Supporting Information to Accompany:

Substitution on the A Ring Confers to Bryopyran Analogues the Unique Biological Activity Characteristic of Bryostatins and Distinct From That of the Phorbol Esters

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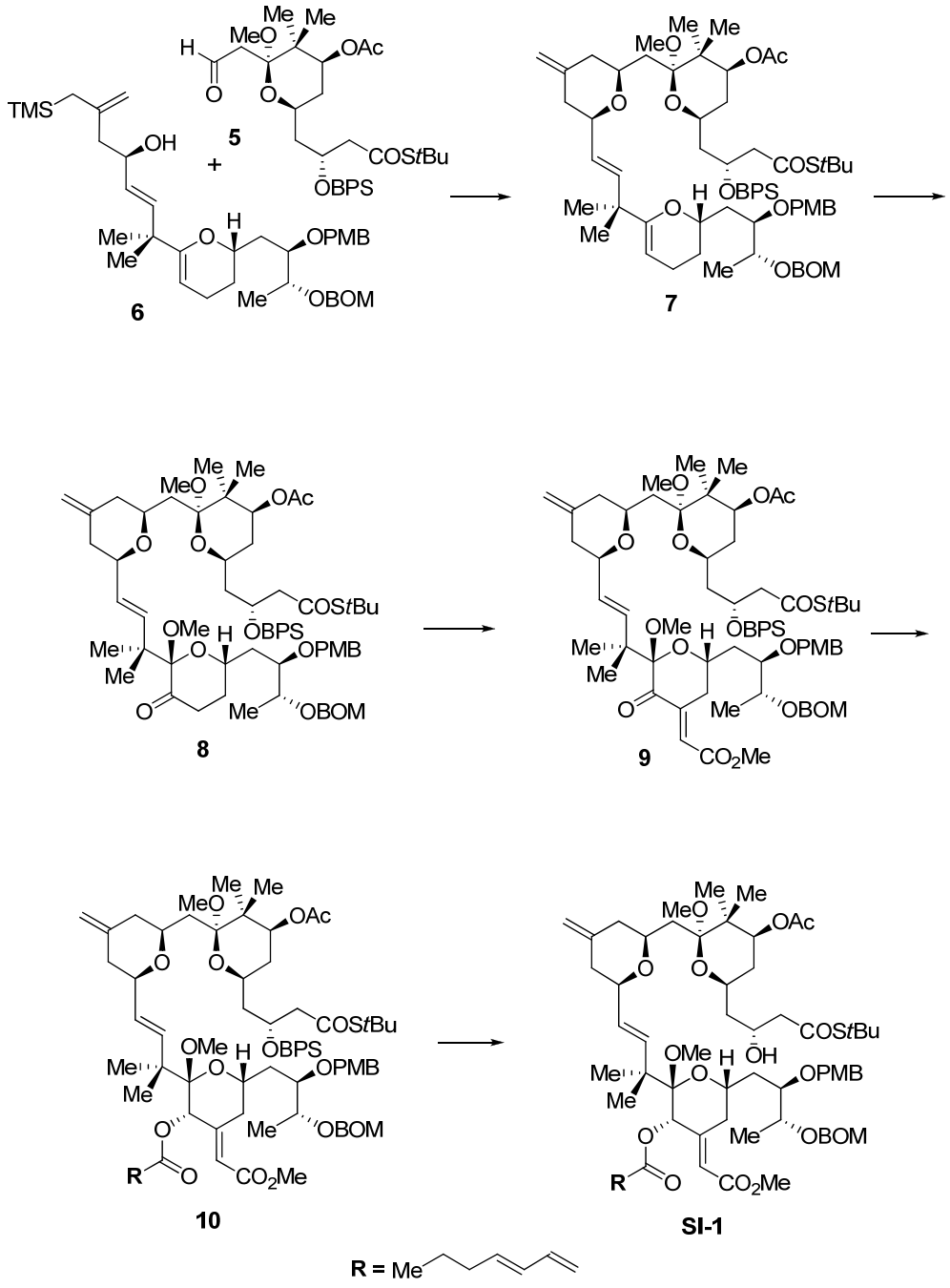
General Experimental Procedures:

Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[1] Diisopropylamine, diisopropylethylamine, pyridine, triethylamine, EtOAc, MeOH, and CH_2Cl_2 were distilled from CaH_2. The titer of *n*-BuLi was determined by the method of Eastham and Watson.[2] All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F_{254} plates or Silicycle 60Å F_{254} eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid. Flash column chromatography was performed with Silicycle Flash Silica Gel 40 – 63 μm or Silicycle Flash Silica Gel 60 – 200 μm, slurry packed with 1% EtOAc/hexanes in glass columns. Preparative thin layer chromatography was performed on Silicycle 60Å F_{254} 20 cm × 20 cm × 250 μm plates. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic resonance spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal residual C_6D_6 at 7.16 ppm or $CDCl_3$ at 7.27 ppm . Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the C_6D_6 triplet at 128.39 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, dd, ddd, t, and m stand for the

resonance multiplicity singlet, doublet, doublet of doublets, doublet of doublet of doublets, triplet and multiplet respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ($[\alpha]_D^{20}$, Unit: °cm^2/g) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unit-less numbers where the concentration c is in g/l00 mL and the path length l is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer or at the mass spectrometry facility of the Department of Chemistry at the University of California, Riverside on an LCTOF mass spectrometer. Compounds were named using AutoNom 2000 for the MDL ISIS^{Tm}/Draw 2.5, or using ChemDraw 11.0.1.

Compounds and Numbering in Supporting Information:



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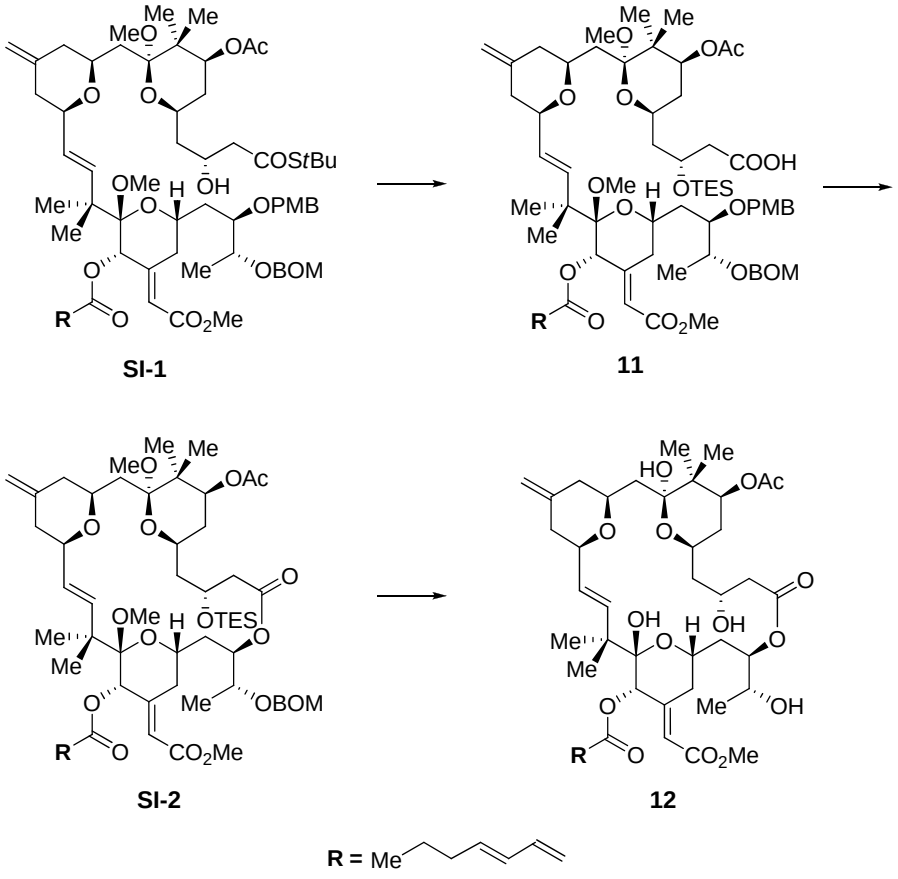
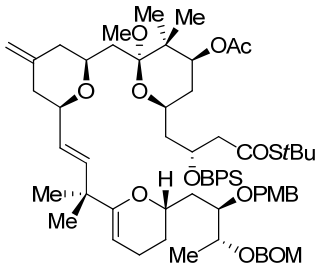
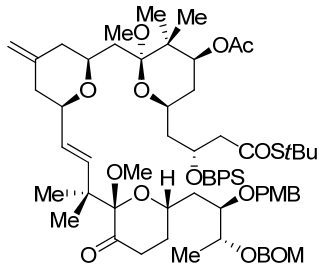


Synthetic Experimental Procedures and Analytical Data:



(2S,4S,6S)-2-(((2S,6R)-6-((E)-3-((S)-2-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-3,4-dihydro-2H-pyran-6-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-6-((R)-2-(tert-butyldiphenylsilyloxy)-4-(tert-butylthio)-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2H-pyran-4-yl acetate (7): To a stirring solution of aldehyde[3] **5** (101 mg, 0.154 mmol, 1.0 equiv) and hydroxyallylsilane[4] **6** (108 mg, 0.169 mmol, 1.1 equiv) in Et_2O (2.2 mL) in a flame dried 25 mL rb flask at -78 ºC was added a solution of TMSOTf in Et_2O (200 μL, 0.926 M, 0.184 mmol, 1.2 equiv). After 1.5 h at -78 ºC, the reaction was quenched by addition of diisopropylethylamine (0.2 mL), followed by addition of saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was warmed to rt, the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 15 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash column chromatography on a 1 x 17 cm silica gel column, eluting with hexanes/EtOAc (9:1), collecting 4 mL fractions. The product containing fractions (20-55) were combined and concentrated under reduced pressure to provide the pyran **7** (107 mg, 58%) as a white foam. The column also furnished a mixture of aldehyde **5** and TMS protected silane **6** which were separately purified

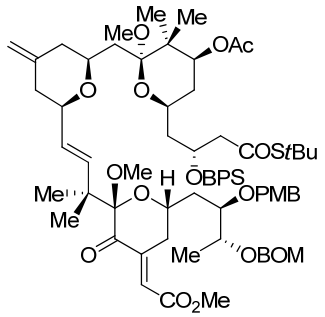
using Hexanes/ EtOAc (95:5) to give 35 mg (35%) of aldehyde **5** and 32 mg (27%) of TMS protected silane **6**. R_f = 0.56 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +18.8 (*c* = 0.65, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.83-7.80 (m, 4H), 7.38-7.09 (m, 13H), 6.82-6.79 (m, 2H), 6.08 (dd, *J* = 15.6, 0.9 Hz, 1H), 5.71 (dd, *J* = 16.1, 5.3 Hz, 1H), 5.35 (dd, *J* = 11.7 Hz, 4.8, 1H), 4.88 (s, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 4.3 Hz, 1H), 4.71-4.66 (m, 3H), 4.64-4.63 (m, 4H), 4.57-4.54 (m, 1H), 4.20-4.16 (m, 1H), 4.08-4.06 (m, 2H), 3.88-3.85 (m, 1H), 3.65-3.63 (m, 1H), 3.30 (s, 3H), 2.93 (s, 3H), 2.91-2.89 (m, 2H), 2.33-2.24 (m, 2H), 2.19-2.15 (m, 1H), 2.11 (t, *J* = 12.4 Hz, 1H), 2.01-1.94 (m, 2H), 1.91-1.76 (m, 4H), 1.72 (d, *J* = 3.9 Hz, 1H), 1.69-1.66 (m, 1H), 1.64 (s, 3H), 1.60-1.52 (m, 4H), 1.43 (s, 9H), 1.34 (s, 3H), 1.33 (s, 3H), 1.23 (d, *J* = 6.3Hz, 3H), 1.19 (s, 9H), 1.07(s, 3H), 1.03 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 198.1, 169.8, 160.0, 159.6, 145.5, 139.2, 138.9, 136.7, 136.6, 135.0, 134.2, 132.0, 130.5, 130.4, 129.9, 128.9, 128.6, 128.4, 128.4, 128.3, 128.0, 114.4, 109.1, 104.7, 94.0, 93.8, 79.1, 78.2, 75.3, 73.9, 73.8, 73.7, 72.5, 70.3, 69.7, 66.9, 55.1, 54.0, 48.5, 48.3, 44.4, 42.9, 42.6, 41.4, 41.2, 39.9, 36.5, 35.5, 30.2, 28.9, 27.6, 26.6, 26.4, 21.2, 21.1, 21.0, 20.0, 17.2, 15.6; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 55.1, 48.5, 30.2, 27.6, 26.6, 26.4, 21.1 (x2), 17.2, 15.6 ; CH_2 δ 109.1, 93.8, 73.6, 69.7, 54.0, 44.4, 42.9, 41.7, 39.9, 36.5, 33.5, 28.9, 21.1; CH δ 138.9, 136.7, 136.6, 130.5 (x2), 129.9, 128.9, 128.4, 128.4, 128.3, 128.0, 114.4, 94.0, 79.1, 78.2, 75.2, 73.8, 72.4, 70.3, 66.9; CH_0 δ 198.0, 169.8, 160.0, 159.6, 145.5, 139.2, 135.0, 134.2, 132.0, 130.4, 104.7, 73.9, 48.3, 42.6; IR (neat) 2959, 2361, 1739, 1681, 1513, 1458, 1365, 1247, 1039, 822, 740, 703 cm^{-1}; HRMS (ESI/APCI) calcd for $C_{71}H_{98}NaO_{12}SSi$ (M+Na): 1225.6446, found: 1225.6462.



(2S,4S,6S)-2-(((2S,6R)-6-((E)-3-((2S,6S)-6-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-methoxy-3-oxotetrahydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-6-((R)-2-(tert-butyldiphenylsilyloxy)-4-(tert-butylthio)-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2H-pyran-4-yl acetate (8): To a stirring solution of dihydropyran **7** (130 mg, 0.108 mmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL) at 0 °C, was added MeOH (0.54 mL). Powdered $NaHCO_3$ (13.6 mg, 0.162 mmol, 1.5 equiv) was added in one portion and the solution was stirred at 0 °C for 10 min. Magnesium monoperoxyphthalate (80 %, 80 mg, 0.129 mmol, 1.2 equiv) was added slowly and the mixture was stirred for 30 min at 0°C. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL), then diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated and taken to the next step without further purification.

To a solution of the previously described crude intermediate alcohol in CH_2Cl_2 (2.2 mL), at rt, were added 4 Å molecular sieves (300 mg), TPAP (3.8 mg, 0.01 mmol, 0.1 equiv), and 4-methylmorpholine-N-oxide (38 mg, 0.324 mmol, 3.0 equiv). The mixture was stirred at rt for 30 min and then diluted with EtOAc (20 mL). The mixture was then filtered through a small plug of Florisil® and washed with copious amounts of EtOAc. The solvent was removed under reduced pressure and purification was accomplished with flash column chromatography, using a 25 x 120 mm silica gel column, eluting with 15% EtOAc/hexanes, collecting 4 mL fractions. The product

containing fractions from 24 to 75 were combined and concentrated under reduced pressure to provide pure methoxy ketone **8** (78 mg, 58% over 2 steps) as a white foam.: R_f = 0.62 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +22 (*c* = 1.0, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.81-7.78 (m, 4H), 7.38-7.09 (m, 13H), 6.79-6.77 (m, 2H), 6.30 (d, *J* = 16.1 Hz, 1H), 5.57 (dd, *J* = 4.8, 16.1 Hz, 1H), 5.32 (dd, *J* = 4.3, 11.2 Hz, 1H), 4.85 (s, 1H), 4.78-4.73 (m, 3H), 4.66-4.54 (m, 7H), 4.44-4.41 (m, 1H), 4.15-4.08 (m, 2H), 4.05-4.02 (m, 1H), 3.76-3.73 (m, 1H), 3.59-3.58 (m, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.93 (s, 3H), 2.90-2.89 (m, 2H), 2.72-2.08 (m, 5H), 1.99 (ddd, *J* = 17.1, 12.4, 12.4, Hz, 2H), 1.86-1.73 (m, 4H), 1.65 (s, 3H), 1.62-1.52 (m, 3H), 1.42 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.17 (s, 9H), 1.04 (s, 3H), 1.02 (s, 3H); 125 MHz ^{13}C NMR (C_6D_6) δ 205.6, 198.1, 169.8, 160.0, 145.3, 139.0, 137.0, 136.7, 136.5, 135.0, 134.2, 131.7, 130.5, 130.4, 129.8, 129.7, 128.9, 128.4 (x2), 128.3, 128.1,128.1, 114.4, 109.1, 104.7, 104.6, 93.8, 78.8, 77.8, 75.1, 73.8, 72.9, 72.5, 70.4, 69.8, 66.9, 55.1, 54.0, 52.8, 48.5, 48.3, 44.8, 44.3, 42.9, 42.6, 41.6, 39.8, 38.1, 36.7, 33.5, 31.1, 30.2, 27.6, 23.6, 23.0, 21.2, 21.1, 20.0, 17.3, 15.0; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.1, 52.8, 48.5, 30.2, 27.6, 23.6, 23.0, 21.2, 21.1, 17.3, 15.0 ; CH_2 δ 109.2, 93.8, 72.4, 69.8, 54.0, 44.3, 42.9, 41.5, 39.9, 38.1, 36.7, 33.5, 31.1; CH δ 137.0, 136.7, 136.6, 130.5, 130.4, 129.8, 129.7, 129.0, 128.6, 128.4 (x2), 128.3, 128.1, 114.4, 78.9, 77.8, 75.1, 73.8, 72.9, 70.4, 66.9; CH_0 δ 205.6, 198.1, 169.8, 160.0, 145.3, 139.0, 135.0, 134.2, 131.7, 104.7, 104.6, 48.3, 44.8, 42.6, 20.0; IR (neat) 3453, 2936, 1734, 1618, 1613, 1588, 1513, 1458, 1428, 1366, 1301, 1246, 1110, 1042, 895, 822, 742, 703 cm^{-1}; HRMS (ESI/APCI) calcd for $C_{72}H_{100}NaO_{14}SSi$ (M+Na): 1271.6501, found: 1271.6491.



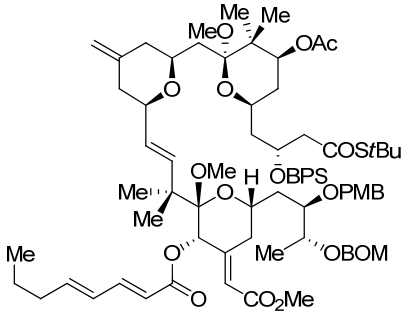
Methyl (E)-methyl 2-((2S,6S)-2-((E)-4-((2R,6S)-6-(((2S,4S,6S)-4-acetoxy-6-((R)-2-(tert-butyldiphenylsilyloxy)-4-(tert-butylthio)-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy)butyl)-2-methoxy-3-oxo-2H-pyran-4(3H,5H,6H)-ylidene)acetate (9): To a stirring solution of $(i\text{Pr})_2\text{NH}$ (0.27 mL, 1.93 mmol) in 6 mL of THF in a 25 mL rb flask at -78 ºC was added *n*-BuLi (2.61 M in hexanes, 0.67 mL, 1.75 mmol) via syringe. The solution stirred at -78 ºC for 30 min and was then allowed to warm to 0 ºC for 20 min. This 0.25 M LDA solution was used immediately in the following aldol reaction.

To a stirring solution of ketone **8** (102 mg, 0.0816 mmol, 1.0 equiv) in THF (2.7 mL, 0.03 M) in a 10 mL rb flask at -78 ºC was added a 0.25 M solution of LDA in THF (0.35 mL, 0.0897 mmol, 1.1 equiv) slowly via syringe down the side of the flask. The resulting light-yellow reaction mixture was allowed to stir at -78 ºC for 12 min and a freshly prepared solution of methyl glyoxylate (ca 3.0 M in THF, 0.54 mL, 1.632 mmol, 20.0 equiv) was added slowly via syringe down the side of the flask upon which the yellow color of the solution disappeared. The reaction mixture stirred at -78 ºC for 40 min and was quenched by addition of 2 mL of saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was then partitioned between 10 mL of EtOAc and 10 mL of brine. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished using flash

column chromatography with a 2 x 8 cm silica gel column, eluting with 20% EtOAc/hexanes (100 mL) then 40% EtOAc/hexanes (100 mL), collecting 4 mL fractions. Fractions 6-20 gave unreacted starting material which were combined and concentrated to provide 48 mg of the starting ketone **8** (47%). The product containing fractions (22-37) were combined and concentrated under reduced pressure to provide the intermediate aldol adduct as a mixture of diastereomers (53.3 mg, 49%). This material was taken into the following elimination reaction.

To a stirring solution of the aforementioned aldol adduct (31.2 mg, 0.0233 mmol, 1.0 equiv) in CH_2Cl_2 (2.3 mL, 0.01 M) in a 5 mL reaction vial at rt was added diisopropylethylamine (23 μL, 0.1631 mmol, 7.0 equiv), DMAP (2.8 mg, 0.0233 mmol, 1.0 equiv), and carbonyldiimidazole (19 mg, 0.1165 mmol, 5.0 equiv). The reaction mixture was allowed to stir at rt for 24 h and was then quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was partitioned between EtOAc (10 mL) and brine (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 1 x 10 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 4 ml fractions. The product containing fractions (27-54) were combined and concentrated under reduced pressure to provide pure enoate **9** (25.3 mg, 82% over 2 steps) as a clear light-yellow oil: R_f = 0.48 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -8.6 (*c* = 0.53, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.84-7.81 (m, 4H), 7.40-7.39 (m, 2H), 7.26-7.11 (m, 11H), 6.79-6.78 (m, 1H), 6.76-6.74 (m, 2H), 6.10 (d, *J* = 16.1 Hz, 1H), 5.50 (dd, *J* = 16.5, 5.3 Hz, 1H), 5.36 (dd, *J* = 11.7, 4.8 Hz, 1H), 4.92-4.80 (m, 3H), 4.74 (dd, *J* = 10.7, 6.8 Hz, 2H), 4.67-4.57 (m, 5H), 4.52 (d, *J* =11.2 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.18-4.02 (m, 4H), 3.76-3.75 (m, 1H), 3.64-3.61 (m, 1H), 3.36 (s, 3H), 3.28 (s, 3H), 3.24 (s, 3H), 2.95 (s, 3H), 2.93-2.92

(m, 2H), 2.31-2.29 (m, 1H), 2.16-1.79 (m, 5H), 1.89-1.78 (m, 3H), 1.66 (s, 3H), 1.61-1.57 (m, 2H), 1.45 (s, 9H), 1.33 (s, 3H), 1.28 (s, 3H), 1.19 (s, 12H), 1.10 (s, 3H), 1.07 (s, 3H); 125 MHz ^{13}C NMR (C_6D_6) δ 198.1, 197.0, 169.9, 166.4, 160.0, 149.2, 145.4, 139.1, 136.7, 136.6, 135.7, 135.1, 134.2, 131.5, 130.8, 130.5, 130.4, 129.6, 129.0, 128.6, 128.4 (x2), 122.9, 114.4, 109.2, 105.6, 104.6, 94.0, 78.8, 77.3, 75.1, 73.9, 72.6, 71.9, 70.7, 70.5, 69.9, 67.0, 55.1, 54.0, 52.7, 51.6, 48.5, 48.4, 45.4, 44.4, 42.9, 42.7, 40.9, 39.9, 37.1, 36.5, 33.6, 30.2, 27.9, 23.1, 22.2, 21.3, 21.1, 20.0, 18.9, 17.4, 14.8; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 55.1, 52.7, 51.6, 48.5, 30.3, 27.6, 23.0, 22.2, 21.2, 21.1, 17.4, 14.8; CH_2 δ 109.2, 94.0, 71.9, 69.9, 54.0, 44.4, 42.9, 40.9, 39.9, 37.1, 36.5, 33.5; CH δ 136.7, 136.6, 135.7, 130.8, 130.5, 130.4, 129.6, 129.0, 128.6, 128.4, 128.3, 128.1, 122.9, 114.4, 78.8, 77.3, 75.1, 73.9, 72.6, 70.7, 70.4, 67.0; CH_0 δ 198.1, 197.0, 169.9, 166.4, 160.0, 149.2, 145.4, 139.1, 135.1, 134.2, 131.5, 105.6, 104.6, 45.4, 42.7, 20.0, 18.9; IR (neat) 3609, 3583, 3531, 3070, 2956, 2936, 2861, 2362, 1727, 1680, 1614, 1514, 1460, 1384, 1365, 1301, 1247, 1208, 1175, 1108, 1079, 1043, 821, 737, 701, 633 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{75}H_{102}NaO_{16}SSi$ (M+Na): 1341.6556, found: 1341.6565.

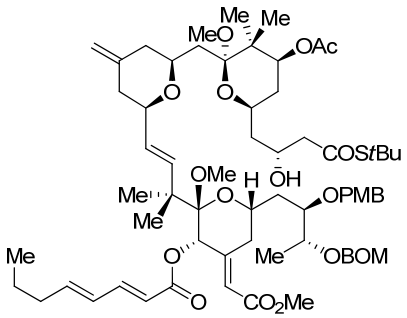


(2E,4E)-((2S,3S,6S,E)-2-((E)-4-((2R,6S)-6-(((2S,4S,6S)-4-acetoxy-6-((R)-2-(tert-butyldiphenylsilyloxy)-4-(tert-butylthio)-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl) octa-2,4-dienoate (10):

To a stirring solution of ketone **9** (10.7 mg, 0.0081 mmol, 1.0 equiv) in MeOH (810 µL, 0.01 M) in a 5 mL reaction vial at rt was added $CeCl_3 \cdot 7H_2O$ (60 mg, 0.162 mmol, 20.0 equiv). The mixture was stirred until all the $CeCl_3 \cdot 7H_2O$ was completely dissolved. The mixture was then cooled to -42 ºC and stirred for 10 min and $NaBH_4$ (3.0 mg, 0.081 mmol, 10.0 equiv) was then added. Stirring continued for 2 h at -42 ºC after which another 10 equiv of $NaBH_4$ was added. The mixture was warmed slowly to 0 ºC over 2 h, and then diluted with 40% EtOAc/hexanes. Saturated aqueous NH_4Cl solution (2 mL) was then added. The layers were separated and the aqueous layer was extracted with 40% EtOAc/hexanes (3 x 5mL). The organic phase was washed with brine (5 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide crude intermediate alcohol which was carried directly to the next step without purification.

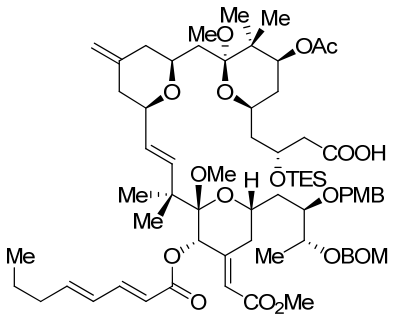
To a stirring solution of the aforementioned intermediate alcohol in CH_2Cl_2 (810 µL, 0.001 M) in a 5 mL reaction vial at rt was added pyridine (7 µL, 0.081 mmol, 10.0 equiv), DMAP (2.0 mg, 0.016 mmol, 2.0 equiv), and octadienoic anhydride (11.0 mg, 0.040 mmol, 5.0 equiv). The reaction mixture stirred at rt for 12 h and was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2.0 mL). The mixture was stirred vigorously for 30 min and was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography using 8% EtOAc/hexanes followed by a preparative TLC with 30% EtOAc/hexanes to provide the ester **10** (10.2 mg, 87%, 2 steps) as a pale yellow liquid. NMR of the product showed essentially a single diastereomer. R_f = 0.43 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +4.4 (*c* = 0.35, EtOAc); 500 MHz ^{1}H

NMR (C_6D_6) δ 7.84-7.81(m, 4H), 7.45 (dd, *J* = 15.1, 10.7 Hz, 1H), 7.40-7.39 (m, 2H), 7.26-7.11 (m, 11H), 6.78-6.76 (m, 2H), 6.39-6.36 (m, 1H), 6.31 (s, 1H), 6.02 (s, 1H), 5.94-5.87 (m, 1H), 5.8 (d, *J* = 15 Hz, 1H), 5.68-5.62 (m, 1H), 5.59 (dd, *J* = 15.6, 4.3 Hz, 1H), 5.37 (dd, *J* = 11.7, 4.8 Hz, 1H), 4.90 (s, 1H), 4.81-4.76 (m, 3H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.34-4.30 (m, 1H), 4.14-4.11 (m, 1H), 4.08-4.05 (m, 1H), 3.83 (s, 2H), 3.66-3.64 (m, 1H), 3.31(s, 6H), 3.30 (s, 3H), 2.97 (s, 3H), 2.92-2.90 (m, 2H), 2.65 (t, *J* = 13.1 Hz, 1H), 2.34-2.25 (m, 2H), 2.20 (dd, *J* = 16.1, 5.3 Hz, 1H), 2.15-2.08 (m, 2H), 1.94-1.70 (m, 8H), 1.66 (s, 3H), 1.63-1.60 (m, 2H), 1.46 (s, 9H), 1.42 (s, 3H), 1.38 (s, 3H), 1.19 (s, 12H), 1.12 (s, 3H), 1.09 (s, 3H), 0.74 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR (C_6D_6) δ 198.0, 169.8, 166.7, 165.7, 160.0, 153.9, 146.8, 145.7, 145.3, 139.2, 137.9, 136.7, 136.6, 135.0, 134.2, 131.7, 130.5, 130.4, 129.8, 129.1, 128.9, 128.6, 128.4(x2), 128.3, 128.0, 119.6, 117.8, 117.7, 114.4, 109.1, 104.7, 93.8, 79.0, 77.6, 75.3, 73.9, 72.9, 72.5, 72.3, 70.3, 69.8, 69.3, 66.9, 55.1, 54.0, 51.7, 51.0, 48.6, 48.3, 46.8, 44.5, 43.1, 42.7, 41.2, 39.9, 37.1, 35.5, 34.1, 33.6, 30.2, 27.6, 25.2, 24.6, 22.4, 21.3, 21.1, 20.0, 17.3, 15.0, 14.1; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 55.1, 51.7, 50.9, 48.6, 30.2, 27.6, 25.2, 24.6, 21.3, 21.1, 17.3, 15.0, 14.1; CH_2 δ 109.1, 93.8, 72.3, 69.8, 54.0, 44.5, 43.1, 41.2, 39.9, 37.1, 35.5, 33.6, 22.4; CH δ 146.8, 145.3, 137.9, 136.7, 136.6, 130.5, 130.4, 129.8, 130.5, 130.4, 129.8, 128.9, 128.6, 128.4, 128.2, 128.0, 119.6, 114.4, 78.9, 77.5, 75.3, 73.9, 72.9, 72.4, 70.3, 69.3, 66.9; CH_0 δ 198.0, 169.8, 166.7, 165.7, 160.0, 145.7, 135.0, 134.2, 131.7, 128.4, 117.8, 104.7, 48.3, 46.8, 42.7, 34.1, 20.0; IR (neat) 3069, 2957, 2933, 2361, 1720, 1681, 1643, 1614, 1513, 1459, 1431, 1383, 1364, 1302, 1246, 1131, 1107, 1041, 1003, 891, 859, 821, 737, 702 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{83}H_{114}NaO_{17}SSi$ (M+Na): 1465.7444, found: 1465.7462.



(2E,4E)-((2S,3S,6S,E)-2-((E)-4-((2R,6S)-6-(((2S,4S,6R)-4-acetoxy-6-((R)-4-(tert-butylthio)-2-hydroxy-4-oxobutyl)-2-methoxy-3,3-dimethyltetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl) octa-2,4-dienoate (SI-1): To a stirring solution of the BPS ether **10** (30.2 mg, 0.02 mmol, 1.0 equiv) in a 5:4:1 THF/MeOH/ pyridine (1.0 mL, 0.02M) at 0 ºC in a 15 mL plastic centrifuge tube was added HF·Py (20 %, 0.46 mL). The reaction mixture was stirred at 0 ºC for 30 min and warmed to rt. Stirring continued for 72 h and the reaction mixture was quenched by pipetting into a mixture of sat. aqueous $NaHCO_3$ solution and EtOAc (10 mL each). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 1 x 10 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 4 ml fractions. The product containing fractions (18-60) were combined and concentrated under reduced pressure to provide alcohol **SI-1** (24.3 mg, 96%) as a clear colorless oil: R_f = 0.25 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +10.3 (*c* = 0.32, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.45 (dd, *J* = 15.1, 10.7 Hz, 1H), 7.41-7.39 (m, 3H), 7.26-7.09 (m, 4H), 6.78-6.76 (m, 2H), 6.35 (d, *J* = 16.1 Hz, 1H), 6.31 (s, 1H), 6.01(s, 1H), 5.93 (dd, *J* = 14.6, 10.7 Hz,

1H), 5.86-5.83 (m, 1H), 5.70-5.56 (m, 3H), 4.89 (s, 1H), 4.81-4.77 (m, 3H), 4.68 (d, *J* = 12.2, Hz, 1H), 4.63 (d, *J* = 12.2, Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.34-4.30 (m, 1H), 4.14-4.11 (m, 1H), 4.08-4.06 (m 1H), 3.90-3.83 (m, 3H), 3.73-3.71 (m, 1H), 3.31 (s, 3H), 3.31 (s, 3H), 3.29 (s, 3H), 3.13 (s, 3H), 2.64 (t, *J* = 14.1 Hz, 1H), 2.53 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.45 (dd, *J* = 15.6, 3.9 Hz, 1H), 2.37 (d, *J* = 13.1 Hz, 1H), 2.31-2.07 (m, 5H), 1.94 (t, *J* = 12.2 Hz, 2H), 1.81-1.71 (m, 5H), 1.70 (s, 3H), 1.52 (d, *J* = 12.2 Hz, 1H), 1.47 (d, *J* = 12.2 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 12H), 1.12-1.18 (m, 6H), 1.12 (s, 3H), 0.74 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR (C_6D_6) δ 199.8, 170.0, 166.7, 165.7, 160.0, 153.9, 146.8, 145.8, 145.3, 139.2, 137.8, 131.6, 129.8, 129.2, 128.9, 128.6, 128.3, 128.0, 127.9, 119.6, 117.8, 114.4, 109.0, 104.6, 93.9, 79.0, 77.5, 75.6, 74.3, 72.9, 72.4, 72.3, 69.8, 69.2, 65.7, 65.5, 55.1, 52.5, 51.7, 51.0, 48.7, 48.5, 46.8, 42.9(x2), 42.5, 41.1, 39.9, 37.0, 35.4, 34.0, 33.4, 30.1, 24.9, 24.8, 22.3, 21.2, 21.1, 17.6, 15.0, 14.0; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 55.1, 51.7, 50.9, 48.7, 30.1, 24.9, 24.8, 21.2, 21.1, 17.6, 15.0, 14.0; CH_2 δ 109.0, 93.9, 72.3, 69.8, 52.5, 42.9, 42.5, 41.1, 39.9, 37.0, 35.4, 34.1, 33.3, 22.3; CH δ 146.8, 145.3, 137.8, 129.8, 129.2, 128.9, 128.3, 128.0, 127.9, 119.6, 117.8, 114.4, 79.0, 77.5, 75.6, 74.2, 72.9, 72.4, 69.2, 65.7, 65.5; CH_0 δ 199.8, 170.0, 166.7, 165.7, 160.0, 153.9, 145.3, 139.2, 131.6, 104.6, 48.5, 46.8, 42.9, 37.0; IR (neat) 3421, 2926, 2361, 1719, 1676, 1643, 1614, 1513, 1456, 1365, 1302, 1248, 1133, 1105, 1041 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{67}H_{96}O_{17}S$ (M+Na): 1227.6266, found: 1227.6262.

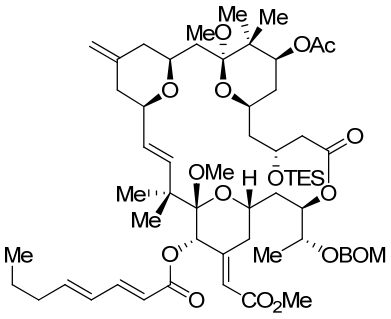


(R)-4-((2S,4S,6S)-4-acetoxy-6-(((2S,6R)-6-((E)-3-((2S,3S,6S,E)-6-((2R,3R)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-((2E,4E)-octa-2,4-dienoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-6-methoxy-5,5-dimethyltetrahydro-2H-pyran-2-yl)-3-(triethylsilyloxy)butanoic acid (11): To a stirring solution of thiolester **SI-1** (6.3 mg, 0.0052 mmol, 1.0 equiv.) in THF (0.4 mL) in a 5 mL vial at 0 ºC was added pH 8 phosphate buffer (0.1 mL). Aqueous lithium hydroxide solution (0.1 M, 104 µL, 0.0104 mmol, 2.0 equiv) was added via syringe followed by 2 drops of 30% H_2O_2 via a 10 µL syringe. The resulting solution stirred at 0 °C for 1 h and another 2 equiv. of LiOH and 2 more drops of H_2O_2 was added. After 1 more hr, the reaction mixture was poured into a mixture of pH 6 phosphate buffer solution and EtOAc (10 mL each). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the hydroxy acid as a sticky pale yellow oil. The product was taken to the next step without further purification.

To a stirring solution of the aftermentioned hydroxy acid in CH_2Cl_2 (0.4 mL) in a 5 mL vial at -15 ºC was added DMAP (3 mg, 0.023 mmol, 4.5 equiv), followed by TESCl (2 µL, 0.013 mmol, 2.5 equiv) via syringe. The solution was stirred at -15 ºC for 1 h and an additional 2.5 equiv of TESCl was added. The mixture was warmed to 0 ºC over 1 h after which it was poured into a mixture of aqueous pH 4 (acetic acid/sodium acetate) buffer and EtOAc (10 mL each). The

layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 1 x 7 cm silica gel column, eluting with 30% EtOAc/hexanes, collecting 2 mL fractions. The product containing fractions (3-9) were combined and concentrated under reduced pressure to provide pure carboxylic acid **11** (4.4 mg, 76% over 2 steps) as a colorless oil: R_f = 0.38 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +7 (*c* = 0.22, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.41-7.39 (m, 3H), 7.26-7.10 (m, 4H), 6.78-6.76 (m, 2H), 6.39 (d, *J* = 15.6 Hz, 1H), 6.32 (s, 1H), 6.02 (s, 1H), 5.95-5.82 (m, 2H), 5.71-5.63 (m, 1H), 5.62-5.58 (m, 2H), 4.86 (s, 1H), 4.83-4.76 (m, 3H), 4.69 (d, *J* = 12.2 Hz, 1H), 4.65(d, *J* = 12.2 Hz, 1H), 4.64-4.59 (m, 2H), 4.50-4.42 (m, 2H), 4.34-4.30 (m, 1H), 4.16-4.12 (m, 1H), 4.09-4.06 (m 1H), 3.90-3.76 (m, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 3.20 (s, 3H), 2.73-2.60 (m, 3H), 2.36-2.21 (m, 3H), 2.14-2.08 (m, 2H), 1.99-1.88 (m, 3H), 1.85-1.1.77 (m, 3H), 1.69 (s, 3H), 1.53 (d, *J* = 12.2, Hz, 1H), 1.48 (d, *J* = 12.2, Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.01 (t, *J* = 3.4 Hz, 9H), 0.75 (t, *J* = 7.3 Hz, 3H), 0.66-0.61 (m, 6H); 125 MHz ^{13}C NMR (C_6D_6) δ 170.1, 166.8, 165.8, 160.0, 153.9, 146.8, 145.7, 145.4, 139.0, 138.0, 131.6, 129.8, 129.1, 129.0, 128.4, 128.1, 127.9,128.6, 119.5, 117.8, 114.4, 109.0, 104.9, 93.8, 79.2, 77.5, 75.4, 74.2, 73.1, 72.5, 72.3, 69.8, 69.3, 68.6, 66.5, 55.1, 51.7, 51.0, 48.8, 46.8, 45.1, 44.0, 42.9, 42.8, 41.3, 40.1, 37.1, 35.5, 34.2, 25.1, 24.7, 22.4, 21.4, 21.1, 17.7, 15.0, 14.1, 7.5, 5.9; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 55.1, 51.8, 51.0, 48.8, 25.0, 24.7, 21.4, 21.1, 17.7, 15.0, 14.1, 7.5; CH_2 δ 109.0, 93.8, 72.3, 69.8, 45.1, 44.0, 42.9, 41.3, 40.1, 37.0, 35.5, 34.2, 22.3, 5.9; CH δ 147.0, 145.5, 138.0, 129.8, 129.1, 128.4, 128.1, 127.9, 119.5, 117.8, 114.4, 103.9, 79.2, 77.5, 75.4, 74.2, 73.1, 72.4, 69.3, 68.6, 66.5; CH_0 δ 170.1, 166.8, 165.8, 160.0, 153.9, 145.7, 139.0, 131.6, 129.0, 128.6,

104.9, 46.8, 42.8; IR (neat) 2933, 1733, 1681, 1612, 1513, 1458, 1365, 1246, 1109, 1041, 821, 736, 701 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{69}H_{102}NaO_{18}Si$ (M+Na): 1269.6733, found: 1269.6770.

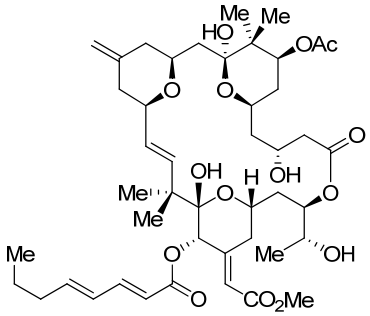


Protected Analogue (SI-2): To a solution of the PMB ether **11** (3.1 mg, 0.0024 mmol, 1 equiv) in CH_2Cl_2 (100 µL) in a 5 mL vial at 0 ºC was added pH 8 phosphate buffer (100 µL) and t-butanol (50 µL) via syringe. To the solution was added DDQ (2.8 mg, 0.0124 mmol, 5 equiv) in one portion and the reaction was stirred vigorously for one hour after which another 5 equiv DDQ was added. After stirring one more hour at 0 ºC, the reaction mixture was poured into a mixture of CH_2Cl_2 and pH 4 acetate buffer (5 mL each). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was quickly passed through a column of silica gel (1 x 7 cm) eluting with 30% EtOAc/hexanes, collecting 4 mL fractions. The product containing fractions 4-11 were combined and concentrated under reduced pressure to give seco acid (2.1 mg) partially mixed with DDQ byproducts which was taken to the next step without further purification.

To a stirring solution of the seco acid in THF (60 µL) in a 5 mL vial at 0 °C was added a 0.1 M solution of triethylamine in THF (112 µL, 0.011 mmol, 6.0 equiv) and a 0.1 M solution of 2,4,6-trichlorobenzoyl chloride in THF (112 µL, 0.0055 mmol, 3.0 equiv). After 10 min, the reaction was warmed to rt and stirring continued for an additional 3 h. The reaction mixture was

diluted with 3:1 toluene/ THF (1 mL) and taken into a 25 mL gas-tight syringe. This solution was added by syringe pump to a stirring solution of DMAP (4.5 mg, 0.037 mmol, 20.0 equiv) in toluene (1.2 mL) at 40 °C over 12 h. The residual contents of the syringe were rinsed into the flask with toluene (0.5 mL) and stirring continued for an additional 2 h. The reaction mixture was cooled to rt and diluted with 30% EtOAc/hexanes (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (2 x 5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 1 x 4 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 2 mL fractions. The product containing fractions (13-25) were combined and concentrated under reduced pressure to provide pure macrolactone **SI-2** as a white solid (1.7 mg, 62% over 2 steps): R_f = 0.48 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +9 (*c* = 0.085, EtOAc); 500 MHz ^{1}H NMR (C_6D_6) δ 7.46 (dd, *J* = 15.1, 10.7 Hz, 1H), 7.33-7.07 (m, 5H), 6.74 (d, *J* = 16.1 Hz, 2H), 6.51 (d, *J* = 1.4 Hz, 1H), 5.92-5.87 (m, 1H), 5.83-5.78 (m, 3H), 5.71 (dd, *J* = 11.7, 4.8 Hz, 1H), 5.63-5.55 (m, 2H), 4.73-4.52 (m, 10H), 4.35-4.31 (m, 2H), 4.05-3.96 (m, 4H), 3.74-3.71 (m, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 3.14 (s, 3H), 2.70 (dd, *J* = 17.5, 3.4 Hz, 1H), 2.47-2.42 (m, 1H), 2.36-2.31 (m, 1H), 2.27-2.18 (m, 2H), 2.12-2.04 (m, 2H), 1.99-1.91 (m, 3H), 1.84-1.80 (m, 2H), 1.73 (s, 3H), 1.54 (s, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.13 (d, *J* = 7.3 Hz, 1H), 1.10 (d, *J* = 7.3 Hz, 1H), 1.09 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.70 (t, *J* = 7.3 Hz, 3H), 0.64-0.59 (m, 6H); 125 MHz ^{13}C NMR (C_6D_6) δ 171.2, 170.1, 167.0, 165.7, 152.2, 147.1, 145.6 (x2), 140.1, 138.9, 128.9 (x2), 128.7, 128.6, 120.5, 119.4, 108.9, 104.1, 103.8, 93.8, 80.6, 74.5, 74.4, 74.2, 74.0, 71.5, 69.9, 67.7, 66.5, 65.3, 53.7, 51.1, 48.6, 45.9, 45.6, 44.0, 42.4 (x2), 42.1, 41.6, 40.7, 36.9, 35.4, 34.7, 31.9, 30.5, 27.6, 22.3, 21.1 (x2), 18.1, 16.2, 14.0, 7.6, 6.3; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 53.7, 51.1 (x2), 48.6 (x2), 21.1 (x2),

18.1, 16.1, 14.0, 7.6; CH_2 δ 108.8, 93.8, 69.9, 45.9, 44.0, 42.1, 40.7, 36.9, 35.4, 34.7, 31.9, 30.5, 22.3, 6.3; CH δ 147.1, 145.5, 140.1, 129.0, 128.9, 128.4, 128.1, 120.5, 119.4, 80.6, 74.5, 74.4, 74.2, 74.0, 71.5, 67.7, 66.5, 65.3; CH_0 δ 171.2, 170.1, 167.0, 165.7, 152.2, 145.6, 128.9, 128.7, 104.1, 45.6, 42.4; IR (neat) 3674, 3526, 1996, 1870, 1846, 1650, 1520, 1159, 819, 789 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{61}H_{92}O_{16}Si$ (M+Na): 1131.6052, found: 1131.6061.



Analogue 12: To a 2 mL reaction vial containing the analogue precursor **(SI-2)** (1.6 mg, 0.00144 mmol, 1 equiv) was added a 0.25 M solution of $LiBF_4$ in 25:1 CH_3CN/ H_2O (260 µL, 0.0648 mmol, 45.0 equiv). The reaction vial was sealed and the mixture was allowed to stir at 80 ºC for 24 h. After cooling to rt, the reaction mixture was diluted with EtOAc (5 mL) and was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification was accomplished using flash column chromatography with a 0.5 x 6 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 6 x 50 mm test tube fractions (1-10) followed by 50% EtOAc/hexanes. The product containing fractions (20-32) were combined and concentrated under reduced pressure to provide analogue **12** (1.0 mg, 83%) as white solid: R_f = 0.25 (50% EtOAc/hexanes; $[\alpha]_D^{20}$ = +4 (*c* = 0.1, EtOAc); 500 MHz ^{1}H NMR ($CDCl_3$) δ 6.18-6.16 (m, 1H), 6.01 (d, *J* = 1.9 Hz, 1H), 5.81 (d, *J* = 11.7 Hz, 1H), 5.78 (d, *J* = 12.2 Hz, 1H), 5.30 (dd, *J* = 15.6,

8.3 Hz, 1H), 5.25 (s, 1H), 5.20 (s, 1H), 5.16 (dd, *J* = 11.7, 4.3 Hz, 1H), 4.75 (d, *J* = 7.8 Hz, 2H), 4.29-4.16 (m, 3H), 4.06-4.01 (m, 1H), 3.85-3.82 (m, 1H), 3.71-3.62 (m 3H), 3.67 (s, 3H), 2.51-2.43 (m, 2H), 2.39 (s, 1H), 2.18-2.13 (m, 2H), 2.10-2.07 (m, 2H), 2.05 (s, 3H), 2.00-1.94 (m, 3H), 1.86-1.81 (m, 1H), 1.79-1.76 (m, 1H), 1.79-1.76 (m, 1H), 1.69-1.62 (m, 2H), 1.57 (s, 3H), 1.51-1.44 (m, 3H), 1.26-1.23 (m, 6H), 1.51 (s, 3H), 1.00 (s, 6H), 0.96 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR (C_6D_6) δ 172.7, 170.3, 167.1, 165.9, 146.9, 145.3, 144.5, 139.8, 130.7, 128.9, 128.7, 128.6, 120.8, 119.7, 109.2, 102.2, 100.2, 80.6, 75.3, 74.4, 73.2, 72.3, 70.6, 69.1, 66.0, 65.7, 50.9, 45.8, 43.2, 42.8, 42.7, 42.0, 40.2, 36.6, 35.4, 33.9, 32.4, 25.7, 22.3, 21.5, 21.0, 20.4, 20.2, 17.2, 14.0; 125 MHz DEPT ^{13}C NMR (C_6D_6) CH_3 δ 50.9, 25.7, 21.5, 21.0, 20.4, 20.2, 17.2, 14.0; CH_2 δ 109.2, 43.2, 42.8, 42.7, 42.0, 40.2, 36.6, 35.4, 33.9, 32.4, 22.3; CH δ 146.9, 145.3, 139.8, 130.7, 129.1, 120.8, 119.7, 80.6, 75.3, 74.4, 73.2, 72.3, 70.6, 69.2, 66.0, 65.7; CH_0 δ 172.7, 170.3, 167.1, 165.9, 144.5, 128.7, 128.6, 102.2, 100.2, 45.8; IR (neat) 3608, 3583, 2932, 2360, 2339, 1736, 1680, 1515, 1459, 1386, 1246, 1109, 820, 663 cm^{-1}; LRMS calcd for $C_{45}H_{66}O_{15}$ (M+Na): 869.4299, found: 869.1.

References:

(1) Armarego, W. L. F.; Perrin, D. D., *Purification of Laboratory Chemicals, Fourth Edition*. Butterworth-Heinemann: Oxford, **1997**.

(2) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(3) Keck, G. E.; Truong, A.P. *Org. Lett.* **2005**, *7*, 2153-2156.

(4) Keck, G. E.; Welch, D. S.; Poudel, Y. B., *Tetrahedron Lett.* **2006**, 47, 8267-8270.

Attachment and cell proliferation of U937 cells

U937 cells (Sundstrom and Nilsson, 1976), purchased from ATCC (Manassas, VA) and cultured in RPMI-1640 medium supplemented with 10 % FBS (ATCC, Manassas, VA), were plated in 35 mm dishes at a density of 1 X 10^5 living cells/ml and treated with different concentrations of the drugs or DMSO. After 72 hours, the number of cells in the supernatant (non-attached cells) and the number of attached cells (after trypsinization) were counted using a particle counter. The number of attached cells is expressed as percent of total cells.

Figure 2: Attachment Assay for Analogue 12

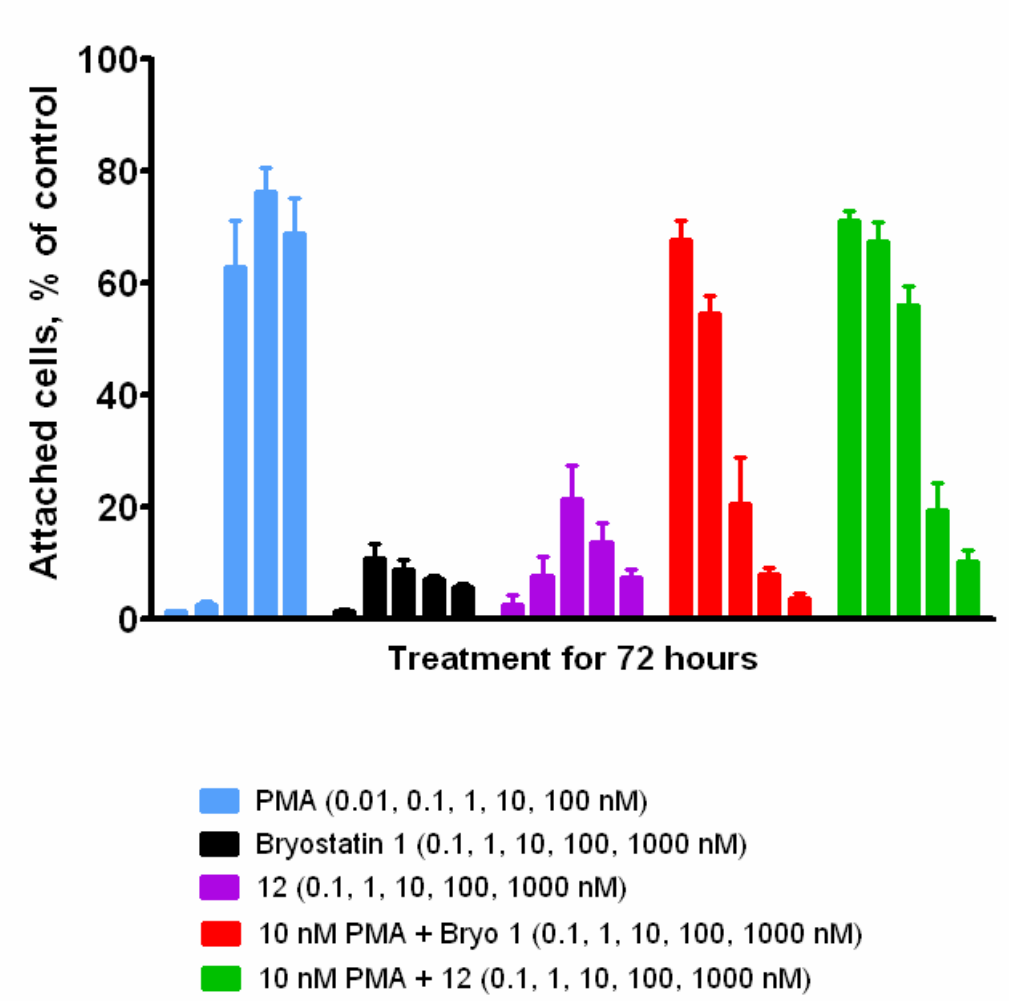
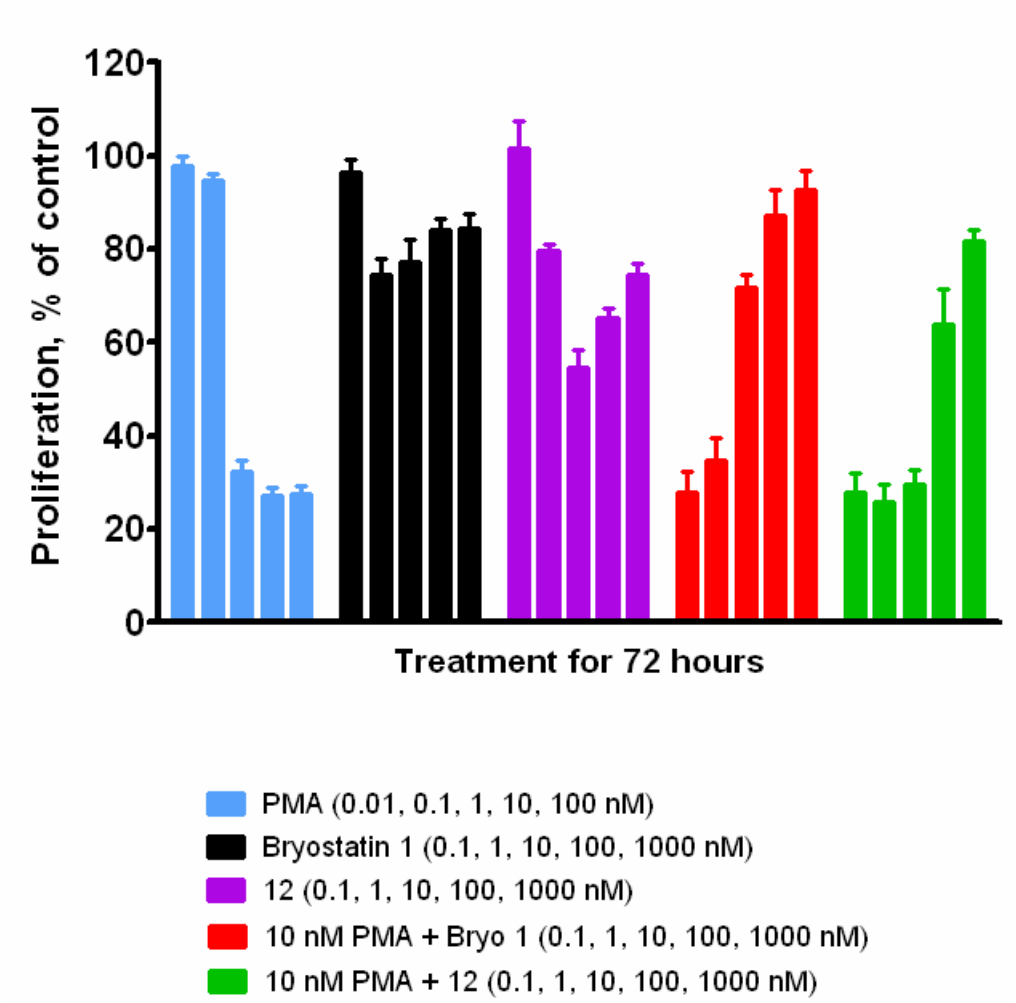


Figure legend for Figure 2: The attachment of U937 cells induced by compound 12 compared to bryostatin 1 and PMA. U937 cells were treated with PMA (0.01-100 nM), bryostatin1 (0.1-1000 nM), analogue **12** (0.1-1000 nM), 10 nM PMA with different concentrations of bryostatin 1 (0.1-1000 nM) or 10 nM PMA with different concentrations of analogue 12 (0.1-1000 nM). The number of attached cells and total cells were counted and the attached cells were graphed as percent of total cells. The bars and error bars represent the average and the standard error of the mean of at least three independent experiments.

Reference: Sundstrom, C. and Nilsson, K. "Establishment and characterization of a human histiocytic lymphoma cell line (U-937)". *Int. J. Cancer* **1976**, *17*, 565-577.

Figure 1S: Inhibition of Proliferation Assay for Analogue 12

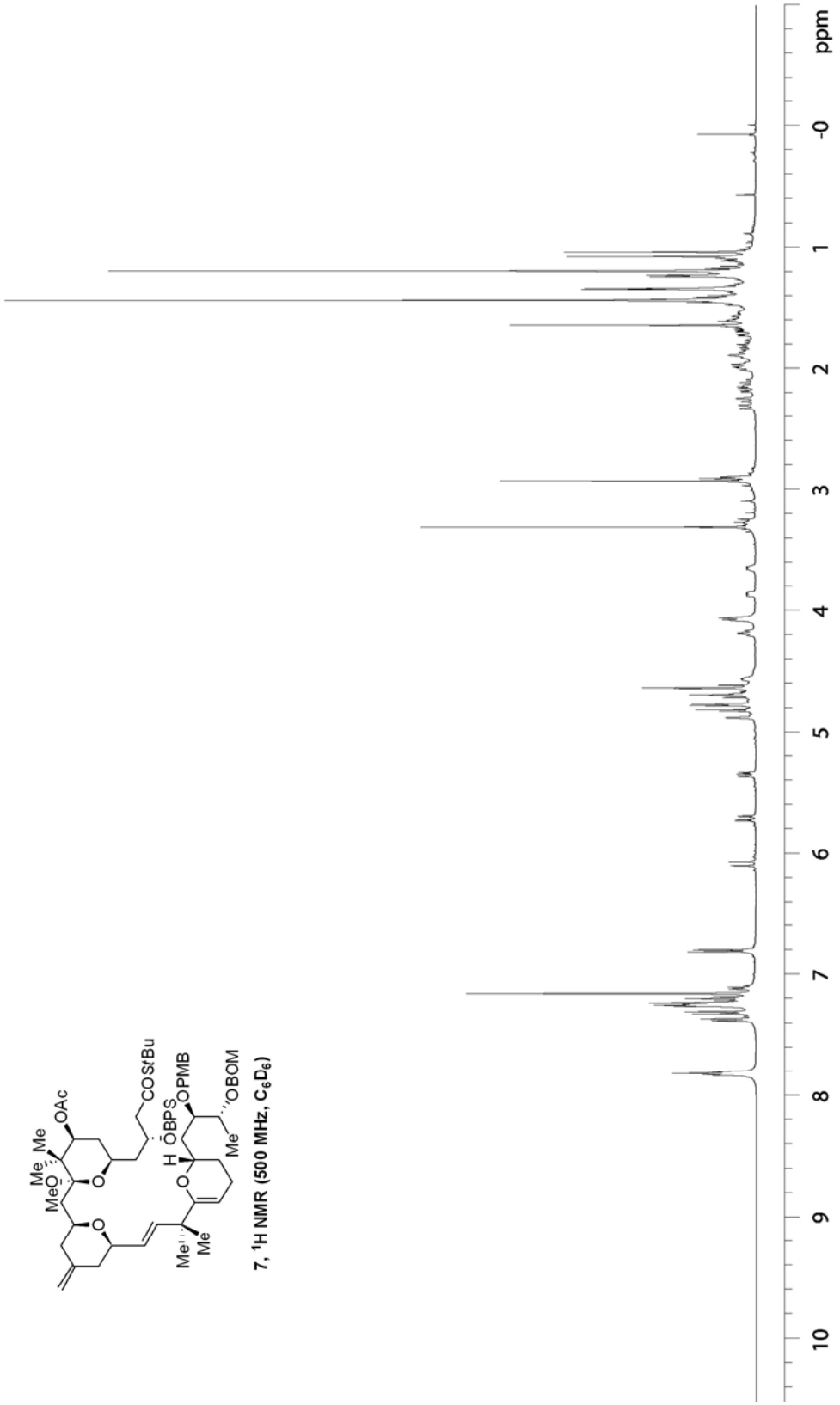


Supplemental figure legend for Figure 1S: The inhibition of U937 cell proliferation induced by compound 12 compared to bryostatin 1 and PMA. U937 cells were treated with PMA (0.01-100 nM), bryostatin1 (0.1-1000 nM), analogue 12 (0.1-1000 nM), 10 nM PMA with different concentrations of bryostatin 1 (0.1-1000 nM) or 10 nM PMA with different concentrations of analogue 12 (0.1-1000 nM). The numbers of attached and non-attached cells were counted and the number of total cells was expressed as % of control. The bars and error bars represent the average and the standard error of the mean of at least three independent experiments.

[^{3}H]PDBu Binding Assay: The inhibitory dissociation constant (K_i) of analogue **12** was determined by the ability of the ligand to displace bound [20-^{3}H]phorbol 12,13-dibutyrate (PDBu) from mouse recombinant isozyme PKCα in the presence of calcium and

phosphatidylserine, using a polyethylene glycol precipitation assay previously described by Blumberg and Lewin. Briefly, the assay mixture (250 µL) contained 50 mM Tris-HCl (pH 7.4 at room temperature), 100 µg/mL phosphatidylserine, 0.1 mM Ca^{2+}, 4 mg/mL bovine immunoglobulin G and .003% Tx-100, 2 nM [^{3}H]PDBu and various concentrations of the competing ligand. The assay tubes were incubated at 37°C for 5 minutes, then chilled for 10 minutes on ice, after which 200 µL of 35% polyethylene glycol 6000 in 50 mM Tris-HCl (pH 7.4) was added. The tubes were vortexed and chilled an additional 10 minutes and then centrifuged in a Beckman Allegra 21R centrifuge at 4°C (12,200 rpm, 15 min). A 100 µL aliquot of each supernatant was removed and placed in a scintillation vial for the determination of the free concentration of [^{3}H]PDBu. Each assay pellet, located in the tip of the assay tube, was carefully dried, cut off, and placed in a scintillation vial for the determination of the total bound [^{3}H]PDBu. The radioactivity was determined by scintillation counting, using Cytoscint (ICN, Costa Mesa, CA). Specific binding was calculated as the difference between total and nonspecific PDBu binding. The inhibitory dissociation constant (K_i) was calculated using the method previously described by Blumberg and Lewin. The K_i for **12** was found to be 0.52 ± 0.06 nM (average of three determinations).

Reference: Lewin, N. E.; Blumberg, P. M. *Methods Mol. Biol.* **2003**, *233*, 129-156.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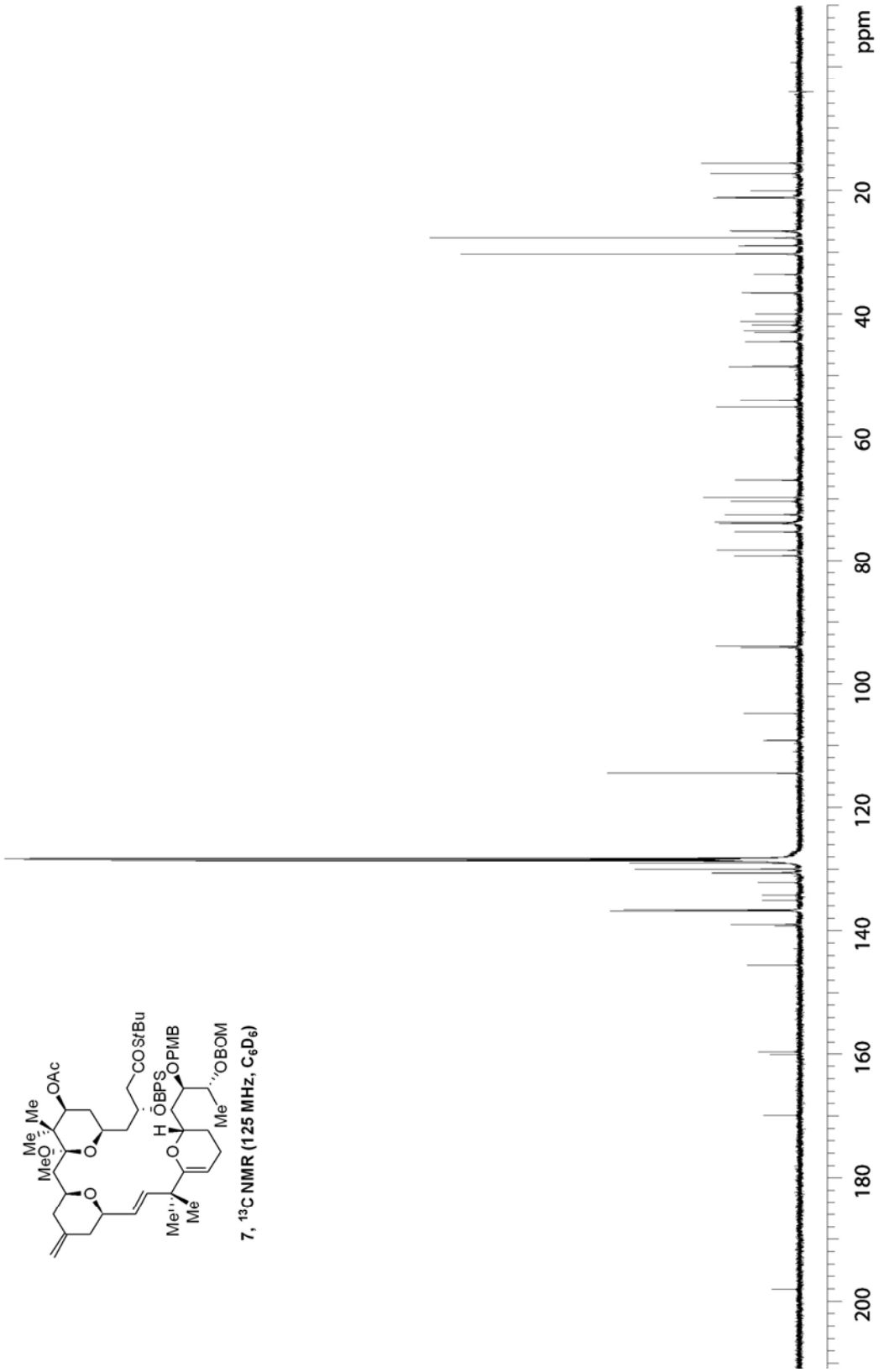
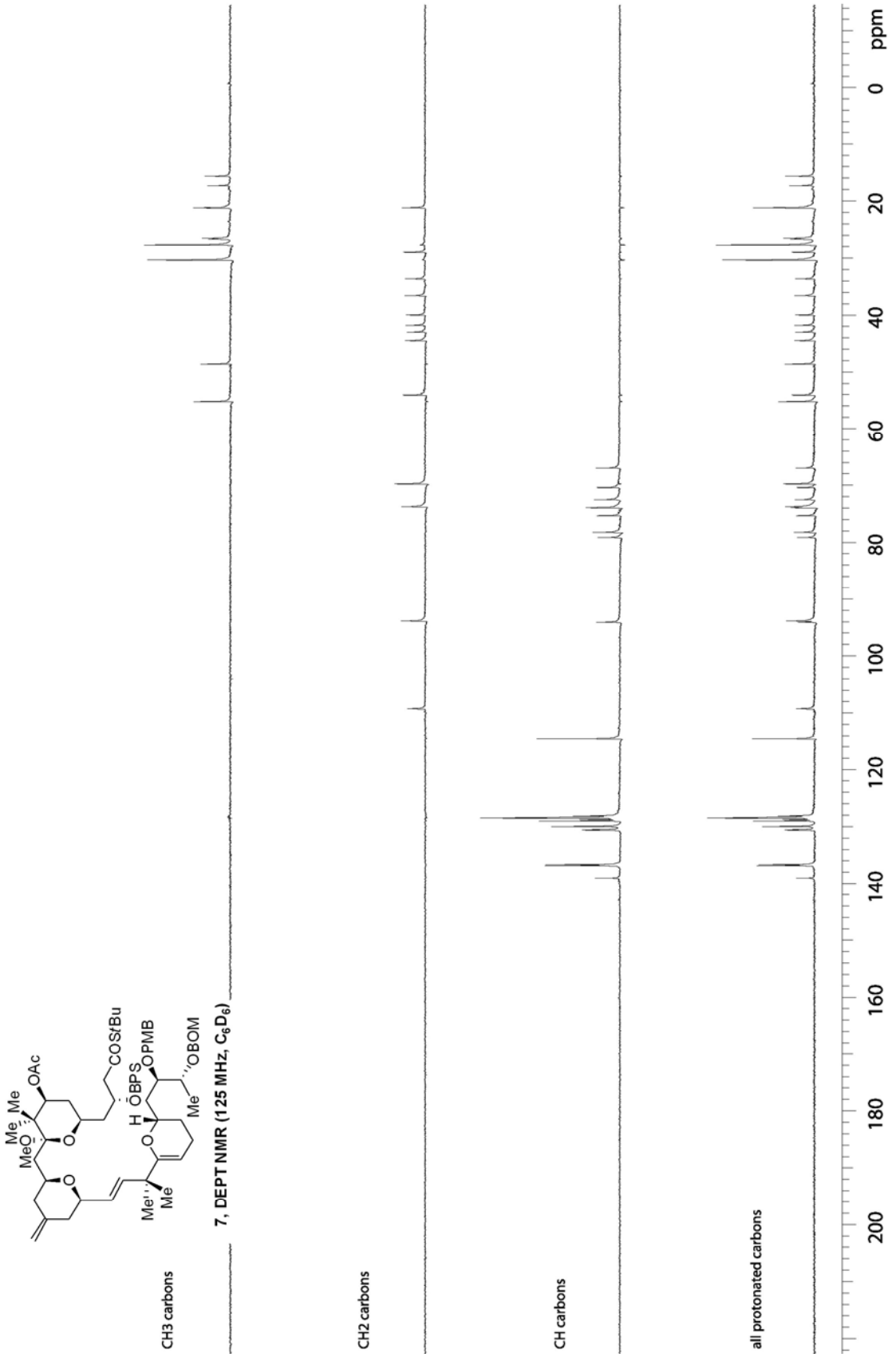


7, ^{13}C NMR (125 MHz, C_6D_6)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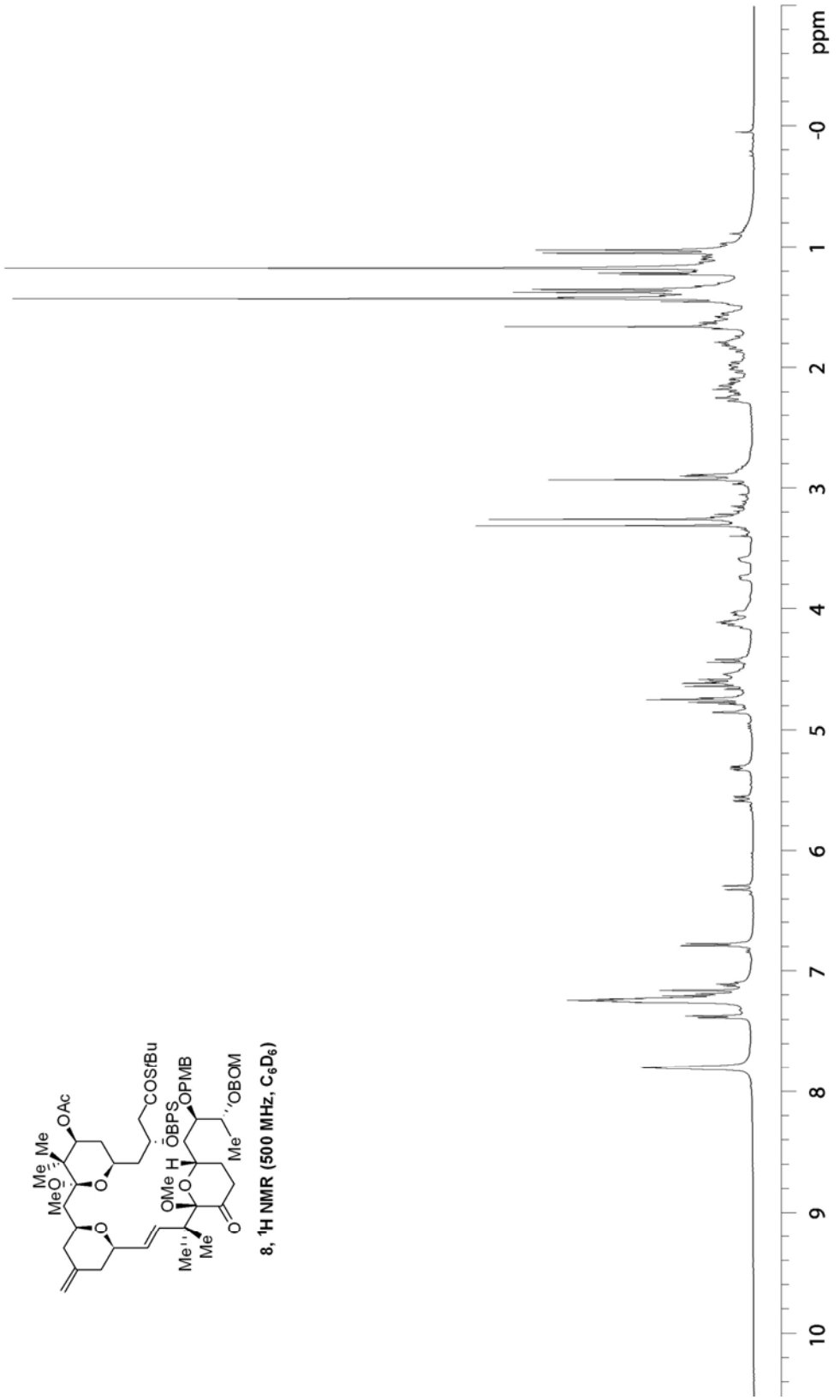

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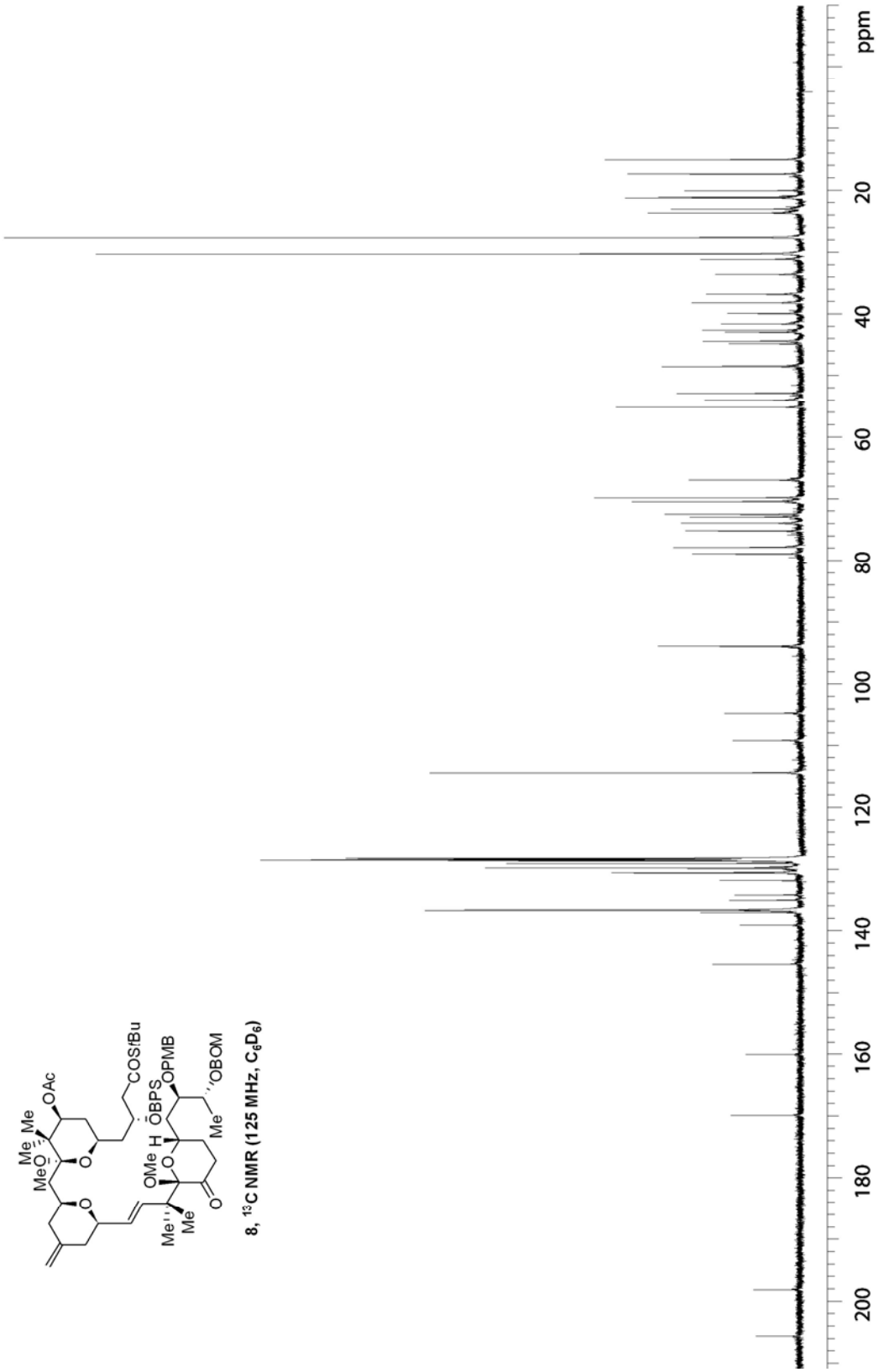

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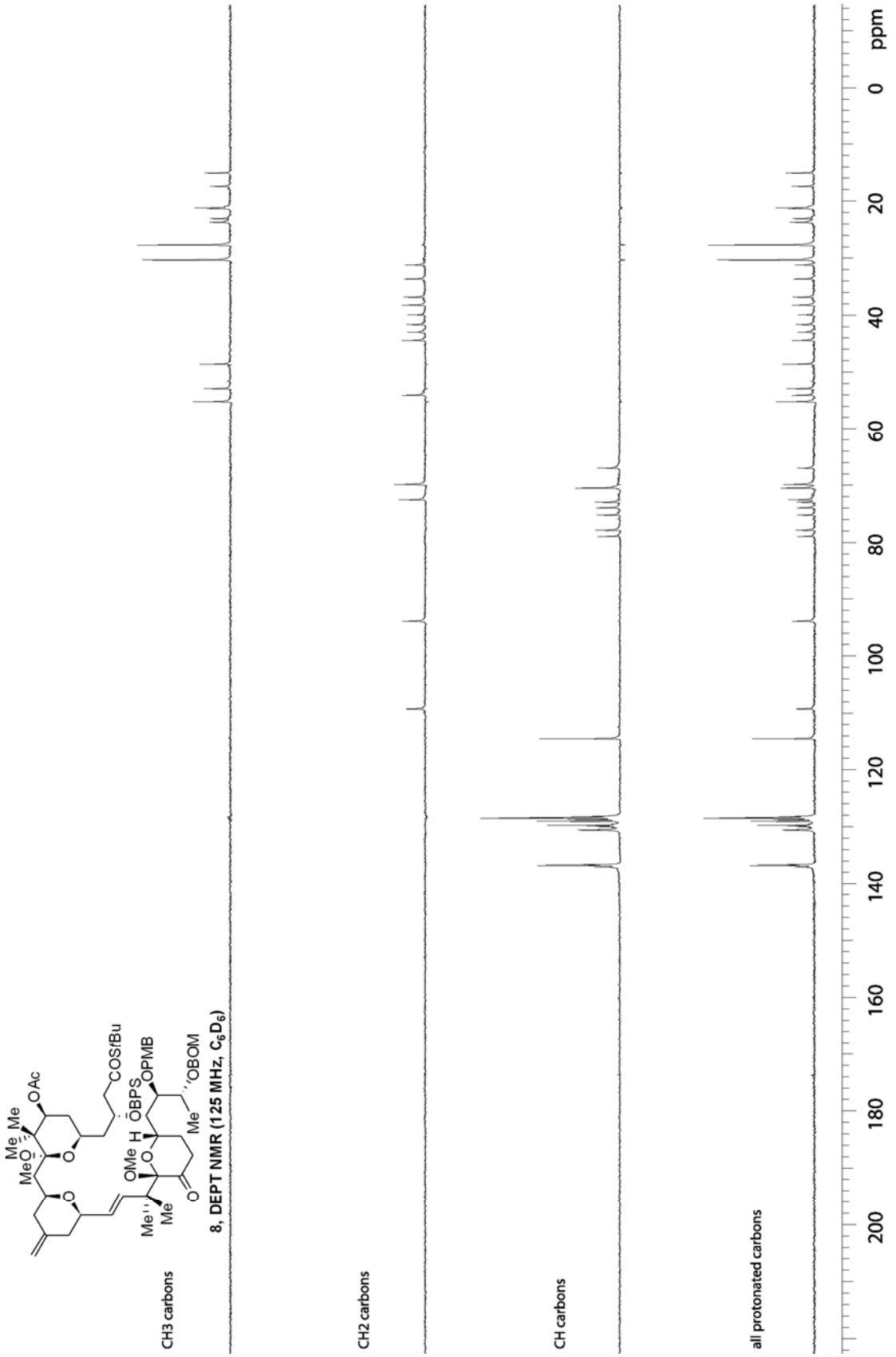
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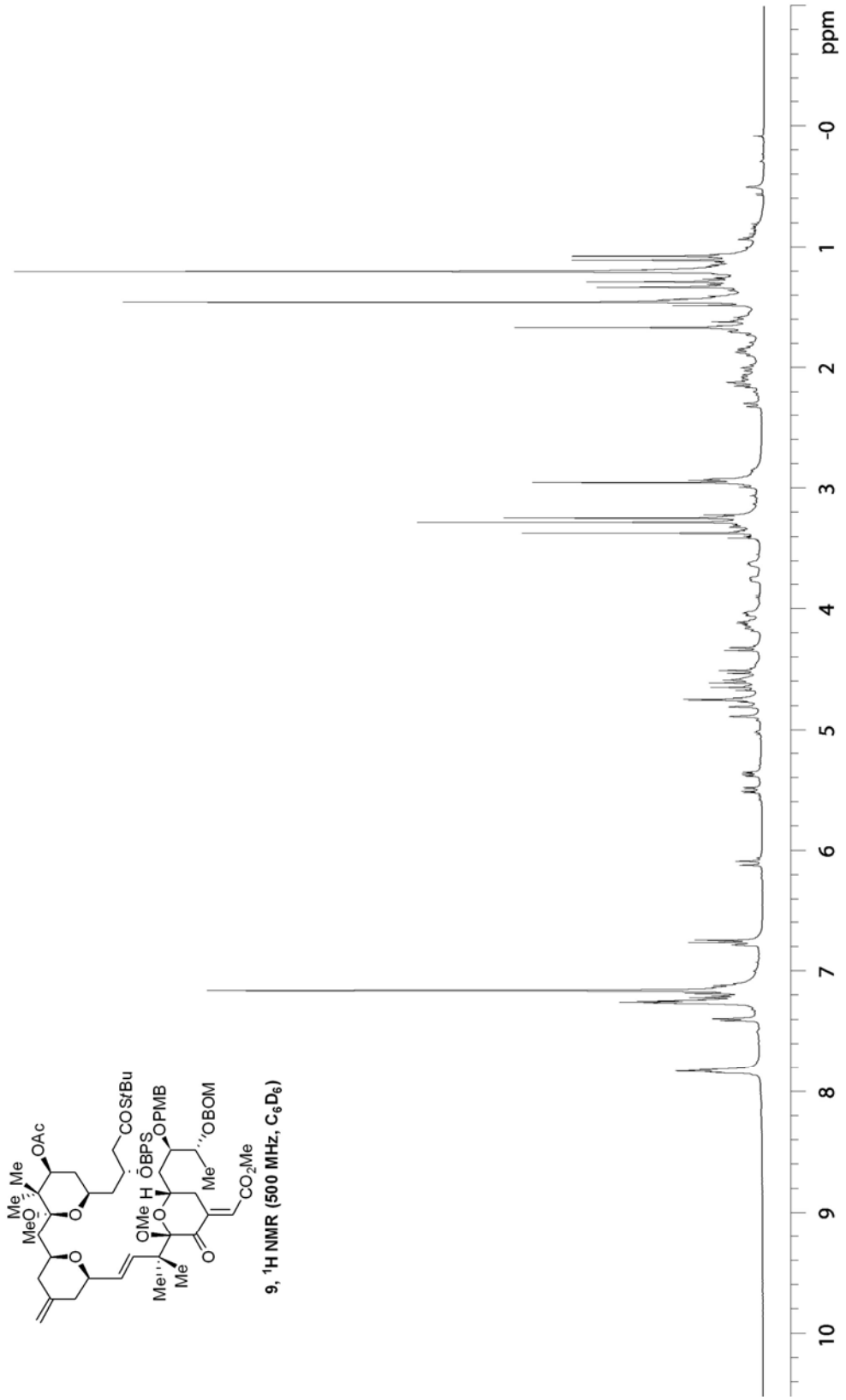
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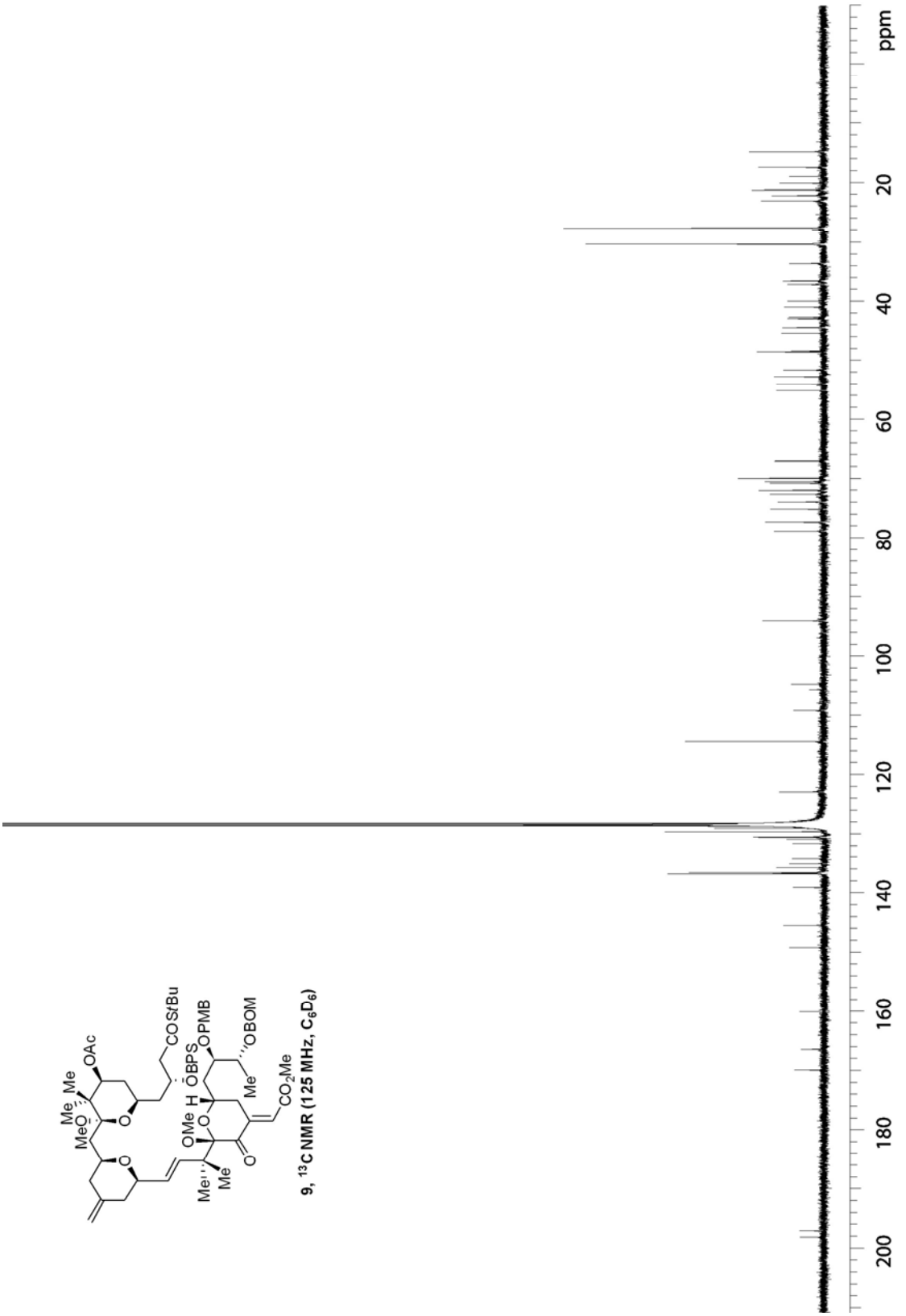

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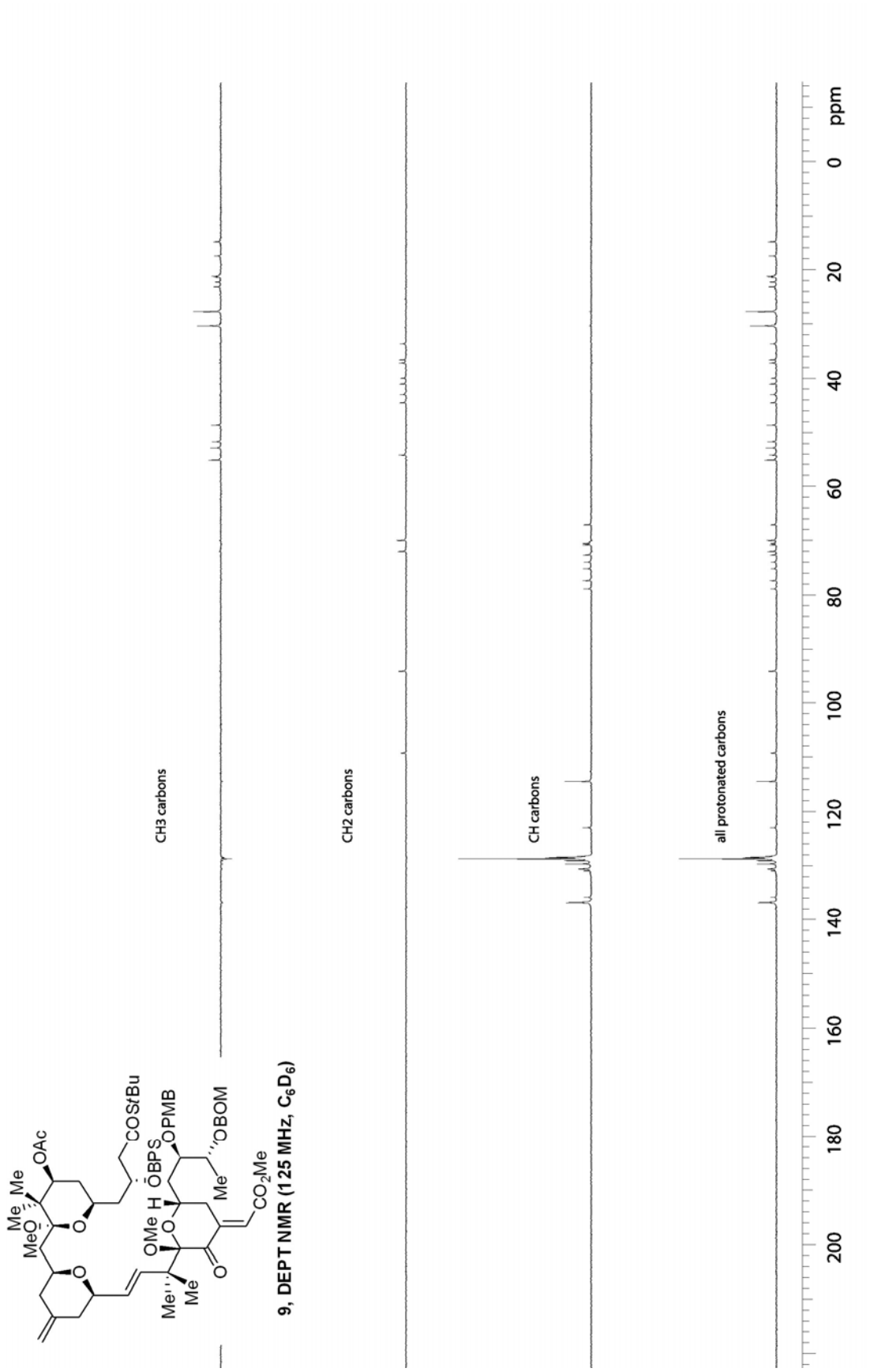
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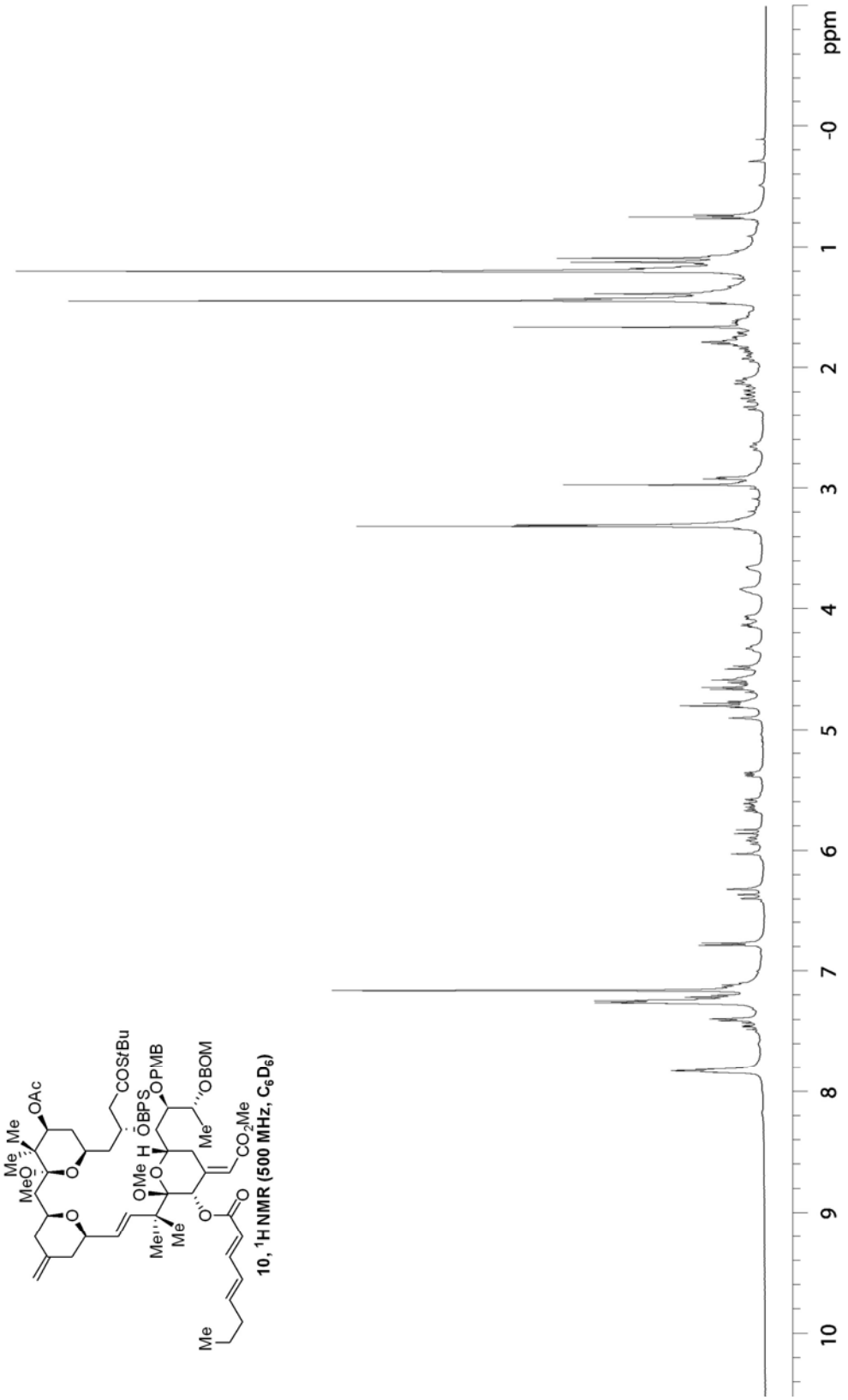
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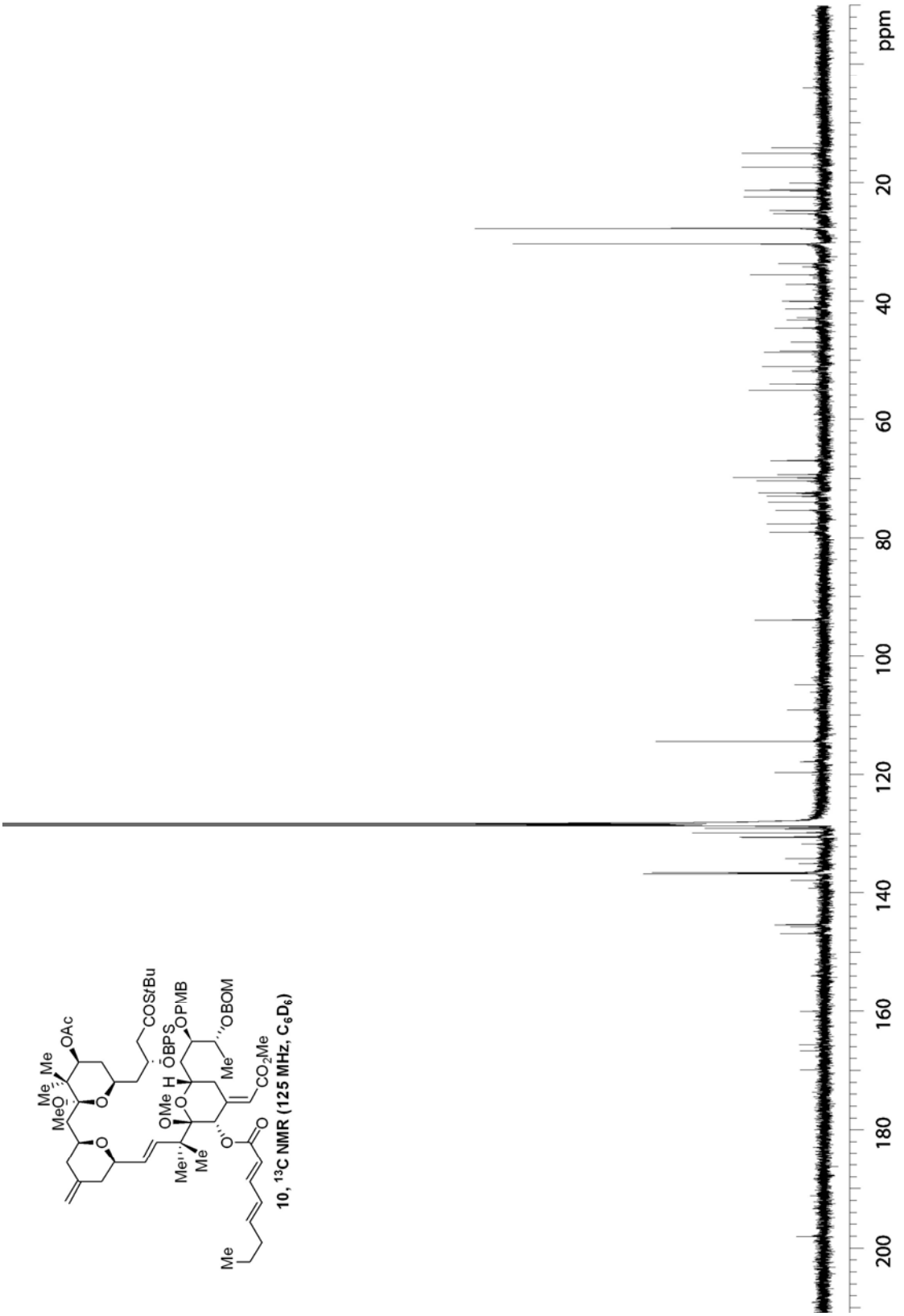
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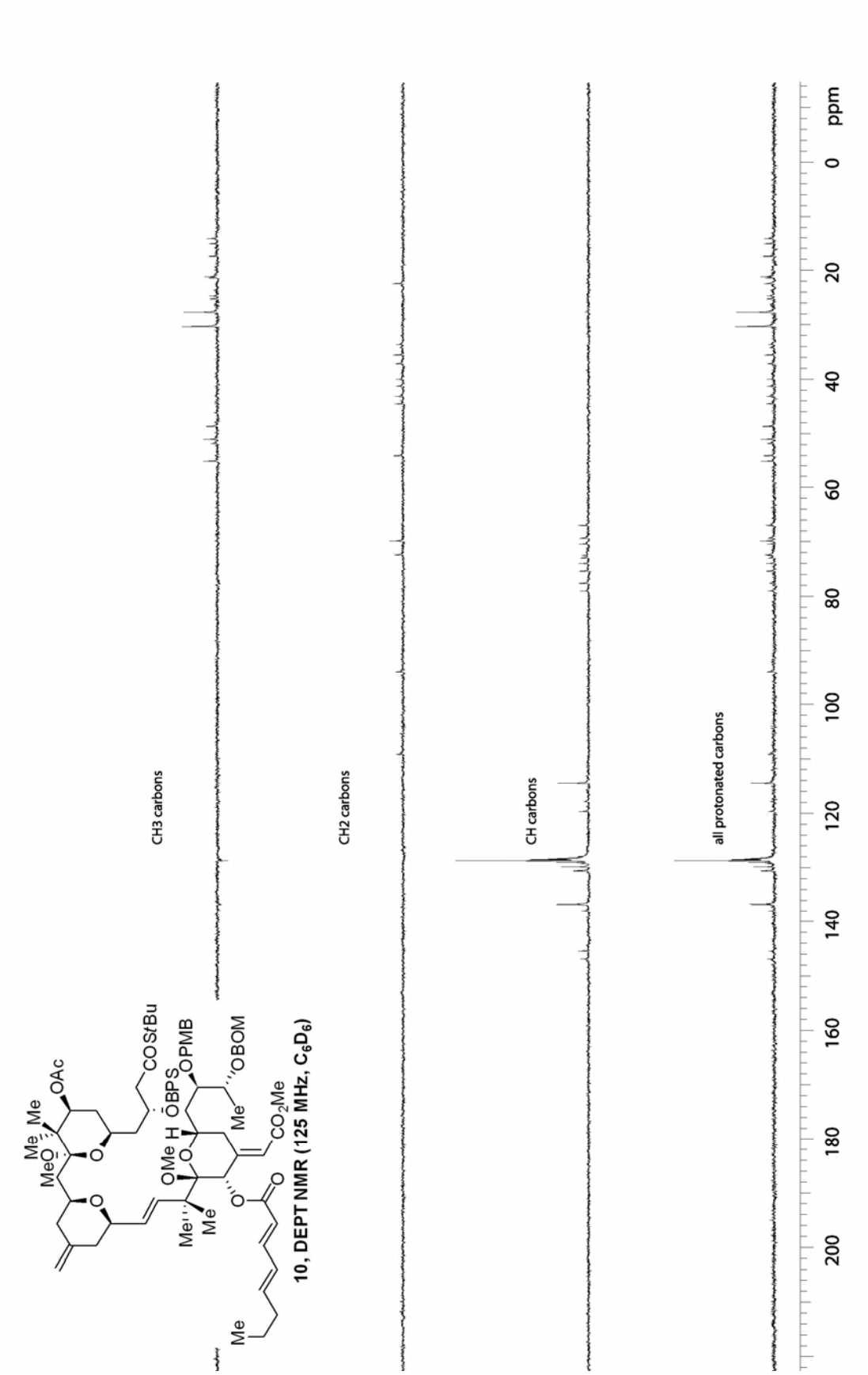
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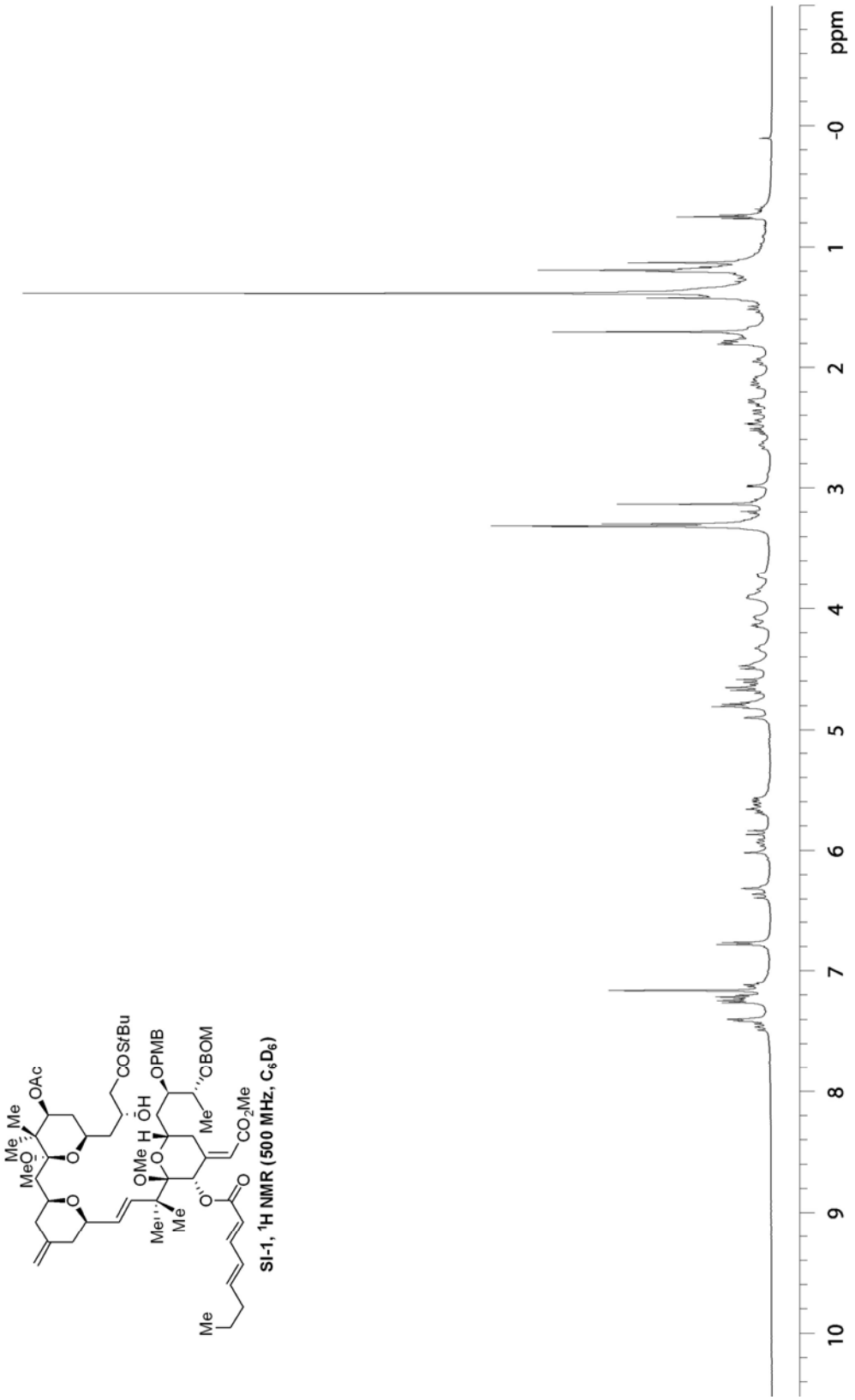
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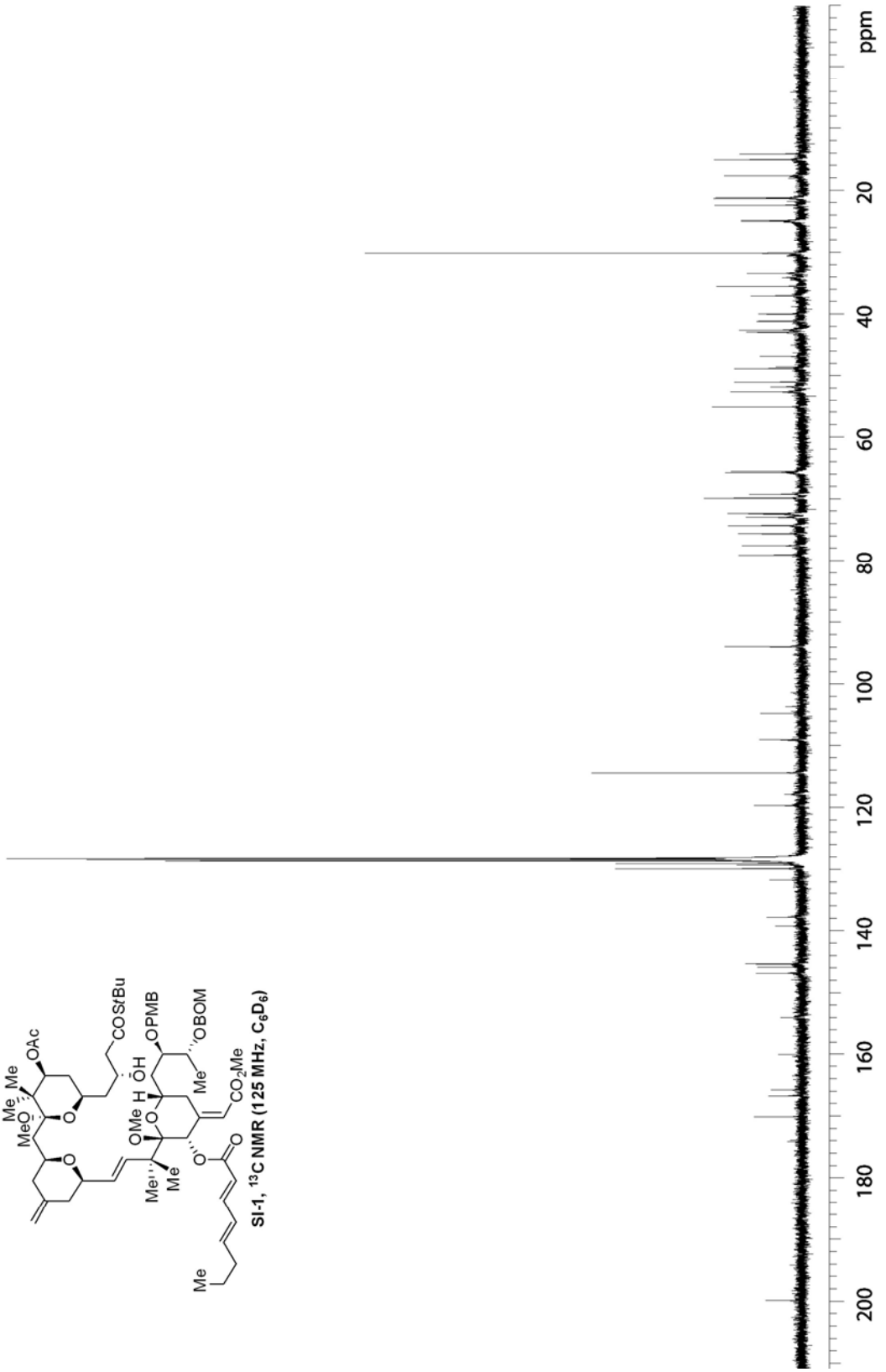
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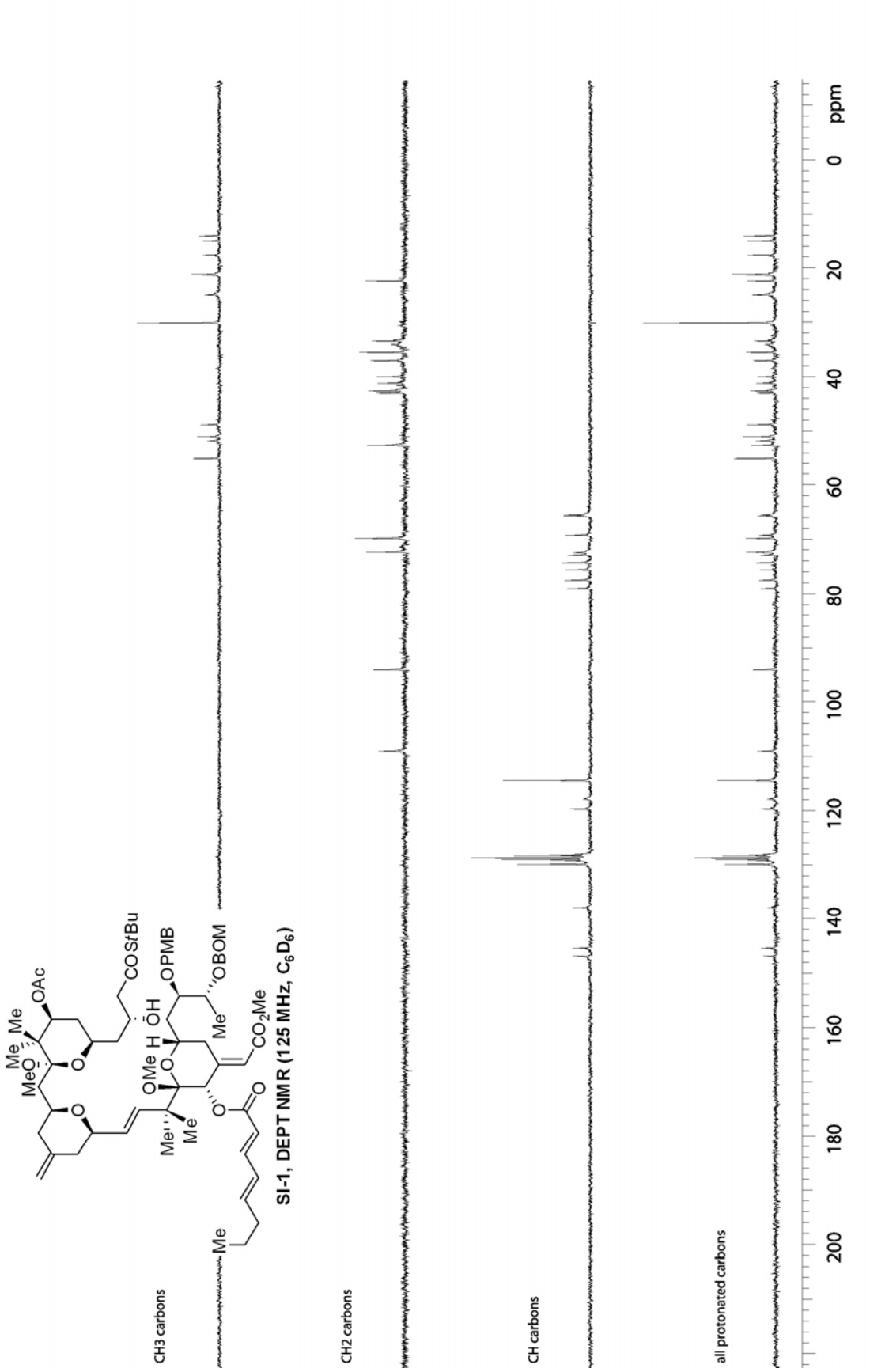
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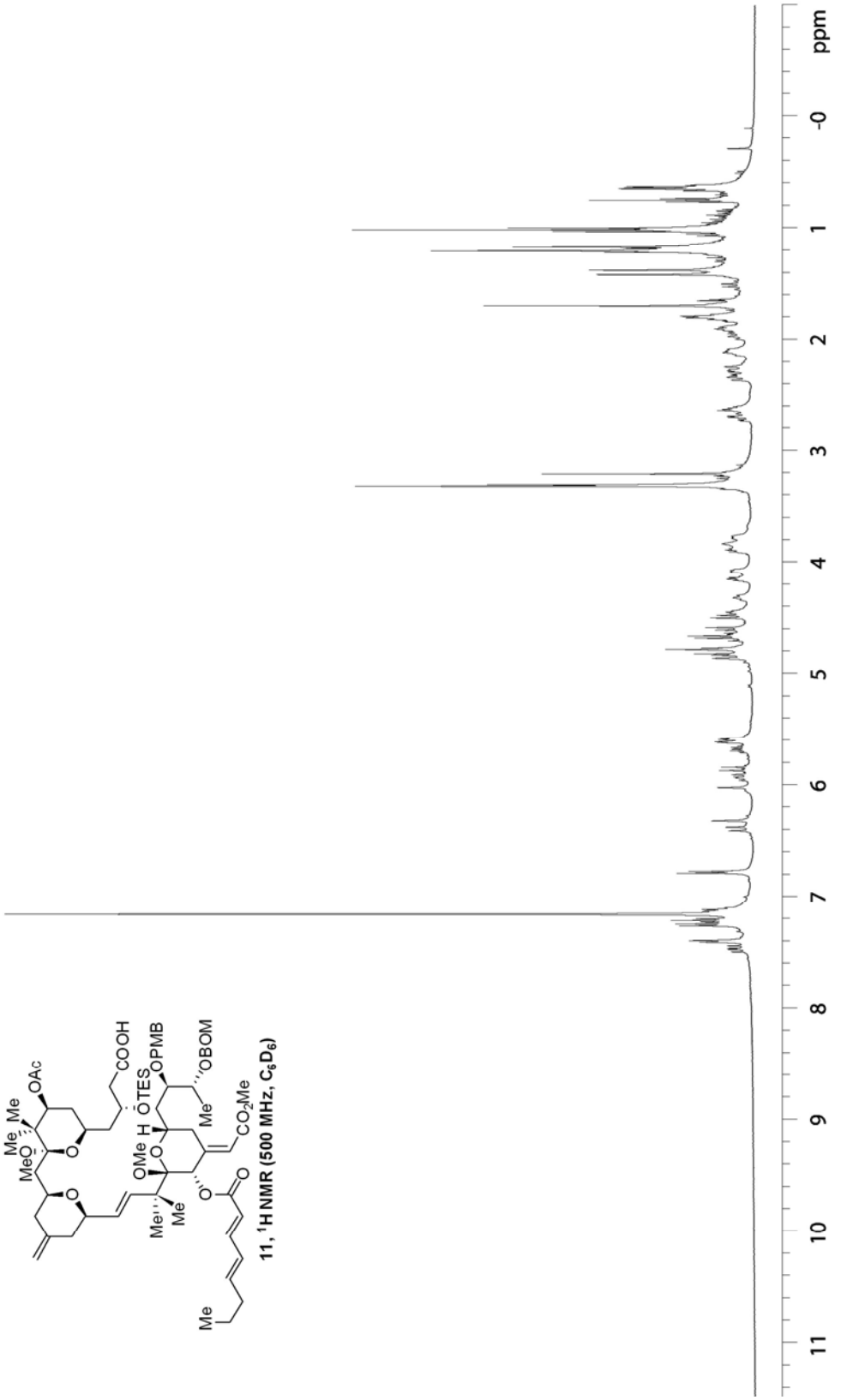
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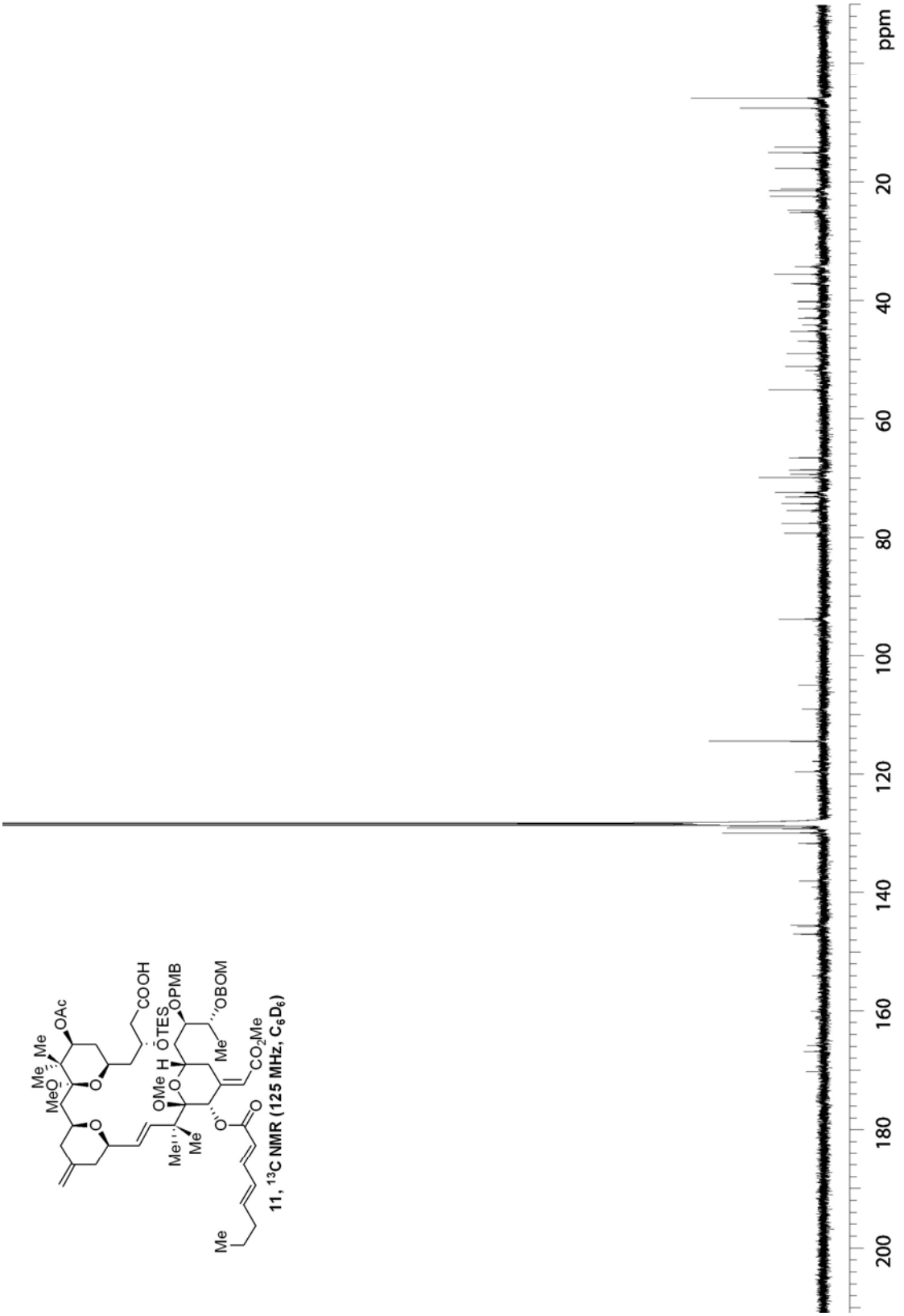
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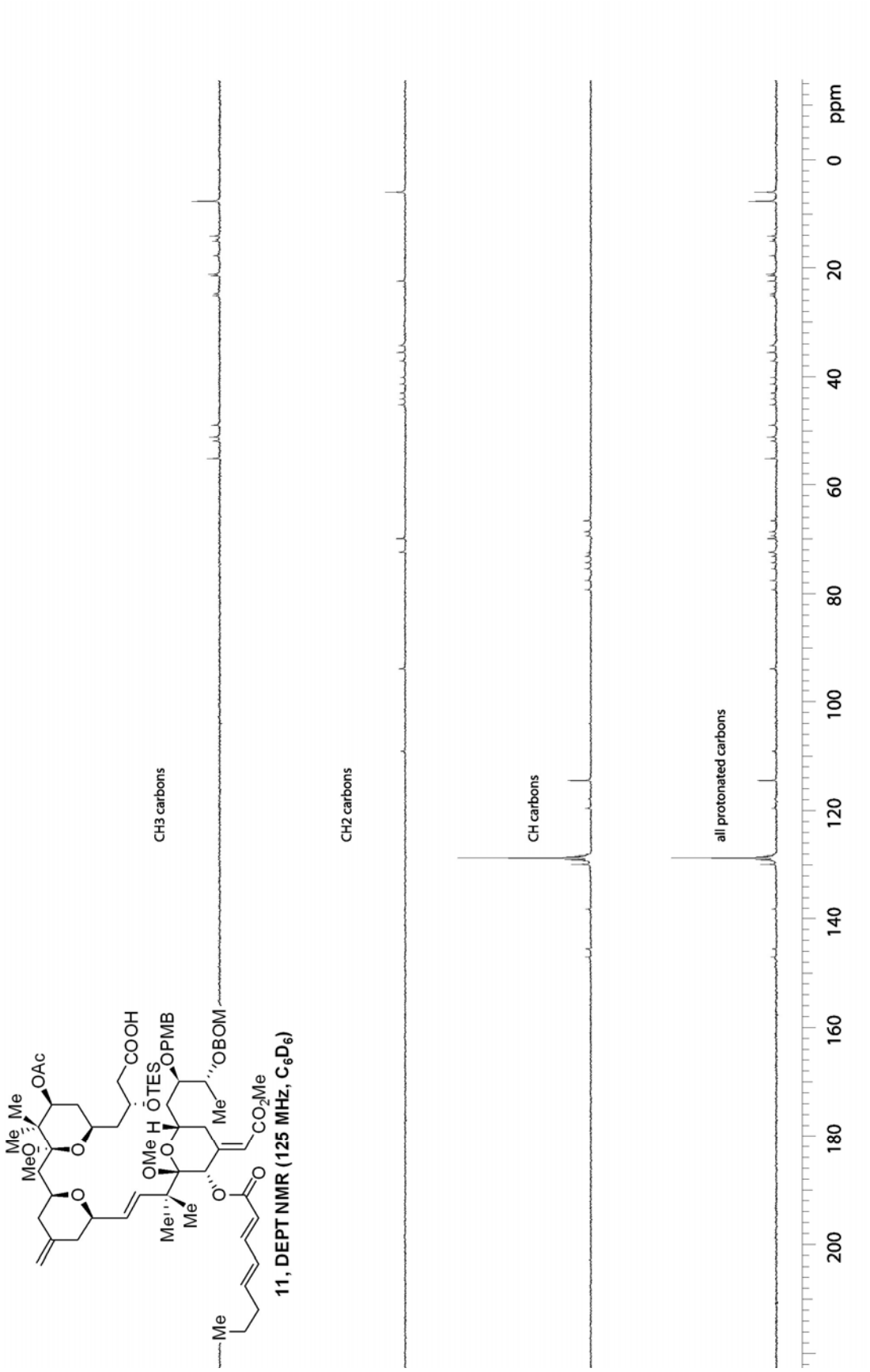
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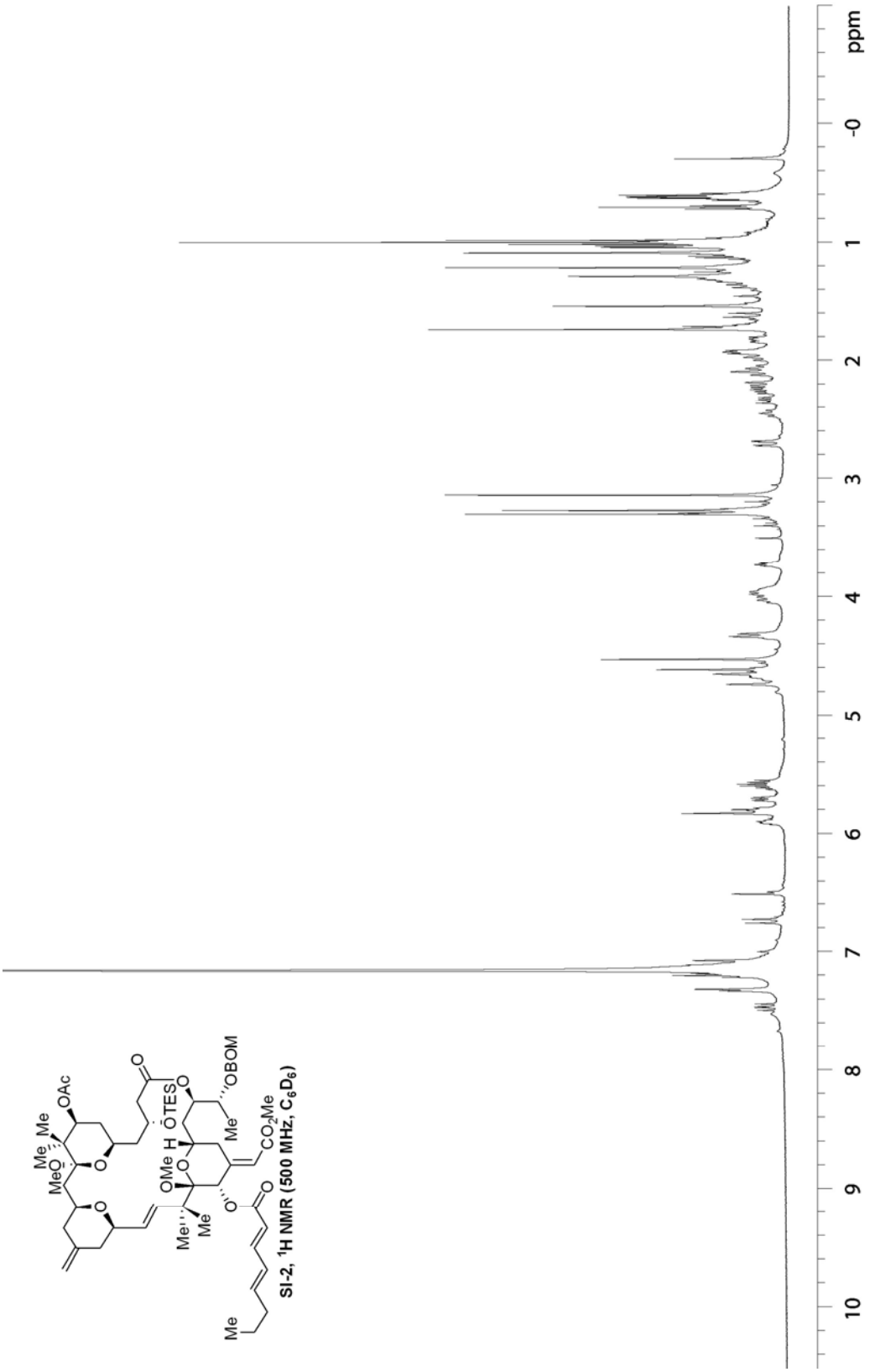
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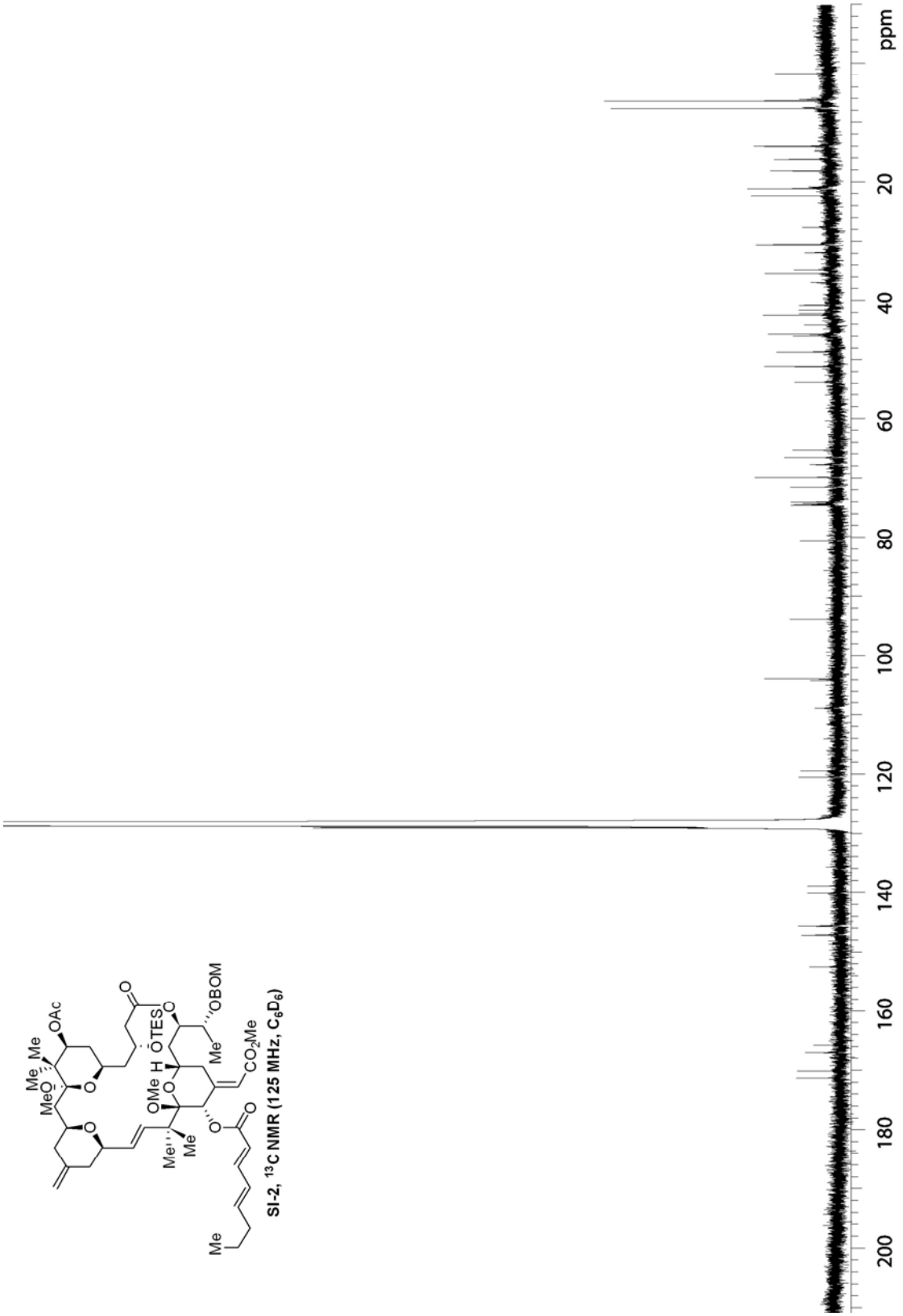

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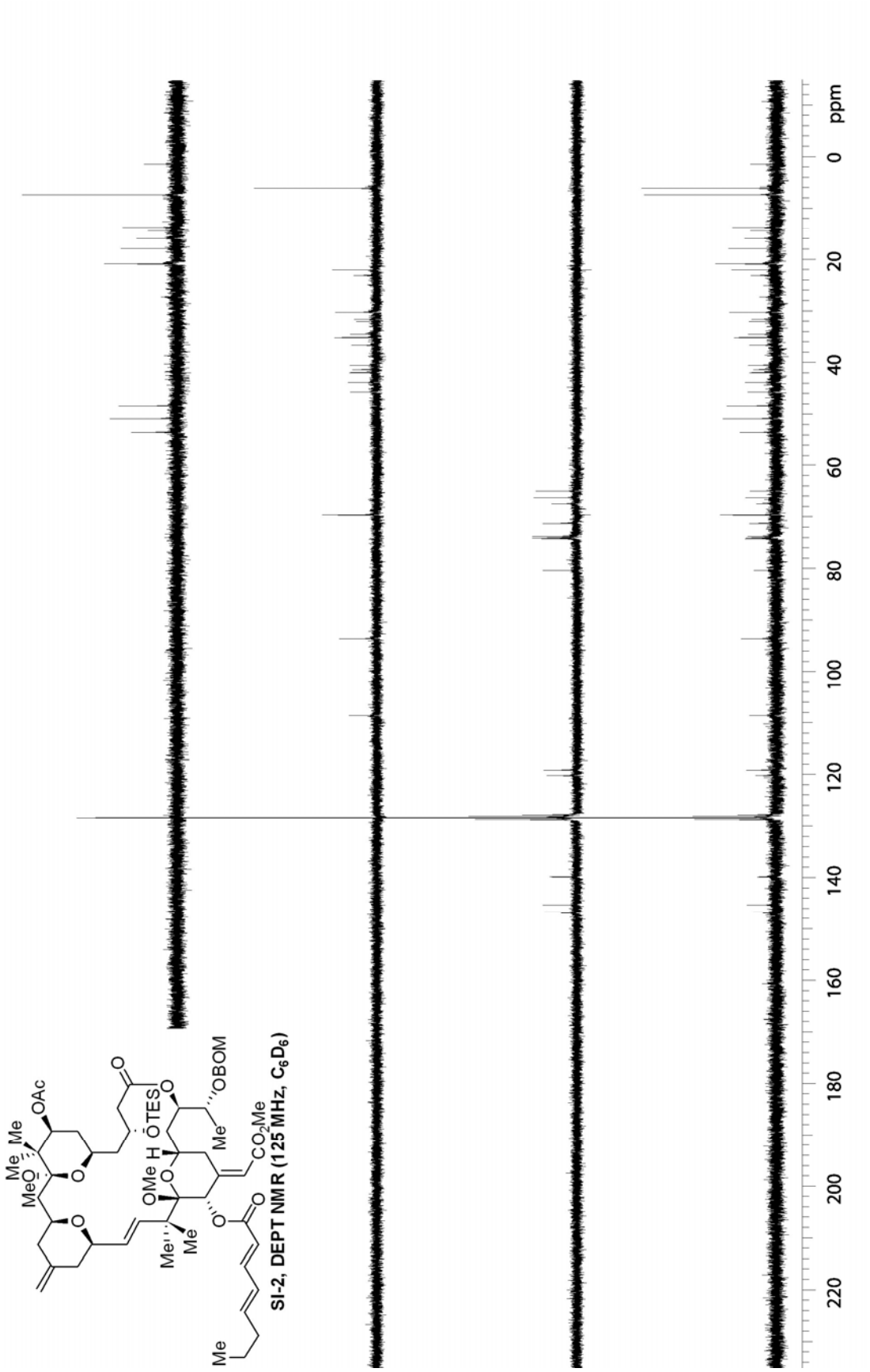
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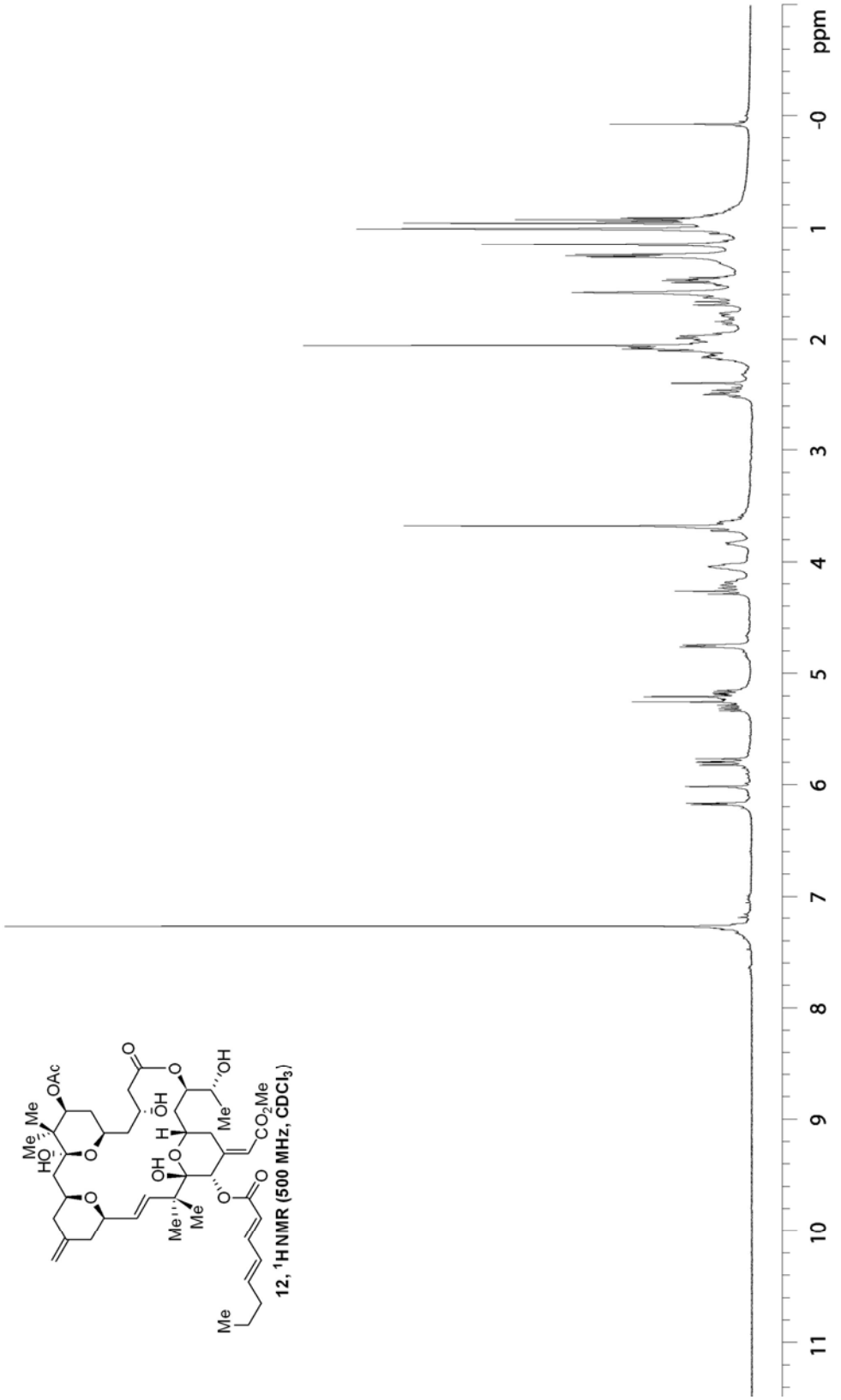
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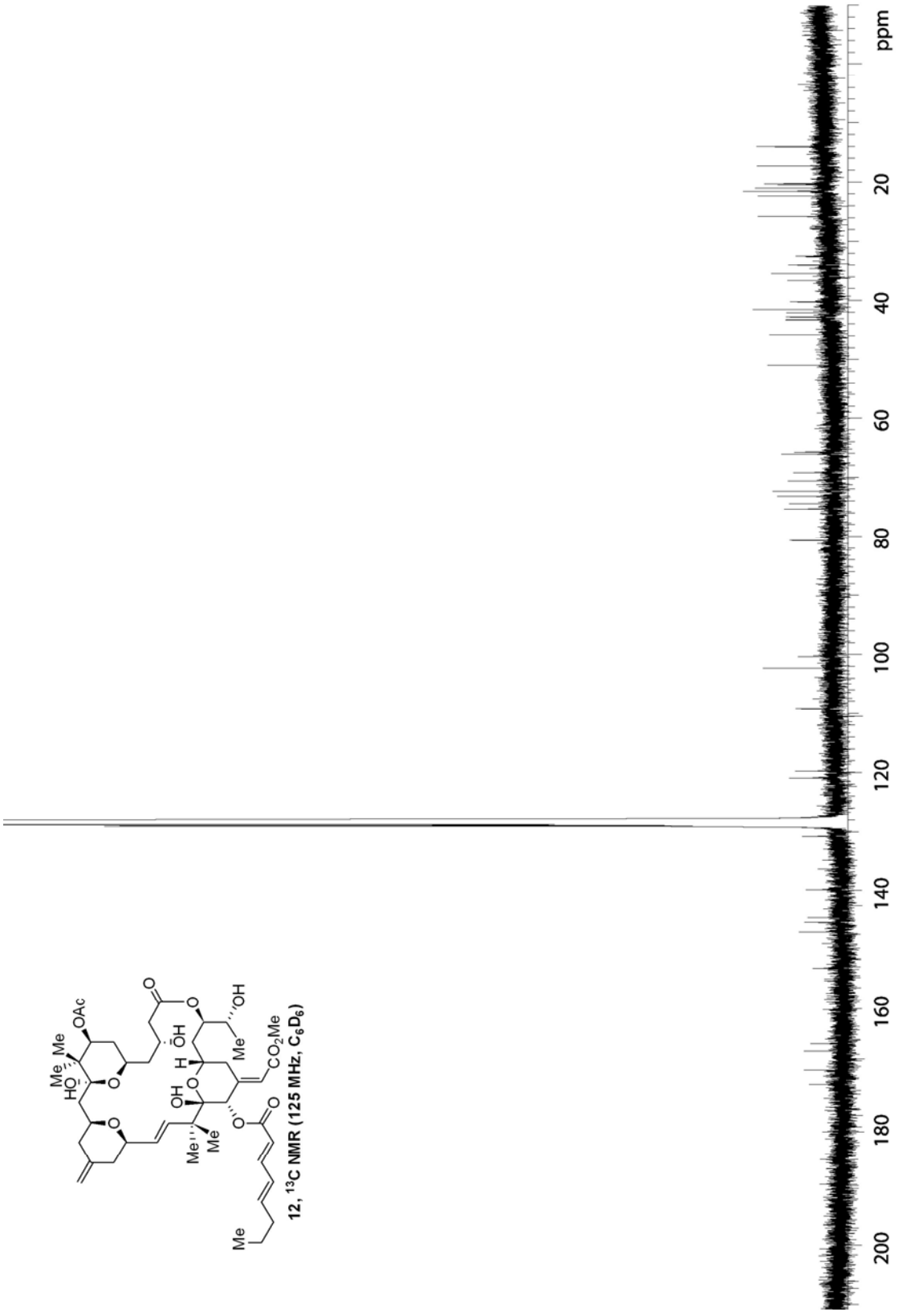
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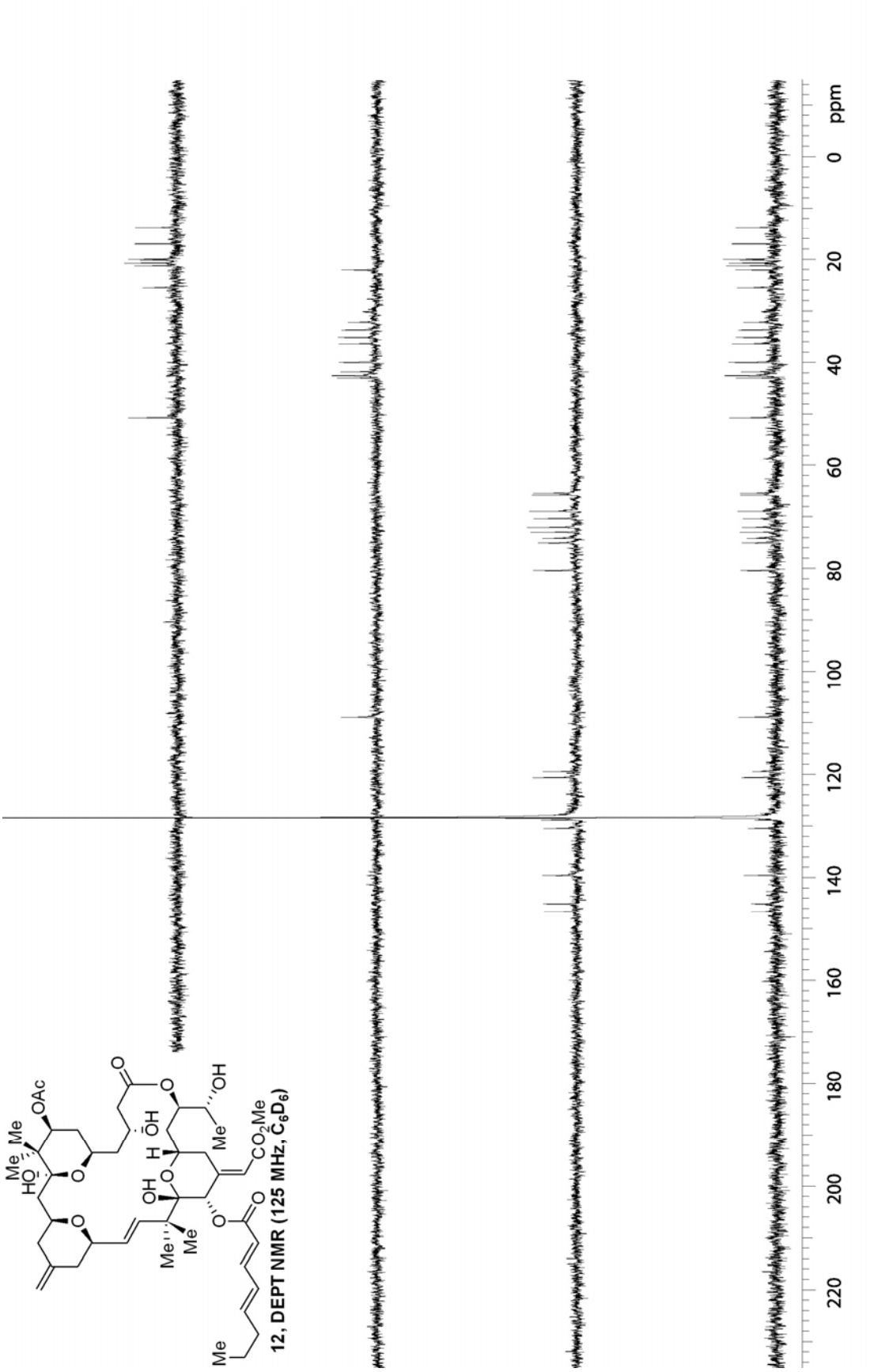
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12, DEPT NMR (125 MHz, C6D6)