Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

An Effective Reagent to Functionalize Alcohols with Phosphocholine

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Supporting Information

General Procedure

All moisture-sensitive reactions were performed in flame-dried or oven-dried glassware under an atmosphere of argon. Oven-dried stainless steel syringes or cannula were used to transfer moisture- and air-sensitive liquids. Reaction temperatures were controlled and monitored using a hot plate stirrer with a thermocouple thermometer. Reactions were conducted at room temperature (rt, approximately 23 °C) unless otherwise noted. Analytical thin-layer chromatography (TLC) were carried out using 250 μm silica plates (SiliCycle). Analytical thin-layer chromatography (TLC) was performed on Sorbtech Silica XHL UV254, glass-backed, 250 μm plated, and visualized using UV, cerium ammonium molybdate stain, anisaldehyde stain, or potassium permanganate stain. Flash column chromatography was performed as described by Still et al. using silica gel 230-400 mesh.[1] Yields were reported as purified, isolated compounds.

Materials

Solvents were dried through a Braun MB-SPS solvent system and used immediately or stored over 3 Å or 4 Å molecular sieves. Other commercial reagents were used as received.

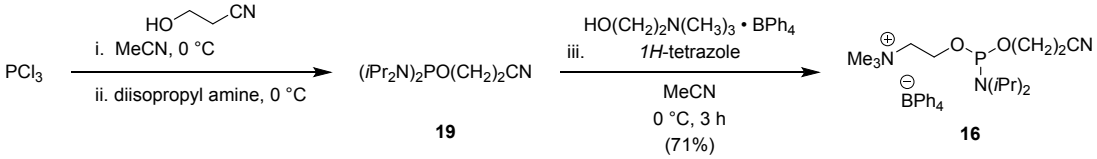
Instrumentation

Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. Deuterated chloroform and methanol were standardized to 7.26 ppm and 3.31 ppm respectively. ^{13}C NMR spectra were recorded on Bruker 75, 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. Deuterated chloroform and methanol were standardized to 77.16 ppm and 49.00 ppm respectively. High-resolution mass spectra were obtained from the Mass Spectrometry Core Lab, Vanderbilt University using a JEOL AX505HA or JEOL LMS-GC mate mass spectrometer. Optical rotations were obtained using a Jasco p-2000 polarimeter with a sodium lamp.

Compound Preparation and Characterization

Synthetic Methods

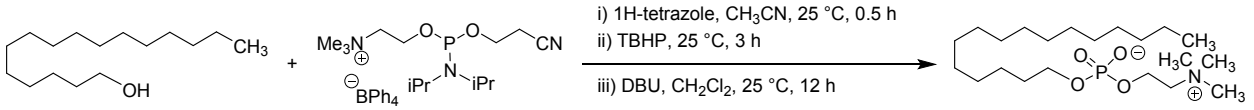
Choline-2-cyanoethyl N, N-diisopropylphosporamidite tetraphenylborate salt (16)



Synthesis of **19**: A solution of PCl_3 (1.0 equiv., 1.0 mL, 11.0 mmol) in anhydrous CH_3CN (110 mL) was added 2-cyanoethanol (1.0 equiv., 0.78 mL, 11.0 mmol) dropwise at 0 °C under an argon atmosphere. The reaction was vented and kept under a constant stream of nitrogen to expel the HCl (g) that was produced. The reaction warmed to room temperature while stirring. At 2 h, the reaction was cooled to 0 °C and added diisopropyl amine (4.0 equiv., 6.4 mL, 44.0 mmol) dropwise. The reaction was warmed to room temperature. At 12 h, the reaction was filtered to remove diisopropyl ammonium chloride salts with a glass fritted filter funnel using positive pressure of an argon balloon, to limit oxidation of the phosphoramidite, to give a crude yellow oil. The crude oil was analyzed by ^{31}P NMR and integration of ^{31}P indicated that the reaction was 72% pure phosphordiamidite **19** (which is commercially available), reagents equivalencies for the last step are normalized for this purity.

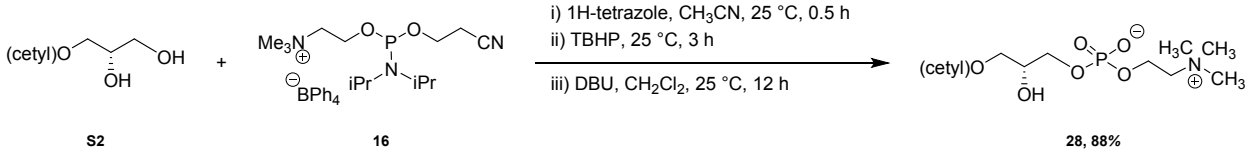
Synthesis of **16**: The crude oil containing phosphordiamidite **19** (1.0 equiv.,2.39 g 7.92 mmol) was diluted in anhydrous CH_3CN (40 mL) and added choline tetraphenylborate salt (1.0 equiv., 4.5 g, 7.86 mmol) and a 4% 1*H*-tetrazole solution (0.5 equiv., 6.74 g, 8.5 mL, 3.85 mmol) dropwise to the reaction at 0 °C under an argon atmosphere. The reaction warmed to room temperature while stirring. At 12 h, the reaction was diluted with EtOAc (100 mL) and transferred to a separatory funnel and washed with sat. aq. $NaHCO_3$ (3 x 20 mL), brine (1 x 20 mL), dried (Na_2SO_4) and filtered through a glass fritted vacuum filter funnel to remove drying agent. The filtrate was concentrated to give phosphoramidite **16** (4.89 g, 7.84 mmol, 71%) as an off-white foam. ^1H NMR (400 MHz, CD_3CN): δ 7.28-7.27 (m, 8H), 7.00 (t, J = 7.0 Hz, 8H), 6.85 (dt, J = 1.2, 8.3 Hz, 4H), 4.03-3.99 (m, 2H), 3.87-3.82 (m, 1H), 3.78-3.73 (m, 1H), 3.65-3.59 (m, 2H), 3.49-3.38 (m, 2H), 3.06 (d, J = 5.6 Hz, 8H), 2.66 (t, J = 6.0 Hz, 2H), 1.18 (dd, J = 4.7, 7.0 Hz, 12 H);^{13}C NMR (100 MHz, CD_3CN): δ 164.9, 164.5, 164.2, 163.9, 136.3, 126.2, 126.2, 126.2, 122.3, 117.9, 67.3, 67.2, 59.1, 59.0, 58.2, 58.1, 54.6, 54.6, 54.5, 43.7, 43.6, 24.5, 24.4, 24.4, 20.6, 20.6; ^{31}P NMR (150 MHz, CD_3CN) δ 150.37. Spectral data for (**16**) was consistent with known values.[2]

General One-pot Procedure: To a round bottom flask, under an argon atmosphere, containing the alcohol (1.0 eq) and phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 eq) dissolved in (0.01 M CH_3CN) was added a 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 eq) at room temperature. At 0.5 h, the crude reaction was filtered through a pad of Celite to remove salts. The filtrate was cooled to 0 °C then added tert-butyl hydroperoxide (1.2 eq). At 1 h, the crude reaction mixture was concentrated to dryness by co-evaporated with toluene (3x). The resulting solid was dissolved with anhydrous CH_2Cl_2 (1.0 mL) and added DBU (5.0 eq) at room temperature under argon. At 12 h, the reaction was diluted with CH_2Cl_2 (1x) and transferred to a separatory funnel and washed with 1 N HCl (3x) satd. aq. $NaHCO_3$ (1 x), brine (1 x), dried (Na_2SO_4) and filtered to remove drying agent. The filtrate was concentrated to a crude solid. The crude material was then dissolved in hot CH_2Cl_2 and allowed to cool to room temperature. At 12 h, the residual amine-phosphate salts were crystalized into thin needles and were removed from the crude reaction mixture. The mother liquor, containing the desired product) was concentrated down and purified by silica gel flash column chromatography (10:90 to 50:50 CH_3OH/CH_2Cl_2) to give the fully protected alcohol.



Miltefosine (27)

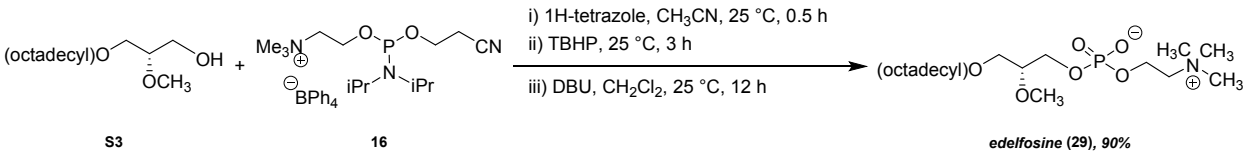
Prepared following the general procedure outlined above using **S1** (1.0 eq., 0.2425 g, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **27** as an off-white solid (0.3709 g, 0.91 mmol, 91%). (**27**): ^{1}H NMR (600 MHz, MeOD) δ 4.27 (ddt, J = 6.9, 4.5, 2.6 Hz, 2H), 3.89 (q, J = 6.6 Hz, 2H), 3.72 – 3.58 (m, 2H), 3.25 (s, 9H), 1.72 – 1.57 (m, 2H), 1.48 – 1.17 (m, 26H), 0.92 (t, J = 7.0 Hz, 3H).; ^{13}C NMR (150 MHz, MeOD) δ 66.1, 66.0, 66.0, 66.0, 65.5, 65.5, 58.8, 58.8, 53.3, 53.2, 53.2, 31.7, 30.5, 30.5, 29.4, 29.3, 29.1, 29.1, 25.5, 22.3, 13.0. Spectral data for **27** was consistent with known values.[3]



(28)

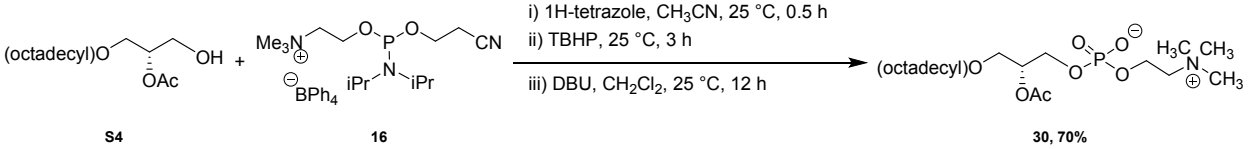
Prepared following the general procedure outlined above using **S2** (1.0 eq., 0.3305, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide

(1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **28** as an off-white solid (0.4362 g, 0.88 mmol, 88%). (**28**): ^{1}H NMR (600 MHz, MeOD) δ 4.31 (tq, *J* = 7.1, 2.6 Hz, 2H), 4.19 (dd, *J* = 11.4, 4.5 Hz, 1H), 4.13 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.99 (ddd, *J* = 10.7, 6.0, 4.5 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.69 – 3.62 (m, 2H), 3.25 (s, 9H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.63 (q, *J* = 7.3 Hz, 2H), 1.31 (s, 25H), 0.92 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (150 MHz, MeOD) δ 173.9, 68.4, 68.4, 66.4, 66.3, 66.1, 66.1, 66.0, 66.0, 64.8, 59.0, 59.0, 53.2, 53.2, 53.2, 33.5, 31.6, 29.3, 29.3, 29.3, 29.2, 29.0, 29.0, 28.8, 24.5, 22.3, 13.0. Spectral data for (**28**) was consistent with known values.[4]



Edelfosine (29)

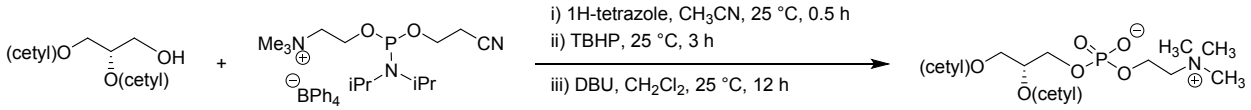
Prepared following the general procedure outlined above using **S3** (1.0 eq., 0.3505 g, 1.0 mmol), phosphoramidite 2-(((2- cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **29** as an off-white solid (0.4641g, 0.90 mmol, 90%). (**29**): ^{1}H NMR (600 MHz, MeOD) δ 4.21 – 4.12 (m, 2H), 3.87 (ddd, *J* = 10.3, 5.9, 4.0 Hz, 1H), 3.79 (dt, *J* = 11.0, 5.8 Hz, 1H), 3.56 – 3.52 (m, 2H), 3.50 – 3.43 (m, 2H), 3.40 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.38 – 3.33 (m, 5H), 3.12 (s, 9H), 1.51 – 1.40 (m, 2H), 1.19 (d, *J* = 5.4 Hz, 30H), 0.80 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (150 MHz, MeOD) δ 79.4, 79.4, 71.3, 69.6, 66.0, 66.0, 66.0, 66.0, 66.0, 66.1, 64.7, 64.7, 58.9, 58.9, 56.8, 53.3, 53.2, 53.2, 31.6, 29.3, 29.3, 29.2, 29.0, 25.8, 22.3, 13.0. Spectral data for (**29**) was consistent with known values.[5]



Platelet Activating Factor 16 (30)

Prepared following the general procedure outlined above using **S4** (1.0 eq., 0.3586 g, 1.0 mmol), phosphoramidite 2-(((2- cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **30** as an off-white solid (0.3666 g, 0.70 mmol, 70%). (**30**): ^{1}H NMR (600 MHz, MeOD) δ 5.15 (tt, *J* = 6.0, 4.5 Hz, 1H), 4.28 (tq, *J* = 7.1, 2.7 Hz, 2H), 4.07 – 3.95 (m, 2H), 3.68 – 3.59 (m, 4H), 3.48 (ddt, *J* = 29.1, 9.4, 6.6 Hz, 2H), 3.24 (s, 9H), 1.61 – 1.51 (m, 2H), 1.31 (d, *J* = 3.2 Hz, 29H), 0.92 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (150 MHz, MeOD) δ 71.89, 71.84, 71.23, 68.77, 66.08, 66.05, 66.0, 66.0, 66.0, 63.98, 63.94, 59.03, 58.99, 53.30, 53.28, 53.25, 31.67,

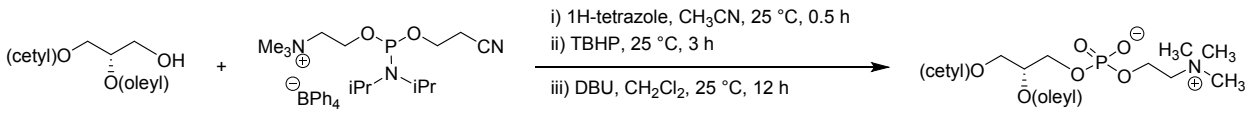
29.38, 29.35, 29.29, 29.19, 29.06, 25.78, 22.33, 19.63, 13.02. Spectral data for (**30**) was consistent with known values.[6]



S5 **16** **31, 69%**

(31)

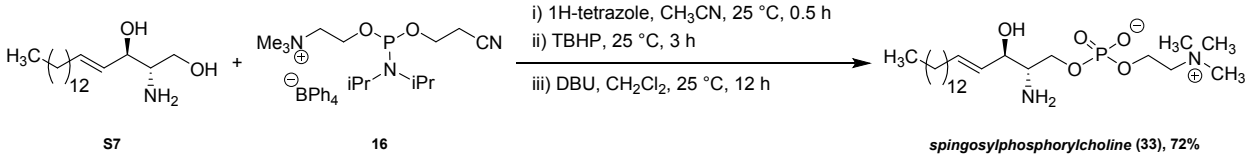
Prepared following the general procedure outlined above using **S5** (1.0 eq., 0.5689 g, 1.0 mmol), phosphoramidite 2-(((2- cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **31** as an off-white solid (0.5065 g, 0.69 mmol, 69%). (**31**): ^{1}H NMR (600 MHz, MeOD) δ 5.27 (dtd, *J* = 6.9, 5.4, 3.1 Hz, 1H), 4.46 (dd, *J* = 12.0, 3.1 Hz, 1H), 4.29 (dh, *J* = 6.4, 2.9 Hz, 2H), 4.02 (ddd, *J* = 6.7, 5.3, 1.3 Hz, 2H), 3.69 – 3.64 (m, 2H), 3.25 (s, 9H), 2.35 (dt, *J* = 15.2, 7.4 Hz, 4H), 1.63 (dtd, *J* = 14.1, 9.2, 8.2, 5.2 Hz, 4H), 1.37 – 1.31 (m, 48H), 0.92 (t, *J* = 7.0 Hz, 6H).; ^{13}C NMR (150 MHz, MeOD) δ 173.5, 173.2, 70.4, 70.3, 66.1, 66.0, 66.0, 66.0, 66.0, 63.5, 63.4, 62.2, 59.0, 59.0, 53.3, 53.2, 53.2, 33.7, 33.5, 31.7, 31.6, 29.4, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.8, 24.6, 24.6, 22.3, 22.3, 13.0, 13.0, 13.0. Spectral data for (**31**) was consistent with known values.[7]



S6 **16** **32, 73%**

(32)

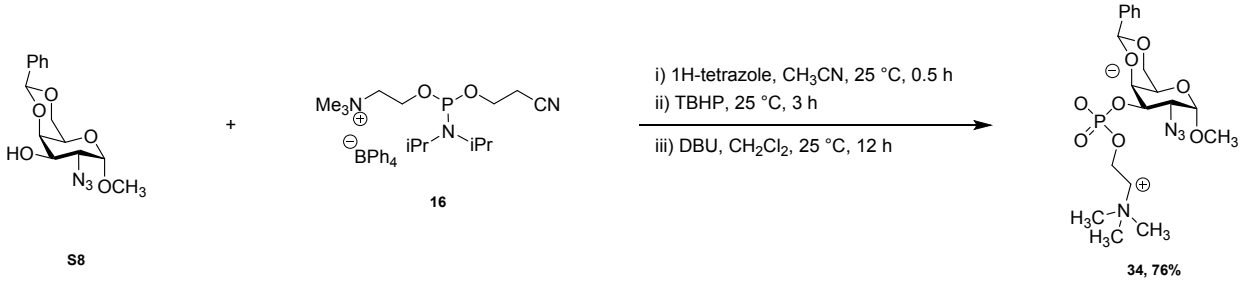
Prepared following the general procedure outlined above using **S6** (1.0 eq., 0.5949 g, 1.0 mmol), phosphoramidite 2-(((2- cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **32** as an off-white solid (0.5549 g, 0.73 mmol, 73%). (**32**): ^{1}H NMR (600 MHz, MeOD) δ 5.37 (td, *J* = 4.8, 4.1, 1.2 Hz, 2H), 5.27 (dtd, *J* = 10.4, 5.4, 3.1 Hz, 1H), 4.46 (dd, *J* = 12.0, 3.1 Hz, 1H), 4.29 (tq, *J* = 6.4, 3.0 Hz, 2H), 4.19 (dd, *J* = 12.0, 7.0 Hz, 1H), 4.02 (ddd, *J* = 6.7, 5.3, 1.2 Hz, 2H), 3.69 – 3.64 (m, 2H), 3.25 (s, 9H), 2.35 (dt, *J* = 16.2, 7.4 Hz, 4H), 2.06 (qd, *J* = 6.9, 3.5 Hz, 4H), 1.68 – 1.58 (m, 4H), 1.41 – 1.35 (m, 10H), 1.32 (d, *J* = 4.3 Hz, 34H), 0.92 (td, *J* = 7.1, 1.4 Hz, 6H).; ^{13}C NMR (150 MHz, MeOD) δ 129.5, 129.3, 70.4, 70.3, 66.0, 66.0, 66.0, 66.0, 66.0, 63.5, 63.4, 62.2, 59.0, 59.0, 53.3, 53.2, 53.2, 33.7, 33.5, 31.7, 31.6, 29.4, 29.4, 29.4, 29.2, 29.2, 29.1, 29.0, 29.0, 28.9, 28.9, 28.8, 28.8, 28.8, 26.7, 24.6, 24.6, 22.3, 13.1, 13.0. Spectral data for (**32**) was consistent with known values.[8]



S7 16 *spingosylphosphorylcholine* (33), 72%

Spingosylphosphorylcholine (33)

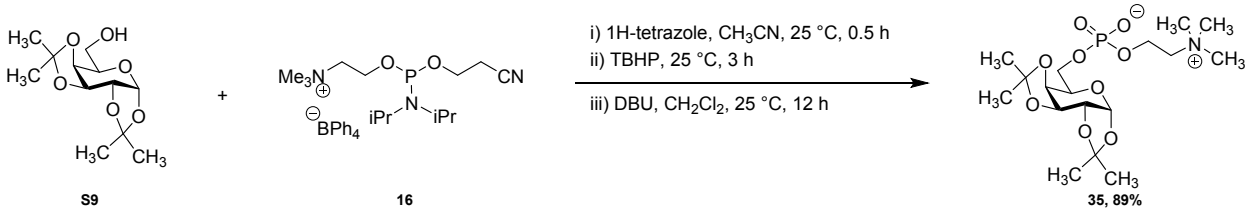
Prepared following the general procedure outlined above using **S7** (1.0 eq., 0.2995 g, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **33** as an off-white solid (0.3345 g, 0.72 mmol, 72%). (**33**): ^{1}H NMR (600 MHz, MeOD) δ 5.85 – 5.69 (m, 1H), 4.87 – 4.81 (m, 17H), 4.28 (dqd, *J* = 7.0, 4.4, 3.0, 2.3 Hz, 2H), 4.03 (dd, *J* = 8.9, 4.0 Hz, 2H), 3.64 (qd, *J* = 4.8, 3.3, 2.6 Hz, 2H), 3.23 (d, *J* = 2.5 Hz, 9H), 2.93 (qt, *J* = 6.7, 3.3 Hz, 1H), 2.09 (q, *J* = 7.3 Hz, 2H), 1.45 – 1.38 (m, 2H), 1.36 – 1.27 (m, 20H), 0.90 (td, *J* = 6.9, 3.1 Hz, 3H).; ^{13}C NMR (150 MHz, MeOD) δ 134.6, 128.9, 78.0, 77.8, 72.4, 72.3, 66.1, 65.8, 59.0, 58.9, 55.6, 55.6, 53.3, 32.0, 31.6, 29.4, 29.3, 29.2, 29.0, 29.0, 28.9, 22.3, 13.1. Spectral data for (**33**) was consistent with known values.[9]



S8 16 34, 76%

(2S,4aR,6S,7R,8R,8aS)-7-azido-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl (2-(trimethylammonio)ethyl) phosphate (34)

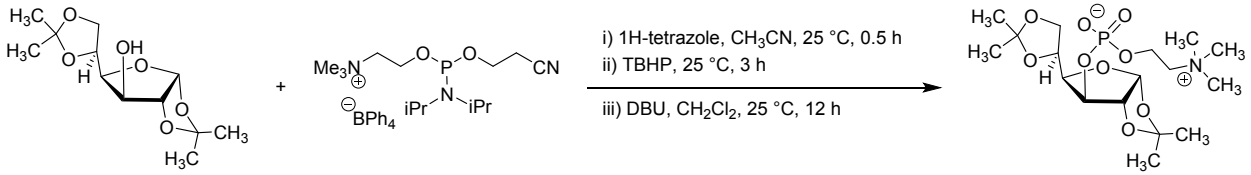
Prepared following the general procedure outlined above using **S8** (1.0 eq., 3.07 g, 10.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 7.48 g, 12.0 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 28 mL, 12.0 mmol), tert-butyl hydroperoxide (1.2 equiv., 2.2 mL, 12.0 mmol), and DBU (5.0 equiv., 7.5 mL, 50.0 mmol). Purification by flash column chromatography gave **34** as an off-white solid (3.55 g, 7.6 mmol, 76%). (**34**): $[\alpha]_D^{24}$ = +25.837° (c = 1.0067, CH_3OH); IR (neat, cm^{-1}): 3382.45, 2924.06, 2853.49, 2113.50, 1241.32, 1078.94, 1047.87; ^{1}H NMR (400 MHz, MeOD) δ 7.56 – 7.49 (m, 2H), 7.37 (dd, *J* = 5.1, 2.0 Hz, 3H), 5.66 (s, 1H), 4.97 (d, *J* = 3.4 Hz, 1H), 4.68 – 4.60 (m, 2H), 4.37 – 4.22 (m, 2H), 4.17 (d, *J* = 1.6 Hz, 2H), 3.82 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.76 (s, 1H), 3.55 (q, *J* = 4.5, 4.5, 4.5 Hz, 2H), 3.45 (s, 3H), 3.12 (s, 9H).; ^{13}C NMR (150 MHz, MeOD) δ 138.3, 128.7, 127.8, 126.2, 100.8, 99.7, 74.9, 71.2, 71.1, 68.9, 66.0, 62.8, 59.2, 59.1, 59.1, 54.4, 53.2, 53.2, 53.2.; HR-ESI-MS (m/z): calcd for $C_{19}H_{29}N_4O_8PH^+$ $[M+H]^+$ 473.1796, found 473.1791.



S9 16 35, 89%

((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl (2-(trimethylammonio)ethyl) phosphate (35)

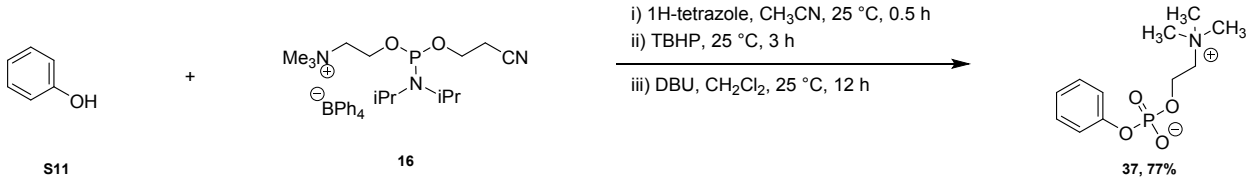
Prepared following the general procedure outlined above using **S9** (1.0 eq., 0.0260 g, 0.1 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.0748 g, 0.12 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 0.28 mL, 0.12 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.02 mL, 1.2 mmol), and DBU (5.0 equiv., 0.07 mL, 0.5 mmol). Purification by flash column chromatography gave **35** as an off-white solid (0.0379 g, 0.089 mmol, 89%). (**35**): $[\alpha]_D^{24}$ = -143.059 ° (c = 0.7636, CH_3OH); IR (neat, cm^{-1}): 3402.37, 2987.26, 2937.59, 1214.95, 1069.19; 1H NMR (600 MHz, MeOD) δ 5.40 (d, J = 5.0 Hz, 1H), 4.54 (dd, J = 7.9, 2.4 Hz, 1H), 4.26 (dd, J = 5.0, 2.4 Hz, 1H), 4.20 (td, J = 8.0, 7.9, 3.2 Hz, 3H), 3.98 – 3.93 (m, 1H), 3.95 – 3.85 (m, 2H), 3.55 (t, J = 4.7, 4.7 Hz, 2H), 3.13 (s, 9H), 1.41 (s, 3H), 1.30 (s, 3H), 1.23 (d, J = 2.8 Hz, 6H).; 13C NMR (150 MHz, MeOD) δ 109.0, 108.5, 96.3, 70.9, 70.6, 70.5, 67.7, 67.6, 66.0, 64.7, 64.7, 62.5, 59.1, 59.0, 53.3, 53.3, 53.3, 25.0, 24.9, 23.7, 23.1.; HR-ESI-MS (m/z): calcd for $C_{17}H_{32}NO_9PH^+$ $[M+H]^+$ 426.1887, found 426.1886.



S10 16 36, 91%

(3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl (2-(trimethylammonio)ethyl) phosphate (36)

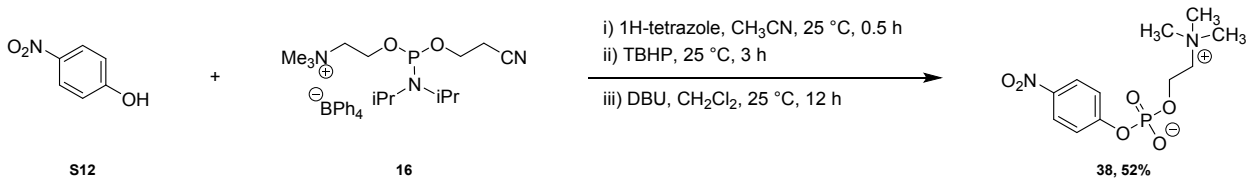
Prepared following the general procedure outlined above using **S10** (1.0 eq., 0.0260 g, 0.1 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.0748 g, 0.12 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 0.28 mL, 0.12 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.02 mL, 1.2 mmol), and DBU (5.0 equiv., 0.07 mL, 0.5 mmol). Purification by flash column chromatography gave **36** as an off-white solid (0.0387 g, 0.091 mmol, 91%). (**36**): $[\alpha]_D^{24}$ = -29.835° (c = 0.97, CH_3OH); IR (neat, cm^{-1}): 3405.08, 2988.53, 2938.69, 1238.40, 1069.70; ^1H NMR (600 MHz, MeOD) δ 5.90 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.58 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.40 (ddd, *J* = 7.3, 6.3, 5.3 Hz, 1H), 4.34 (dh, *J* = 6.0, 3.1 Hz, 2H), 4.19 – 4.10 (m, 2H), 4.01 (dd, *J* = 8.6, 5.3 Hz, 1H), 3.67 – 3.61 (m, 2H), 3.25 (s, 9H), 1.48 (s, 3H), 1.42 (s, 3H), 1.34 (d, *J* = 15.2 Hz, 6H).; ^{13}C NMR (150 MHz, MeOD) δ 111.6, 108.8, 105.0, 83.9, 80.5, 80.4, 77.8, 77.7, 72.5, 66.3, 66.1, 59.1, 59.0, 53.3, 53.3, 53.2, 25.6, 25.6, 25.0, 24.2.; HR-ESI-MS (m/z): calcd for $C_{17}H_{32}NO_9PH^+$ $[M+H]^+$ 426.1887, found 426.1883.



S11 16 37, 77%

(37)

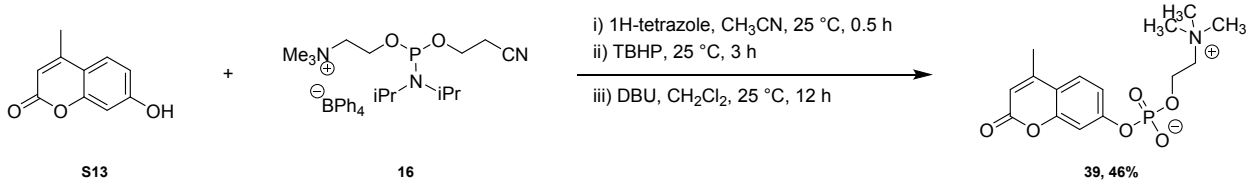
Prepared following the general procedure outlined above using **S11** (1.0 eq., 0.0941 g, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **37** as an off-white solid (0.1996 g, 0.77 mmol, 77%). (**37**): ^{1}H NMR (600 MHz, MeOD) δ 7.23 – 7.17 (m, 2H), 7.13 (dt, *J* = 8.6, 1.2, 1.2 Hz, 2H), 6.98 (t, *J* = 7.4, 7.4 Hz, 1H), 4.25 (ddt, *J* = 7.0, 4.6, 2.5, 2.5 Hz, 2H), 3.55 – 3.51 (m, 2H), 3.07 (s, 10H).; ^{13}C NMR (150 MHz, MeOD) δ 152.7, 152.6, 129.0, 123.2, 119.9, 119.8, 66.0, 66.0, 66.0, 65.9, 65.9, 59.5, 59.5, 53.3, 53.2, 53.2. Spectral data for (**37**) was consistent with known values.[10]



S12 16 38, 52%

(38)

Prepared following the general procedure outlined above using **S12** (1.0 eq., 0.1391 g, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash column chromatography gave **38** as an off-white solid (0.1570 g, 0.52 mmol, 52%). (**38**): ^{1}H NMR (600 MHz, MeOD) δ 8.27 – 8.21 (m, 2H), 7.47 – 7.41 (m, 2H), 4.42 (ddq, *J* = 7.2, 5.1, 2.5 Hz, 2H), 3.73 – 3.69 (m, 2H), 3.25 (s, 9H). ^{13}C NMR (150 MHz, MeOD) δ 158.1, 158.0, 143.3, 125.0, 120.1, 120.1, 65.9, 65.9, 65.9, 65.9, 65.8, 59.7, 59.7, 53.3, 53.3, 53.2. Spectral data for (**38**) was consistent with commercially available material from Millipore Sigma.



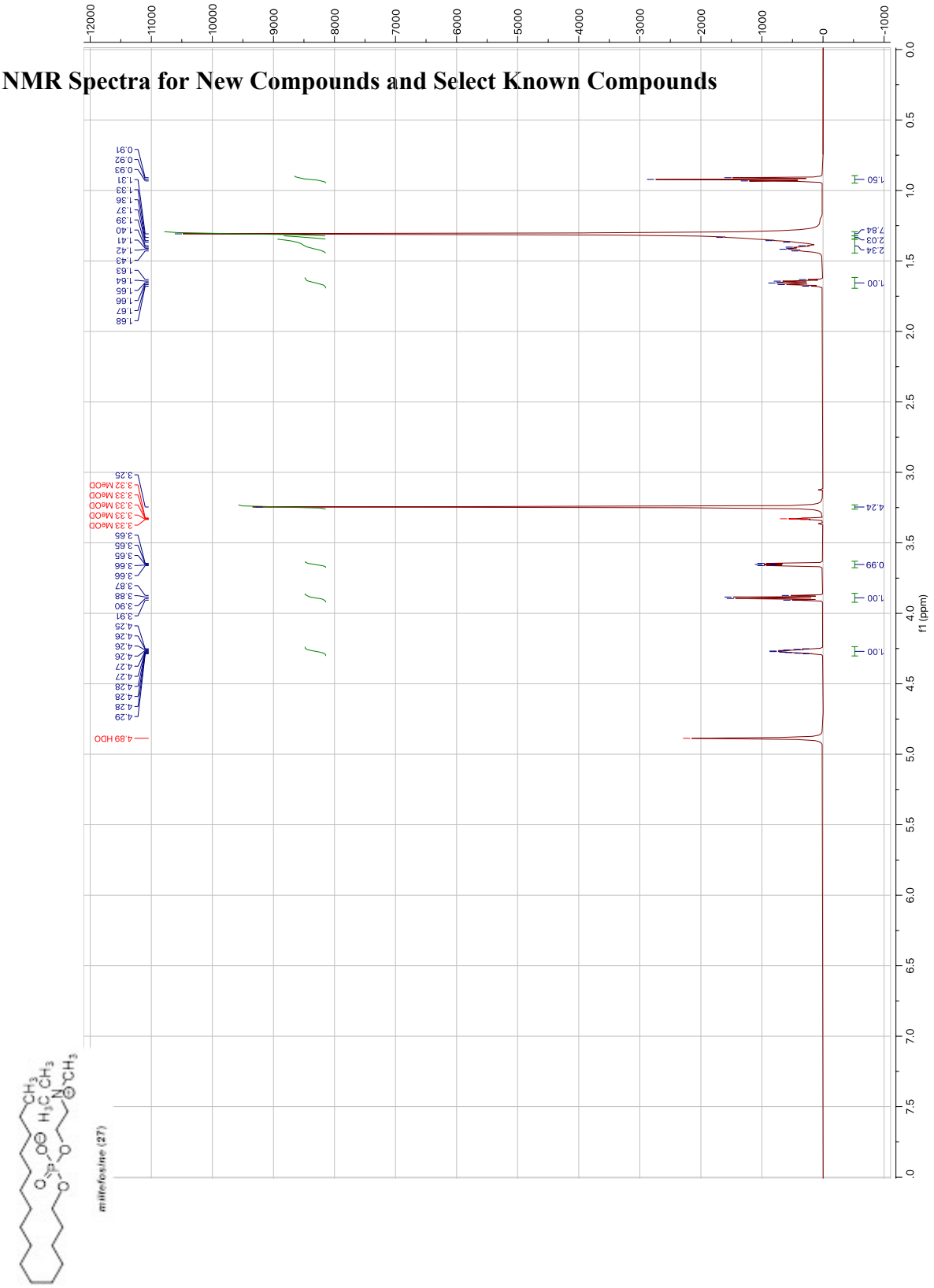
S13 16 39, 46%

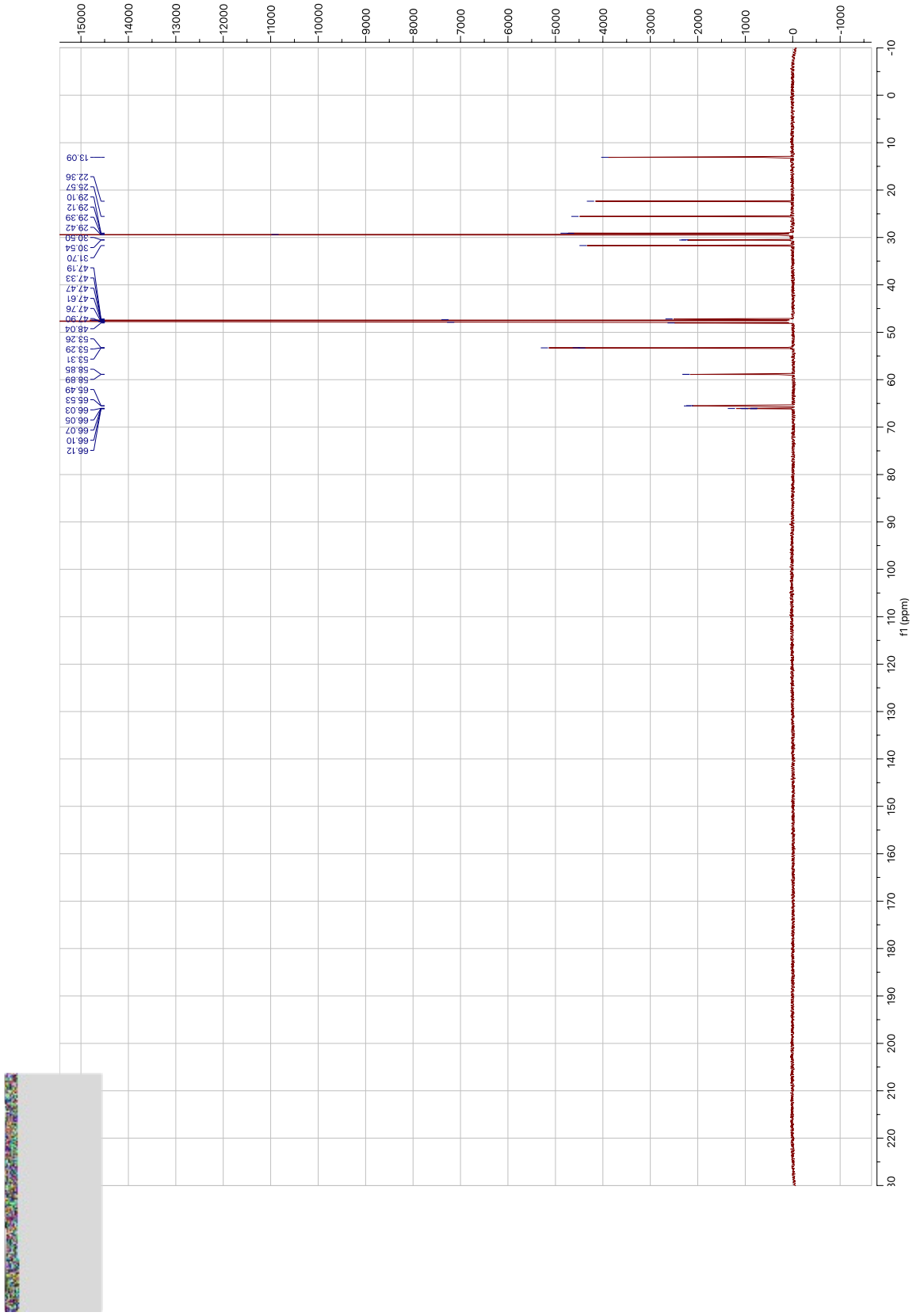
(39)

Prepared following the general procedure outlined above using **S13** (1.0 eq., 0.1762 g, 1.0 mmol), phosphoramidite 2-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)-N,N,N-trimethylethan-1-aminium tetraphenylborate salt **16** (1.2 equiv., 0.7484 g, 1.2 mmol), 3% 1*H*-tetrazole solution in anhydrous CH_3CN (1.2 equiv., 2.8 mL, 1.2 mmol), tert-butyl hydroperoxide (1.2 equiv., 0.22 mL, 1.2 mmol), and DBU (5.0 equiv., 0.75 mL, 5.0 mmol). Purification by flash

column chromatography gave **39** as an off-white solid (0.1570 g, 0.46 mmol, 46%). (**39**): ^{1}H NMR (600 MHz, MeOD) δ 7.77 – 7.72 (m, 1H), 7.27 (dd, *J* = 7.5, 1.0 Hz, 2H), 6.26 (q, *J* = 1.3 Hz, 1H), 4.47 – 4.41 (m, 2H), 4.41 (dd, *J* = 4.9, 2.4 Hz, 1H), 3.72 – 3.67 (m, 2H), 3.24 (s, 9H), 2.48 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (150 MHz, MeOD) δ 125.8, 116.7, 116.7, 115.7, 112.1, 107.5, 107.4, 78.0, 65.9, 65.9, 65.9, 65.9, 65.9, 59.7, 59.6, 59.5, 53.2, 53.2, 53.2, 17.2. Spectral data for (**39**) was consistent with commercially available material from Carbosynth.

^{1}H and ^{13}C NMR Spectra for New Compounds and Select Known Compounds

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7000
6000
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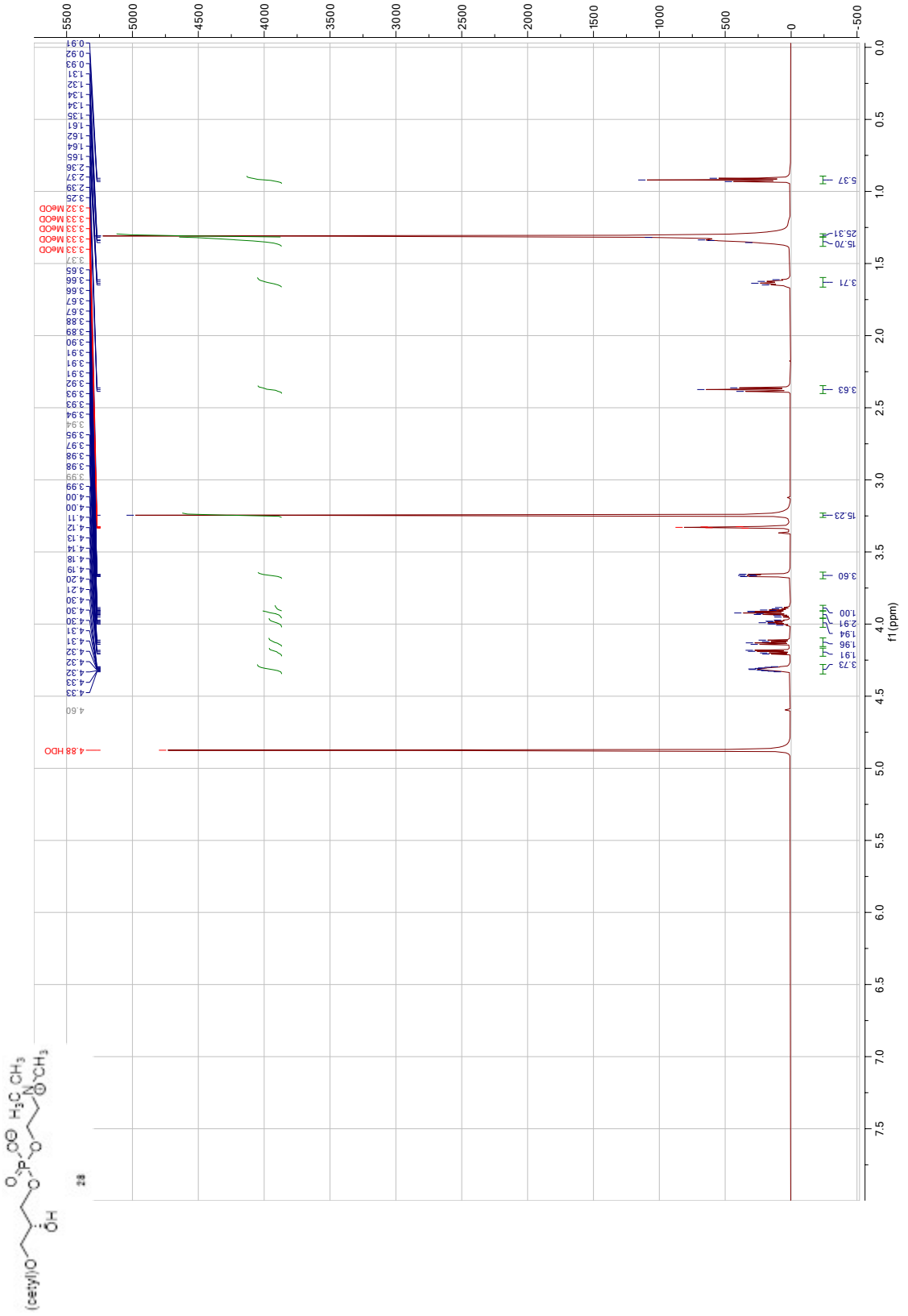
4000
3000
2000
1000
0
-1000
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
13.09
22.36
25.57
29.10
29.12
29.39
29.42
30.60
30.54
31.70
47.19
47.33
47.47
47.61
47.76
47.90
48.04
53.26
53.29
53.31
58.85
58.89
65.49
65.53
66.03
66.05
66.07
66.10
66.12


f1 (ppm)
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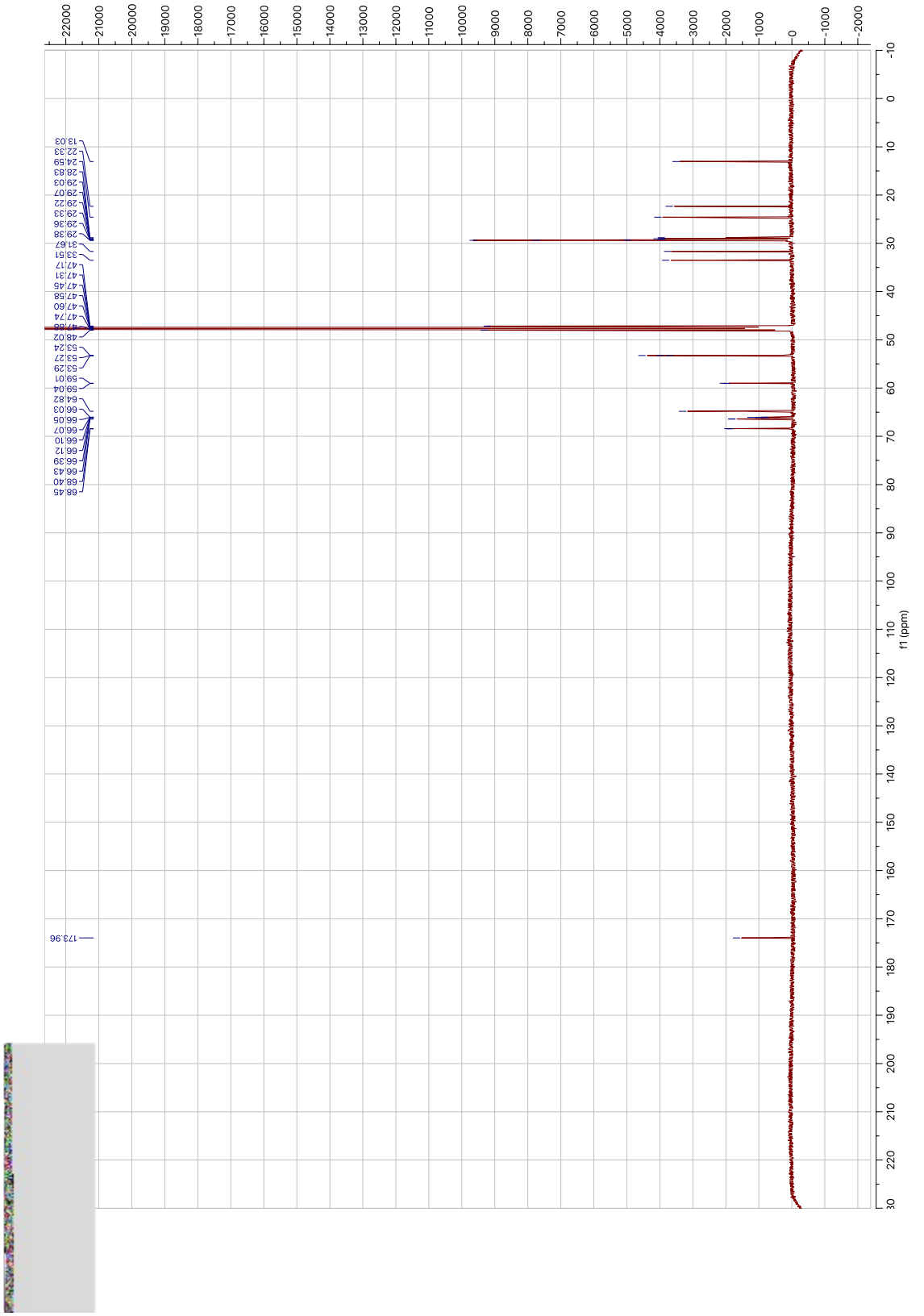
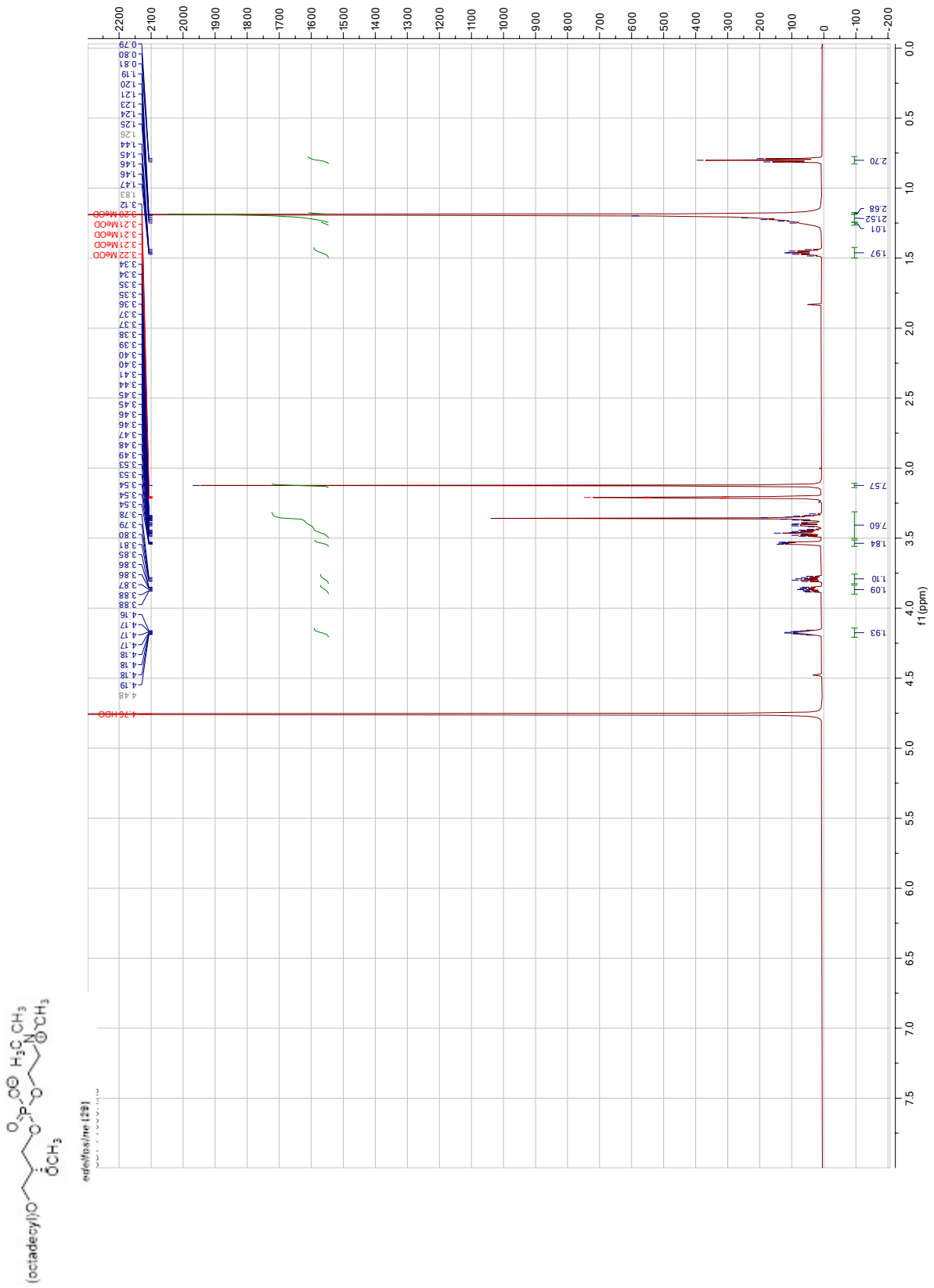
3.30 MeOD
3.32 MeOD
3.33 MeOD
5.37
15.70
3.71
3.63
15.23
3.60
1.00
2.91
1.94
1.96
1.91
3.73
(cetyl)O
OH
O
P
O
O
N
CH3
H3C
CH3


13.03
22.33
24.59
28.83
29.03
29.07
29.22
29.33
29.36
29.38
31.67
33.51
47.17
47.31
47.45
47.58
47.60
47.74
48.02
53.24
53.27
53.29
59.01
59.04
64.82
66.03
66.05
66.07
66.10
66.12
66.39
66.43
68.40
68.45
173.96
f1 (ppm)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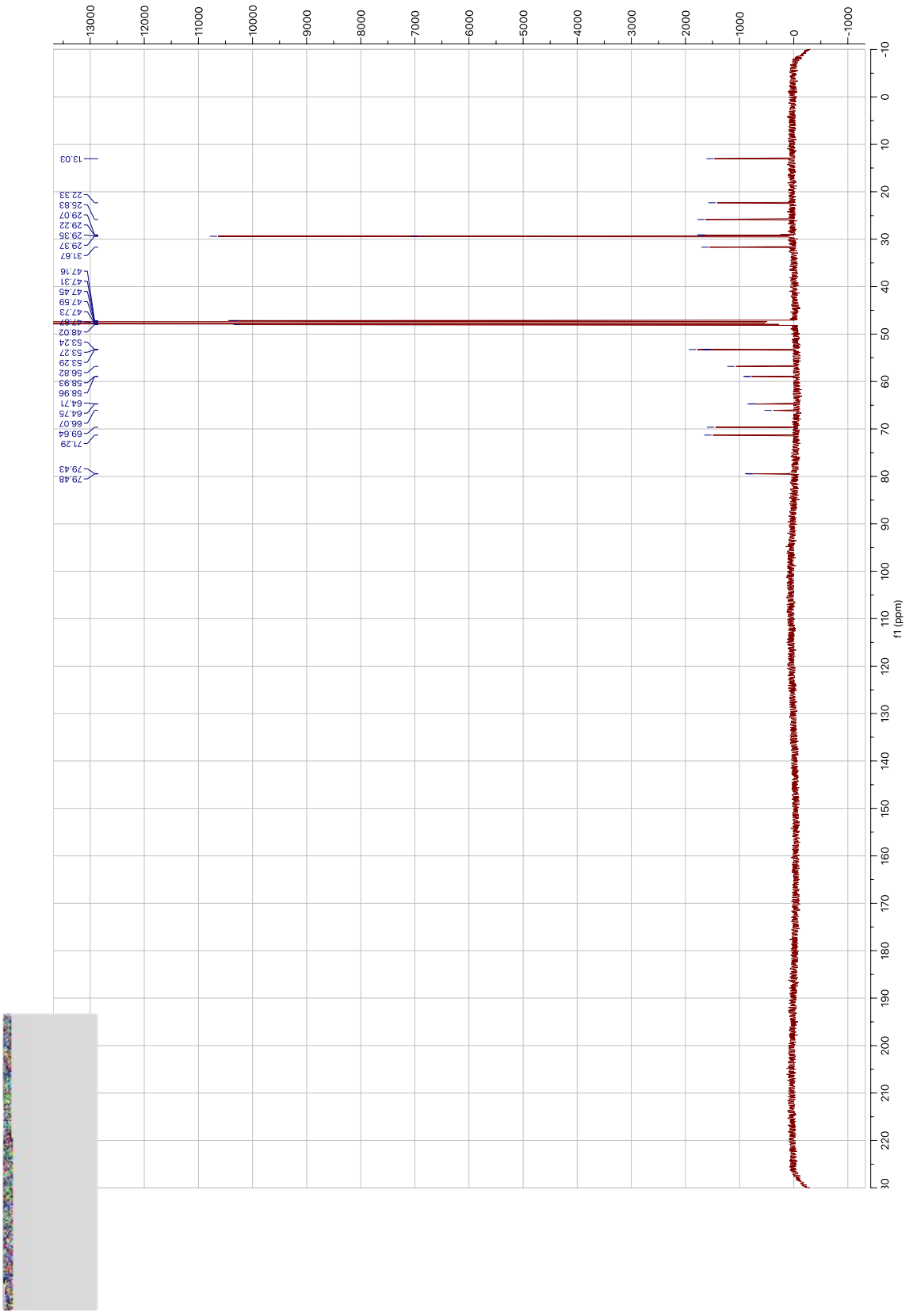
OCH3
H3C CH3
N
OCH3
f1 (ppm)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7000
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3000
2000
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0
-1000
13.03
22.33
25.83
29.07
29.22
29.35
29.37
31.67
47.16
47.31
47.45
47.59
47.73
48.02
53.24
53.27
53.29
56.82
58.93
58.96
64.71
64.75
66.07
69.64
71.29
79.43
79.48
-10
0
10
20
30
40
50
60
70
80
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100
110
120
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140
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160
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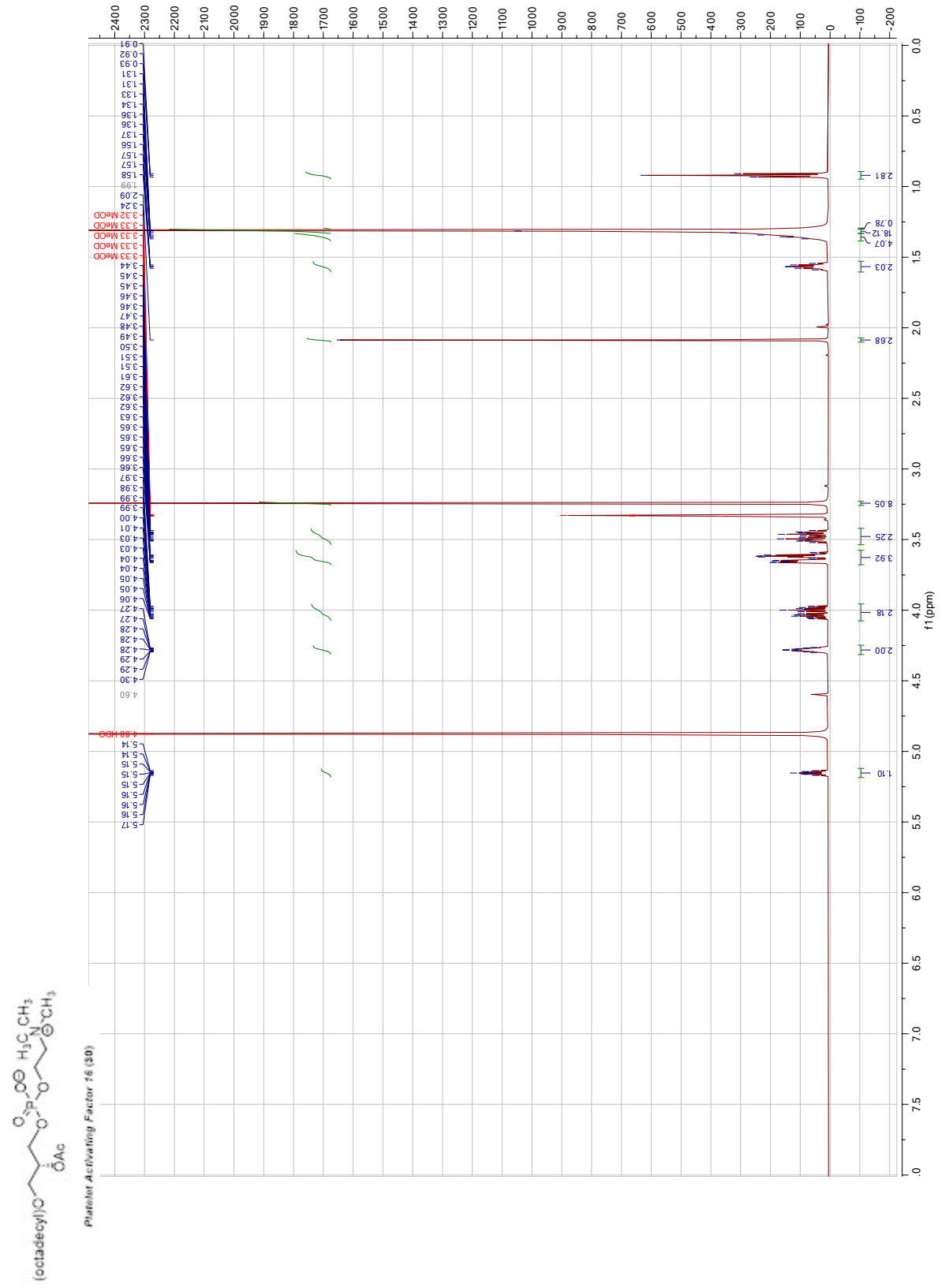
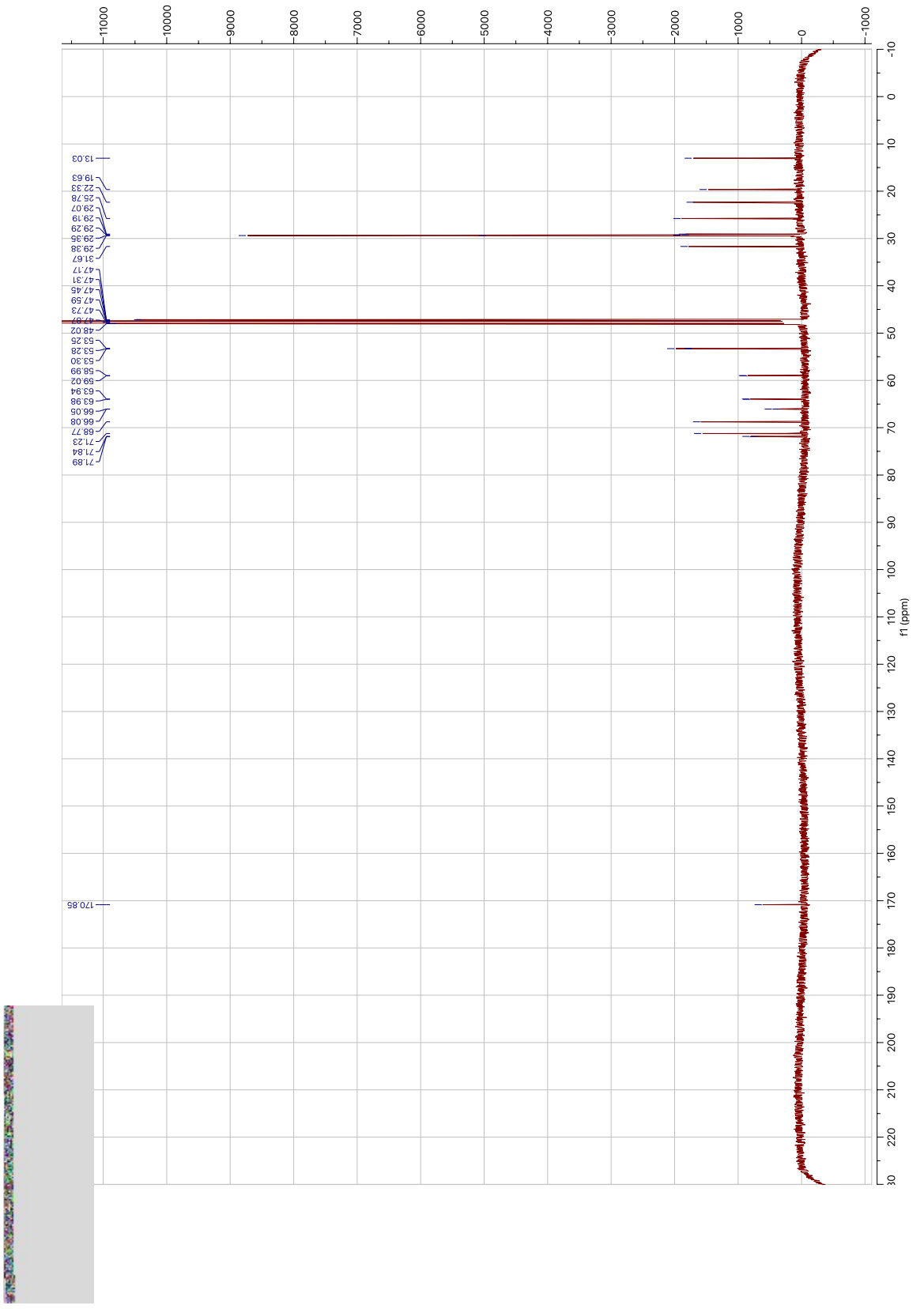
180
190
200
210
220
230
f1 (ppm)


Platelet Activating Factor 16 (30)
(octadecyl)O
OAc
f1 (ppm)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50
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70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
13.03
19.63
22.33
25.78
29.07
29.19
29.29
29.35
29.38
31.67
47.17
47.31
47.45
47.59
47.73
48.02
53.25
53.28
53.30
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63.98
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66.08
68.77
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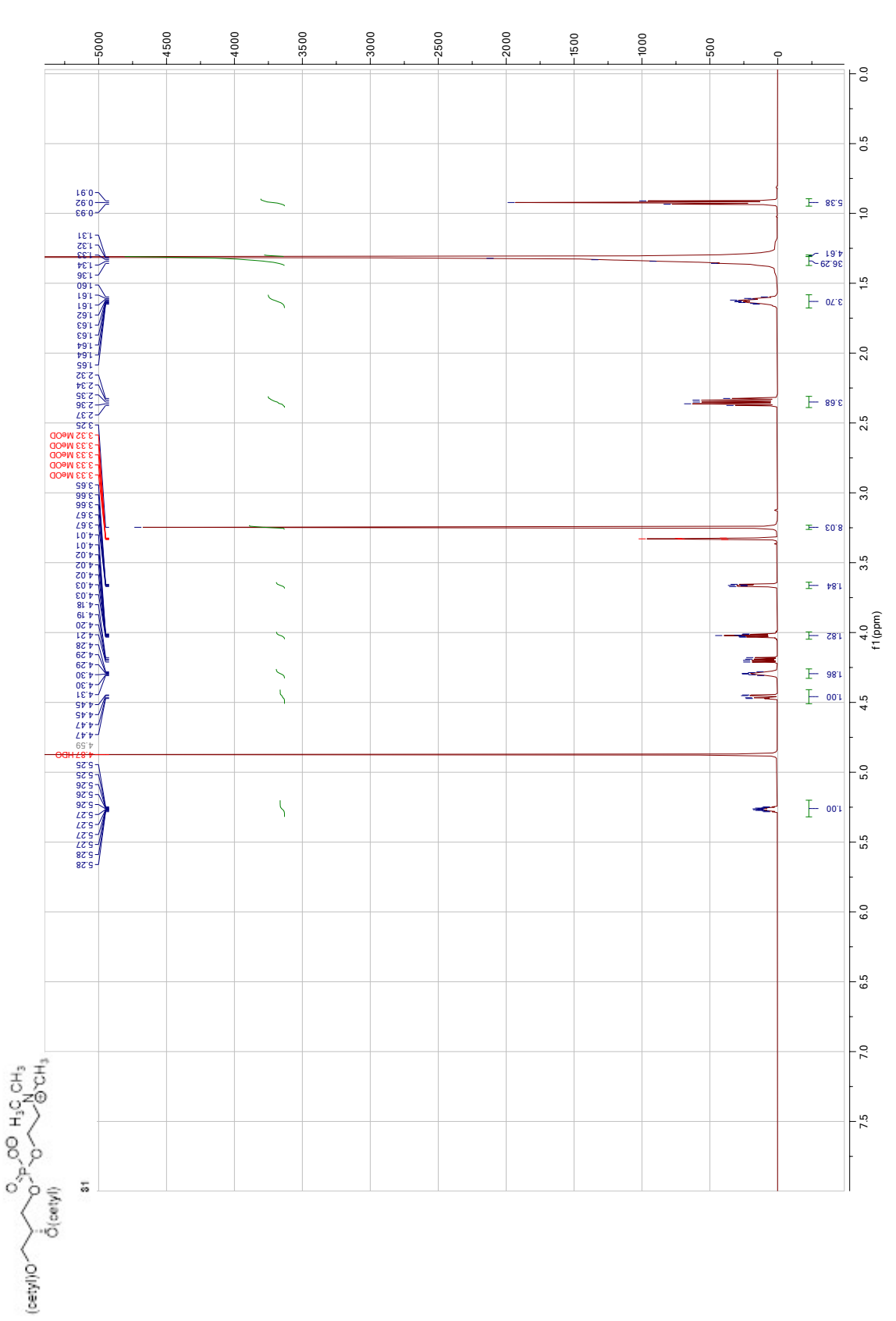
71.84
71.89
170.85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4.61
36.29
3.70
3.68
8.03
1.84
1.82
1.86
1.00
1.00
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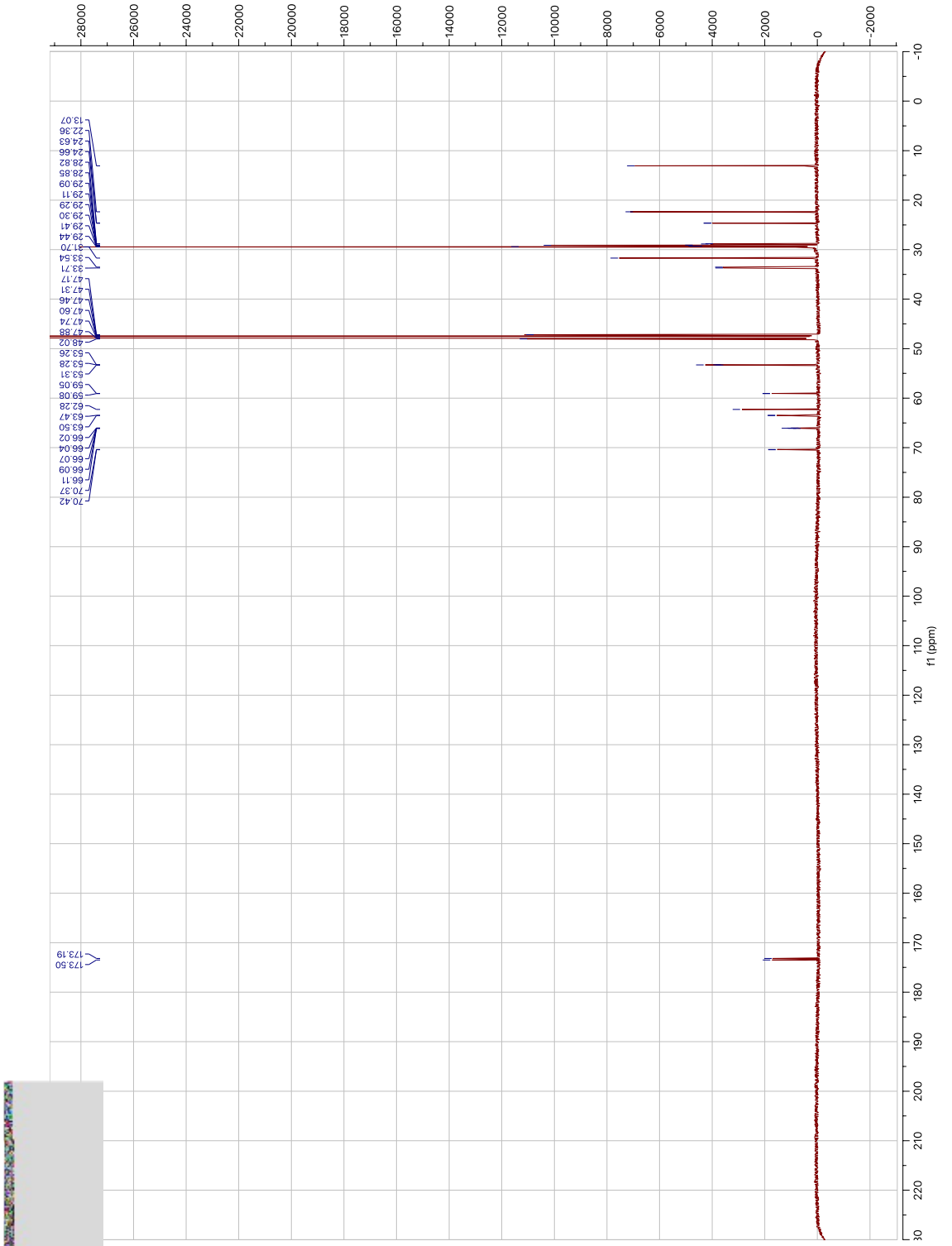
O(cetyl)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4000
2000
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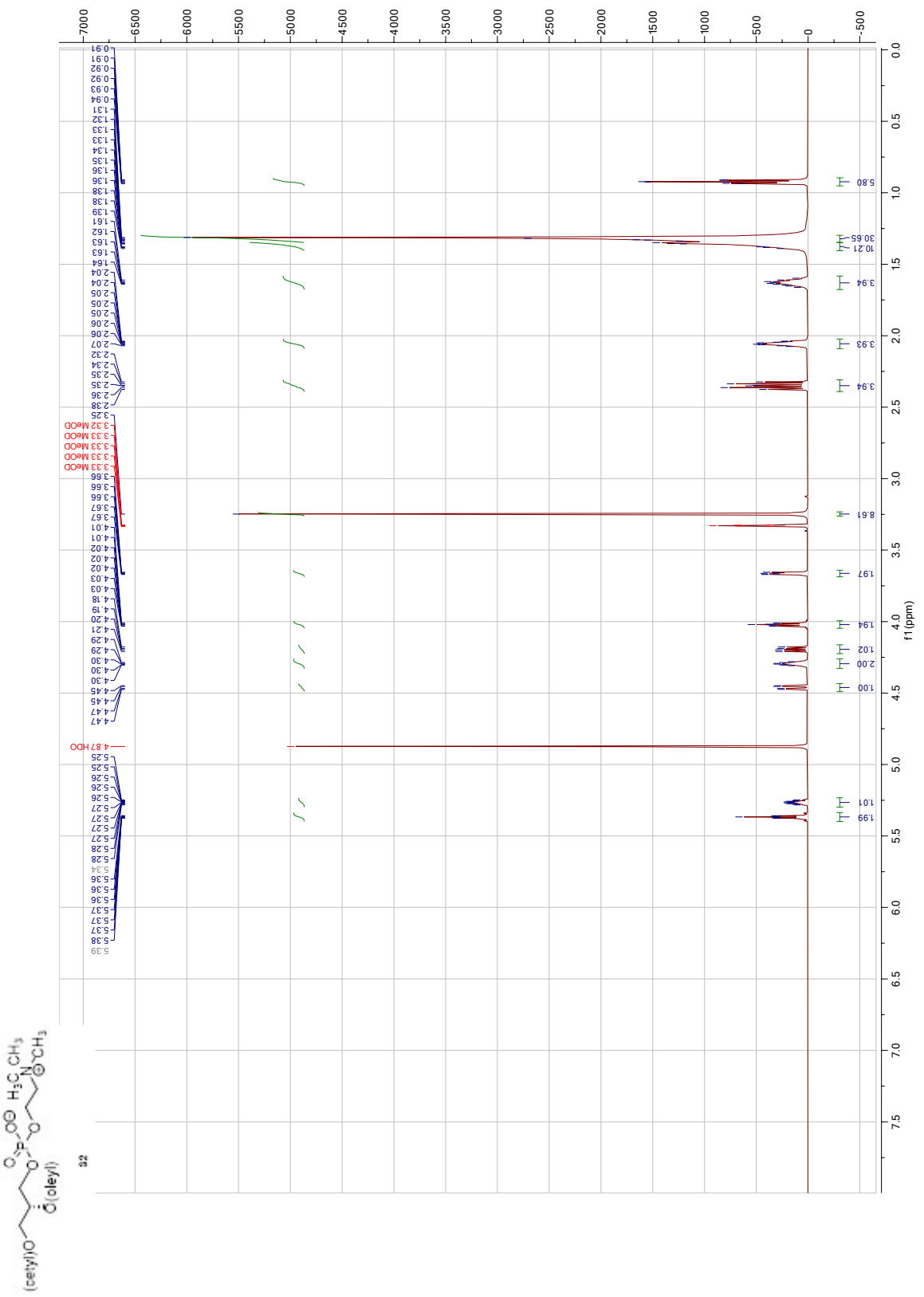
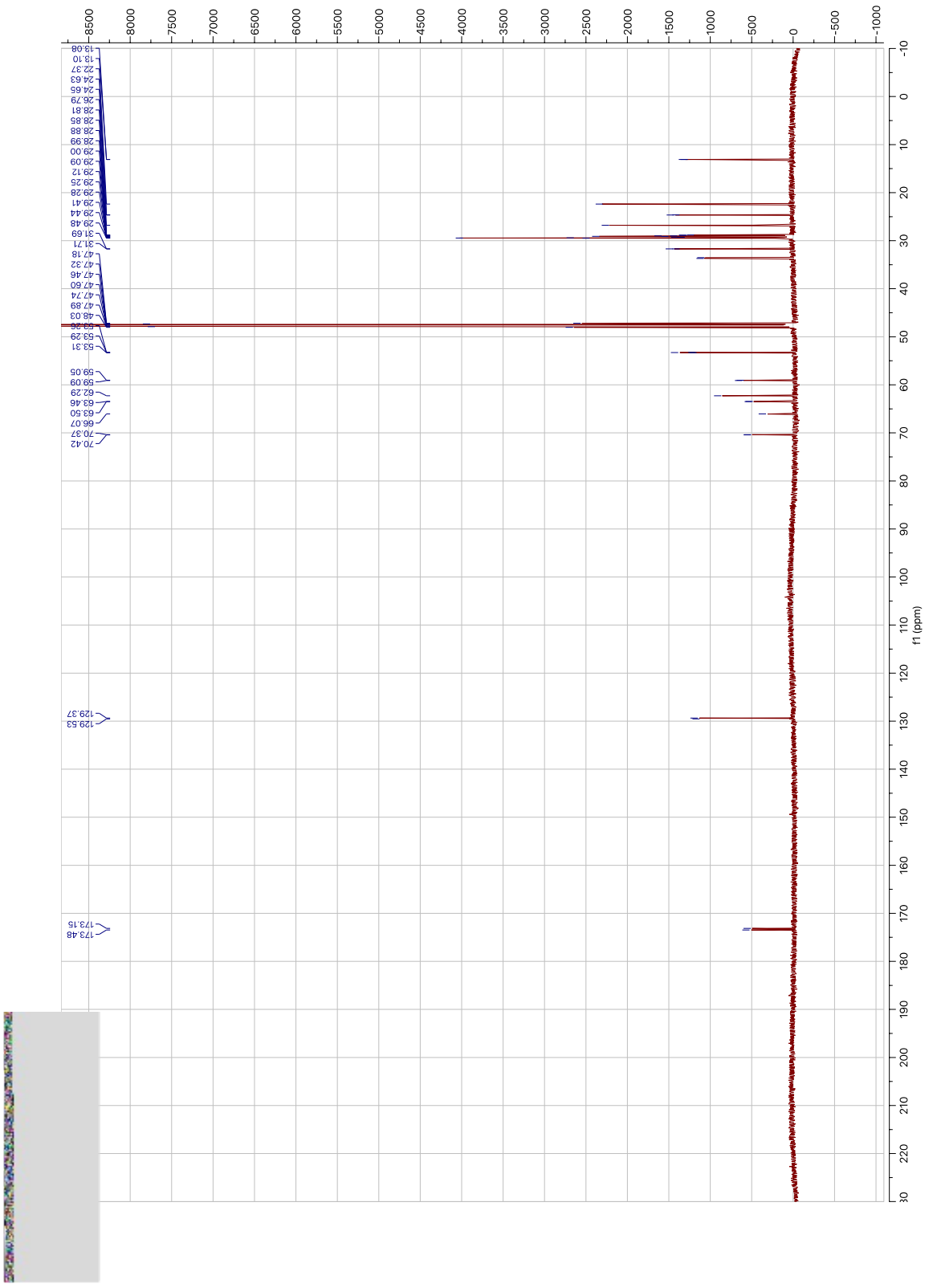
−2000
13.07
22.36
24.63
24.66
28.82
28.85
29.09
29.11
29.29
29.30
29.41
29.44
31.70
33.54
33.71
47.17
47.31
47.46
47.60
47.74
47.88
48.02
53.26
53.28
53.31
59.05
59.08
62.28
63.47
63.50
66.02
66.04
66.07
66.09
66.11
70.37
70.42
173.19
173.50
f1 (ppm)


f1 (ppm)
(cetyl)O
O(oleyl)
S2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5500
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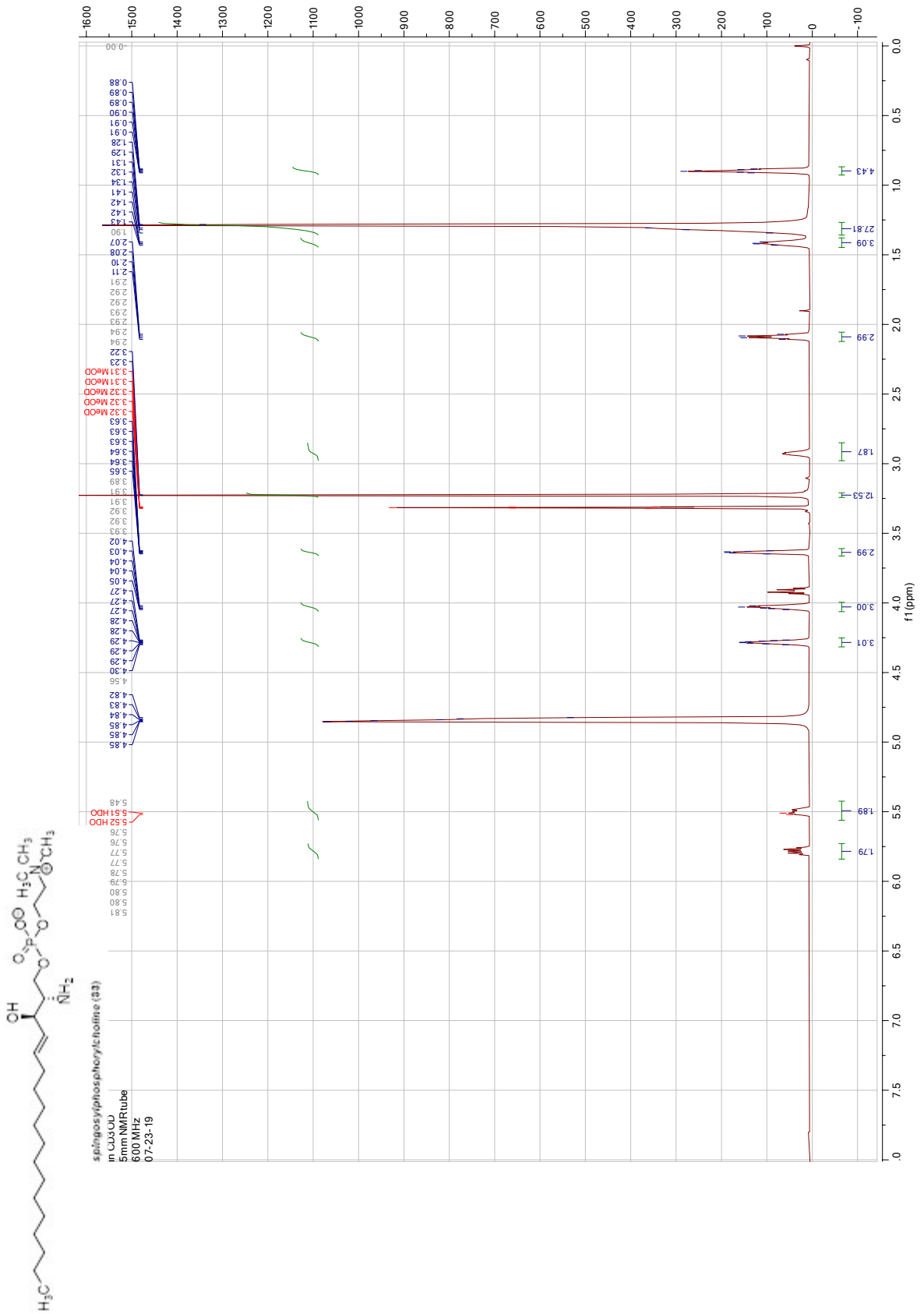
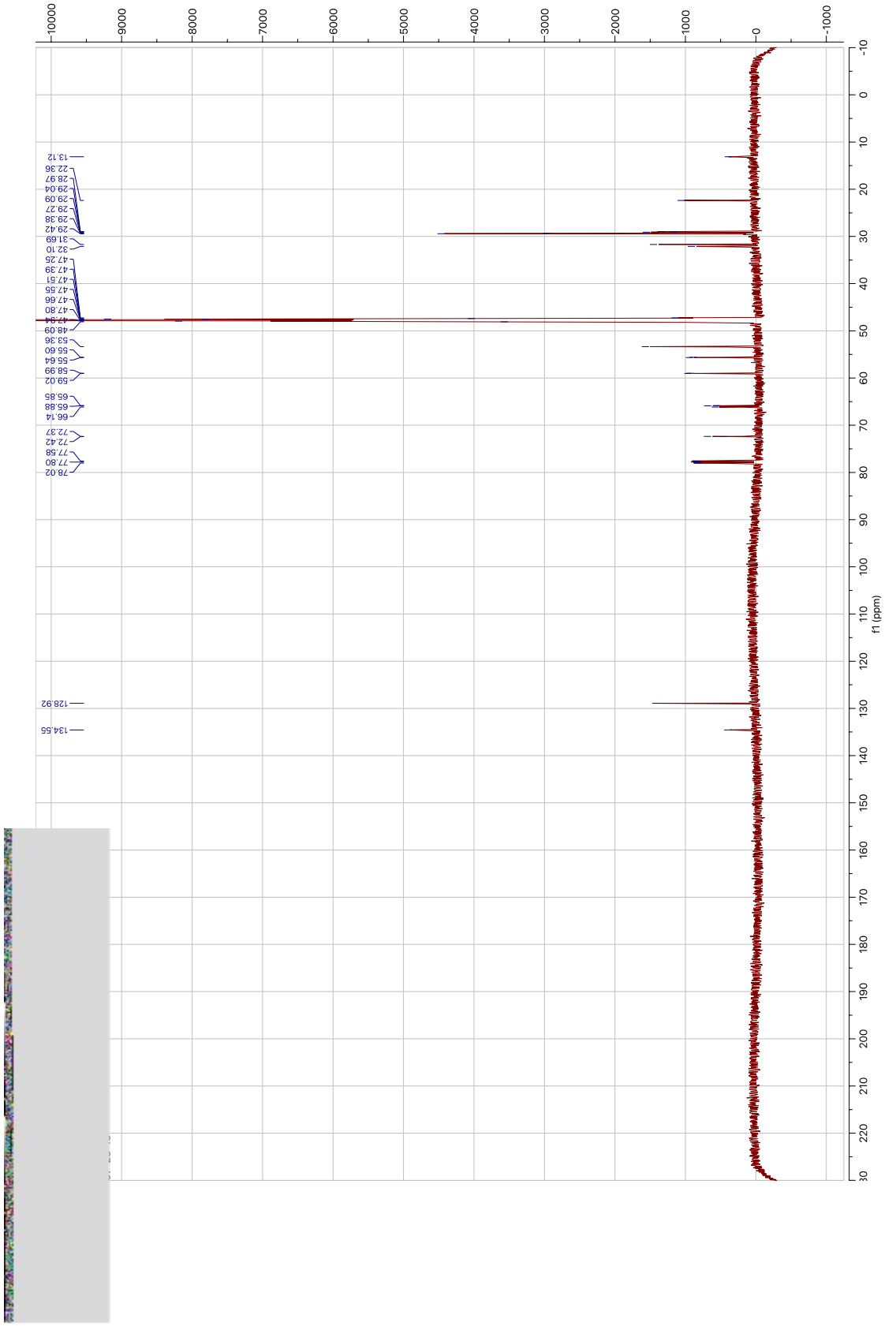
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
13.08
13.10
22.37
24.63
24.65
26.79
28.81
28.85
28.88
28.99
29.00
29.09
29.12
29.25
29.28
29.41
29.44
29.48
31.69
31.71
47.18
47.32
47.46
47.60
47.74
47.89
48.03
52.26
53.29
53.31
59.05
59.09
62.29
63.46
63.50
66.07
70.37
70.42
129.37
129.53
173.15
173.48
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)


sphingosyiphosphorylcholine (83)
in CD3OD
5mm NMR tube
600 MHz
07-23-19
f1 (ppm)


13.12
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28.97
29.04
29.09
29.27
29.38
29.42
31.69
32.10
47.26
47.39
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47.55
47.66
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53.36
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55.84
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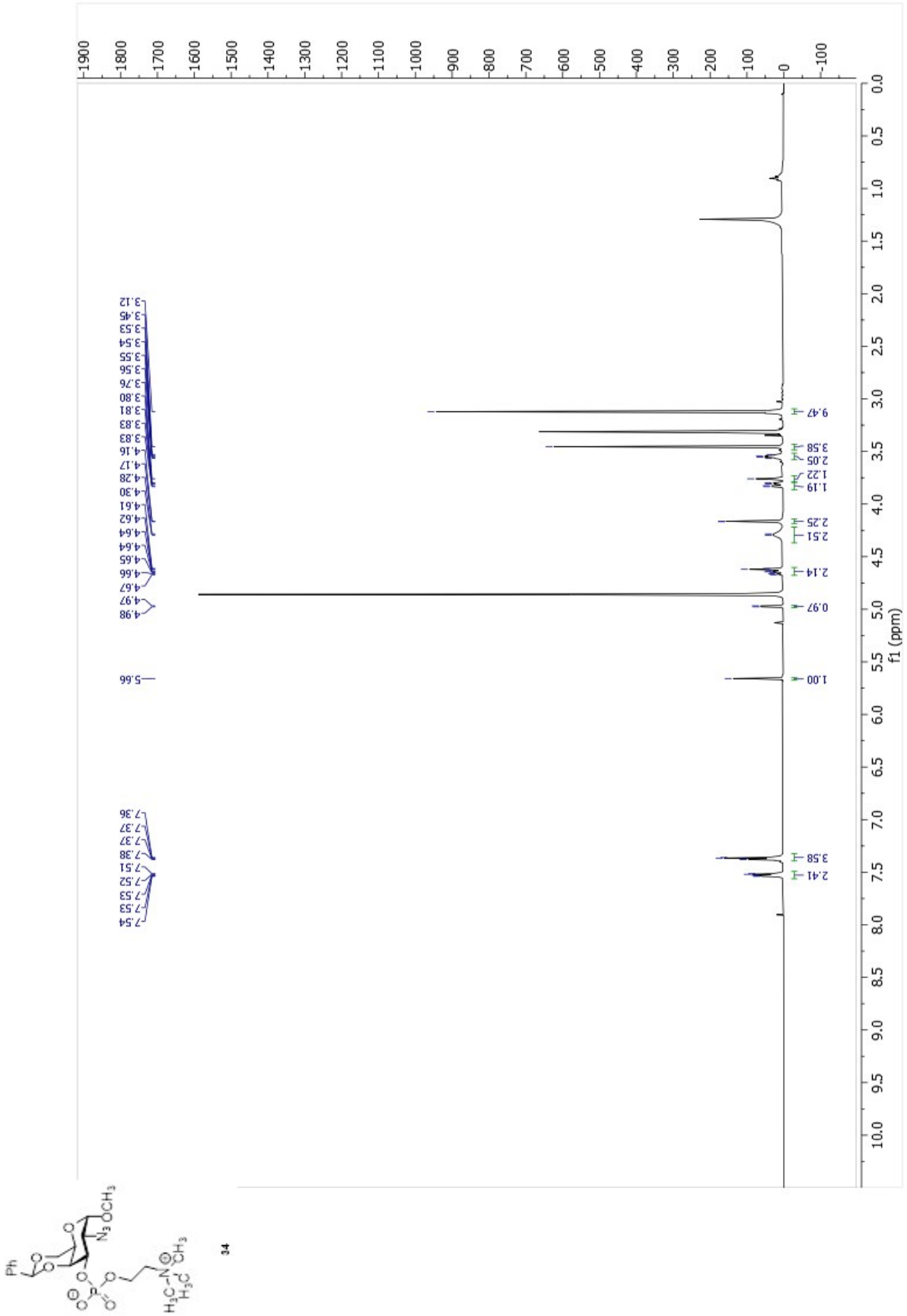
77.80
78.02
128.92
134.55
f1 (ppm)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1.22
1.19
2.25
2.51
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0.97
1.00
3.58
2.41
5.66
4.98
4.97
4.67
4.66
4.65
4.64
4.64
4.62
4.61
4.30
4.28
4.17
4.16
3.83
3.83
3.81
3.80
3.76
3.56
3.55
3.54
3.53
3.45
3.12
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7.53
7.53
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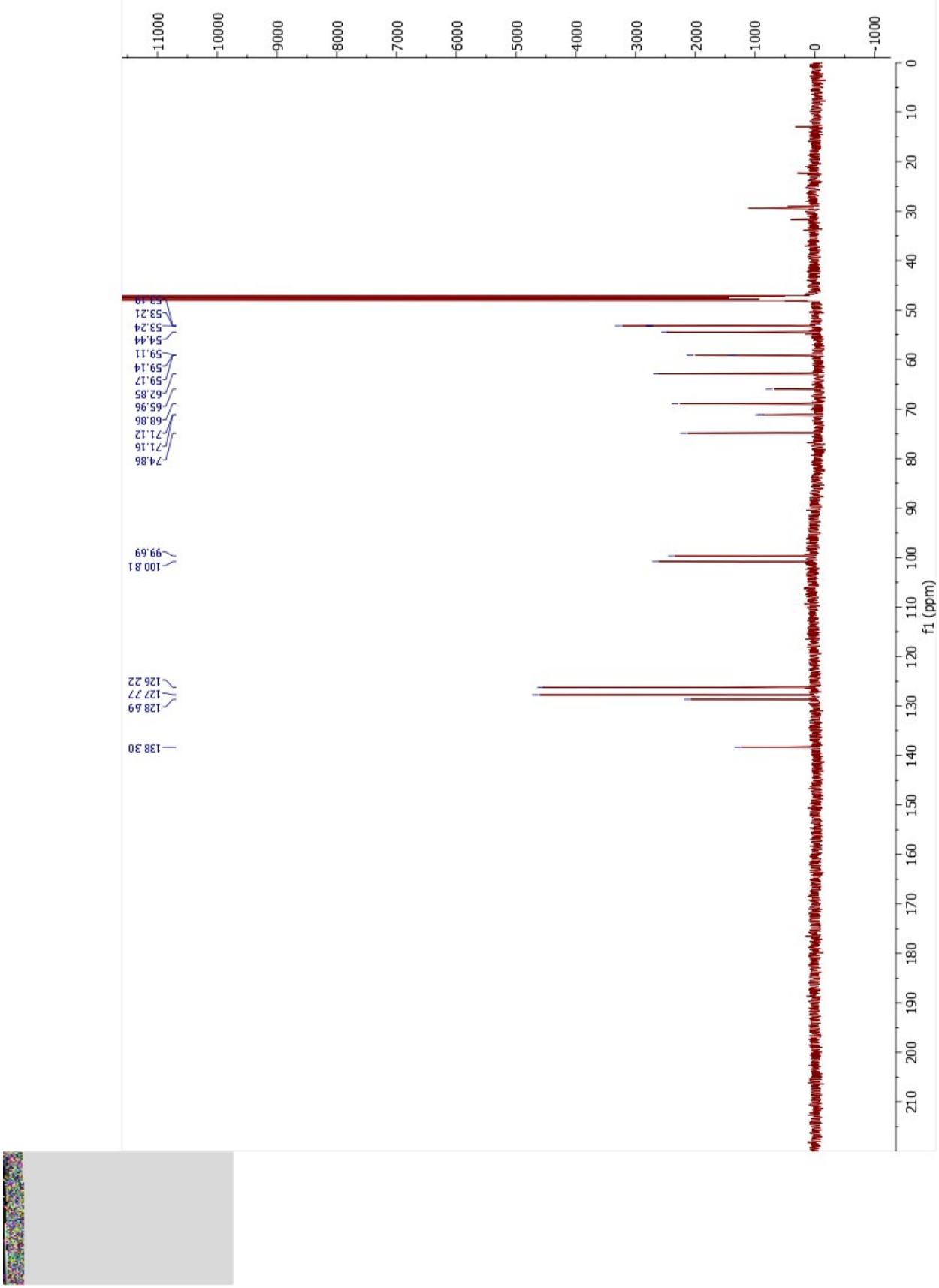
OCH_3
H_3C
CH_3
CH_3

34


53.19
53.21
53.24
54.44
59.11
59.14
59.17
62.85
65.96
68.86
71.12
71.16
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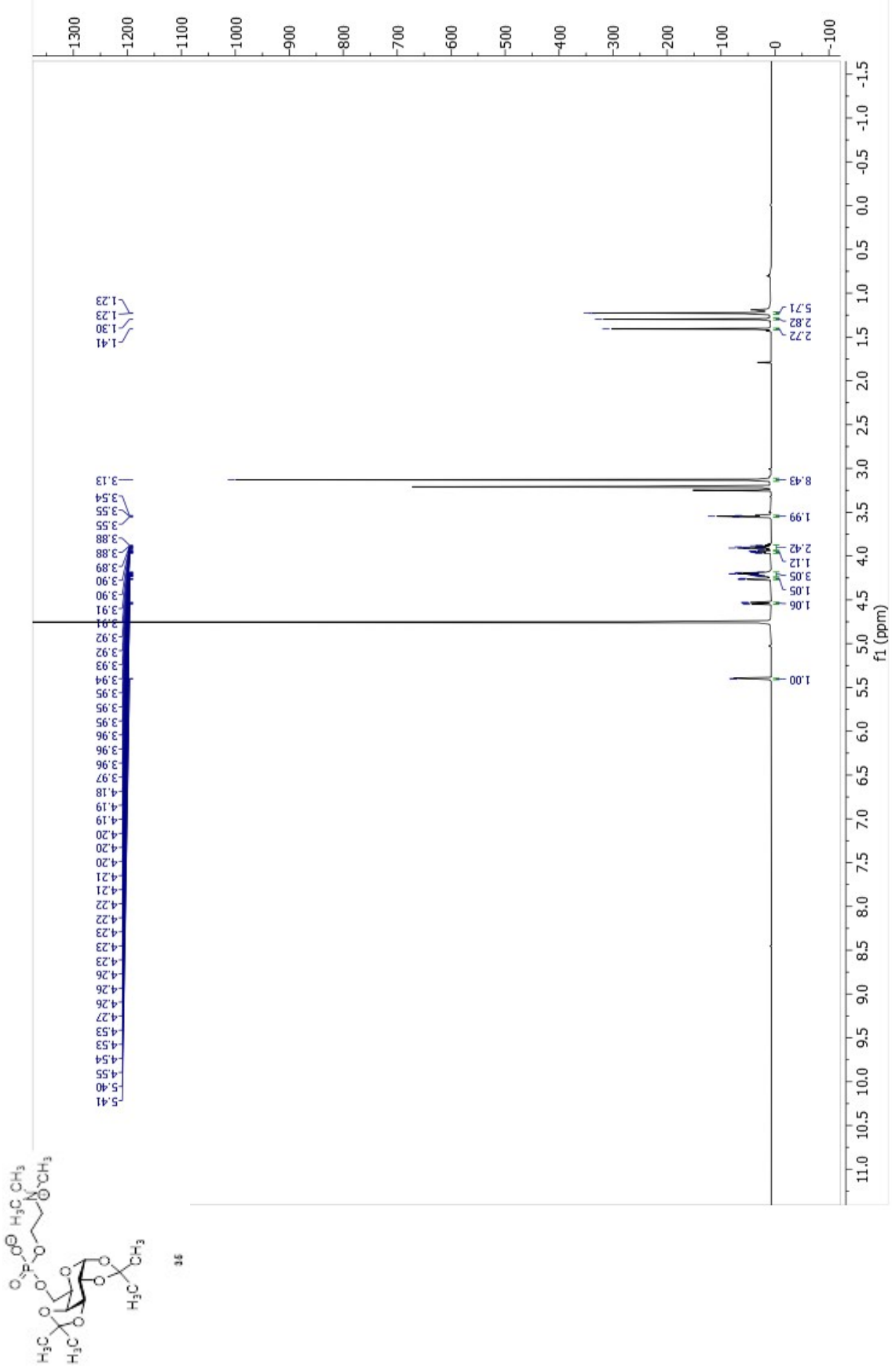
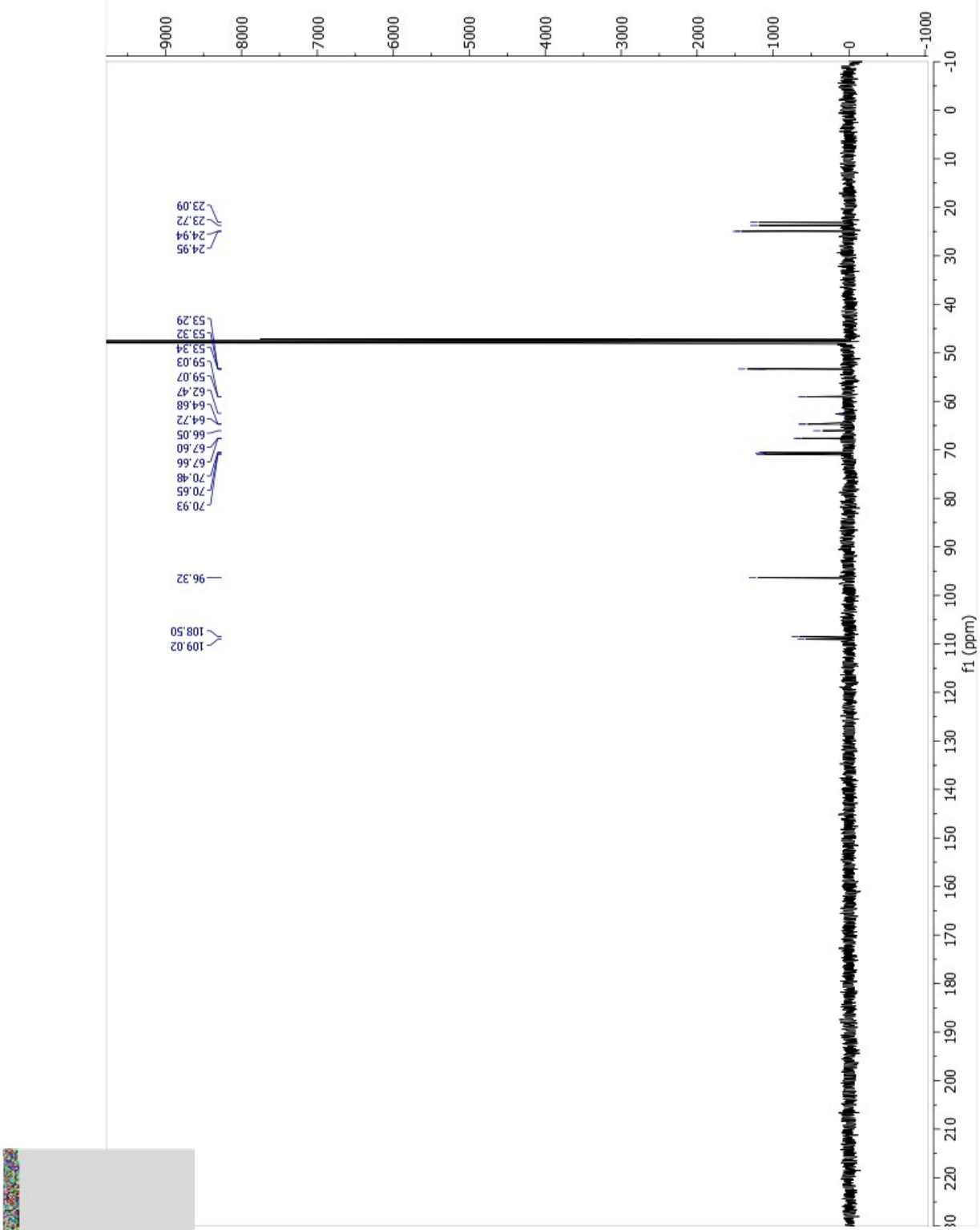
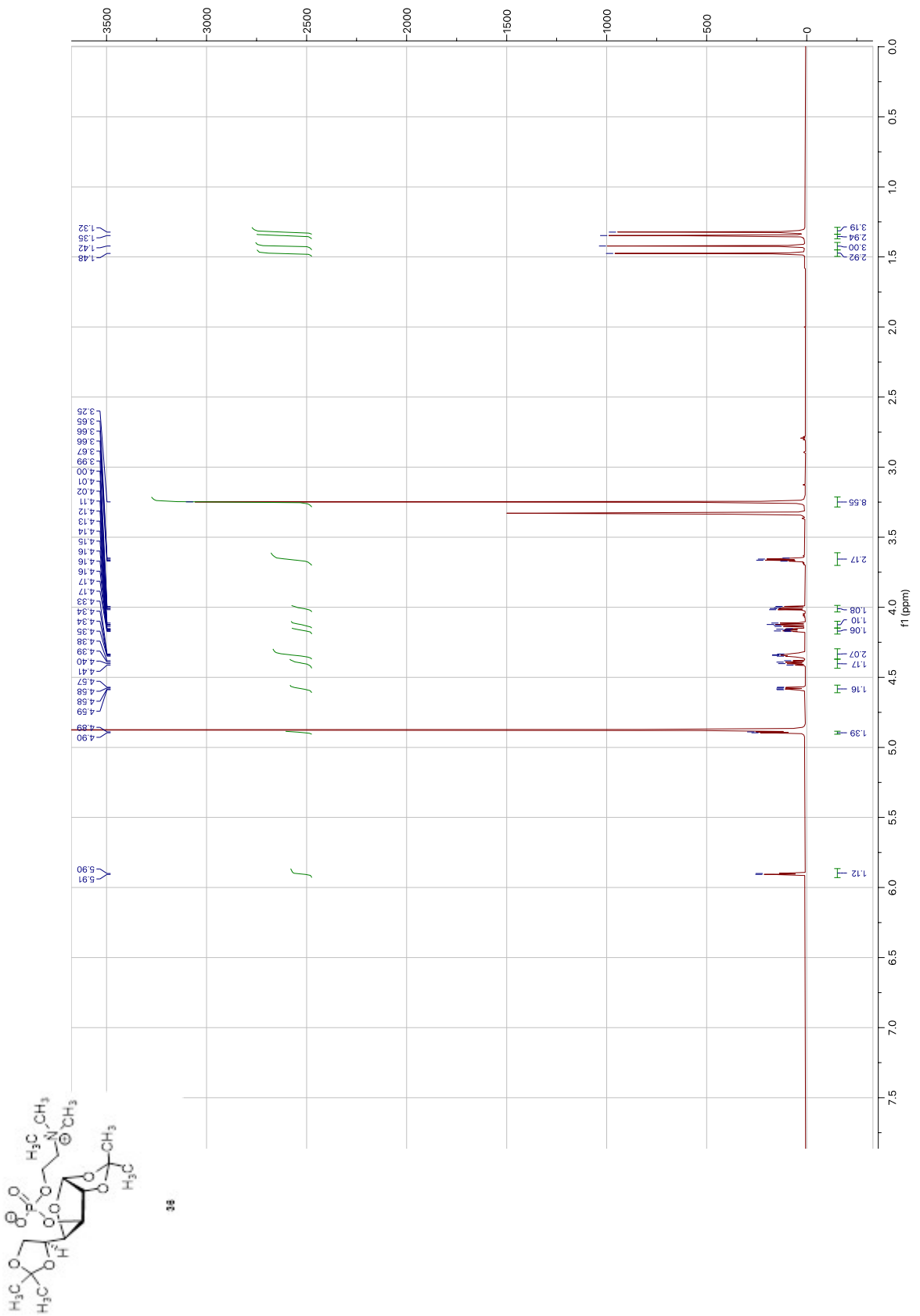
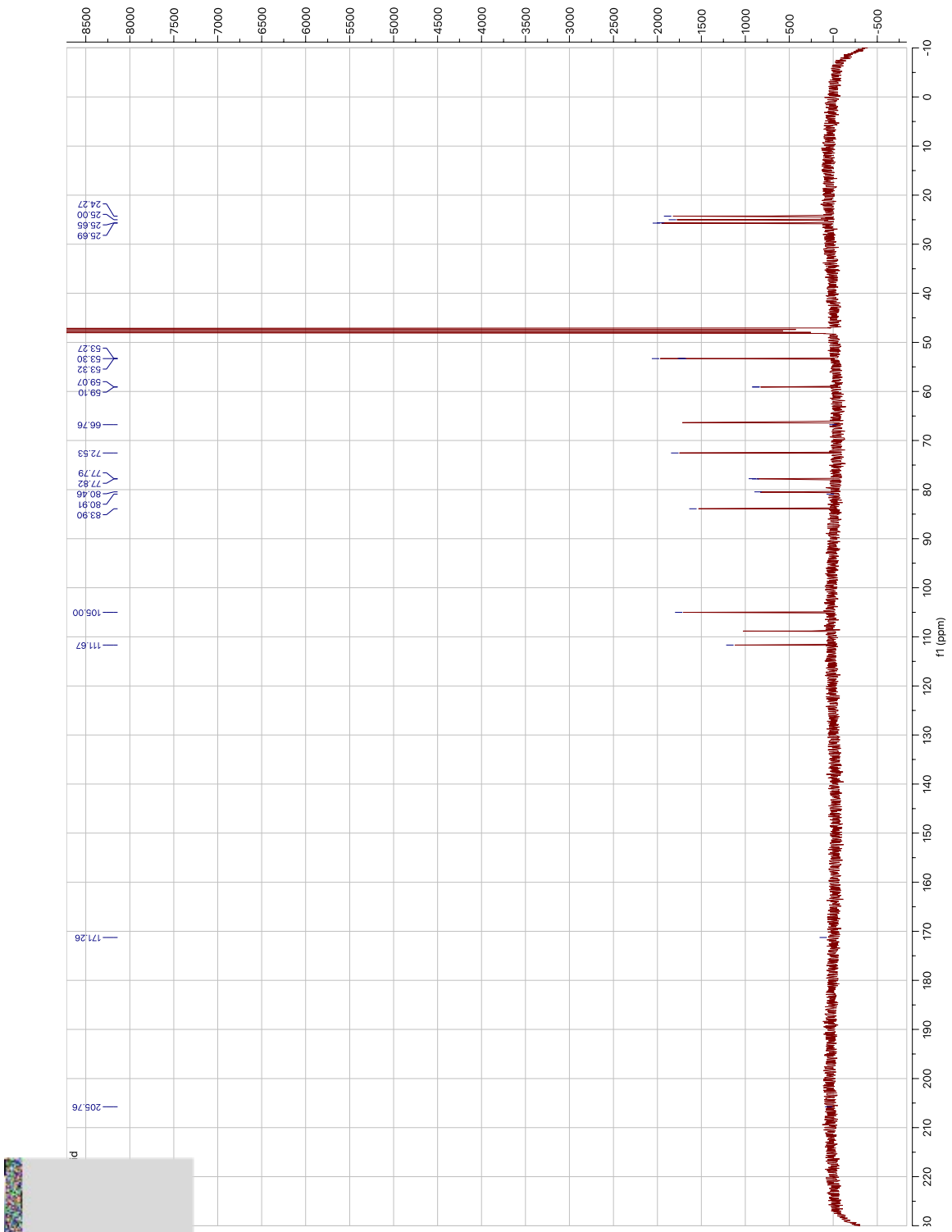
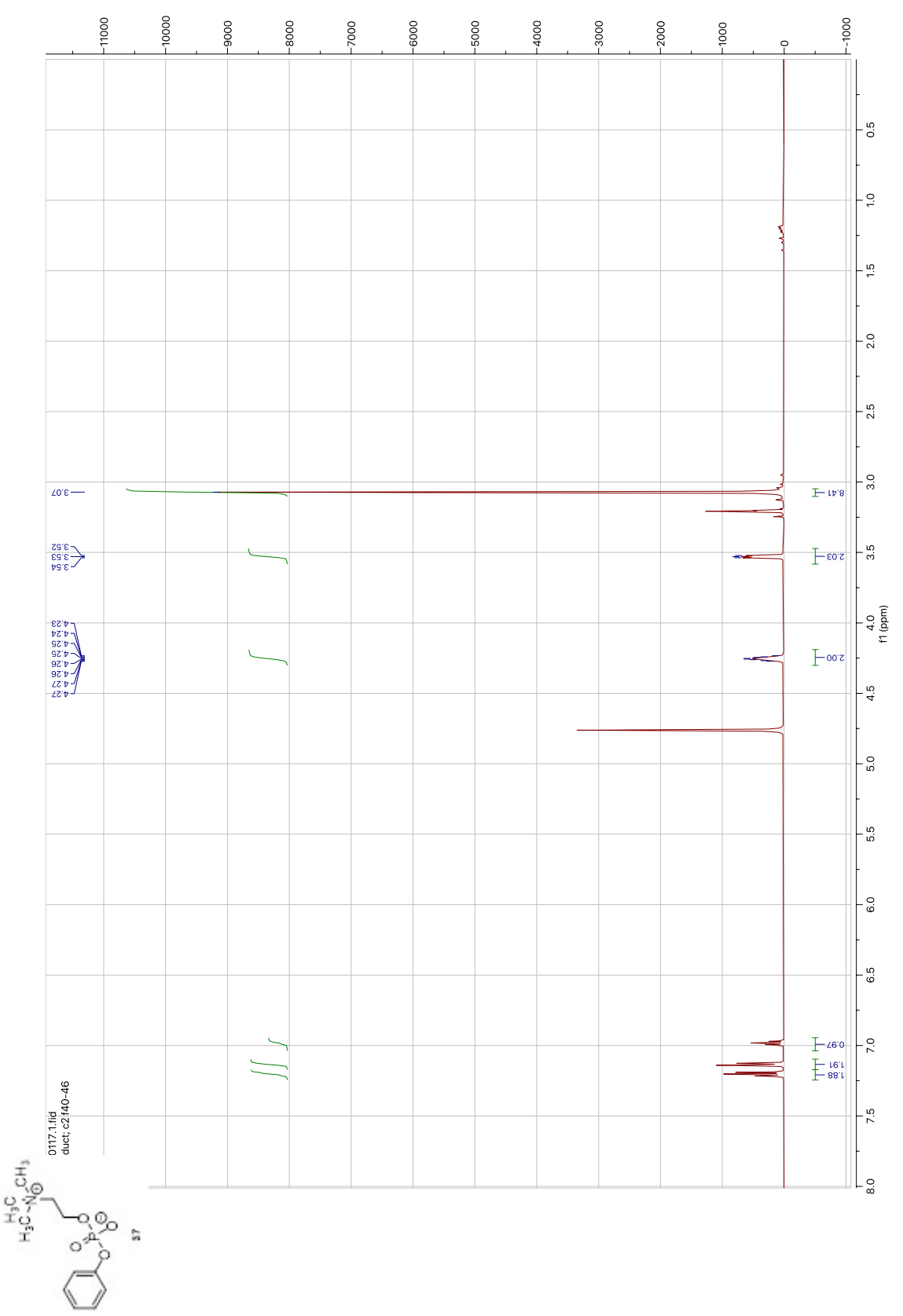
127.77
128.59
138.30
f1 (ppm)

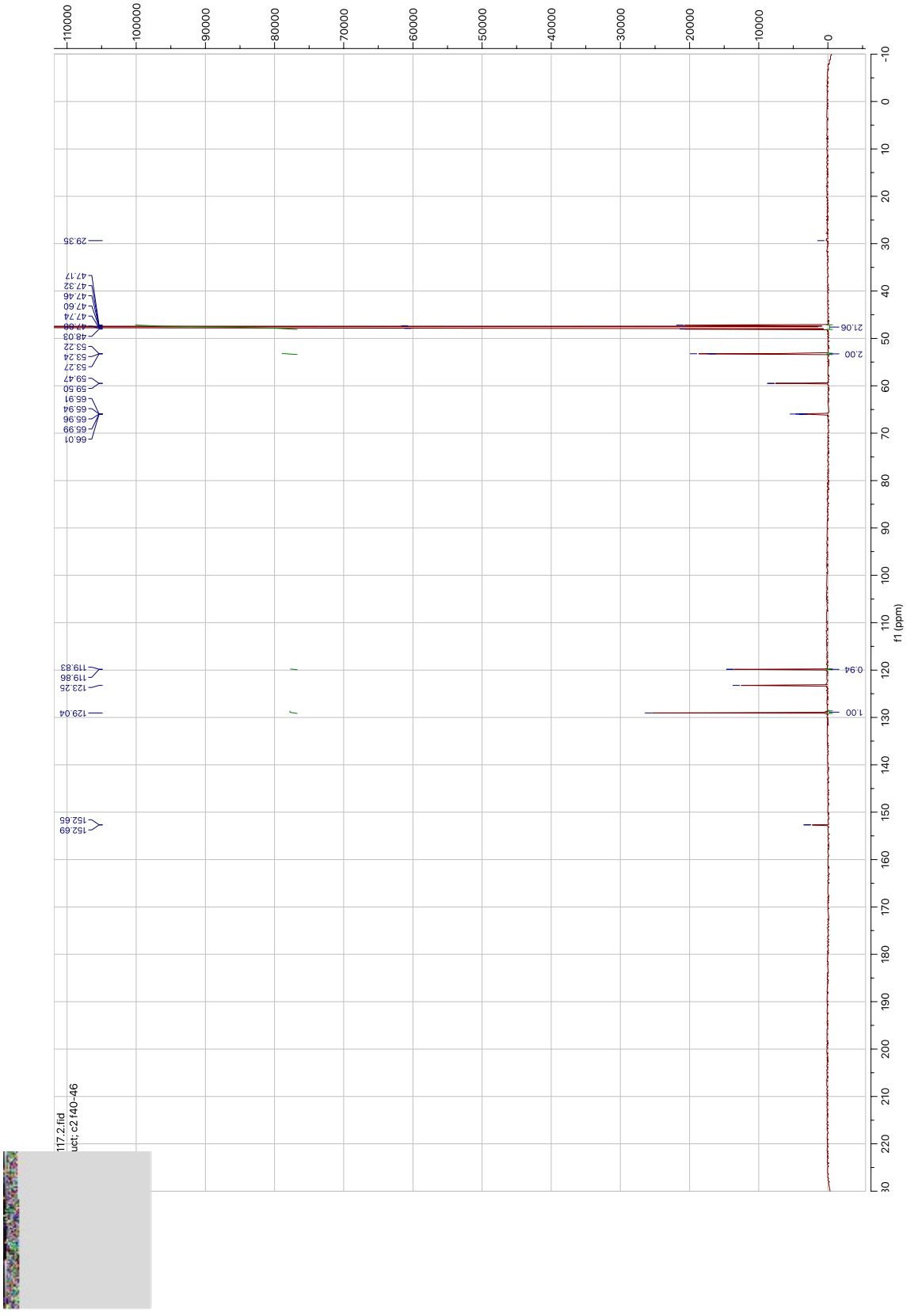

f1 (ppm)

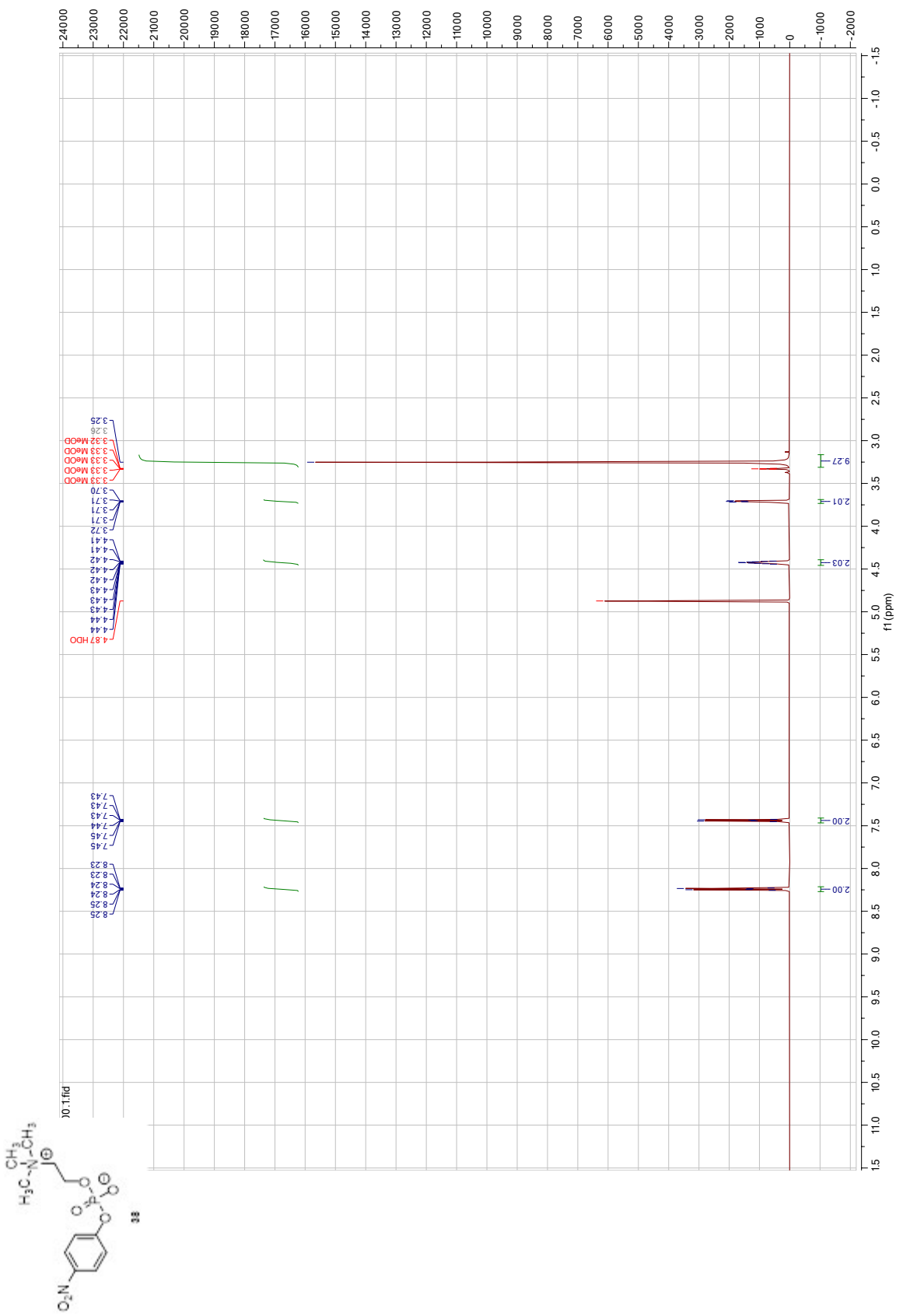

23.09
23.72
24.94
24.95
53.29
53.32
53.34
59.03
59.07
62.47
64.68
64.72
66.05
67.60
67.66
70.48
70.65
70.93
96.32
108.50
109.02
f1 (ppm)

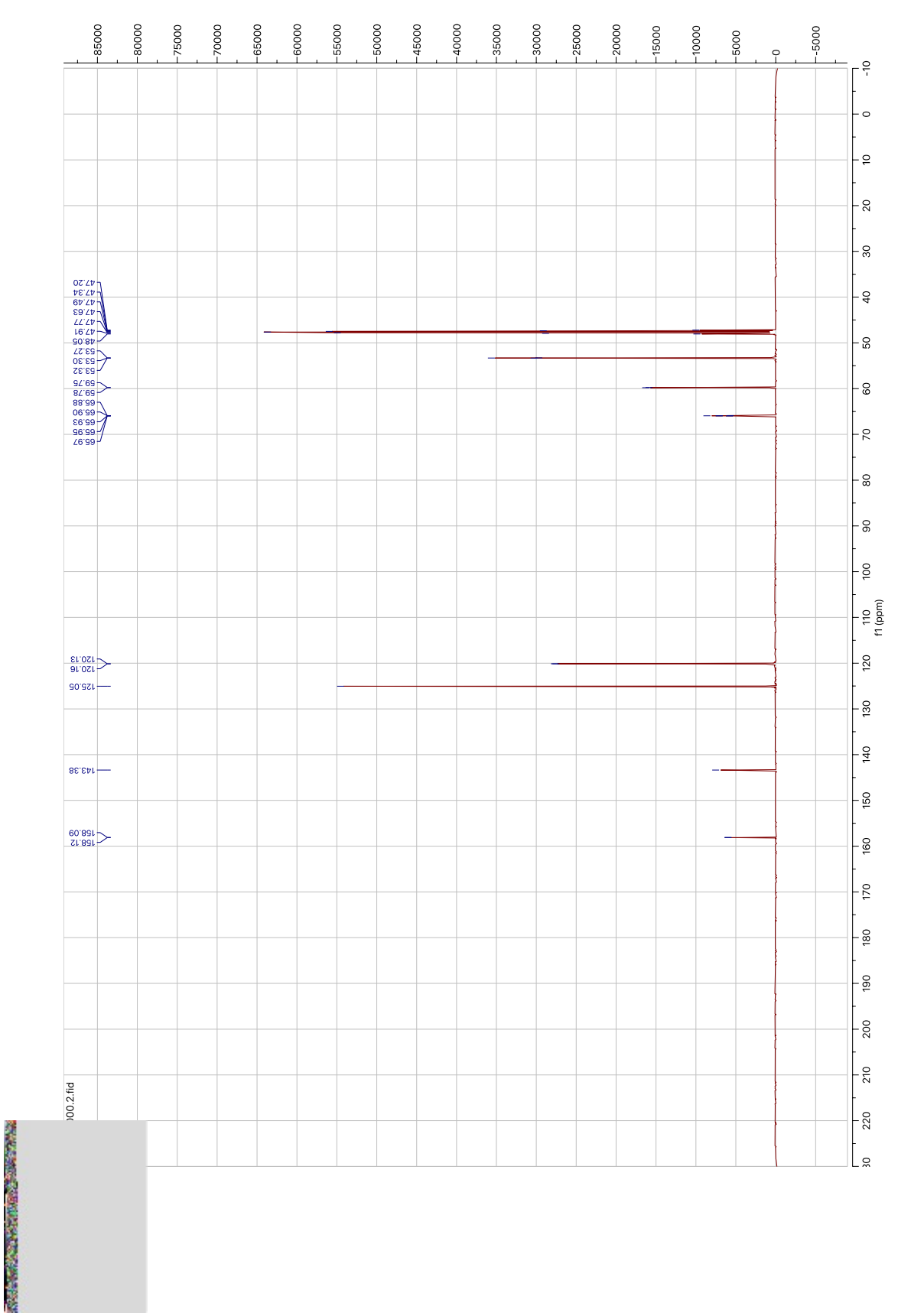

f1 (ppm)


8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
24.27
25.00
25.65
25.89
53.27
53.30
53.32
59.07
59.10
66.76
72.53
77.79
77.82
80.46
80.91
83.90
105.00
111.67
171.26
205.76


0117.1.fid
duct; c2.f40-46
3.07
3.54
3.53
3.52
4.23
4.24
4.25
4.25
4.26
4.26
4.27
4.27
8.41
2.03
2.00
0.97
1.91
1.88
f1 (ppm)
S7


29.35
47.17
47.32
47.46
47.60
47.74
48.03
53.22
53.24
53.27
59.47
59.50
66.91
66.94
66.96
66.99
66.01
119.83
119.86
123.25
129.04
152.65
152.69
21.06
2.00
0.94
1.00
f1 (ppm)


f1 (ppm)
9.27
2.01
2.03
2.00
2.00
4.87 HDO
3.33 MeOD
3.32 MeOD
3.25
3.26
3.70
3.71
3.72
4.41
4.42
4.43
4.44
7.43
7.44
7.45
8.23
8.24
8.25
3B


47.20
47.34
47.49
47.63
47.77
47.91
48.05
53.27
53.30
53.32
59.75
59.78
65.88
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65.96
65.97
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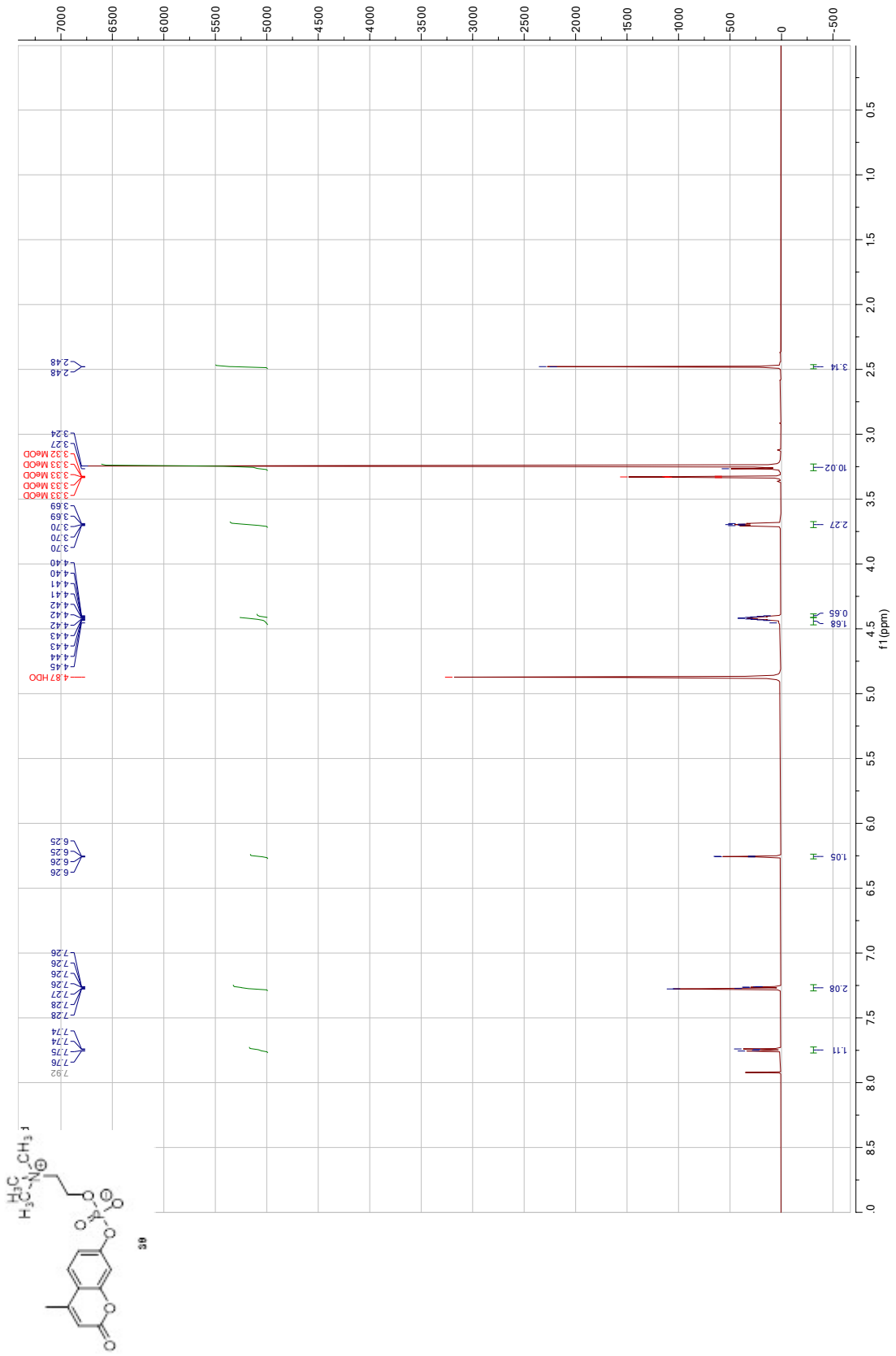
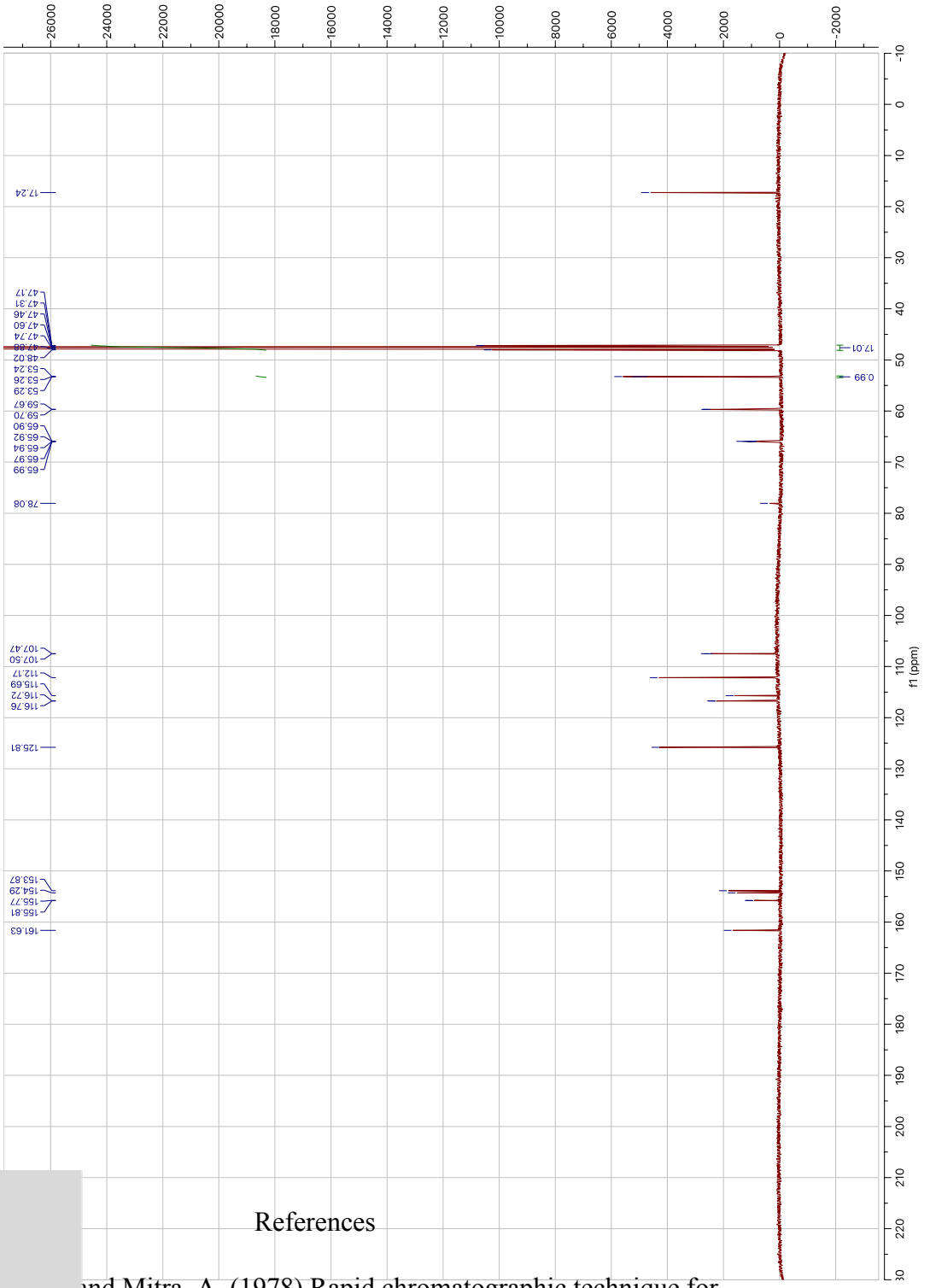
120.16
126.05
143.38
158.09
158.12
f1 (ppm)


f1 (ppm)
4.87 HDO
3.32 MeOD
3.33 MeOD
3.35 MeOD
3.14
10.02
2.27
1.68
0.65
1.05
2.08
1.11



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