0, 6.6 Hz, 1H), 2.24 (d, *J* = 6.8 Hz, 2H), 2.05 (s, 3H), 2.02 (s, 0H), 2.01 (s, 3H), 1.97-1.85 (m, 3H), 1.59 (dddd, *J* = 13.4, 9.1, 7.3, 4.3 Hz, 1H), 1.45 (d, *J* = 11.1 Hz, 6H), 1.40-1.32 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 170.4, 146.7, 142.1, 141.2, 128.5, 128.4, 128.3, 128.3, 126.0, 125.7, 113.6, **99.1**, 77.2, 74.3, 72.8, 72.7, 42.2, 39.3, 36.4, 34.5, 33.6, 33.3, 32.0, 31.7, **30.1**, 21.1, **19.8**, 17.8, 9.9, 5.3; IR (cast film) 2986, 2939, 1736, 1455, 1373, 1233, 1199, 1020, 970 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>36</sub>H<sub>51</sub>O<sub>6</sub> [M+H]<sup>+</sup> 579.79, found 579.33.

The proof of the C(10) relative stereochemistry in product **27** was carried out as follows:



To a cooled (-78 °C) solution of **27** (60 mg, 0.113 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> was added 2,6-lutidine (20  $\mu$ L, 0.170 mmol, 1.5 equiv) followed by TBSOTf (31  $\mu$ L, 1.2 equiv). After 20 min the reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub>. The dry ice/acetone bath was removed, and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted 3 x with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (15% EtOAc/Hexanes) to afford **37** (61 mg, 0.094 mmol, 83% yield) as a colorless oil. [ $\alpha$ ]<sub>D</sub> =

+23° (*c* 0.9, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.3 (15% EtOAc/Hexanes, PMA); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36-7.25 (m, 2H), 7.25-7.14 (m, 3H), 5.07 (ddd, *J* = 9.2, 5.3, 3.6 Hz, 1H), 5.04-4.94 (m, 2H), 4.91 (s, 1H), 4.24 (dt, *J* = 11.0, 5.5 Hz, 1H), 3.66 (dt, *J* = 8.5, 3.4 Hz, 1H), 2.83-2.51 (m, 4H), 2.35 (dq, *J* = 13.8, 6.1, 4.8 Hz, 2H), 2.21 (dd, *J* = 14.3, 9.7 Hz, 1H), 2.12 (d, *J* = 3.7 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.91 (dq, *J* = 11.1, 7.7, 6.9 Hz, 3H), 1.55-1.39 (m, 2H), 1.31 (qd, *J* = 6.2, 5.2, 2.4 Hz, 5H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.00 (dd, *J* = 6.9, 2.1 Hz, 6H), 0.95-0.80 (m, 12H), 0.10 (s, 3H), 0.05 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 213.5, 170.6, 170.4, 147.8, 141.2, 128.5, 128.3, 126.0, 114.3, 74.0, 73.0, 71.9, 67.8, 51.1, 48.7, 40.4, 40.3, 38.6, 37.3, 33.6, 32.1, 27.2, 25.9, 22.8, 21.1, 21.0, 18.0, 14.1, 13.0, 11.4, 10.2, -4.6; IR (cast film) 3517, 2956, 2931, 2858, 1738, 1459, 1373, 1239, 1025, 976 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>37</sub>H<sub>63</sub>O<sub>7</sub>Si [M+H]<sup>+</sup> 647.98, found 647.51.

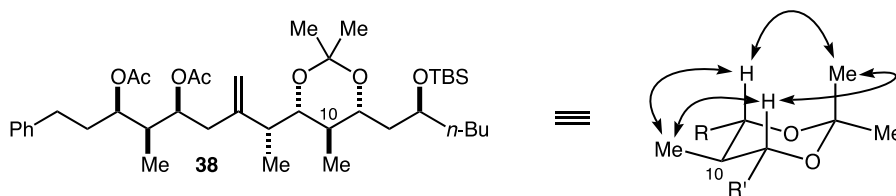


To a cooled (-78 °C) solution of **37** (51 mg, 0.079 mmol, 1.0 equiv) in THF (1.6 mL) was added DIBAL-H (0.24 mL, 0.237 mmol, 1 M in hexanes, 3.0 equiv) slowly over 1 min. After 30 min, the reaction was quenched by the addition of a 1 M aqueous solution of tartaric acid. The resulting mixture was allowed to warm to room temperature. The mixture was extracted 3 x with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (20% EtOAc/Hexanes) to afford a 2:1 mixture of diastereomeric diols.

The mixture of diols (~51mg, 0.079 mmol, 1.0 equiv) was treated with 2,2-dimethoxypropane (1 mL) and *p*-TsOH·H<sub>2</sub>O (~1 mg). After 20 min, the reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> and the mixture was extracted 3 x with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to afford a 2:1 mixture of *syn/anti*-acetonides (45 mg, 0.065 mmol, 83% yield over 2 steps) as a pale yellow oil. The mixture of diastereomers was repurified by silica gel chromatography (15% Et<sub>2</sub>O/Hexanes) to afford a small amount of the major acetonide **38** for full characterization. The stereochemistry of acetonide **38** (1,3-*syn*) was verified by <sup>13</sup>C NMR analysis (see **bolded** peaks below) according to the Rychnovsky method.<sup>3</sup> [ $\alpha$ ]<sub>D</sub> = +20° (*c* 0.9, CH<sub>2</sub>Cl<sub>2</sub>); *R<sub>f</sub>* = 0.4 (10% EtOAc/Hexanes, PMA); <sup>1</sup>H

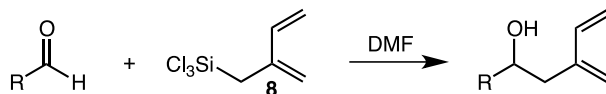
NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.25 (d,  $J$  = 4.6 Hz, 2H), 7.25-7.14 (m, 3H), 5.12 (dt,  $J$  = 9.0, 4.6 Hz, 1H), 5.00 (q,  $J$  = 6.0 Hz, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 3.90 (qd,  $J$  = 8.0, 6.8, 4.0 Hz, 1H), 3.66-3.47 (m, 2H), 2.70-2.52 (m, 2H), 2.46-2.31 (m, 2H), 2.25 (dd,  $J$  = 14.7, 8.6 Hz, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.99-1.85 (m, 3H), 1.72 (ddd,  $J$  = 13.8, 9.2, 1.5 Hz, 1H), 1.48 (dddd,  $J$  = 9.1, 7.0, 4.9, 3.0 Hz, 2H), 1.39 (s, 3H), 1.37-1.22 (m, 9H), 1.01 (dd,  $J$  = 7.1, 2.0 Hz, 6H), 0.92 (s, 12H), 0.79 (d,  $J$  = 6.5 Hz, 3H), 0.08 (d,  $J$  = 3.2 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 170.3, 147.9, 141.3, 128.4, 128.3, 125.9, 112.7, **97.4**, 75.4, 74.4, 72.3, 71.2, 68.5, 41.7, 39.7, 39.0, 38.0, 37.8, 35.7, 33.6, 32.0, **30.1**, 26.6, 26.0, 23.0, 21.1, 21.1, **19.9**, 18.1, 14.1, 12.4, 11.8, 10.0, -3.9, -4.4; IR (cast film) 2956, 2931, 2858, 1738, 1461, 1376, 1240, 1202, 1026 cm<sup>-1</sup>; LRMS (FAB+) calc'd for C<sub>40</sub>H<sub>68</sub>O<sub>7</sub> [M]<sup>+</sup> 689.05, found 689.48.

An nOe analysis was carried out on **38**, and the illustrated enhancements confirmed the relative configuration of the C(10) stereocenter:

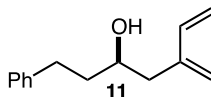


### Determination of Enantiomeric Excess for **11**, **30**, **31**, **32**, and **28**.

Authentic samples of racemic isoprenylation products were generated as follows:

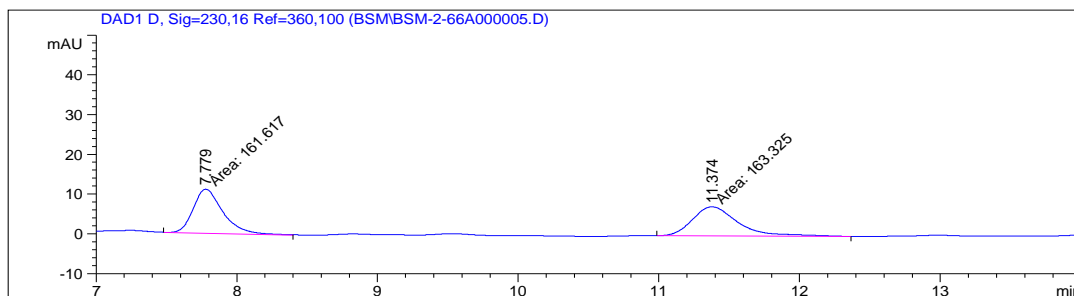


Enantiomeric excesses (ee's) were determined by chiral HPLC analysis.



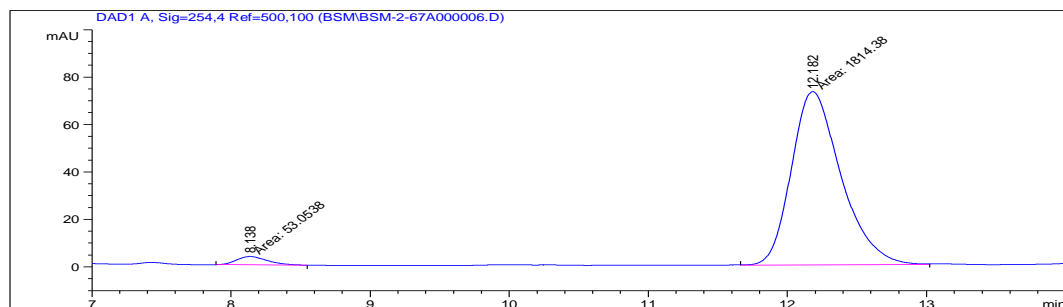
Alcohol **11**: Chiralcel OD Column, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm.

Racemic:

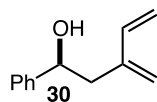


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.779	1	MM	161.61710	11.06059	49.7372
2	11.374	1	MM	163.32510	7.30261	50.2628

**11**:



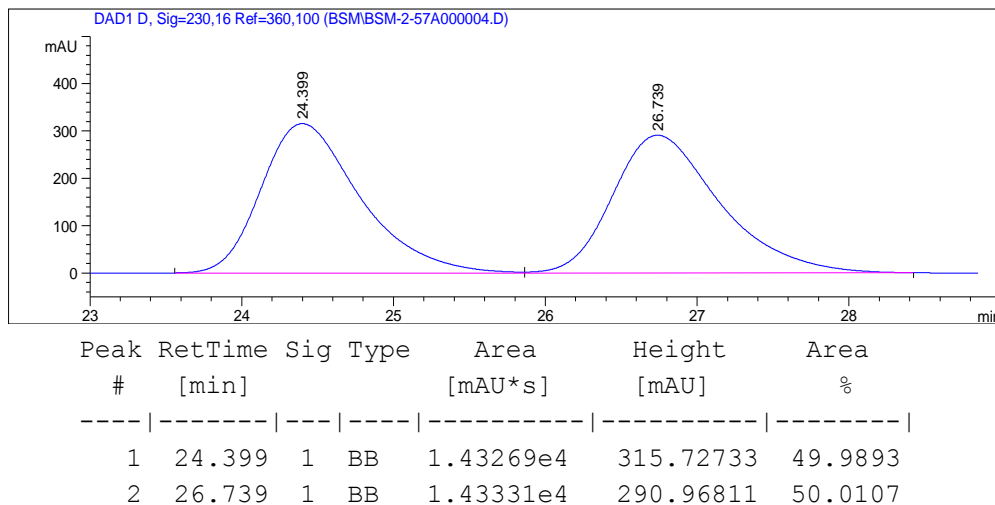
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	8.138	1	MM	53.05380	3.50956	2.8410
2	12.182	1	MM	1814.38416	73.03902	97.1590



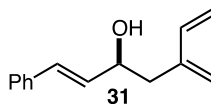
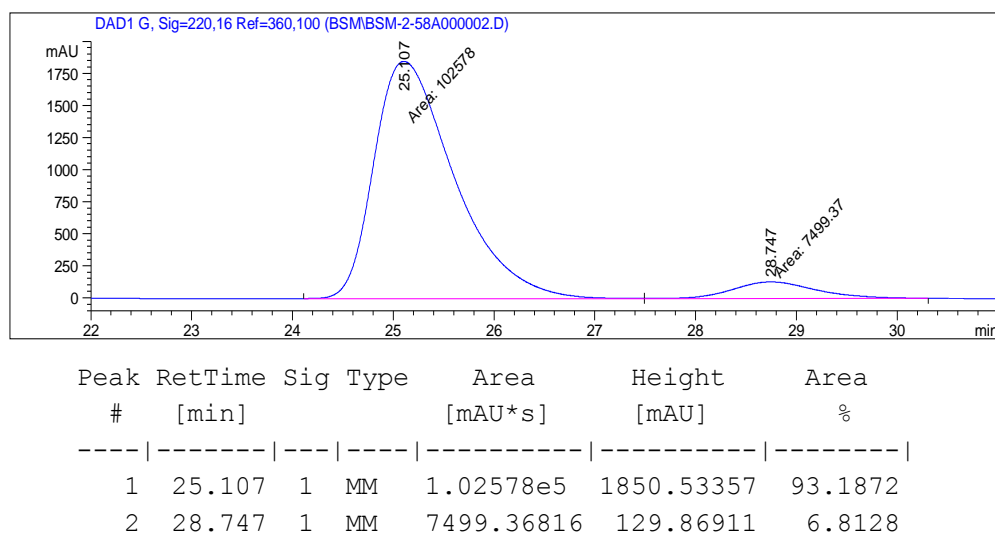


Alcohol **30**: Chiralcel OD Column, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm.

Racemic:

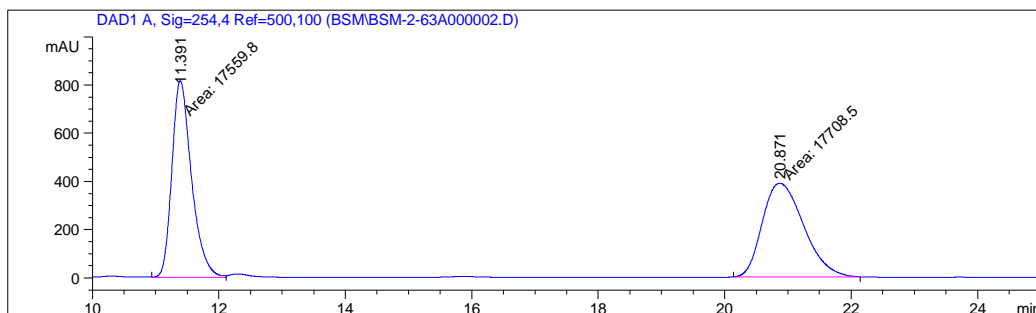


**30**:



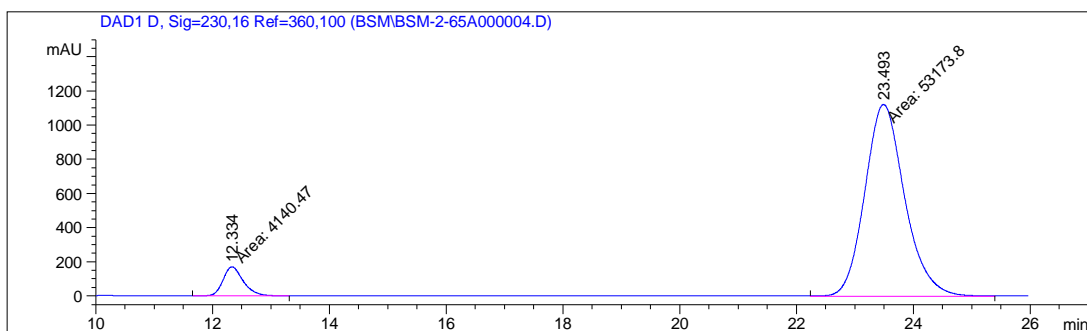
Alcohol **31**: Chiralcel OD Column, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm.

Racemic:

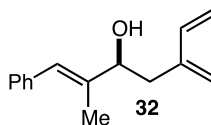


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	11.391	1	MM	1.75598e4	815.82251	49.7891
2	20.871	1	MM	1.77085e4	389.36655	50.2109

**31**:

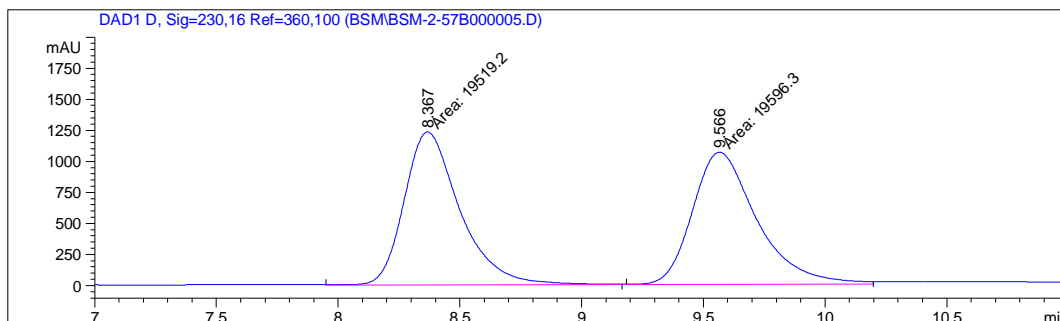


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	12.334	1	MM	4140.47070	170.59232	7.2241
2	23.493	1	MM	5.31738e4	1121.85962	92.7759



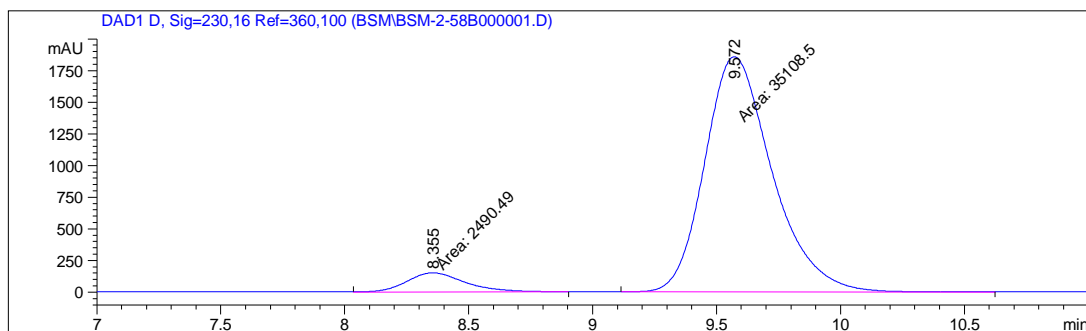
Alcohol **32**: Chiralcel OD Column, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm.

Racemic:

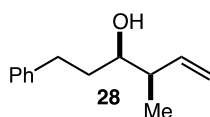


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	8.367	1	MM	1.95192e4	1229.96985	49.9015
2	9.566	1	MM	1.95963e4	1064.27173	50.0985

**32**:

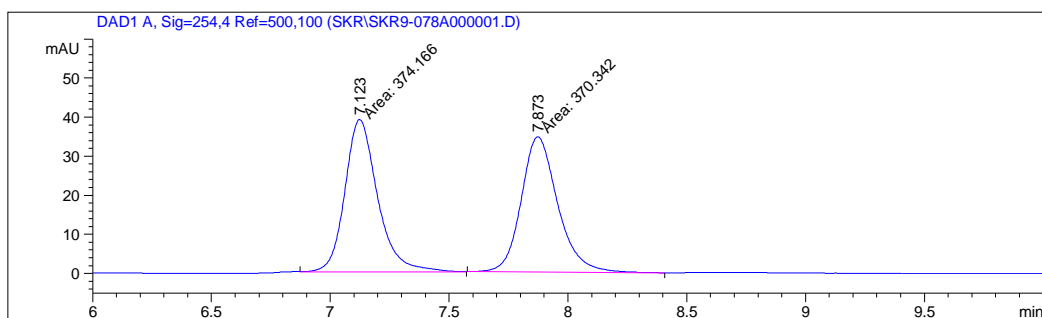


Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	8.355	1	MM	2490.49487	151.44154	6.6238
2	9.572	1	MM	3.51085e4	1857.52759	93.3762



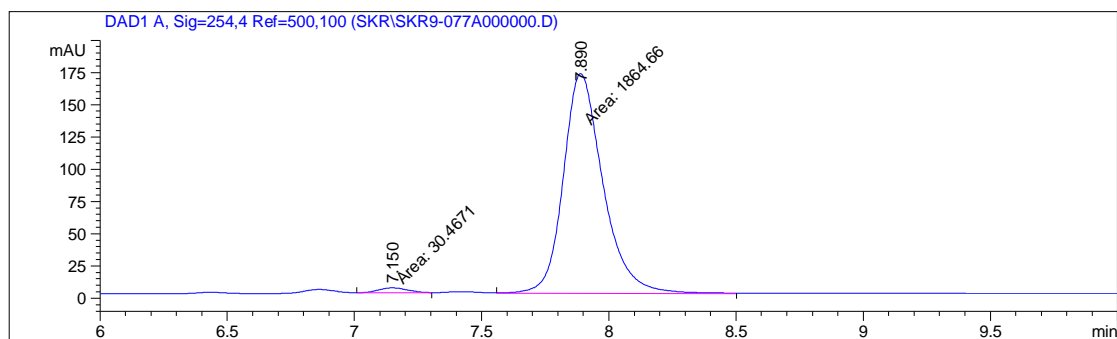
Alcohol **28**: Chiralcel AD-H Column, 5% *i*-PrOH in hexanes, 1 mL/min, 254 nm.

Racemic:



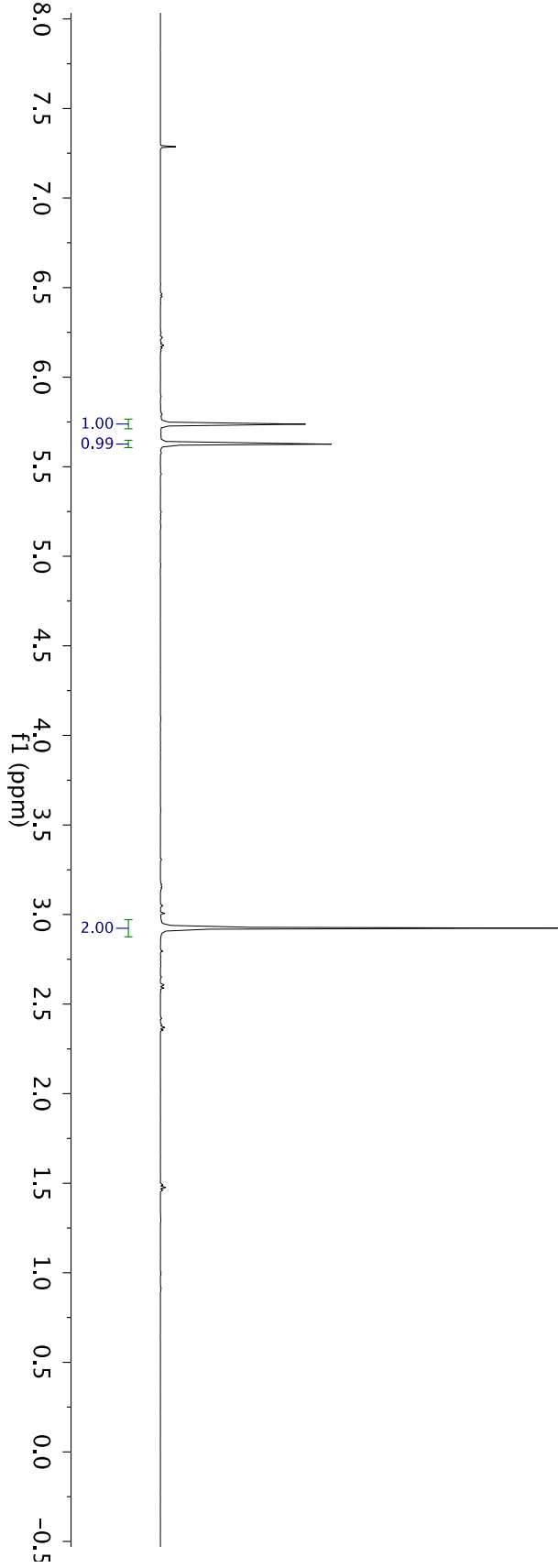
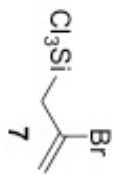
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.123	1	MM	374.16617	39.00862	50.2568
2	7.873	1	MM	370.34189	34.64413	49.7432

**28:**

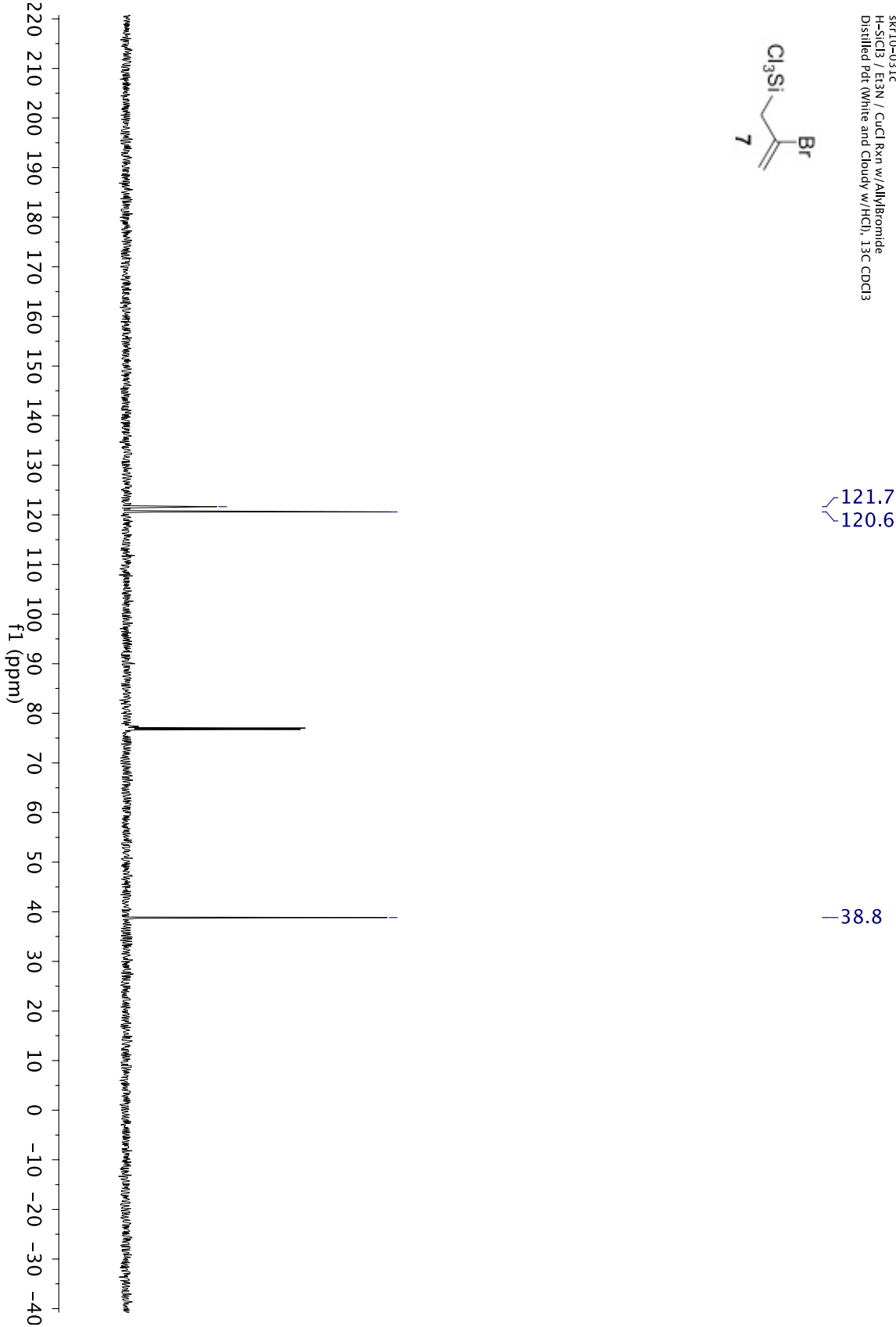
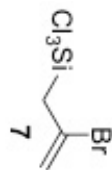


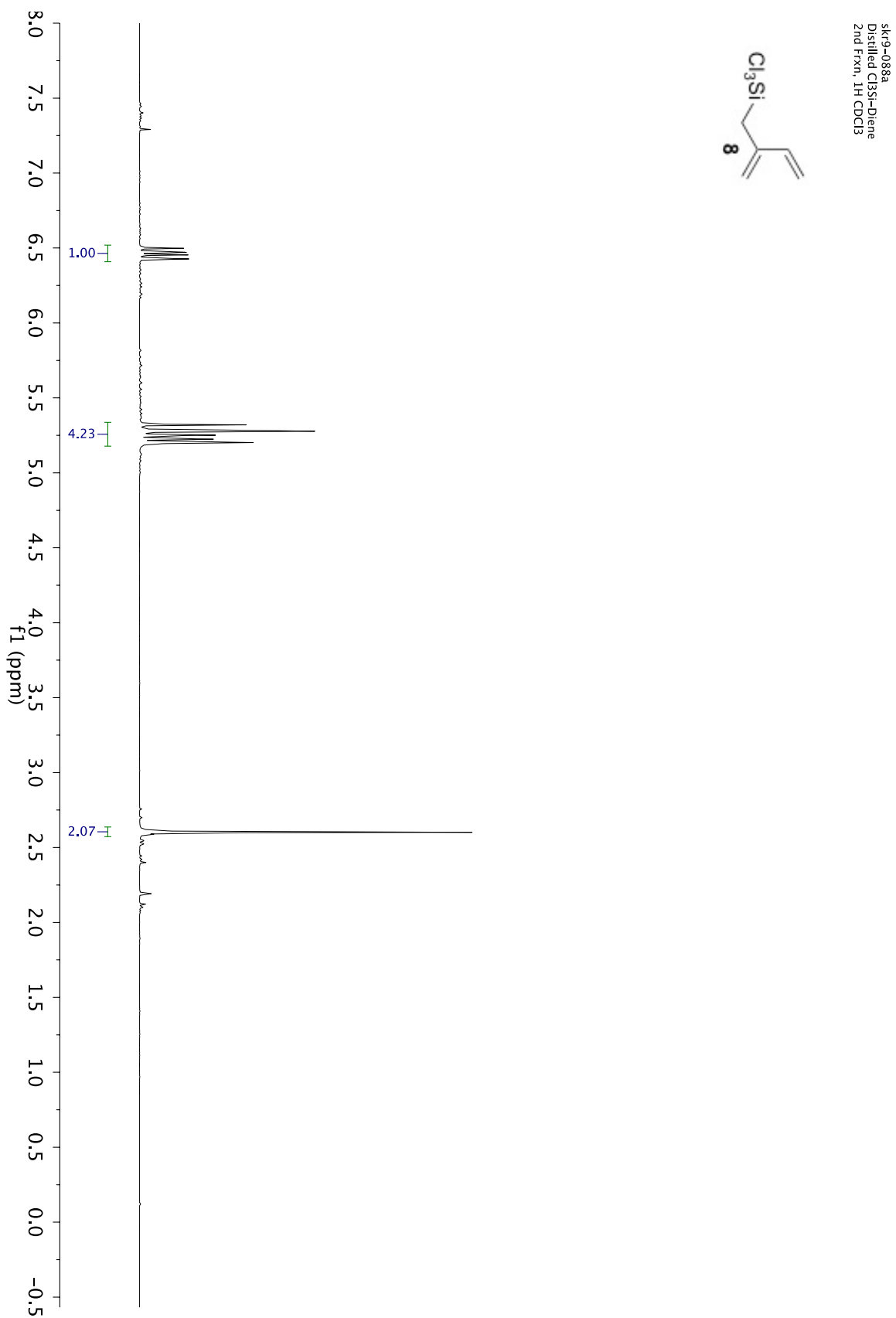
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.150	1	MM	30.46707	3.78520	1.6076
2	7.890	1	MM	1864.66418	170.56212	98.3924

skr10-031b  
H-SiCl<sub>3</sub> / Et<sub>3</sub>N / CuCl Rxn w/ Alkylbromide  
Distilled Pd (White and Cloudy), CDCl<sub>3</sub>

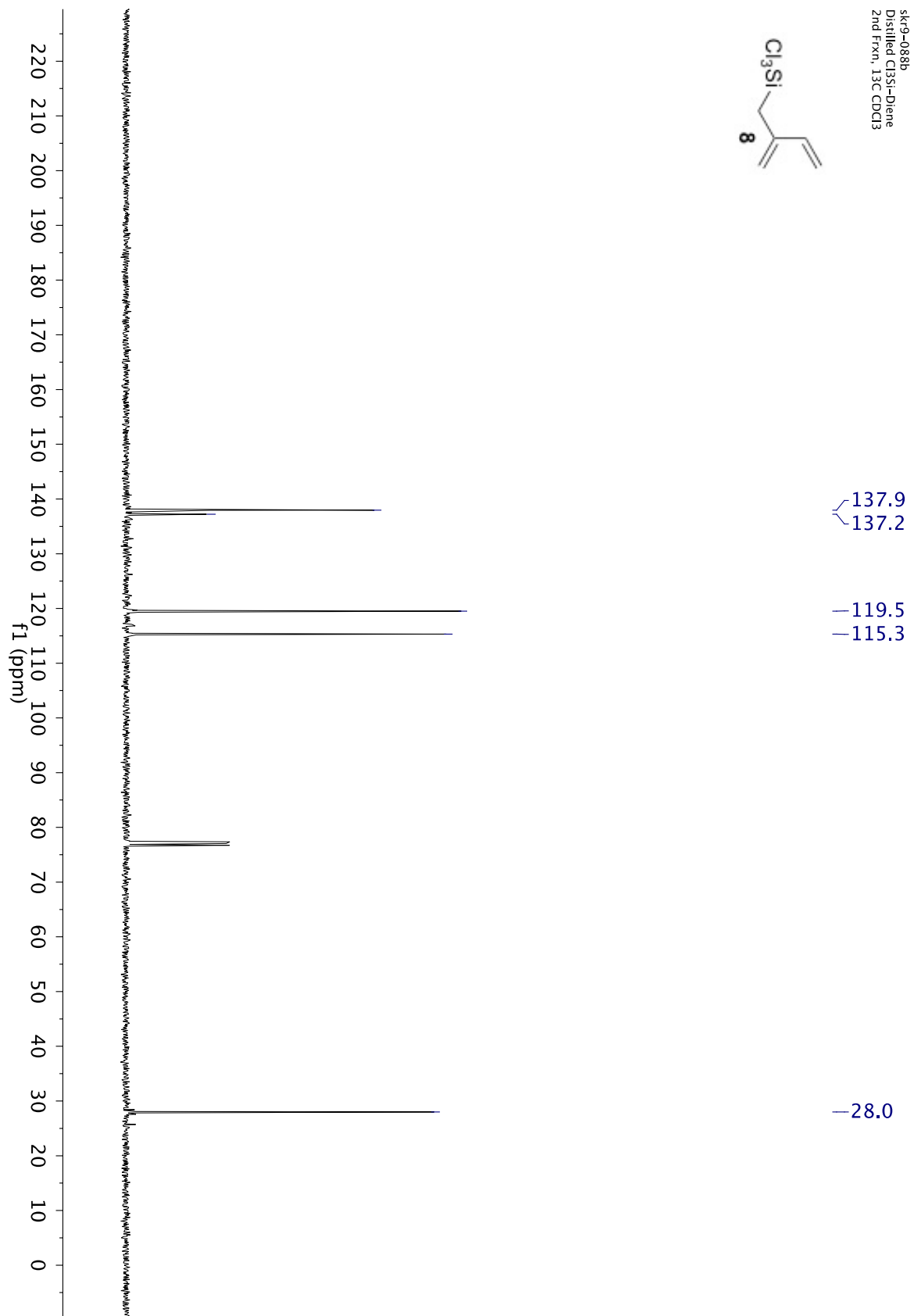


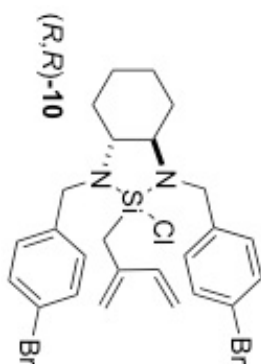
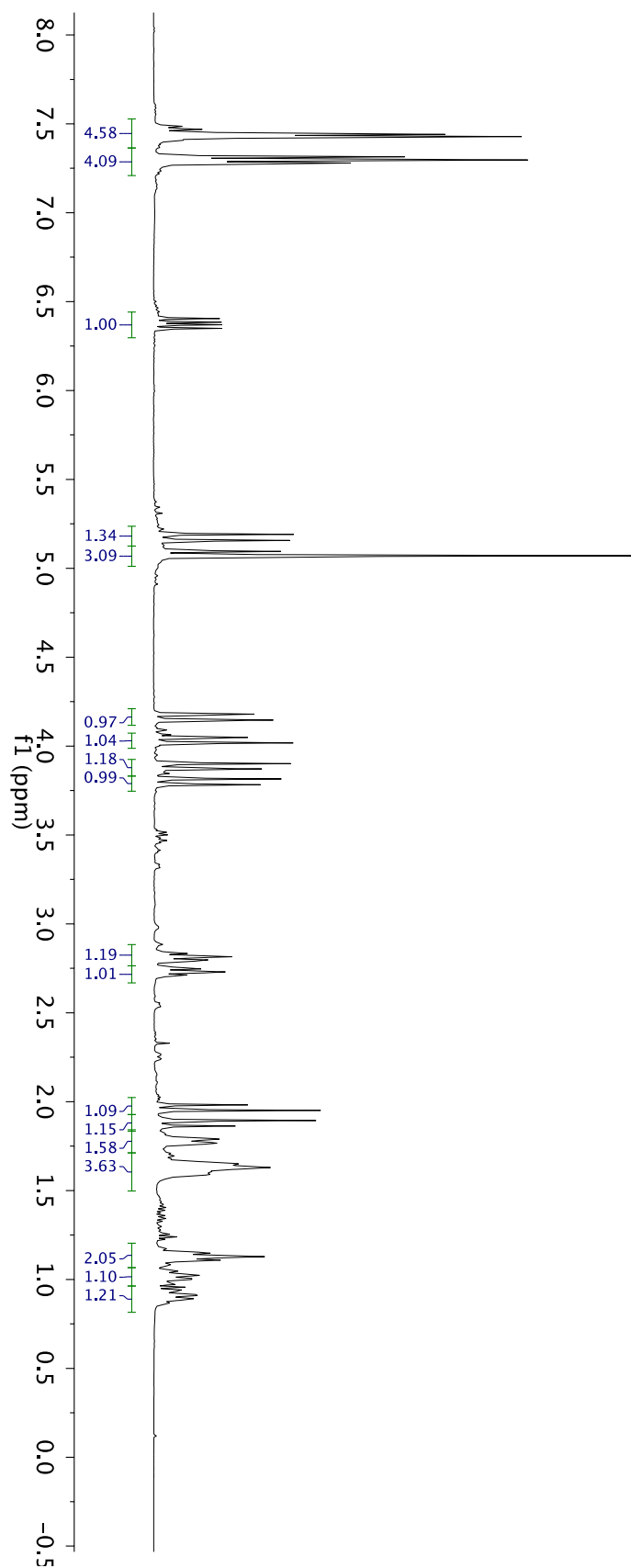
SKT10-031C  
H-SiCl<sub>3</sub> / Et<sub>3</sub>N / CuCl Rxn w/ Allyl Bromide  
Distilled Pot (White and Cloudy w/ HCl), 13C CDCl<sub>3</sub>





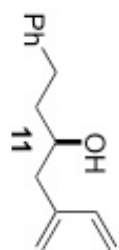
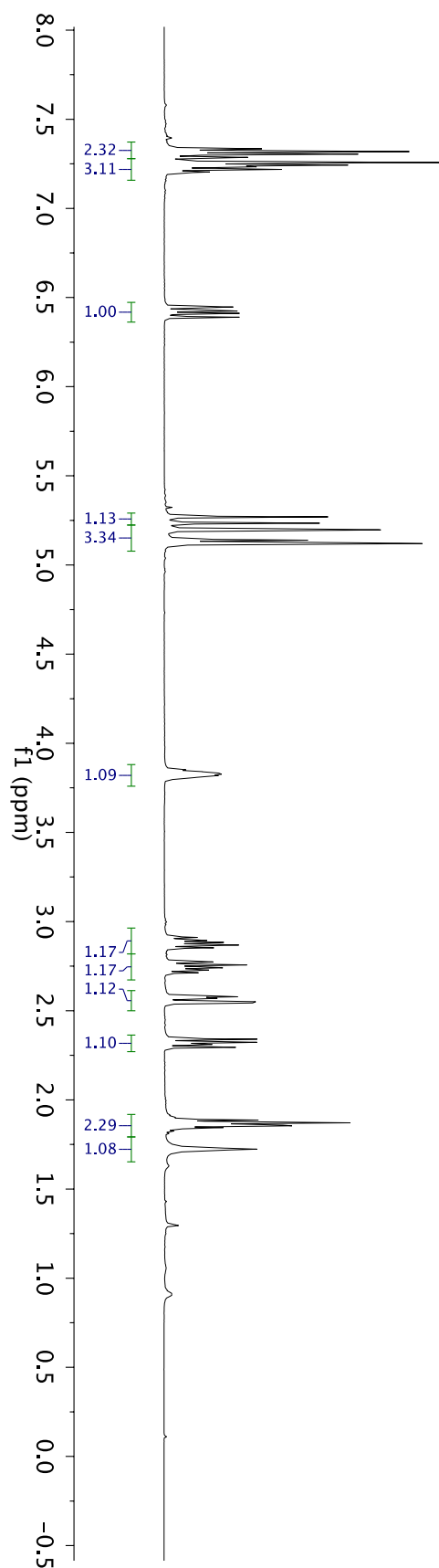




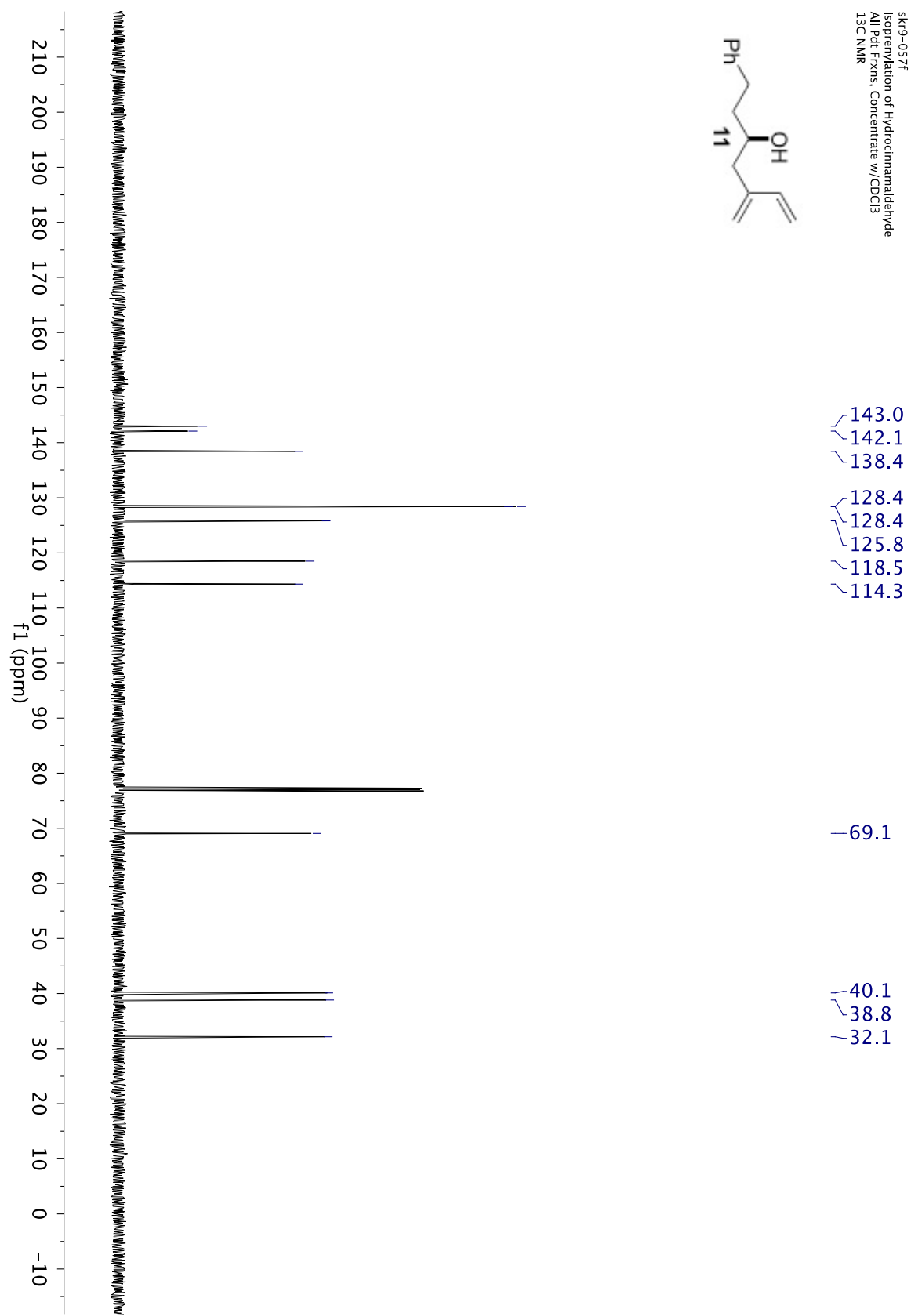


sk10-032a  
(R,R) Isoprenylation Silane Reagent  
Stored in a solution of CDCl<sub>3</sub>

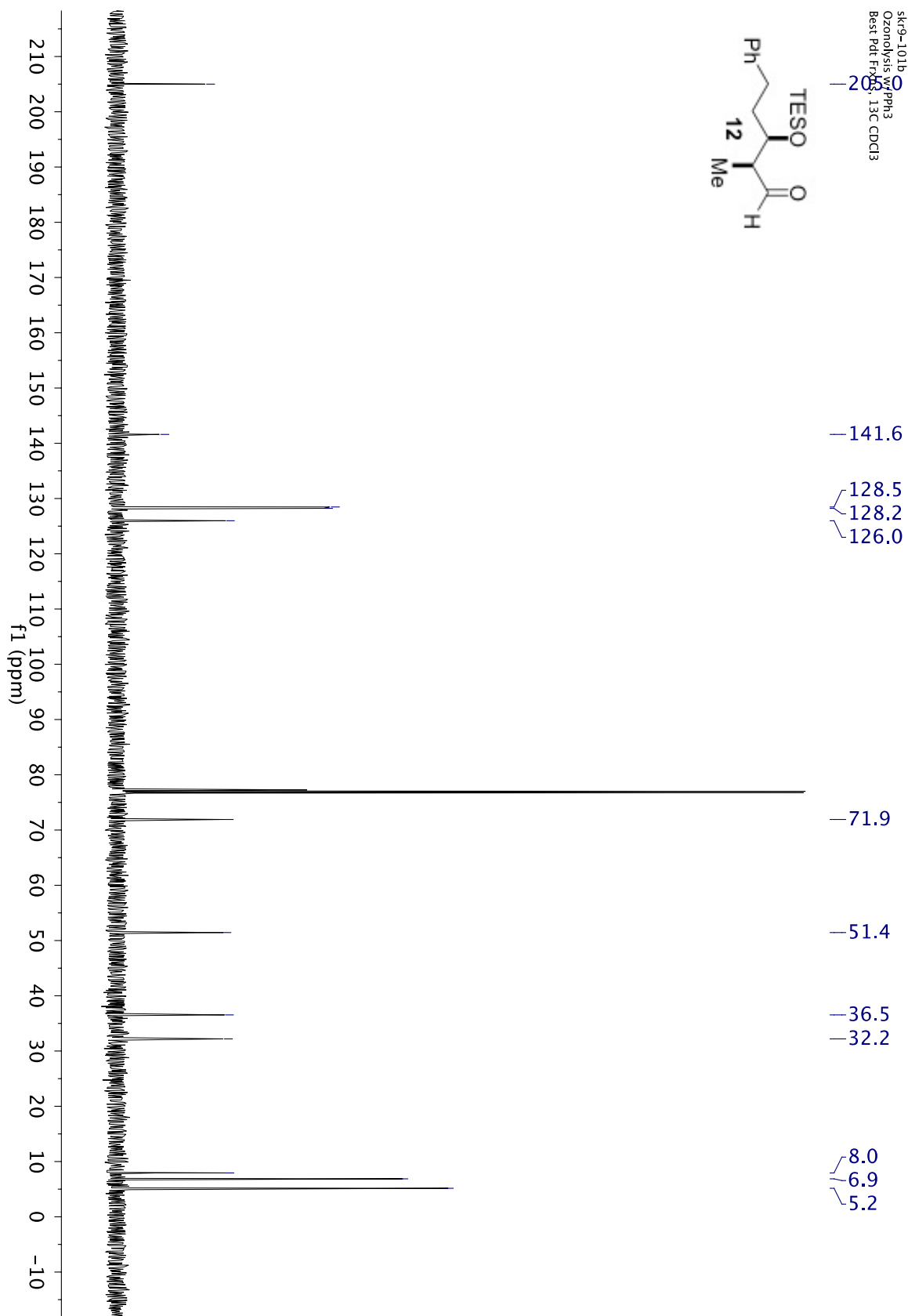




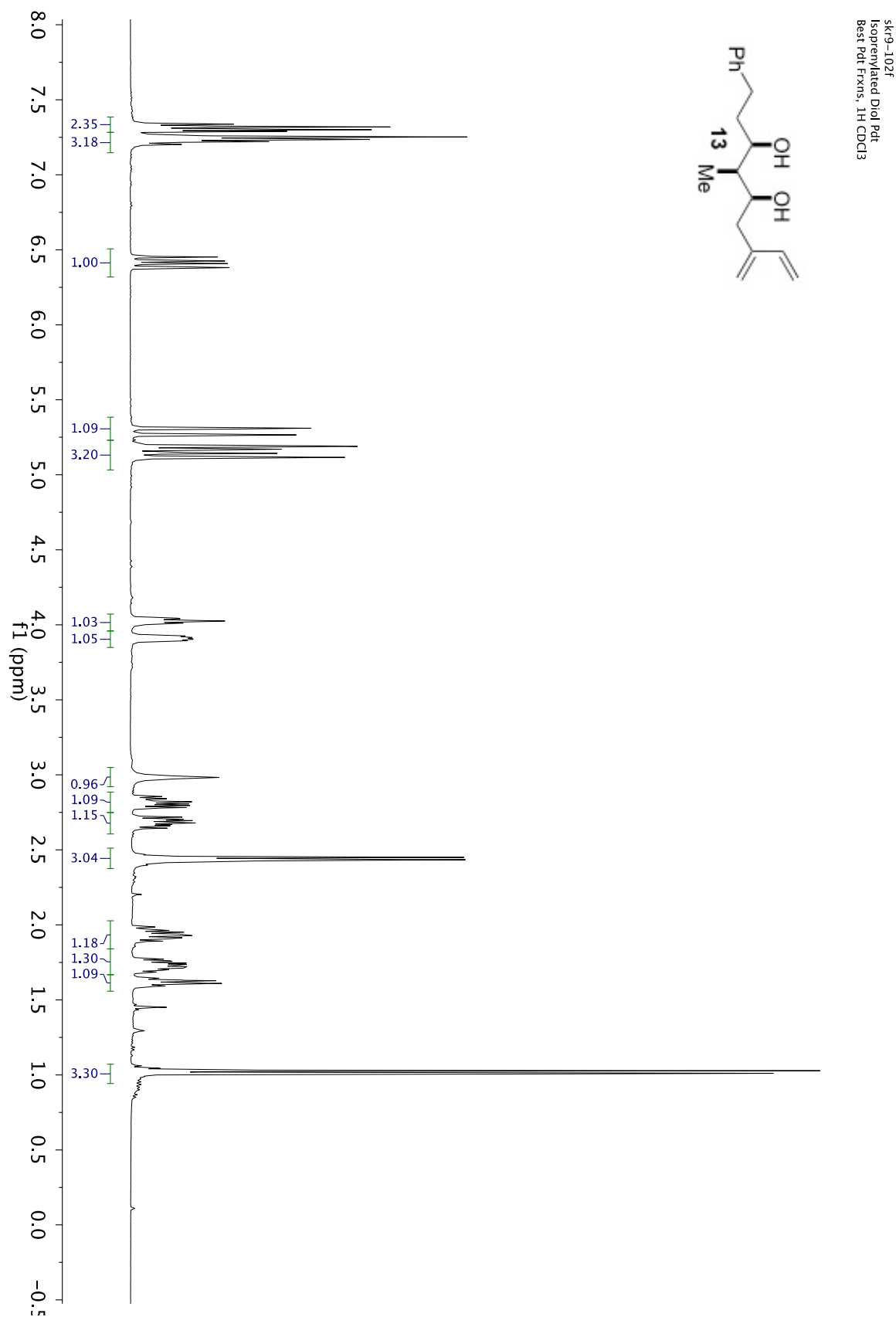
sk9-057e  
Isoprenylation of Hydrocinamaldehyde  
All Pdt Frxns, Concentrate w/CDCl<sub>3</sub>

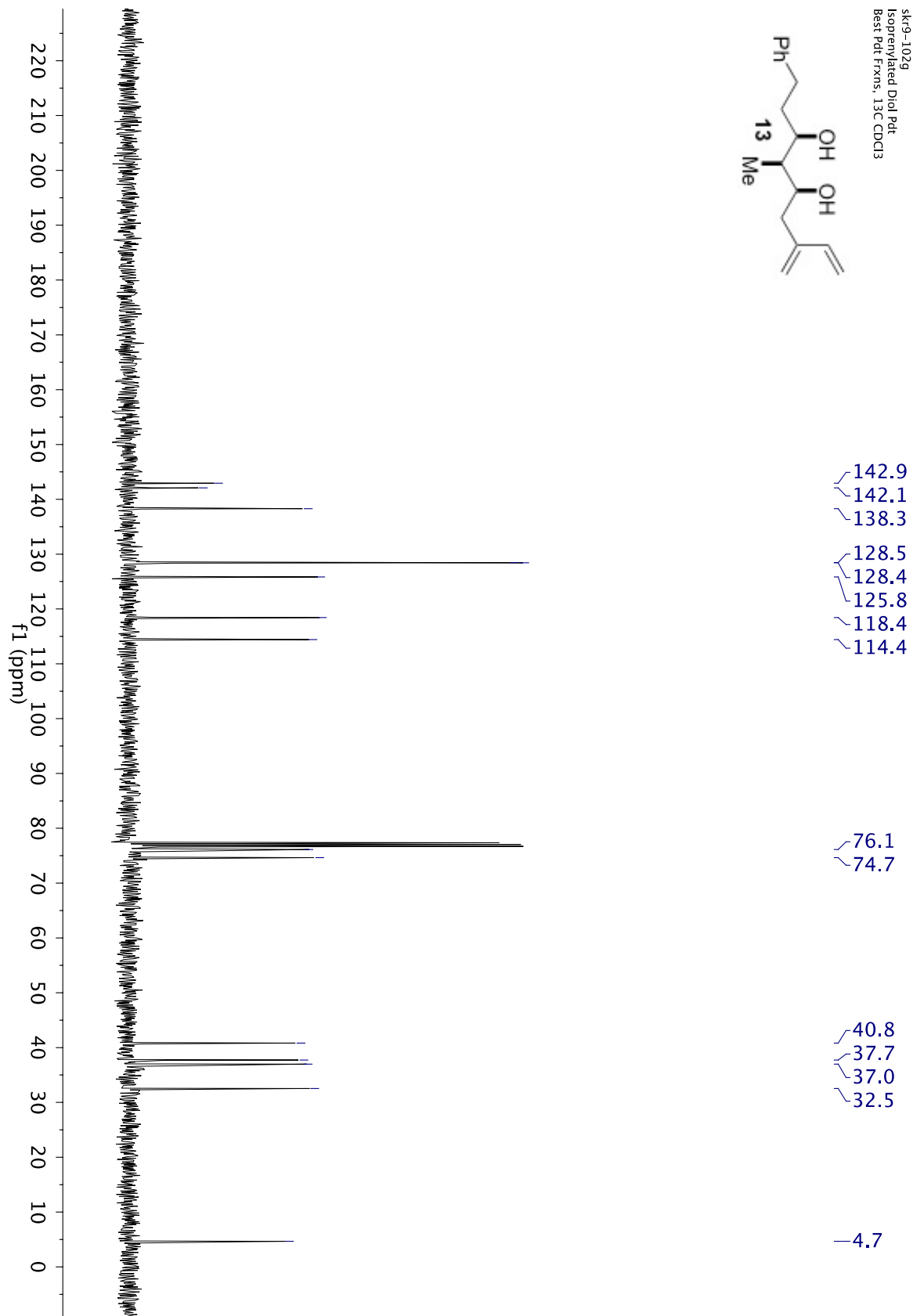


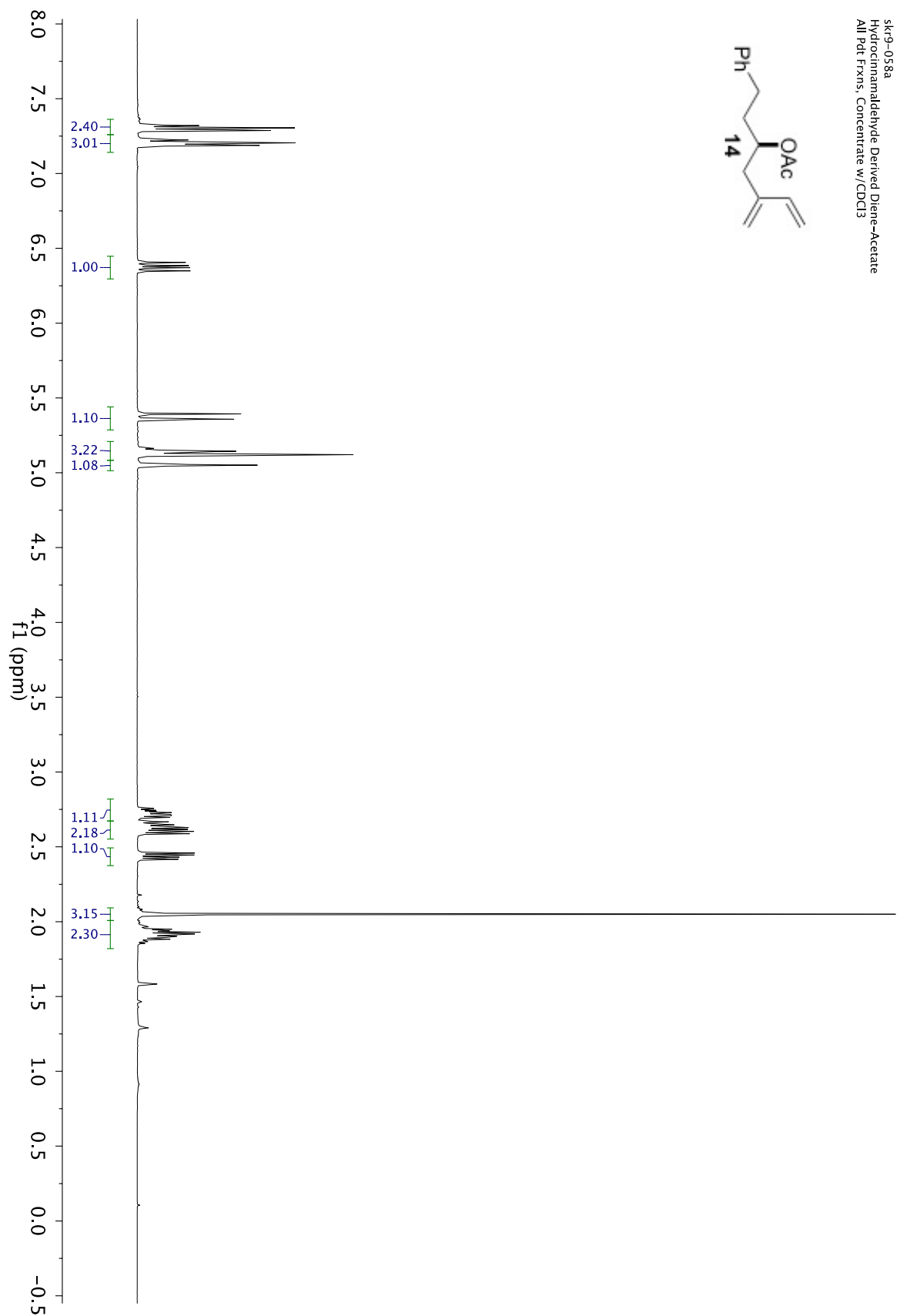
[illegible]

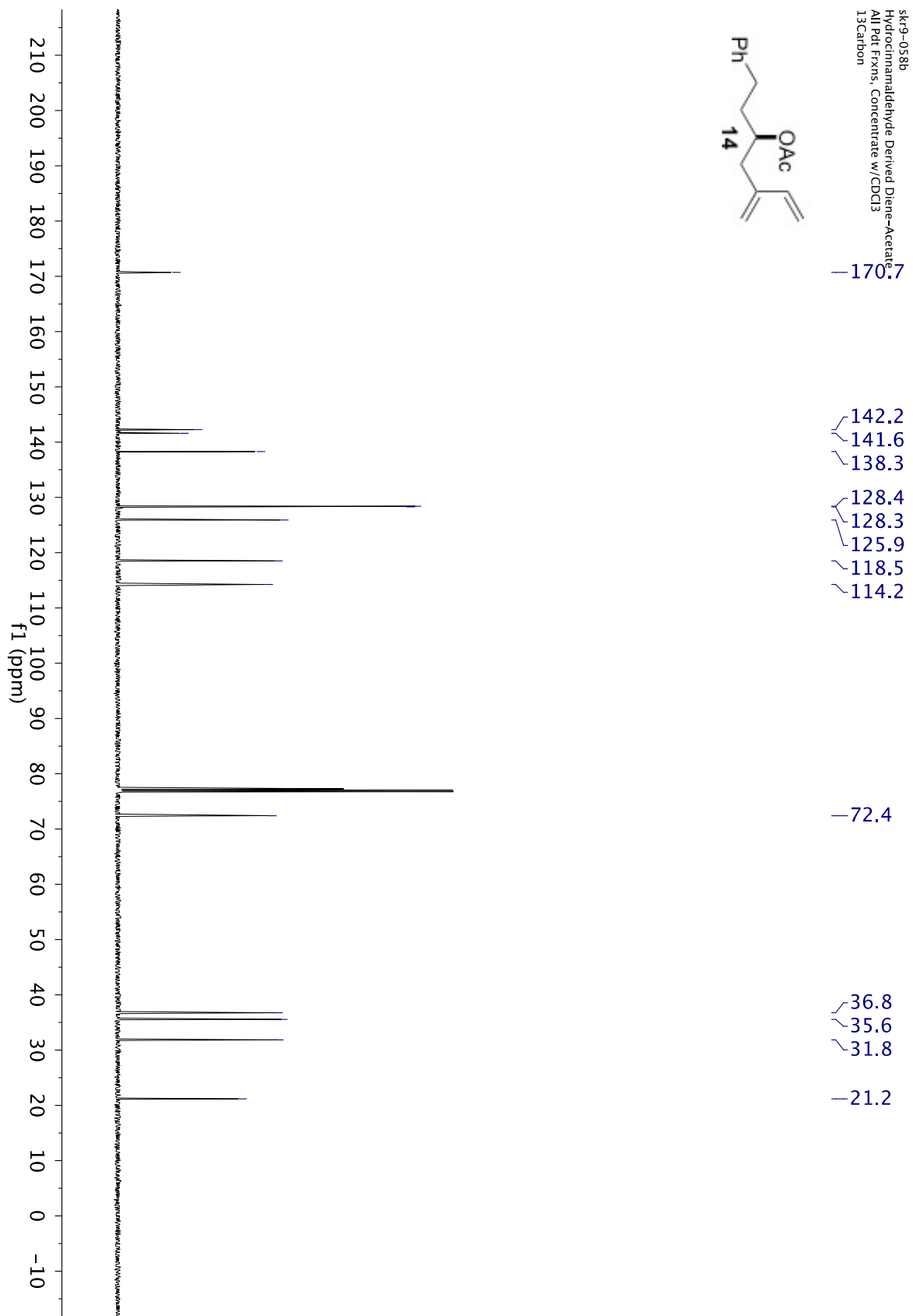


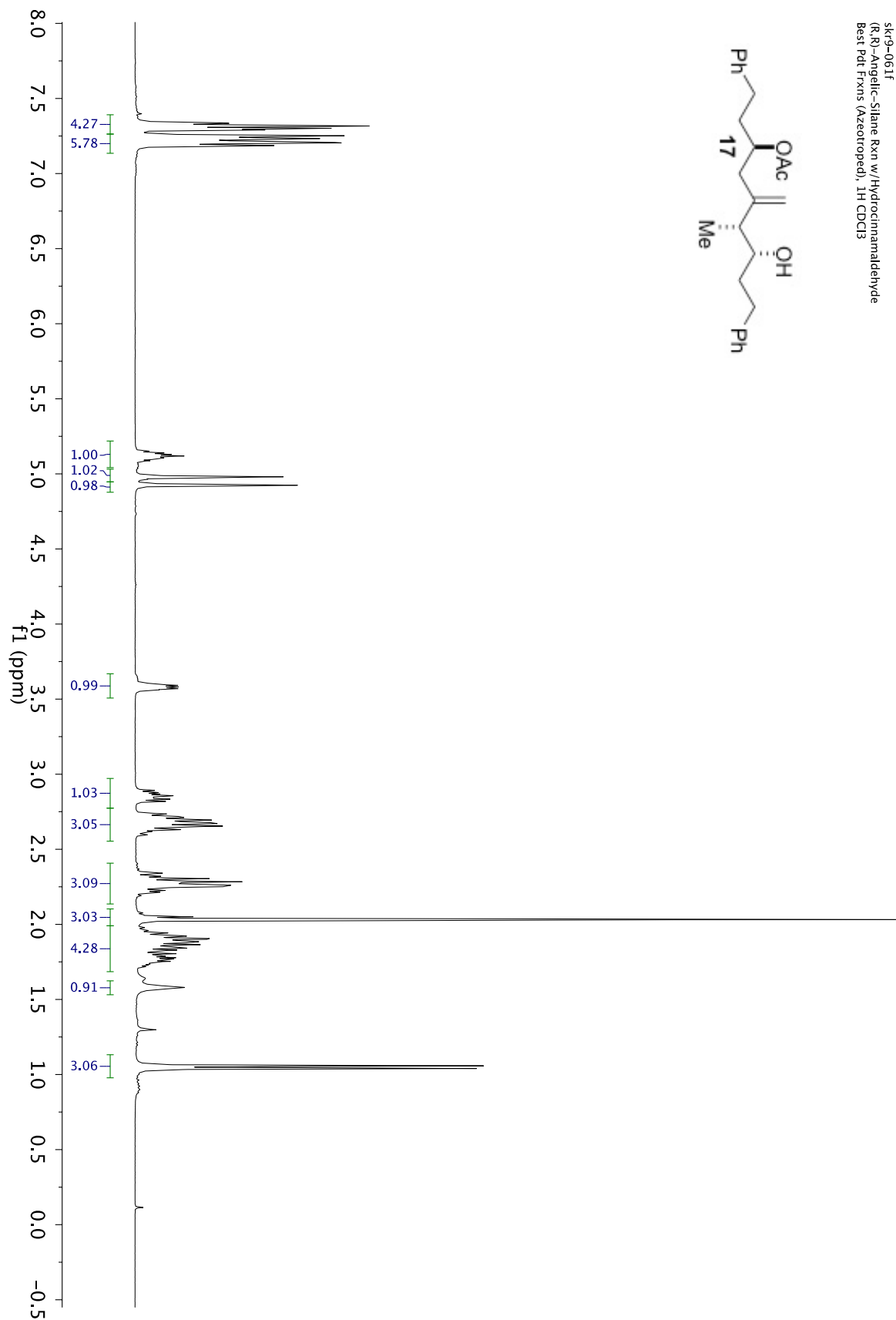


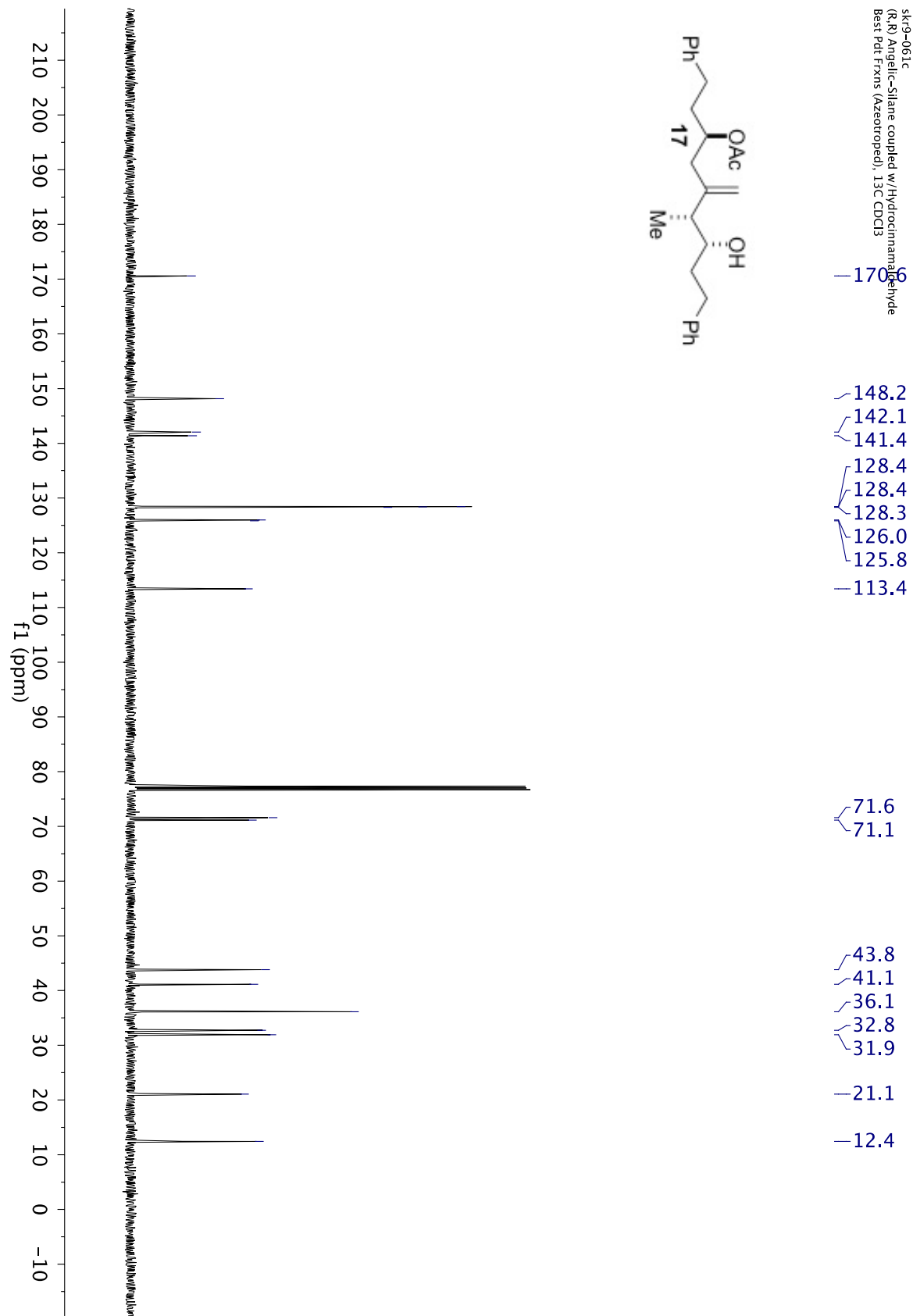


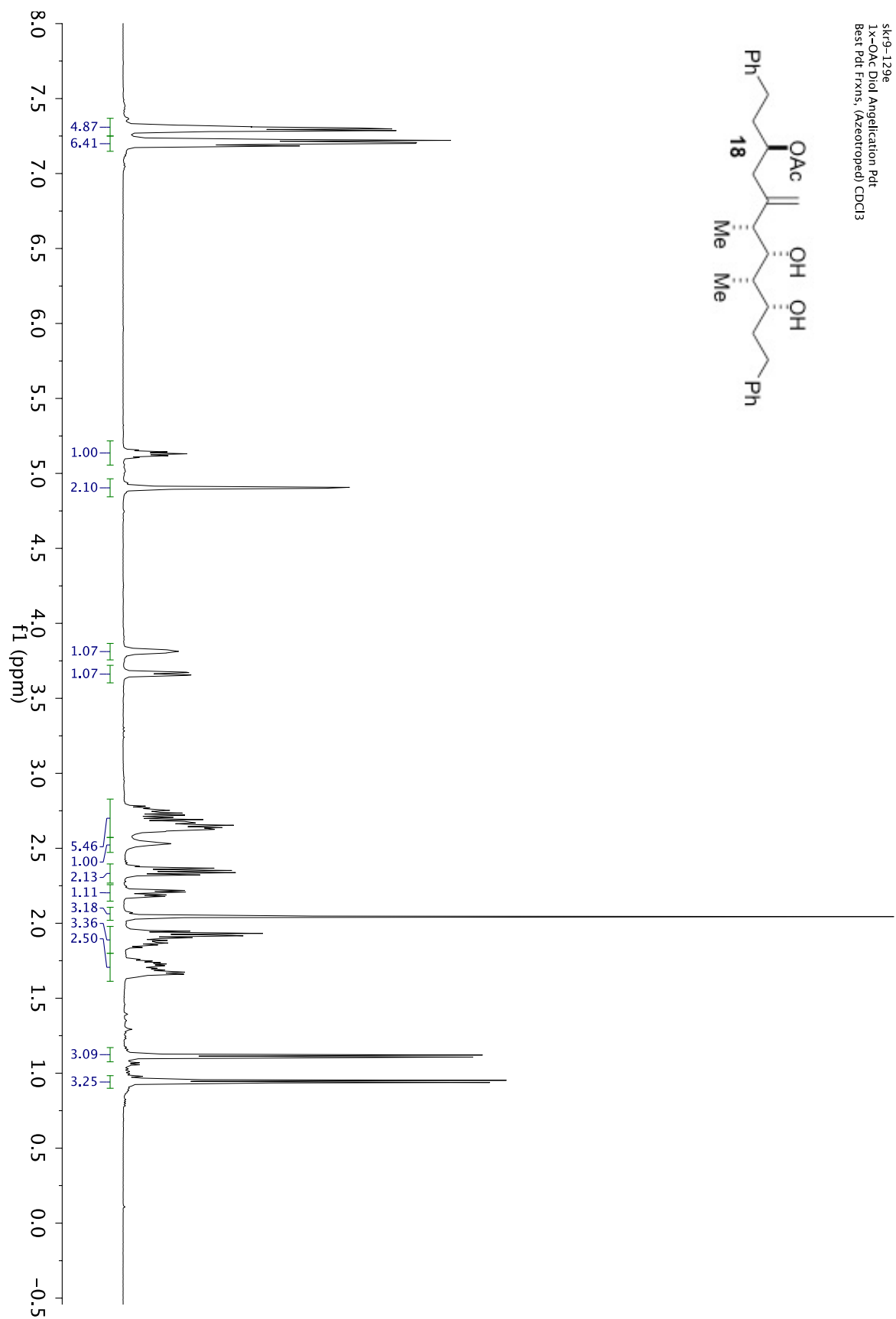


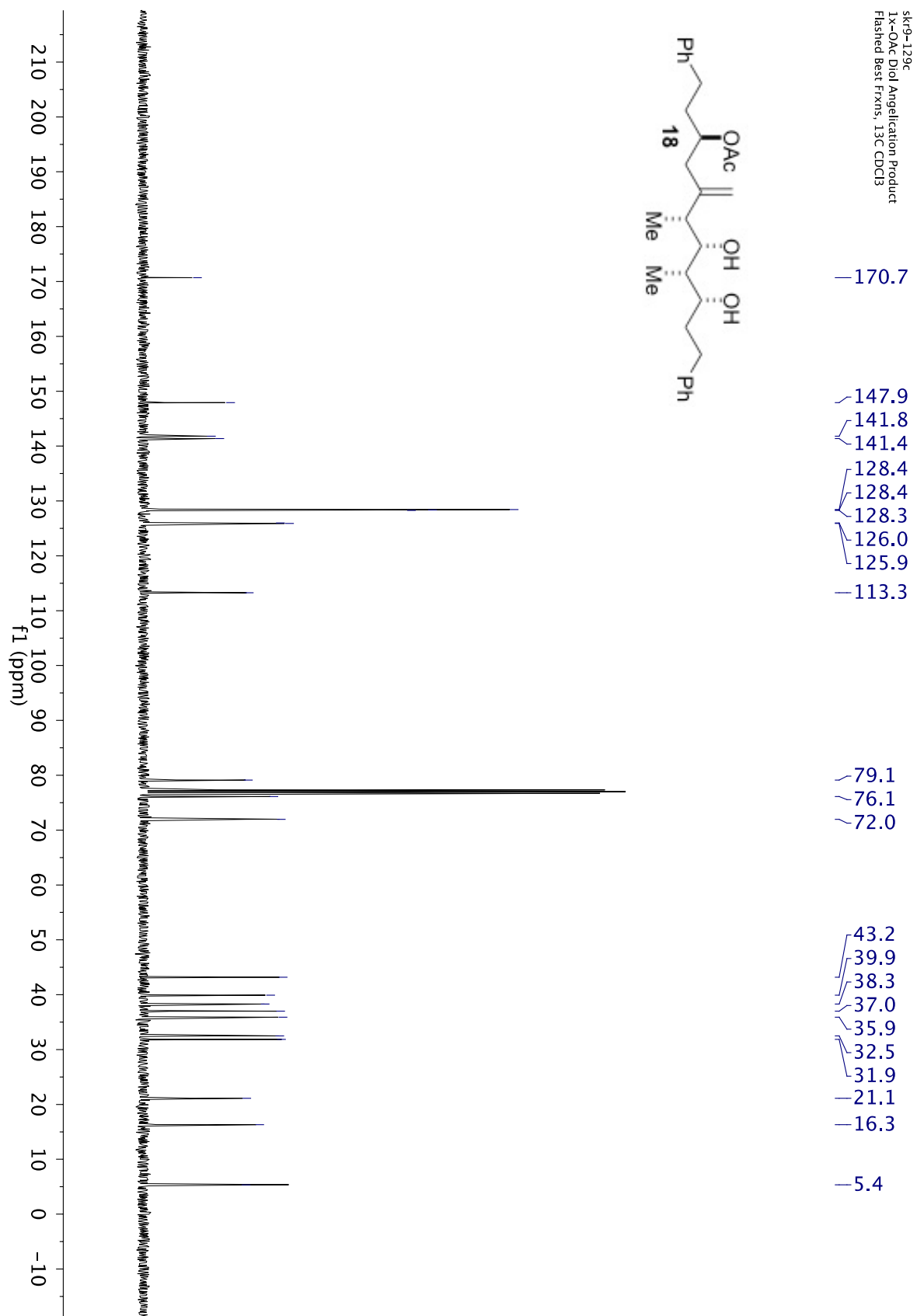




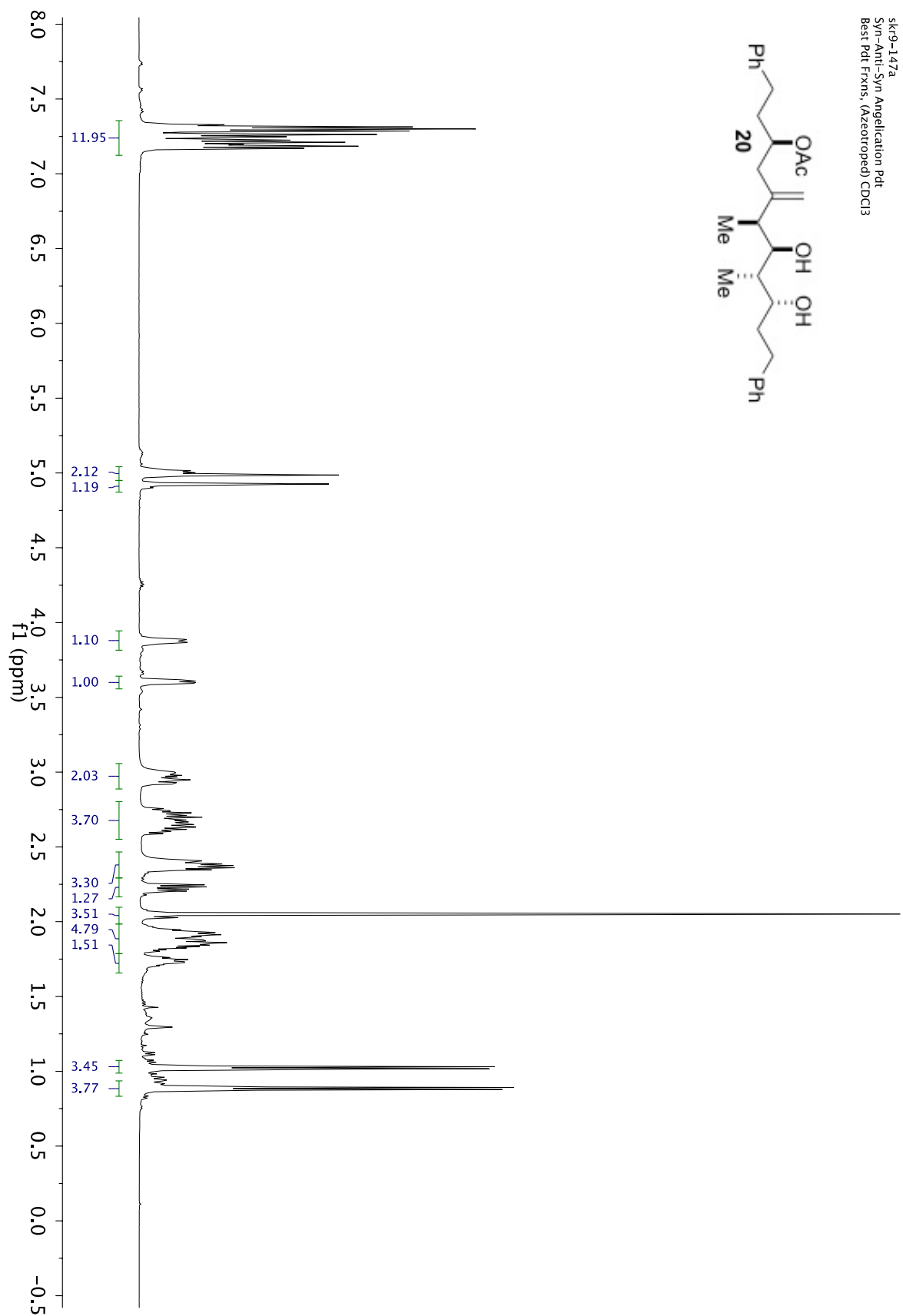


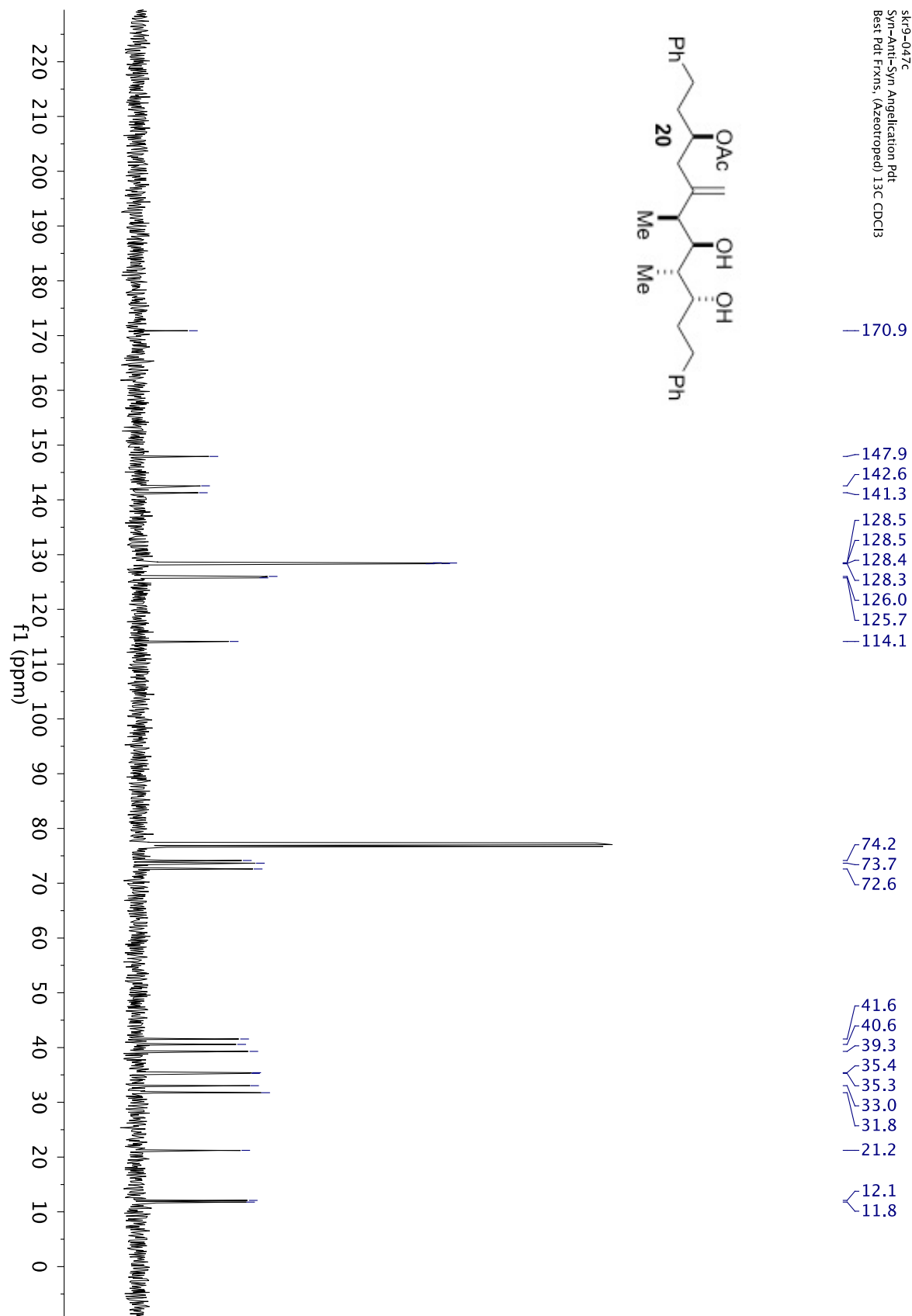


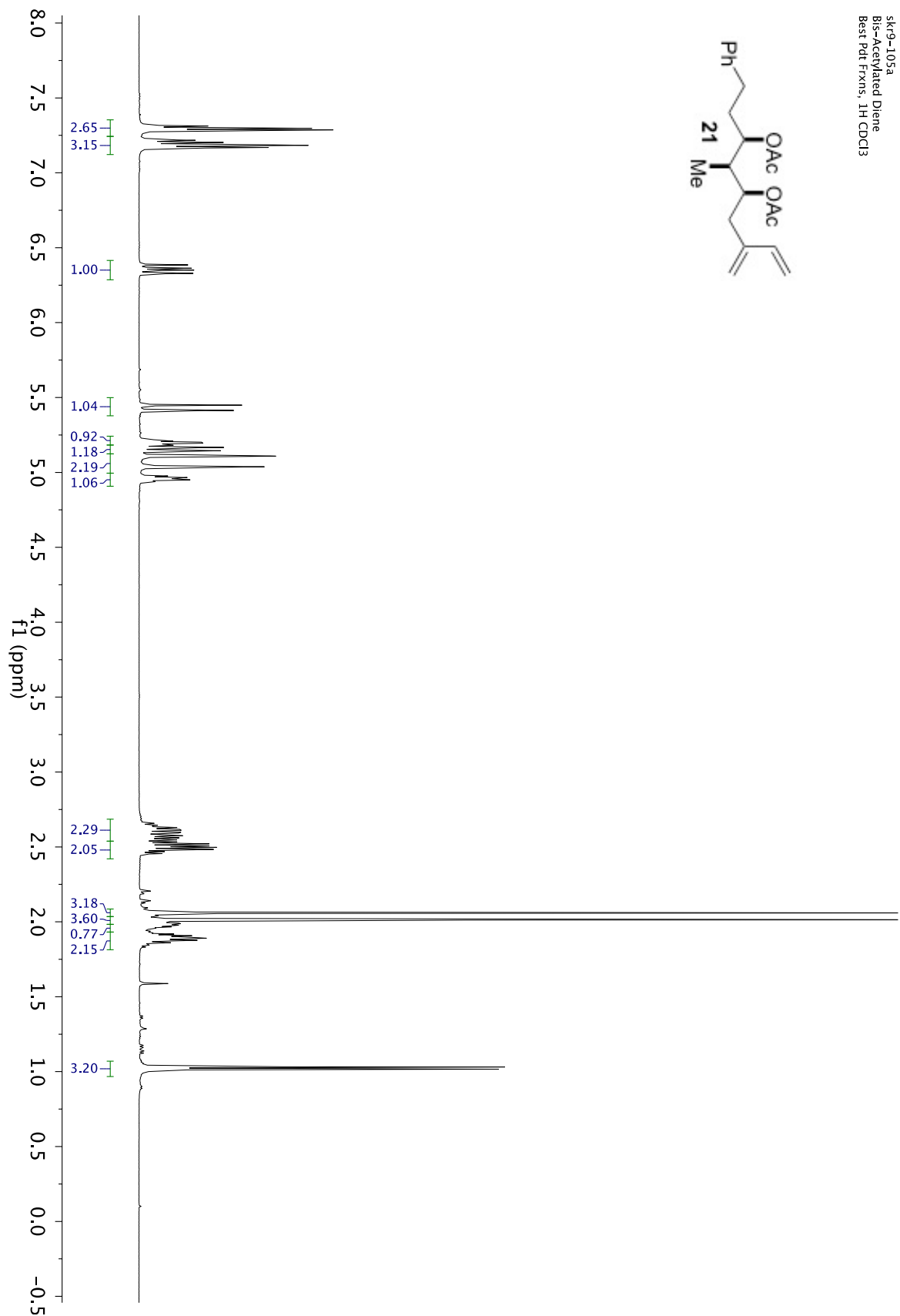


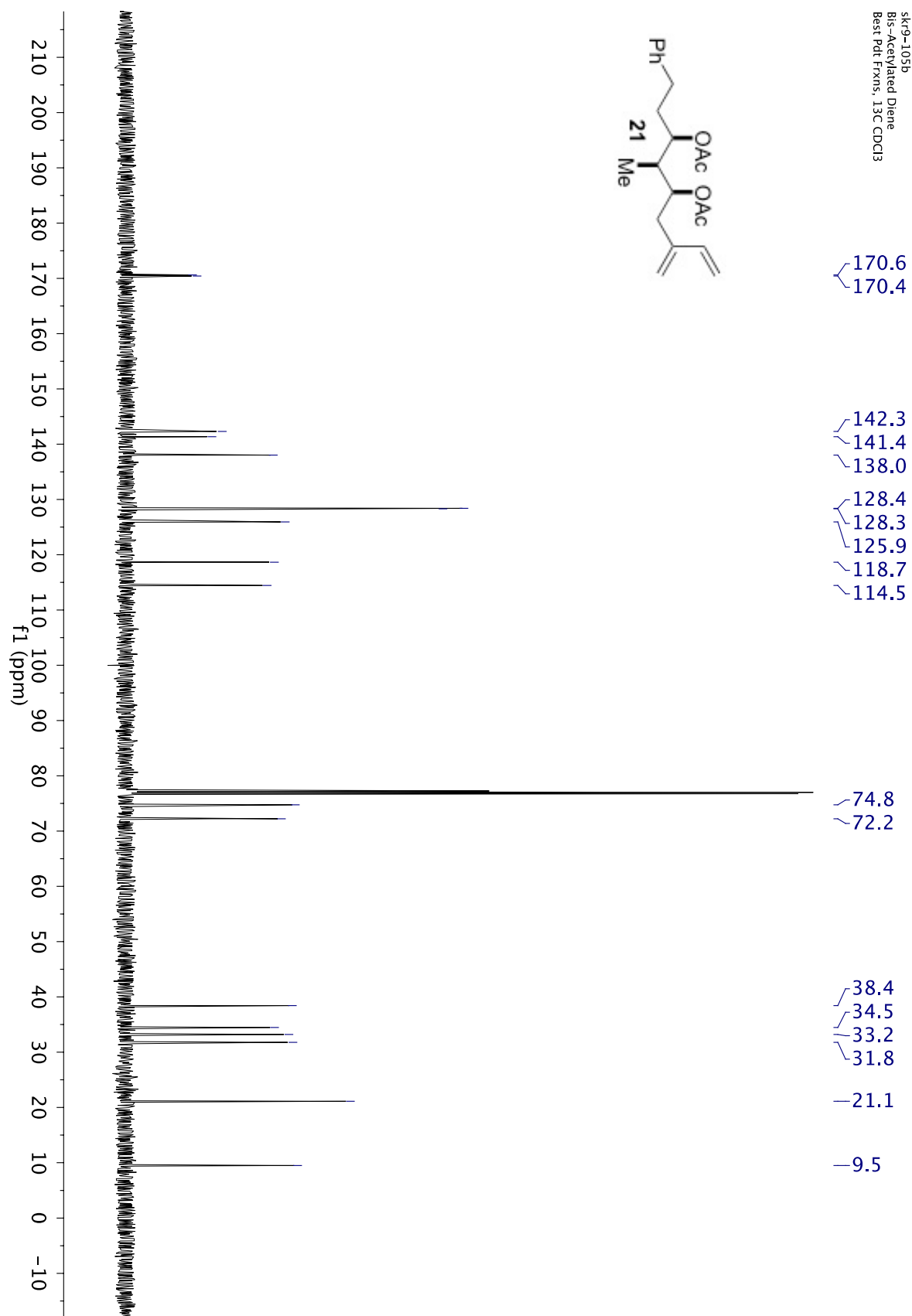




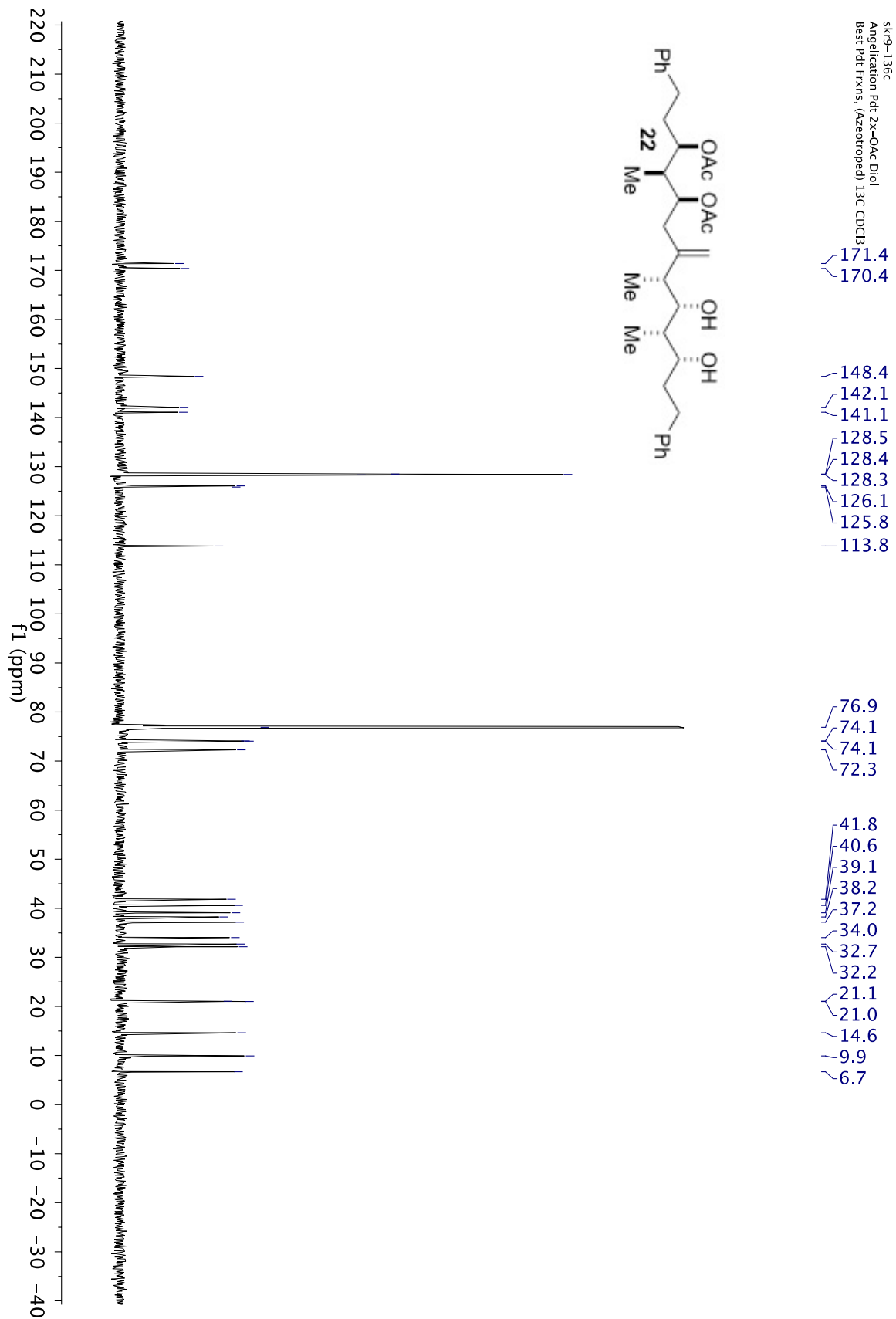


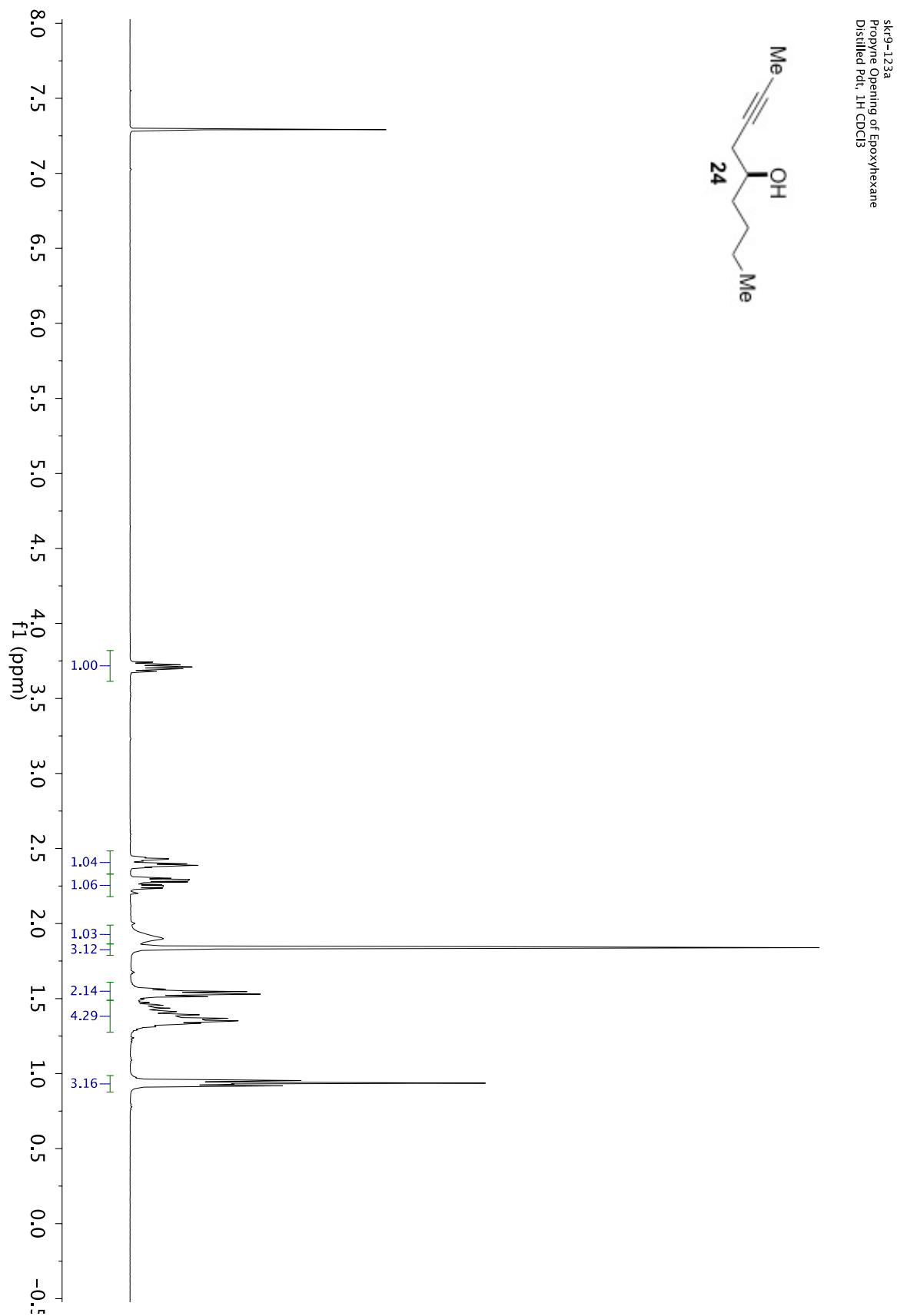


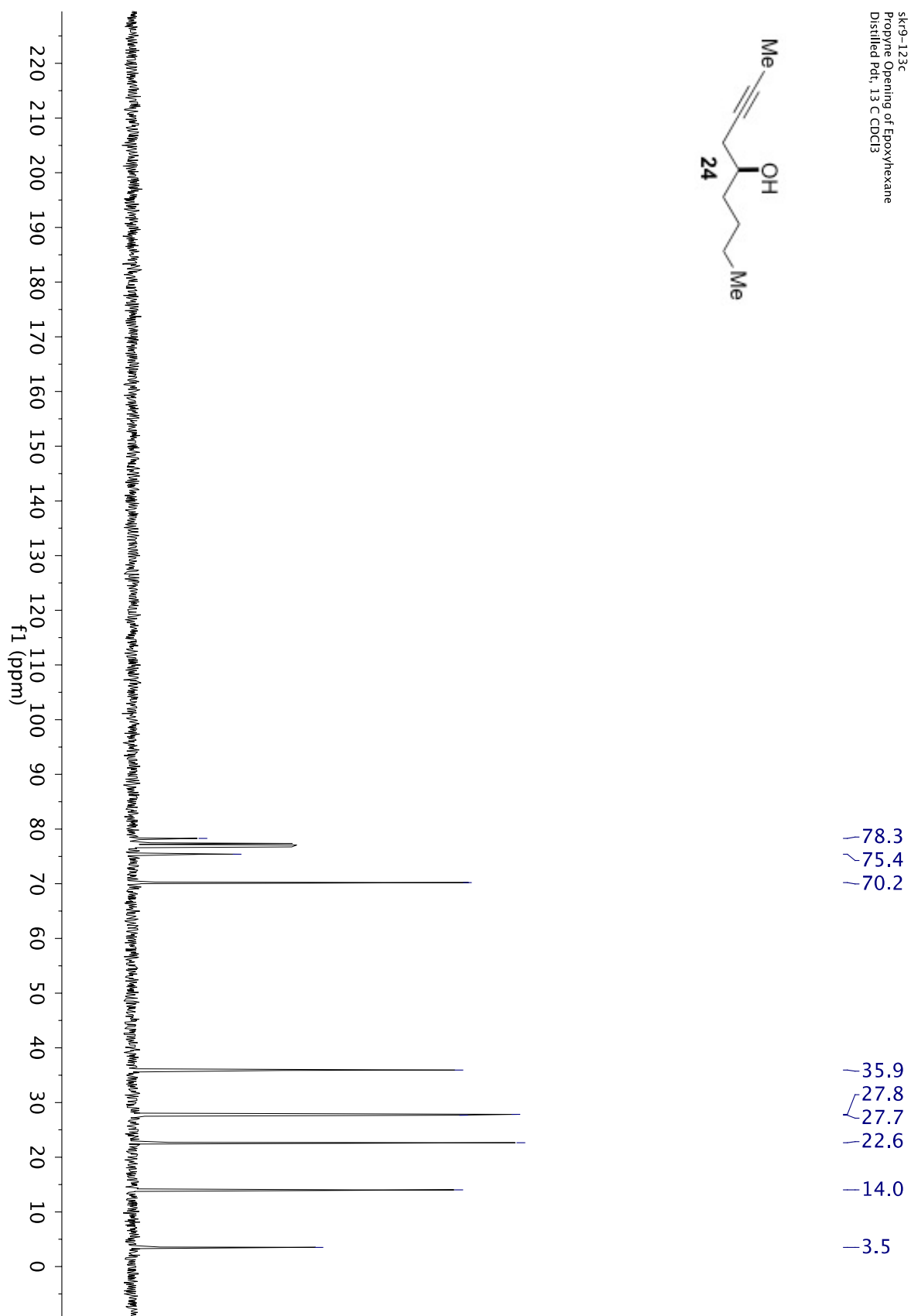




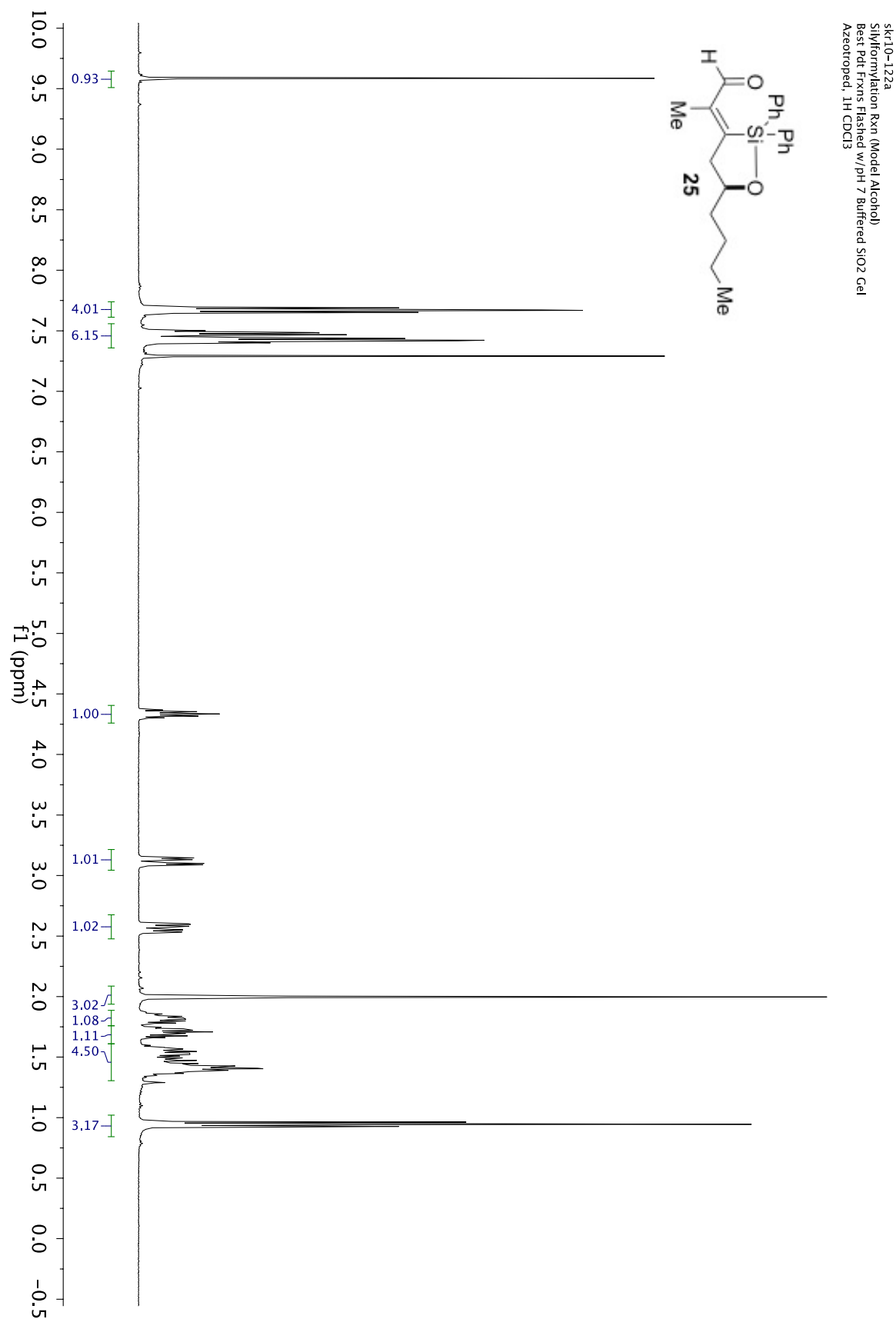


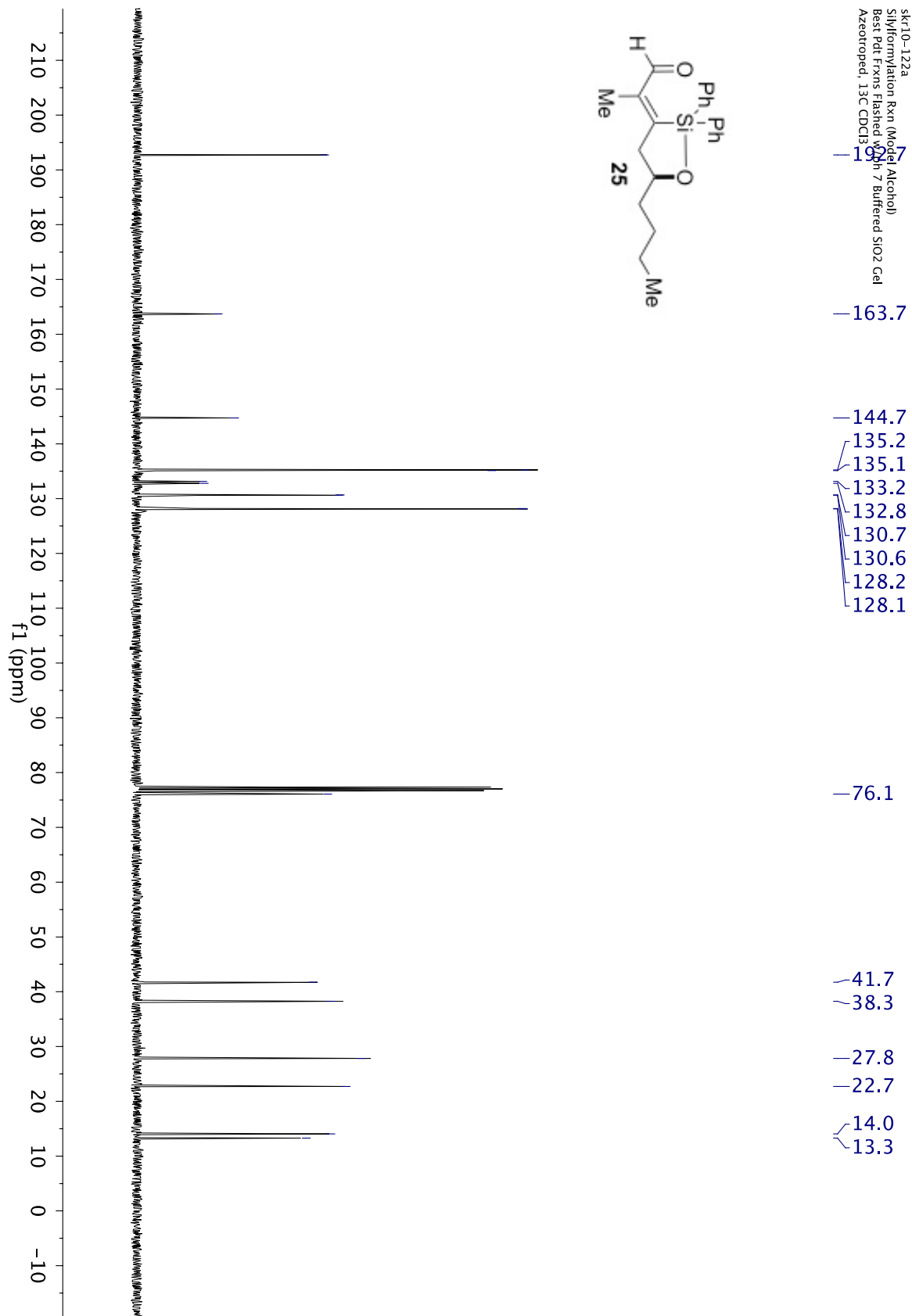




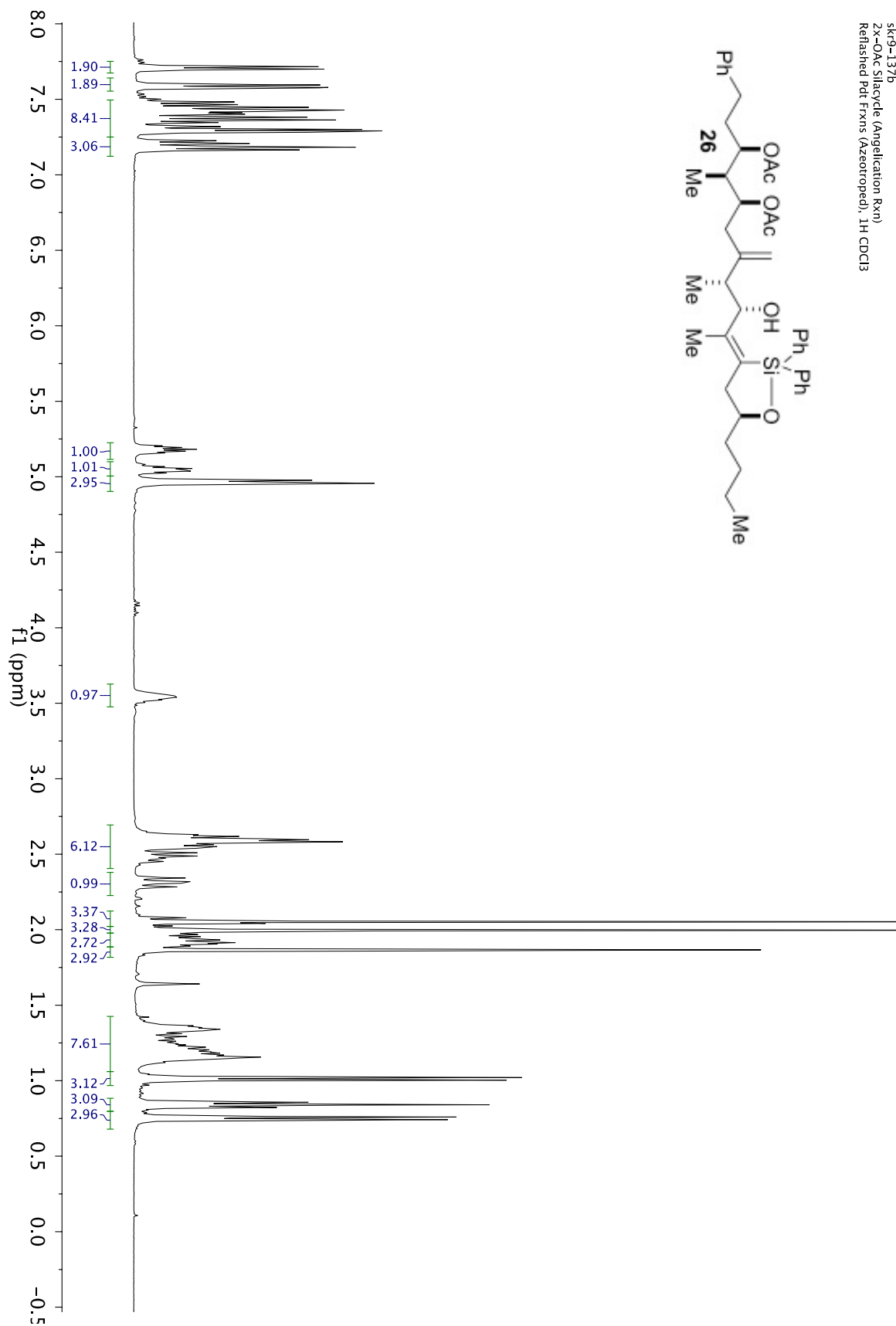
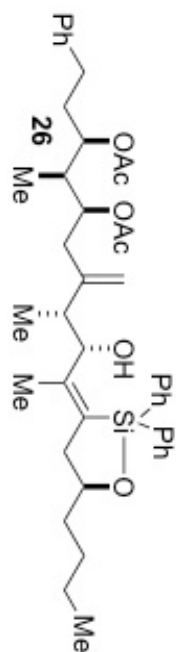




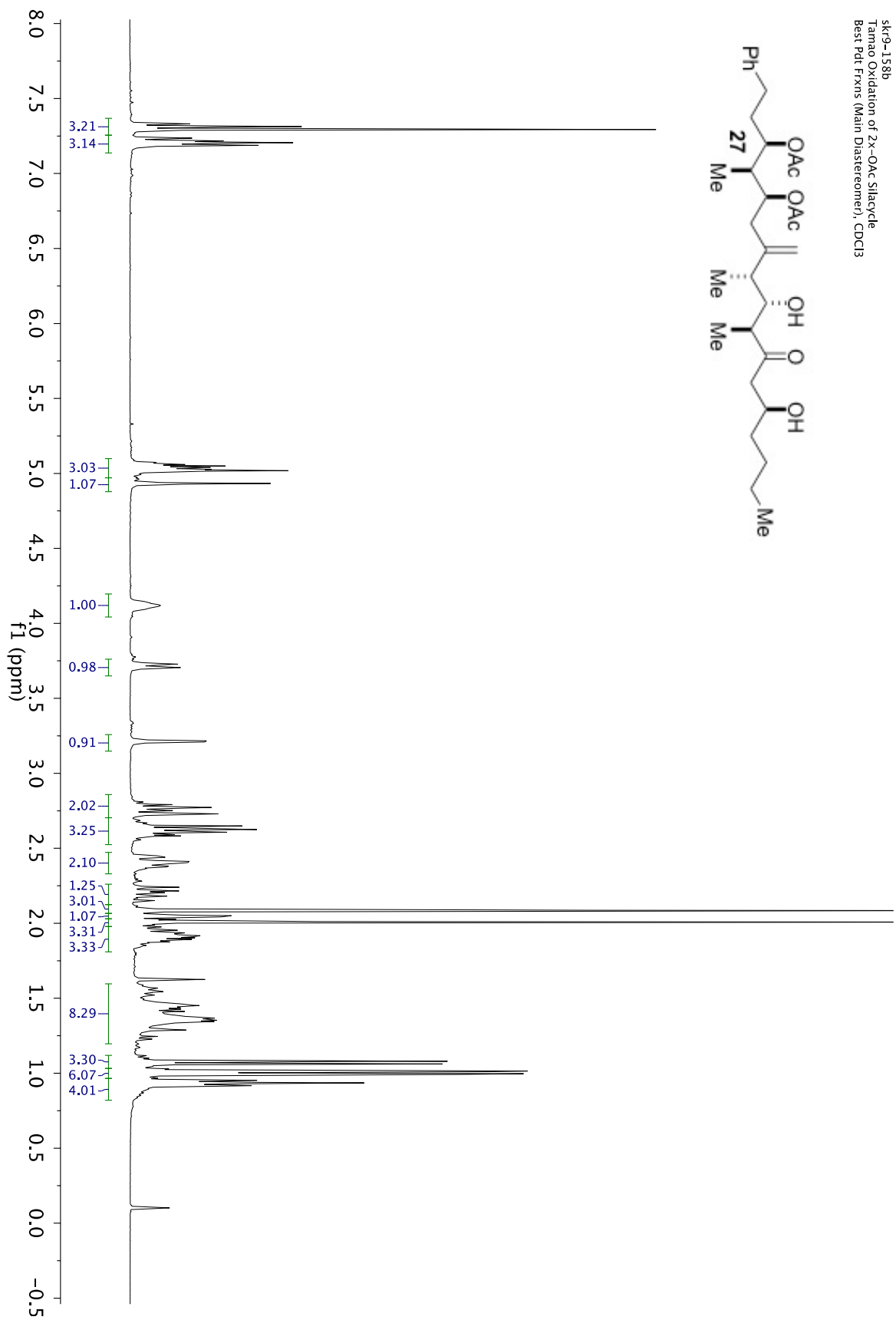


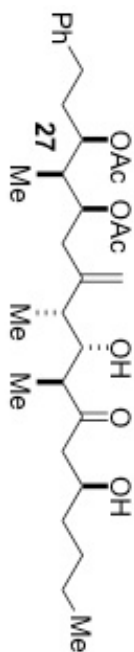
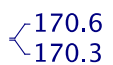


skr9-137b  
 2x-OAc Silacycle (Angelcation Rxn)  
 Refreshed Pdt. Frxns (Azeotroped), <sup>1</sup>H CDCl<sub>3</sub>









—147.7

—141.1

✓128.4

128.3  
126.0

—114.6

73.9

73.0

71.9

67.5

## 50.1

48.4

-40.5

39.9

38.9

36.1

33.7

32.1

27.7

22.6

21.0

20.9  
14.0

14.0  
12.113.1  
11.011.0  
10.1

