Supporting Information to Accompany:

The Bryostatin 1 A-Ring Acetate is Not the Critical Determinant for Antagonism of Phorbol Ester-Induced Biological Responses

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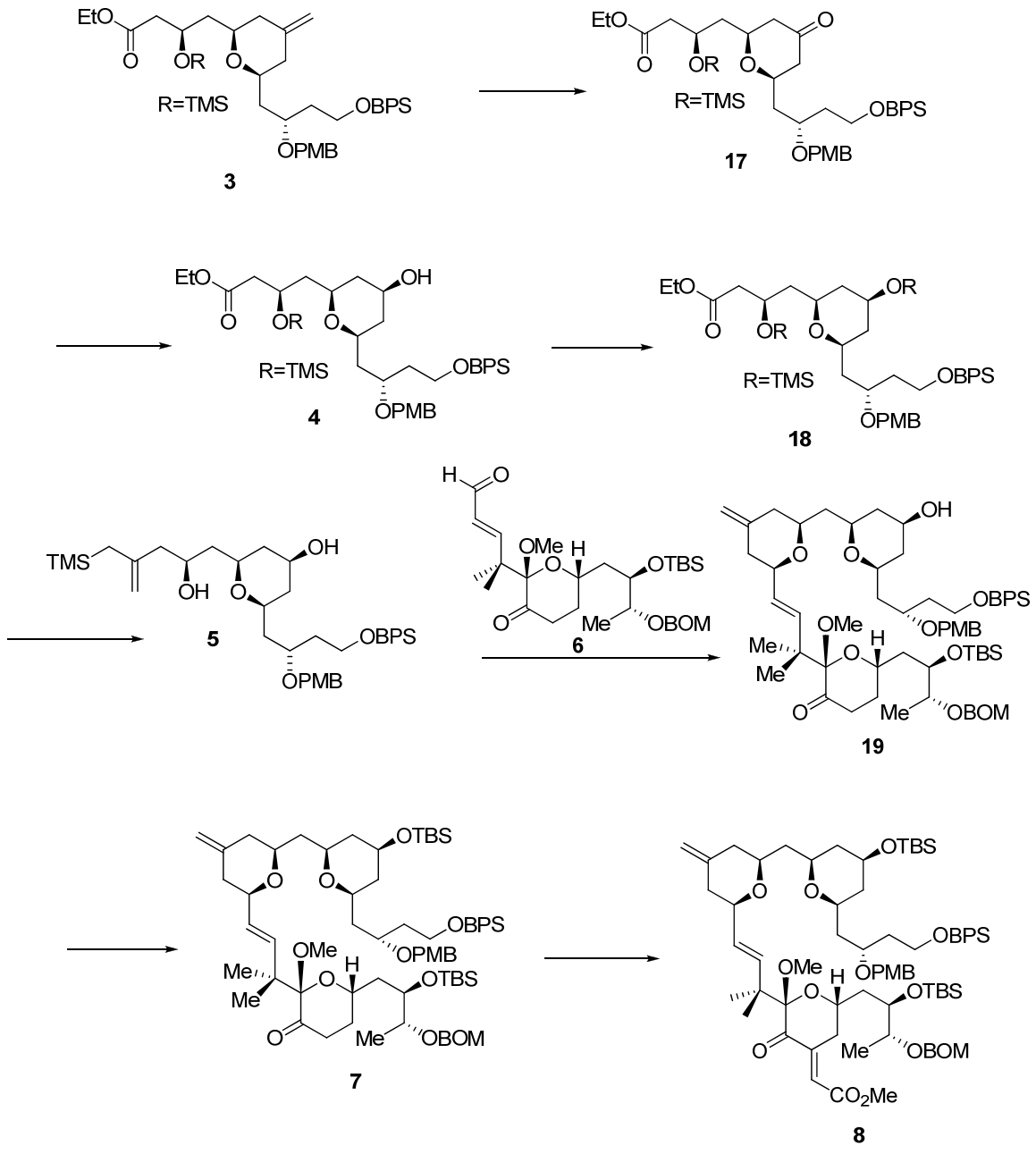
General Experimental Procedures:

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 F254 plates or Silicycle 60Å F254 eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid, or 4-anisaldehyde. 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. 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 of relative to the signal of residual $CHCl_3$ 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 $CDCl_3$ triplet at 77.23 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, apd, dd, ddd, dddd, ddddd, dddddd, t, td,

tt, q, dq, bs, and m stand for the resonance multiplicity singlet, doublet, apparent doublet, doublet of doublets, doublet of doublet of doublets, doublet of doublet of doublet of doublets, doublet of doublet of doublet of doublets of doublets, doublet of doublet of doublet of doublets of doublets of doublets, triplet, triplet of doublets, triplet of triplets, quartet, doublet of quartets, broad singlet, and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ($[\alpha]$, 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 ChemDraw 11.0.

Compounds and Numbering in Supporting Information:



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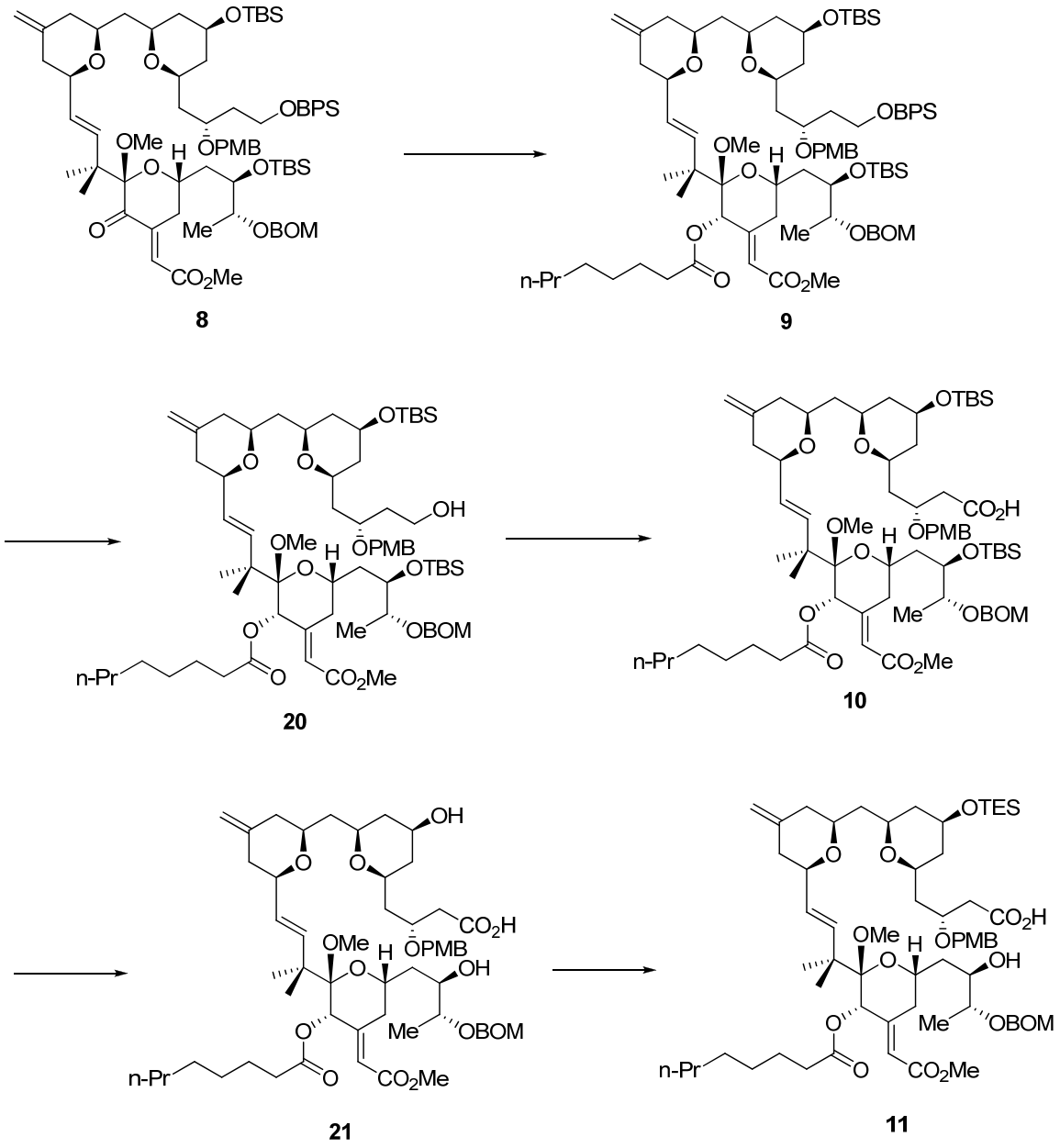

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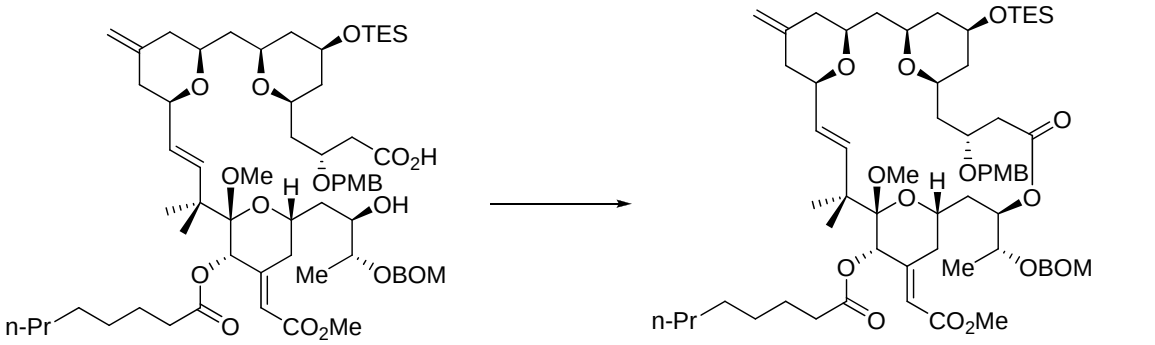

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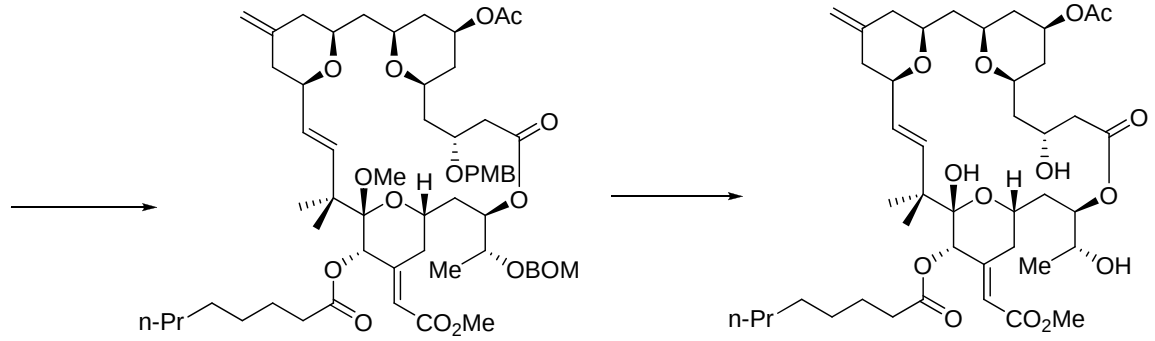

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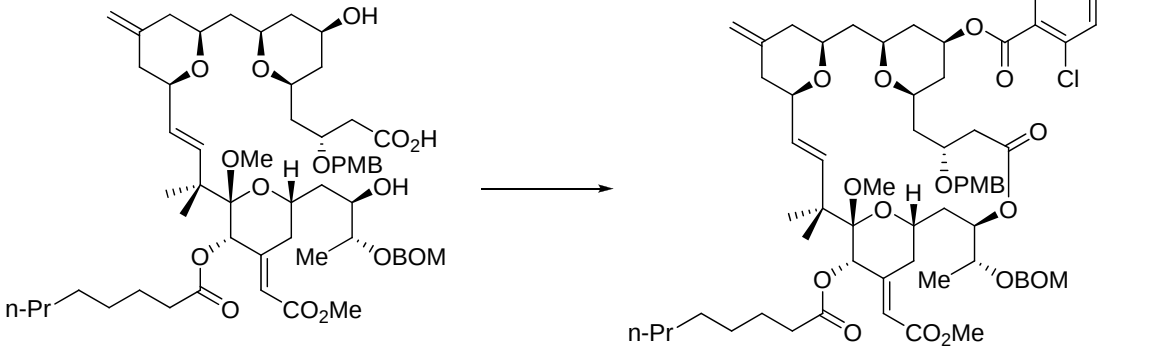

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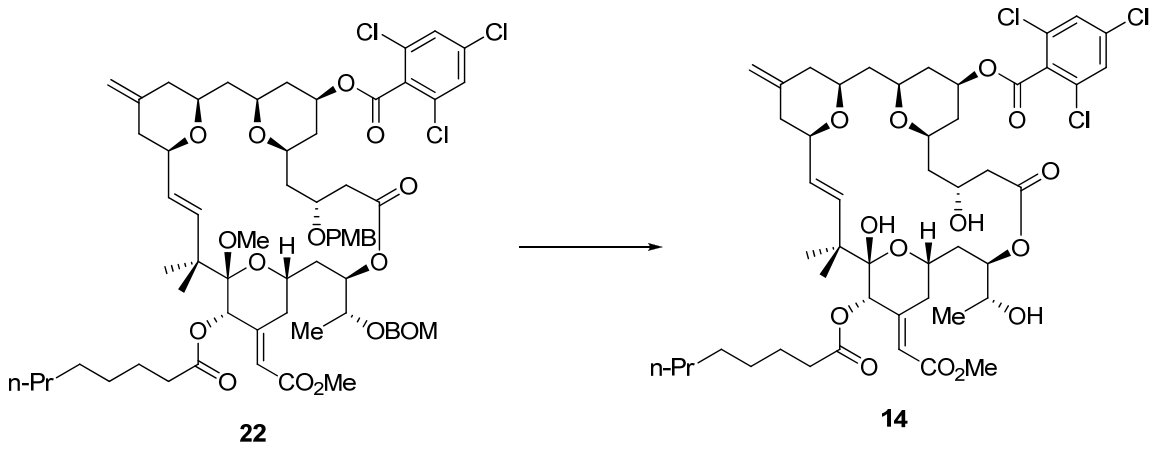

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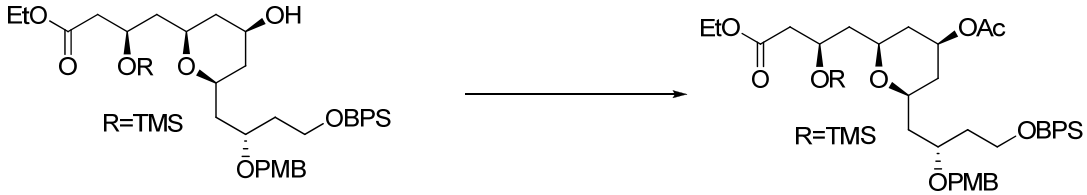

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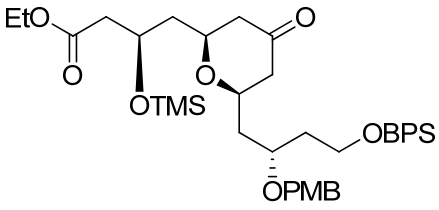
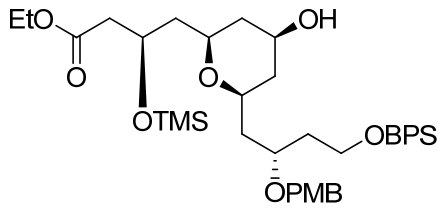
Synthetic Experimental Procedures and Analytical Data:



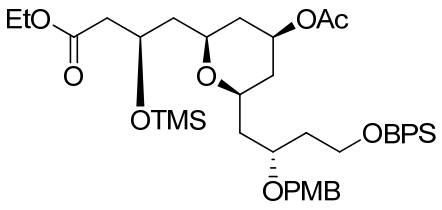
Preparation of (*R*)-ethyl 4-((2*S*,6*R*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)-4-oxotetrahydro-2H-pyran-2-yl)-3-(trimethylsilyloxy)butanoate (17): To a stirring solution of alkene **3**[3] (109.0 mg, 0.146 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL, 0.058 M) in a 50 ml rb flask was added $NaHCO_3$ (109.0 mg). The reaction mixture was cooled to -78 ºC, and then a steady stream of ozone was bubbled through the solution for 1 min, during which time the solution developed a light grey color. The solution was then purged with a steady stream of oxygen until the grey color disappeared. Triphenylphosphine (115 mg, 0.438 mmol, 3.0 equiv) was added in one portion, and the reaction mixture was allowed to warm to rt and stir overnight. The solid $NaHCO_3$ was removed by filtration and the reaction was concentrated under reduced pressure to give a yellow oil. Purification was accomplished by flash chromatography on a 2 x 17 cm column, eluting with 20% EtOAc/hexanes, collecting 13 x 100 mm test tube fractions. The product containing fractions (6-10) were combined and concentrated under reduced pressure to give the product (98.8 mg, 91% yield) as colorless oil: R_f = 0.27 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +13.7 (c=1.65, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 7.69 (dd, *J* = 3.0, 1.4 Hz, 2H), 7.67 (dd, *J* = 3.0, 1.4 Hz, 2H), 7.45-7.36 (m, 6H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.38-4.32 (m, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.08 (dddddd, *J* = 19.1, 10.7, 10.7, 7.1, 7.1, 7.1 Hz, 2H), 3.91 (dddd, *J* = 9.1, 5.7, 5.7, 3.0 Hz, 1H), 3.83 (dddd, *J* = 9.1, 9.1,

2.7, 2.7 Hz, 1H), 3.80 (m, 5H), 3.76-3.70 (m, 2H), 2.50 (dddd, *J* = 14.8, 14.8, 14.8, 7.7 Hz, 2H), 2.40 (ddd, *J* = 14.4, 2.0, 2.0 Hz, 1H), 2.33 (ddd, *J* = 14.4, 2.0, 2.0 Hz, 1H), 2.25 (dd, *J* = 14.1, 11.8 Hz, 1H), 2.20 (dd, *J* = 14.1, 11.8 Hz, 1H), 1.96-1.86 (m, 2H), 1.84-1.73 (m, 2H), 1.72-1.62 (m, 2H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 9H), 0.10 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.1, 171.5, 159.3, 135.8, 135.8, 134.0, 134.0, 131.0, 129.8, 129.5, 127.9, 127.9, 114.0, 73.8, 73.6, 72.7, 71.6, 66.4, 60.6, 60.5, 55.5, 48.3, 48.1, 44.0, 42.8, 42.6, 37.4, 27.1, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 14.4, 0.5; CH_2 δ 71.6, 60.6, 60.6, 48.3, 48.1, 44.0, 42.8, 42.6, 37.4; CH δ 135.8, 129.8, 129.5, 129.5, 127.9, 73.8, 73.6, 72.7, 66.4; C δ 207.1, 171.5, 159.3, 19.3; IR (neat) 2956, 1732, 1612, 1513, 1428, 1377, 1302, 1249, 1173, 1111, 1037, 842, 742, 703, 614, 542 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{42}H_{60}O_8NaSi_2$ (M+Na) 771.3719, found 771.3715.



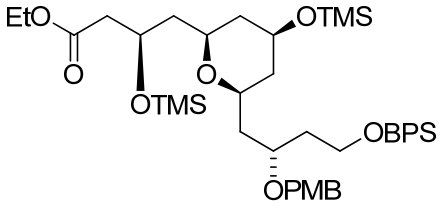
Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)-4-hydroxytetrahydro-2H-pyran-2-yl)-3-(trimethylsilyloxy)butanoate (4): To a solution of ketone **17** (59.0 mg, 0.0788 mmol, 1.0 equiv) in MeOH (5.0 mL, 0.015M) in a 15 mL rb flask at 0 ºC was added $NaBH_4$ (6.0 mg, 0.158 mmol, 2.0 equiv) in one portion. After 30 min at 0 ºC, the reaction was quenched by addition of acetone (0.1 mL), and then concentrated under reduced pressure. Purification was accomplished by flash chromatography column on a 3 x 12 cm column, eluting with 40% EtOAc/hexanes, collecting 18 x 150 mm test tube fractions. The product containing fractions (6-10) were combined and concentrated under

reduced pressure to give the alcohol product **4** (55.6 mg, 94% yield) as colorless oil: R_f = 0.40 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +16 (c=0.29, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.46-7.37 (m, 6H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.40-4.32 (m, 1H), 4.15-4.02 (dddddd, *J* = 18.1, 10.7, 10.7, 7.1, 7.1, 7.1 Hz, 2H), 3.91-3.86 (m, 1H), 3.82-3.74 (m, 7H), 3.56-3.50 (m, 1H), 3.46-3.39 (m, 1H), 2.50 (d, *J* = 5.5 Hz, 1H), 2.49 (d, *J* = 3.0 Hz, 1H), 1.97 (ddd, *J* = 12.4, 4.4, 2.4 Hz, 1H), 1.90-1.76 (m, 4H), 1.68-1.45 (m, 5H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 0.12 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8, 159.3, 135.8, 135.8, 134.1, 134.1, 131.2, 129.8, 129.5, 127.9, 127.9, 114.0, 72.9, 72.1, 72.1, 71.7, 68.3, 66.8, 60.7, 60.5, 55.5, 43.9, 42.9, 42.3, 41.8, 41.5, 37.8, 27.1, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 14.4, 0.5; CH_2 δ 71.7, 60.7, 60.5, 43.9, 42.9, 42.3, 41.8, 41.5, 37.8; CH δ 135.8, 135.8, 129.8, 129.5, 127.9, 127.9, 114.0, 72.9, 72.1, 68.4, 66.8; C δ 171.8, 159.3, 134.1, 134.1, 131.2, 19.4; IR (neat) 3440, 2940, 1735, 1612, 1513, 1428, 1376, 1250, 1175, 1109, 1037, 741, 704, 613, 536 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{42}H_{62}O_8Na$ (M+Na) 773.3881, found 773.3886.



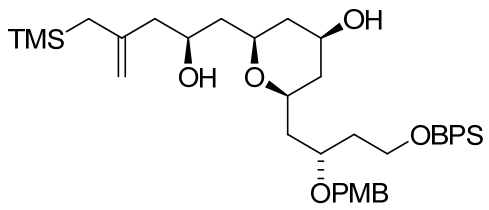
Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*R*)-4-acetoxy-6-((*S*)-4-(*tert*-butyldiphenyl silyloxy) -2-(4-methoxy benzyloxy) butyl) tetrahydro-2H-pyran-2-yl)-3-(trimethyl silyloxy) butanoate (23): To a stirring solution of alcohol **4** (25.0 mg, 0.0333 mmol, 1.0 equiv.) in CH_2Cl_2 (3.3 mL, 0.01 M) in a 15 mL rb flask at rt was added DMAP (4.1 mg, 0.0333 mmol, 1.0 equiv.), pyridine (105.4 mg, 1.332 mmol, 40.0 equiv.), and Ac_2O (68.0 mg, 0.666 mmol, 20.0 equiv.) via syringe. The reaction was

stirred at rt overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 x 12 cm column, eluting with 50% EtOAc/hexane, collecting 13 x 100 mm test tube fractions. The product containing fractions (2-4) were combined and concentrated under reduced pressure to give the product **24** (12.1 mg, 46% yield) as colorless oil: R_f = 0.34 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = + 9 (c=0.27, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.45-7.36 (m, 6H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.88 (dddd, *J* = 11.2, 11.2, 4.9, 4.9 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.33 (dddd, *J* = 6.3, 6.3, 6.3, 6.3 Hz, 1H), 4.07 (dddddd, *J* = 18.1, 10.7, 10.7, 7.3, 7.3, 7.3 Hz, 2H), 3.86 (m, 1H), 3.82-3.74 (m, 5H), 3.62-3.56 (m, 1H), 3.52-3.46 (m, 1H), 2.48 (d, *J* = 2.9 Hz, 1H), 2.47 (s, 1H), 2.05 (s, 3H), 2.03-2.00 (m, 1H), 1.92-1.76 (m, 5H), 1.70-1.56 (m, 4H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.07 (s, 9H), 0.12 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.7, 170.6, 159.3, 135.8, 134.0, 134.0, 131.1, 129.8, 129.5, 127.8, 114.0, 72.8, 72.1, 72.0, 71.8, 70.6, 66.7, 60.7, 60.5, 55.5, 43.9, 42.9, 42.2, 37.8, 37.7, 37.6, 27.1, 21.5, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 21.5, 14.4, 0.5; CH_2 δ 71.8, 60.7, 60.5, 43.9, 42.9, 42.2, 37.8, 37.7, 37.6; CH δ 135.8, 129.8, 129.5, 127.8, 114.0, 72.8, 72.1, 72.0, 70.6, 66.7; C δ 171.7, 170.6, 159.3, 134.0, 134.0, 131.1, 19.4; IR (neat) 2953, 2859, 1738, 1612, 1513, 1428, 1365, 1247, 1175, 1109, 1033, 842, 741, 704, 612, 536 cm^{-1}; HRMS (ESI/ APCI) calcd $C_{44}H_{64}O_9NaSi_2$ for (M+Na) 815.3987, found 815.4017.



Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*R*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)-4-(trimethylsilyloxy) tetrahydro-2H-pyran-2-yl)-3-(trimethylsilyloxy)butanoate (18): To a solution of alcohol **4** (83.1 mg, 0.111mmol, 1.0 equiv) in CH_2Cl_2 (11 mL, 0.01 M) in a 25 mL rb flask was added TMSCl (60.3 mg, 0.555 mmol, 5.0 equiv) and NEt_3 (112.3 mg, 1.11 mmol, 10.0 equiv) dropwise via syringe. After 12 h at rt, the reaction was quenched by the addition of water (5.0 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3.5 x 13 cm column, eluting with 10% EtOAc/hexanes, collecting 18 mm x 150 mm test tube fractions. The product containing fractions (5-9) were combined and concentrated under reduced pressure to give the product **18** (87.6 mg, 96% yield) as colorless oil: R_f = 0.52 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +12.5 (c=2.71, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (ddd, *J* = 4.4, 1.4, 1.4 Hz, 2H), 7.67 (dd, *J* = 4.0, 1.7 Hz, 2H), 7.45-7.35 (m, 6H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.37-4.30 (m, 1H), 4.14-4.02 (m, 2H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 3.80-3.71 (m, 3H), 3.56-3.50 (m, 1H), 3.45-3.38 (m, 1H), 2.50 (d, *J* = 4.7 Hz, 1H), 2.48 (d, *J* = 2.7 Hz, 1H), 1.86-1.72 (m, 5H), 1.66-1.54 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.13 (s, 9H), 0.11 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8, 159.3, 135.8, 135.8, 134.1, 134.1, 129.8, 129.6, 127.9, 114.0, 72.9, 72.2, 72.1,

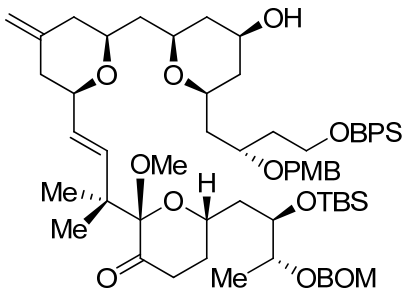
71.8, 68.8, 66.8, 60.7, 60.5, 55.5, 44.0, 43.1, 42.3, 42.3, 41.9, 37.7, 27.1, 19.4, 14.4, 0.5, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 14.4, 0.5, 0.5; CH_2 δ 71.8, 60.7, 60.5, 44.0, 43.1, 42.3, 42.3, 41.9, 37.7; CH δ 135.8, 129.8, 129.6, 127.9, 114.0, 72.9, 72.2, 72.1, 68.8, 66.8; C δ 171.8, 159.3, 135.8, 134.1, 134.1, 19.4; IR (neat) 3071, 2952, 2859, 1613, 1588, 1467, 1428, 1377, 1302, 1250, 1175, 1110, 744 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{45}H_{70}O_8NaSi_3$ (M+Na) 845.4271, found 845.4263.



Preparation of (2*S*,4*R*,6*S*)-2-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)-6-((S)-2-hydroxy-4-((trimethylsilyl) methyl)pent-4-enyl)tetrahydro-2H-pyran-4-ol (5): Powered $CeCl_3 \cdot 7H_2O$ (757.0 mg, 2.03 mmol, 10.0 equiv) was placed in a 10 mL rb flask and heated to 170 ºC under vacuum. After 16 h at 170 ºC, the dried $CeCl_3$ was cooled to rt, and the flask was purged with N_2. THF (2.5 mL) was added, and the mixture was stirred at rt for 2 h. Meanwhile, a 25 mL three-necked rb flask equipped with condenser and magnetic stir bar was charged with magnesium turnings (124.0 mg, 5 mmol, 1.0 equiv), and a crystal of iodine. The flask was heated with a heat gun for 5 min while stirring. THF (5.0 mL) was added into the reaction via syringe, and the reaction mixture was heated with the heat gun to reflux. $TMSCH_2Cl$ (0.613 g, 5.0 mmol, 1.0 equiv) was then added to the reaction dropwise via syringe. The reaction was stirred at rt for 1.5 h to give an assumed 1.0 M solution of $TMSCH_2MgCl$. The $CeCl_3$/THF mixture was cooled to -78 ºC, then a solution of $TMSCH_2MgCl$ (2.03 mL, 2.03 mmol, 10.0 equiv) was added to the reaction dropwise via syringe. After 1 h at -78 ºC, ester **18** (167.2 mg, 0.203 mmol, 1.0 equiv) in

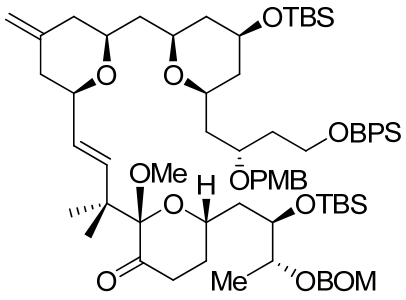
THF (1.0 mL) was added to the reaction via cannula. An additional THF (0.6 mL) rinse was used to transfer the remaining ester residue into the reaction mixture. The solution was allowed to warm to rt and stirred overnight. The mixture was then cooled to -78 ºC, and then a 1N aqueous HCl solution (4.0 mL) was added to the mixture dropwise via syringe. The reaction mixture was then allowed to warm to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 x 12 cm column, eluting with 50% EtOAc/hexanes, collecting 18 x 150 mm test tube fractions. The product containing fractions (19-22) were combined and concentrated under reduced pressure to give the product **5** (103.4 mg, 71% yield) as a colorless oil: R_f = 0.31 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +15.8 (c=1.04, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, *J* = 11.4, 1.7 Hz, 2H), 7.68 (dd, *J* = 4.4, 1.3 Hz, 2H), 7.46-7.38 (m, 6H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.67 (dd, *J* = 14.1, 2.0 Hz, 2H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.00-3.94 (m, 1H), 3.81-3.74 (m, 6H), 3.60-3.50 (m, 2H), 3.44 (bs, 1H), 2.22 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.07 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.96 (ddd, *J* = 12.1, 2.4, 2.0 Hz, 1H), 1.87 (ddd, *J* = 12.4, 2.4, 2.4 Hz, 1H), 1.84-1.78 (m, 3H), 1.72-1.60 (m, 5H), 1.57 (s, 2H), 1.07 (s, 9H), 0.05 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 159.3, 144.6, 135.8, 134.0, 134.0, 131.1, 129.8, 129.7, 127.8, 127.8 114.0, 110.1, 76.3, 72.8, 72.5, 71.6, 69.5, 67.8, 60.5, 55.4, 46.6, 42.4, 41.8, 41.6, 41.5, 37.5, 27.1, 27.1, 19.3, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 27.1, -1.2; CH_2 δ 101.1, 71.6, 60.5, 46.6, 42.4, 41.8, 41.6, 41.5, 37.5, 27.1; CH δ 135.8, 129.8, 129.7, 127.8, 127.8, 114.0, 76.3, 72.8, 72.5, 69.5, 67.8 C

δ 159.3, 144.6, 134.0, 134.0, 131.1, 19.3; IR (neat) 3441, 2941, 1612, 1513, 1427, 1248, 1111, 1037, 848, 738, 702, 614, 541, 505 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{42}H_{62}O_6NaSi_2$ (M+Na) 741.3977, found 741.3979.



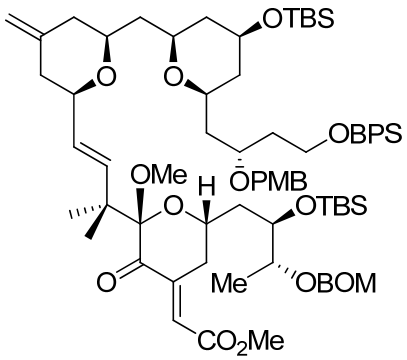
Preparation of (2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxy methoxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-2-((*E*)-4-(6-(((4*S*)-6-((*S*)-4-(*tert*-butyl diphenylsilyloxy)-2-(4-methoxy benzyloxy)butyl)-4-hydroxytetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxydihydro-2H-pyran-3(4H)-one (19): To a solution of hydroxyallylsilane **5** (31.6 mg, 0.0439 mmol, 1.1 equiv) and aldehyde **6**[3] (21.9 mg, 0.0399 mmol, 1.0 equiv) in Et_2O (4.0 mL) in a 10 mL rb flask at -78 ºC was added a 1.0 M solution of TMSOTf in Et_2O (47.9 μL, 0.0479 mmol, 1.2 equiv) dropwise via syringe. After 1 h at -78 ºC, the reaction was quenched by the addition of diisopropylethylamine (0.2 mL), followed by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was warmed to rt, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash chromatography column on a 3 x 12 cm column, eluting with 40% EtOAc/hexanes, collecting 13 x 100 mm test tube fractions. The product containing fractions (7-15) were combined and concentrated under reduced pressure to give the product **19** (43.0 mg, 92% yield) as colorless oil. R_f = 0.38 (50%

EtOAc/Hexanes); $[\alpha]_D^{20}$ = +14 (c=0.08, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.45-7.34 (m, 11H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.06 (dd, *J* = 16.1, 1.0 Hz, 1H), 5.45 (dd, *J* = 16.1, 6.0 Hz, 1H), 4.79 (d, *J* = 1.3 Hz, 2H), 4.66-4.58 (m, 2H), 4.63 (s, 2H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.13-4.04 (m, 2H), 3.95-3.89 (m, 1H), 3.84-3.76 (m, 9H), 3.60-3.46 (m, 3H), 3.29 (s, 3H), 2.45 (d, *J* = 6.4 Hz, 1H), 2.43 (d, *J* = 5.7 Hz, 1H), 2.24 (d, *J* = 13.1 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.02-1.91 (m, 6H), 1.91-1.84 (m, 2H), 1.83-1.71 (m, 2H), 1.68-1.48 (m, 6H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.7, 159.3, 144.3, 138.0, 137.2, 135.8, 135.8, 134.1, 134.0, 131.2, 129.8, 129.6, 129.1, 128.6, 128.6, 128.0, 128.0, 127.9, 127.9, 114.0, 109.1, 104.1, 93.4, 79.1, 75.2, 75.0, 72.7, 72.1, 72.0, 72.0, 70.7, 69.9, 69.6, 68.4, 60.6, 55.5, 55.5, 52.8, 44.4, 42.5, 42.3, 41.8, 41.4, 41.2, 40.5, 38.2, 37.9, 37.7, 30.6, 27.1, 26.1, 23.2, 22.1, 19.4, 18.3, 13.9, -3.8, -4.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 27.1, 26.1, 23.2, 22.1, 13.9, -3.9, -4.5; CH_2 δ 109.1, 93.4, 72.0, 69.6, 60.6, 42.5, 42.3, 41.8, 41.4, 41.2, 40.5, 38.2, 37.9, 37.7, 30.6; CH δ 137.2, 135.8, 135.8, 129.8, 129.6, 129.1, 128.6, 128.6, 128.0, 128.0, 127.9, 127.9, 114.0, 79.1, 75.2, 75.0, 72.7, 72.1, 72.0, 70.7, 69.9, 68.4, C δ 207.7, 159.3, 144.3, 138.0, 134.1, 134.0, 131.2, 104.1, 44.4, 19.4, 18.3; IR (neat) 3445, 2931, 2857, 1724, 1612, 1513, 1465, 1383, 1251, 1110, 1042, 835, 776, 739, 702, 612, 536 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{69}H_{100}O_{12}NaSi_2$ (M+Na) 1199.6646, found 1199.6636.



Preparation of (2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethyl silyloxy) butyl)-2-((*E*)-4-((2R,6S)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethyl silyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl) tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetra hydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxydihydro-2H-pyran-3(4H)-one (7): To a solution of alcohol **19** (83.8 mg, 0.0712 mmol, 1.0 equiv) in CH_2Cl_2 (7.1 mL, 0.001M) in a 25 mL rb flask at 0 ºC was added diisopropylethylamine (45.8 mg, 0.427 mmol, 6.0 equiv) and TBSOTf (47.0 mg, 0.178 mmol, 2.5 equiv) via syringe. The solution was stirred at 0 ºC for 40 min, then quenched by the addition of 1.0 mL of methanol. Stirring was continued for another 10 min, and then saturated aqueous $NaHCO_3$ solution (5 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4 x 10 cm column, eluting with 10% EtOAc/hexanes, collecting 18 x 150 mm test tube fractions. The product containing fractions (6-13) were combined and concentrated under reduced pressure to give the product **7** (89.3 mg, 98% yield) as a colorless oil. R_f = 0.73 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +8.1 (c=0.40, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.44-7.35 (m, 11H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.02 (d, *J* = 5.6 Hz, 1H), 5.47 (dd, *J* = 16.1, 6.3 Hz, 1H), 4.78 (dd, *J* = 10.3, 6.8 Hz, 2H), 4.65 (s, 1H), 4.63 (s, 2H), 4.56 (s, 1H), 4.46 (d, *J* = 10.7

Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.14-4.04 (m, 2H), 3.95-3.88 (m, 1H), 3.85-3.71 (m, 8H), 3.60-3.50 (m, 2H), 3.50-3.44 (m, 1H), 3.29 (s, 3H), 2.43 (dd, *J* = 8.3, 5.9 Hz, 2H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.04-1.90 (m, 6H), 1.86-1.72 (m, 5H), 1.68-1.48 (m, 5H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.4, 159.3, 144.4, 138.1, 137.1, 135.8, 135.8, 134.1, 134.0, 131.3, 129.8, 129.8, 129.6, 129.4, 128.6, 128.0, 127.9, 127.9, 114.0, 109.0, 104.1, 93.4, 79.2, 75.3, 75.1, 72.9, 72.2, 72.0, 72.0, 70.8, 69.9, 69.6, 69.1, 60.6, 55.5, 52.8, 44.4, 42.8, 42.5, 42.5, 42.1, 41.2, 40.4, 38.2, 38.0, 37.7, 30.7, 27.2, 26.1, 23.3, 21.9, 19.4, 18.3, 18.3, 14.0, -3.9, -4.2, -4.3, -4.4; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 27.2, 26.1, 23.3, 21.9, 14.0, -3.9, -4.2, -4.3, -4.4; CH_2 δ 109.0, 93.4, 72.2, 69.6, 60.6, 42.8, 42.5, 42.5, 42.1, 41.2, 40.4, 38.2, 38.0, 37.7, 30.7; CH δ 137.1, 135.8, 135.8, 129.8, 129.8, 129.6, 129.4, 128.6, 128.0, 127.9, 127.9, 114.0, 79.2, 75.3, 75.1, 72.9, 72.0, 72.0, 70.8, 69.9, 69.1, C δ 207.4, 159.3, 144.4, 138.1, 134.1, 134.0, 131.3, 104.1, 44.4, 19.4, 18.3, 18.3; IR (neat) 2930, 2856, 1728, 1513, 1465, 1382, 1250, 1110, 835, 775, 738, 703, 536cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{75}H_{114}O_{12}NaSi_3$ (M+Na) 1313.7516, found 1313.7560.



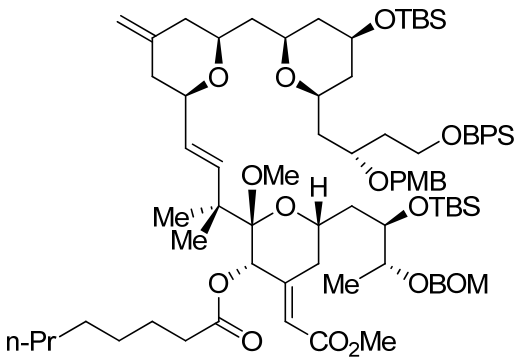
Preparation of (*E*)-methyl 2-((2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-

(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-3-oxo-2H-pyran-4(3H,5H,6H)-ylidene)acetate (8): To a stirring solution of ketone **7** (63.2 mg, 0.0489 mmol, 1.0 equiv.) in THF (0.98 mL, 0.05M) in a 10 mL rb flask at -78 °C was added a freshly prepared 0.25M solution of LDA in THF (0.587 mL, 0.147 mmol, 3.0 equiv.). The mixture was stirred at -78 °C for 30 min, then a 3.0 M solution of methyl glyoxylate in THF (0.489 mL, 1.47 mmol, 30 equiv) was added via syringe. The reaction mixture stirred at -78 ºC for 30 min and was then quenched by addition of 1.0 mL of saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was then partitioned between 5 mL of EtOAc and 5 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 by flash chromatography on a 4 x 11 cm column, eluting with 15% EtOAc/hexanes, collecting 18 x 150 mm test tube fractions. The product containing fractions (9-23) were combined and concentrated under reduced pressure to give a diastereomeric mixture of products (62.1 mg, 92% yield), which were carried into the next step.

To a stirring solution of the aforementioned product (62.1mg, 0.0450 mmol, 1.0 equiv) in pyridine (4.5 mL, 0.01 M) in a 25 mL rb flask with condenser was added DMAP (5.5 mg, 0.040 mmol, 1.0 equiv) and a solution of 0.5 M Ac_2O in CH_2Cl_2 (1.80 mL, 0.890 mmol, 20 equiv) by syringe. The reaction mixture was heated to 60 °C and stirred overnight. The solution was cooled to rt, then diluted with 10 mL of CH_2Cl_2 and 5 mL of saturated

aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 x 12 cm column, eluting with 10% EtOAc/hexanes, collecting 18 x 150 mm test tube fractions. The product containing fractions (4-9) were combined and concentrated under reduced pressure to give the product **8** (57.2 mg, 93% yield) as a colorless oil. R_f = 0.71 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = -16.1 (c=0.90, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.67 (m, 4H), 7.45-7.28 (m, 11H), 7.19 (d, *J* = 8.1Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.55 (t, *J* = 1.7 Hz, 1H), 5.82 (d, *J* = 15.8 Hz, 1H), 5.38 (dd, *J* = 16.1, 6.4Hz, 1H), 4.79 (dd, *J* = 11.1, 4.0 Hz, 2H), 4.65-4.60 (m, 4H), 4.55 (s, 1H), 4.47 (d, *J* = 10.4 Hz, 1H), 4.37 (d, *J* = 10.4 Hz, 1H), 4.11-.4.05 (m, 2H), 3.95-3.89 (m, 1H), 3.86-3.77 (m, 5H), 3.77-3.71 (m, 4H), 3.71-3.65 (m, 1H), 3.59-3.50 (m, 2H), 3.50-3.43 (m, 1H), 3.32 (s, 3H), 2.86 (ddd, *J* = 15.8, 12.4, 3.0 Hz, 1H), 2.28 (d, *J* = 12.8 Hz, 1H), 2.09 (ddd, *J* = 10.1, 7.7, 2.4Hz, 1H), 2.04 (d, *J* = 13.8 Hz, 1H), 1.98 (ddd, *J* = 13.8, 8.1, 5.7 Hz, 1H), 1.90 (t, *J* = 11.1 Hz, 2H), 1.85-1.72 (m, 4H), 1.69-1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.29-1.20 (m, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 9H), 1.04 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.5, 166.3, 159.3, 148.3, 144.2, 138.0, 136.1, 135.8, 134.1, 134.0, 131.2, 130.1, 129.8, 129.6, 128.6, 128.0, 128.0, 127.9, 123.2, 114.0, 109.0, 104.6, 93.5, 79.2, 75.3, 75.1, 72.9, 72.3, 72.0, 71.9, 71.0, 69.9, 69.6, 69.0, 60.5, 55.5, 52.4, 52.0, 44.8, 42.7, 42.5, 42.4, 42.0, 40.6, 40.3, 38.4, 37.9, 36.6, 27.2, 26.1, 26.0, 22.8, 21.4, 19.4, 18.3, 18.2, 13.9, -3.8, -4.3, -4.3, -4.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.4, 52.0, 27.2, 26.1, 26.0, 22.8, 21.4, 13.9, -3.8, -4.3, -4.3, -4.5 ; CH_2 δ 109.0, 93.5, 72.3,

69.6, 60.5, 42.7, 42.5, 42.4, 42.0, 40.6, 40.3, 38.4, 37.9, 36.6; CH δ 136.1, 135.8, 130.1, 129.8, 129.6, 128.6, 128.0, 128.0, 127.9, 123.2, 114.0, 79.2, 75.3, 75.1, 72.9, 72.0, 71.9, 71.0, 69.9, 69.0; C δ 197.5, 166.3, 159.3, 148.3, 144.2, 138.0, 134.1, 134.0, 131.2, 104.6, 44.8, 19.4, 18.3, 18.2; IR (neat) 2934, 2857, 1724, 1513, 1466, 1381, 1250, 1111, 835, 775, 738, 703, 536 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{78}H_{116}O_{14}NaSi_3$ (M+Na) 1383.7565, found 1383.7555.

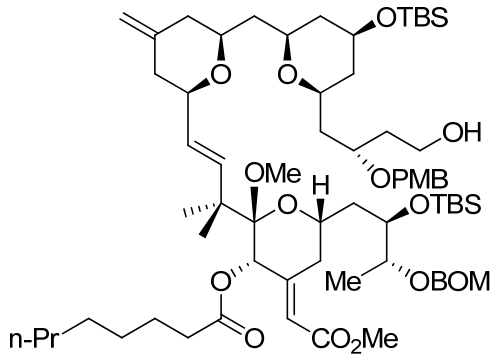


Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethyl silyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylene tetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-ethoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl octanoate (9): To a stirring solution of ketone **8** (14.1 mg, 0.0104 mmol, 1.0 equiv.) in MeOH (2.1 mL, 0.005M) in a 10 mL rb flask at rt was added $CeCl_3 \cdot 7H_2O$ (77.5 mg, 0.208 mmol, 20 equiv). The reaction mixture was stirred at rt until all the $CeCl_3 \cdot 7H_2O$ crystals dissolved. Then the reaction mixture was cooled to -40 °C and kept for 15 min. $NaBH_4$ (3.9 mg, 0.104 mmol, 10 equiv) was then added in one portion. The reaction continued at -40 °C for 3 h. The mixture was diluted with 40% EtOAC/hexanes (10 mL), then quenched by the addition of saturated aqueous NH_4Cl solution (5.0 mL). The mixture was poured into a separatory

funnel with the aid of 50 mL of 40% EtOAc/hexanes. The organic phase was separated, then washed with 10 mL of H_2O and 10 mL of brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was used in the next step without further purification.

To a stirring solution of the previously described crude alcohol in CH_2Cl_2 (1.1 mL, 0.01M) in a 10 mL rb flask at rt, was added pyridine (8.2 mg, 0.104 mmol, 10 equiv), DMAP (2.5 mg, 0.0208 mmol, 2.0 equiv), and octanoic anhydride (14.1 mg, 0.052 mmol, 5.0 equiv). The reaction mixture stirred at rt overnight, after which the solution was diluted with 10 mL of CH_2Cl_2. The mixture was poured into a separatory funnel containing 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 15 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 x 16 cm column, eluting with 8% EtOAc/hexanes, collecting 13 x 100 mm test tube fractions. The product containing fractions (9-15) were combined and concentrated under reduced pressure to give the product **9** (12.6 mg, 82% yield) as a colorless oil. R_f = 0.60 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +3.2 (c=1.45, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69-7.65 (m, 4H), 7.44-7.34 (m, 11H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.93 (d, *J* = 16.1 Hz), 5.88 (s, 1H), 5.57 (s, 1H), 5.43 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.80 (s, 2H), 4.64 (s, 3H), 4.55 (s, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.12-4.06 (m, 2H), 3.92-3.86 (m, 1H), 3.84 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.81 (s, 3H), 3.80-3.70 (m, 3H), 3.79 (s, 3H), 3.57-3.44 (m, 4H), 3.30 (s, 3H), 2.35 (ddd, *J* = 7.3, 7.3, 1.5 Hz, 2H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.17 (d, *J* = 12.7 Hz, 1H), 2.03-1.95 (m, 3H), 1.90 (t, *J* = 12.2 Hz, 1H), 1.85-1.72

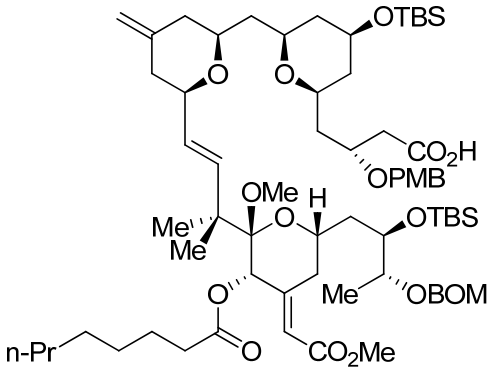
(m, 4H), 1.65-1.52 (m, 7H), 1.33-1.28 (m, 10H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.04 (s, 9H), 0.92-0.85 (m, 21H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 166.6, 159.4, 153.1, 144.4, 138.2, 138.0, 135.8, 135.8, 134.1, 134.1, 131.3, 129.8, 129.8, 129.5, 128.6, 128.0, 127.9, 127.8, 127.5, 117.0, 114.1, 109.0, 102.7, 93.3, 79.1, 75.2, 75.1, 73.0, 72.2, 72.0, 71.6, 70.4, 69.5, 69.1, 68.5, 60.6, 55.5, 51.6, 51.3, 46.1, 42.8, 42.5, 42.5, 42.1, 40.8, 40.4, 38.8, 38.0, 34.6, 33.6, 31.9, 29.3, 29.2, 27.2, 26.1, 25.0, 24.2, 24.2, 22.8, 19.4, 18.3, 18.3, 14.3, 14.0, -3.8, -4.2, -4.3, -4.4; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 27.2, 26.1, 26.1, 24.2, 24.2, 14.3, 14.0, -3.8, -4.2, -4.3, -4.4; CH_2 δ 109.0, 93.3, 72.2, 69.5, 60.6, 42.8, 42.5, 42.5, 42.1, 40.8, 40.4, 38.8, 38.0, 34.6, 33.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.0, 135.8, 135.8, 129.8, 129.5, 128.6, 128.0, 127.9, 127.5, 117.0, 114.0, 79.1, 75.2, 75.1, 73.0, 72.0, 71.6, 70.4, 69.1, 68.5; C δ 172.3, 166.6, 159.4, 153.1, 144.4, 138.2, 134.1, 134.1, 131.3, 127.8, 102.7, 46.1, 19.4, 18.3, 18.3; IR (neat) 2931, 2857, 1722, 1513, 1465, 1381, 1251, 1154, 1111, 836, 775, 739, 702 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{86}H_{132}O_{15}NaSi_3$ (M+Na) 1511.8772, found 1511.8793.



Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-((*S*)-4-hydroxy-2-(4-methoxy benzyloxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-

pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene) tetrahydro-2H-pyran-3-yl octanoate (20): To a stirring solution of TBDPS silyl ether **9** (11.0 mg, 0.00738 mmol, 1.0 equiv) in DMF (0.389 mL, 0.01 M) in a 4 mL reaction vial, was added a solution of 1.0 M TBAF solution in THF (7.4 μL, 0.00738 mmol, 1.0 equiv) and a solution of 1.0 M AcOH solution in DMF (7.4 μL, 0.00738 mmol, 1.0 equiv). The reaction was stirred at rt overnight, then diluted with 40% EtOAc/hexanes (5 mL) and quenched with water (5 mL). The phases were separated and the aqueous phase was extracted three times with 40% EtOAc/hexanes (5 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 2 x 13 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 13 x 100 mm test tube fractions. The product containing fractions (10-20) were combined and concentrated under reduced pressure to provide pure alcohol **20** (8.2 mg, 89%) as colorless oil. R_f = 0.44 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +7.4 (c=0.575, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.36-7.34 (m, 5H), 7.27 (d, *J* = 8.3 Hz), 6.89 (d, *J* = 8.3 Hz, 2H), 5.94 (d, *J* = 16.1 Hz, 1H), 5.89 (s, 1H), 5.57 (s, 1H), 5.42 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.80 (s, 1H), 4.66 (s, 1H), 4.65 (s, 2H), 4.57 (s, 1H), 4.50 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.12-4.06 (m, 2H), 3.92-3.82 (m, 2H), 3.82-3.75 (m, 5H), 3.75-3.65 (m, 5H), 3.55-3.40 (m, 4H), 3.30 (s, 3H), 2.39-2.32 (m, 3H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.18 (d, *J* = 13.2 Hz, 1H), 2.00 (q, *J* = 12.2 Hz, 2H), 1.95-1.86 (m, 3H), 1.84-1.66 (m, 4H), 1.66-1.50 (m, 6H), 1.38-1.20 (m, 8H), 1.22 (dd, *J* = 11.2, 6.3 Hz, 2H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 6H), 0.90-0.84 (m, 21H), 0.08 (s, 3H), 0.06 (s, 3H). 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.4, 166.7, 159.6, 153.1, 144.5, 138.4, 138.1, 130.7, 129.7, 128.6, 128.0, 127.9, 127.3, 117.0, 114.2, 109.0, 102.6,

93.3, 79.4, 75.5, 75.2, 75.1, 72.5, 72.2, 72.2, 71.6, 70.3, 69.5, 68.9, 68.4, 60.4, 55.5, 51.6, 51.3, 46.1, 42.8, 42.5, 42.0, 41.7, 40.9, 40.4, 38.7, 36.9, 36.8, 34.6, 31.9, 29.3, 29.2, 26.1, 26.1, 25.0, 24.2, 24.1, 22.8, 18.3, 18.3, 14.3, 14.0, -3.8, -4.3, -4.4; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 26.1, 26.1, 24.2, 24.1, 14.3, 14.0, -3.8, -4.3, -4.4 ; CH_2 δ 109.0, 93.3, 72.2, 69.5, 60.4, 42.8, 42.5, 42.0, 41.7, 40.9, 40.4, 38.7, 36.9, 36.8, 34.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.4, 129.7, 128.6, 128.0, 127.9, 127.3, 117.0, 114.2, 79.4, 75.5, 75.2, 75.1, 72.5, 72.2, 71.6, 70.3, 68.9, 68.4; C δ 172.4, 166.7, 159.6, 153.1, 144.5, 138.1, 130.7, 102.6, 46.1, 18.3, 18.3; IR (neat) 2930, 2857, 1722, 1514, 1463, 1380, 1250, 1155, 1044, 836, 775 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{70}H_{114}O_{15}NaSi_2$ (M+Na) 1273.7594, found 1273.7595.

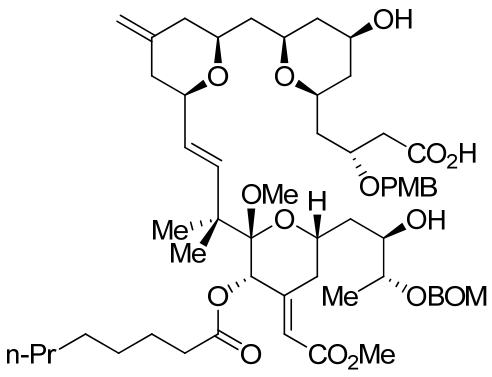


Preparation of (*R*)-4-((2*R*,4*S*,6*S*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy) butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-(octanoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-4-(tert-butyldimethylsilyloxy) tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyloxy) butanoic acid (10): To a stirring solution of alcohol **20** (7.1 mg, 0.0057 mmol, 1.0 equiv) in CH_2Cl_2 (570 μL), in a 4 mL reaction vial at 0 °C, was added diisopropylethylamine (21 μL, 0.119 mmol, 21.0 equiv) and DMSO (12 μL, 0.171 mmol, 30.0 equiv). The

solution stirred at 0 °C for 5 min and SO_3·Py (5.4 mg, 0.0340 mmol, 6.0 equiv) was added in one portion. Stirring continued at 0 °C for 1.25 h, after which the reaction mixture was diluted with CH_2Cl_2 (1 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture stirred at room temperature for 10 min until effervescence was complete. The reaction mixture was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was washed through a small plug of silica gel with 20 % EtOAc/hexanes (30 mL), and the solvent was removed under reduced pressure to provide the aldehyde, which was used in the next step without further purification.

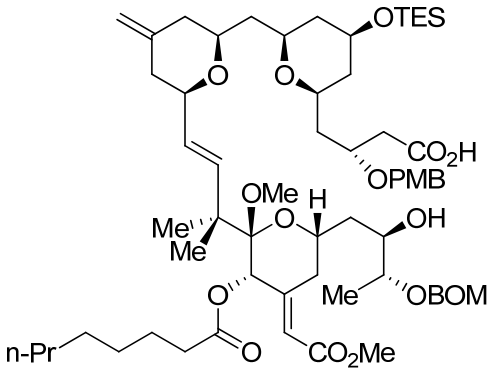
To a stirring solution of the aforementioned aldehyde (7.1 mg, 0.0057 mmol, 1.0 equiv) in 2-methyl-2-butene (570 μL) and *t*-BuOH (570 μL), in a 4 mL reaction vial at rt, was added a 1.25 M aqueous solution of KH_2PO_4 (109 μL). The mixture was cooled to -10 °C, and $NaClO_2$ (80% Aldrich, 13 mg, 0.114 mmol, 20.0 equiv) was added in one portion. The reaction mixture stirred vigorously at -10 °C for 4 h, and was then quenched with aqueous pH 4 buffer solution (1 mL). The reaction mixture was partitioned between CH_2Cl_2 (5 mL) and aqueous pH 4 buffer solution (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 0.8 x 6.5 cm silica gel column, eluting with 20 % EtOAc/hexanes then 1 % MeOH / 30 % EtOAc/ hexanes, collecting 6 x 50 mm test tube fractions. The product containing fractions (10-21) were combined

and concentrated under reduced pressure to provide pure carboxylic acid **10** (8.0 mg, quant. yield over 2 steps) as a colorless oil: R_f = 0.38 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +12 (c = 0.27, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.28 (m, 5H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 5.8 Hz, 1H), 5.88 (s, 1H), 5.59 (s, 1H), 5.44 (dd, *J* = 15.8, 6.1 Hz, 1H), 4.82 (dd, *J* = 10.1, 7.1 Hz, 2H), 4.66 (s, 2H), 4.60 (s, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.14-4.05 (m, 3H), 3.87 (ddd, *J* = 12.4, 6.4, 6.4 Hz, 1H), 3.81 (s, 3H), 3.77 (t, *J* = 5.0 Hz, 1H), 3.75-3.68 (m, 4H), 3.57-3.40 (m, 4H), 3.31 (s, 3H), 2.61 (dddd, *J* = 15.4, 15.4, 15.4, 5.4 Hz, 2H), 2.40-2.31 (m, 3H), 2.28 (d, *J* = 13.1 Hz, 1H), 2.17 (d, *J* = 12.4 Hz, 1H), 2.08-1.88 (m, 5H), 1.84-1.72 (m, 3H), 1.70-1.52 (m, 5H), 1.35-1.25 (m, 8H), 1.24 (dd, *J* = 11.8, 4.0 Hz, 2H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 6H), 0.90-0.86 (m, 21H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.2, 172.5, 166.8, 159.6, 153.2, 144.3, 138.8, 137.9, 130.3, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.2, 109.1, 102.6, 93.1, 79.6, 75.3, 75.1, 73.3, 72.5, 72.2, 72.1, 71.6, 70.1, 69.5, 68.8, 68.4, 55.5, 51.6, 51.4, 46.1, 42.8, 42.2, 42.0, 42.0, 40.8, 40.4, 40.0, 38.7, 34.6, 33.6, 31.9, 29.3, 29.2, 26.1, 26.1, 25.0, 24.4, 24.0, 22.8, 18.3, 14.3, 14.0, -3.8, -4.3, -4.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.4, 26.1, 26.1, 24.4, 24.0, 14.3, 14.0, -3.8, -4.3, -4.5 ; CH_2 δ 109.1, 93.1, 72.5, 69.5, 42.8, 42.2, 42.0, 42.0, 40.8, 40.4, 40.0, 38.7, 34.6, 33.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.8, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.1, 79.6, 75.3, 75.1, 73.3, 72.2, 72.1, 71.6, 70.1, 68.8, 68.4; C δ 173.2, 172.5, 166.8, 159.6, 153.2, 144.3, 137.9, 130.3, 102.6, 46.1, 18.3; IR (neat) 2930, 2857, 1722, 1514, 1463, 1380, 1250, 1156, 1111, 836, 775, 542 cm^{-1} ; HRMS (ESI/ APCI) calcd for $C_{70}H_{112}O_{16}NaSi_2$ (M+Na) 1287.7381, found 1287.7361.



Preparation of (*R*)-4-((2*S*,4*S*,6*R*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-(octanoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-4-hydroxy tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyloxy)butanoic acid (21): To a stirring solution of TBS ether **10** (7.6 mg, 0.0060 mmol, 1.0 equiv) in 9:1 THF/ pyridine (600 μL, 0.01 M) in a 4 mL plastic vial was added HF·Py (20 %, 240 μL). The solution was stirred at rt for 48 h, then diluted with 50 % EtOAc/hexanes (50 mL), and washed with brine (2 x 10 mL). The solution was dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 2 x 14 cm silica gel column, eluting with 10% MeOH/40% EtOAc/hexanes, collecting 10 x 130 mm test tube fractions. The product containing fractions (6-8) were combined and concentrated under reduced pressure to provide pure product **21** (5.4 mg, 87%) as a colorless oil. R_f = 0.48 (MeOH/EtOAc/Hexanes = 10:40:50); $[\alpha]_D^{20}$ = +6 (c=0.20, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.29 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.00 (d, *J* = 16.1 Hz, 1H), 5.87 (s, 1H), 5.54 (s, 1H), 5.40 (dd, *J* = 16.1, 6.4 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 4.70 (s, 2H), 4.66 (d, *J* = 2.9 Hz, 2H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.46 (d, *J* = 10.7 Hz, 1H), 4.22-4.16 (m, 1H), 4.14-4.06 (m, 2H), 3.86 (m, 1H), 3.80 (s, 3H), 3.78-3.72 (m, 1H), 3.70-3.62 (m, 5H),

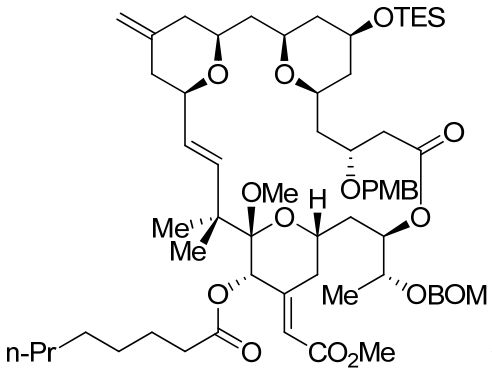
3.52-3.40 (m, 4H), 3.33 (s, 3H), 2.61 (dddd, J = 15.6, 15.6, 15.6, 5.9 Hz, 2H), 2.40-2.32 (m, 3H), 2.22 (t, J = 14.6 Hz, 3H), 2.05-1.85 (m, 5H), 1.80-1.55 (m, 7H), 1.34-1.24 (m, 10H), 1.18-1.08 (m, 9H), 0.90-0.87 (m, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.5, 172.3, 166.9, 159.6, 153.2, 144.4, 139.7, 137.7, 130.2, 129.7, 128.7, 128.1, 128.1, 127.0, 116.8, 114.2, 109.1, 102.9, 93.9, 80.0, 77.9, 75.1, 72.9, 72.5, 72.2, 72.2, 71.3, 70.1, 68.2, 68.2, 60.6, 55.5, 51.5, 51.4, 46.2, 42.2, 41.8, 41.5, 41.1, 40.8, 40.8, 39.9, 34.7, 31.9, 29.9, 29.3, 29.1, 25.0, 24.9, 24.9, 23.0, 22.8, 17.0, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.5, 51.4, 25.0, 23.0, 17.0, 14.3; CH_2 δ 109.1, 93.9, 72.2, 70.1, 42.2, 41.8, 41.5, 41.1, 40.8, 40.8, 39.9, 34.7, 31.9, 29.9, 29.3, 29.1, 24.9, 24.9, 22.8; CH δ 139.7, 129.7, 128.7, 128.1, 128.1, 127.0, 116.8, 114.2, 80.0, 77.9, 75.1, 72.9, 72.5, 72.2, 72.2, 71.3, 68.2, 68.2; C δ 173.5, 172.3, 166.9, 159.6, 153.3, 144.4, 137.7, 130.2, 102.9, 46.2; IR (neat) 3426, 2930, 1719, 1514, 1458, 1379, 1247, 1156, 1105, 1038, 745 cm^{-1}; HRMS (ESI/ APCI) calcd $C_{58}H_{84}O_{16}Na$ for (M+Na) 1059.5657, found 1059.5675.



Preparation of (*R*)-4-((2*R*,4*S*,6*S*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-(octanoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)-4-(triethyl silyloxy)tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyloxy)butanoic acid (11): To a stirring solution of alcohol **21** (3.0 mg, 0.0029 mmol, 1.0 equiv) in CH_2Cl_2 (116 μL,

0.025 M) in a 4 mL reaction vial at rt was added DMAP (1.6 mg, 0.013 mmol, 4.5 equiv). The reaction was cooled to -15 °C, then a 1.0 M solution of TESCl in CH_2Cl_2 (6.1 μL, 0.0061 mmol, 2.1 equiv) was added by syringe. Stirring was continued for 90 min. The reaction was then quenched by addition of 1 mL of saturated aqueous $NaHCO_3$ solution, and the mixture was partitioned between 10 mL of EtOAc and 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 0.6 x 4 cm silica gel column, eluting with 5% MeOH/35% EtOAc/hexanes, collecting 6 x 50 mm test tube fractions. The product containing fractions (11-25) were combined and concentrated under reduced pressure to provide pure product **11** (2.5 mg, 76%) as a colorless oil. R_f = 0.63 (MeOH/EtOAc/Hexanes = 5:35:60); $[\alpha]_D^{20}$ = +5 (c=0.085, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 5H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.98 (d, *J* = 15.6 Hz, 1H), 5.88 (s, 1H), 5.56 (s, 1H), 5.42 (dd, *J* = 16.1, 6.3 Hz, 1H), 4.90 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.70-4.60 (m, 4H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.47 (d, *J* = 10.7 Hz, 1H), 4.26-4.18 (m, 1H), 4.15-4.05 (m, 1H), 3.90-3.85 (m, 1H), 3.81 (s, 3H), 3.74-3.62 (m, 6H), 3.56-3.40 (m, 4H), 3.34 (s, 3H), 2.62 (dddd, *J* = 15.6, 15.6, 15.6, 5.4 Hz, 2H), 2.35 (ddd, *J* = 7.3, 7.3, 2.9 Hz, 3H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.20 (d, *J* = 12.2 Hz, 1H), 2.10-2.00 (m, 2H), 2.00-1.88 (m, 3H), 1.86-1.80 (m, 1H), 1.80-1.55 (m, 7H), 1.34-1.22 (m, 10H), 1.12 (s, 6H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.88 (m, 6H), 0.60 (q, *J* = 7.8 Hz, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0, 172.3, 166.8, 159.5, 153.2, 144.3, 139.2, 139.2, 137.7, 129.6, 128.7, 128.1, 128.1, 126.9, 116.8, 114.1, 109.1, 102.8, 93.9, 79.7, 78.0, 77.4, 75.7, 73.6, 72.4, 72.2, 72.1, 71.1, 70.1, 68.6,

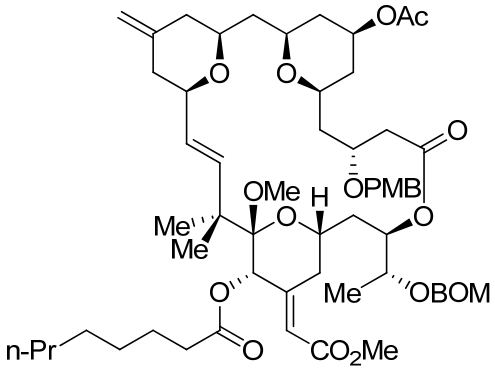
68.2, 55.5, 51.4, 51.4, 46.2, 42.9, 42.3, 42.1, 40.8, 40.7, 39.8, 34.6, 31.9, 31.8, 29.9, 29.3, 29.2, 25.0, 24.6, 23.6, 22.9, 22.8, 17.0, 14.4, 7.1, 5.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.4, 51.4, 24.6, 23.6, 17.0, 14.4, 7.1; CH_2 δ 109.1, 93.9, 72.4, 70.1, 42.9, 42.3, 42.1, 40.8, 40.7, 39.8, 34.6, 31.9, 29.9, 29.3, 29.2, 25.0, 23.6, 22.9, 22.8, 5.2; CH δ 139.2, 139.2, 129.6, 128.7, 128.1, 128.1, 126.9, 114.1, 79.7, 78.0, 75.7, 73.6, 72.4, 72.2, 72.1, 71.1, 68.6, 68.2; C δ 174.0, 172.3, 166.8, 159.5, 153.2, 144.3, 137.7, 116.8, 102.8, 46.2; IR (neat) 2930, 1719, 1513, 1459, 1380, 1247, 1154, 1040, 822, 742 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{64}H_{98}O_{16}NaSi$ (M+Na) 1173.6522, found 1173.6545.



Preparation of macrolactone (12): To a stirring solution of seco-acid **11** (2.0 mg, 0.0017 mmol, 1.0 equiv) in THF (58 μL, 0.03 M) at 0 °C in a 4 mL reaction vial was added triethylamine (1.1 mg, 0.010 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (1.3 mg, 0.0052 mmol, 3.0 equiv) by syringe. The reaction was stirred at 0 °C for 5 min, then warmed to rt and stirred for 2 h. The reaction mixture was diluted with 1:3 THF/toluene (696 μL, 0.0025 M), and taken up into a 1.0 mL gas-tight syringe. The resulting solution was added into a stirring solution of DMAP (4.3 mg, 0.035 mmol, 20 equiv) in toluene (1.2 mL, 0.0015 M) at 40 °C over 12 h by a syringe pump. The vial was rinsed with toluene (0.2 mL) and the rinsing solution was added into reaction by syringe pump over 2 h. The reaction was cooled to rt, and diluted with 50 mL of 40% EtOAc/Hexanes. The solution was washed with 5 mL of saturated

aqueous $NaHCO_3$ solution and 5 mL of brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash column chromatography with a 1.6 x 10 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 12 x 75 mm test tube fractions. The product containing fractions (7-10) were combined and concentrated under reduced pressure to provide pure product **12** (1.8 mg, 91%) as a colorless oil. R_f = 0.45 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +21 (c = 0.075, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 7.40-7.28 (m, 5H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 6.1 Hz, 1H), 5.95 (s, 1H), 5.57 (ddd, *J* = 12.2, 4.0, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.15 (s, 1H), 4.82 (dd, *J* = 12.2, 5.8 Hz, 2H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.51 (s, 2H), 4.17 (m, 1H), 3.95 (m, 2H), 3.75 (s, 3H), 3.73-3.66 (m, 5H), 3.50 (m, 1H), 3.35 (t, *J* = 11.7 Hz, 1H), 3.15-3.05 (m, 4H), 3.08 (s, 3H), 2.54 (d, *J* = 15.6 Hz, 1H), 2.46 (dd, *J* = 15.6, 9.8 Hz, 1H), 2.32-2.26 (m, 3H), 2.20 (d, *J* = 12.7 Hz, 1H), 2.15-2.03 (m, 4H), 1.99 (d, *J* = 12.2 Hz, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.85 (t, *J* = 13.2 Hz, 1H), 1.83-1.67 (m, 3H), 1.64-1.55 (m, 2H), 1.52 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.46-1.38 (m, 1H), 1.30-1.22 (m, 10H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 172.2, 167.0, 159.3, 151.5, 144.7, 141.8, 138.1, 131.1, 129.6, 128.6, 128.1, 127.8, 125.7, 119.4, 113.9, 108.9, 103.4, 93.7, 81.5, 76.5, 75.3, 73.8, 73.7, 73.4, 73.2, 72.2, 70.7, 69.8, 68.6, 67.3, 55.5, 52.8, 51.4, 45.3, 44.2, 43.0, 42.2, 42.1, 42.1, 41.5, 41.0, 34.8, 31.9, 31.1, 30.0, 29.2, 29.1, 26.4, 24.9, 22.8, 20.2, 15.3, 14.3, 7.1, 5.1; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.4, 20.2, 15.3, 14.3, 7.1; CH_2 δ 108.9, 93.7, 72.2, 69.8, 44.2, 43.0, 42.2, 42.1, 42.1, 41.5, 41.0, 34.8, 31.9, 31.1, 30.0, 29.2, 29.1, 24.9, 22.8, 5.1; CH δ

141.8, 129.6, 128.6, 128.1, 127.8, 125.7, 119.4, 113.9, 81.5, 76.5, 75.3, 73.8, 73.7, 73.4, 73.2, 70.7, 68.6, 67.3 ; C δ 172.3, 172.2, 167.0, 159.3, 151.5, 144.7, 138.1, 131.1, 103.4, 45.3; IR (neat) 2930, 1725, 1513, 1459, 1377, 1246, 1156, 1088, 1044, 824, 742, 644, 590, 535 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{64}H_{96}O_{15}NaSi$ (M+Na) 1155.6416, found 1155.6415.

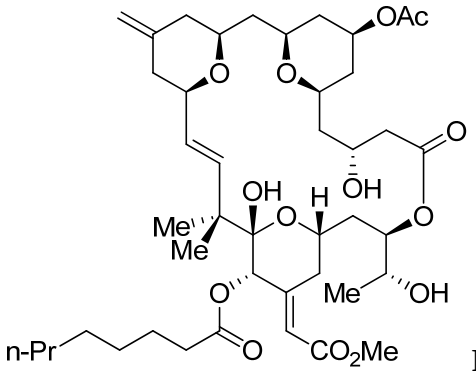


Preparation of Protected Analogue (13): To a stirring solution of TES ether **12** (2.0 mg, 0.0018 mmol, 1.0 equiv) in 9:1 THF/ pyridine (272 μL, 0.0067 M) in a 4 mL plastic vial was added HF·Py (20 %, 108 μL). The solution was stirred at rt for 48 h, then diluted with 50 % EtOAc/hexanes (50 mL), and washed with brine (3 x 5 mL). The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was carried into the next step without further purification.

To a stirring solution of the aforementioned alcohol in CH_2Cl_2 (352 μL, 0.005 M) in a 4 mL reaction vial at rt was added pyridine (7.0 mg, 0.088 mmol, 50 equiv), DMAP (2.2 mg, 0.018 mmol) and Ac_2O (5.4 mg, 0.053 mmol, 30 equiv). The mixture was stirred at rt overnight, then diluted with 1 mL of CH_2Cl_2 and quenched with 1 mL of saturated aqueous $NaHCO_3$ solution. The mixture was then partitioned between 10 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (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 chromatography with a 1 x 9 cm silica gel column, eluting with 50% EtOAc/hexanes, collecting 12 x 75 mm test tube fractions. The product containing fractions (4-7) were combined and concentrated under reduced pressure to provide pure product **13** (1.8 mg, 95% over 2 steps) as a colorless oil: R_f = 0.45 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +13 (c = 0.080, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 5.58 (ddd, *J* = 11.7, 4.4, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.18 (s, 1H), 4.86-4.80 (m, 3H), 4.77 (d, *J* = 7.3 Hz, 2H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 10.7 Hz, 1H), 4.47 (d, *J* = 10.7 Hz, 1H), 4.22-4.16 (m, 1H), 3.99-3.92 (m, 2H), 3.76 (s, 3H), 3.73-3.66 (m, 5H), 3.52-3.40 (m, 2H), 3.18 (t, *J* = 10.7 Hz, 1H), 3.08 (s, 3H), 2.52 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.47 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.32-2.26 (m, 3H), 2.20 (d, *J* = 13.2 Hz, 1H), 2.13-2.07 (m, 2H), 2.05 (s, 3H), 1.99 (d, *J* = 14.7 Hz, 1H), 1.94 (d, *J* = 11.7 Hz, 1H), 1.64-1.50 (m, 3H), 1.46-1.38 (m, 1H), 1.34-1.22 (m, 10H), 1.09 (s, 6H), 1.07 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.2, 171.3, 170.7, 167.0, 159.3, 151.5, 144.4, 141.7, 138.1, 130.9, 129.6, 128.6, 128.1, 127.9, 125.7, 119.4, 113.9, 109.1, 103.4, 93.7, 81.5, 76.3, 74.8, 73.7, 73.5, 73.3, 73.2, 72.3, 70.8, 70.4, 69.8, 67.3, 55.5, 52.8, 51.4, 45.2, 44.0, 42.9, 41.9, 41.4, 41.0, 37.6, 34.8, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 26.5, 24.9, 22.8, 21.5, 20.2, 15.3, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.5, 21.5, 20.2, 15.3, 14.3; CH_2 δ 109.1, 93.7, 72.3, 69.8, 44.0, 42.9, 41.9, 41.4, 41.0, 37.6, 34.8, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 24.9, 22.8; CH δ 141.7, 129.6, 128.6, 128.1, 127.9, 125.7, 119.4, 113.9, 81.5, 76.3, 74.8, 73.7, 73.5, 73.3, 73.2, 70.8, 70.4, 67.3; C δ 172.2, 171.3,

170.7, 167.0, 159.3, 151.5, 144.4, 138.1, 130.9, 103.4, 45.2; IR (neat) 2929, 2856, 1665, 1613, 1514, 1436, 1377, 1309, 1243, 1158, 1091, 1040, 892, 815, 753, 699, 536 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{60}H_{84}O_{16}Na$ (M+Na) 1083.5657, found 1083.5643.



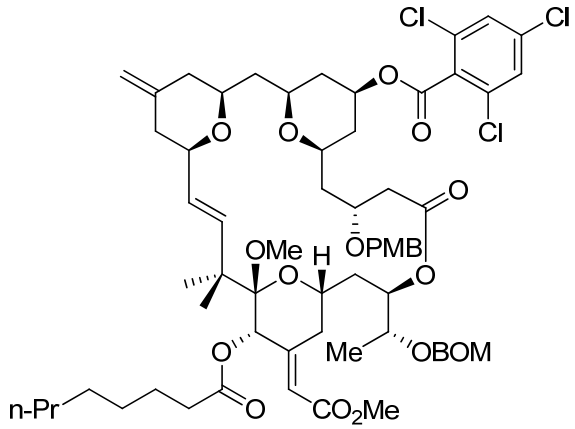
Preparation of MERLE 27

To a stirring solution of **13** (1.4 mg, 0.0013mmol, 1.0 equiv) in CH_2Cl_2 (0.26 mL, 0.005 M) in a 4 mL reaction vial at 0 ºC was added aqueous pH 7 buffer (0.15 mL) and DDQ (1.5 mg, 0.0068 mmol, 5.0 equiv). The reaction mixture stirred at 0 ºC for 2 h and additional DDQ (1.5 mg, 0.0068 mmol, 5.0 equiv) was then added. Stirring continued for 1.5 h and the reaction mixture was diluted with CH_2Cl_2 (1 mL) and quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). After stirring vigorously for 10 min at rt the mixture was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was taken on to the next step without purification.

To a 4 mL reaction vial containing the aforementioned analogue precursor was added a 0.25 M solution of $LiBF_4$ in 25:1 CH_3CN/ H_2O (238 µL, 0.059 mmol, 45.0 equiv). The reaction vial was sealed and the mixture was allowed to stir at 80 ºC for 10 h. After cooling to rt, the reaction mixture was diluted with EtOAc (1 mL) and was quenched by

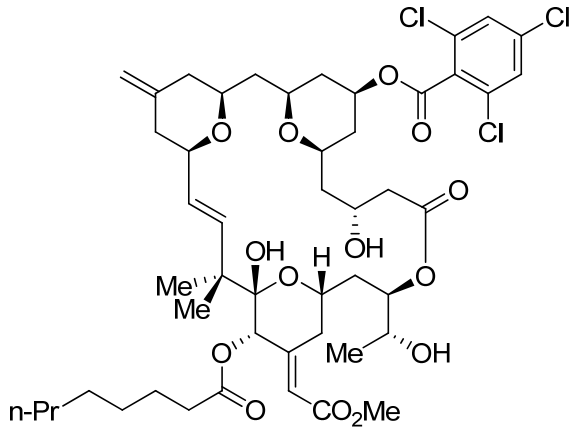
addition of saturated aqueous $NaHCO_3$ solution (0.5 mL). The mixture was partitioned between EtOAc (10 mL) and saturated $NaHCO_3$ aqueous solution (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 0.6 x 4 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 6 x 50 mm test tube fractions. The product containing fractions (4-13) were combined and concentrated under reduced pressure to provide analogue **MERLE 27** (0.93 mg, 87% over 2 steps) as a colorless oil: R_f = 0.11 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +20 (c=0.047, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.99 (d, *J* = 2.0 Hz, 1H), 5.79 (d, *J* = 16.1 Hz, 1H), 5.33 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.23 (ddd, *J* = 11.7, 5.9, 2.9 Hz, 1H), 5.13 (s, 1H), 4.90-4.80 (m, 1H), 4.72 (d, *J* = 4.4 Hz, 2H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.23 (t, *J* = 11.7 Hz, 1H), 4.08-4.00 (m, 2H), 3.83 (q, *J* = 6.3 Hz, 1H), 3.73-3.71 (m, 1H), 3.68 (s, 3H), 3.65-3.50 (m, 3H), 2.51 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.45 (t, *J* = 11.7 Hz, 1H), 2.31 (ddd, *J* = 7.8, 3.9, 3.9 Hz, 2H), 2.13-2.06 (m, 2H), 2.06-2.00 (m, 5H), 2.00-1.96 (m, 2H), 1.96-1.92 (m, 6H), 1.78-1.68 (m, 1H), 1.66-1.60 (m, 2H), 1.56-1.48 (m, 2H), 1.36-1.22 (m, 10H), 1.14 (s, 3H), 1.01 (s, 3H), 0.92-0.84 (m, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 172.2, 170.7, 167.2, 152.1, 143.9, 139.0, 130.0, 119.9, 108.9, 99.1, 80.2, 77.8, 76.9, 74.4, 73.9, 73.6, 70.5, 69.6, 68.7, 64.7, 51.3, 45.1, 43.1, 42.8, 41.5, 40.0, 37.5, 36.1, 34.9, 31.9, 31.8, 31.5, 29.2, 29.1, 25.0, 24.9, 22.9, 22.8, 21.4, 20.0, 20.0, 4.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 51.3, 25.0, 21.4, 20.0, 20.0, 14.3; CH_2 δ 108.9, 43.1, 42.8, 41.5, 40.0, 37.5, 36.1, 34.9, 31.9, 31.8, 31.5, 29.2, 29.1, 24.9, 22.9, 22.8; CH δ 139.0, 130.0, 119.9, 80.2, 77.8, 76.9, 74.4, 73.9, 73.6, 70.5, 69.6, 68.7, 64.7; C δ 172.3, 172.2, 170.7, 167.2,

152.1, 143.9, 99.1, 45.1; IR (neat) 3583, 3458, 3070, 2955, 2932, 2857, 1734, 1612, 1513, 1472, 1463, 1377, 1250, 1172, 1105, 843, 823, 742, 703, 688 cm^{-1}; HRMS (ESI/ APCI) calcd for $C_{43}H_{66}O_{14}Na$ (M+Na) 829.4350, found 829.4372.



Preparation of macrolactone (22): Prepared from **21** (2.8 mg) in the same manner as **12** to provide product **22** (2.6 mg, 79 %) as a white film: R_f = 0.20 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +5 (c=0.10, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.28 (m, 7H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.93 (d, *J* = 1.0 Hz, 1H), 5.58 (ddd, *J* = 11.7, 4.4, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.20-5.11 (m, 2H), 4.83 (s, 1H), 4.78 (d, *J* = 8.8 Hz, 2H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.48 (d, *J* = 10.7 Hz, 1H), 4.24-4.15 (m, 1H), 4.00-3.90 (m, 2H), 3.77 (s, 3H), 3.72-3.66 (m, 4H), 3.62 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.54-3.46 (m, 2H), 3.24 (t, *J* = 11.3 Hz, 1H), 3.06 (s, 3H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.33-2.23 (m, 3H), 2.20 (d, *J* = 12.7 Hz, 1H), 2.13-1.95 (m, 6H), 1.90-1.81 (m, 2H), 1.80-1.75 (m, 1H), 1.65-1.50 (m, 6H), 1.34-1.20 (m, 10H), 1.10 (s, 6H), 1.08 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.2, 172.1, 167.0, 164.9, 159.3, 151.5, 144.4, 141.7, 138.1, 134.7, 133.2, 132.3, 130.9, 129.9, 129.8, 129.6, 128.6, 128.1, 127.9, 127.8, 125.8, 119.5, 113.9, 109.1, 103.4, 93.7, 81.5, 76.3, 74.6, 73.7, 73.5, 73.3, 73.2, 72.3, 71.5, 70.9, 69.8, 67.3, 55.5, 52.8, 51.4, 45.3,

44.0, 42.9, 42.0, 41.5, 41.0, 37.3, 34.8, 31.9, 31.1, 29.9, 29.2, 26.5, 24.9, 22.8, 20.3, 15.4, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.5, 15.3, 14.3; CH_2 δ 109.1, 93.7, 72.3, 69.8, 44.0, 42.9, 42.0, 41.5, 41.0, 37.3, 34.8, 31.9, 31.1, 29.9, 29.2, 29.1, 24.9, 22.8, 20.3; CH δ 141.7, 129.6, 128.6, 128.1, 127.9, 127.9, 125.8, 119.5, 113.9, 81.5, 76.3, 74.6, 73.7, 73.5, 73.3, 73.2, 71.5, 70.9, 67.3; C δ 172.2, 172.1, 167.0, 164.9, 159.3, 151.5, 144.4, 138.1, 134.7, 133.2, 132.3, 130.9, 129.9, 129.8, 103.4, 45.3; IR (neat) 2926, 2853, 1738, 1651, 1580, 1548, 1514, 1435, 1382, 1249, 1160, 1103, 1042, 819, 668, 541 cm^{-1}; LRMS (EI) Calcd for $C_{65}H_{83}Cl_3O_{16}Na$ (M+Na): 1247.5, Found: 1247.5.

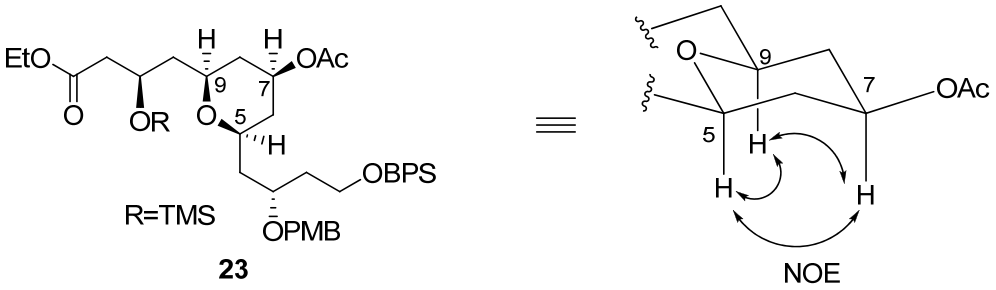


Preparation of Analogue (14): Prepared from **22** (2.6 mg) in the same manner as **MERLE 27** to provide the analogue **14** (1.3 mg, 63 %) as a white film: R_f = 0.45 (50% EtOAc/Hexanes); $[\alpha]_D^{20}$ = +3 (c=0.065, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.40 (m, 2H), 5.99 (s, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 5.33 (dd, *J* = 16.1, 8.8 Hz, 1H), 5.22 (m, 1H), 5.14 (s, 1H), 4.76-4.70 (m, 3H), 4.40 (d, *J* = 12.2 Hz, 1H), 4.27-4.20 (m, 1H), 4.07-4.00 (m, 2H), 3.85-3.80 (m, 1H), 3.73-3.70 (m, 1H), 3.68 (s, 3H), 3.62-3.55 (m, 3H), 2.54 (d, *J* = 12.2 Hz,1H), 2.47 (q, *J* = 12.7 Hz, 1H), 2.31 (ddd, *J* = 3.4, 7.3, 7.3 Hz, 2H), 2.18-1.80 (m, 12H), 1.66-1.40 (m, 5H), 1.32-1.22 (m, 10H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90-0.84 (m, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ

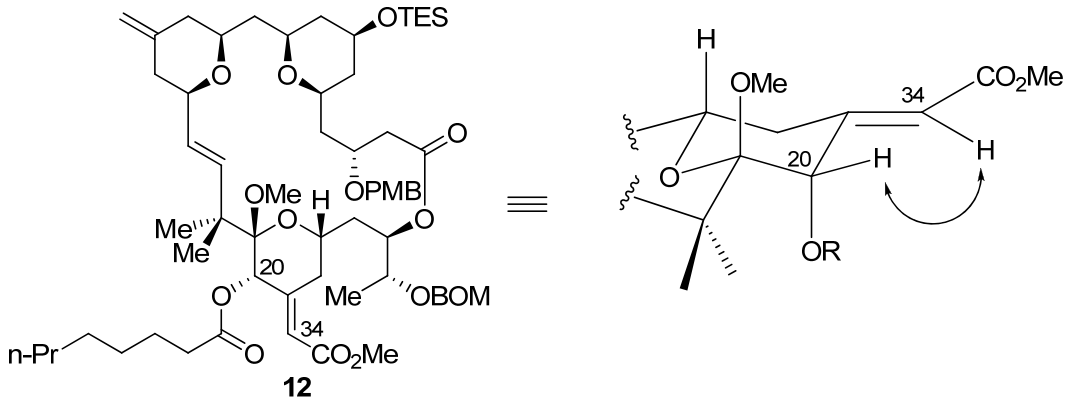
172.4, 172.2, 167.2, 163.6, 159.7, 152.1, 143.8, 139.0, 132.7, 129.9, 128.3, 119.9, 108.9, 99.1, 95.0, 80.2, 77.8, 77.4, 74.4, 73.9, 73.6, 72.0, 70.5, 68.7, 64.7, 51.3, 45.1, 43.1, 42.8, 42.3, 41.6, 40.0, 37.1, 36.7, 36.1, 34.9, 31.9, 31.5, 29.3, 29.1, 25.0, 24.9, 22.8, 20.1, 20.0, 14.3; IR (neat) 3458, 2933, 2859, 1732, 1611, 1513, 1466, 1428, 1376, 1250, 1172, 1106, 843, 742, 704, 613 cm^{-1}. LRMS (EI) Calcd for $C_{48}H_{65}Cl_3O_{14}Na$ (M+Na): 993.3, Found: 993.3.

Summary of Stereochemical Evidence:

The relative stereochemistry of the **C7** hydroxyl group on A-ring pyran in alcohol **4** was confirmed by the observation of a NOE among **C5, C7** and **C9** protons on acetate **23**, which was prepared from alcohol **4** by acetylation.



The **C20** stereochemistry was determined using NOE experiments on intermediate **12**. A NOE was observed between the equatorial **C20** proton and the nearby **C34** proton.



[3H]PDBu Binding Assay: The inhibitory dissociation constant (Ki) of each bryologue ligand was determined by the ability of the ligand to displace bound [20-3H]phorbol 12,13-dibutyrate (PDBu) from mouse recombinant isozyme PKC α in the presence of calcium and phosphatidylserine, using a polyethylene glycol precipitation assay previously described by Blumberg and Lewin.[4] Briefly, the assay mixture (250 μL) contained 50 mM Tris-HCl (pH 7.4 at room temperature), 100 μg/mL phosphatidylserine, 0.1 mM Ca2+, 4 mg/mL bovine immunoglobulin G and .003% Tx-100, 2 nM [3H]PDBu and various concentrations of the competing ligand. The assay tubes were incubated at 37 °C for 5 min, then chilled for 10 min 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 min 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 [3H]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 [3H]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 constants (Ki) were calculated using the method previously described by Blumberg and Lewin.

MERLE 27: $K_i = 3.0 \pm 0.06$ nM

Analogue 14: $K_i = 16.8 \pm 4.2$ nM

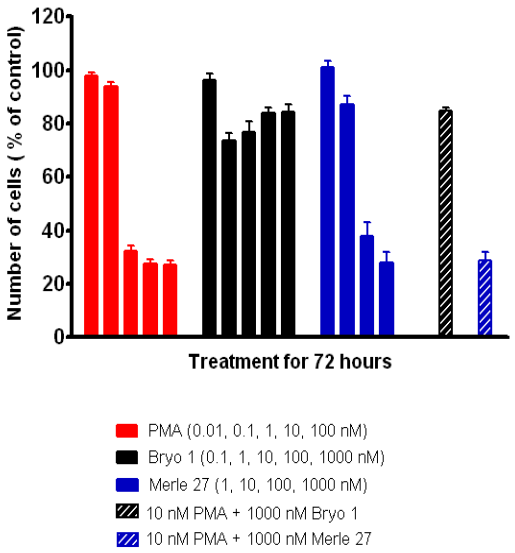
Attachment and cell proliferation of U937 cells: U937 cells [5] (Sundstrom and Nilsson, 1976), purchased from ATCC (Manassas, VA) and cultured in RPMI-1640 medium supplemented with 10 % FBS (ATCC, Manassas, VA), were plated in 35 mm dishes at a density of 1 X 105 living cells/ml and treated with different 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.

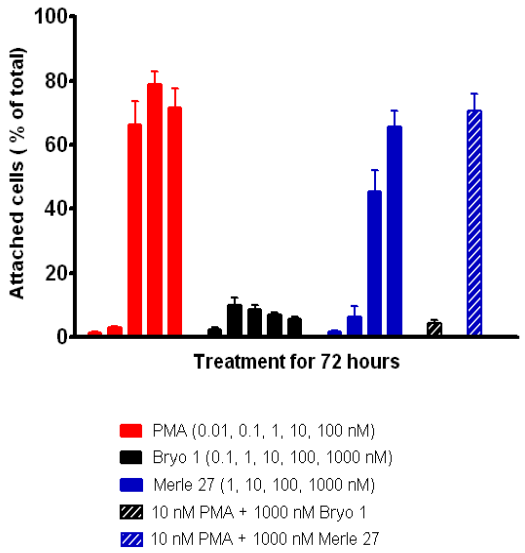
The attachment of U937 cells induced by the indicated compounds compared to bryostatin 1and PMA: U937 cells were treated with PMA (0.1-100 nM), bryostatin 1 (1-1000 nM), the indicated compound (1-1000 nM), 10 nM PMA with different concentrations of bryostatin 1 (1-1000 nM) or 10 nM PMA with different concentrations of indicated compound (1-1000 nM) for 72 hours. 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.

The inhibition of U937 cell proliferation induced by the indicated compounds compared to bryostatin 1 and PMA: U937 cells were treated with PMA (0.1-100 nM), bryostatin 1 (1-1000nM), the indicated compound (1-1000 nM), 10 nM PMA with

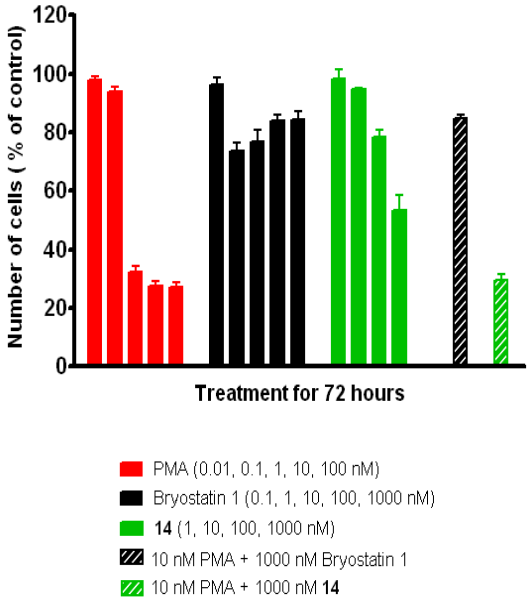
different concentrations of bryostatin 1 (1-1000 nM) or 10 nM PMA with different concentrations of indicated compound (1-1000 nM). The number of attached and non-attached cells was counted and the number of total cells was expressed as % of control. The bars and error bars represent the average and the standard error of the mean of at least three independent experiments.

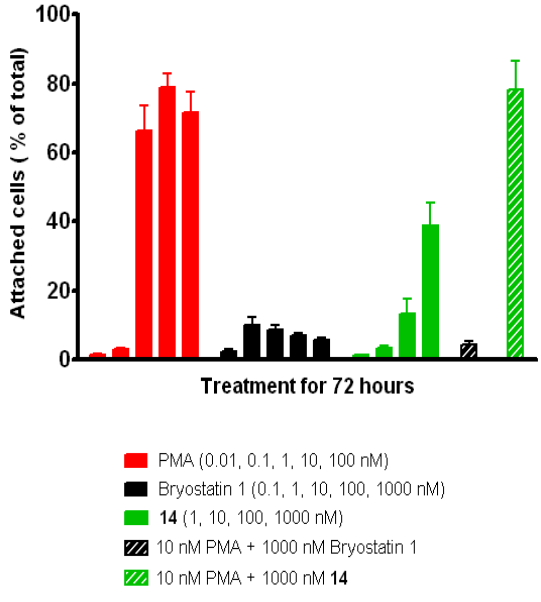
Results of U937 Proliferation and Attachment Assays with MERLE 27:



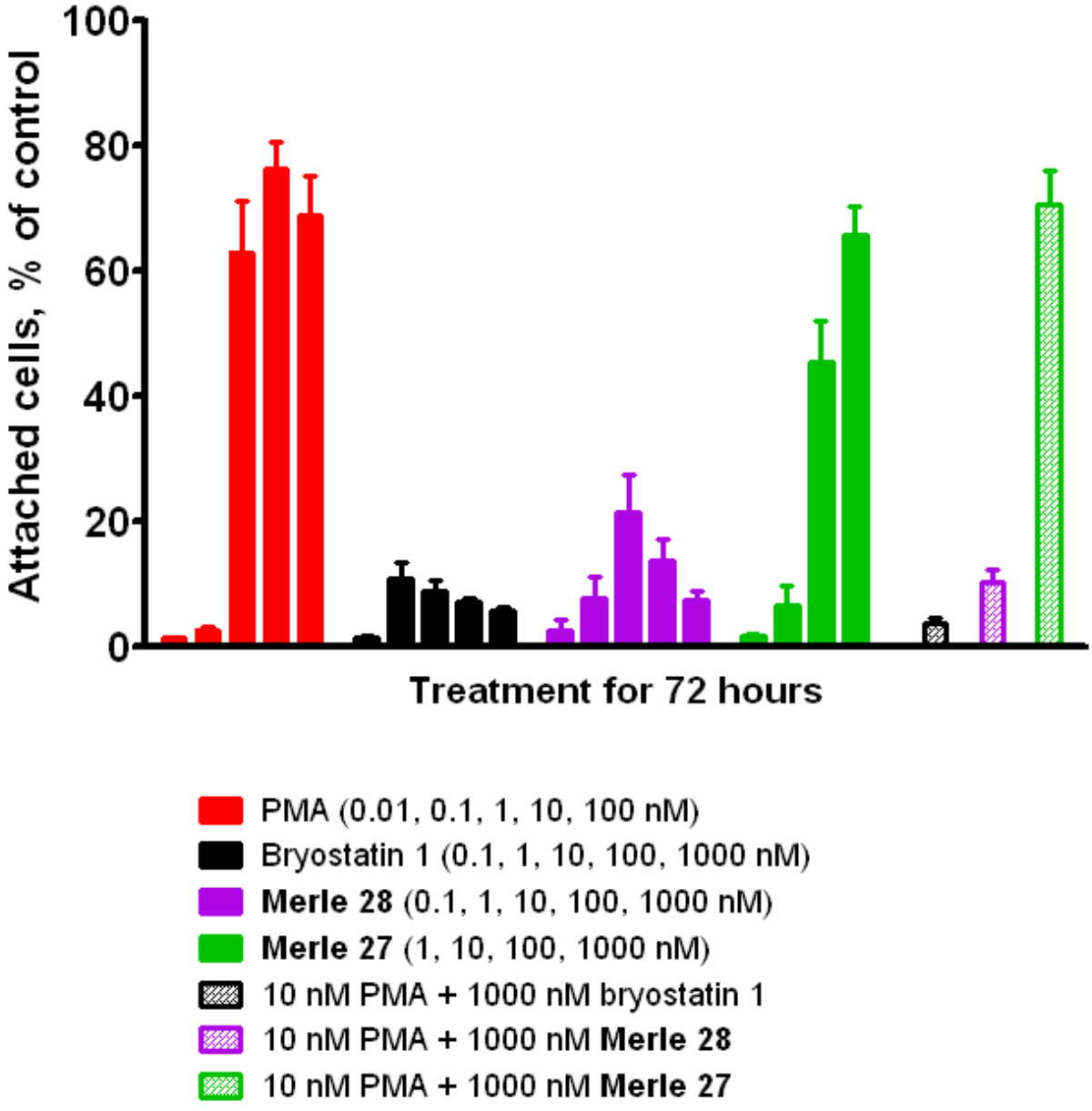


Results of U937 Proliferation and Attachment Assays with Analogue 14:

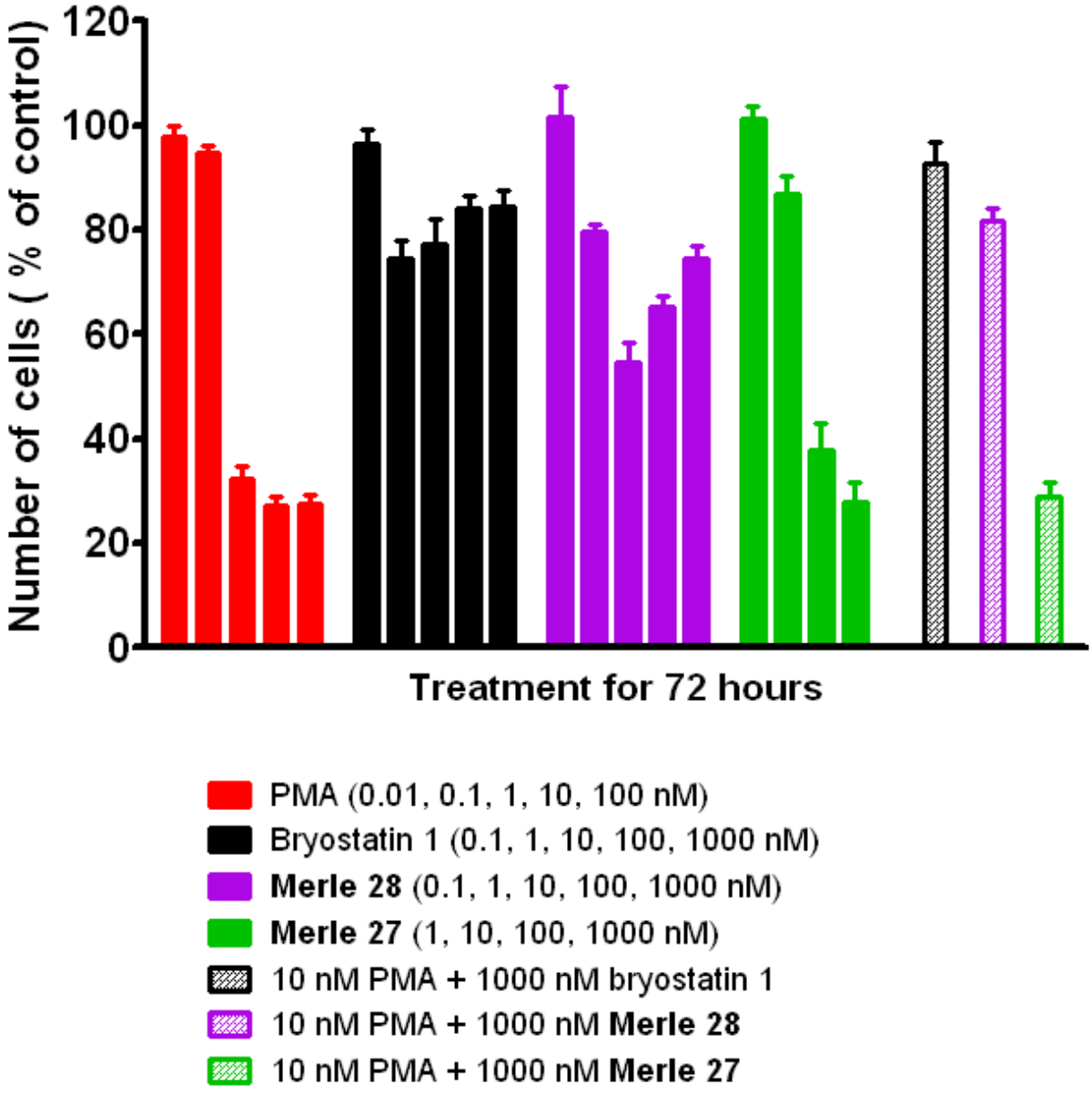




Results of U937 Attachment Assay With Merle 27 and Merle 28



Results of U937 Proliferation Assay With Merle 27 and Merle 28



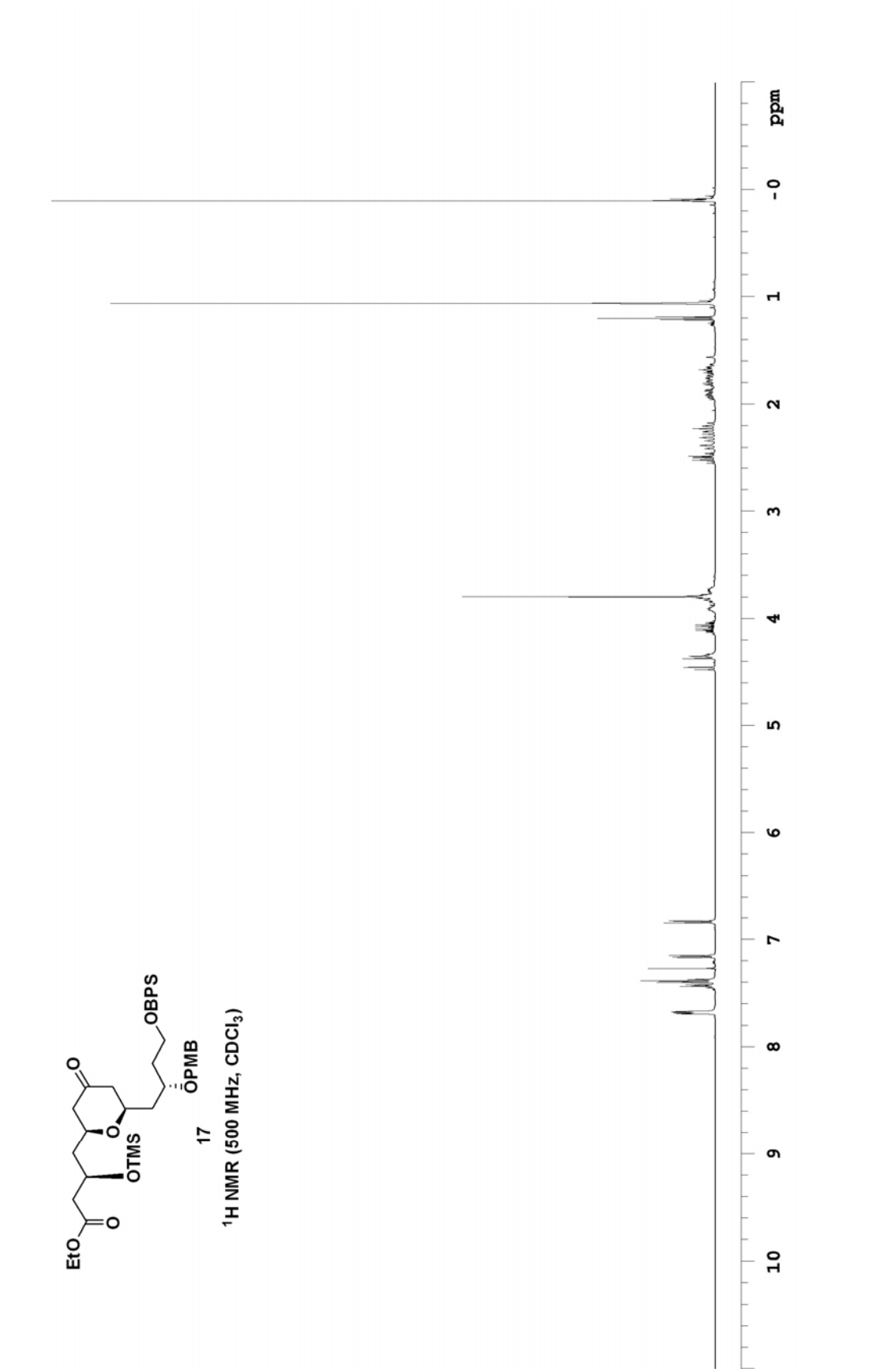
(1) Armarego, W. L. F.; Perrin, D. D., *Purification of Laboratory Chemicals, Fourth Edition*. Butterworth-Heinemann: Oxford, **1997**.

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

(3) Keck, G. E.; Kraft, M. B.; Truong, A. P.; Li, W.; Sanchez, C. C.; Kedei, N.; Lewin, N.; Blumberg, P. M. *J. Am. Chem. Soc.* **2008**, *130*, 6660–6661.

(4) Lewin, N. E.; Blumberg, P. M. *Methods Mol. Biol.* **2003**, *233*, 129-156.

(5) Sundstrom, C.; Nilsson, K. *Int. J. Cancer* **1976**, *17*, 565-577.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OTMS
O
O
OPMB
OBPS
17
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ppm
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9
8
7
6
5
4
3
2
1
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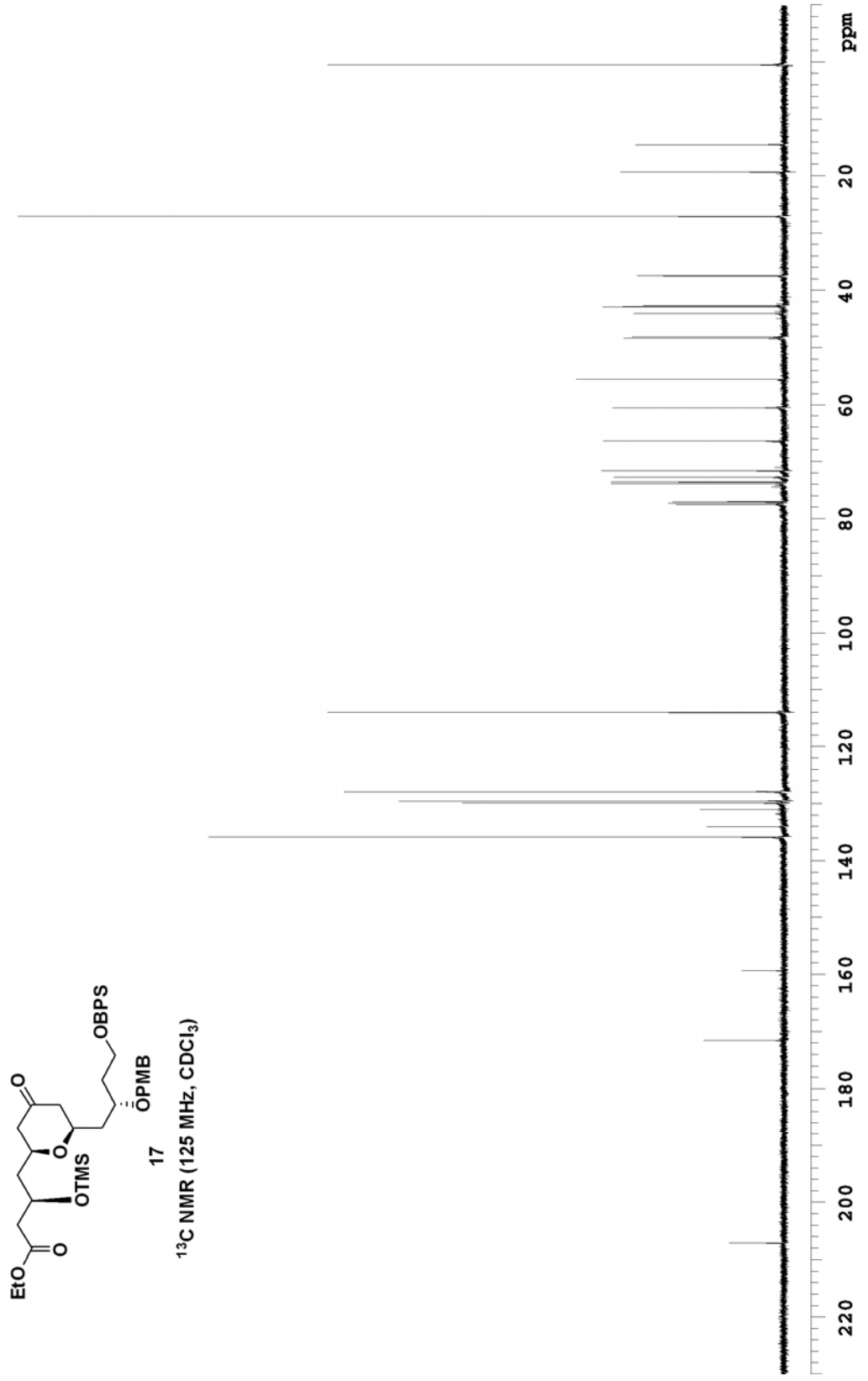
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140
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80
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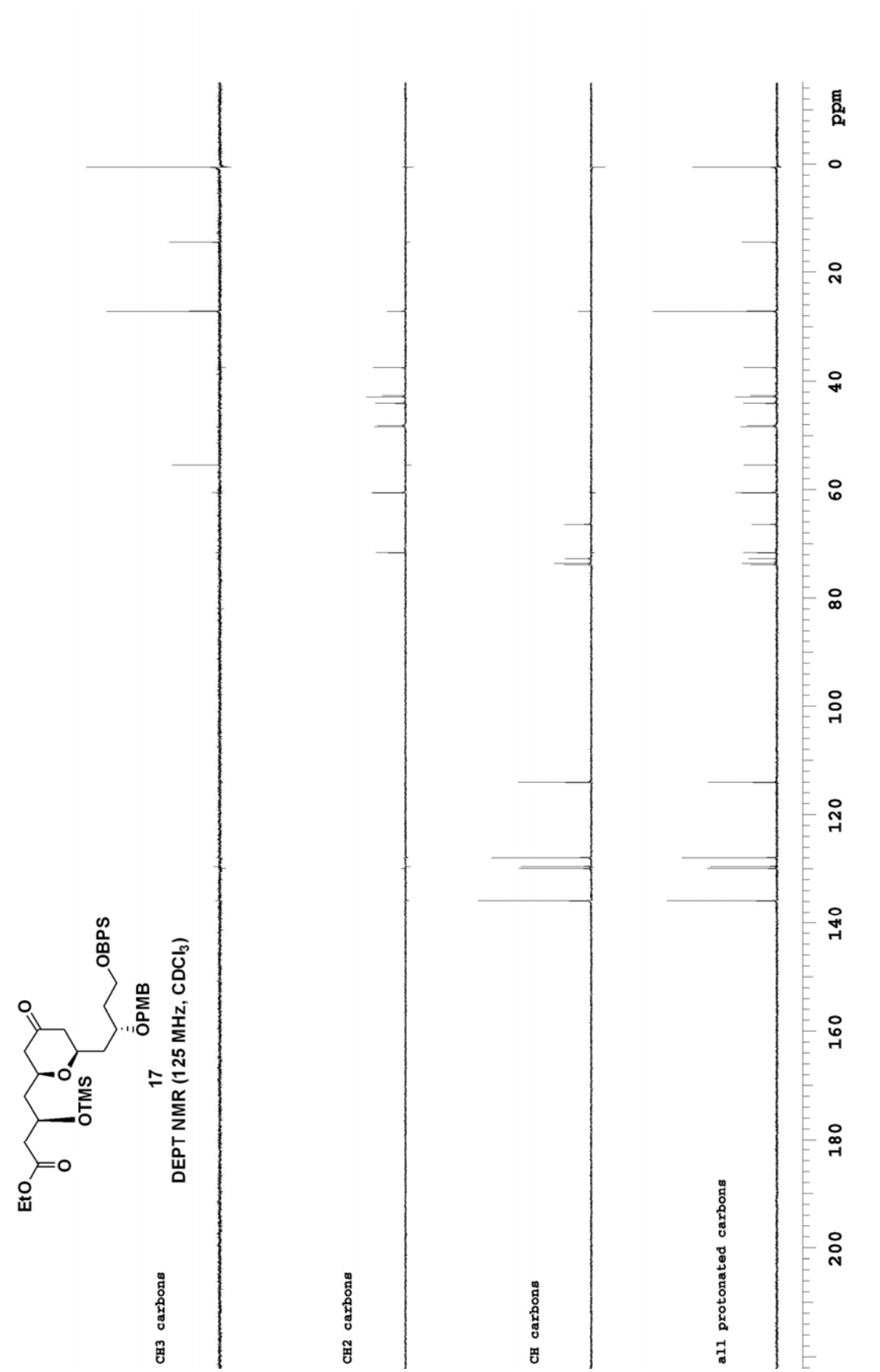
40
20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CH carbons
all protonated carbons
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180
160
140
120
100
80
60
40
20
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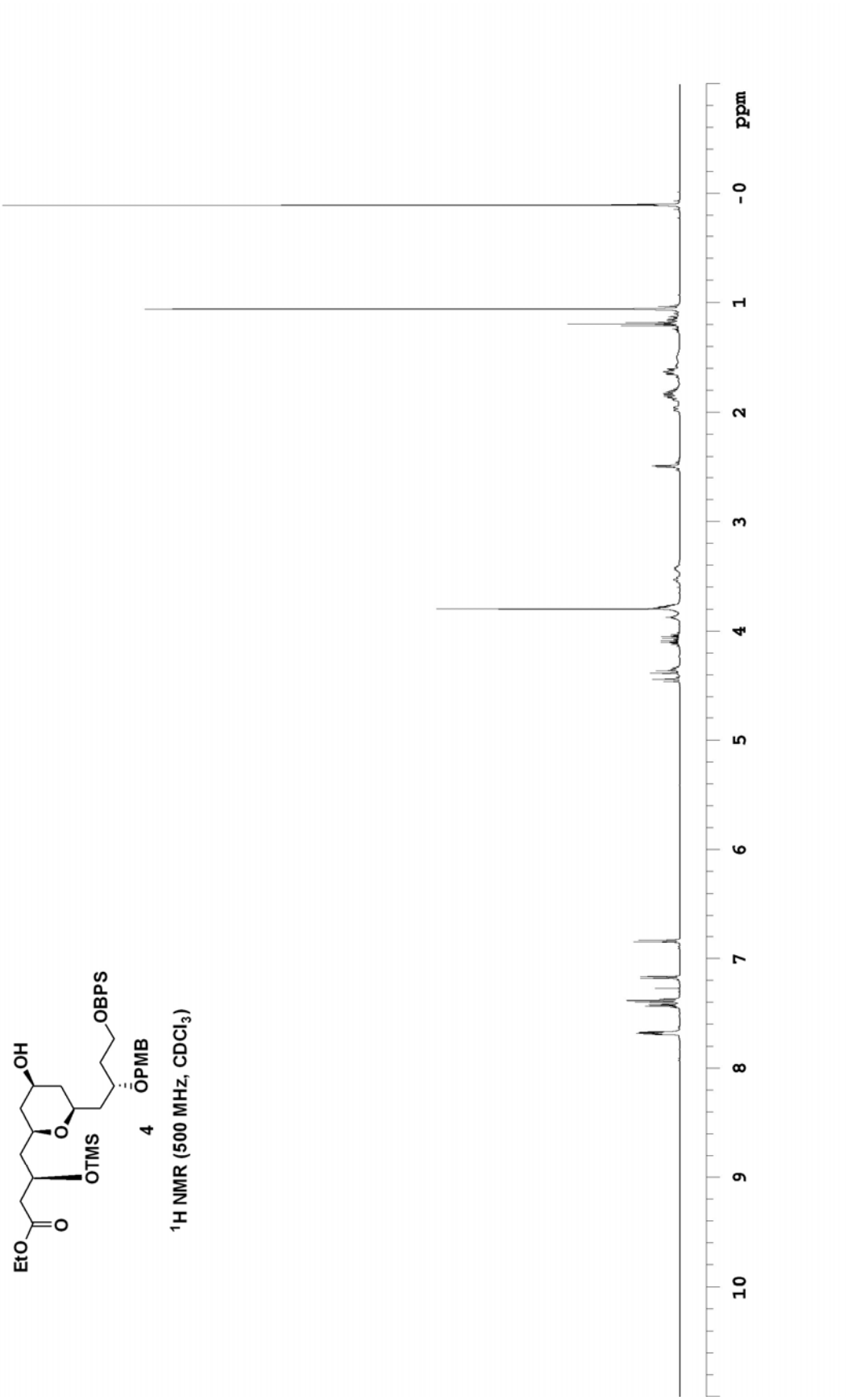
ppm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ppm
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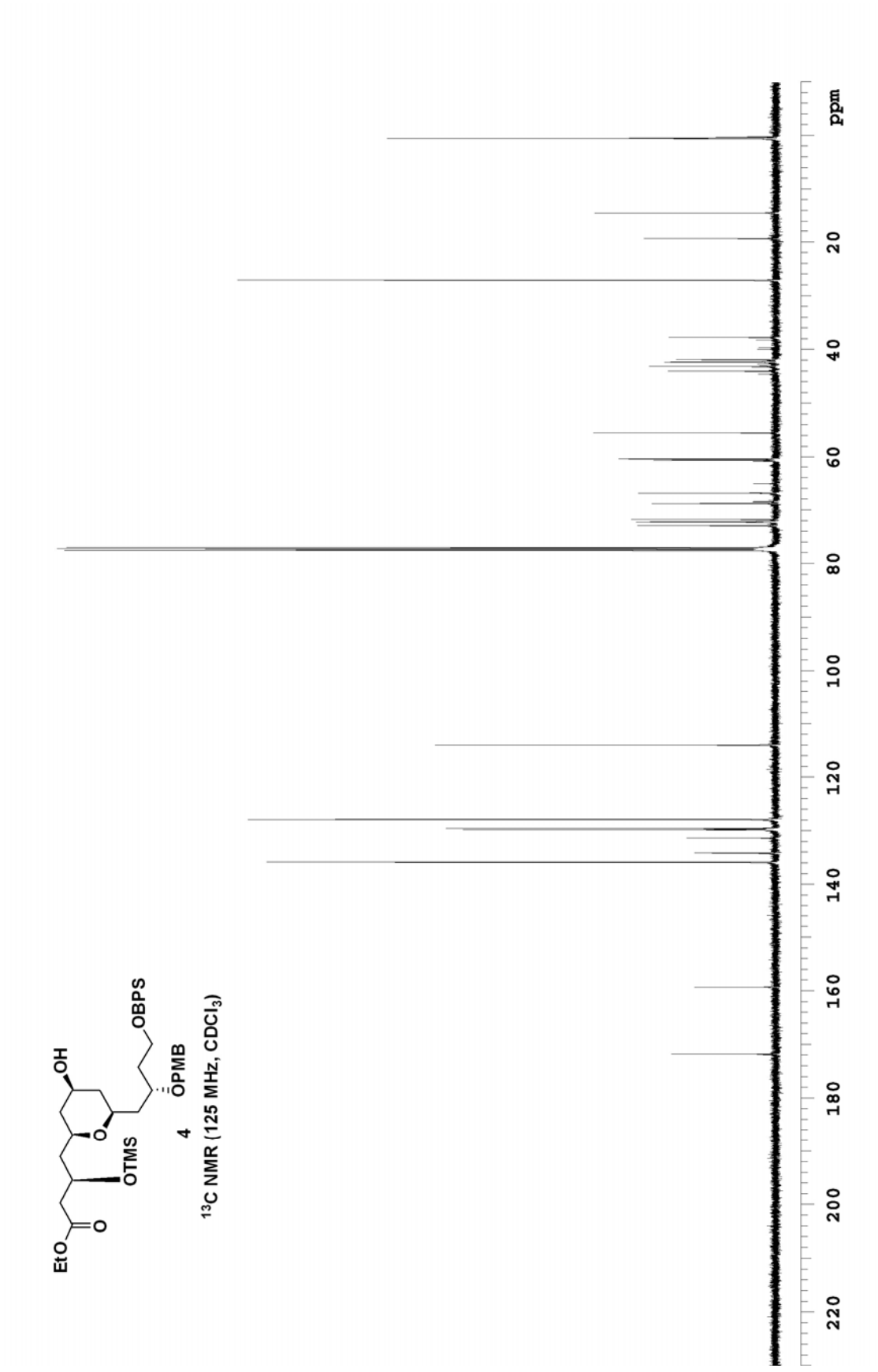
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OH
OPMB
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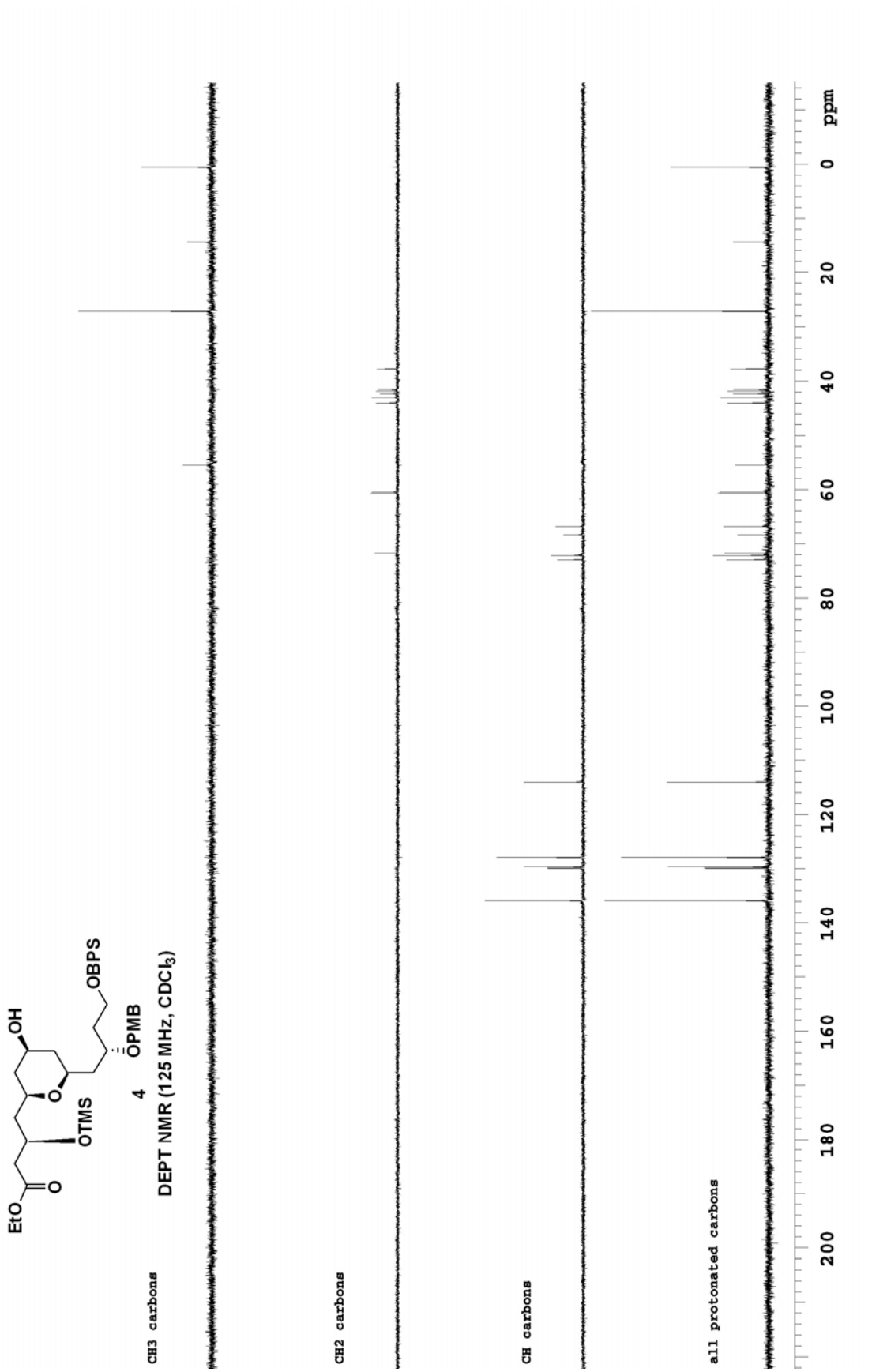
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OPMB
OBPS
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CH carbons
all protonated carbons
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180
160
140
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100
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60
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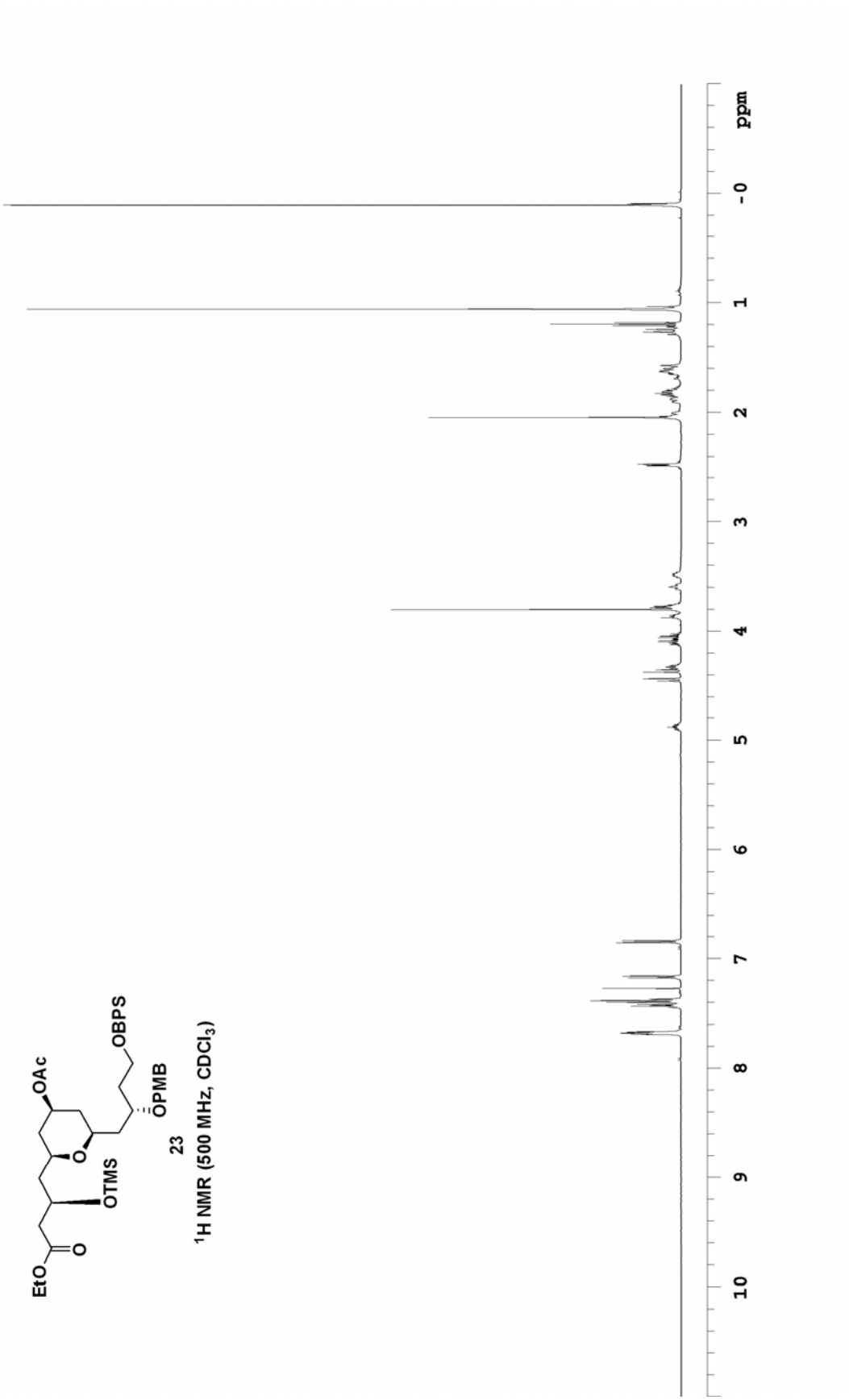
ppm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OBPS
OPMB
OTMS
EtO
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ppm
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6
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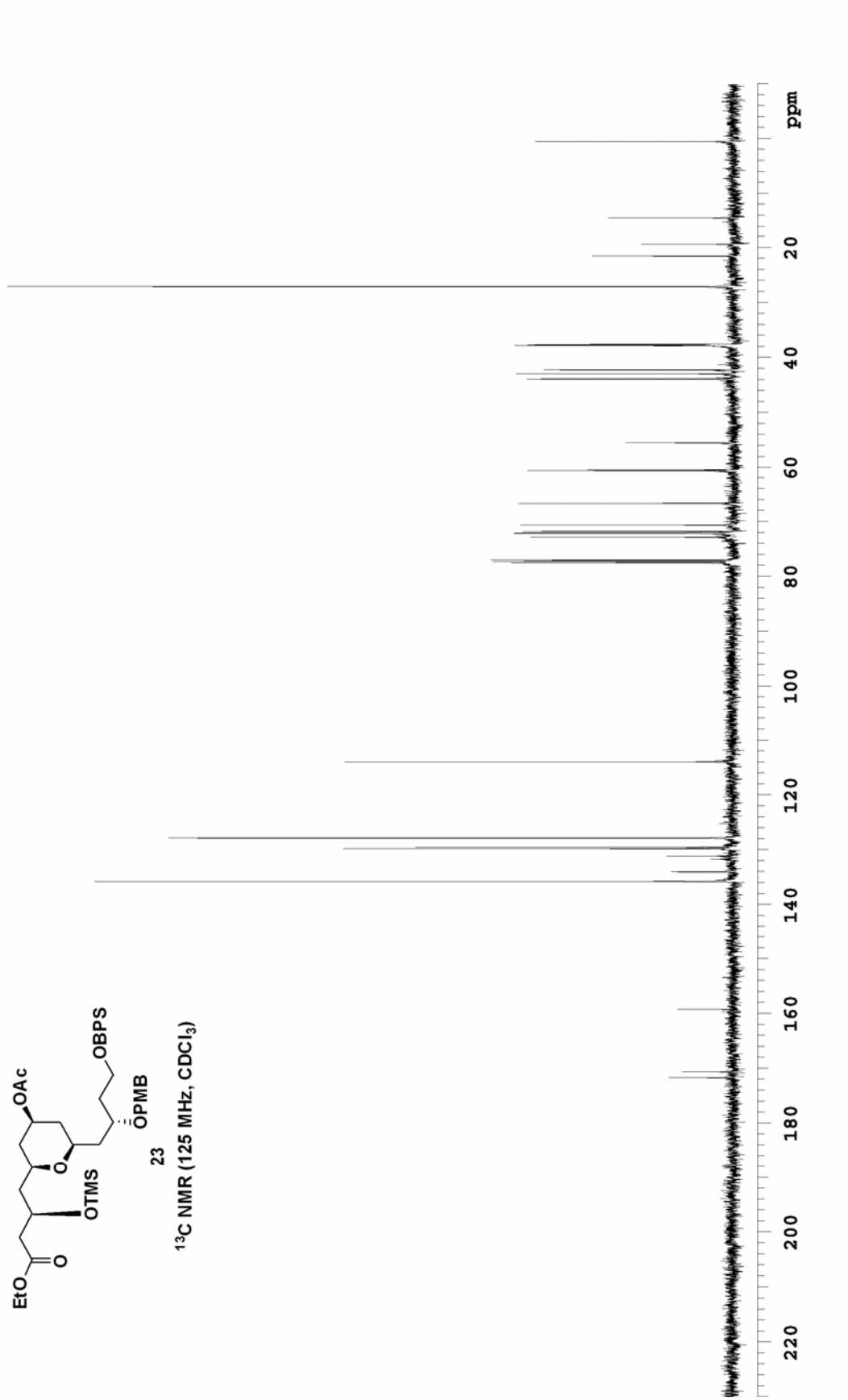
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OAc
OPMB
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140
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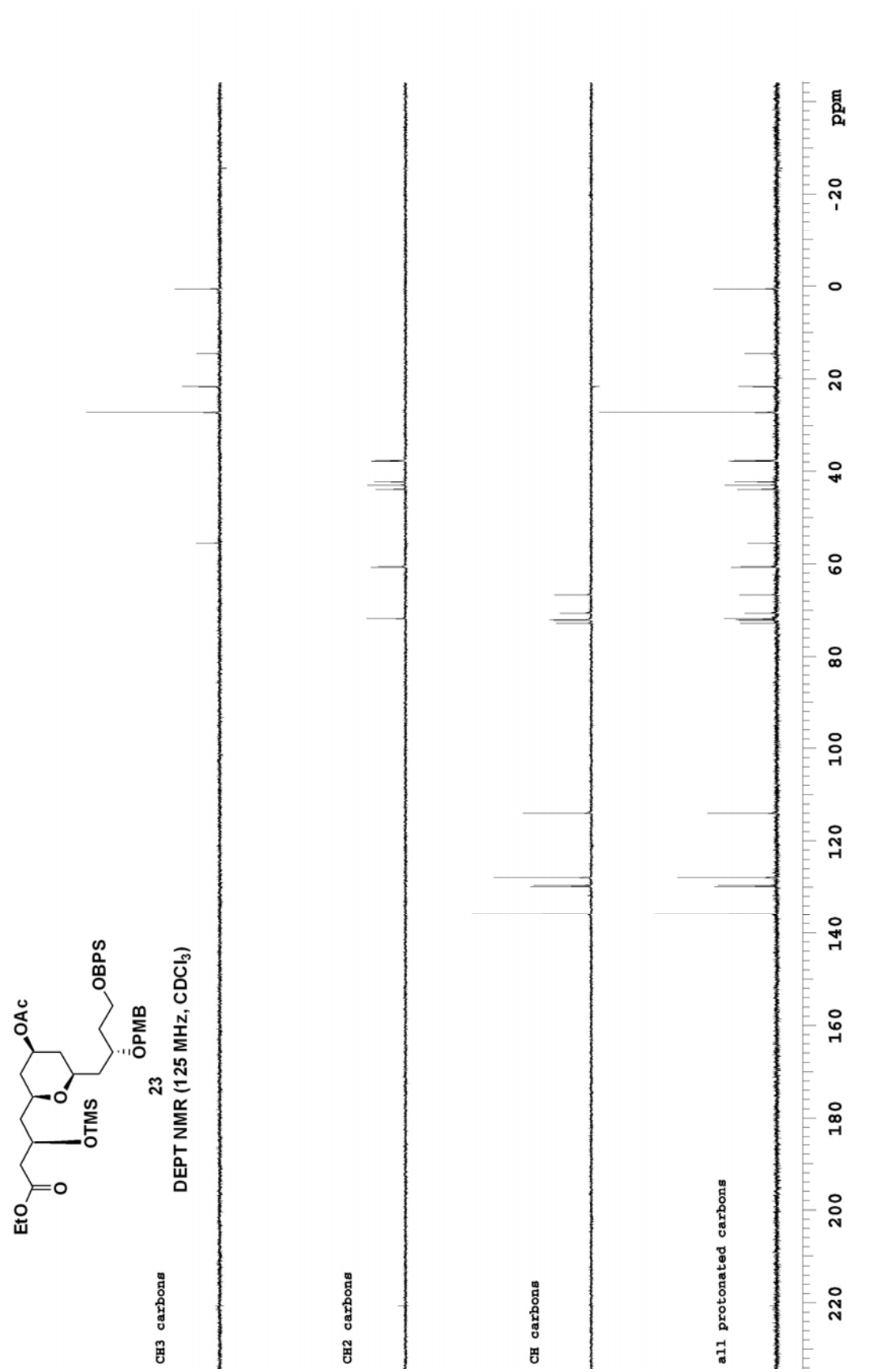
60
40
20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OPMB
OBPS
OAc
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160
140
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80
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20
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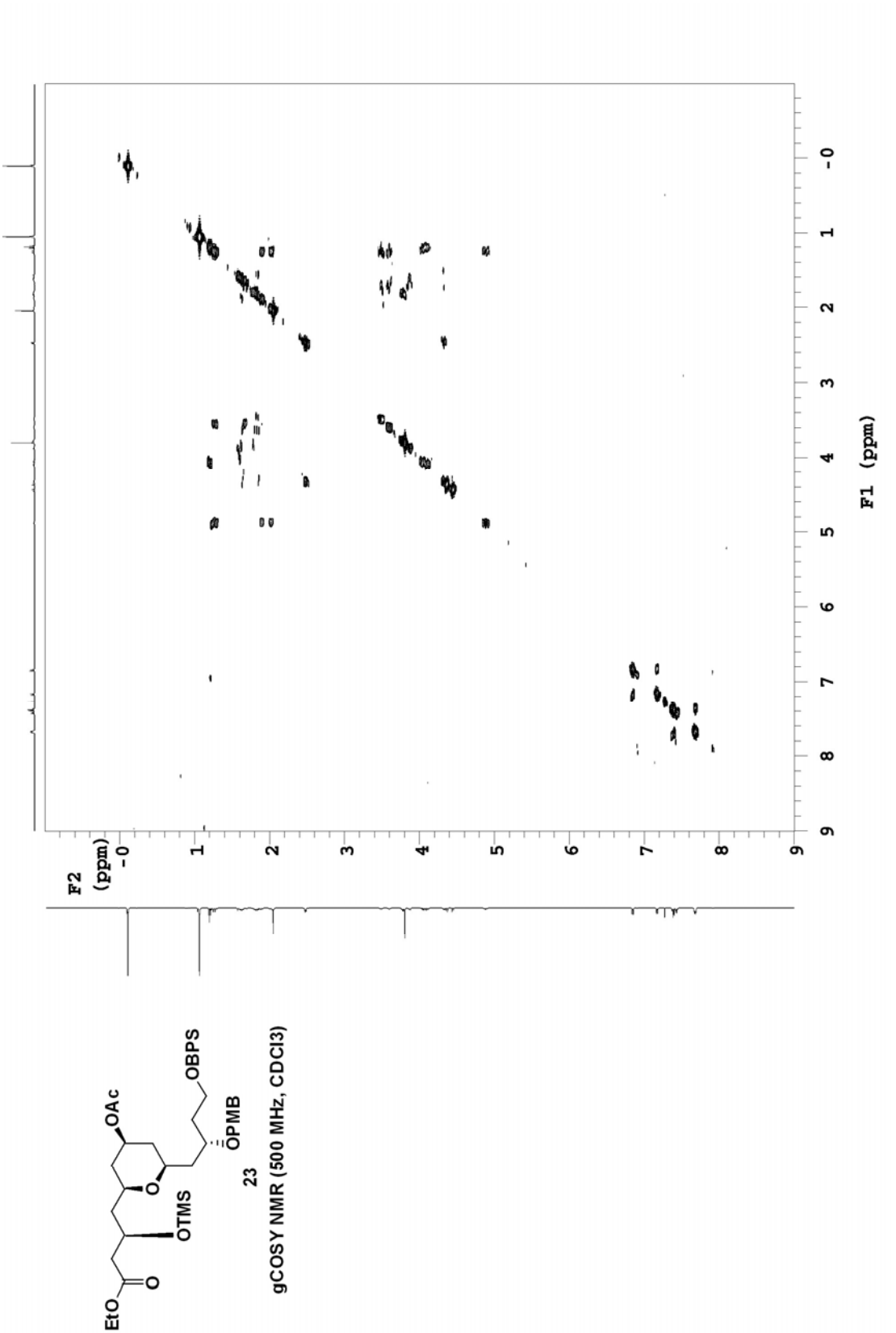
ppm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F1 (ppm)
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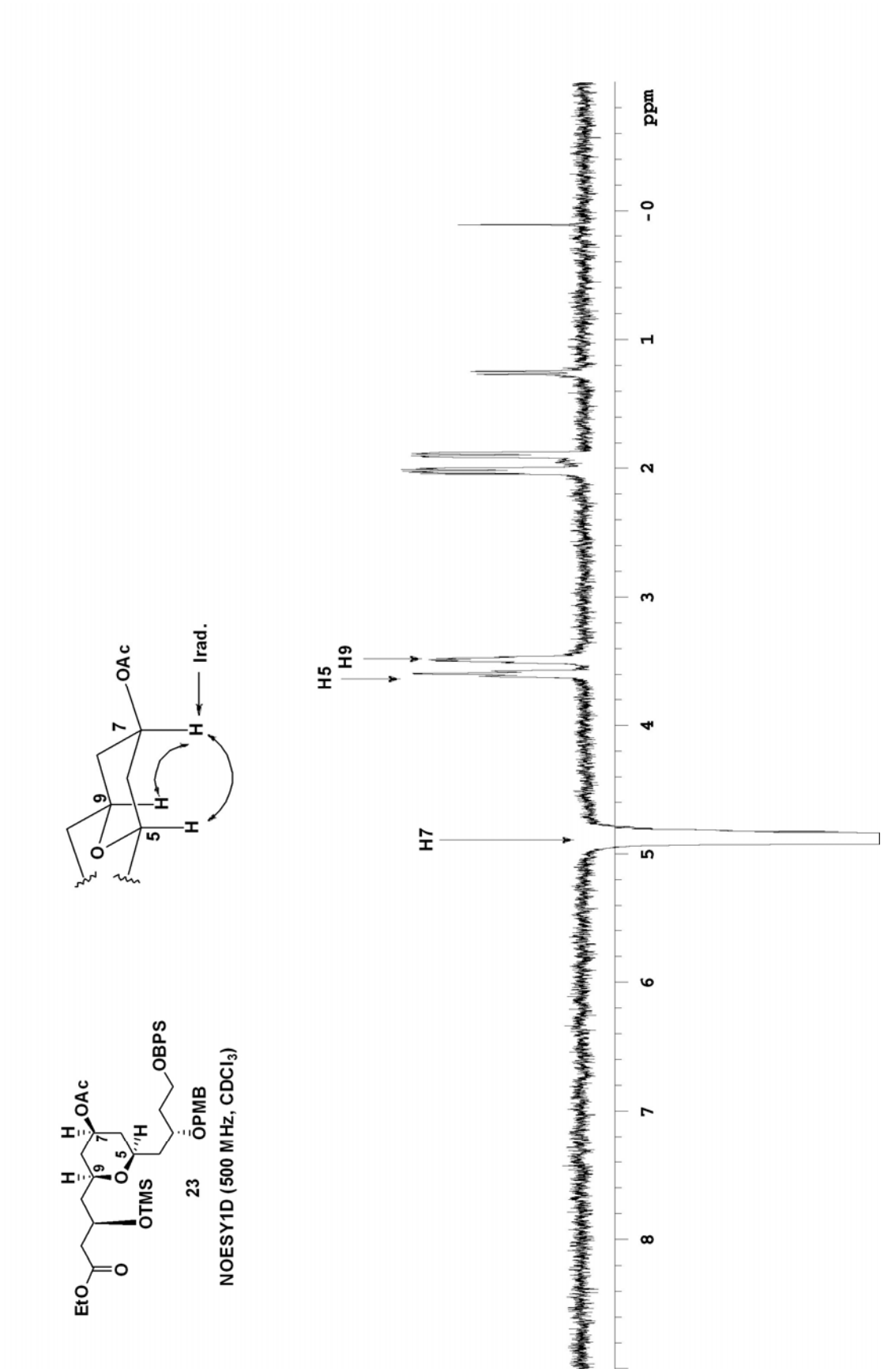
OTMS
OAc
OPMB
OBPS
23
gCOSY NMR (500 MHz, CDCl3)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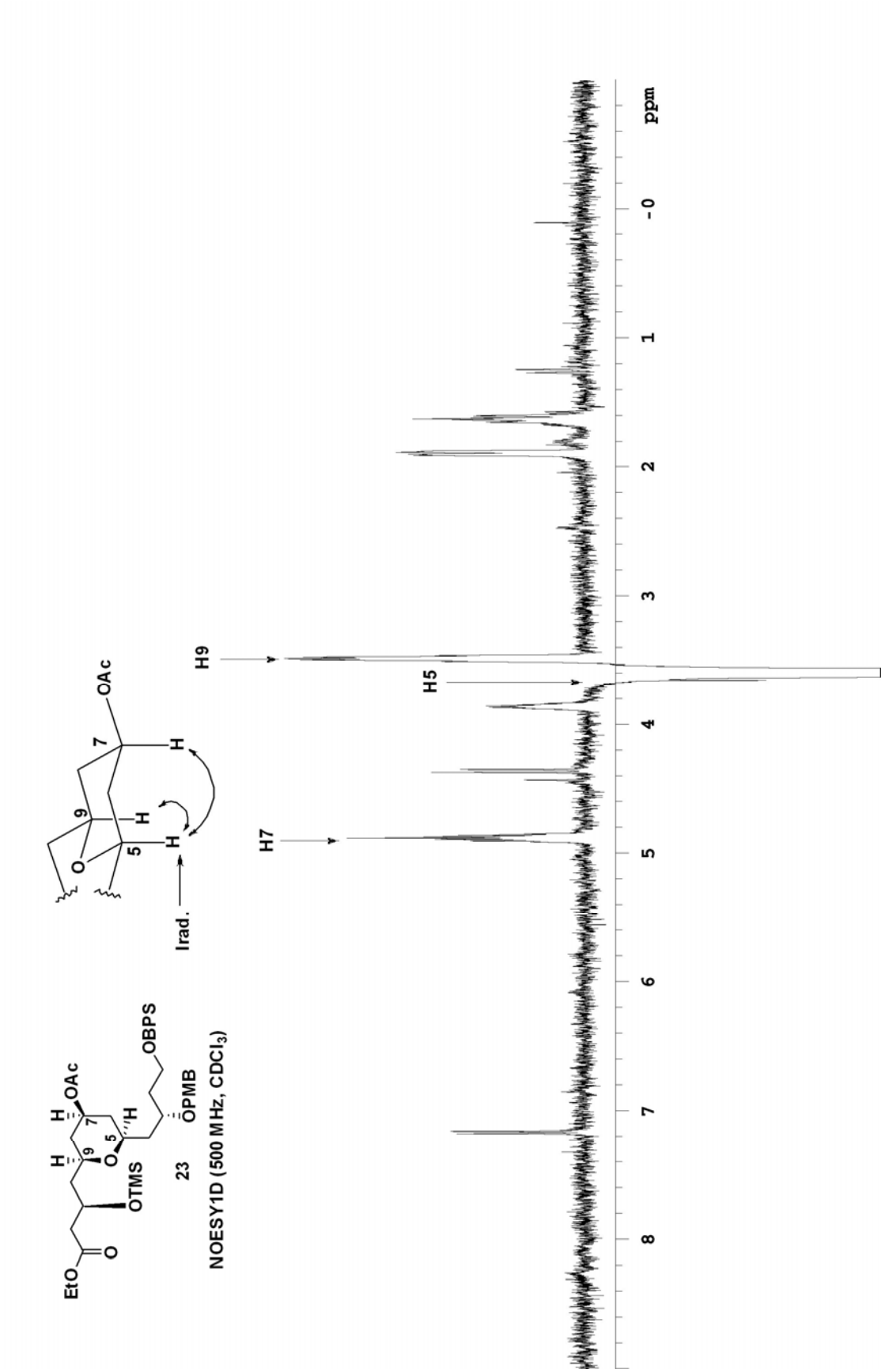
OAc
H
OPMB
OBPS
Irad.
H5
H9
H7
ppm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ppm
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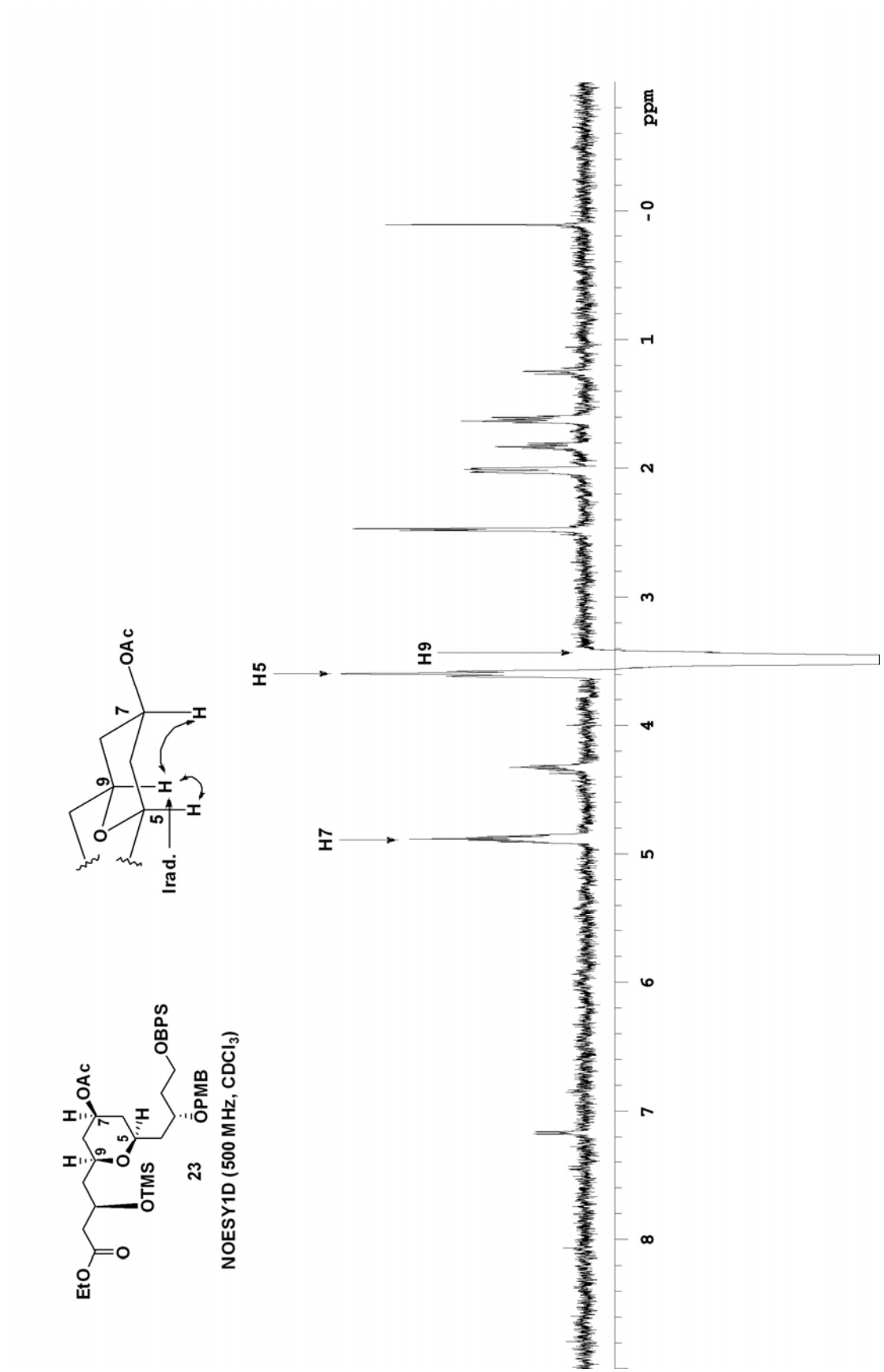
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H9
H7
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OAc
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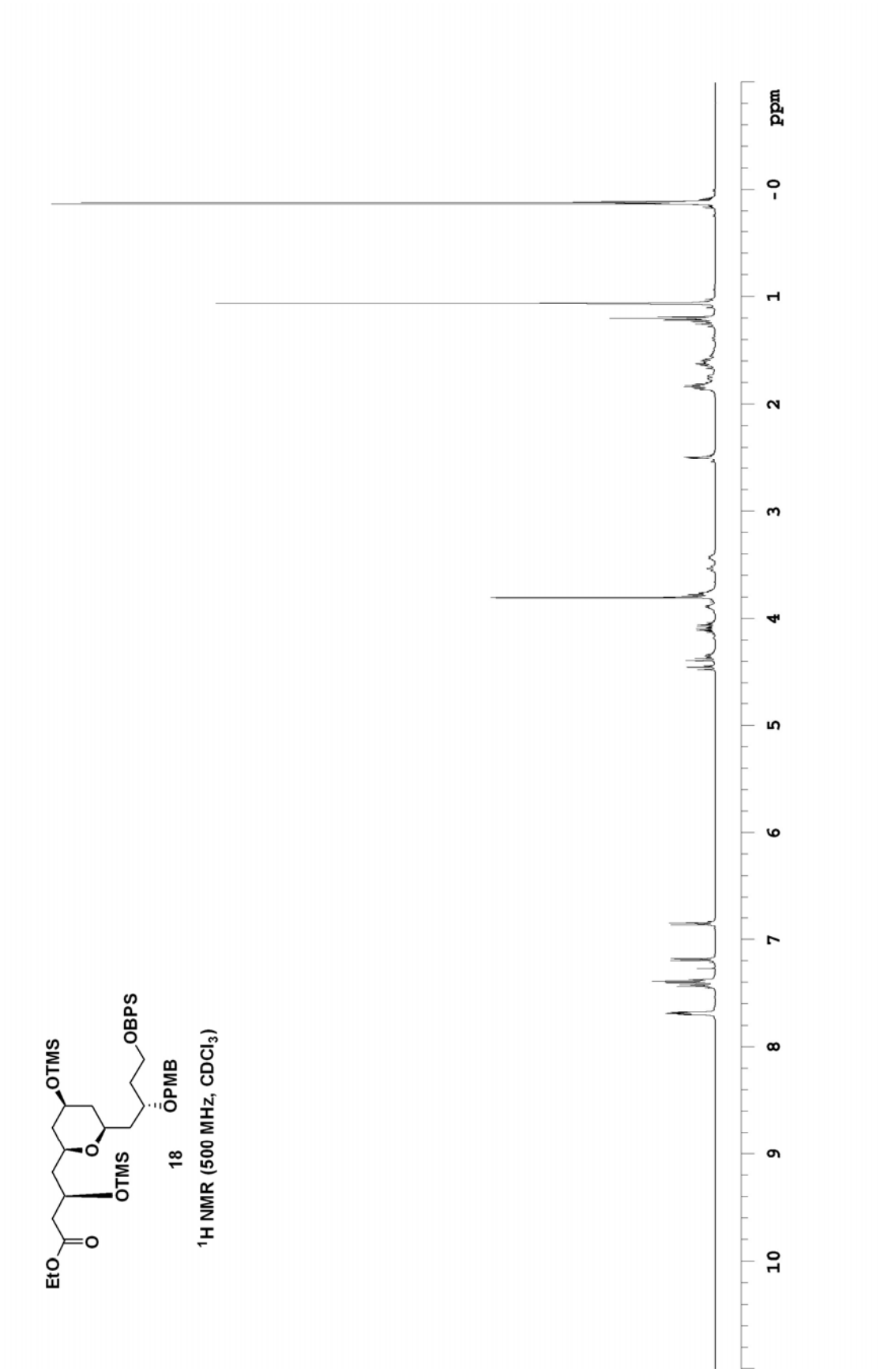
OPMB
OTMS
EtO
ppm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OBPS
OTMS
OPMB
EtO
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ppm
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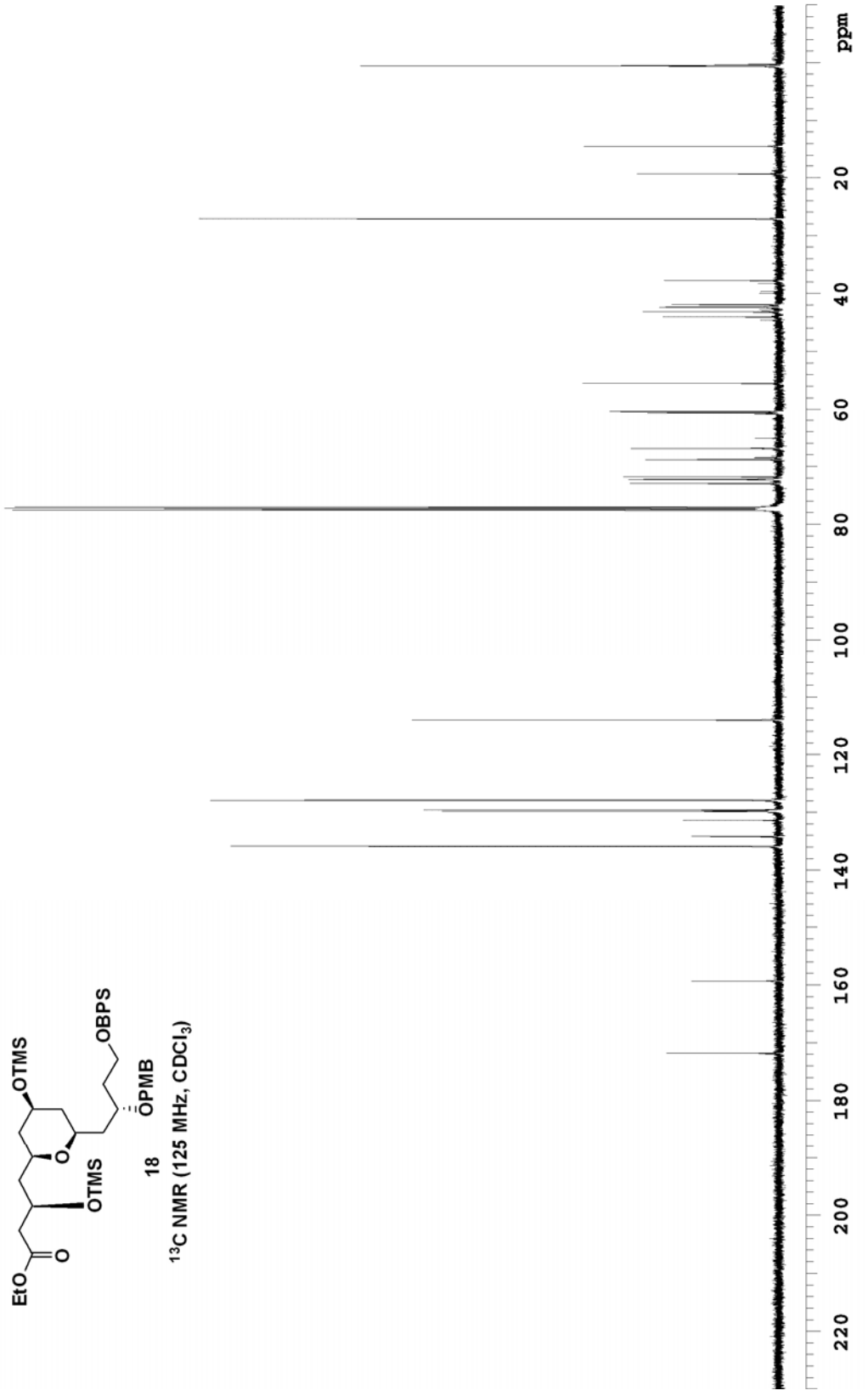
10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OTMS
OPMB
OBPS
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ppm
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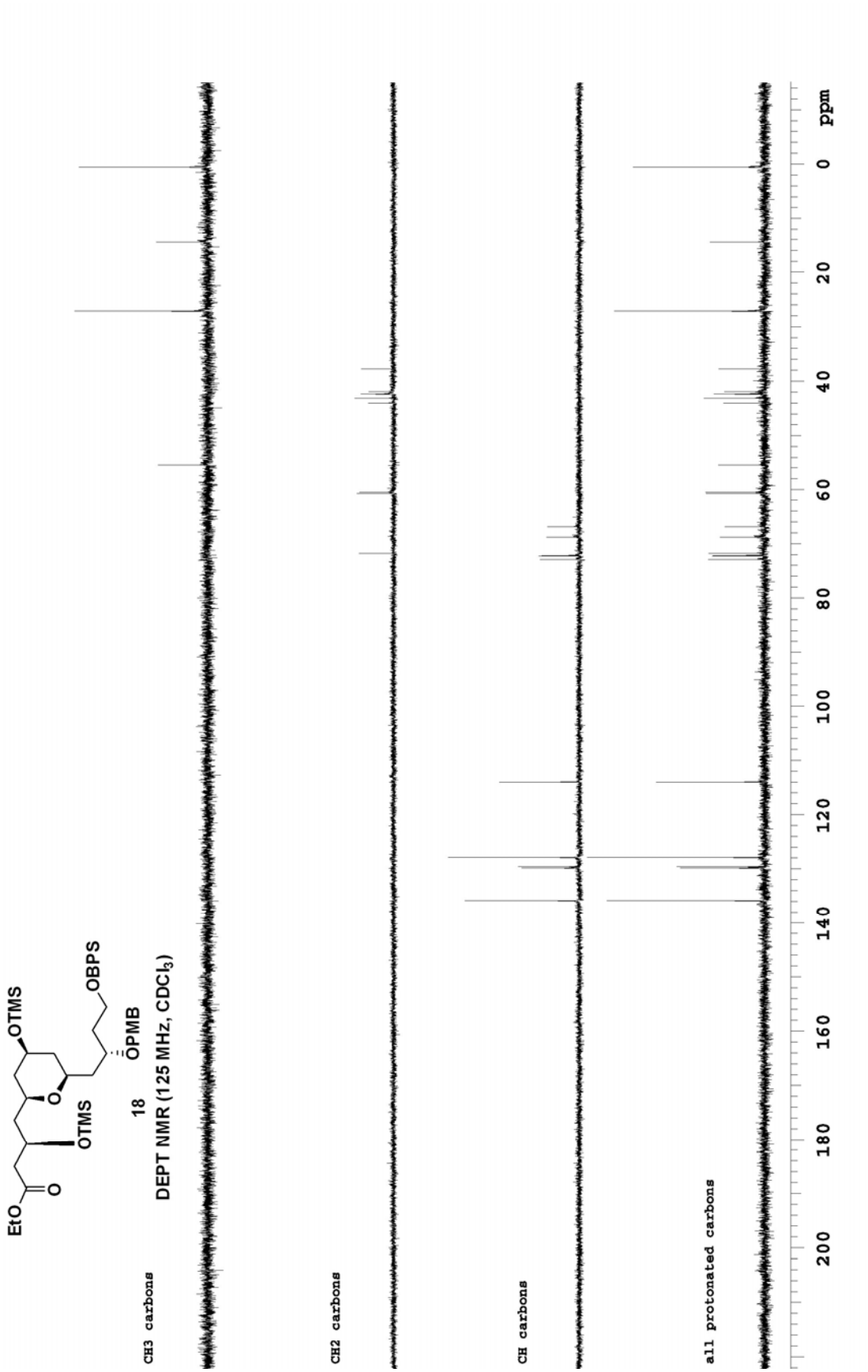
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OPMB
OBPS
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DEPT NMR (125 MHz, CDCl3)
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CH2 carbons
CH carbons
all protonated carbons
200
180
160
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120
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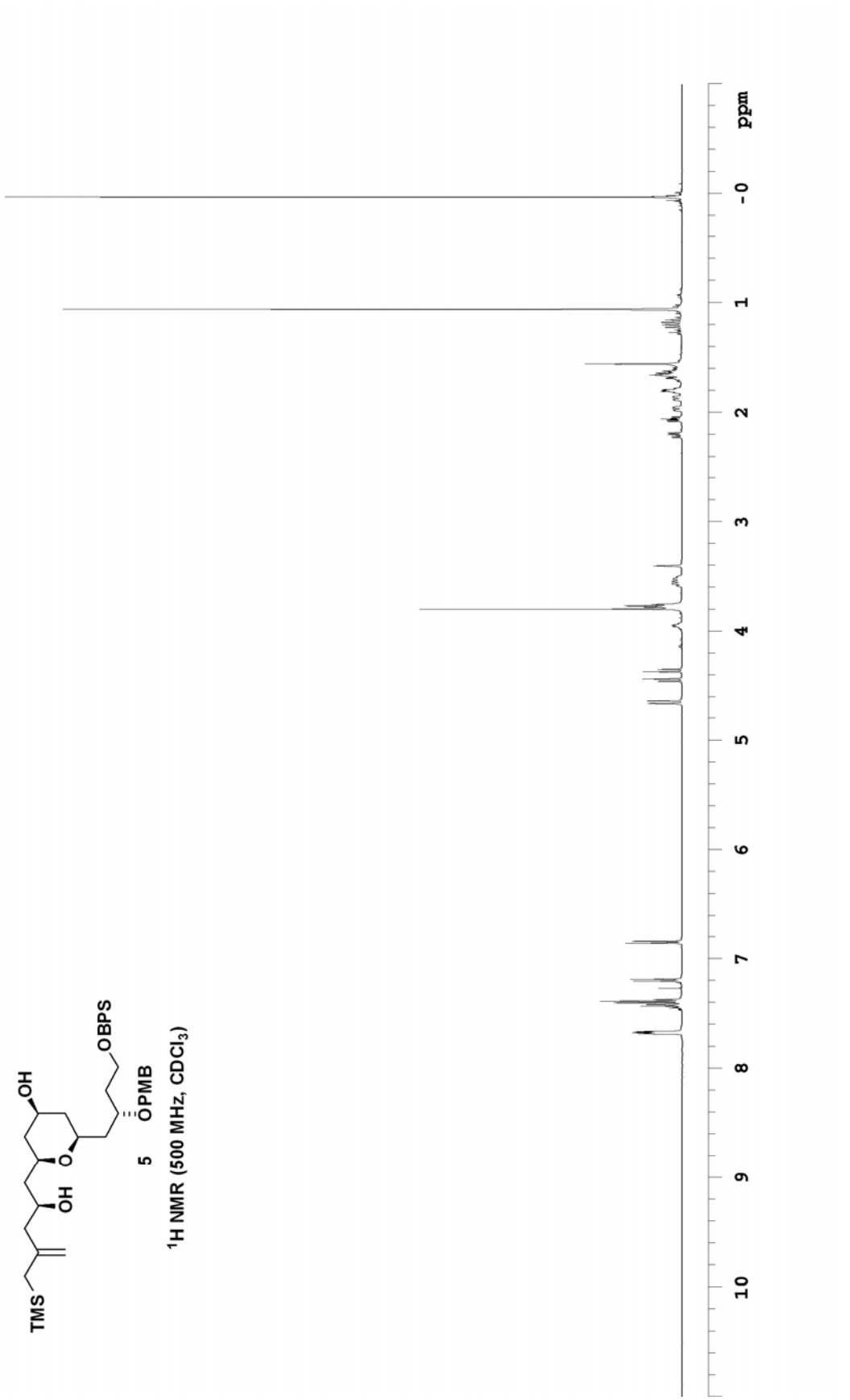
0
ppm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OH
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OPMB
TMS
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ppm
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9
8
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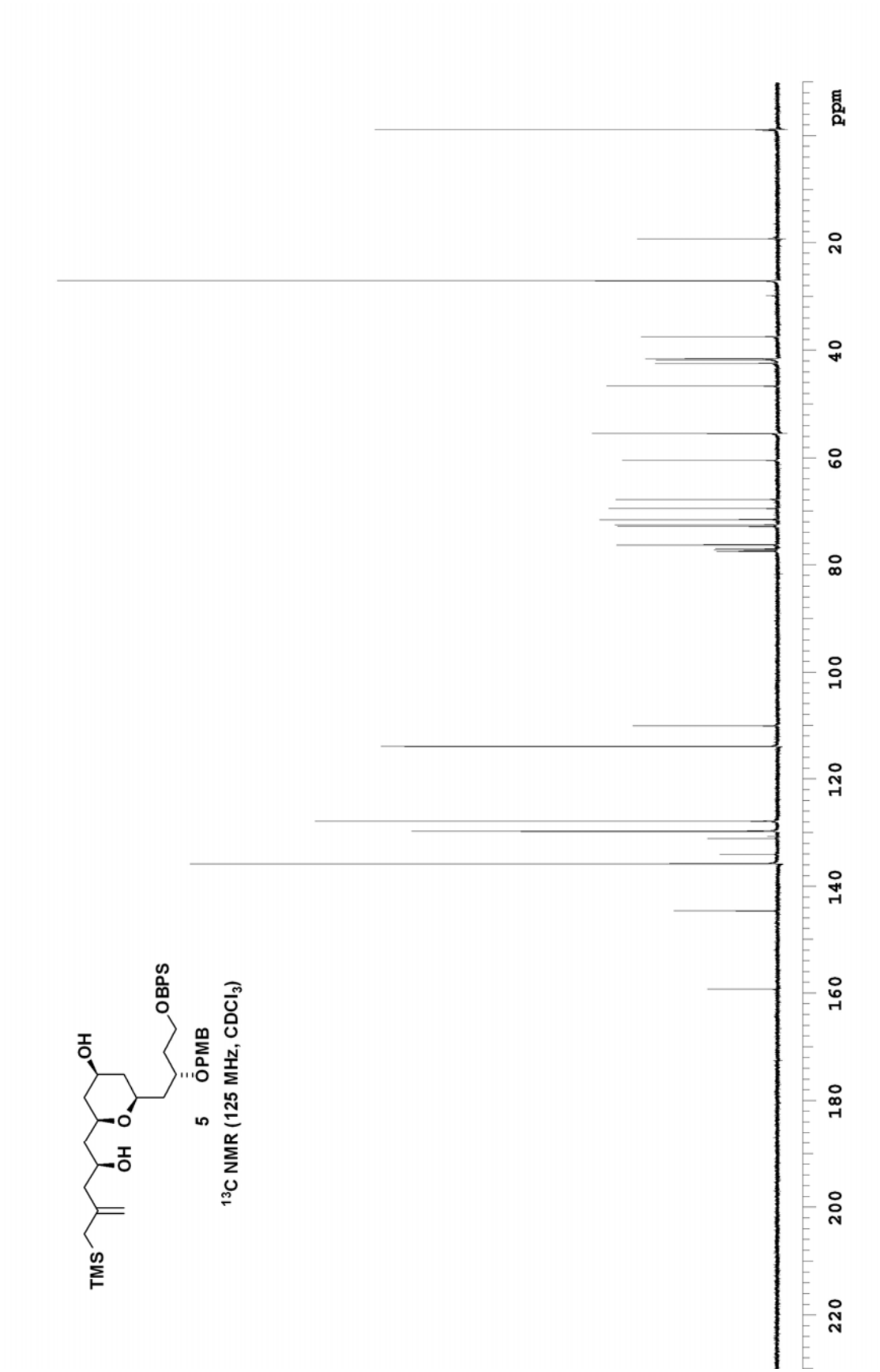
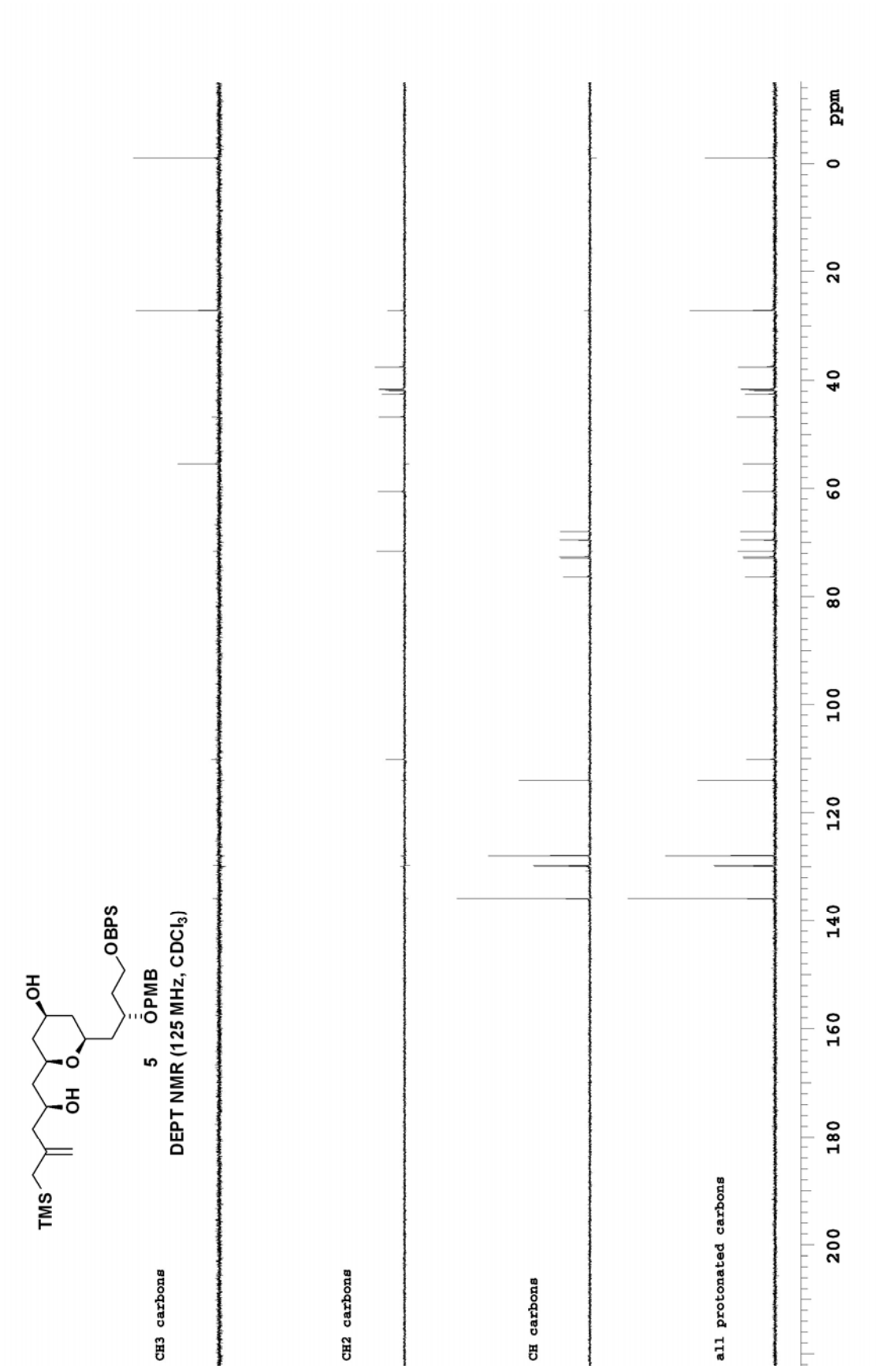
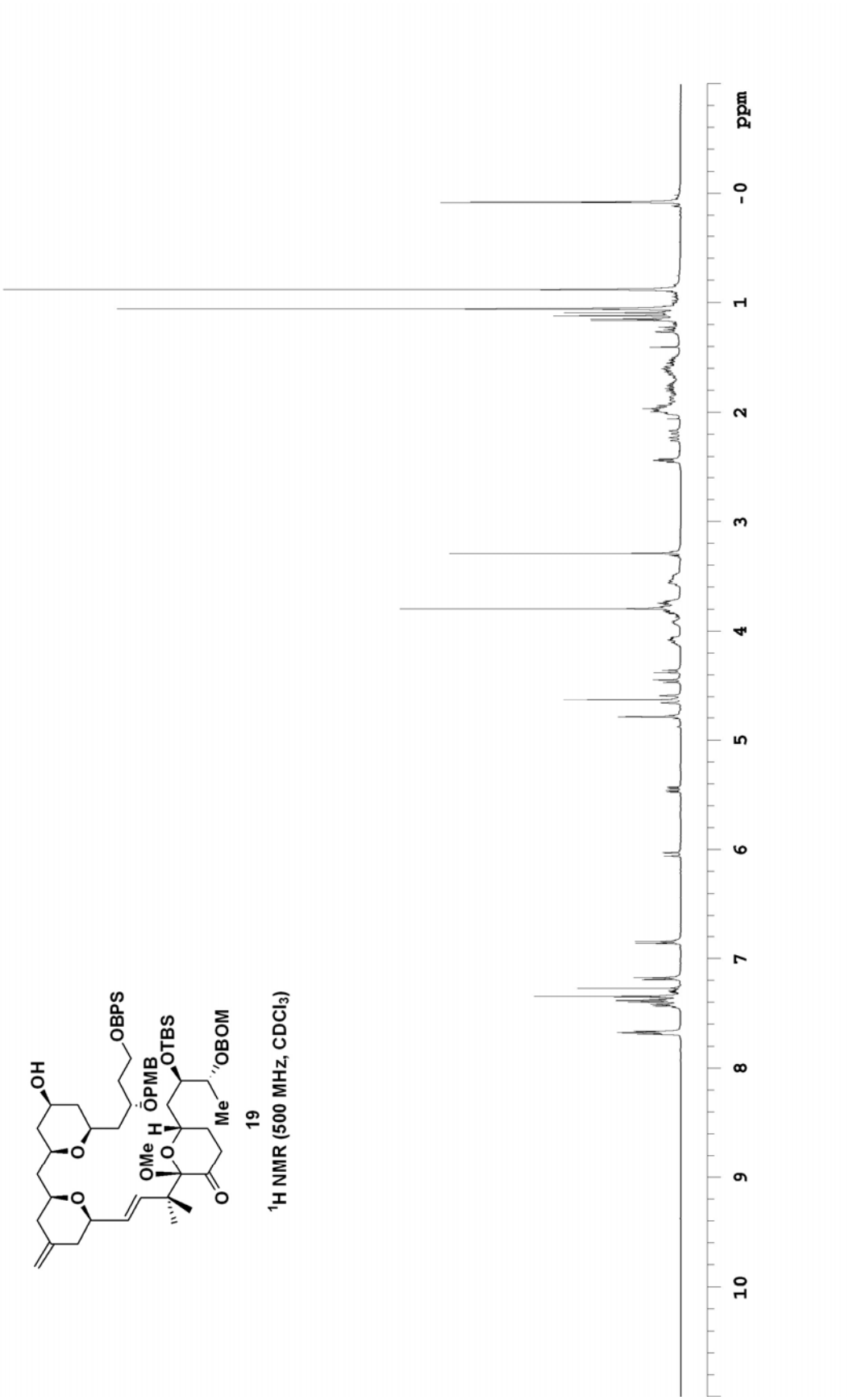
6
5
4
3
2
1
-0


TMS
OH
O
OH
OPMB
OBPS
5
^{13}C NMR (125 MHz, $CDCl_3$)
ppm
220
200
180
160
140
120
100
80
60
40
20


TMS
OH
OH
O
OPMB
OBPS
5
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm


OBPS
OH
OMe
H
OPMB
OTBS
OBOM
Me
O
O
O
O
19
^{1}H NMR (500 MHz, CDCl$_3$)
ppm
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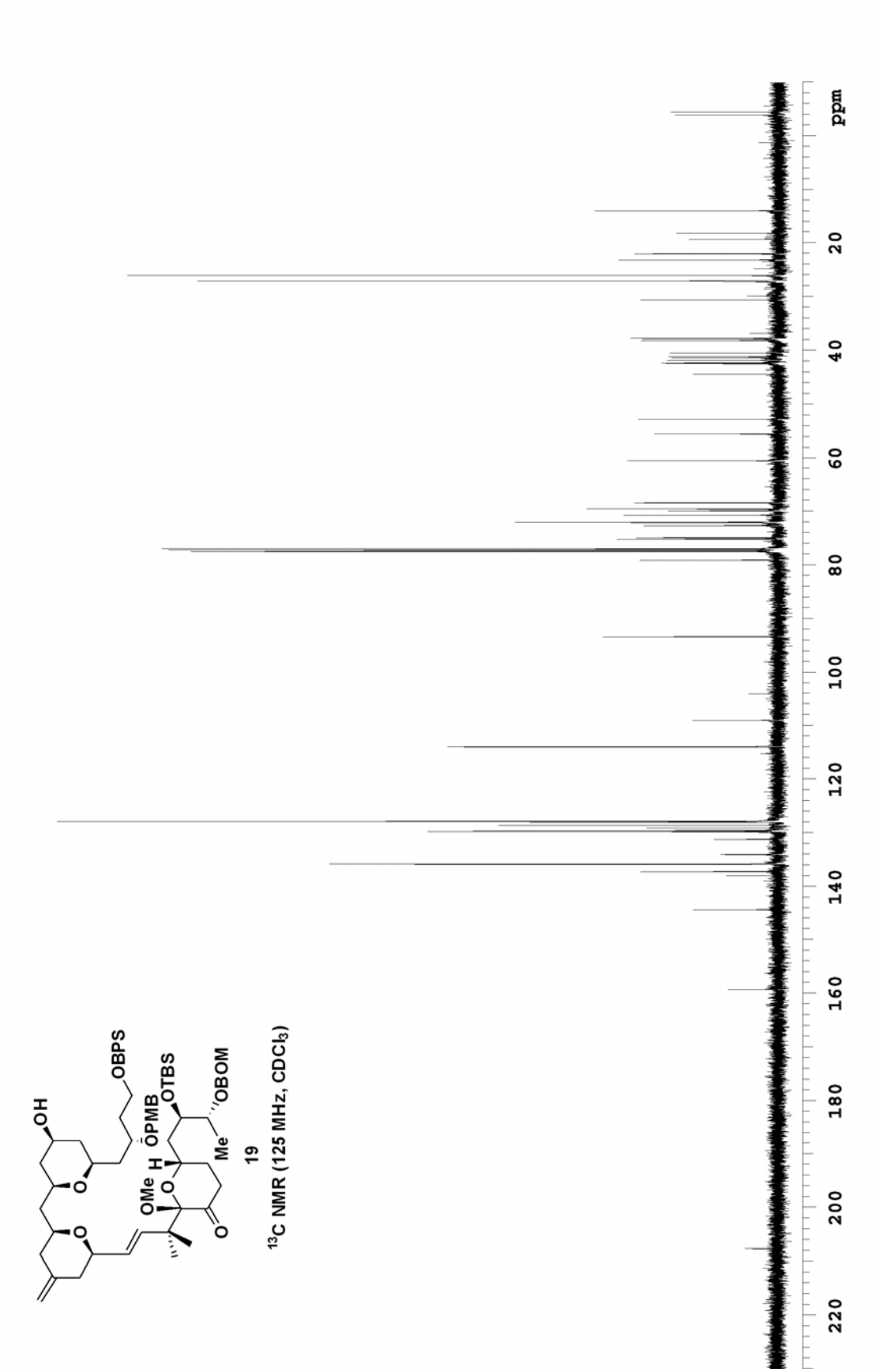
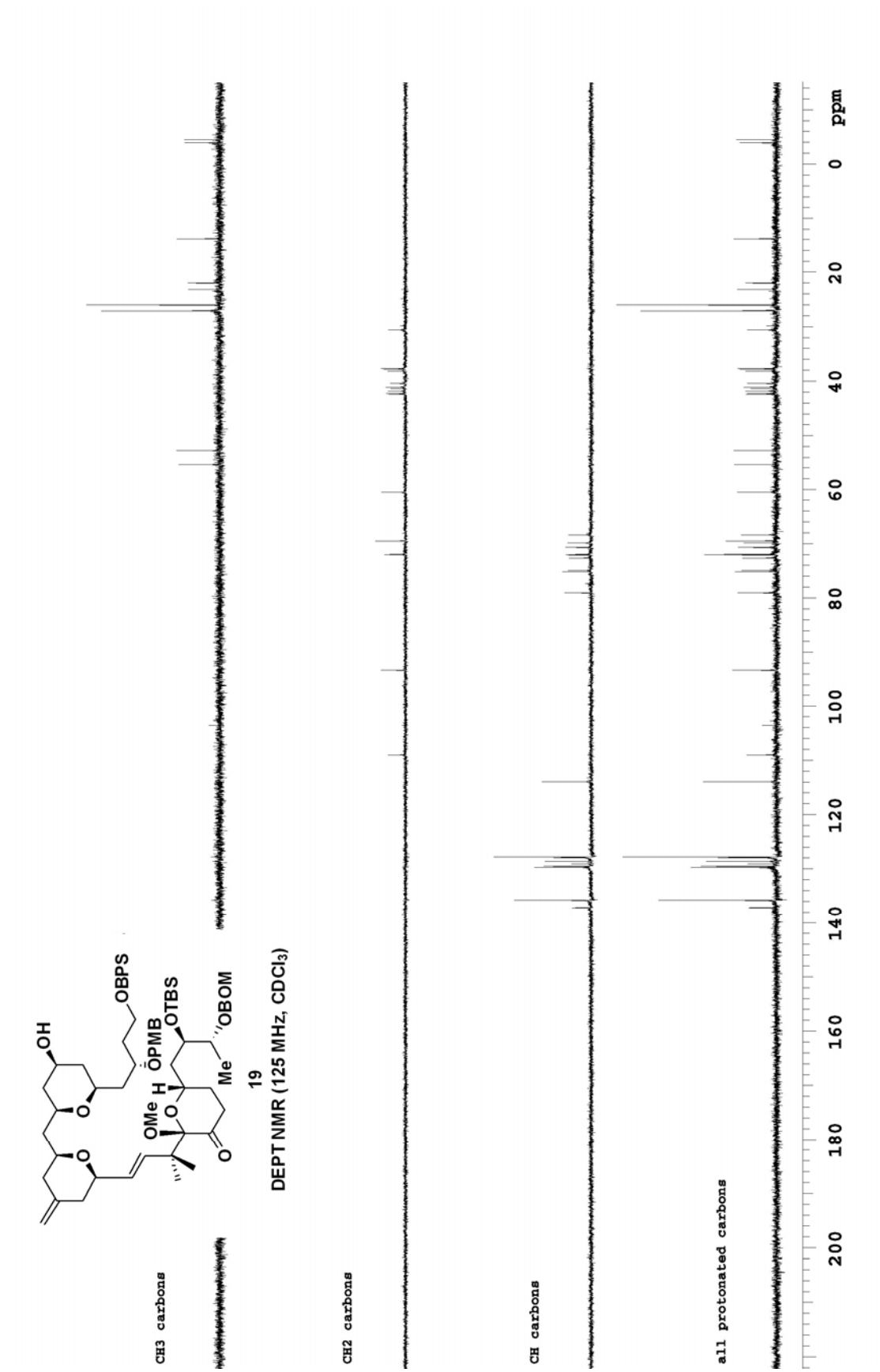
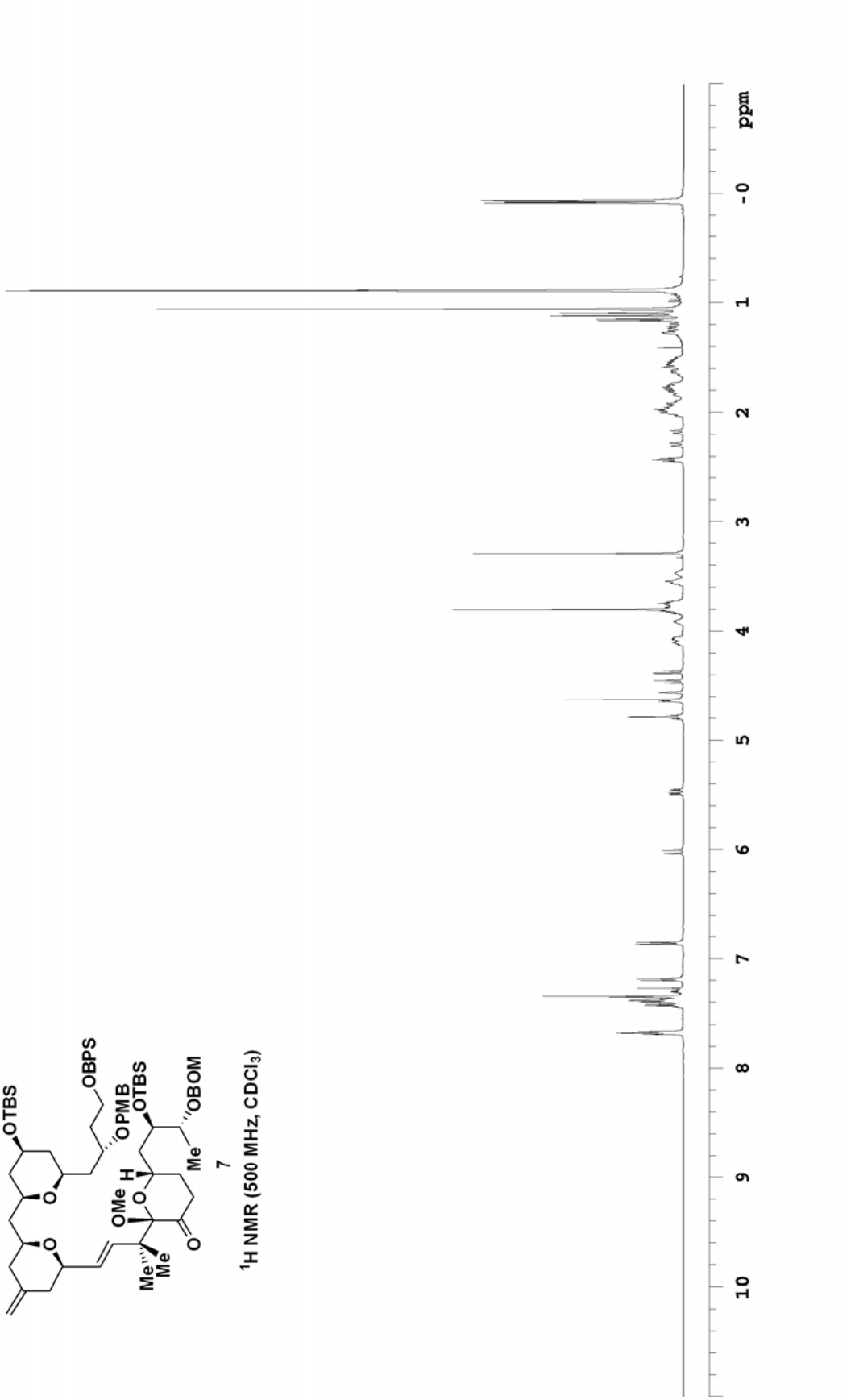
9
8
7
6
5
4
3
2
1
-0


OH
OBPS
OPMB
OTBS
OBOM
OMe
H
O
Me
O
19
^{13}C NMR (125 MHz, $CDCl_3$)
ppm
220
200
180
160
140
120
100
80
60
40
20


OBPS
OH
OPMB
OTBS
OMe
H
O
Me
OBOM
O
19
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
O
Me
Me
Me
O
7
^{1}H NMR (500 MHz, $CDCl_3$)
ppm
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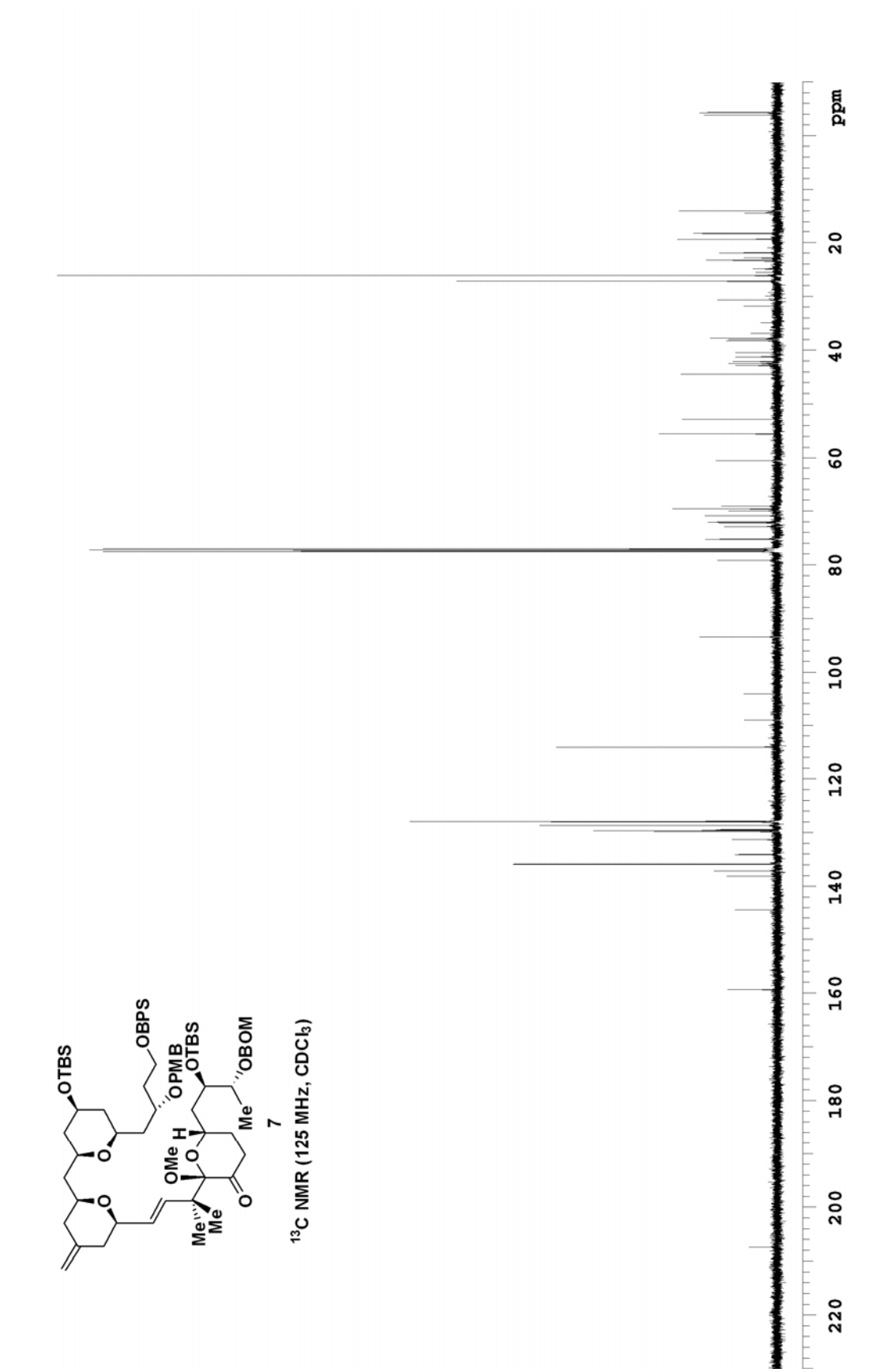
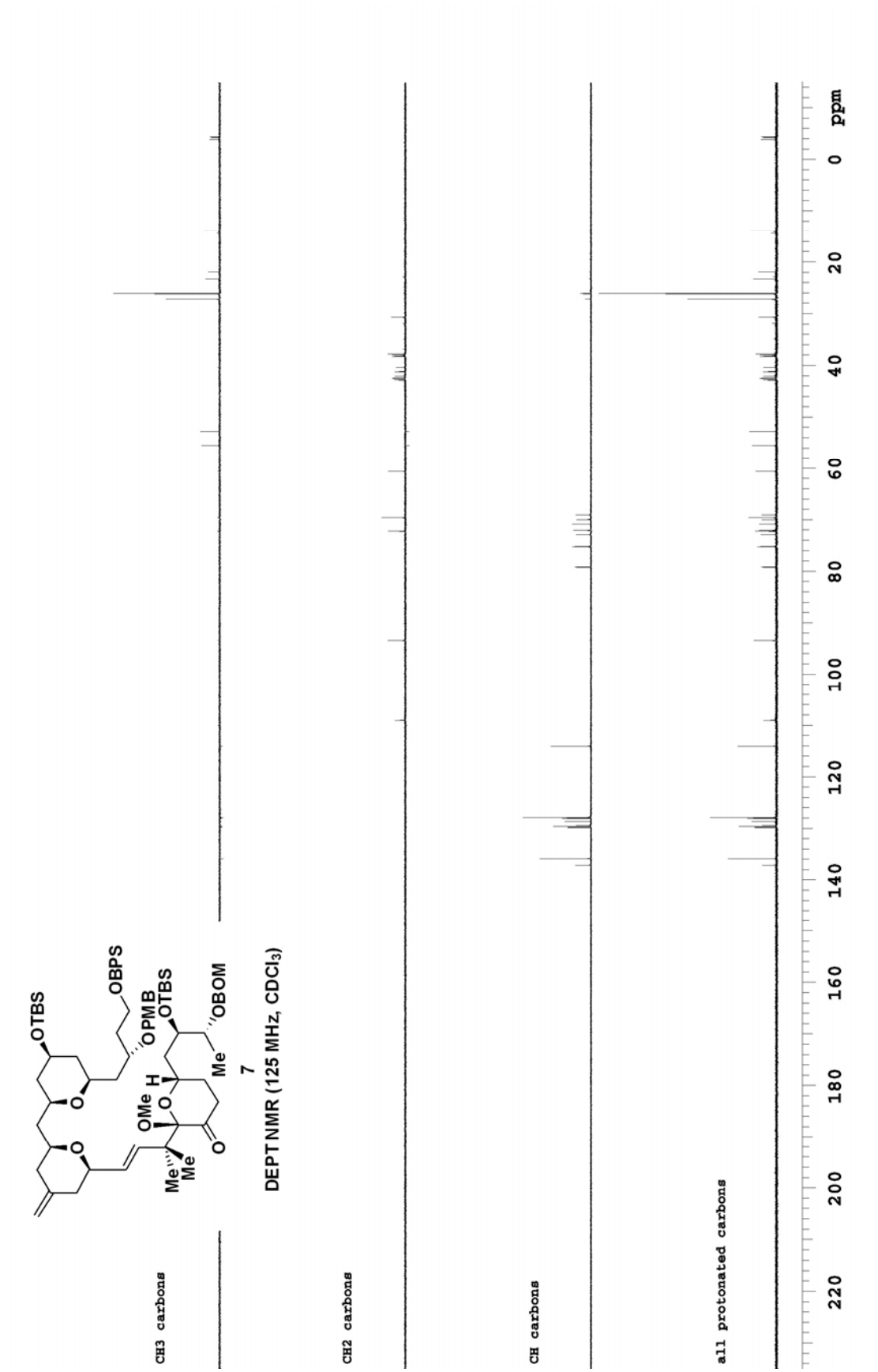
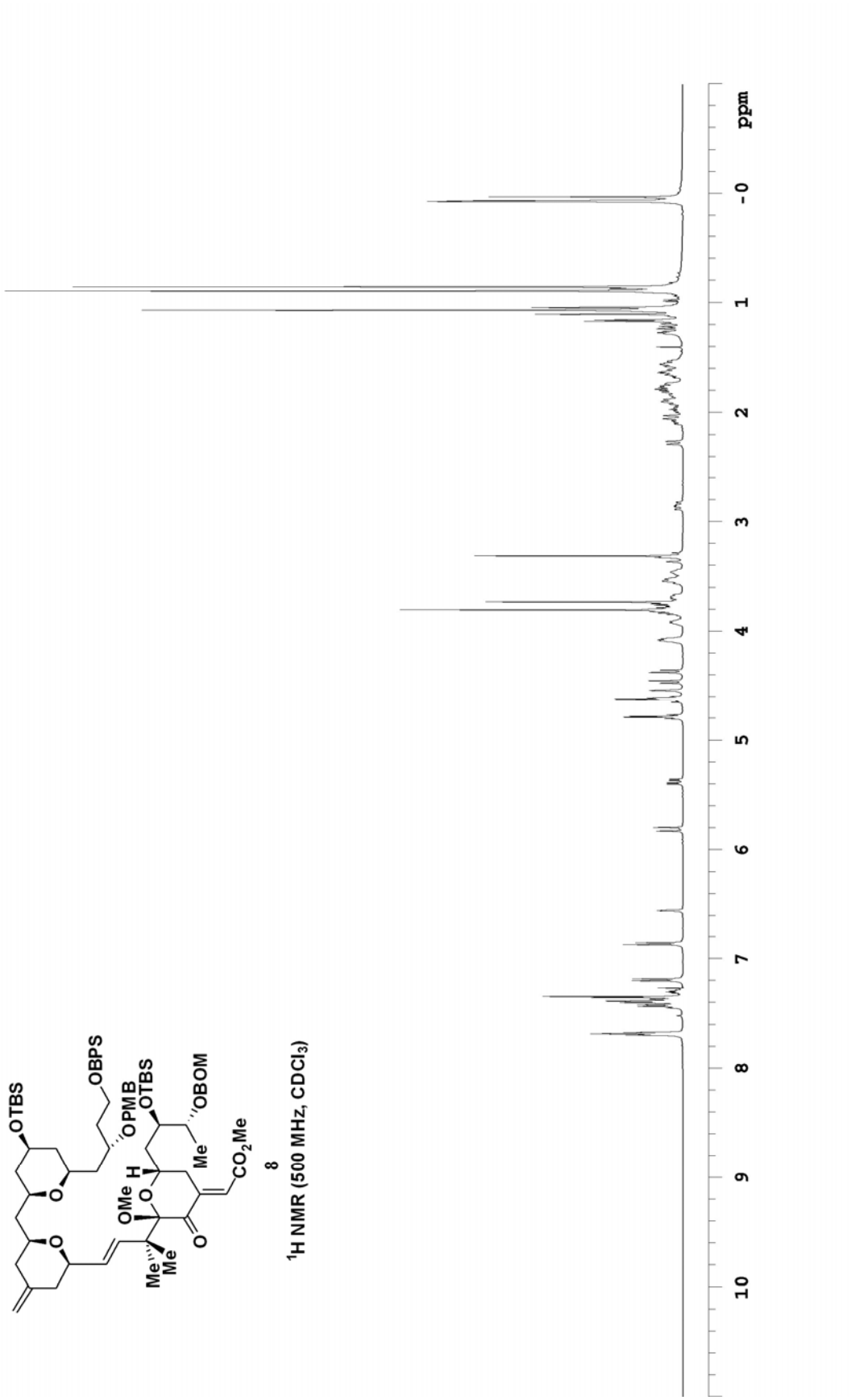
8
7
6
5
4
3
2
1
-0


OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
O
O
O
O
O
7
^{13}C NMR (125 MHz, CDCl$_3$)
ppm
220
200
180
160
140
120
100
80
60
40
20


OTBS
OBPS
OPMB
OTBS
OMe
H
O
Me
Me
Me
OBOM
O
O
O
7
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
O
Me
CO2Me
O
Me
Me
8
1H NMR (500 MHz, CDCl3)
ppm
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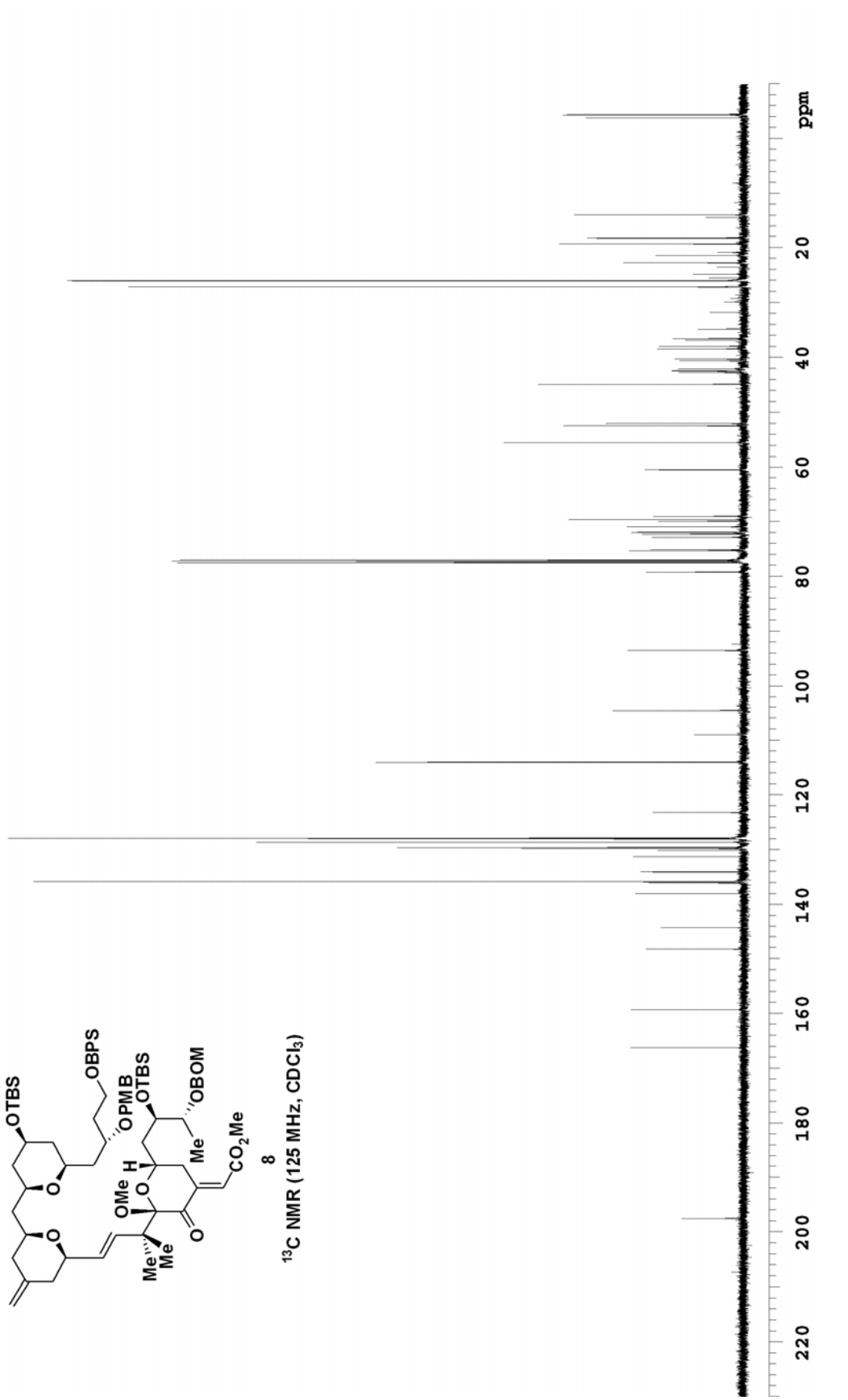
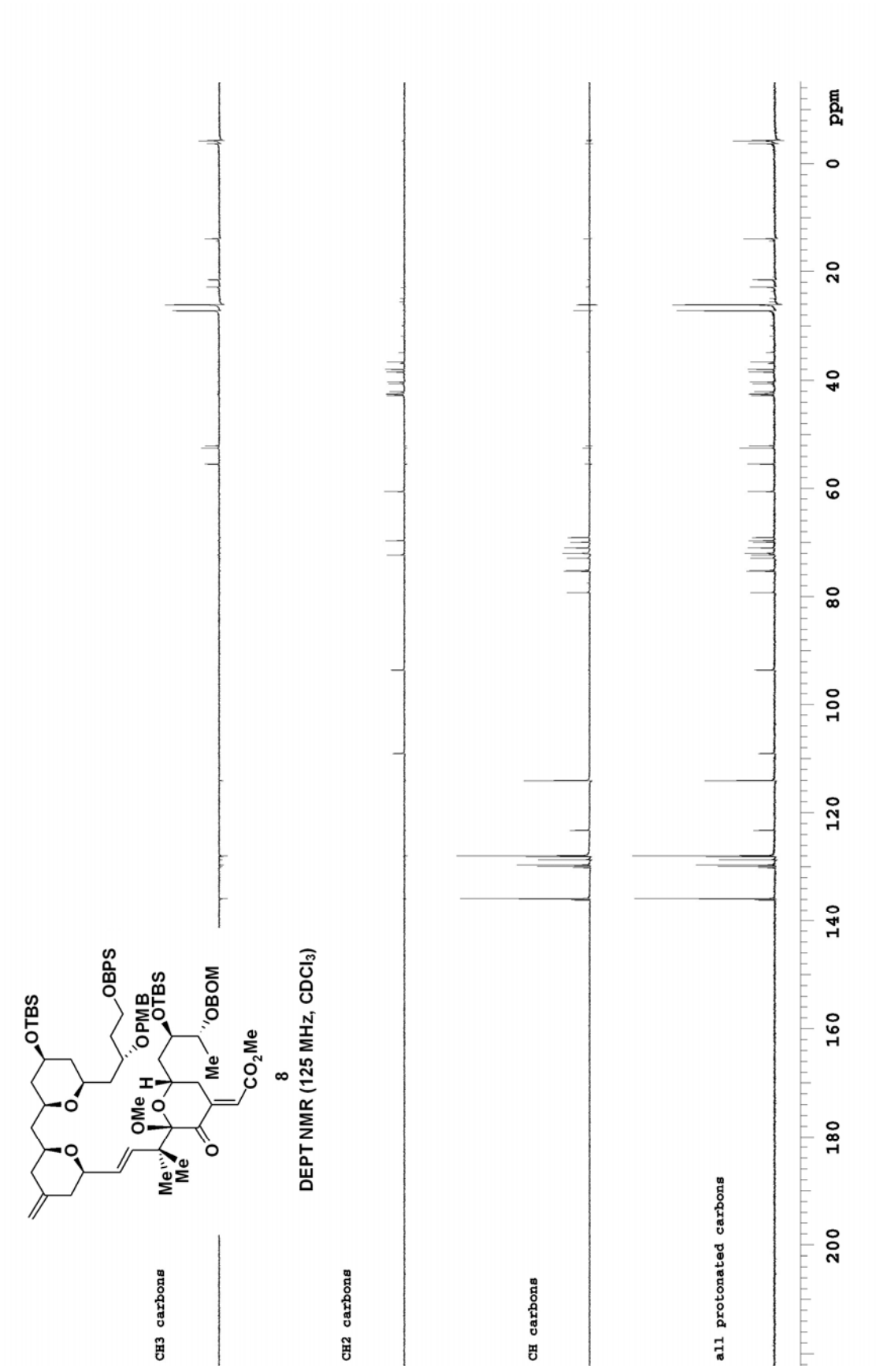
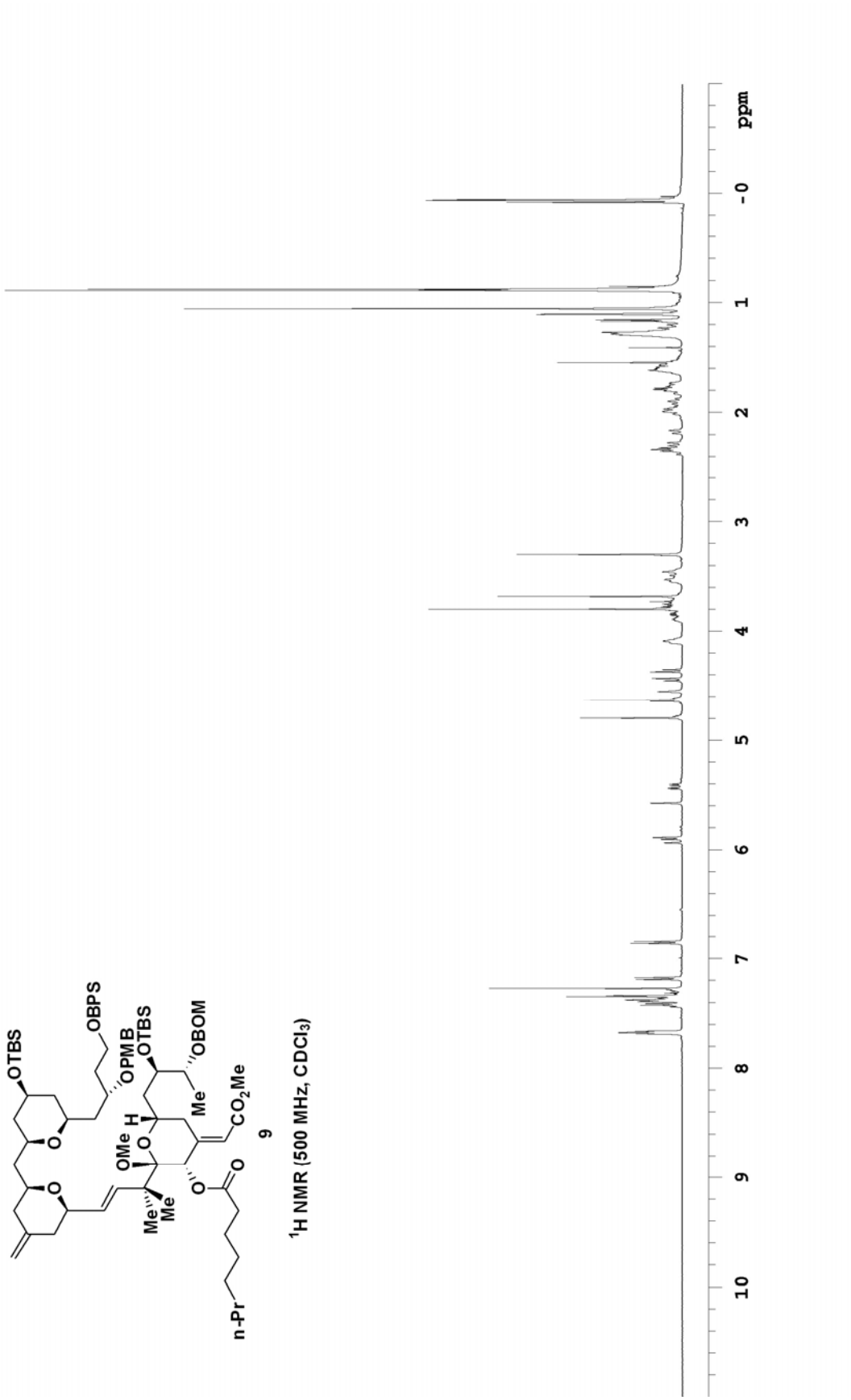
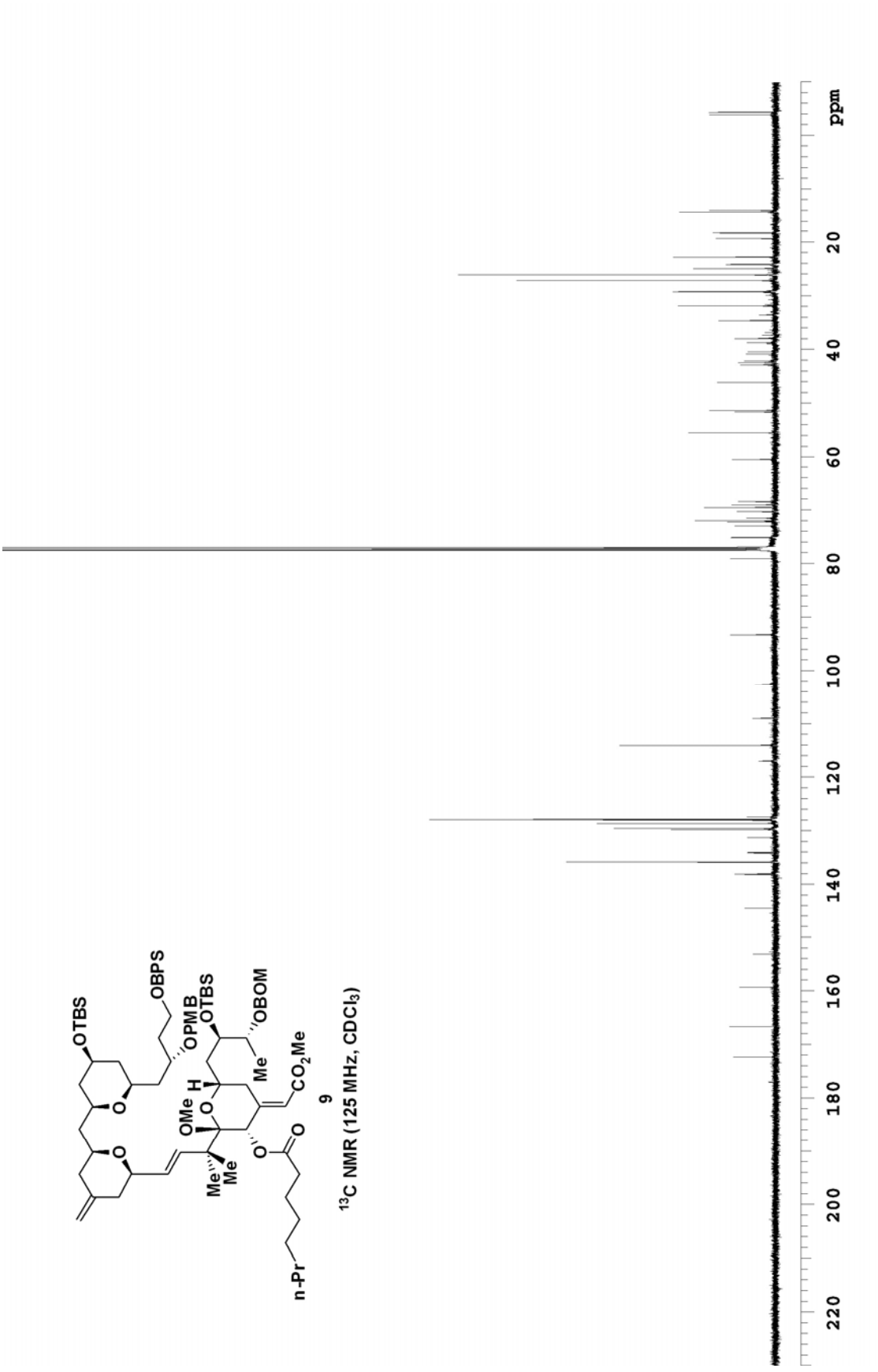
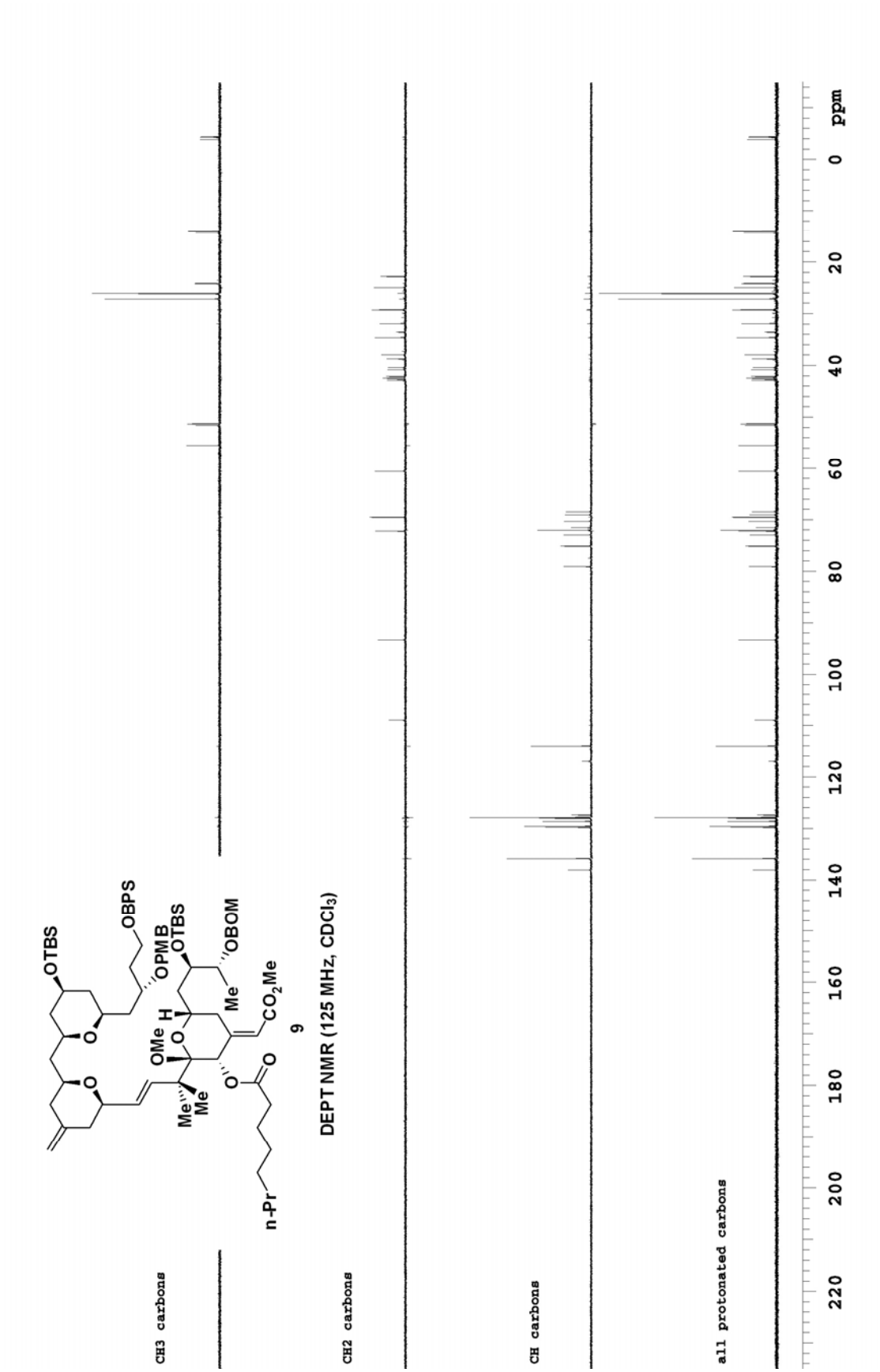
8
7
6
5
4
3
2
1
-0

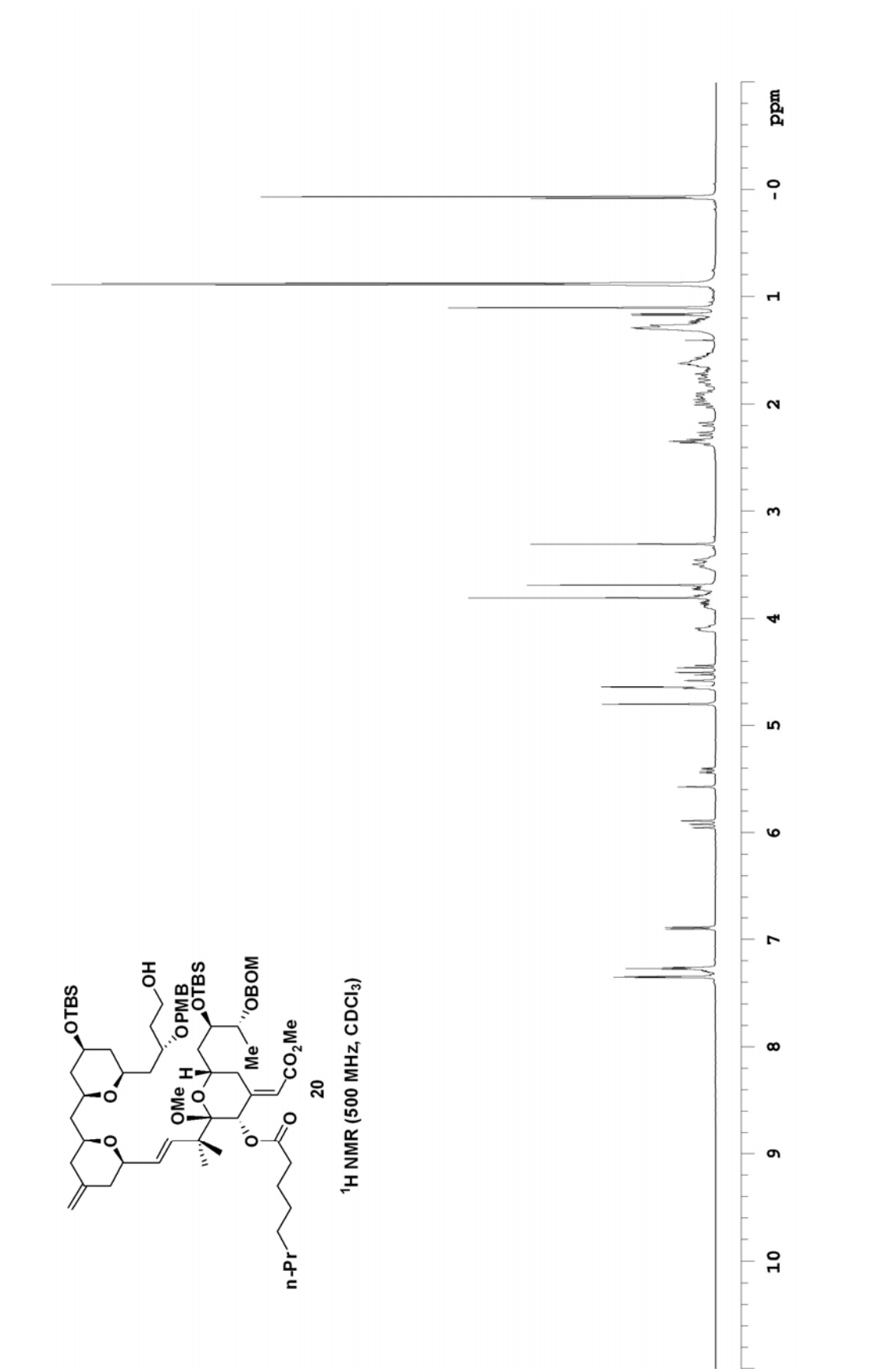

OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
CO2Me
O
O
O
O
O
8
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20

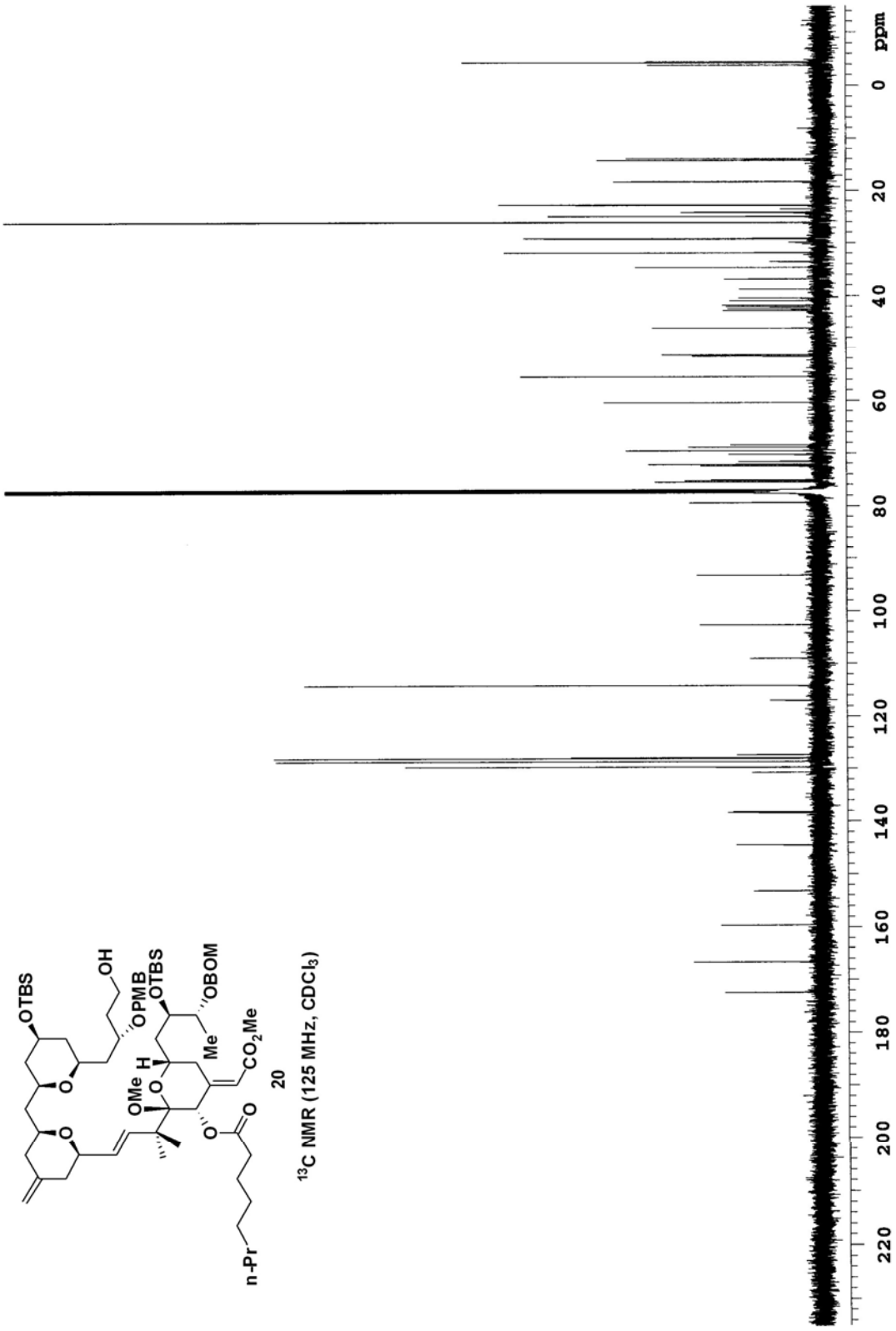

OTBS
OBPS
OPMB
OTBS
OMe
H
O
Me
OBOM
Me
Me
CO2Me
O
O
O
O
8
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

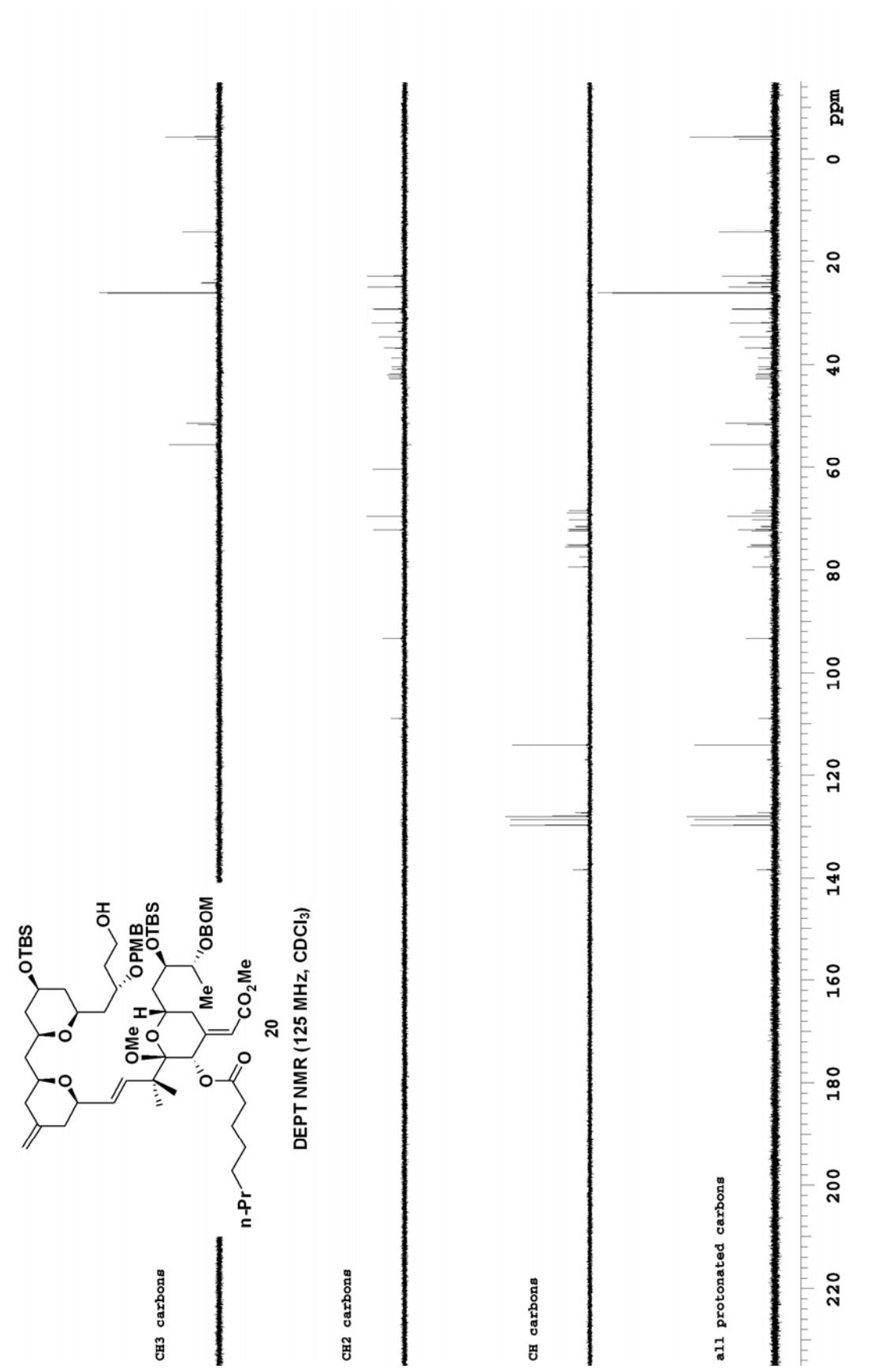

OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
CO2Me
n-Pr
9
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0

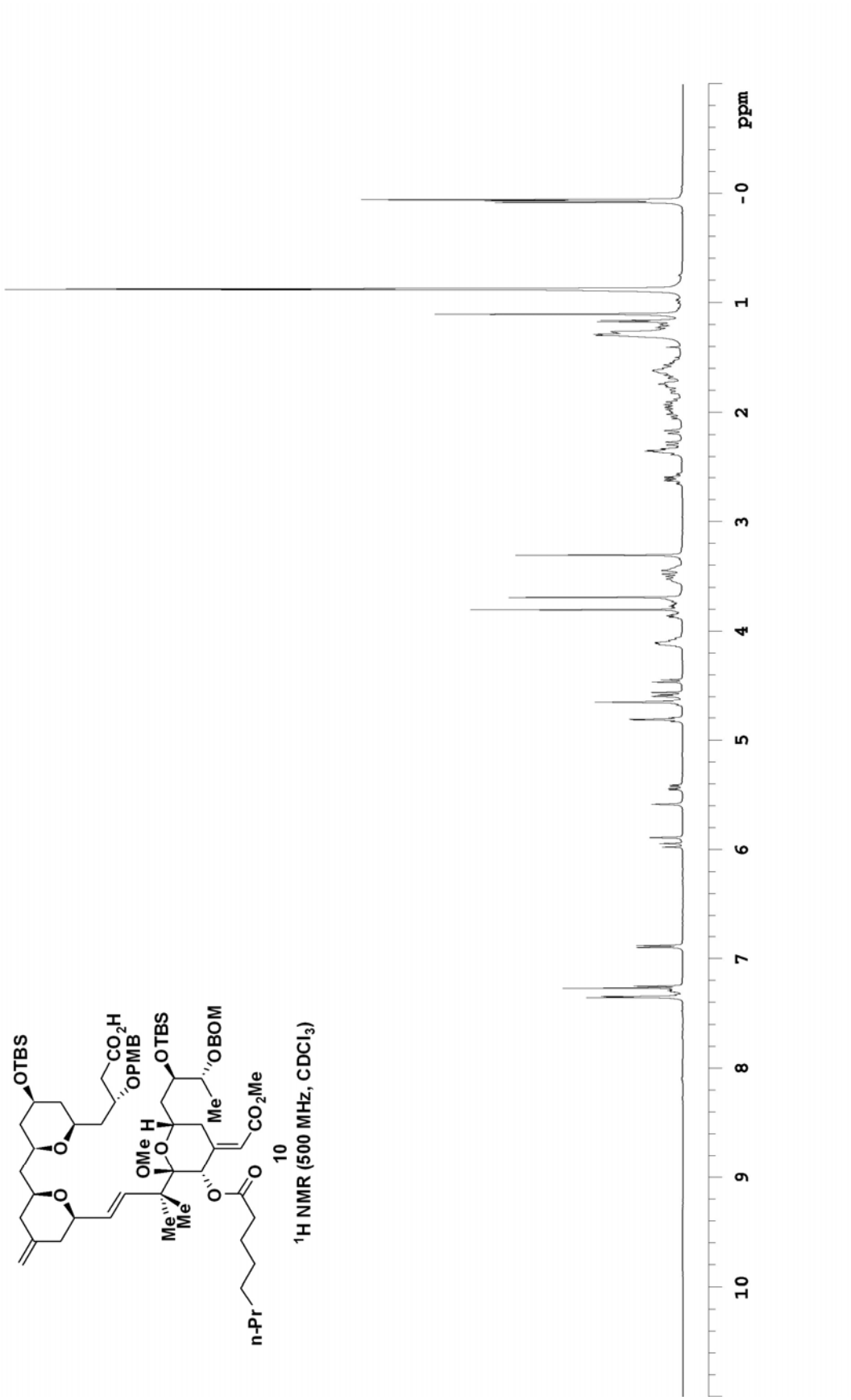

OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
CO2Me
n-Pr
9
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20

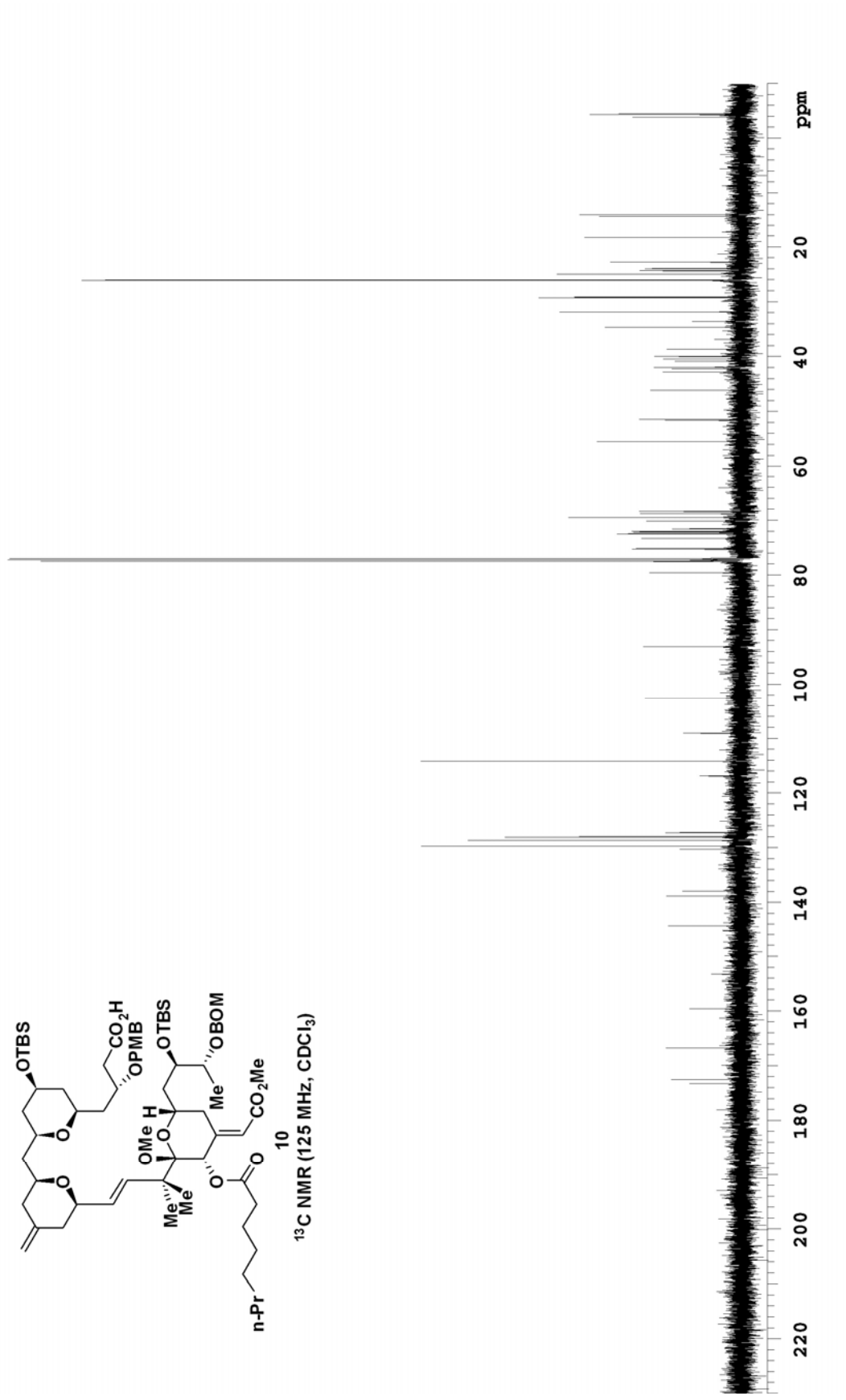

DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTBS
OBPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
CO2Me
n-Pr
9
220
200
180
160
140
120
100
80
60
40
20
0
ppm

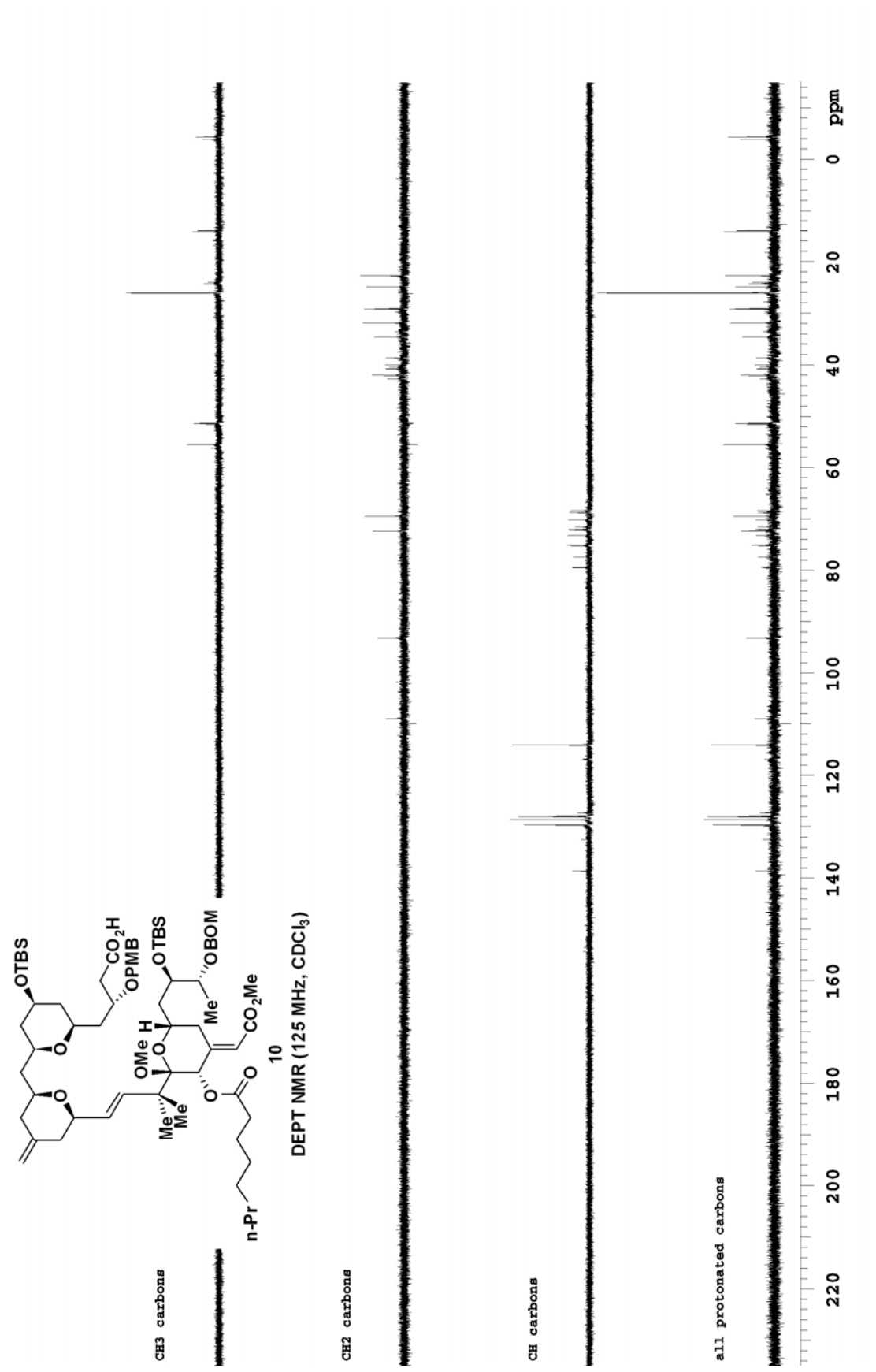

OTBS
OH
OPMB
OTBS
OBOM
OMe
H
Me
CO2Me
O
O
O
O
O
n-Pr
20
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0

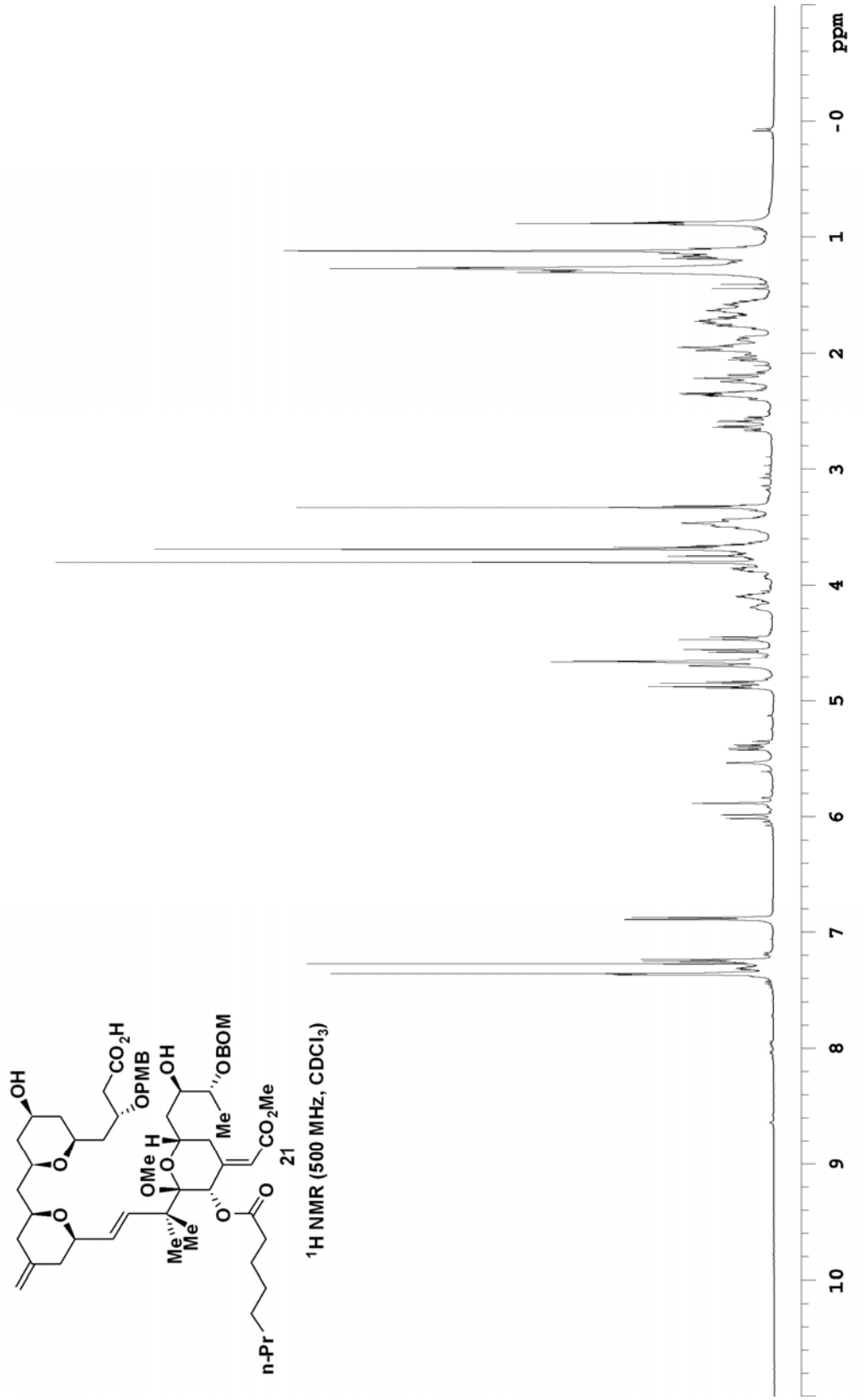

OTBS
OH
OPMB
OTBS
OBOM
Me
CO_2Me
OMe
H
O
n-Pr
20
^{13}C NMR (125 MHz, $CDCl_3$)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

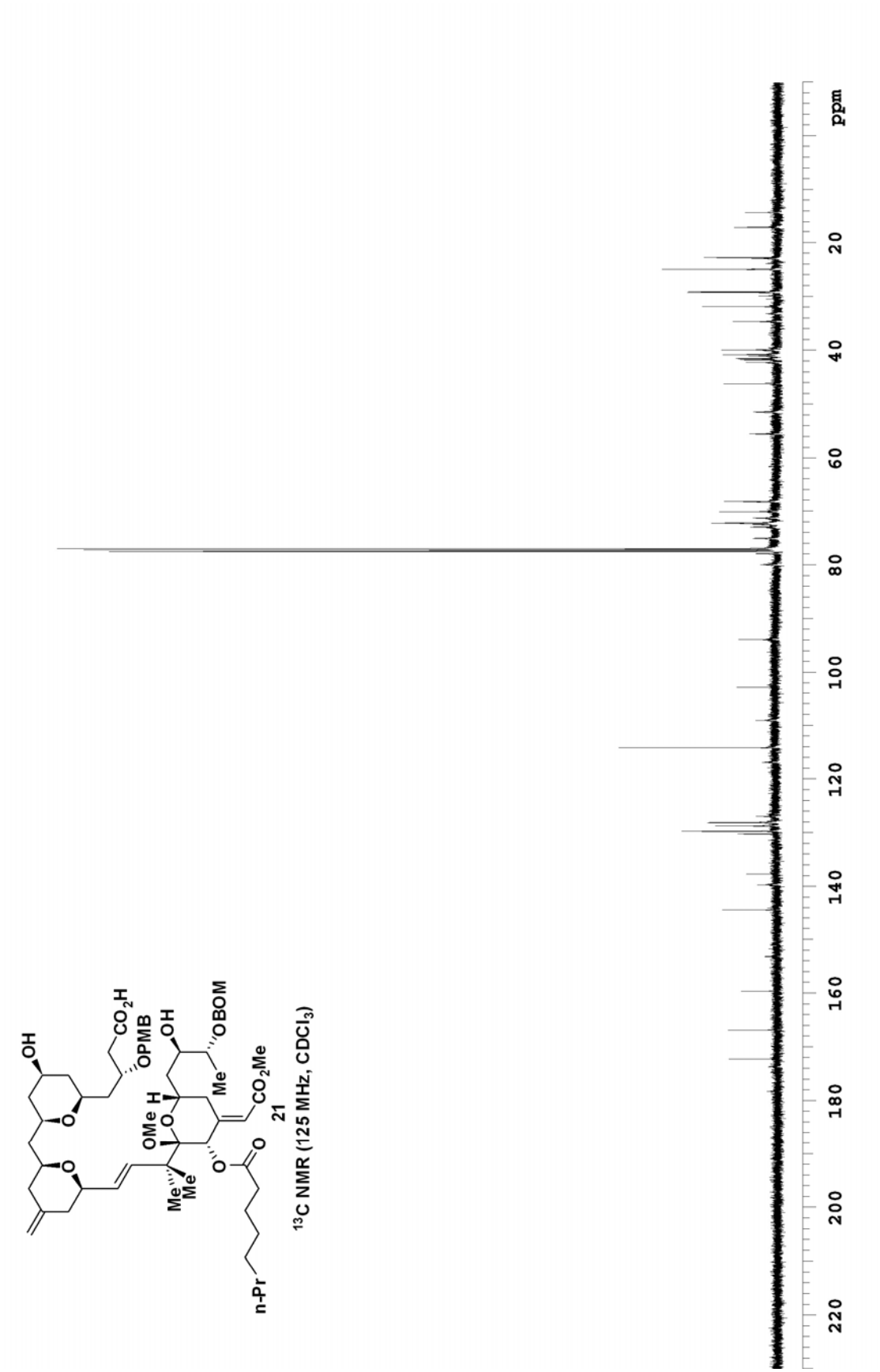

OTBS
OH
OPMB
OTBS
OBOM
OMe
H
Me
CO2Me
n-Pr
20
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

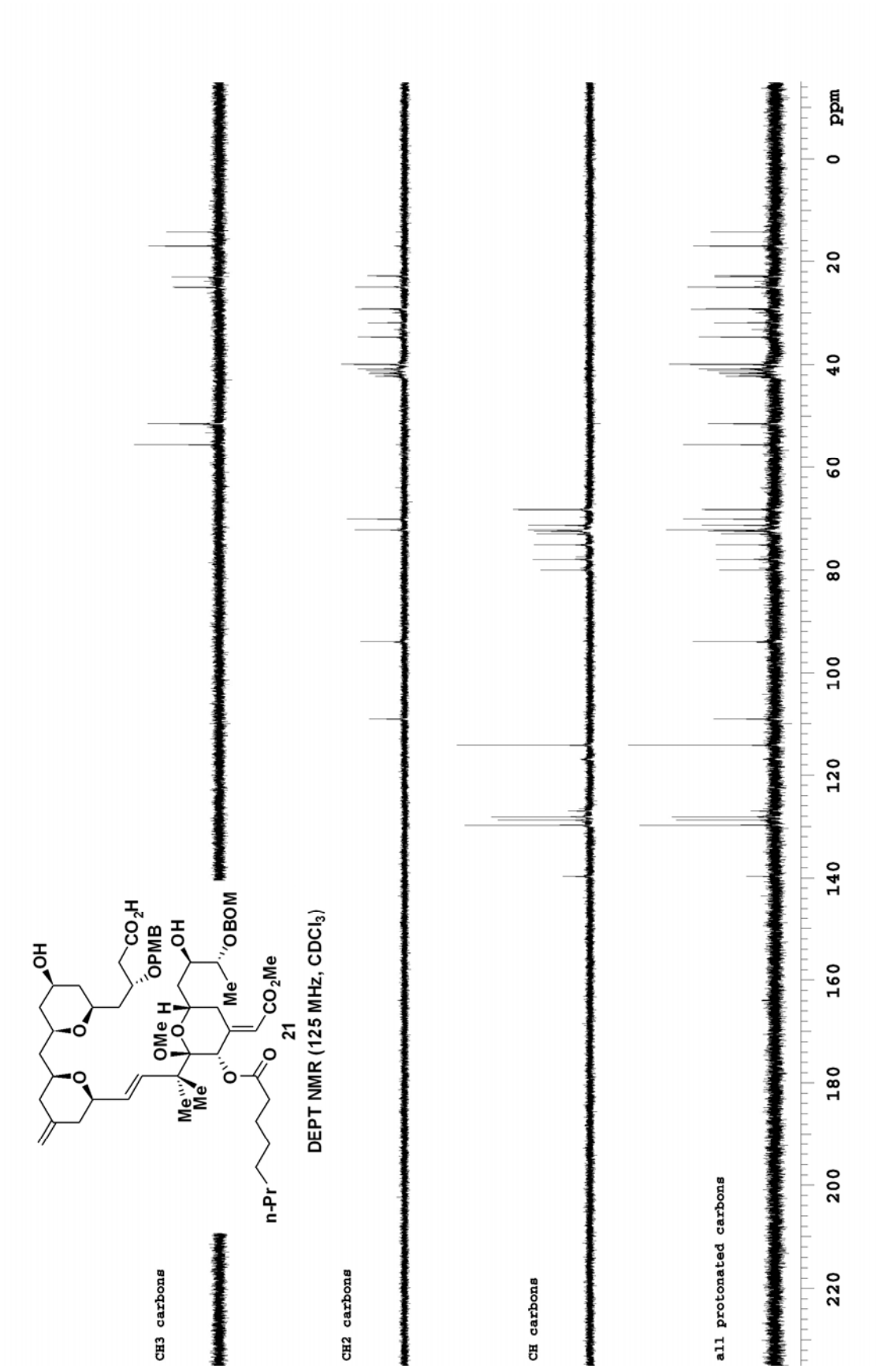

OTBS
CO2H
OPMB
OTBS
OBOM
OMe H
Me
CO2Me
Me
Me
n-Pr
10
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0

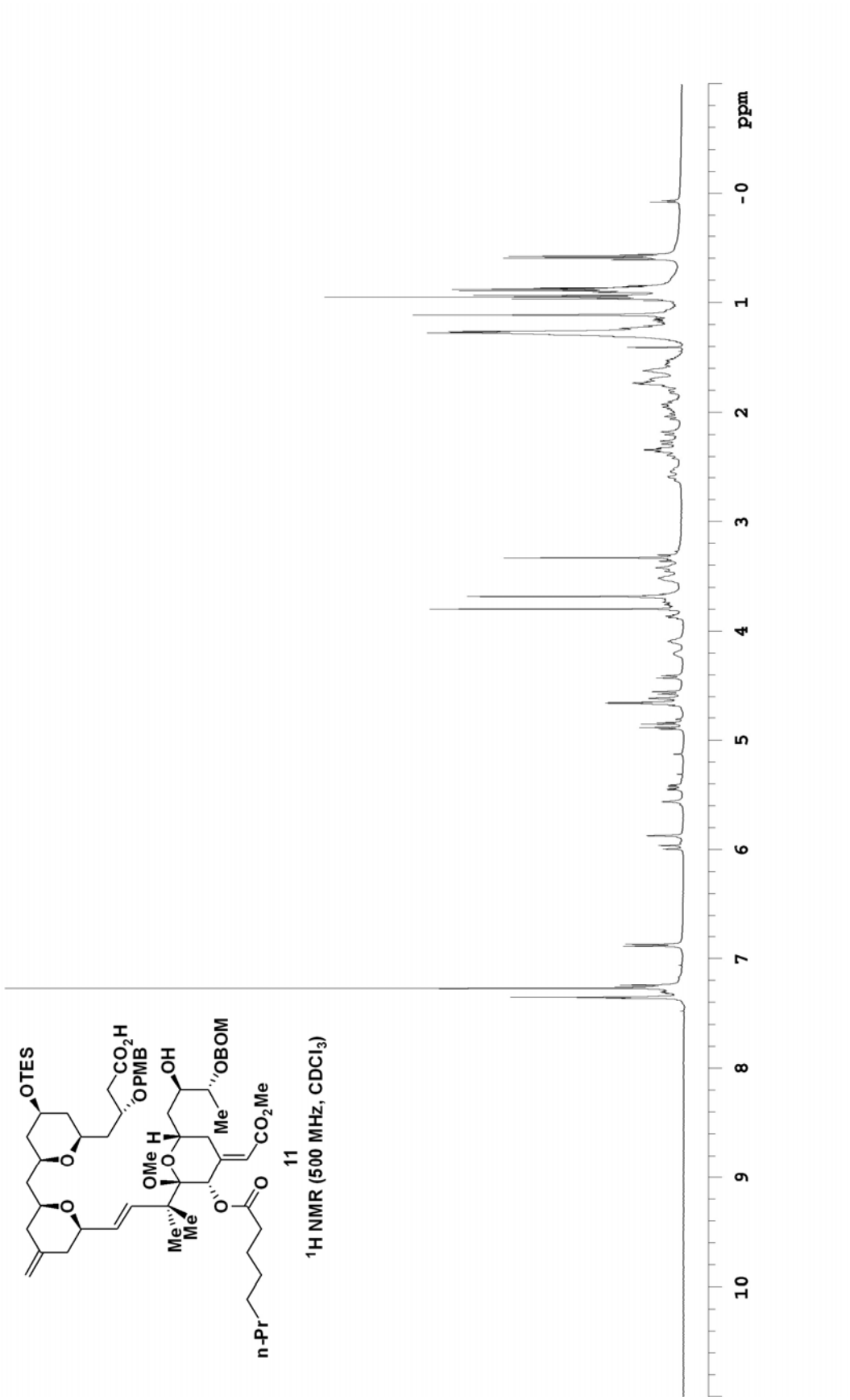

OTBS
CO2H
OPMB
OTBS
OBOM
OMe
H
Me
CO2Me
Me
Me
O
O
O
O
O
n-Pr
10
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20


OTBS
CO2H
OPMB
OTBS
OBOM
OMe
H
Me
CO2Me
Me
Me
n-Pr
10
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
CO2H
OPMB
OH
OBOM
OMe H
Me
CO2Me
Me
Me
O
O
n-Pr
21
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0


OH
CO2H
OPMB
OH
OBOM
Me
CO2Me
OMe H
O
O
O
O
Me
Me
n-Pr
21
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20


DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm
21


OTES
CO2H
OPMB
OMe H
OH
OBOM
Me
CO2Me
Me
Me
O
n-Pr
11
1H NMR (500 MHz, CDCl3)
ppm
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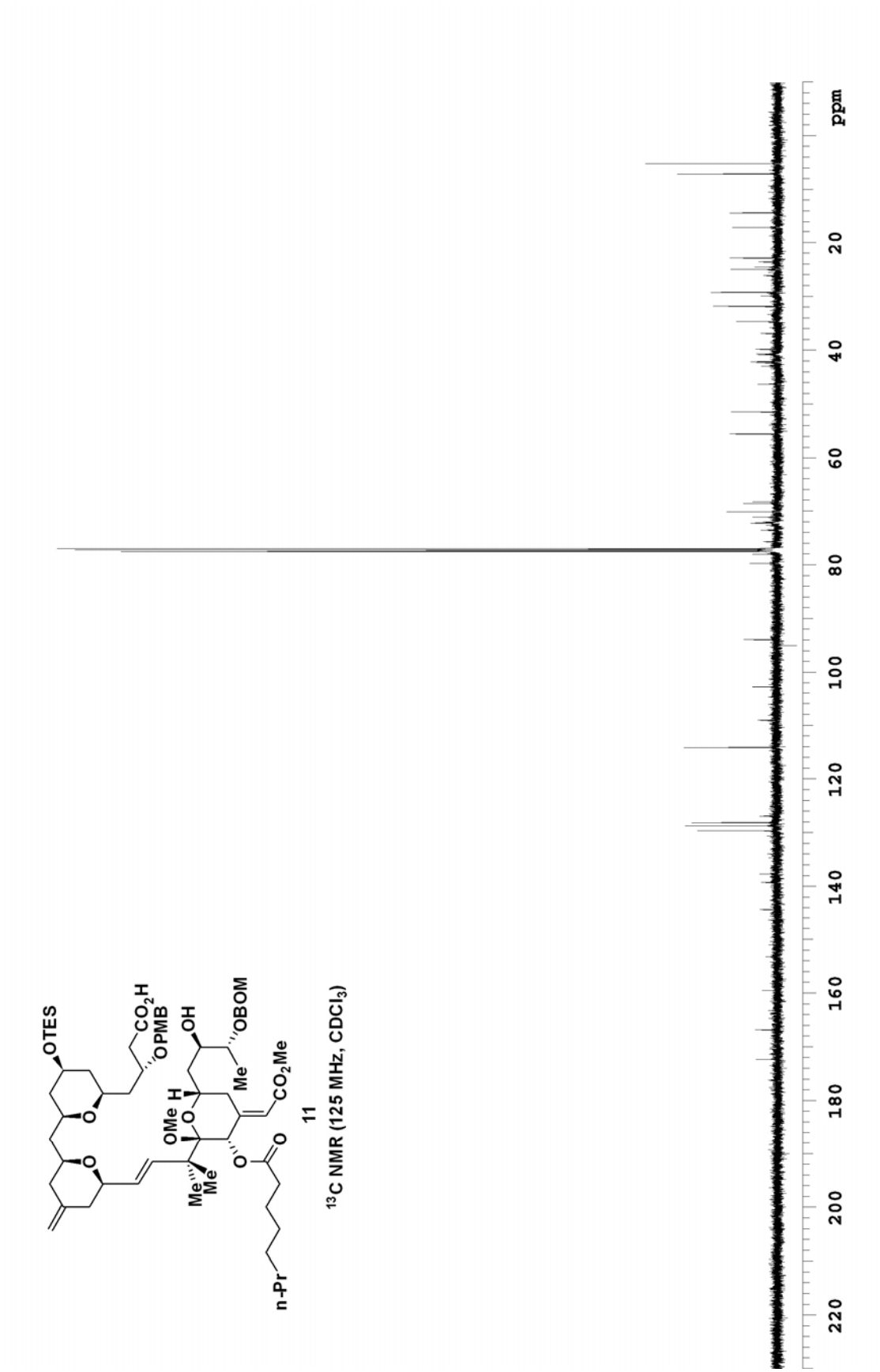
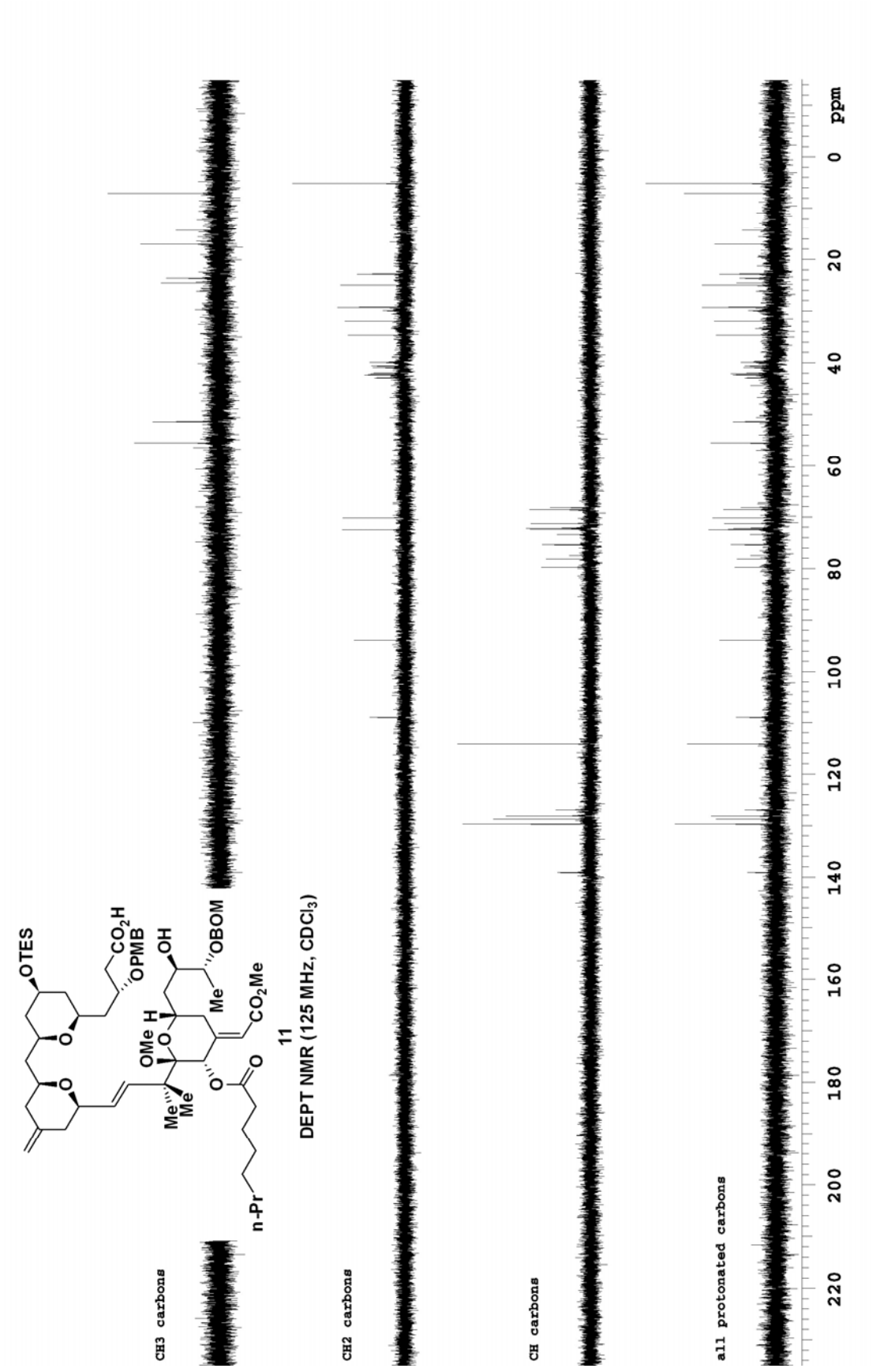
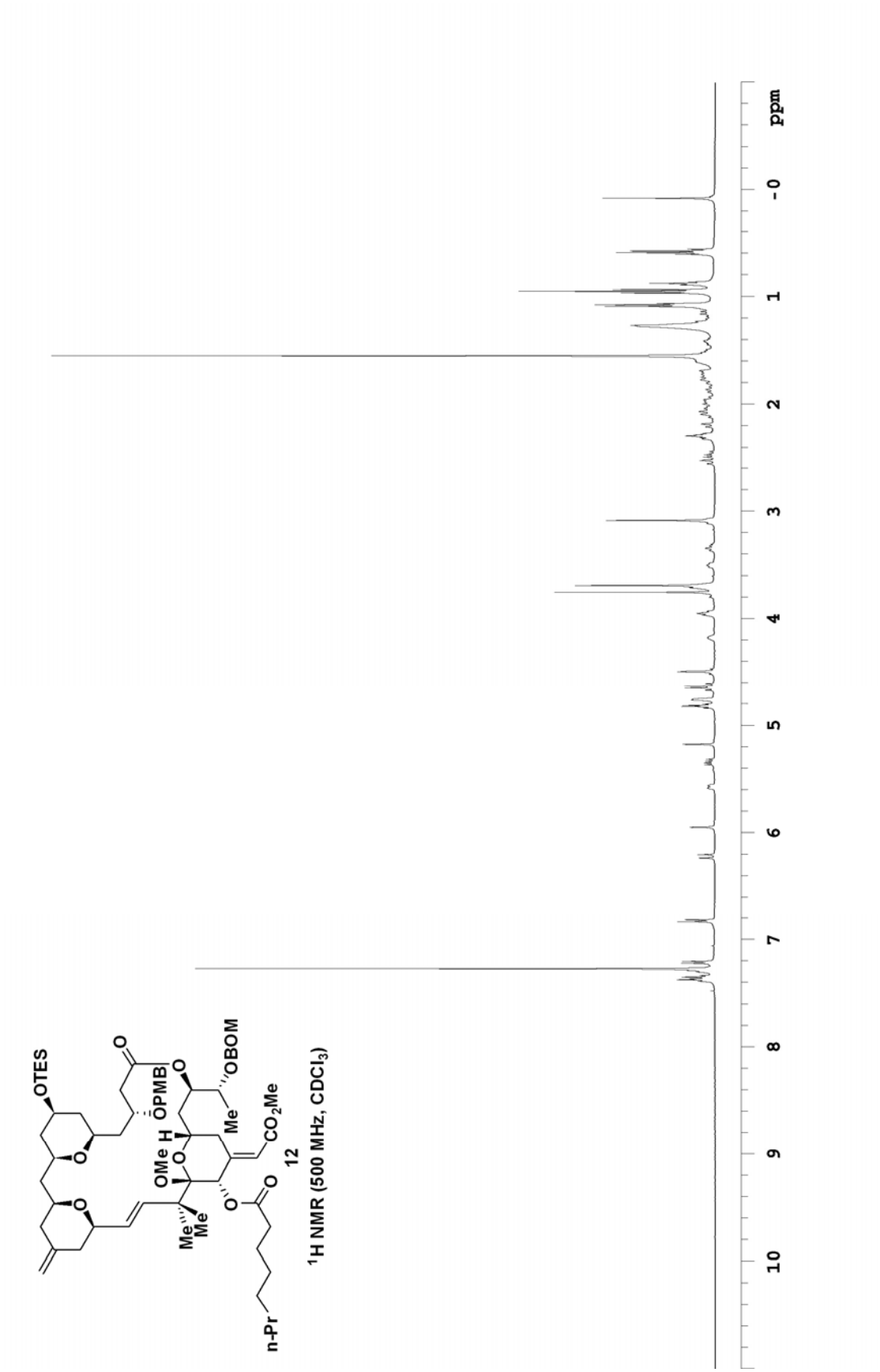
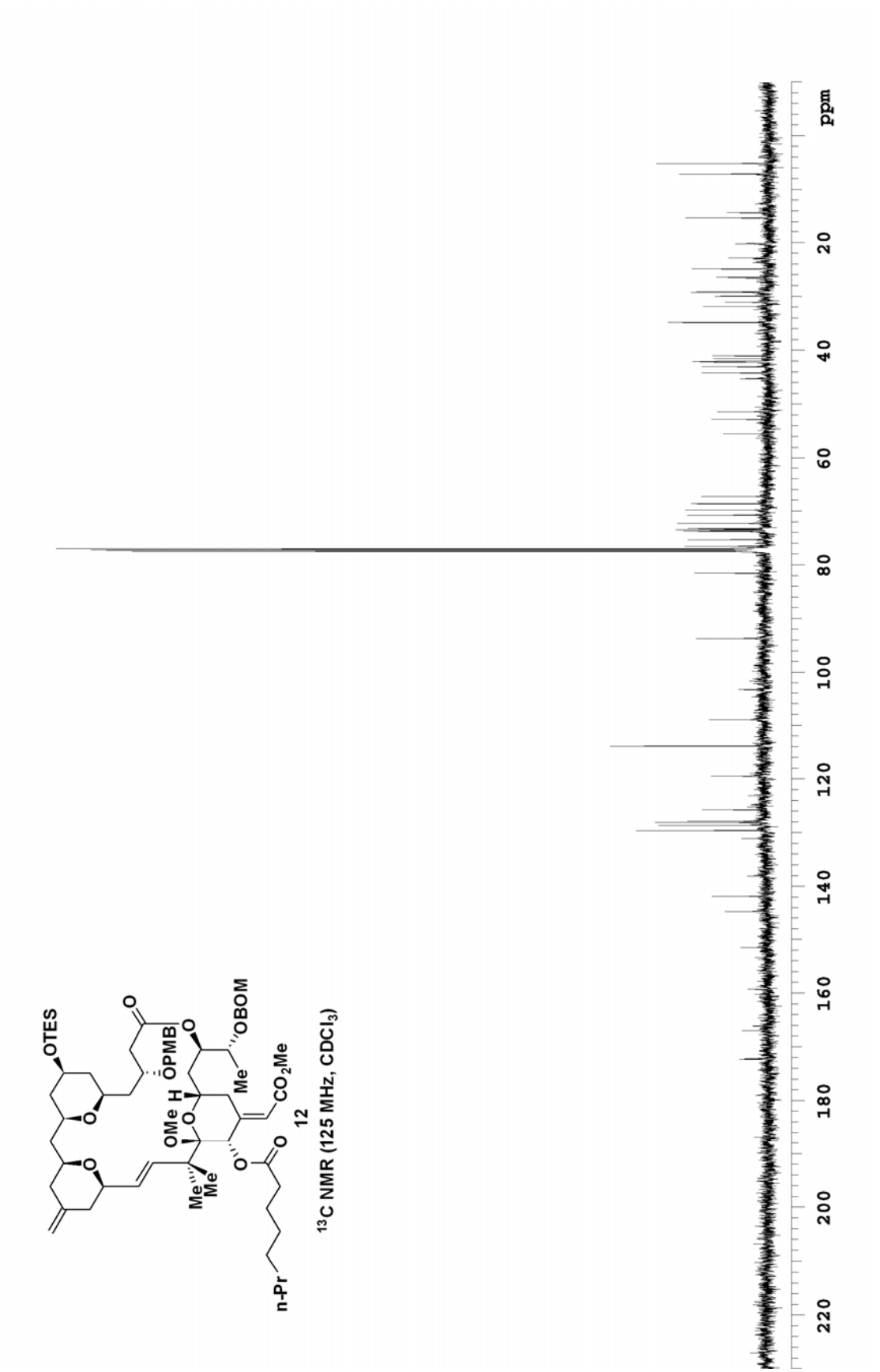
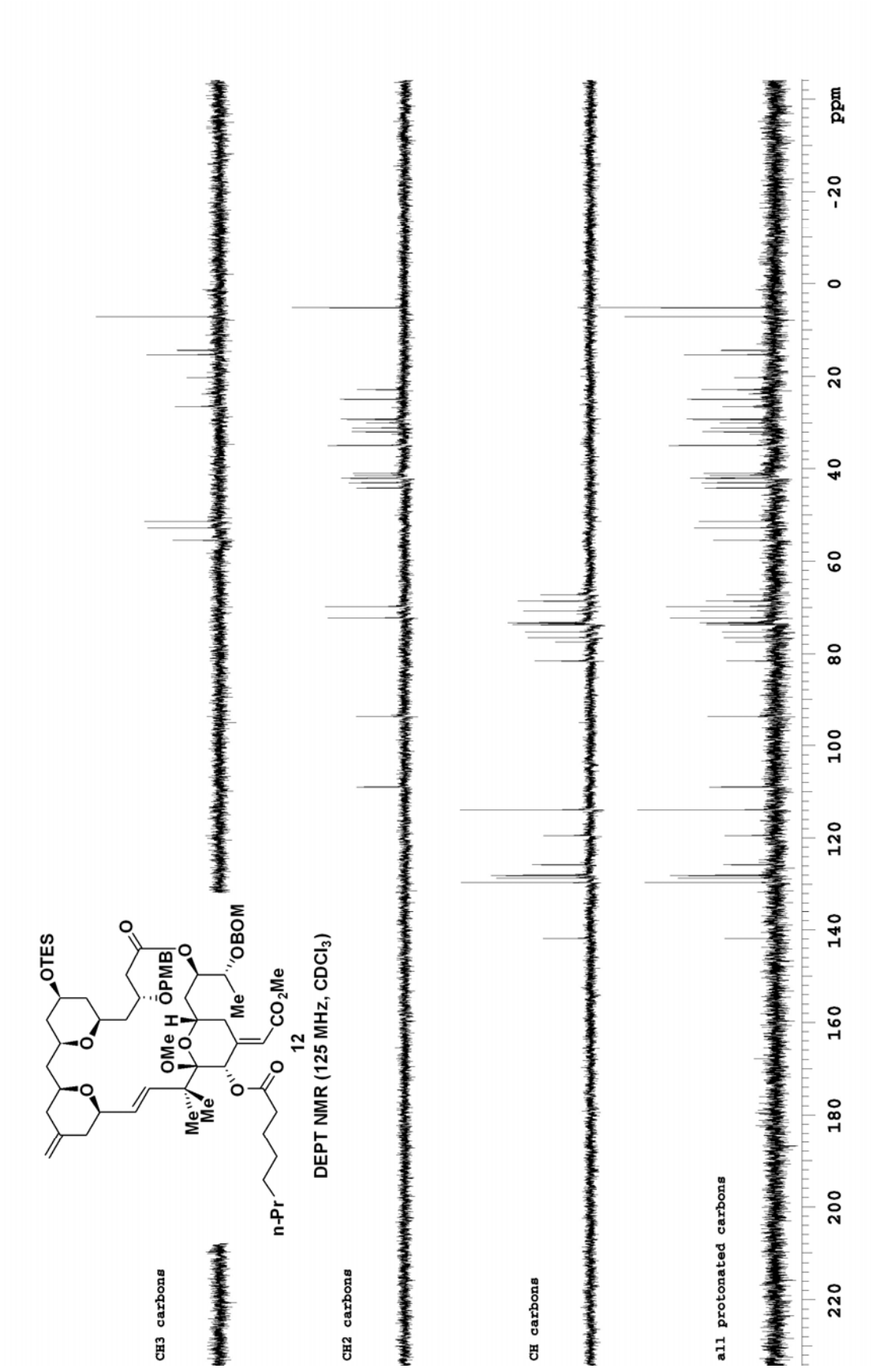
8
7
6
5
4
3
2
1
-0

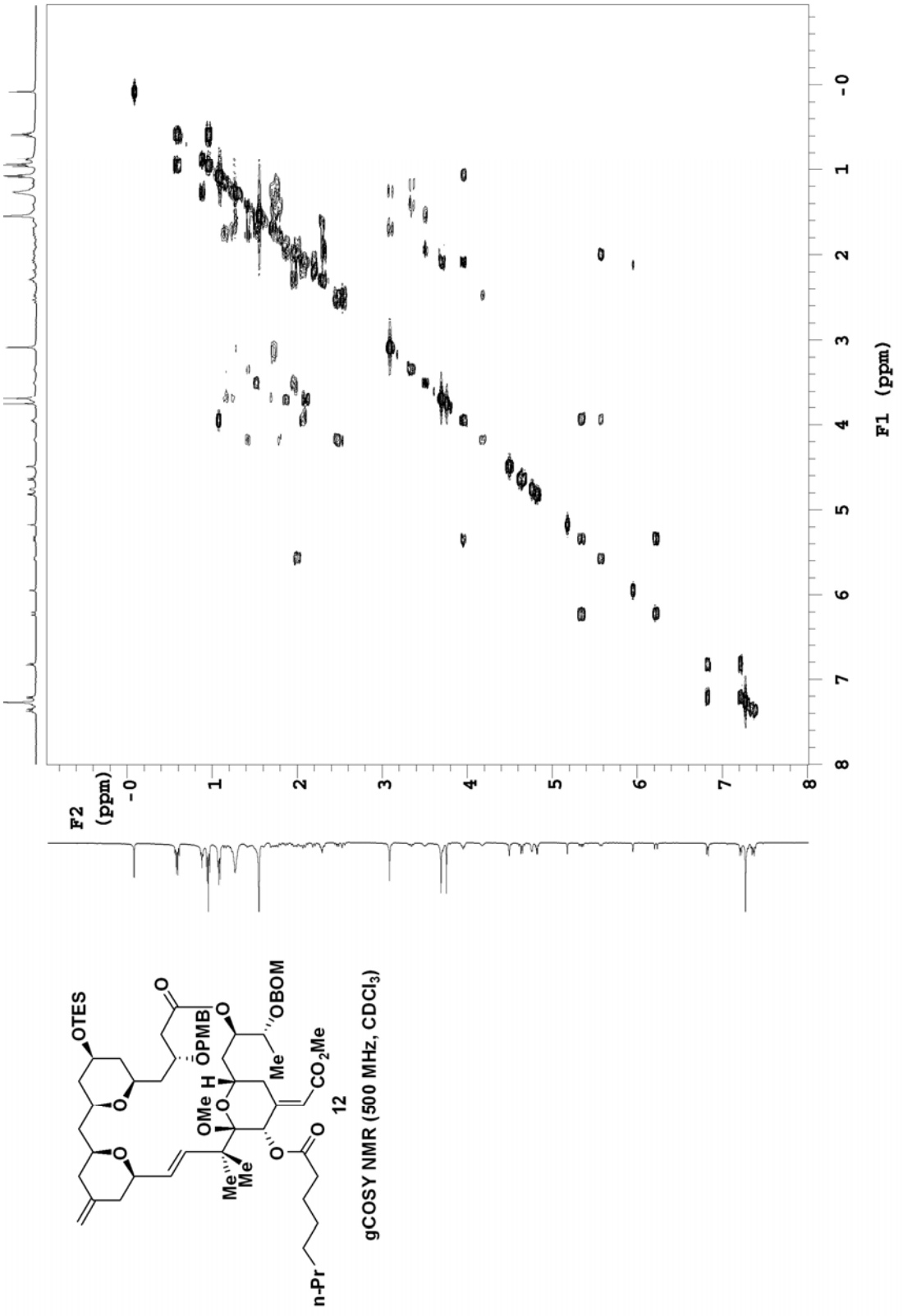

OTES
CO2H
OPMB
OH
OBOM
OMe H
O
Me
CO2Me
Me
Me
O
O
O
n-Pr
11
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20

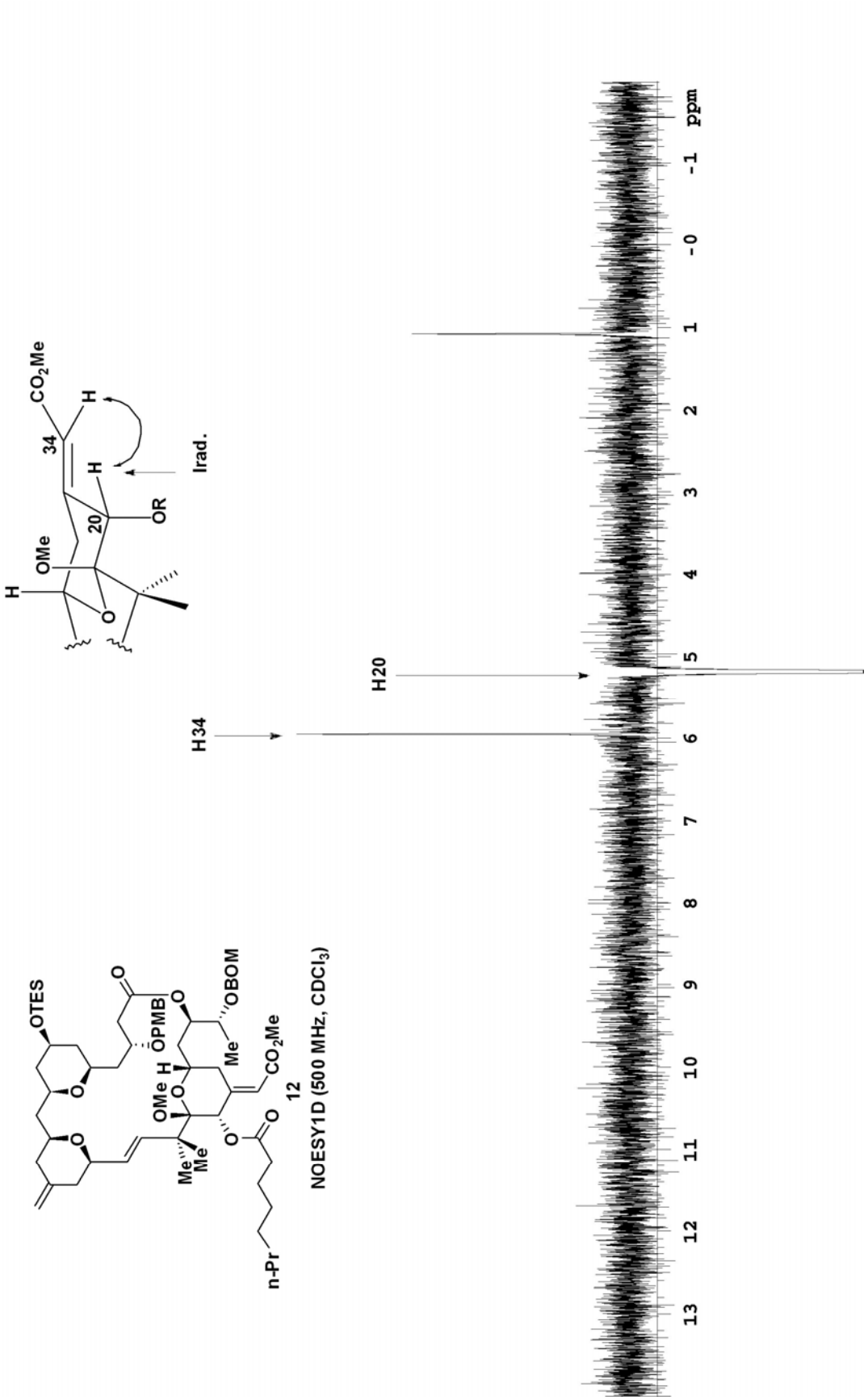

OTES
CO2H
OPMB
OMe
H
OH
OBOM
Me
Me
Me
CO2Me
n-Pr
11
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

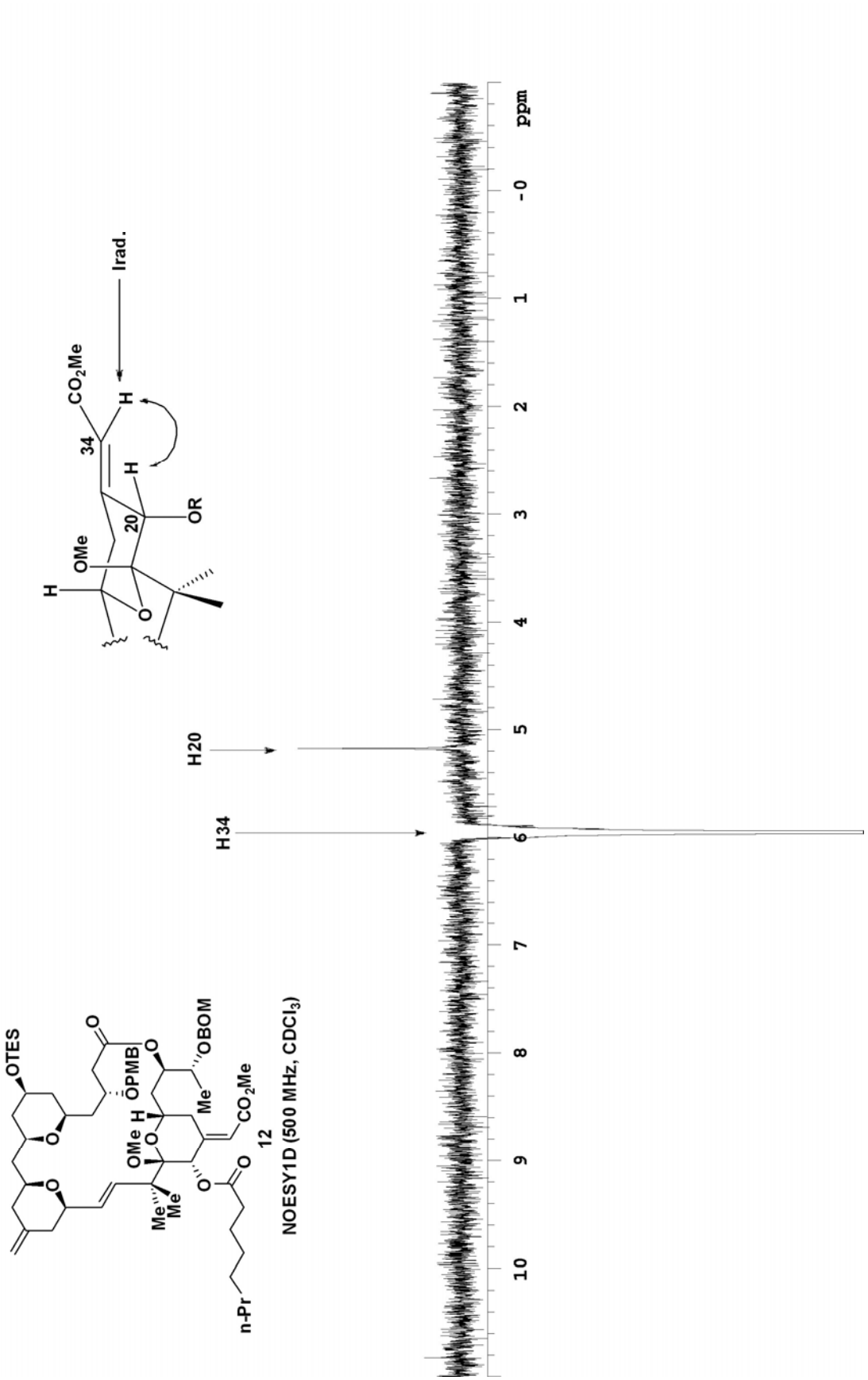

OTES
OPMB
OMe H
Me
Me
OBOM
Me
CO2Me
n-Pr
12
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0

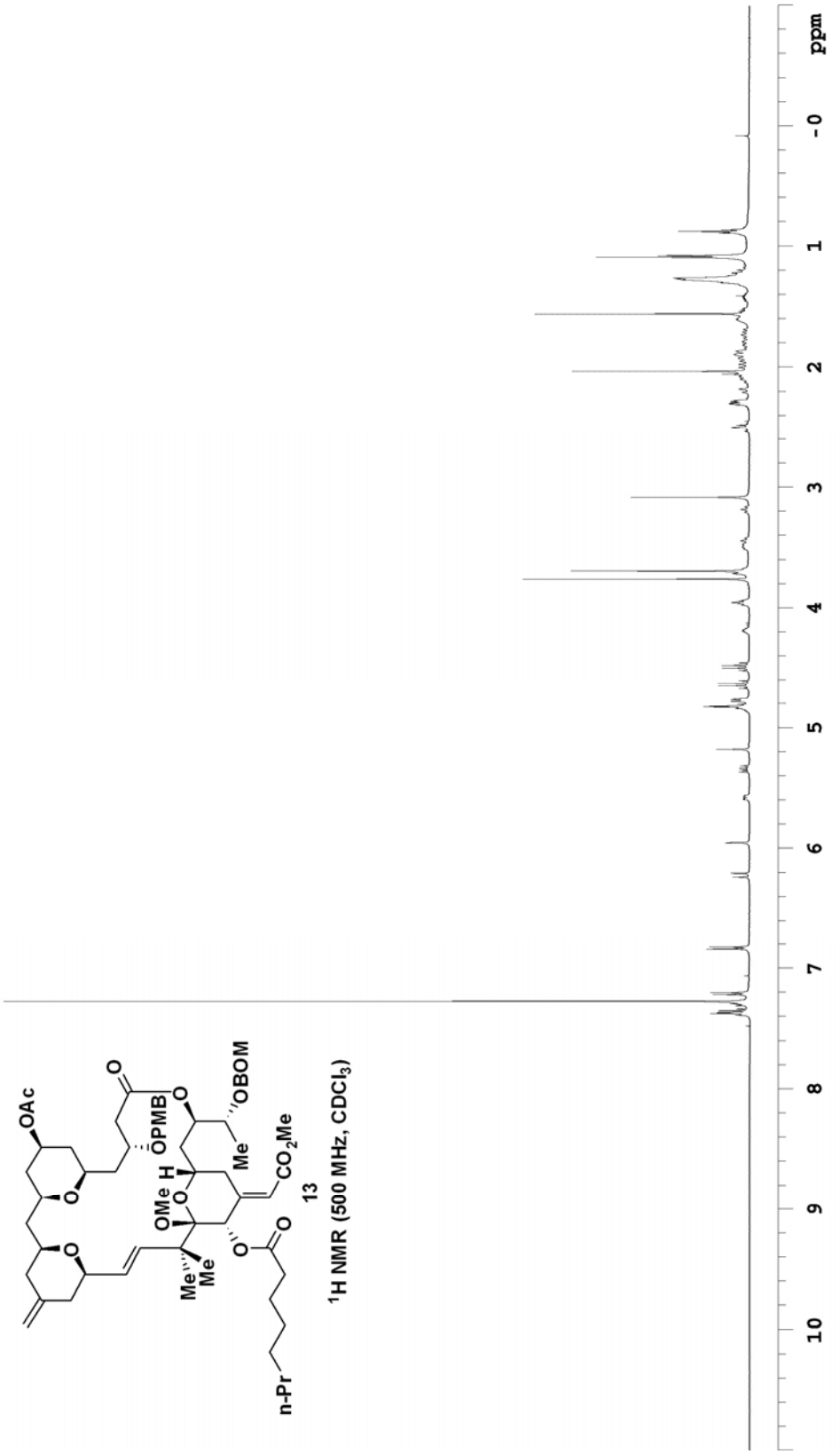

OTES
OPMB
OMe
H
OBOM
Me
CO2Me
Me
Me
n-Pr
12
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20

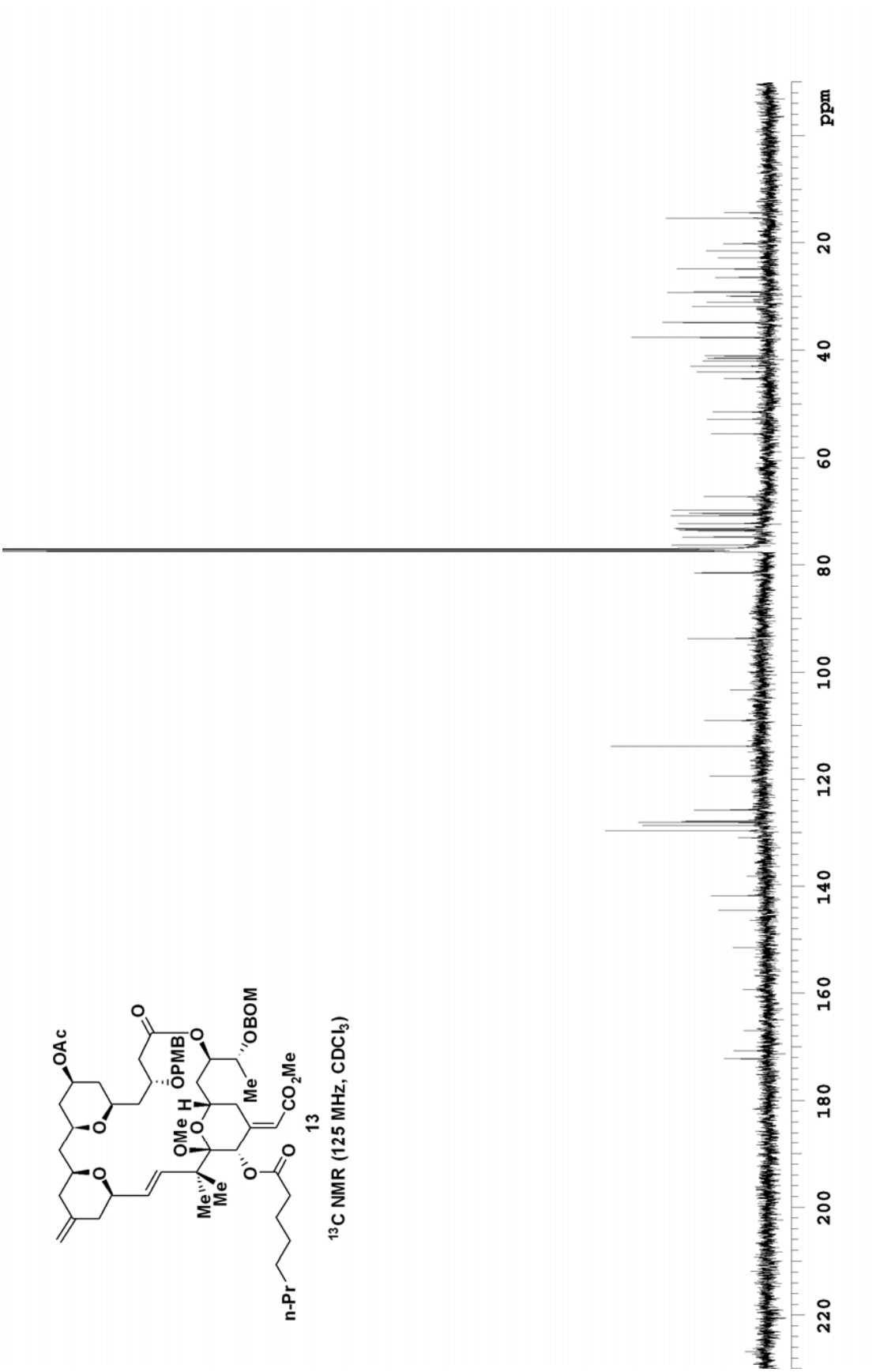

DEPT NMR (125 MHz, CDCl3)
12
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
ppm
220
200
180
160
140
120
100
80
60
40
20
0
-20
OTES
OPMB
OMe
H
OBOM
Me
CO2Me
Me
Me
n-Pr

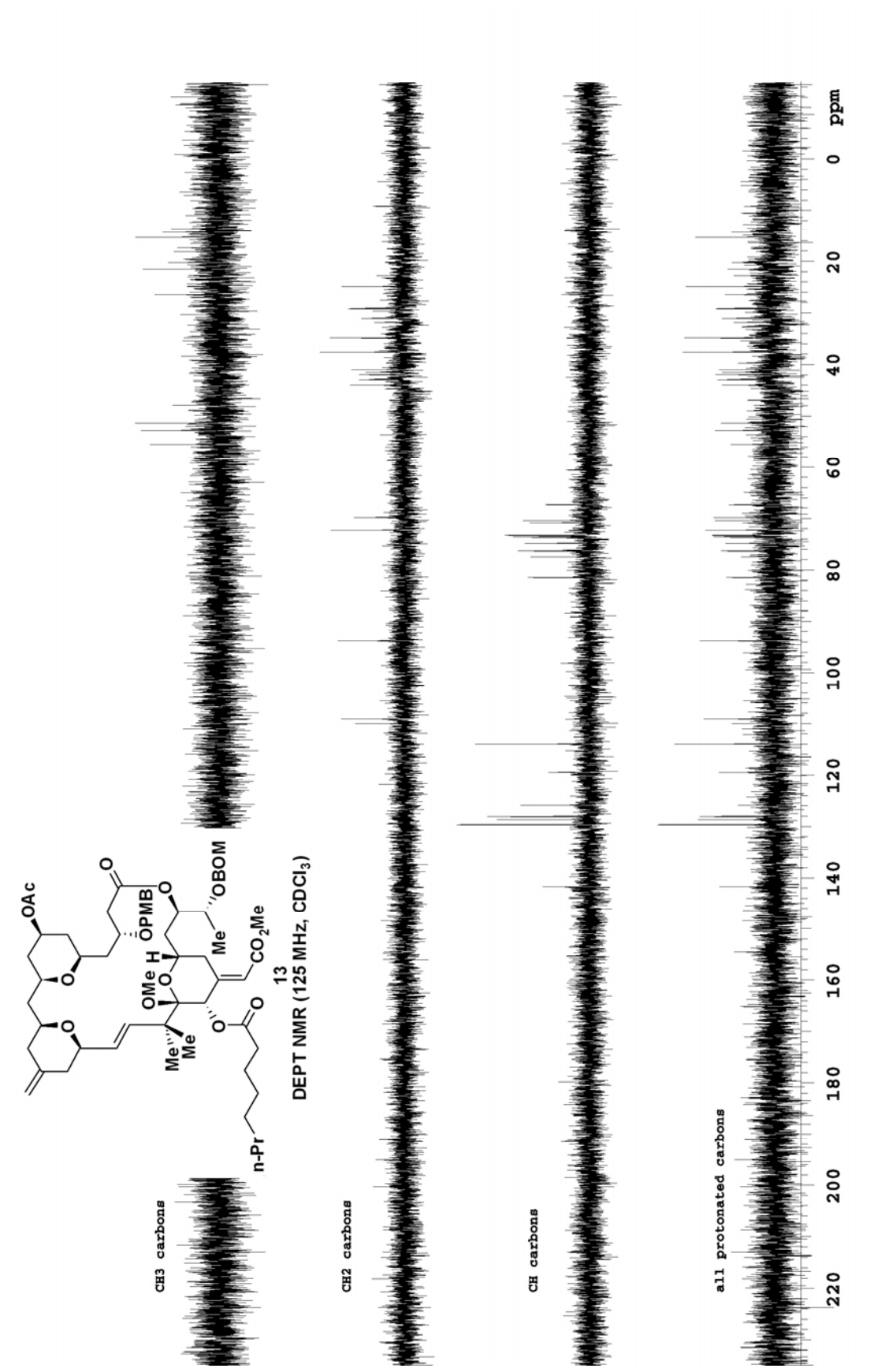

F2 (ppm)
F1 (ppm)
OTES
OPMB
OMe H
OBOM
Me
CO2Me
12
Me
Me
n-Pr
gCOSY NMR (500 MHz, CDCl3)

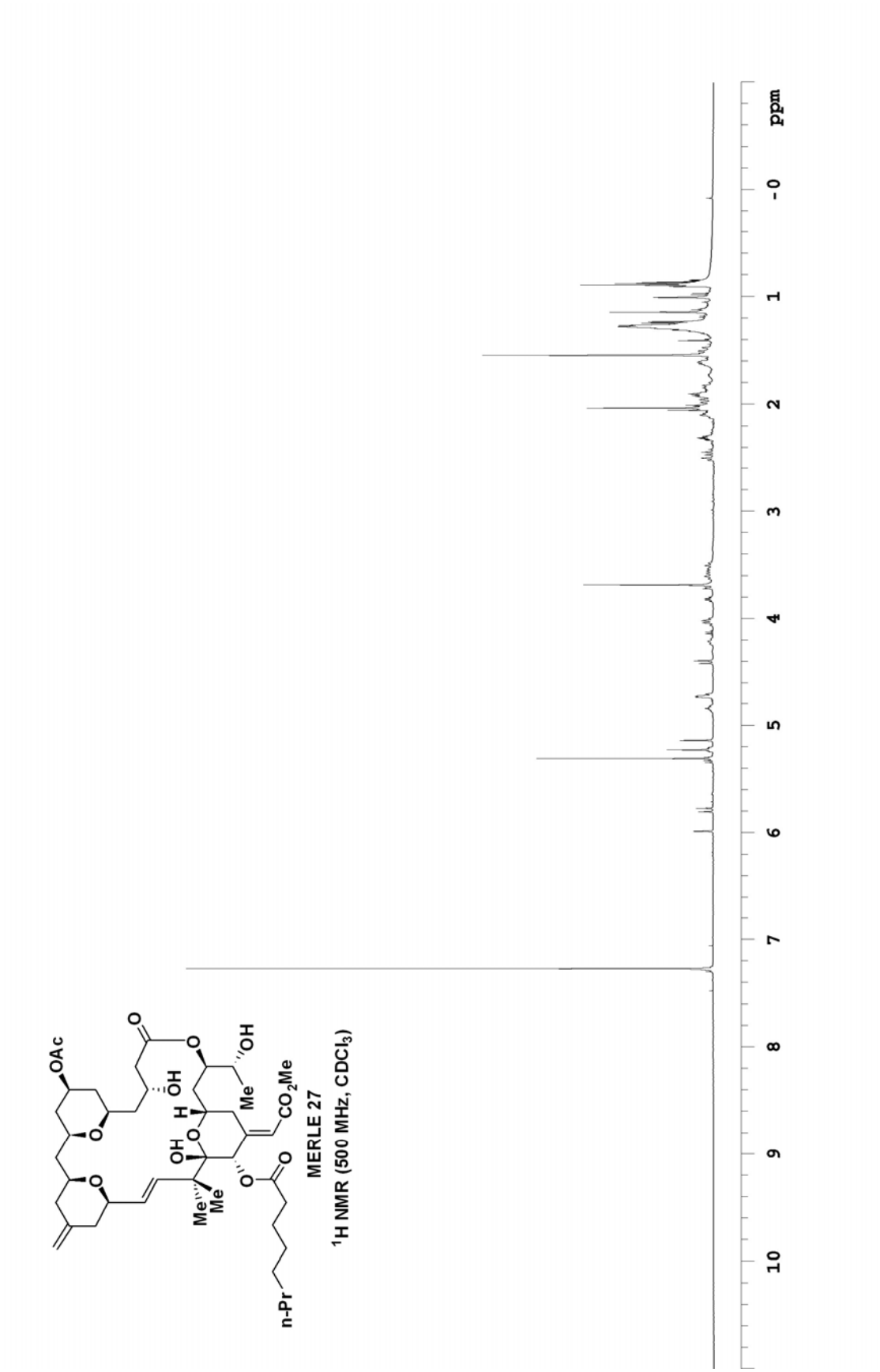

CO2Me
34
H
H
20
OR
Irad.
OMe
H
O
H34
H20
OTES
OPMB
OBOM
Me
CO2Me
OMe
H
O
12
Me
Me
n-Pr
NOESY1D (500 MHz, CDCl3)
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

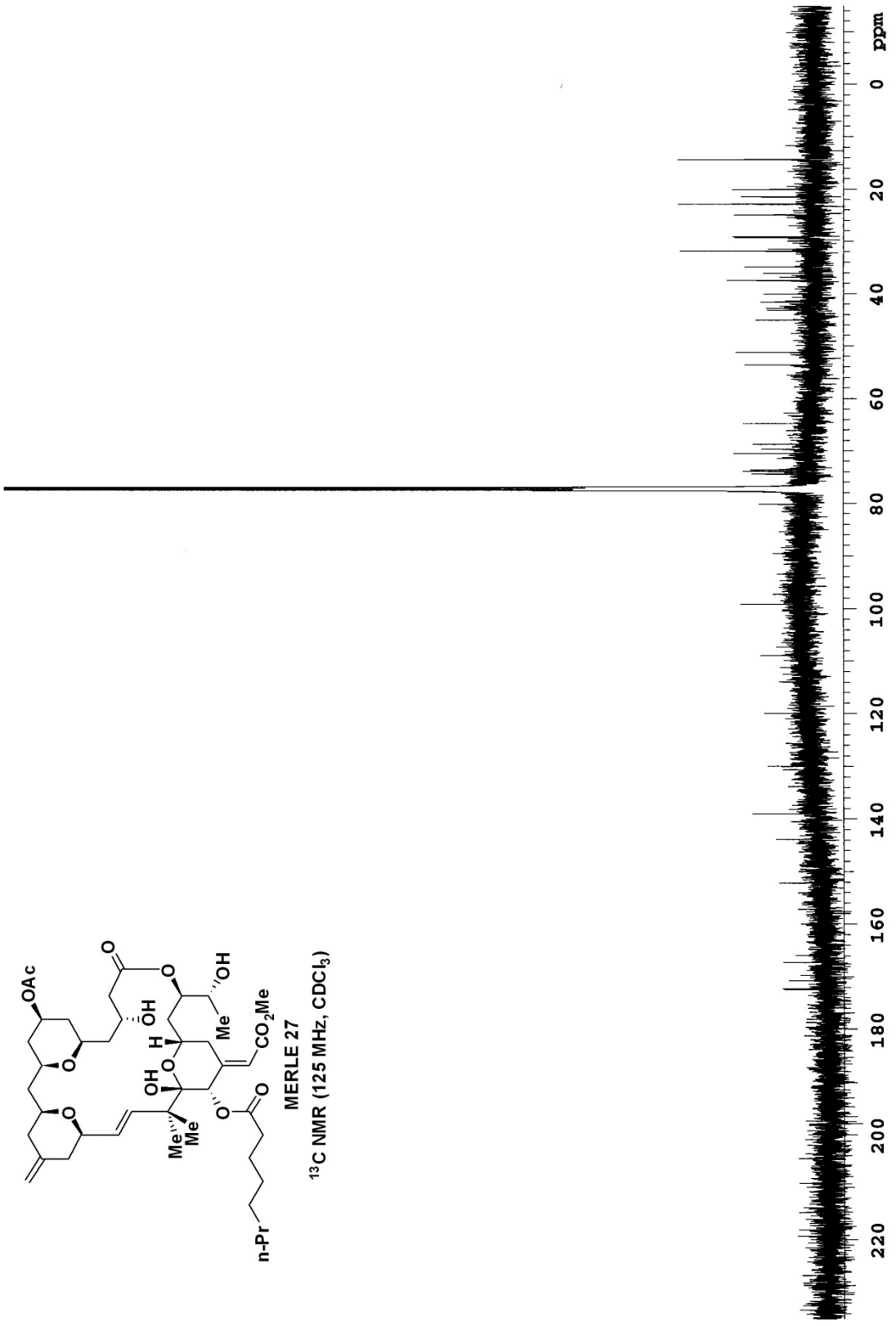

Irad.
CO2Me
34
H
H
20
OR
OMe
H
O
H20
H34
ppm
OTES
OPMB
OBOM
OMe
H
Me
CO2Me
12
Me
Me
n-Pr
NOESY1D (500 MHz, CDCl3)

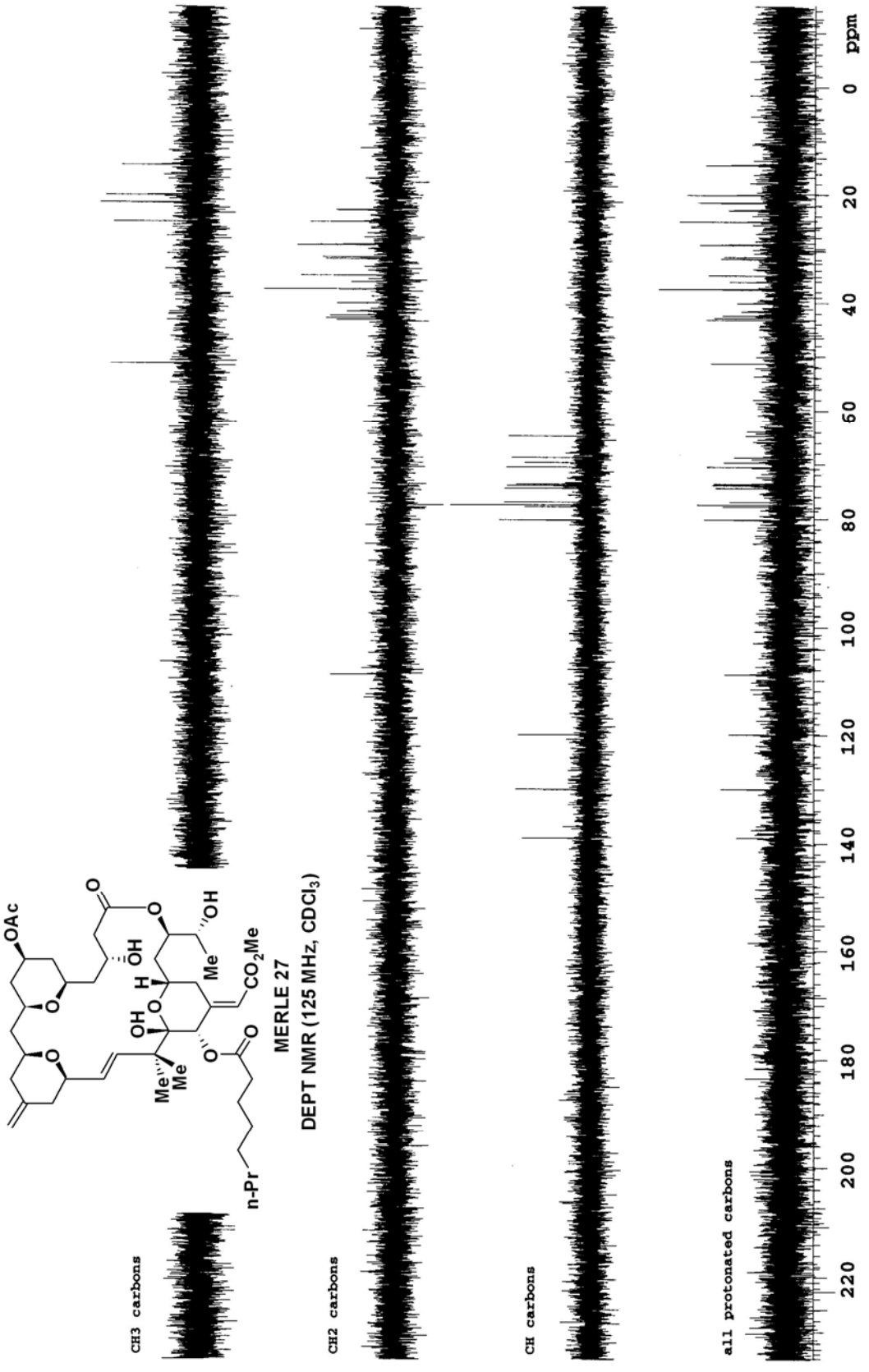

OAc
OPMB
OMe
H
Me
Me
OBOM
Me
CO2Me
n-Pr
13
1H NMR (500 MHz, CDCl3)
ppm
10
9
8
7
6
5
4
3
2
1
-0

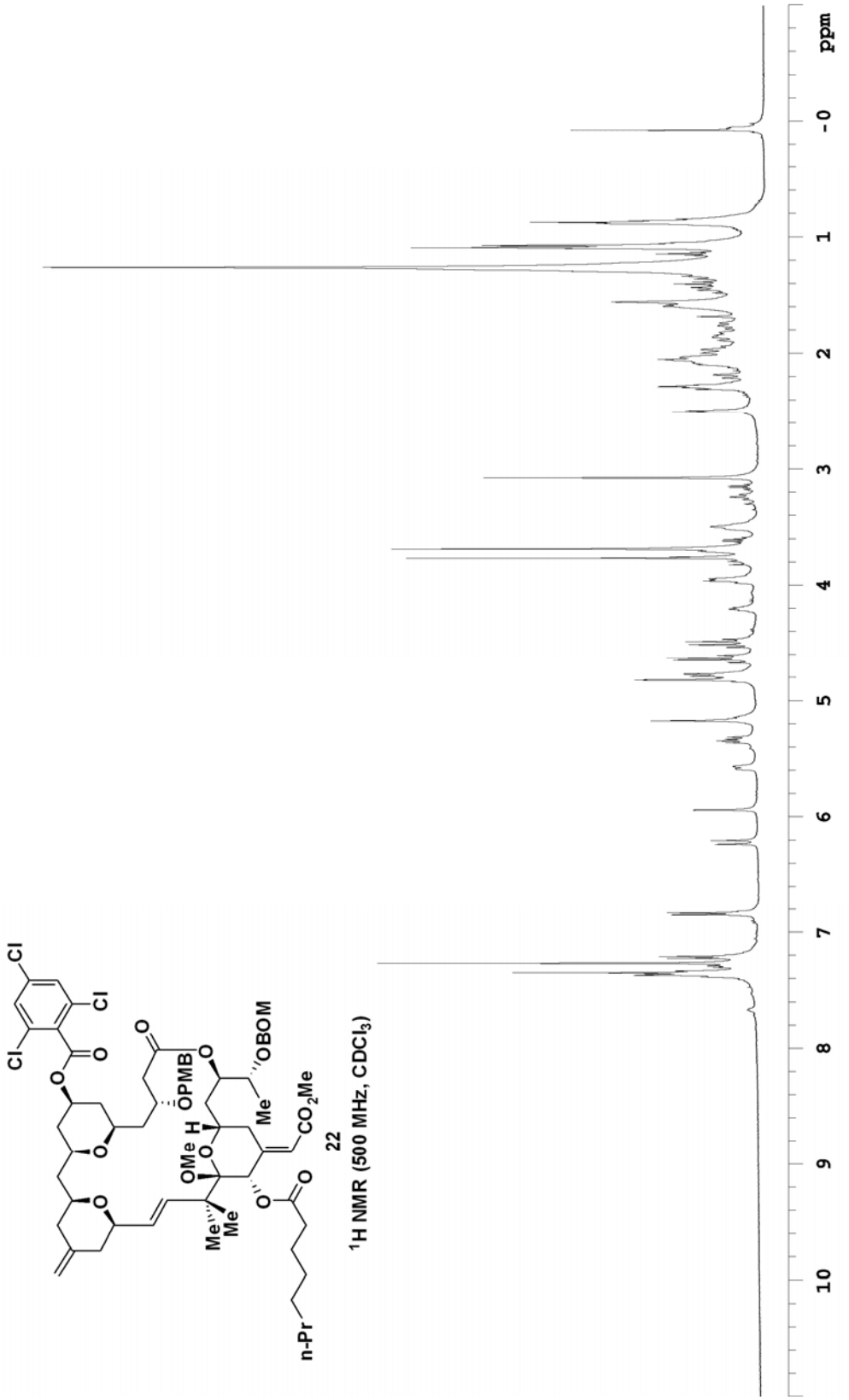

OAc
OPMB
OMe
H
OBOM
Me
CO2Me
Me
Me
n-Pr
13
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20

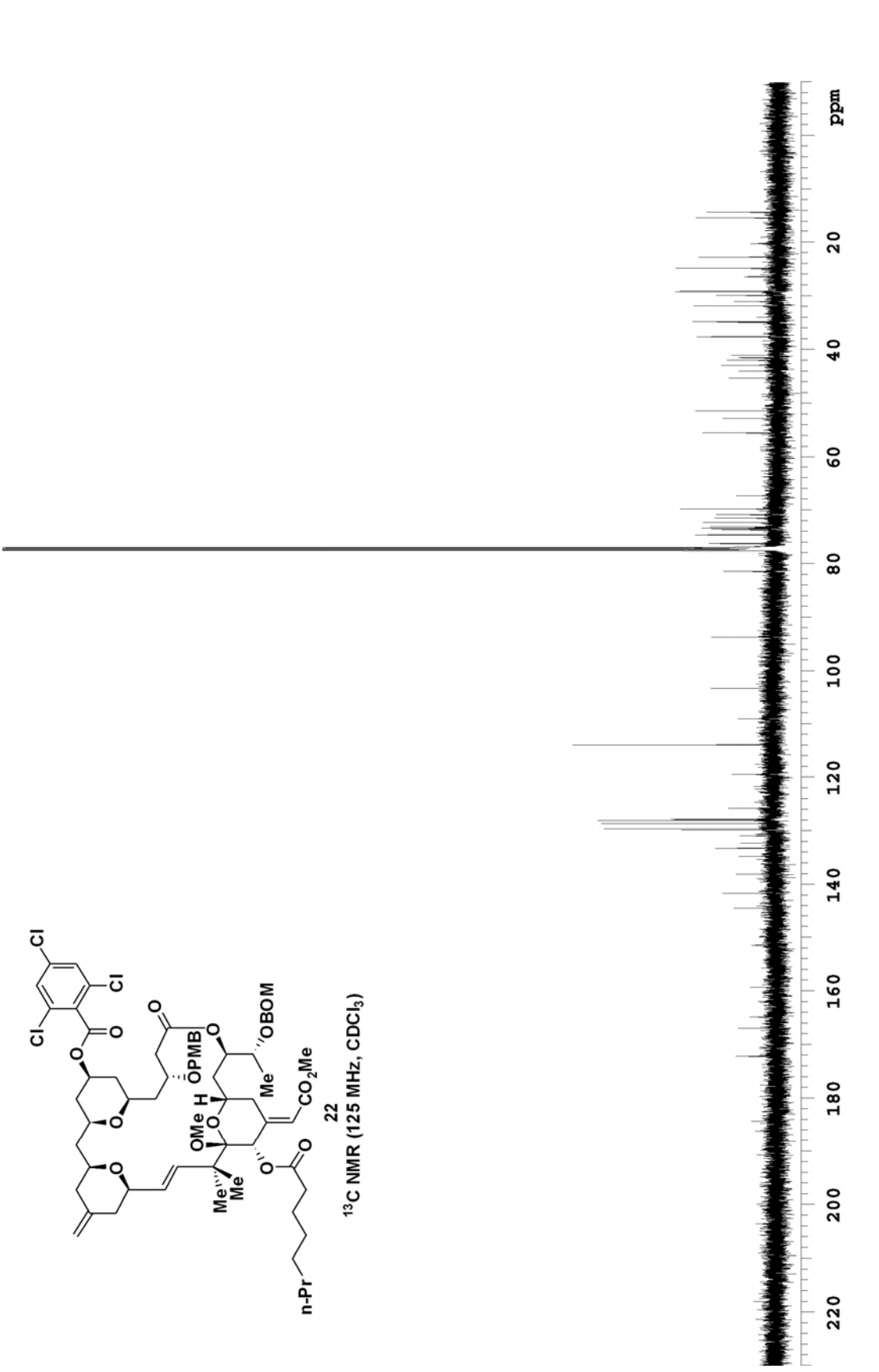

OAc
OPMB
OMe
H
OBOM
Me
Me
Me
CO2Me
n-Pr
13
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

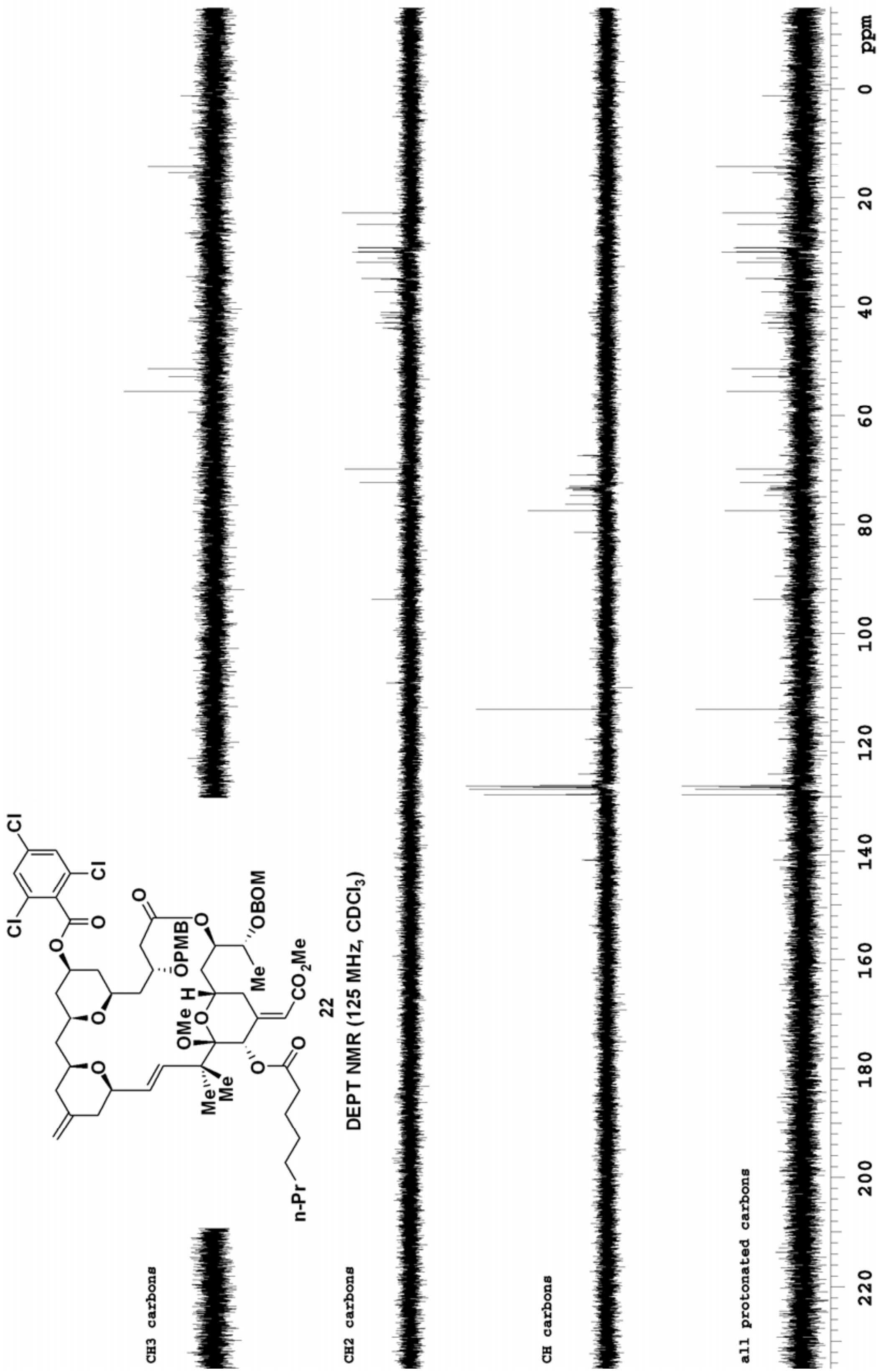

OAc
OH
H
OH
Me
Me
Me
OH
CO2Me
n-Pr
MERLE 27
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
-0
ppm

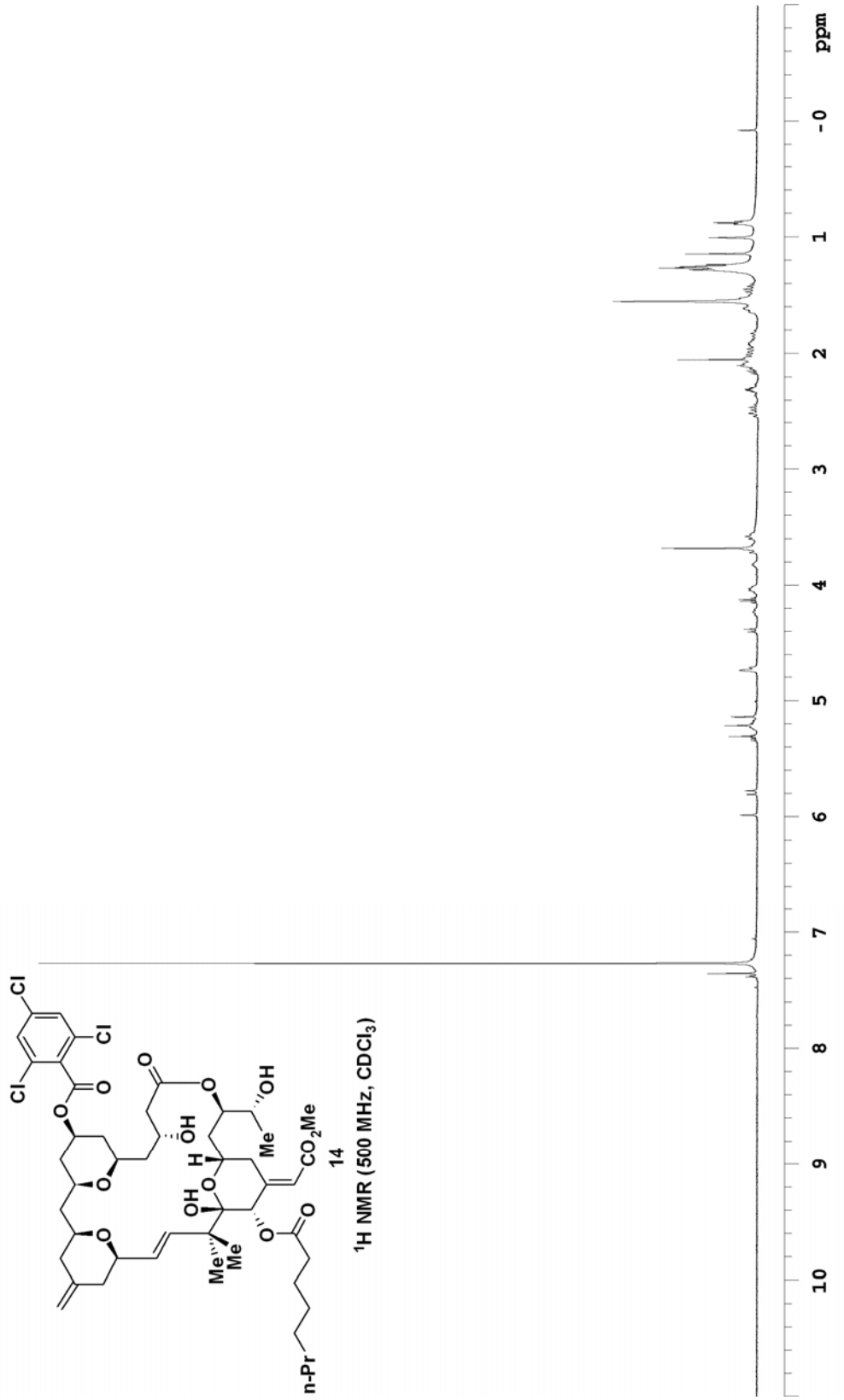

OAc
OH
H
OH
Me
Me
Me
OH
CO2Me
n-Pr
MERLE 27
13C NMR (125 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

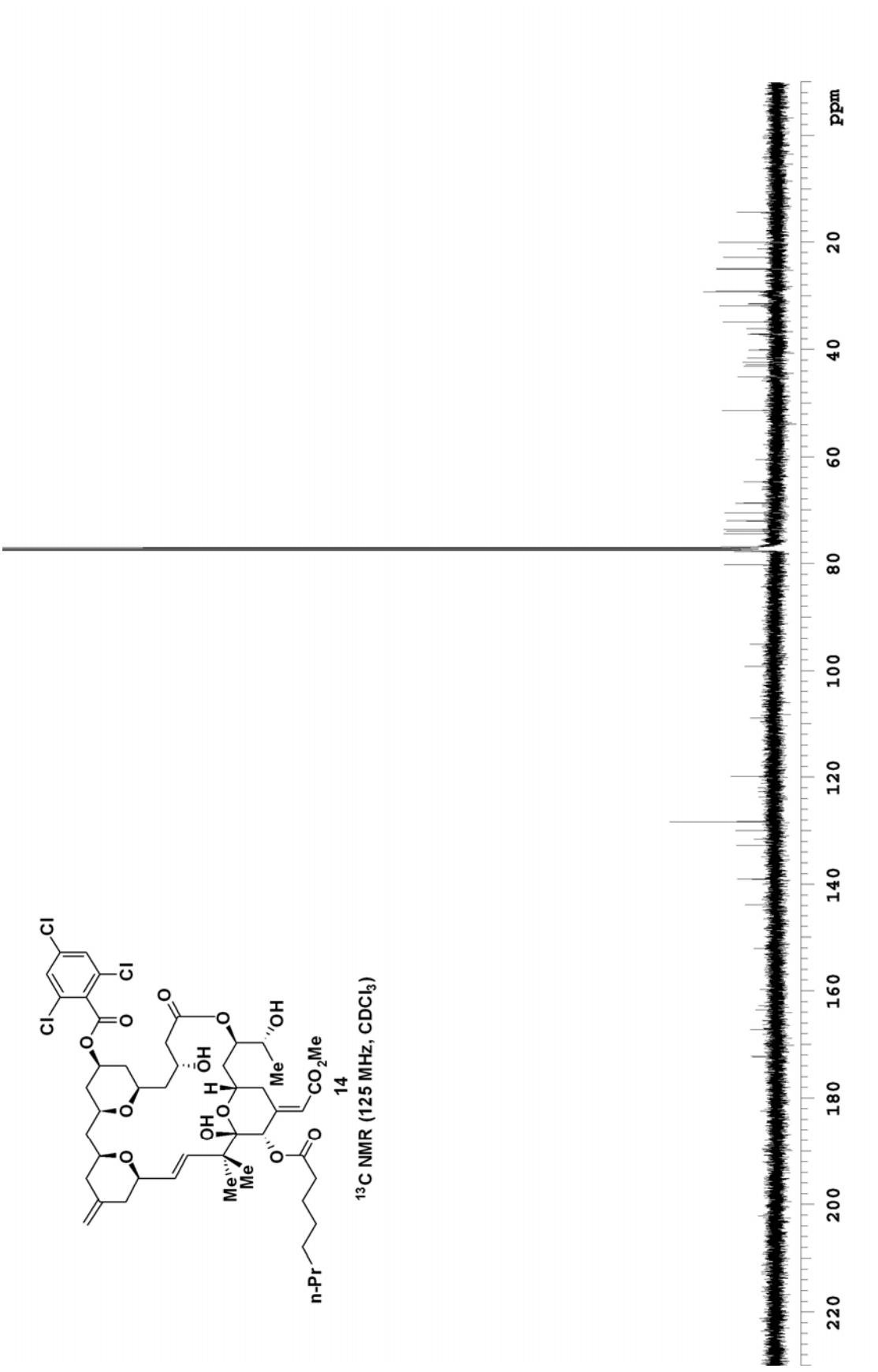

MERLE 27
DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OAc
OH
H
OH
Me
Me
Me
OH
CO2Me
n-Pr
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Cl
Cl
Cl
O
O
O
O
O
O
O
O
OPMB
OMe
H
O
Me
Me
Me
OBOM
CO2Me
n-Pr
22
1H NMR (500 MHz, CDCl3)
ppm
-0
1
2
3
4
5
6
7
8
9
10


Cl
Cl
Cl
O
O
O
O
OPMB
OMe
H
O
O
OBOM
Me
CO2Me
Me
Me
O
O
O
n-Pr
22
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20


CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
22
DEPT NMR (125 MHz, CDCl$_3$)
ppm


Cl
Cl
Cl
O
O
O
O
O
O
O
O
OH
H
OH
Me
Me
Me
OH
CO2Me
14
n-Pr
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
-0
ppm


Cl
Cl
Cl
O
O
O
O
O
O
O
O
OH
H
OH
Me
CO2Me
Me
Me
n-Pr
14
13C NMR (125 MHz, CDCl3)
ppm
220
200
180
160
140
120
100
80
60
40
20