

Supporting Information for

Total Synthesis of Sulfolipid-I

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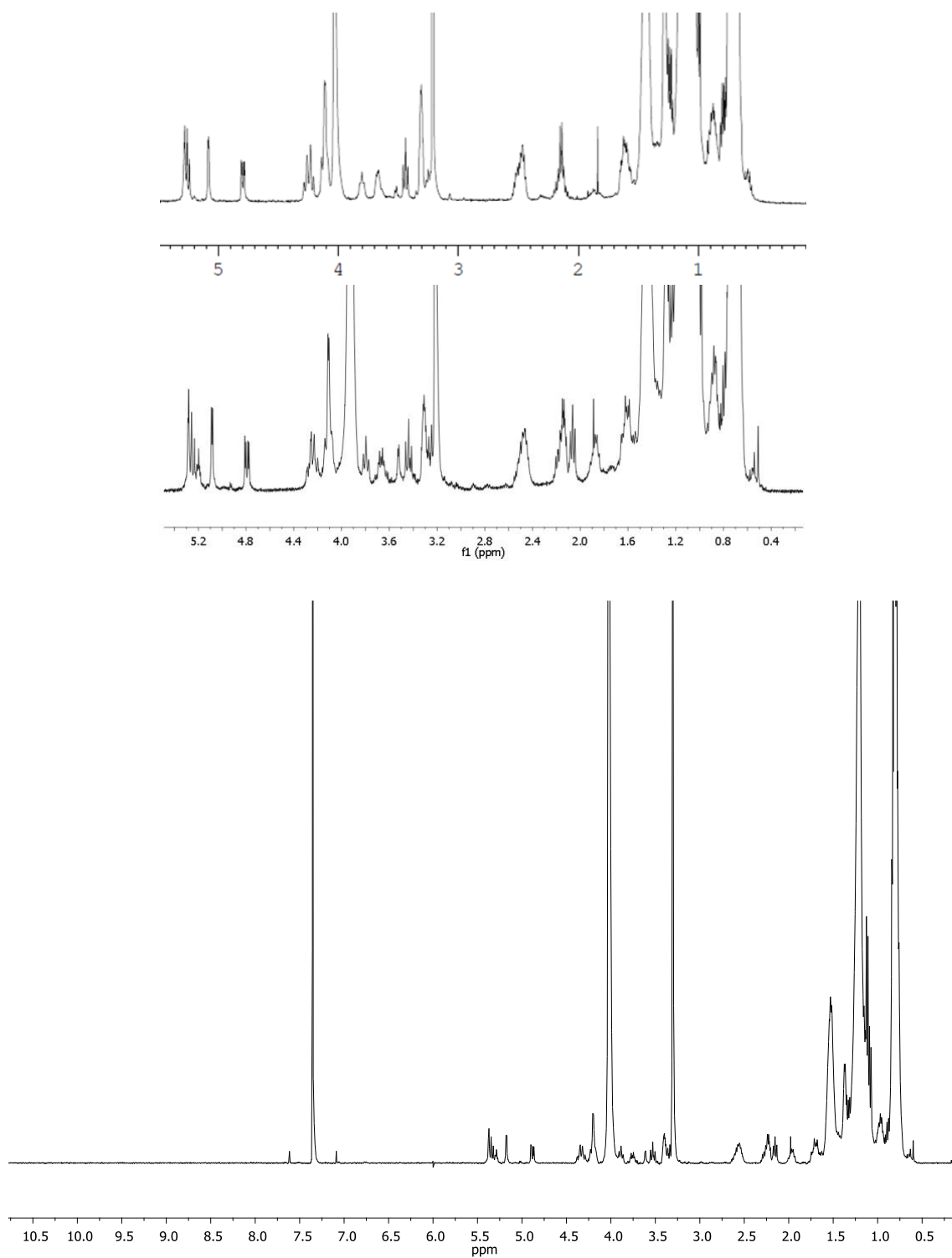


Figure 1SI ^1H -NMR spectra of natural (*up*) and synthetic (*middle and bottom*) sulfolipid-1

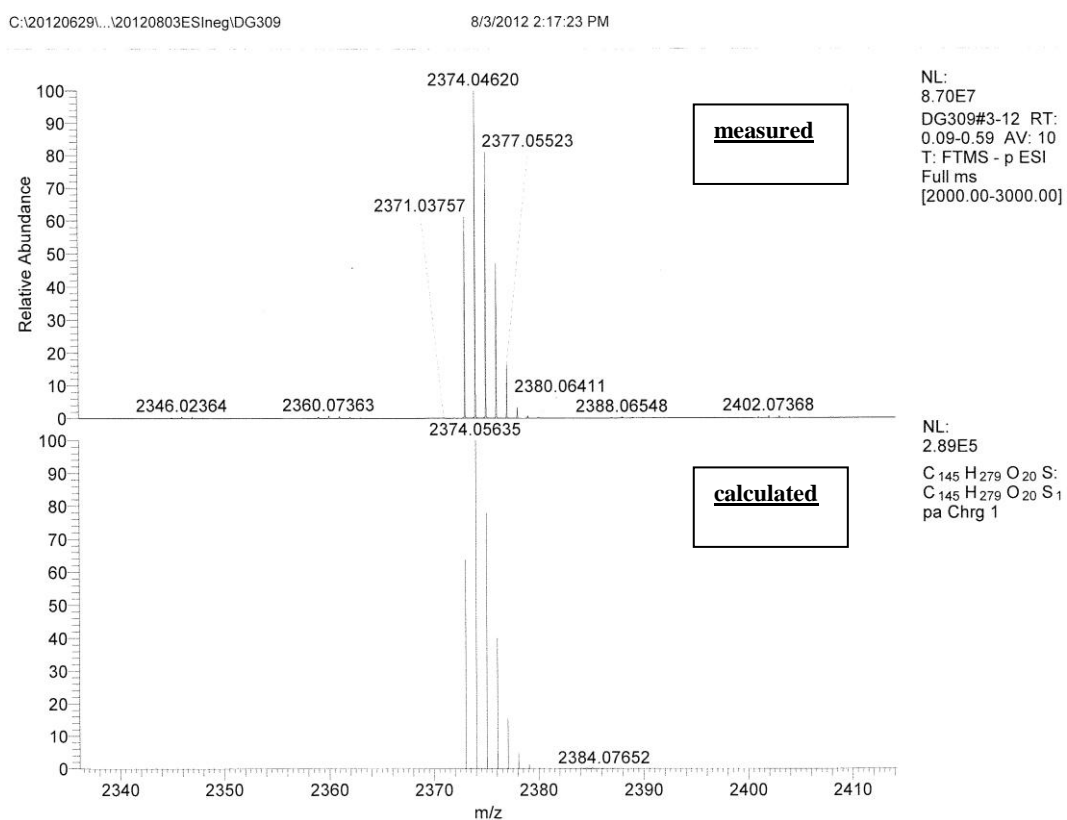
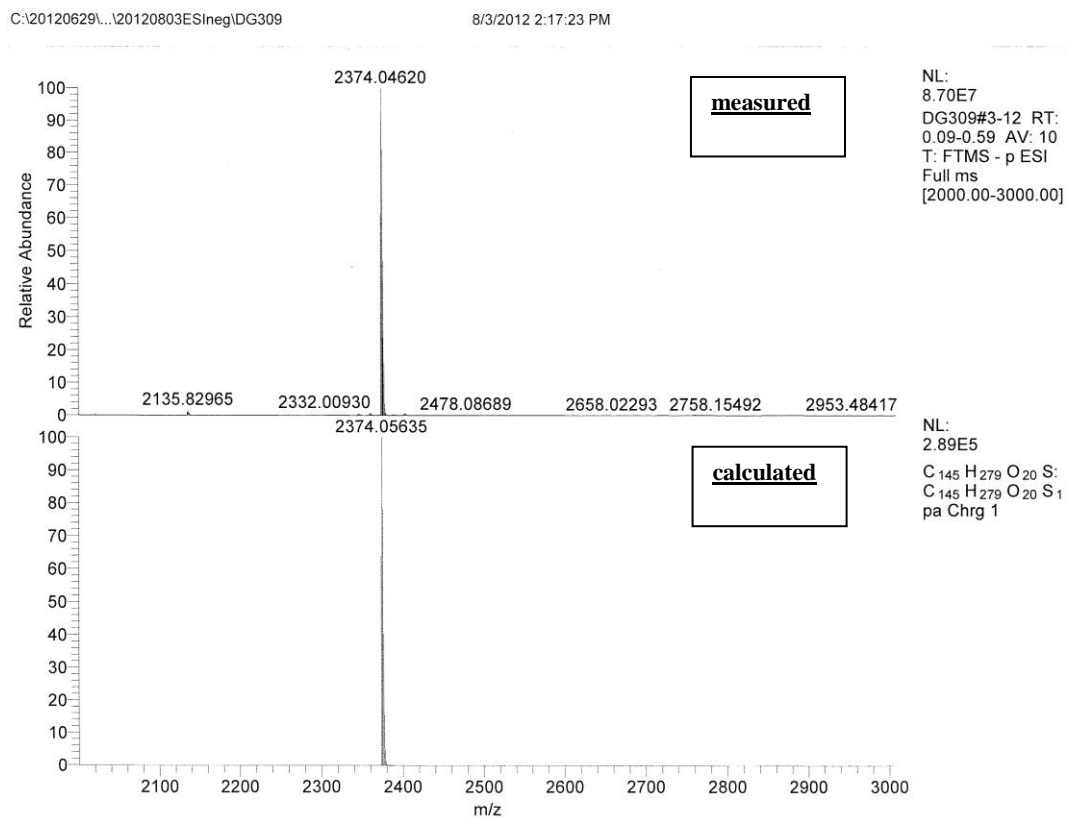


Figure 2SI Mass spectra of synthetic sulfolipid-1

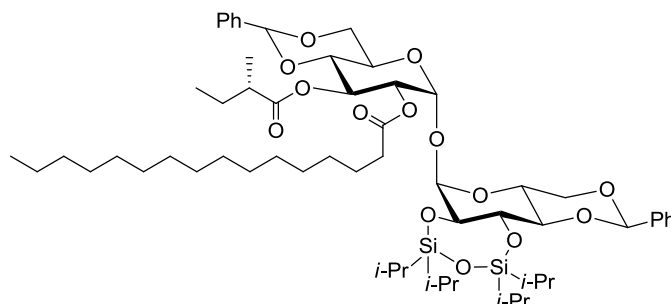
General remarks

All reactions were performed using oven or flame-dried glassware and dry solvents. Solvents were taken from a MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma Aldrich, Acros, TCI Europe, Alfa Aesar, Chempur or Fluorochem and used without any further purification unless noted otherwise. Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline. Fatty acids **3** and **5** were prepared according to a previously reported route.¹

¹H- and ¹³C-NMR spectra were recorded on a Varian AMX400 or a Varian 400-MR (400, 100.59 MHz, respectively) using CDCl₃ or CD₃OD as solvent, unless stated otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CDCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C, CD₃OD: δ 3.31 for ¹H) or using TMS. Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz), and integration. Due to the (multiple) long alkyl chains in some of the compounds we unfortunately could not resolve all individual signals for every carbon atom in the ¹³C NMR spectra. High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL or on a AEI-MS-902 spectrometer.

Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230 – 400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash purification system purchased from Grace Davison Discovery Sciences. TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL)) or a KMnO₄ stain (K₂CO₃ (40 g), KMnO₄ (6 g), H₂O (600 mL) and 10% NaOH (5 mL)).

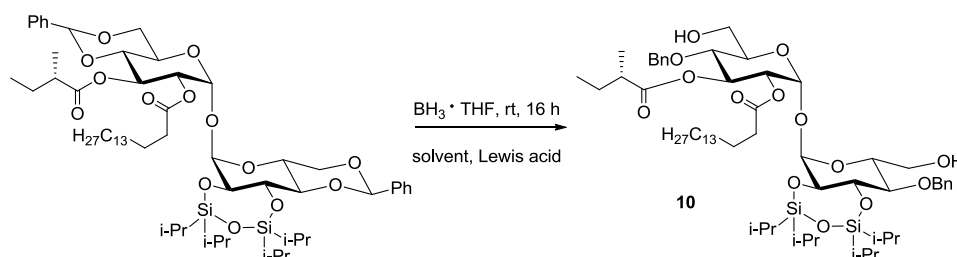
(2*R*,4*aR*,6*R*,7*R*,8*S*,8*aR*)-8-(((*S*)-2-methylbutanoyl)oxy)-2-phenyl-6-(((5*aR*,6*R*,7*aR*,10*R*,11*aR*,11*bS*)-2,2,4,4-tetraisopropyl-10-phenylhexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,4-*f*][1,3,5,2,4]trioxadisilepin-6-yl)oxy)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl palmitate (**7a**):



To (*S*)-methylbutyric acid (1.2 eq, 24 mg, 0.24 mmol) in benzene (3 mL) was added Et₃N (2.2 eq, 44 mg, 0.44 mmol) and 2,4,6-trichlorobenzoyl chloride (1.2 eq, 58 mg, 0.24 mmol). The mixture was stirred for 1 h and subsequently **6** (1 eq, dissolved in 1 mL benzene) and DMAP (1.3 eq, 32 mg, 0.26 mmol) were added, upon which the mixture turned into a white suspension. After 48 h the suspension was quenched with a sat. aq. solution of NaHCO₃ (4 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried, filtered and all volatiles were evaporated. Purification using column chromatography (pentane/EtOAc, 20:1) afforded **7a** as a colorless oil with traces of an inseparable impurity (161 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.39 (m, 4H), 7.39 – 7.30 (m, 6H), 5.69 (t, *J* = 9.8, 1H), 5.54 (s, 1H), 5.50 (s, 1H), 5.40 (d, *J* = 3.8, 1H), 5.15 (d, *J* = 4.1, 1H), 5.04 (dd, *J* = 9.9, 3.9, 1H), 4.34 (td, *J* = 10.0, 4.9, 1H), 4.27 – 4.19 (m, 2H), 4.15 (dd, *J* = 10.1, 4.7, 1H), 3.93 (dd, *J* = 8.4, 4.2, 1H), 3.85 (td, *J* = 10.0, 4.7, 1H), 3.78 – 3.66 (m, 3H), 3.53 (t, *J* = 9.3, 1H), 2.41 – 2.25 (m, 3H), 1.72 – 1.53 (m, 3H), 1.47 – 1.38 (m, 1H), 1.34 – 1.00 (m, 55H), 0.90 (t, *J* = 6.8, 3H), 0.86 (t, *J* = 7.4, 3H); HRMS-(ESI⁺) calculated for C₅₉H₉₅O₁₄Si₂ [M + H]⁺ 1083.6260 Da, found 1083.6251 Da.

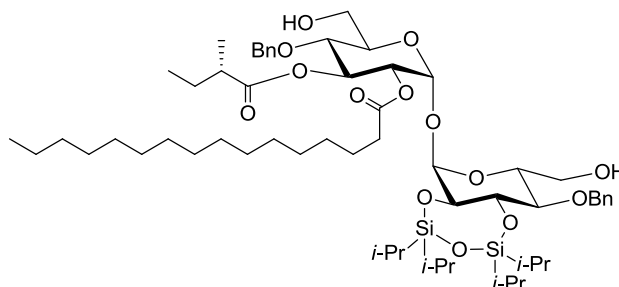
Table 1SI. Optimization of the regioselective reductive ring-opening



entry ^a	solvent	lewis acid (eq)	eq. BH ₃ ·THF	yield ^b (%)
1	THF	CoCl ₂ (5)	6	0 ^c
2	DCM	Cu(OTf) ₂ (0.25)	10	31
3	DCM	TMSOTf (0.3)	4	16
4	DCM	TMSOTf (0.3)	12	59

^a Reactions were performed at 0.018 mmol scale. ^b Yield of the isolated product. ^c No conversion

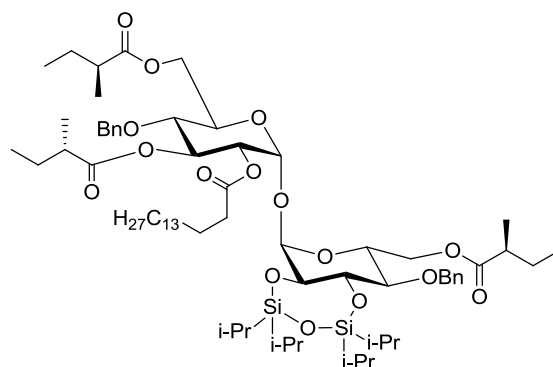
(2*R*,3*R*,4*S*,5*R*,6*R*)-5-(benzyloxy)-2-(((5*aR*,6*R*,8*R*,9*R*,9*aS*)-9-(benzyloxy)-8-(hydroxymethyl)-2,2,4,4-tetraisopropyltetrahydro-5*aH*-pyrano[3,4-*f*][1,3,5,2,4]trioxadisilepin-6-yl)oxy)-6-(hydroxymethyl)-4-(((*S*)-2-methylbutanoyl)oxy)tetrahydro-2*H*-pyran-3-yl palmitate (10**):**



To a solution of **7a** (20 mg, 0.018 mmol, stripped three times with toluene) in DCM (1 mL) under argon atmosphere, was added $\text{BH}_3 \cdot \text{THF}$ complex (12 eq, 0.221 mL, 1 M solution in THF) and after 5 min, freshly distilled (N_2 -atmosphere) TMSOTf (0.3 eq, 0.8 μL). After stirring for 16 h, the reaction was quenched with Et_3N (0.1 mL) and MeOH (2 mL). The mixture was concentrated and the crude material was purified using column chromatography (pentane/EtOAc, 2:1) affording **10** as a colorless oil (11.3 mg, 59% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.22 (m, 10H), 5.64 (t, J = 9.7, 1H), 5.27 (d, J = 3.7, 1H), 5.04 (d, J = 3.9, 1H), 4.97 (d, J = 11.2, 1H), 4.87 (dd, J = 10.2, 3.7, 1H), 4.70 – 4.57 (m, 3H), 4.26 (t, J = 8.7, 1H), 4.16 (d, J = 10.0, 1H), 3.82 – 3.70 (m, 4H), 3.69 – 3.57 (m, 3H), 3.45 (t, J = 8.9, 1H), 2.29 – 2.22 (m, 3H), 1.75 – 1.34 (m, 4H), 1.28 – 0.94 (m, 55H), 0.88 (t, J = 7.0, 3H), 0.86 (t, J = 7.5, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ 175.05, 173.34, 138.18, 137.98, 128.35, 128.28, 128.19, 128.14, 127.78, 127.47, 127.16, 127.13, 94.01, 91.45, 77.65, 77.47, 75.49, 75.19, 74.58, 74.07, 71.35, 71.10, 71.05, 70.88, 61.70, 61.13, 41.05, 33.93, 31.90, 29.68, 29.66, 29.64, 29.60, 29.55, 29.45, 29.34, 29.22, 29.12, 26.59, 24.50, 22.67, 17.49, 17.44, 17.34, 17.29, 17.26, 17.23, 17.15, 17.13, 17.11, 16.21, 14.09, 12.81, 12.68, 12.22, 12.00, 11.59; **HRMS**-(ESI+) calculated for $\text{C}_{59}\text{H}_{98}\text{O}_{14}\text{Si}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 1109.6387 Da, found 1109.6380 Da.

(2*R*,3*R*,4*S*,5*R*,6*R*)-5-(benzyloxy)-2-(((5*aR*,6*R*,8*R*,9*R*,9*aS*)-9-(benzyloxy)-2,2,4,4-tetraisopropyl-8-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-5*aH*-pyrano[3,4-*f*][1,3,5,2,4]trioxadisilepin-6-yl)oxy)-4-(((*S*)-2-methylbutanoyl)oxy)-6-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-2*H*-pyran-3-yl palmitate (11**):**

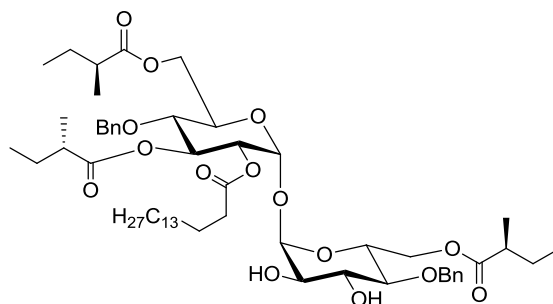


To a solution of diol **10** (128 mg, 0.12 mmol) in DCM (4 mL) was added EDC·HCl (2.2 eq., 49.6 mg, 0.26 mmol), DMAP (4.1 eq, 59 mg, 0.48 mmol) and (*S*)-methylbutyric acid (2.15 eq, 27.6 μL , 0.25 mmol) at rt. The mixture was stirred for 16 h and was then diluted with 10 mL EtOAc. The organic layer was washed with sat. aq. NaHCO_3 (10 mL), brine (10 mL) and dried over MgSO_4 . After filtration, all volatiles were evaporated and the crude product was

purified using flash column chromatography (silica, pentane/EtOAc 20:1) to afford **11** as a colorless oil (127 mg, 86% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.17 (m, 10H), 5.66 (t, *J* = 9.4, 1H), 5.21 (d, *J* = 3.6, 1H), 5.08 (d, *J* = 3.8, 1H), 4.99 (AB-6, *J* = 11.0, 1H), 4.96 (dd, *J* = 10.2, 3.7, 1H), 4.63 (AB-6', *J* = 11.1, 1H), 4.57 (AB-6, *J* = 11.0, 1H), 4.51 (AB-6', *J* = 11.1, 1H), 4.37 – 4.14 (m, 6H), 3.87 – 3.81 (m, 1H), 3.79 (dd, *J* = 9.0, 3.8, 1H), 3.65 (t, *J* = 9.5, 1H), 3.36 (dd, *J* = 10.1, 8.5, 1H), 2.48 – 2.35 (m, 2H), 2.32 – 2.21 (m, 3H), 1.77 – 1.34 (m, 6H), 1.32 – 1.01 (m, 63H), 0.99 – 0.83 (m, 12H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.36, 176.29, 174.91, 172.85, 137.95, 137.58, 128.31, 128.20, 127.90, 127.72, 127.54, 127.04, 93.22, 90.82, 78.41, 77.46, 76.35, 75.32, 74.48, 74.16, 71.53, 70.54, 69.01, 68.64, 62.77, 62.20, 41.03, 40.95, 40.79, 33.98, 31.91, 29.68, 29.67, 29.65, 29.64, 29.58, 29.42, 29.34, 29.19, 29.12, 26.76, 26.56, 24.54, 22.67, 17.49, 17.43, 17.38, 17.29, 17.18, 17.14, 17.12, 16.51, 16.45, 16.13, 14.10, 12.83, 12.74, 12.32, 12.05, 11.58, 11.57, 11.52; **HRMS**-(ESI+) calculated for C₆₉H₁₁₆O₁₆Si₂ [M + H]⁺ 1255.7724 Da, found 1255.7718 Da.

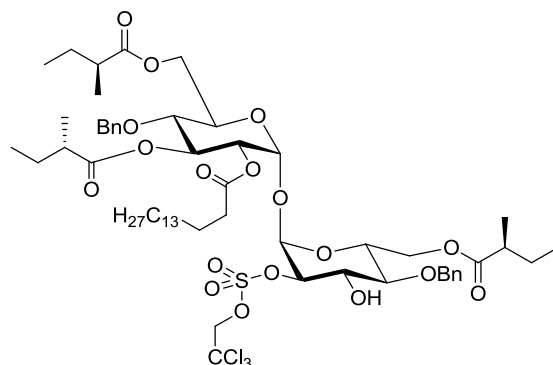
(2*R*,3*R*,4*S*,5*R*,6*R*)-5-(benzyloxy)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-5-(benzyloxy)-3,4-dihydroxy-6-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-4-(((*S*)-2-methylbutanoyl)oxy)-6-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-2H-pyran-3-yl palmitate (15**):**



To compound **11** (30 mg, 0.024 mmol) in THF (0.5 mL) was added TBAF (40 eq, 0.96 mL, 1 M solution in THF, acidified to pH 6.5 with TFA). The mixture was heated to 40 °C for 24 h, and diluted with EtOAc (2 mL) afterwards. The organic layer was washed with water (2 mL) and then dried over MgSO₄. After filtration, the solvent was evaporated and the product was purified using flash column chromatography (pentane/EtOAc 3:2) to afford **15** (22 mg, 91% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.20 (m, 10H), 5.62 (t, *J* = 9.6 1H), 5.24 (d, *J* = 3.8, 1H), 5.11 (d, *J* = 3.7, 1H), 4.97 (dd, *J* = 10.3, 3.8, 1H), 4.82 (AB-6, *J* = 11.3, 1H), 4.66 (AB-6, *J* = 11.3, 1H), 4.62 (AB-6', *J* = 10.8, 1H), 4.52 (AB-6', *J* = 10.8, 1H), 4.38 (d, *J* = 10.2, 1H), 4.26 – 4.16 (m, 4H), 4.01 (t, *J* = 9.2, 1H), 3.81 (dt, *J* = 9.7, 3.7, 1H), 3.65 (t, *J* = 9.5, 1H), 3.61 – 3.54 (m, 1H), 3.37 (t, *J* = 9.7, 1H), 2.49 – 2.35 (m, 2H), 2.34 – 2.21 (m, 3H), 1.77 – 1.37 (m, 8H), 1.28 – 1.19 (m, 24H), 1.17 (d, *J* = 7.0, 3H), 1.13 (d, *J* = 7.0, 3H), 1.10 (d, *J* = 7.0, 3H), 0.95 – 0.84 (m, 12H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.30, 176.23, 175.50, 172.73, 137.94, 137.04, 128.53, 128.50, 128.07, 127.96, 127.86, 127.84, 127.79, 93.53, 91.36, 77.69, 76.29, 74.77, 74.66, 74.41, 71.95, 71.37, 70.30, 69.63, 69.14, 62.50, 62.13, 41.01, 40.97, 40.88, 33.93, 31.92, 29.69, 29.68, 29.65, 29.60, 29.45, 29.35, 29.24, 29.16, 26.77, 26.72, 26.59, 24.60, 22.68, 16.57, 16.46, 16.11, 14.11, 11.62, 11.57; **HRMS**-(ESI+) calculated for C₅₇H₈₈O₁₅Na [M + Na]⁺ 1035.6021 Da, found 1035.6024 Da.

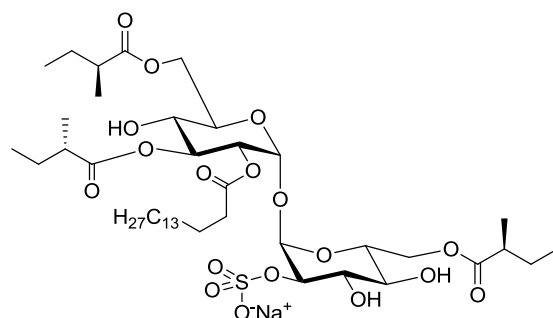
(2*R*,3*R*,4*S*,5*R*,6*R*)-5-(benzyloxy)-2-(((2*R*,3*R*,4*S*,5*S*,6*R*)-5-(benzyloxy)-4-hydroxy-6-(((*S*)-2-methylbutanoyl)oxy)methyl)-3-(((2,2,2-trichloroethoxy)sulfonyl)oxy)tetrahydro-2H-pyran-2-yl)oxy)-4-(((*S*)-2-methylbutanoyl)oxy)-6-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-2H-pyran-3-yl palmitate (16):



To **15** (32 mg, 0.032 mmol) in DCM (1 mL) was added imidazolium salt **13** (2 eq, 29 mg, 0.063 mmol, prepared according to a previously reported procedure).^[1] The mixture was cooled to 0 °C and 1,2-dimethylimidazole (2.5 eq, 7.6 mg, 0.079 mmol) was added as a solution in DCM (0.5 mL) over 4 h. The reaction was allowed to reach rt after which it was stirred for 72 h. The mixture was diluted with DCM (3 mL) and the organic layer was washed with brine. The organic layer was dried over MgSO₄, filtered and all volatiles were evaporated. The product was purified using flash chromatography (pentane/EtOAc 10:1) to afford **16** as a colorless oil (19 mg, 49% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.20 (m, 10H), 5.60 (t, *J* = 9.4, 1H), 5.40 (d, *J* = 3.7, 1H), 5.21 (d, *J* = 3.8, 1H), 5.00 (dd, *J* = 10.3, 3.8, 1H), 4.87, 4.76 (AB-CH₂CCl₃, *J* = 10.8, 2H), 4.71 (d, *J* = 4.6, 2H), 4.59, 4.54 (AB system, *J* = 10.8, 2H), 4.50 (dd, *J* = 10.0, 3.7, 1H), 4.37 (ddd, *J* = 16.0, 12.6, 2.8, 2H), 4.30 – 4.20 (m, 3H), 4.17 (dt, *J* = 10.1, 2.7, 1H), 3.95 – 3.89 (m, 1H), 3.69 (t, *J* = 9.7, 1H), 3.45 (t, *J* = 7.2, 1H), 2.52 – 2.36 (m, 3H), 2.35 – 2.20 (m, 2H), 1.80 – 1.35 (m, 8H), 1.27 – 1.22 (m, 24H), 1.17 (d, *J* = 7.0, 3H), 1.15 (d, *J* = 7.0, 3H), 1.09 (d, *J* = 7.0, 3H), 0.96 – 0.81 (m, 12H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.20 (2 x C), 175.42, 172.57, 137.25, 137.13, 128.82, 128.44, 128.42, 127.94, 127.91, 127.71, 92.66, 92.45, 92.00, 81.02, 81.00, 79.90, 78.41, 75.89, 75.27, 74.35, 71.05, 70.67, 70.20, 69.54, 69.27, 61.82, 40.93, 40.90, 40.87, 33.91, 31.91, 29.69, 29.68, 29.66, 29.65, 29.60, 29.44, 29.35, 29.25, 29.18, 26.79, 26.56, 24.58, 22.68, 16.54, 16.51, 16.06, 14.12, 11.63, 11.60; **HRMS**-(ESI⁺) calculated for C₉₁H₁₄₆Cl₃O₁₇S [M + H]⁺ 1647.9346 Da, found 1647.9355 Da.

sodium (2*R*,3*R*,4*S*,5*S*,6*R*)-4,5-dihydroxy-2-(((2*R*,3*R*,4*S*,5*R*,6*R*)-5-hydroxy-4-(((*S*)-2-methylbutanoyl)oxy)-6-(((*S*)-2-methylbutanoyl)oxy)methyl)-3-(palmitoyloxy)tetrahydro-2H-pyran-2-yl)oxy)-6-(((*S*)-2-methylbutanoyl)oxy)methyl)tetrahydro-2H-pyran-3-yl sulfate (17):

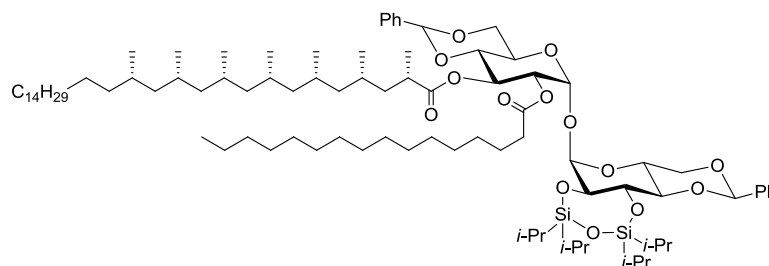


To compound **16** (16 mg, 0.013 mmol) was added DCM (0.5 mL) and MeOH (1 mL). Ammonium formate (20 eq, 16.5 mg, 0.26 mmol) was added and after everything had dissolved, Pd(OH)₂ (1 eq, 9 mg, 20% weight on carbon) was added. The mixture was placed under a H₂ atmosphere (1 bar, balloon) using three vacuum/N₂ cycles

followed by four vacuum/H₂ cycles. After 16 h, TLC showed complete conversion of the starting material and the mixture was filtered over Celite and concentrated. ¹H NMR spectroscopy showed complete removal of the TCE group but incomplete deprotection of the benzyl ethers. The crude product was redissolved in DCM (0.5 mL) and MeOH (1 mL). Pd(OH)₂ (1.2 eq, 11 mg) was added and the reaction was placed under a H₂ atmosphere (1 bar, balloon) and left for 48 h. After this period, TLC indicated the appearance of one major product, which was purified using column chromatography (8% MeOH in DCM). The ammonium salt was flushed over a DOWEX Na⁺ ion-exchange column (DCM/MeOH 9:1) to give **17** as a viscous colorless oil (6.0 mg, 49%).

¹H NMR (400 MHz, CDCl₃/MeOD 9:1) δ 5.33 (d, *J* = 4.0, 1H), 5.31 (t, *J* = 9.7, 1H), 5.13 (d, *J* = 3.4, 1H), 4.86 (dd, *J* = 10.3, 3.5, 1H), 4.31 (m, 2H), 4.25 – 4.11 (m, 4H), 3.83 (t, *J* = 9.3, 1H), 3.76 – 3.69 (m, 1H), 3.49 (t, *J* = 9.8, 1H), 3.32 (t, *J* = 9.6, 1H), 2.41 – 2.25 (m, 3H), 2.23 – 2.15 (m, 2H), 1.66 – 1.31 (m, 8H), 1.24 – 1.13 (m, 24H), 1.07 (d, *J* = 7.0, 3H), 1.06 (d, *J* = 7.0, 3H), 1.04 (d, *J* = 7.0, 3H), 0.87 – 0.76 (m, 12H); **HRMS**-(ESI-) calculated for C₄₃H₇₅O₁₈SNa₂ [M + Na]⁺ 957.4470 Da, found 957.4468 Da.

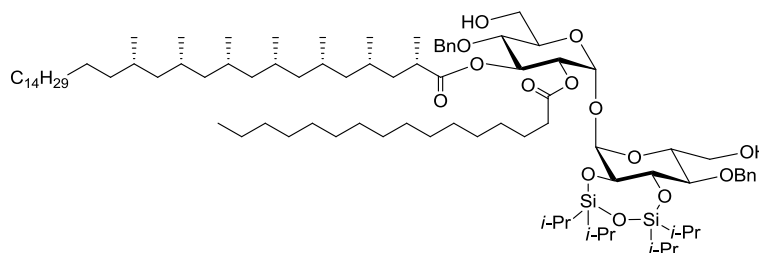
(2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,14*S*)-(2*R*,4*aR*,6*R*,7*R*,8*S*,8*aR*)-7-(palmitoyloxy)-2-phenyl-6-(((5*aR*,6*R*,7*aR*,10*R*,11*aR*,11*bS*)-2,2,4,4-tetraisopropyl-10-phenylhexahydro [1,3]dioxino[4',5':5,6]pyrano[3,4-f][1,3,5,2,4]trioxadisilepin-6-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-8-yl 2,4,6,8,10,12,14-heptamethyltriacontanoate (7**):**



To carboxylic acid **3** (1.05 eq, 40 mg, 0.073 mmol)^[2] in benzene (1 mL) was added Et₃N (2.2 eq, 15.4 mg, 0.152 mmol) and 2,4,6-trichlorobenzoyl chloride (1.1 eq, 5.2 mg, 0.021 mmol). The mixture was stirred for 1 h, and **6** (1 eq, dissolved in 0.4 mL benzene) and DMAP (1.1 eq, 9.3 mg, 0.076 mmol) were added, upon which the mixture turned into a white suspension. After 48 h, the suspension was quenched with sat. aq. NaHCO₃ (4 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried, filtered and all volatiles were evaporated. Purification using column chromatography (pentane/EtOAc 20:1) afforded **7** as a colorless oil (81 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.46 (dd, *J* = 6.6, 3.0, 2H), 7.40 (dd, *J* = 6.7, 3.0, 2H), 7.36 – 7.31 (m, 6H), 5.67 (t, *J* = 9.8, 1H), 5.54 (s, 1H), 5.47 (s, 1H), 5.39 (d, *J* = 3.8, 1H), 5.13 (d, *J* = 4.1, 1H), 5.03 (dd, *J* = 10.0, 3.8, 1H), 4.32 (td, *J* = 9.9, 5.0, 1H), 4.27 – 4.18 (m, 2H), 4.17 – 4.11 (m, 1H), 3.91 (dd, *J* = 8.5, 4.1, 1H), 3.82 (td, *J* = 10.0, 4.6, 1H), 3.78 – 3.61 (m, 3H), 3.52 (t, *J* = 9.2, 1H), 2.63 – 2.52 (m, 1H), 2.41 – 2.24 (m, 2H), 1.83 – 1.72 (m, 1H), 1.65 – 1.45 (m, 8H), 1.37 – 1.03 (m, 93H), 0.92 – 0.75 (m, 27H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.22, 173.15, 137.60, 137.06, 128.80, 128.56, 127.98, 127.93, 126.11, 125.90, 101.42, 101.09, 94.44, 91.92, 81.10, 79.43, 75.24, 73.40, 70.88, 68.73, 68.71, 68.38, 62.82, 62.51, 45.63, 45.42, 45.04, 44.95, 39.83, 37.55, 36.44, 33.90, 31.93, 30.06, 29.99, 29.76, 29.70, 29.68, 29.66, 29.56, 29.48, 29.38, 29.36, 29.15, 29.11, 27.82, 27.48, 27.40, 27.30, 27.02, 26.88, 26.55, 24.61, 22.69, 21.26, 21.13, 21.05, 20.66, 20.60, 20.56, 18.52, 17.45, 17.40, 17.32, 17.21, 17.15, 17.12, 17.00, 14.12, 12.89, 12.65, 12.29, 11.70; **HRMS**-(ESI+) calculated for C₉₁H₁₅₉O₁₄Si₂ [M + H]⁺ 1532.1268 Da, found 1532.1263 Da.

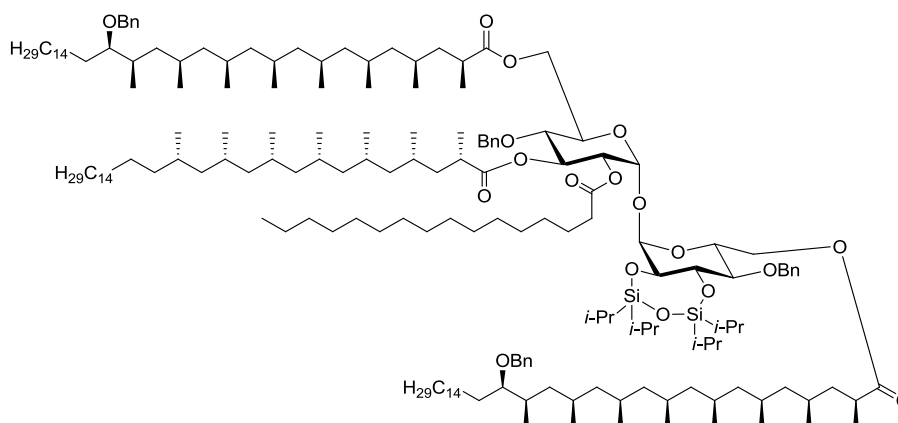
(2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,14*S*)-(2*R*,3*R*,4*S*,5*R*,6*R*)-3-(benzyloxy)-6-(((5*aR*,6*R*,8*R*,9*R*,9*aS*)-(benzyloxy)-8-(hydroxymethyl)-2,2,4,4-tetraisopropyltetrahydro-5*aH*-pyrano[3,4-*f*][1,3,5,2,4]trioxadisilepin-6-yl)oxy)-2-(hydroxymethyl)-5-(palmitoyloxy)tetrahydro-2*H*-pyran-4-yl 2,4,6,8,10,12,14-heptamethyltriacontanoate (8):



To a solution of **7** (48 mg, 0.031 mmol, stripped three times with toluene) in DCM (1 mL) under argon atmosphere, was added BH₃•THF complex (12 eq, 0.38 mL, 1 M solution in THF) and after 5 minutes, freshly distilled TMSOTf (0.3 eq, 3.40 µL). After stirring for 16 h, the reaction was quenched with Et₃N (0.1 mL) and MeOH (2 mL). The mixture was concentrated and the crude material was purified using column chromatography (pentane/EtOAc, 3:1) affording **8** as a colorless oil (28 mg, 59%).

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.17 (m, 10H), 5.64 (t, *J* = 9.6, 1H), 5.28 (d, *J* = 3.6, 1H), 5.04 (d, *J* = 3.8, 1H), 4.97 (AB-6, *J* = 11.2, 1H), 4.86 (dd, *J* = 12.1, 5.6, 1H), 4.67 (AB-6', *J* = 11.4, 1H), 4.66 (AB-6, *J* = 11.2, 1H), 4.61 (AB-6', *J* = 11.6, 1H), 4.27 (t, *J* = 8.8, 1H), 4.15 (d, *J* = 10.0, 1H), 3.82 – 3.69 (m, 4H), 3.69 – 3.56 (m, 3H), 3.45 (t, *J* = 9.0, 1H), 2.48 (q, *J* = 14.5, 6.9, 1H), 2.24 (td, *J* = 7.1, 1.8, 2H), 1.79 – 1.65 (m, 2H), 1.63 – 1.46 (m, 8H), 1.34 – 1.12 (m, 78H), 1.11 – 0.95 (m, 14H), 0.91 – 0.76 (m, 27H); **¹³C NMR** (101 MHz, CDCl₃) δ 175.33, 173.24, 138.17, 137.95, 130.26, 128.38, 128.20, 128.17, 128.10, 127.82, 127.47, 127.10, 93.92, 91.28, 77.58, 77.42, 77.20, 75.60, 75.21, 74.57, 73.99, 71.29, 71.09, 70.78, 61.70, 61.23, 45.46, 45.39, 45.33, 45.02, 44.80, 41.58, 41.35, 40.48, 37.91, 37.88, 37.05, 36.43, 33.91, 32.12, 31.92, 30.06, 29.99, 29.76, 29.70, 29.67, 29.65, 29.52, 29.37, 29.36, 29.28, 29.20, 27.82, 27.48, 27.45, 27.41, 27.29, 27.17, 26.87, 24.91, 24.48, 22.69, 21.31, 21.20, 21.14, 21.01, 20.79, 20.60, 18.47, 17.77, 17.50, 17.45, 17.36, 17.26, 17.17, 17.14, 14.12, 14.05, 12.82, 12.70, 12.24, 12.02; **HRMS**-(ESI+) calculated for C₉₁H₁₆₂O₁₄Si₂Na [M + Na]⁺ 1558.1401 Da, found 1558.1395 Da.

(2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-((5*aR*,6*R*,8*R*,9*R*,9*aS*)-9-(benzyloxy)-6-((2*R*,3*R*,4*S*,5*R*,6*R*)-5-(benzyloxy)-6-(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-(benzyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontanoyloxy)methyl)-4-((2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,14*S*)-2,4,6,8,10,12,14-heptamethyltriacontanoyloxy)-3-(palmitoyloxy)tetrahydro-2H-pyran-2-yloxy)-2,2,4,4-tetraisopropyltetrahydro-5*aH*-pyrano[3,4-*f*][1,3,5,2,4]trioxadisilepin-8-yl)methyl 17-(benzyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontanoate (9):

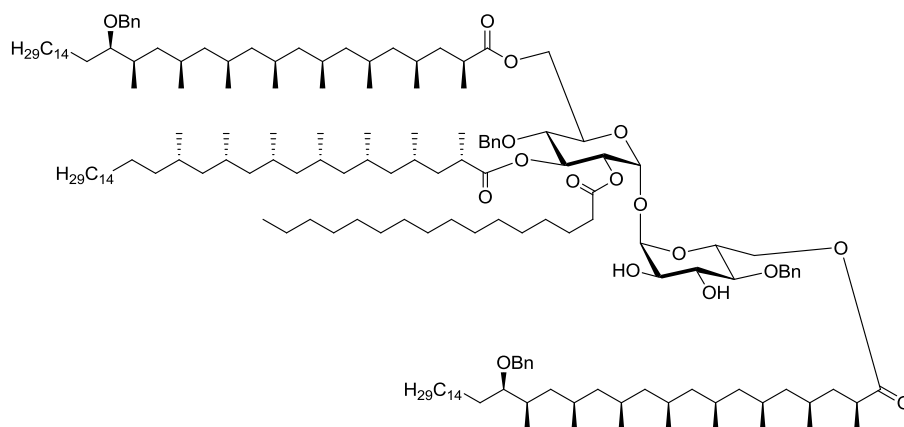


To a solution of diol **8** (27 mg, 0.018 mmol) in DCM (1 mL) was added EDC•HCl (2.1 eq, 7.1 mg, 0.037 mmol),

DMAP (4.1 eq, 8.8 mg, 0.072 mmol) and acid **5** (2.1 eq, 25.8 mg, 0.037 mmol)^[1] at rt. The mixture was stirred for 16 h, after which TLC showed incomplete conversion. Additional EDC·HCl (6 eq) and DMAP (4 eq) were added and stirring was continued for 6 h. The reaction was diluted with EtOAc (5 mL), and the organic layer was washed with a sat. aq. NaHCO₃ solution (10 mL), brine (10 mL) and dried over MgSO₄. After filtration, all volatiles were evaporated and the crude product was purified using flash column chromatography (silica, pentane/EtOAc 40:1) to afford **9** as a colorless oil (36 mg, 71% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.17 (m, 20H), 5.65 (t, *J* = 9.6, 1H), 5.23 (d, *J* = 3.6, 1H), 5.06 (d, *J* = 3.7, 1H), 4.99 (d, *J* = 10.8, 1H), 4.93 (dd, *J* = 10.2, 3.6, 1H), 4.63 (d, *J* = 11.1, 1H), 4.54 (d, *J* = 10.9, 1H), 4.51 (s, 4H), 4.50 (d, *J* = 11.0, 1H), 4.33 – 4.24 (m, 5H), 4.15 (dd, *J* = 11.5, 1.6, 1H), 3.83 – 3.74 (m, 2H), 3.65 (t, *J* = 9.5, 1H), 3.37 (dd, *J* = 10.0, 8.5, 1H), 3.26 – 3.19 (m, 2H), 2.66 – 2.57 (m, 2H), 2.48 (q, *J* = 14.7, 6.9, 1H), 2.22 (t, *J* = 7.8, 1H), 1.85 – 1.76 (m, 4H), 1.75 – 1.66 (m, 2H), 1.65 – 1.38 (m, 24H), 1.35 – 1.12 (m, 153H), 1.11 – 0.94 (m, 18H), 0.93 – 0.73 (m, 81H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.70, 176.63, 175.20, 172.74, 139.35, 138.00, 137.57, 128.30, 128.19, 127.85, 127.70, 127.57, 127.51, 127.23, 126.97, 93.15, 90.62, 82.84, 78.38, 76.37, 75.38, 74.47, 74.05, 71.81, 71.42, 70.64, 69.07, 68.59, 62.61, 62.22, 52.62, 45.48, 45.38, 45.34, 45.27, 45.22, 45.22, 45.18, 45.02, 44.92, 44.89, 44.75, 40.68, 40.62, 40.54, 40.41, 38.73, 37.24, 37.12, 37.03, 36.44, 33.97, 31.93, 30.76, 30.07, 29.99, 29.89, 29.76, 29.70, 29.68, 29.66, 29.52, 29.38, 29.38, 29.36, 29.26, 29.20, 28.12, 28.10, 27.87, 27.79, 27.65, 27.53, 27.47, 27.44, 27.40, 27.36, 27.34, 27.14, 27.10, 26.88, 26.20, 24.56, 22.69, 21.58, 21.48, 21.41, 21.31, 21.19, 21.17, 21.14, 20.96, 20.82, 20.81, 20.71, 20.64, 20.60, 18.47, 18.38, 17.75, 17.50, 17.45, 17.41, 17.30, 17.23, 17.17, 15.69, 14.12, 12.84, 12.77, 12.33, 12.06; **HRMS**-(APPI+) calculated for C₁₈₅H₃₃₀O₁₈Si₂Na [M + Na]⁺ 2921.4405 Da, found 2921.4186 Da.

(2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-((2*R*,3*R*,4*S*,5*R*,6*R*)-3-(benzyloxy)-6-((2*R*,3*R*,4*R*,5*S*,6*R*)-5-(benzyloxy)-6-(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-(benzyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontanoyloxy)methyl)-3,4-dihydroxytetrahydro-2H-pyran-2-yloxy)-4-((2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,14*S*)-2,4,6,8,10,12,14-heptamethyltriacontanoyloxy)-5-(palmitoyloxy)tetrahydro-2H-pyran-2-yl)methyl 17-(benzyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontanoate (12**):**

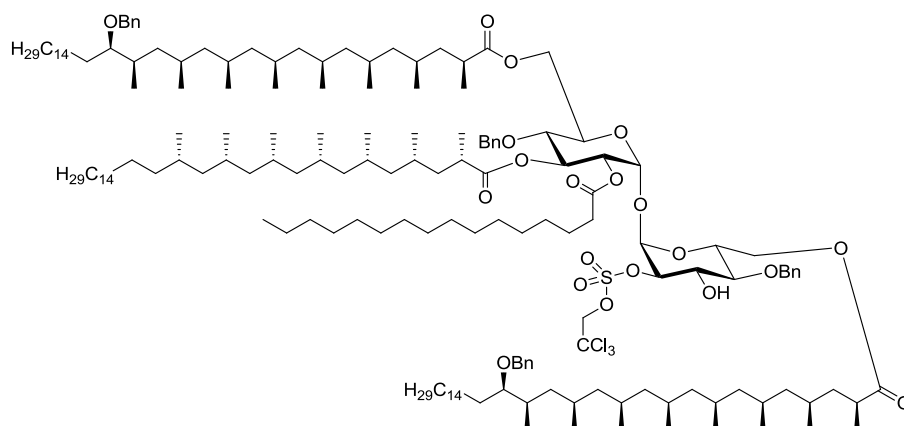


To compound **9** (32 mg, 0.011 mmol) in THF (0.5 mL), was added TBAF (40 eq, 0.44 mL, 1 M solution in THF, acidified to pH = 6.5 with TFA). The mixture was heated to 40 °C for 24 h and then EtOAc (2 mL) was added. The organic layer was washed with water (2 mL) and subsequently dried over MgSO₄. After filtration, the solvent was evaporated, and the product was purified using flash column chromatography (pentane/EtOAc 5:1) to afford **12** (25 mg, 84% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.20 (m, 20H), 5.61 (t, *J* = 9.7, 1H), 5.25 (d, *J* = 3.3, 1H), 5.10 (d, *J* = 3.4, 1H), 4.96 (dd, *J* = 10.2, 3.5, 1H), 4.82 (d, *J* = 11.2, 1H), 4.70 – 4.59 (m, 2H), 4.53 (d, *J* = 11.0, 1H), 4.51 (s, 4H), 4.36 (d, *J* = 11.5, 1H), 4.25 – 4.17 (m, 4H), 4.01 (t, *J* = 8.9, 1H), 3.82 – 3.76 (m, 1H), 3.66 (t, *J* = 9.5, 1H), 3.61 –

3.51 (m, 1H), 3.40 (t, $J = 9.1$, 1H), 3.26 – 3.18 (m, 2H), 2.69 – 2.55 (m, 3H), 2.51 (q, $J = 13.9$, 7.0, 1H), 2.33 (d, $J = 7.6$, 1H), 2.23 (t, $J = 7.8$, 2H), 1.89 – 1.71 (m, 4H), 1.64 – 1.36 (m, 24H), 1.35 – 1.12 (m, 130H), 1.12 – 0.96 (m, 14H), 0.95 – 0.74 (m, 81H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.65, 176.58, 175.80, 172.59, 139.34, 137.95, 137.05, 128.53, 128.47, 128.19, 128.01, 127.95, 127.82, 127.66, 127.57, 127.24, 93.51, 91.28, 82.84, 77.72, 77.20, 76.37, 74.84, 74.42, 71.98, 71.81, 71.30, 70.36, 69.58, 69.00, 62.44, 62.20, 45.39, 45.31, 45.26, 45.22, 45.17, 45.02, 44.89, 44.70, 40.74, 40.63, 40.54, 37.26, 37.16, 37.03, 36.44, 33.94, 32.88, 31.92, 31.90, 30.76, 30.07, 29.99, 29.89, 29.76, 29.70, 29.68, 29.66, 29.56, 29.51, 29.42, 29.36, 29.33, 29.30, 29.24, 28.14, 28.10, 27.88, 27.80, 27.66, 27.54, 27.47, 27.46, 27.37, 27.36, 27.21, 27.15, 27.12, 26.88, 26.55, 26.20, 25.86, 24.63, 22.69, 21.58, 21.49, 21.42, 21.32, 21.25, 21.19, 21.15, 21.13, 20.85, 20.82, 20.80, 20.71, 20.64, 20.60, 18.44, 18.35, 17.67, 17.07, 17.05, 15.69, 14.12, 14.10, 13.05, 13.03; HRMS-(ESI+) calculated for $\text{C}_{173}\text{H}_{304}\text{O}_{17}\text{Na}_2$ [$\text{M} + 2\text{Na}$] $^+$ 2700.2719 Da, found 2700.2637 Da.

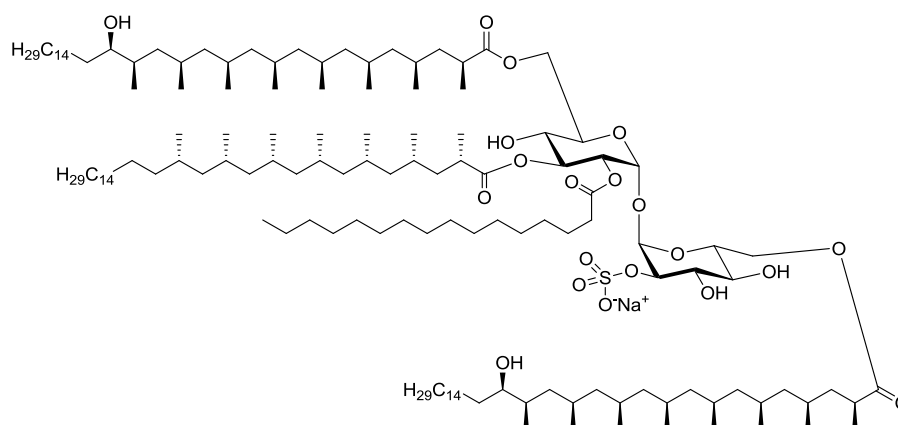
Compound 14:



To **12** (24 mg, 9.7 μmol) in DCM (1 mL) was added imidazolium salt **13** (2 eq, 8.3 mg, 0.018 mmol, prepared according to a previously reported procedure).^[2] The mixture was cooled to 0 $^{\circ}\text{C}$ and 1,2-dimethylimidazole (2.8 eq, 2.4 mg, 0.025 mmol) was added as a solution in DCM (0.5 mL) over 4 h. The reaction was allowed to reach rt, after which it was stirred for 24 h, and more imidazolium (0.5 eq) salt was added. After an additional 48 h the mixture was diluted with DCM (3 mL) and the organic layer was washed with brine (2 mL). The organic layer was dried over MgSO_4 , filtered and all volatiles were evaporated. The product was purified using flash chromatography (pentane/EtOAc 20:1) to afford **14** as a colorless oil (15 mg, 58% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.17 (m, 20H), 5.59 (t, $J = 9.7$, 1H), 5.39 (d, $J = 3.1$, 1H), 5.22 (d, $J = 3.3$, 1H), 4.98 (dd, $J = 10.2$, 3.2, 1H), 4.86, 4.75 (AB- CH_2CCl_3 , $J = 10.8$, 2H), 4.70 (s, 2H), 4.59, 4.54 (AB system, $J = 10.7$, 2H), 4.52 – 4.48 (m, 5H), 4.42 – 4.20 (m, 5H), 4.17 (d, $J = 10.2$, 1H), 3.91 (d, $J = 7.3$, 1H), 3.70 (t, $J = 9.6$, 1H), 3.47 (t, $J = 9.3$, 1H), 3.24 – 3.19 (m, 2H), 2.69 – 2.60 (m, 2H), 2.52 – 2.45 (m, 2H), 2.25 – 2.18 (m, 2H), 1.85 – 1.73 (m, 4H), 1.65 – 1.35 (m, 24H), 1.35 – 1.13 (m, 130H), 1.08 – 0.97 (m, 14H), 0.93 – 0.74 (m, 81H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.54, 176.50, 175.68, 172.43, 139.35, 137.28, 137.17, 128.81, 128.40, 128.19, 127.86, 127.57, 127.24, 92.64, 92.48, 92.02, 82.84, 81.03, 79.91, 78.43, 75.94, 75.30, 74.04, 71.81, 70.99, 70.67, 70.30, 69.35, 69.23, 61.88, 61.80, 45.38, 45.33, 45.30, 45.26, 45.22, 45.17, 45.01, 44.92, 44.83, 44.65, 40.67, 40.62, 40.54, 37.23, 37.18, 36.99, 36.44, 33.93, 32.88, 31.93, 30.76, 30.07, 29.99, 29.95, 29.90, 29.85, 29.82, 29.76, 29.70, 29.68, 29.66, 29.51, 29.36, 29.34, 29.32, 29.27, 28.14, 27.87, 27.80, 27.64, 27.53, 27.47, 27.35, 27.23, 27.12, 26.88, 26.20, 24.62, 22.69, 21.58, 21.48, 21.41, 21.33, 21.27, 21.17, 20.83, 20.81, 20.72, 20.66, 20.61, 18.49, 18.39, 17.58, 15.69, 14.12; HRMS-(ESI-) calculated for $\text{C}_{175}\text{H}_{305}\text{Cl}_3\text{O}_{20}\text{S}$ [$\text{M} - \text{H}$] $^-$ 2866.1556 Da, found 2866.1323 Da.

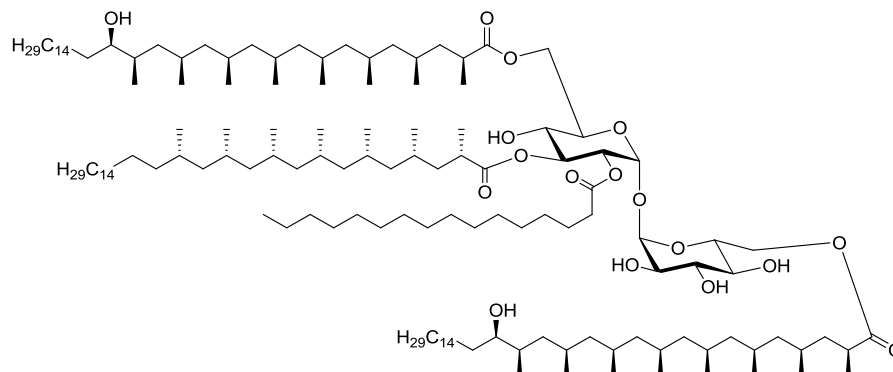
Sulfolipid-1 (1):



To a solution of **14** (13 mg, 4.5 μ mol) in DCM/MeOH (1:1, 1.2 mL) was added ammonium formate (15 eq, 4.3 mg, 0.07 mmol). After everything had dissolved, Pd(OH)₂ (1.2 eq, 3.8 mg, 20% weight on carbon) was added. The mixture was placed under a H₂ atmosphere (1 bar, balloon) using three vacuum/N₂ cycles followed by four vacuum/H₂ cycles. After 16 h, TLC showed complete conversion of the starting material and the mixture was filtered over Celite and concentrated. ¹H NMR spectroscopy showed complete removal of the TCE group but incomplete deprotection of the benzyl ethers. The crude product was redissolved in DCM (0.5 mL) and MeOH (1 mL). Pd(OH)₂ (1.2 eq, 11 mg) was added and the reaction was placed under a H₂ atmosphere (1 bar, balloon) and left for 48 h. After this period, TLC indicated the formation of multiple products. ¹H NMR still indicated the presence of benzyl ethers. The procedure was repeated, first with 250 psi of hydrogen for 3 h (little change) and then at 500 psi for 3 h in a Parr bomb. After this, ¹H NMR showed complete removal of all protecting groups, however with substantial amounts of side products. The crude product was flushed over a DOWEX Na⁺ ion-exchange column (DCM/MeOH 9:1) and further purified by flash column chromatography (silica, first DCM/MeOH 99:1, then DCM/MeOH 97:3). **1** was obtained as a glass-like colorless oil (1.6 mg, 15%).

¹H NMR (400 MHz, CDCl₃/MeOD - 4:1) δ 5.28 (d, J = 3.8, 1H), 5.25 (t, J = 9.7, 1H), 5.07 (d, J = 3.5, 1H), 4.77 (dd, J = 10.2, 3.5, 1H), 4.27, 4.21 (AB system, J = 12.2, 2H), 4.14 – 4.06 (m, 4H), 3.78 (t, J = 9.5, 1H), 3.68 – 3.63 (m, 1H), 3.44 (t, J = 10.1, 1H), 3.33 – 3.27 (m, 2H), 3.24 (t, J = 9.2, 1H), 2.55 – 2.42 (m, 3H), 2.20 – 2.10 (m, 3H), 1.64 – 1.55 (m, 4H), 1.50 – 1.35 (m, 20H), 1.33 – 0.95 (m, 147H), 0.92 – 0.63 (m, 81H); **HRMS**-(ESI⁻) calculated for C₁₄₅H₂₇₉O₂₀S [M – Na]⁻ 2374.0564 Da, found 2374.0462 Da.

Desulfated side-product, isolated after the conversion of 14 to 1.



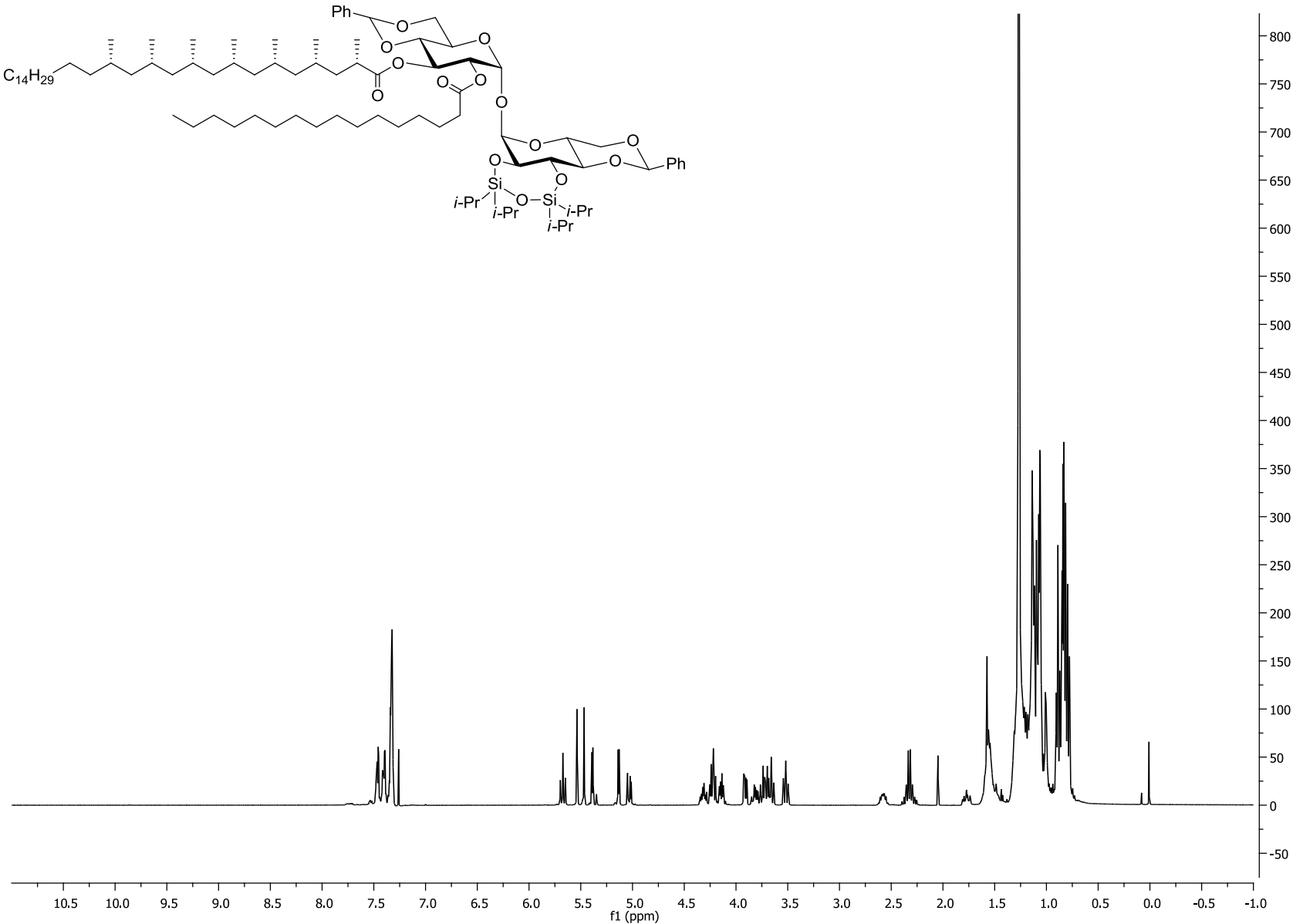
¹H NMR (400 MHz, CDCl₃) 5.39 (t, J = 9.4, 1H), 5.28 (d, J = 2.6, 1H), 5.12 (d, J = 2.7, 1H), 4.95 (dd, J = 10.0, 2.7, 1H), 4.49 (dd, J = 12.4, 4.0, 1H), 4.40 (dd, J = 12.8, 4.1, 1H), 4.34 – 4.28 (m, 1H), 4.17 – 4.06 (m, 2H), 3.92 (t, J = 8.7, 1H), 3.78 – 3.71 (m, 1H), 3.63 – 3.56 (m, 1H), 3.54 – 3.44 (m, 3H), 3.36 – 3.23 (m, 3H), 2.68 – 2.55 (m, 3H),

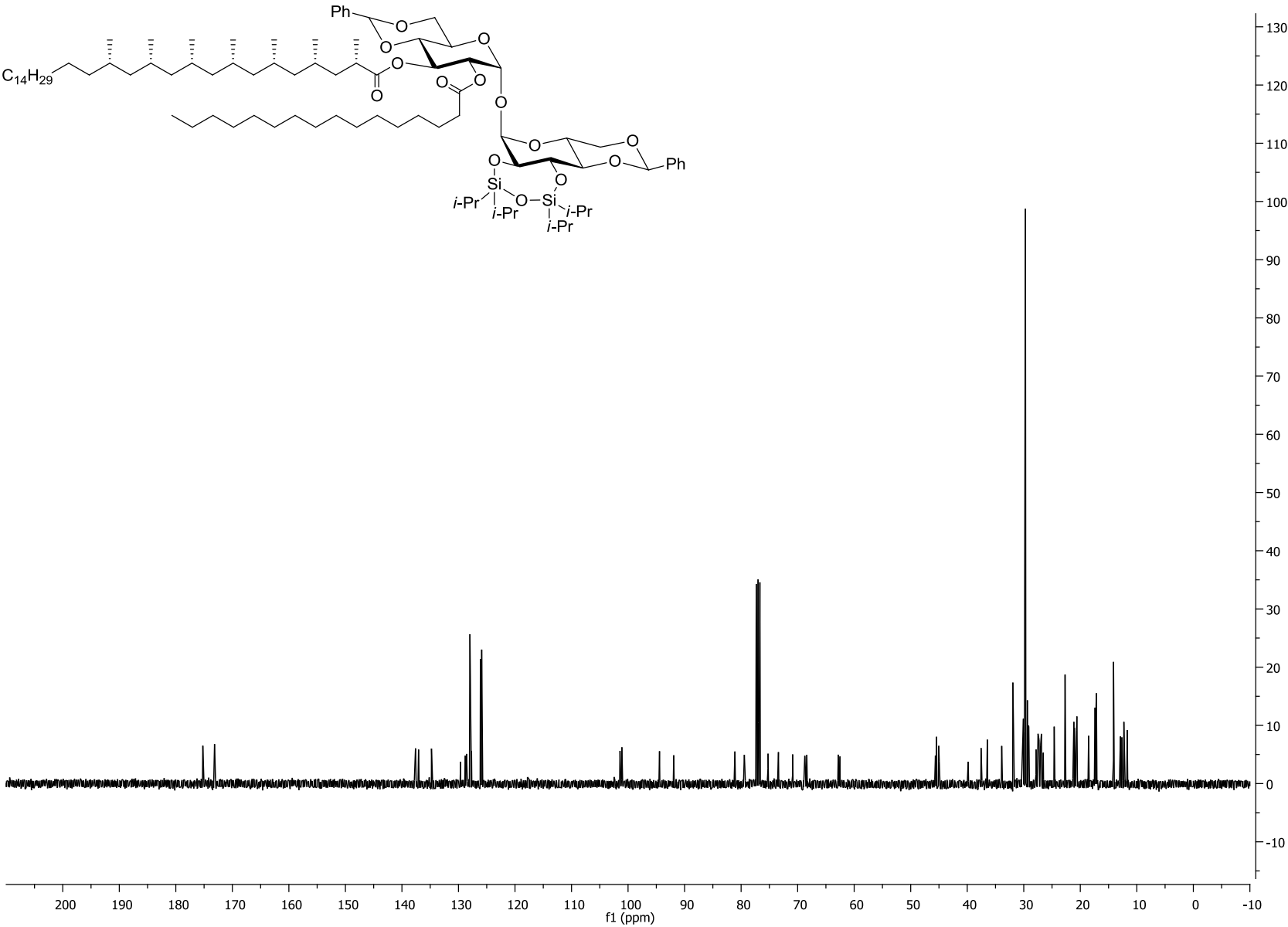
2.29 – 2.18 (m, 3H), 1.82 – 1.70 (m, 4H), 1.68 – 1.38 (m, 22H), 1.35 – 0.97 (m, 145H), 0.93 – 0.77 (m, 81H);

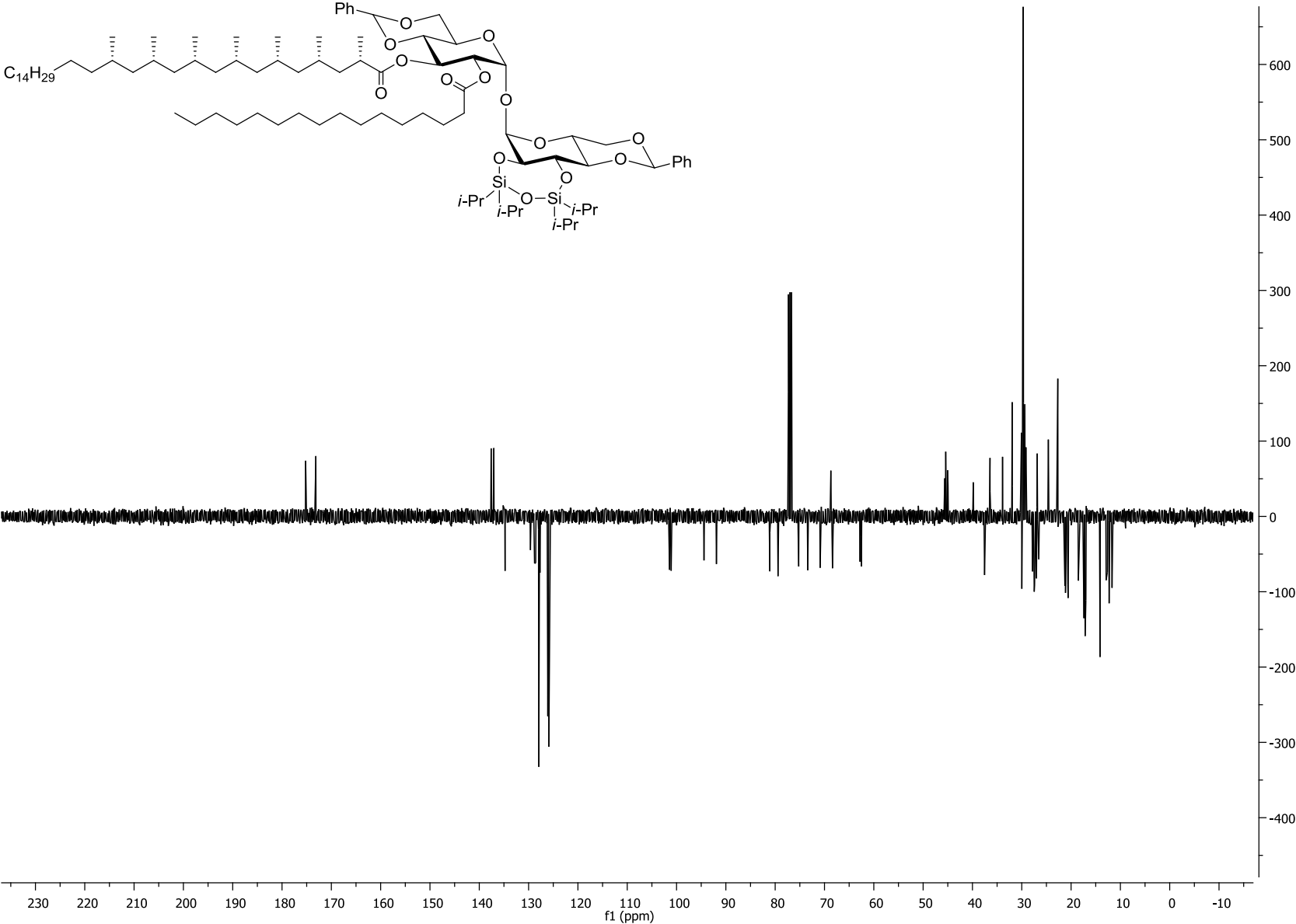
HRMS-(ESI+) calculated for C₁₄₅H₂₈₁O₁₇ [M + H]⁺ 2296.1152 Da, found 2296.0999 Da.

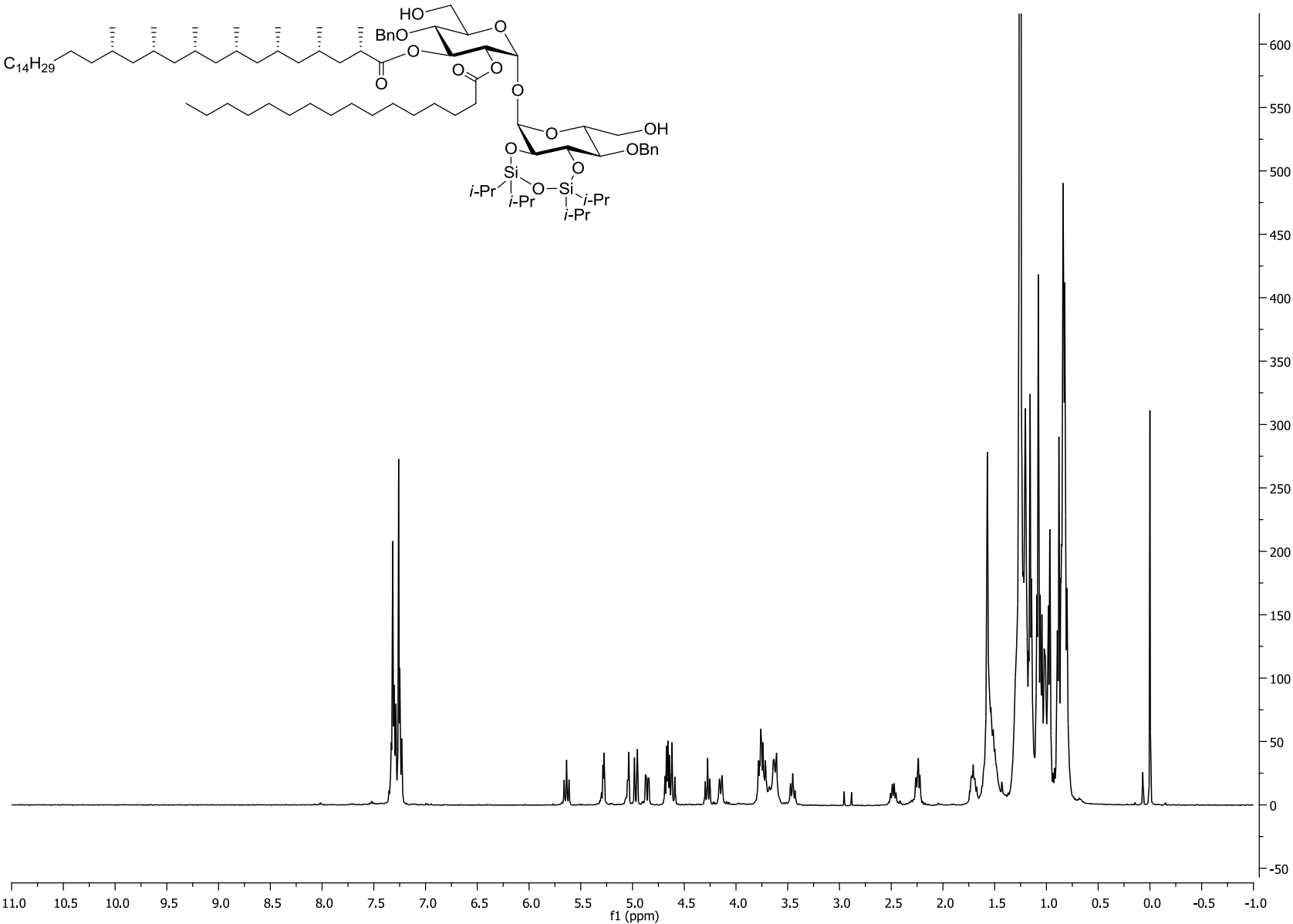
[1] D. Geerdink, B. ter Horst, M. Lepore, L. Mori, G. Puzo, A. K. H. Hirsch, M. Gilleron, G. de Libero and A. J. Minnaard, *Chem. Sci.* 2013, 709-716

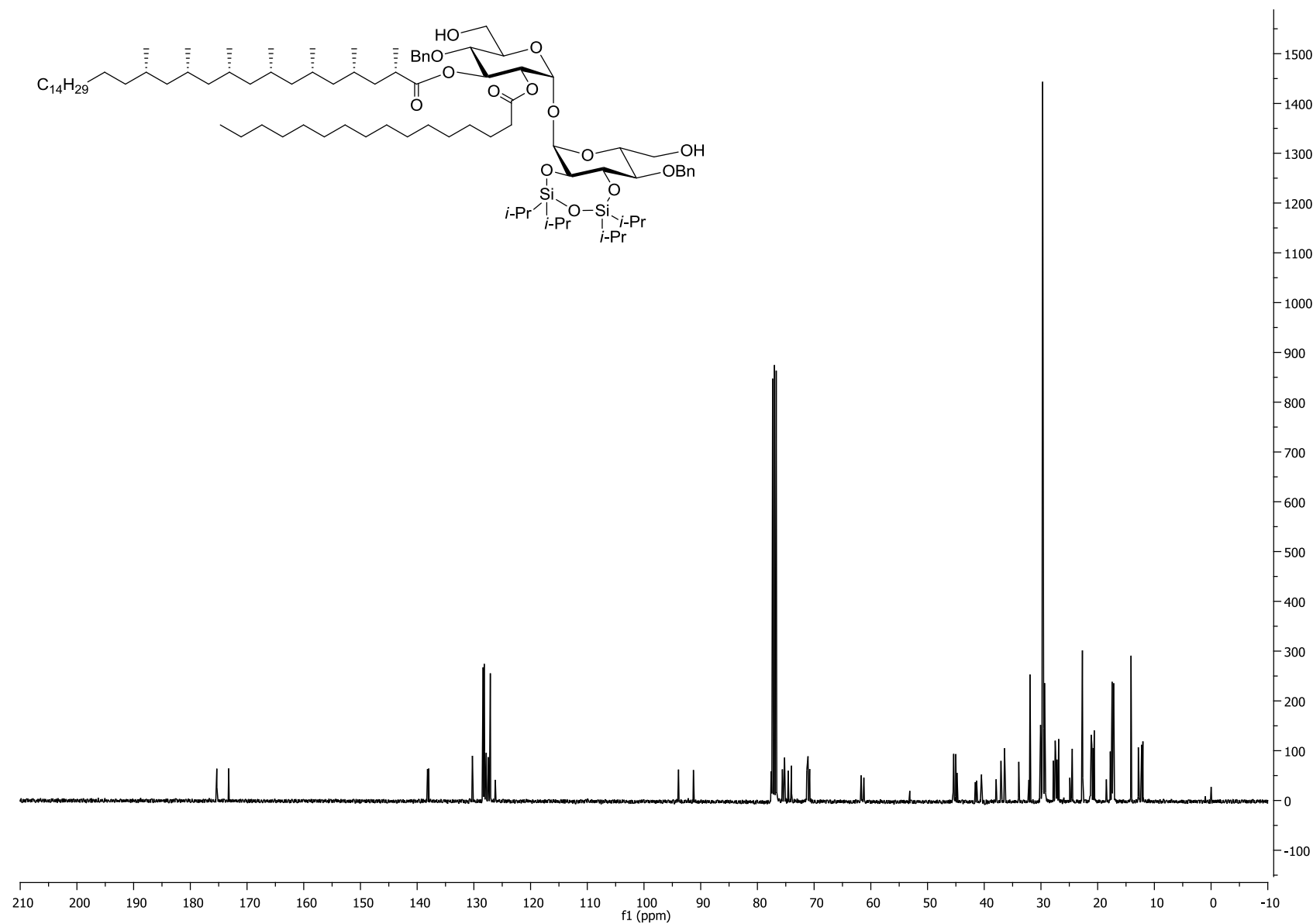
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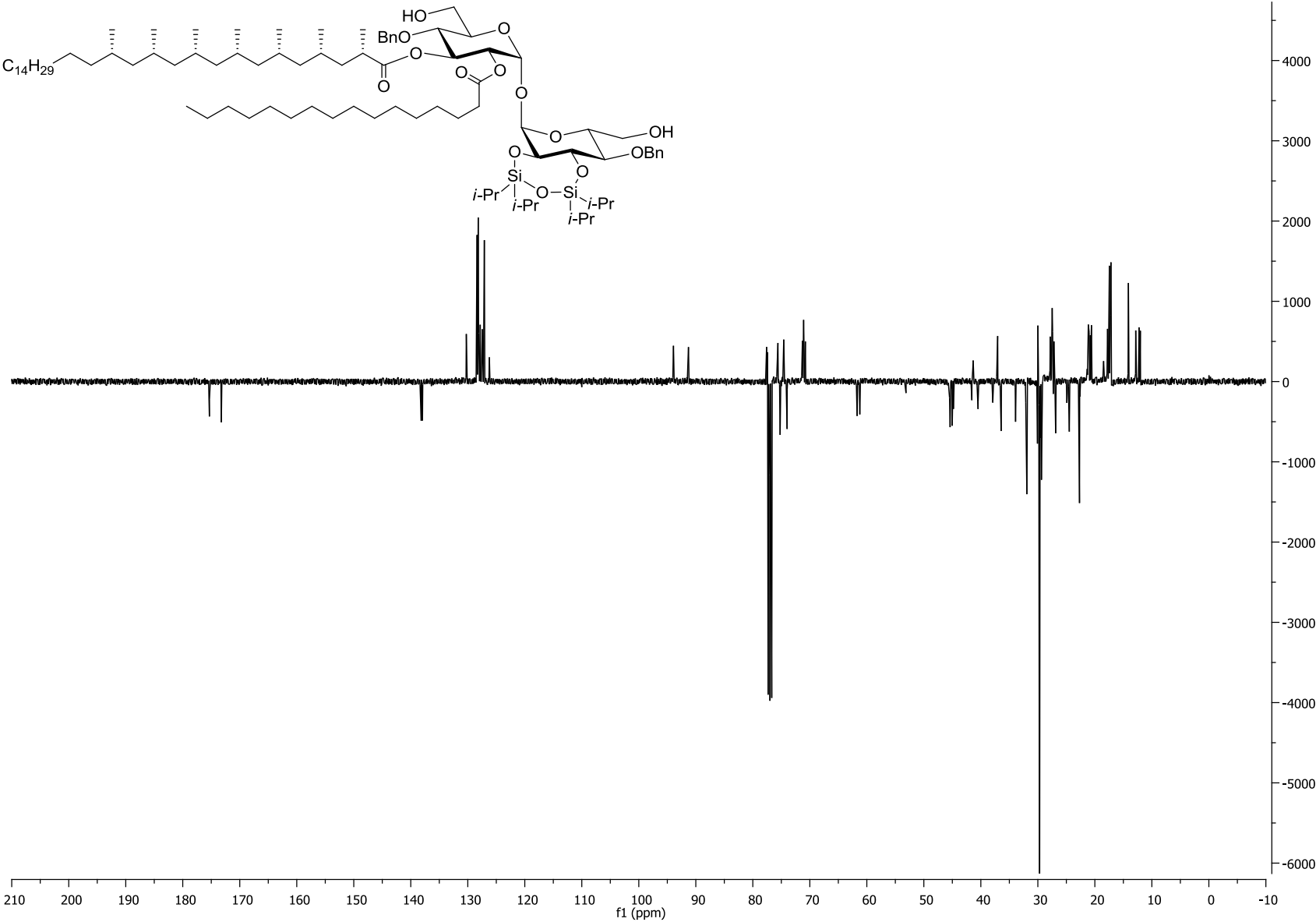


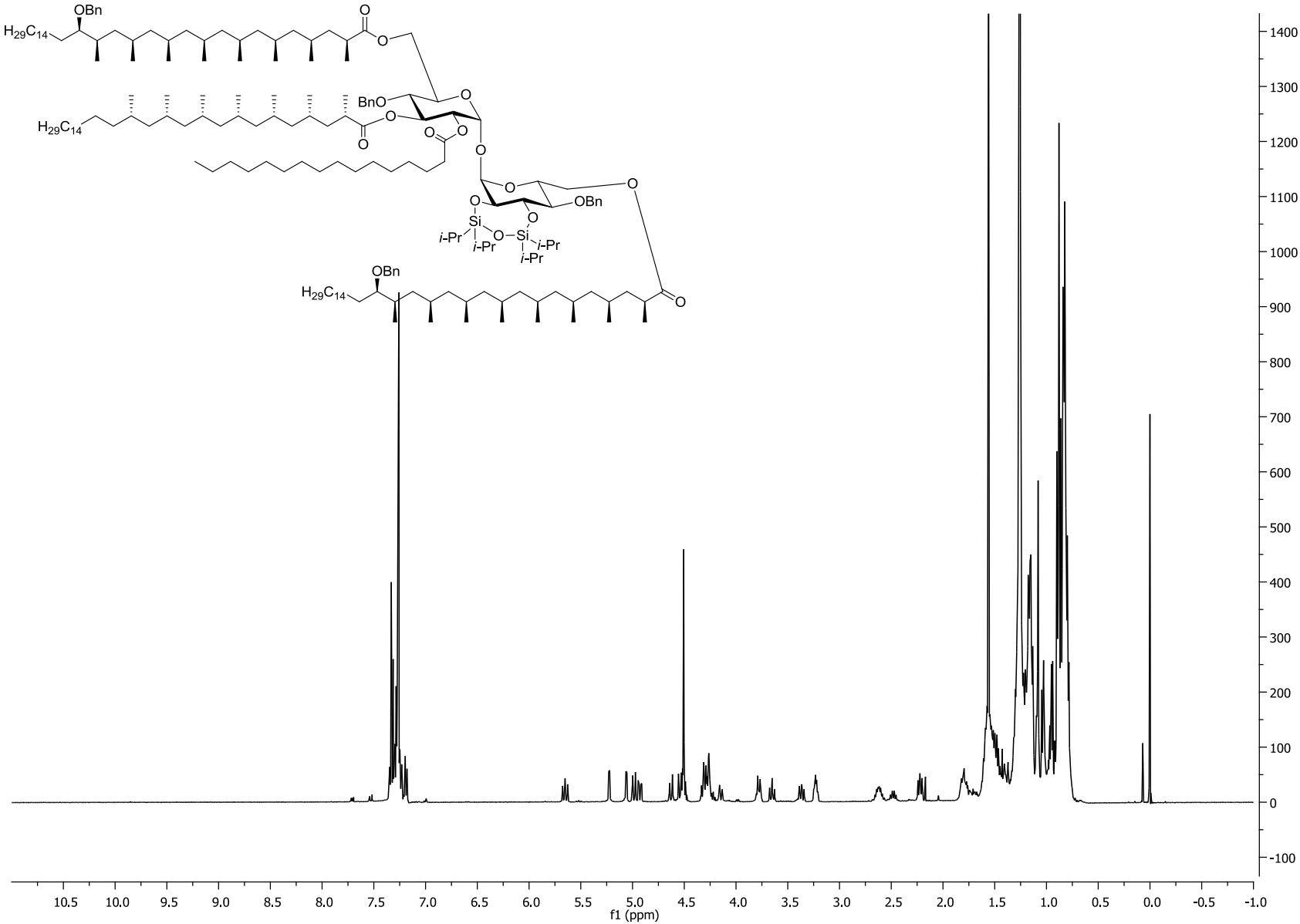


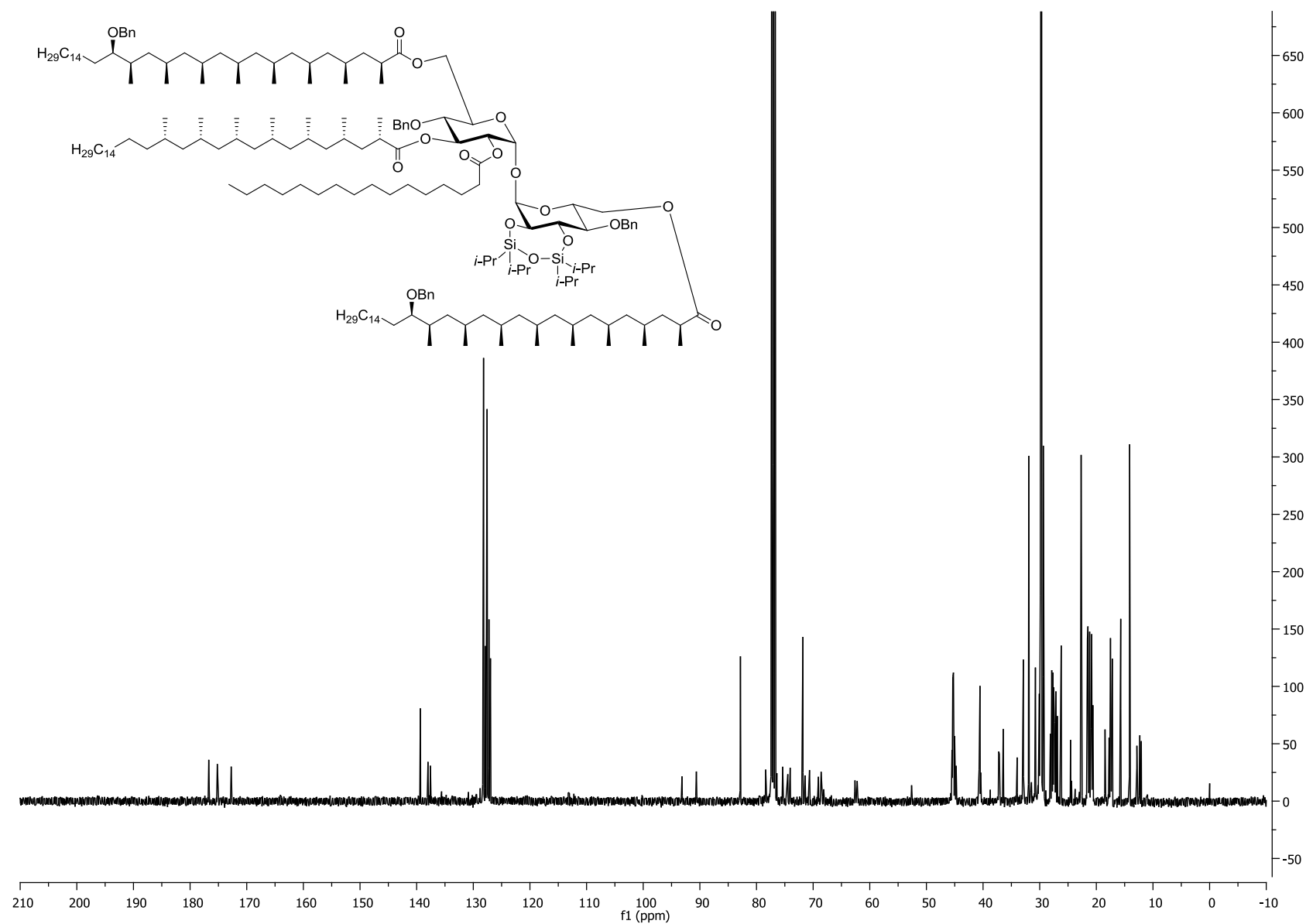


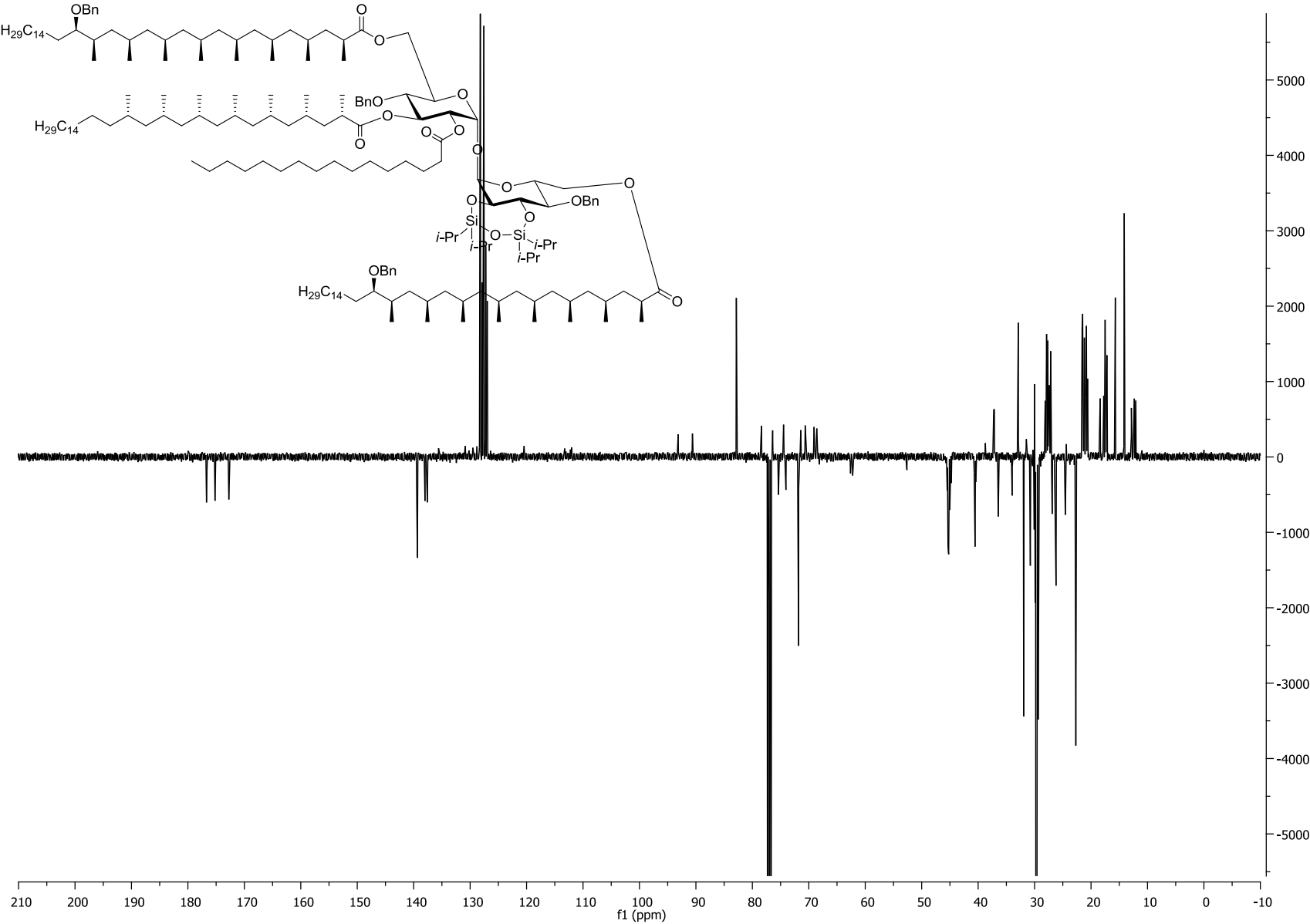


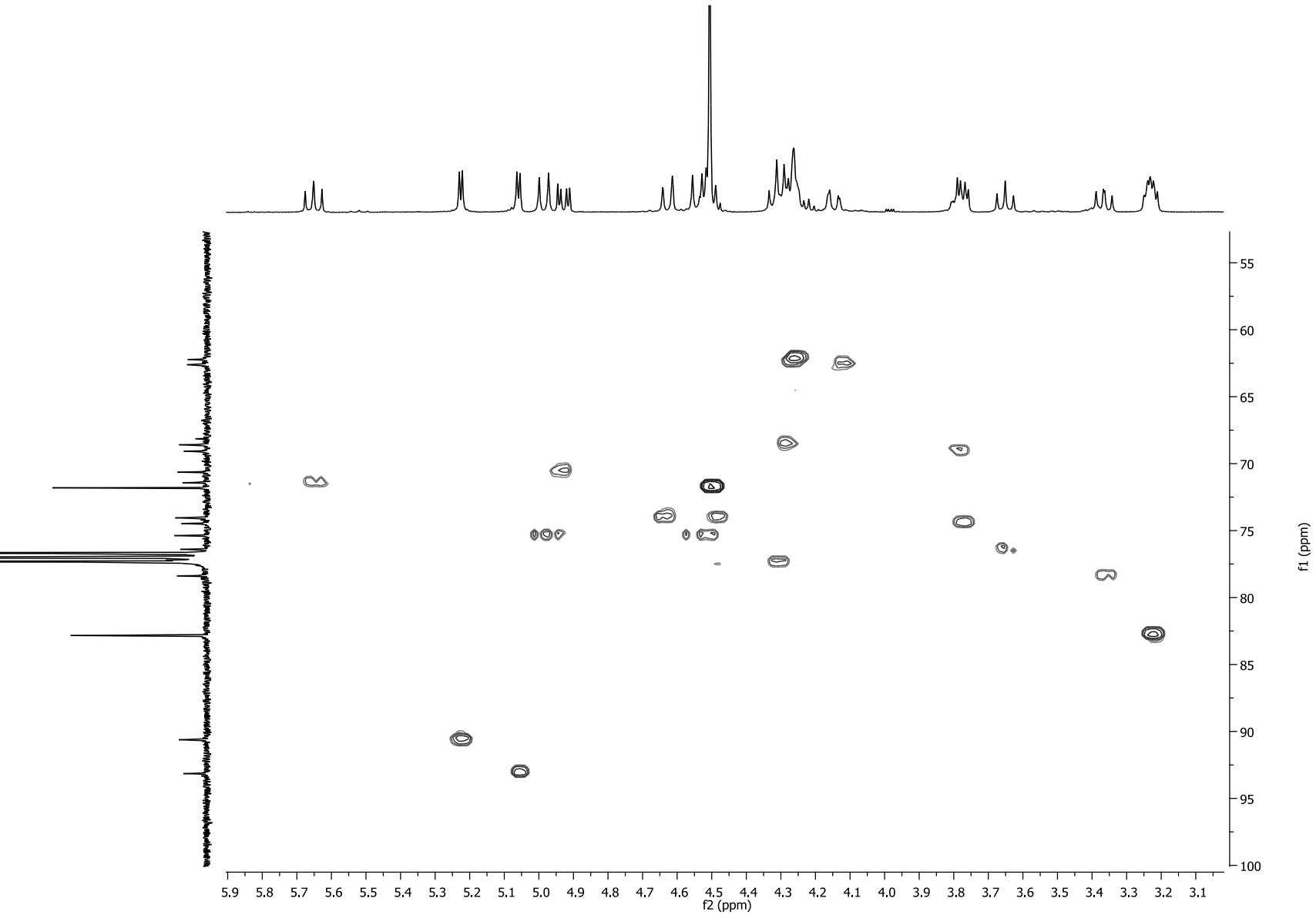




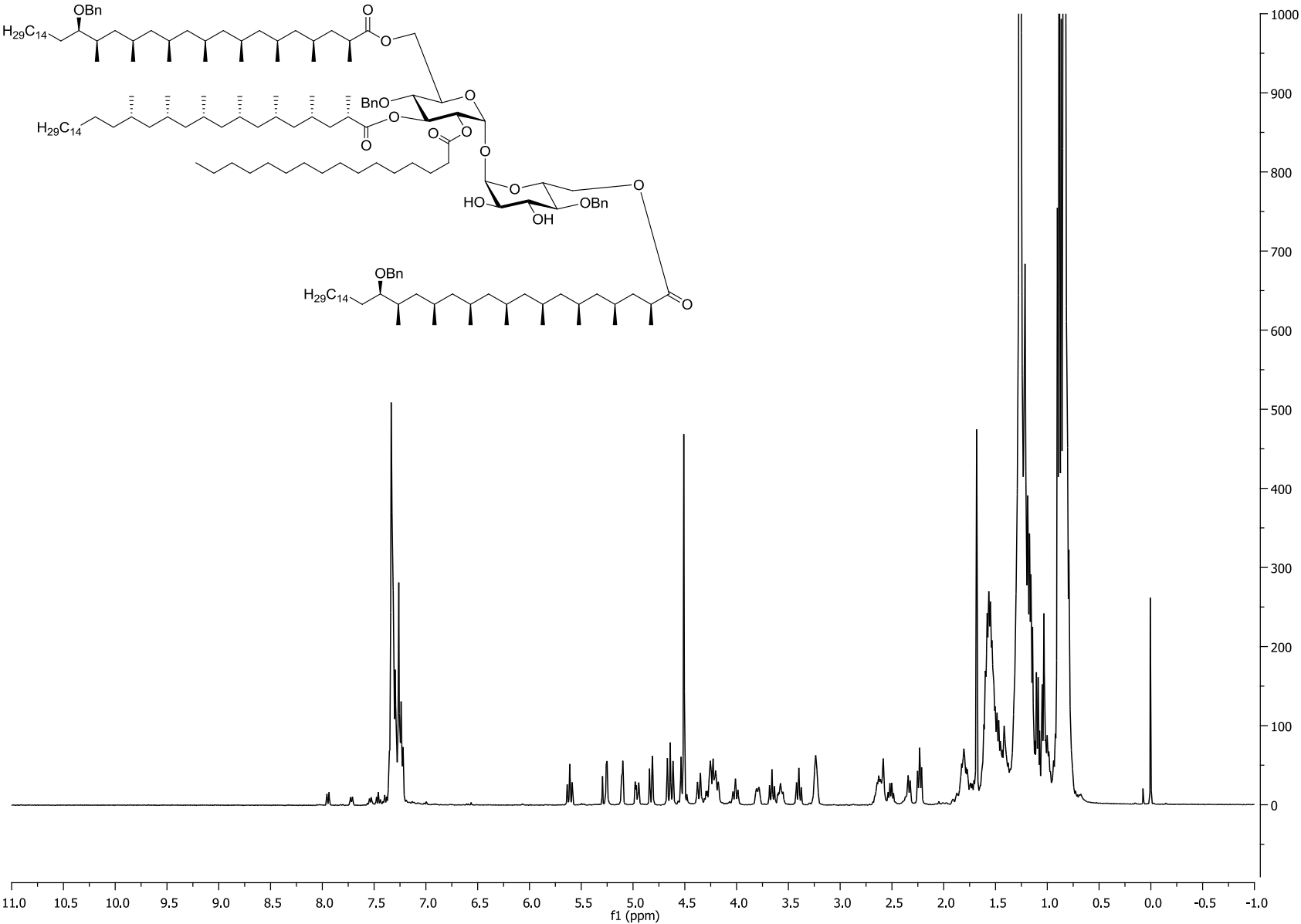


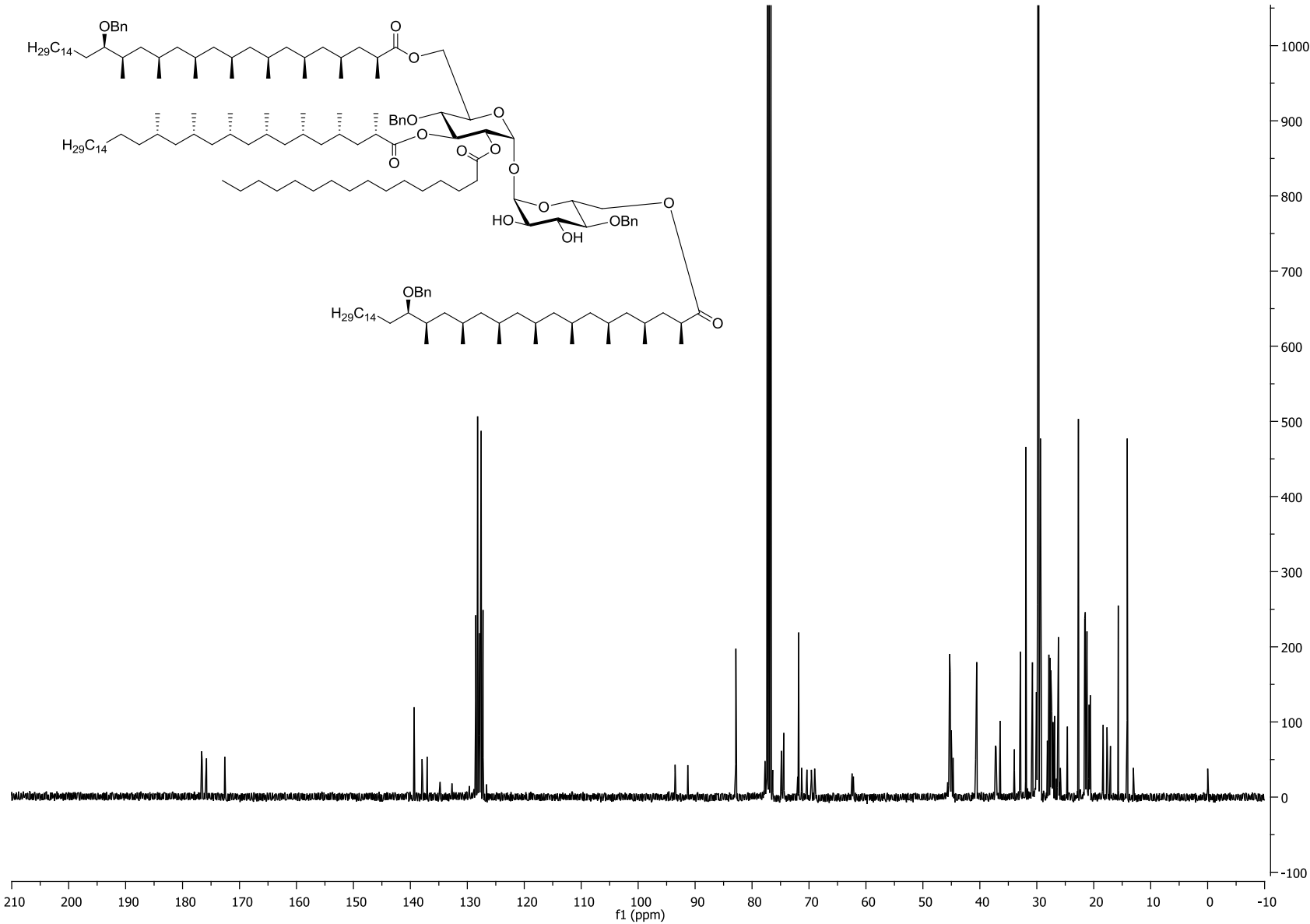


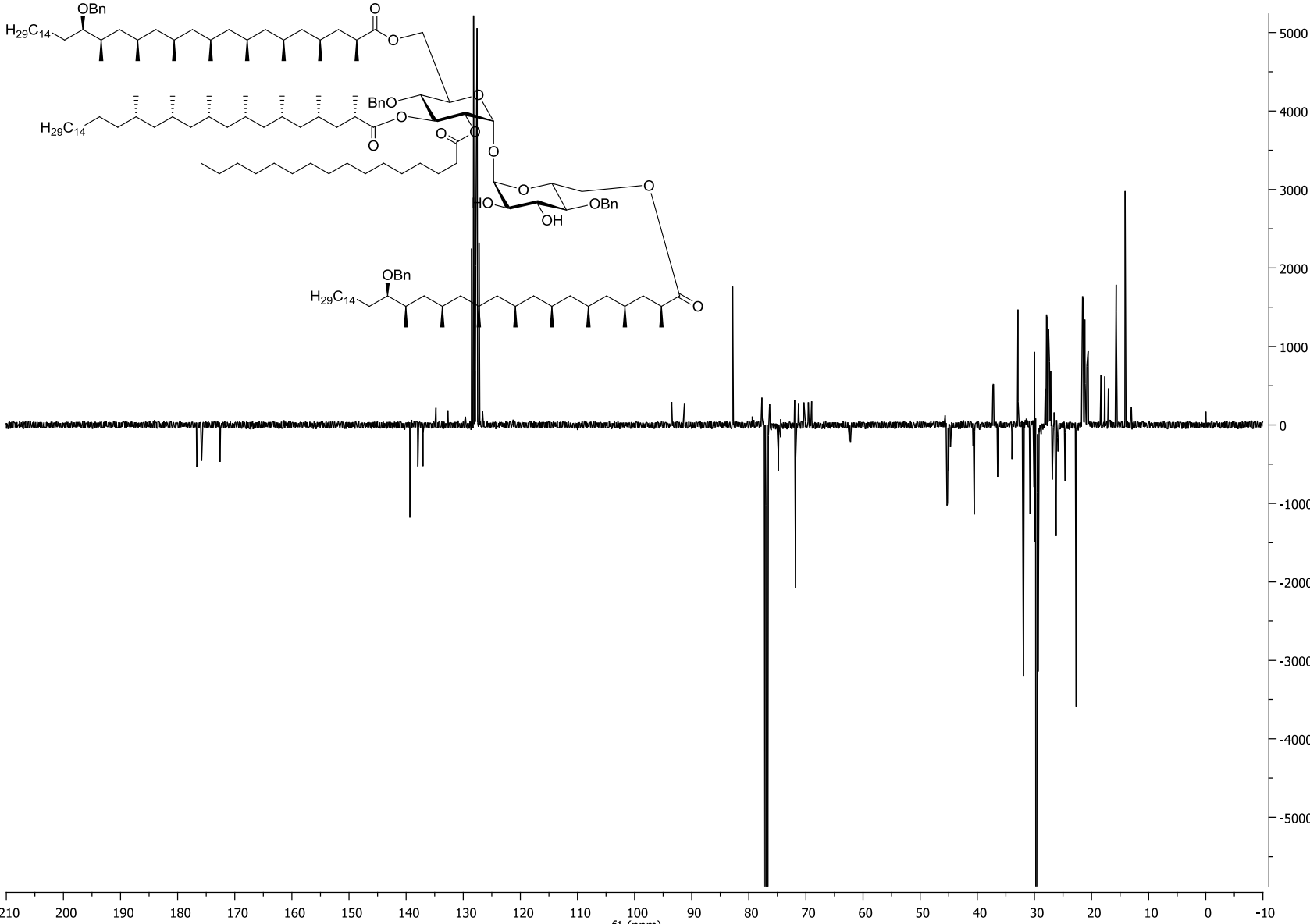


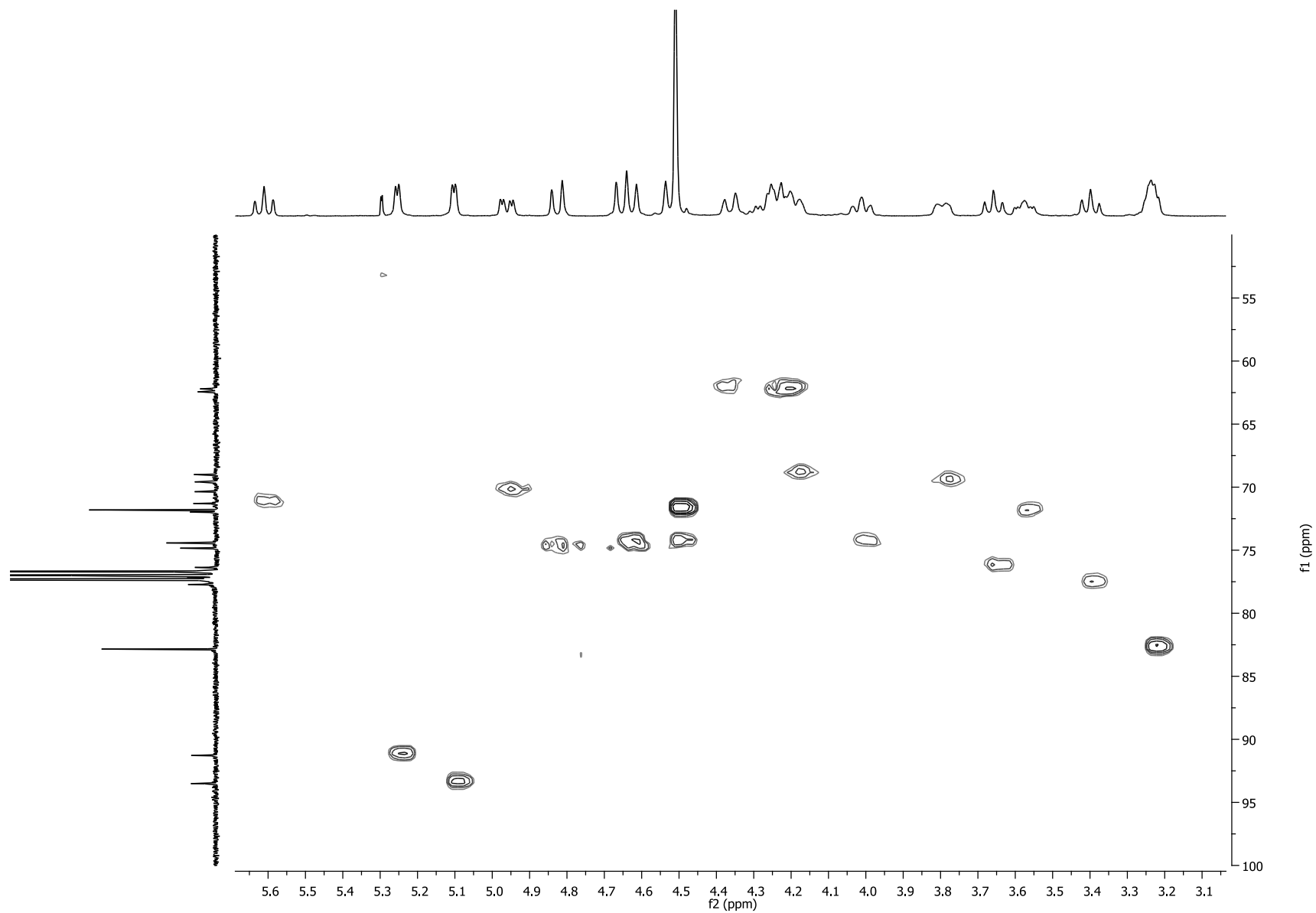


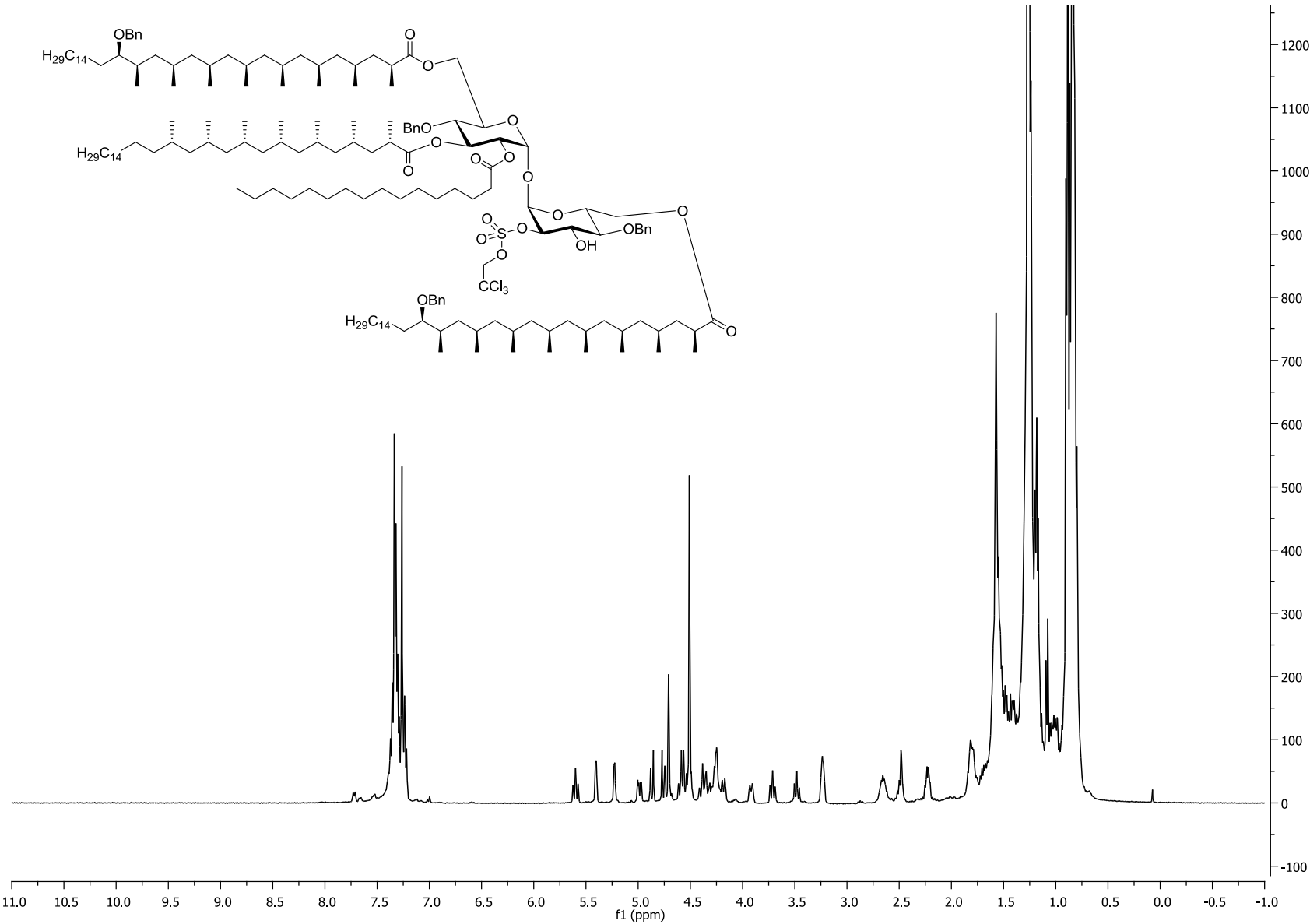
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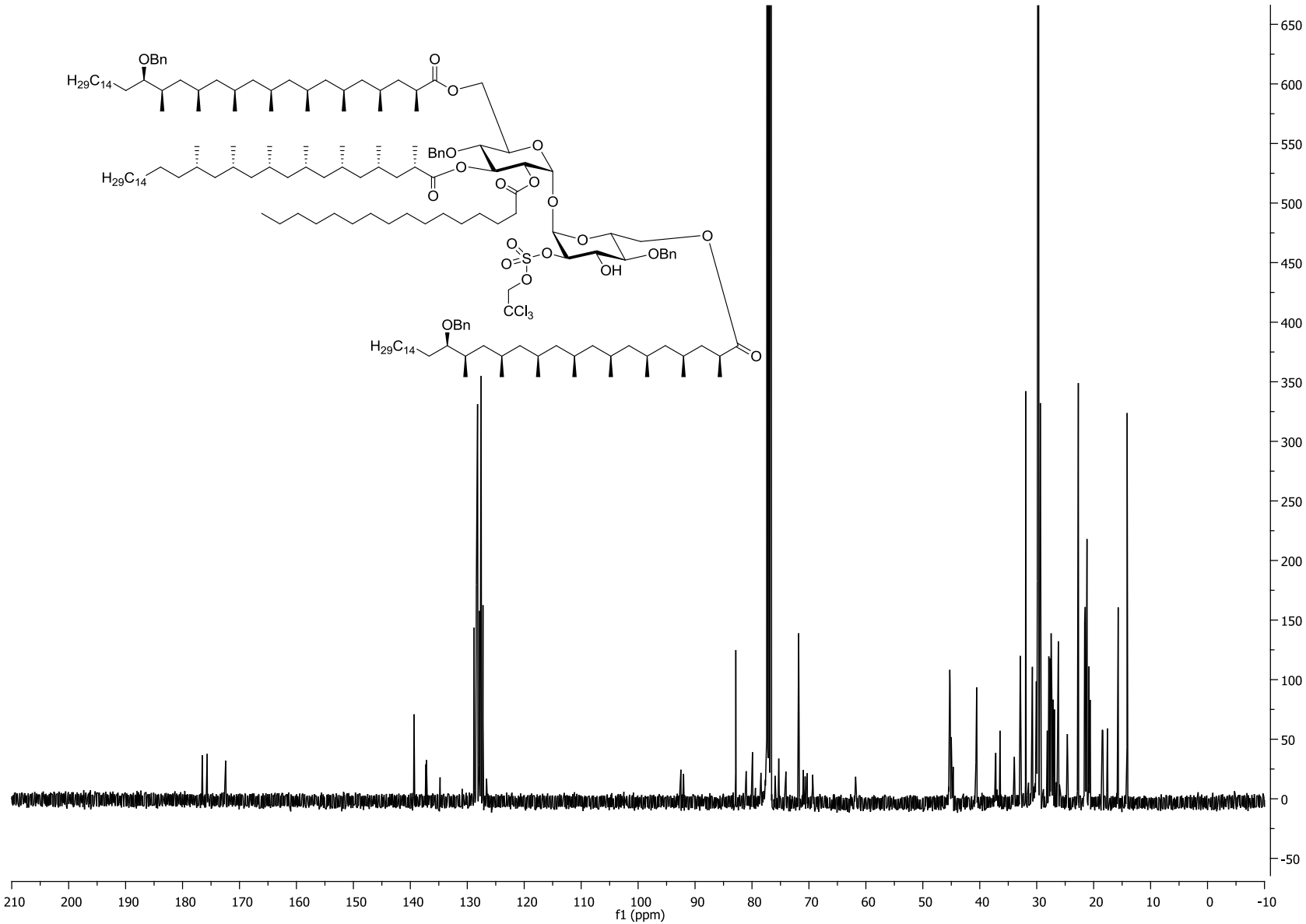


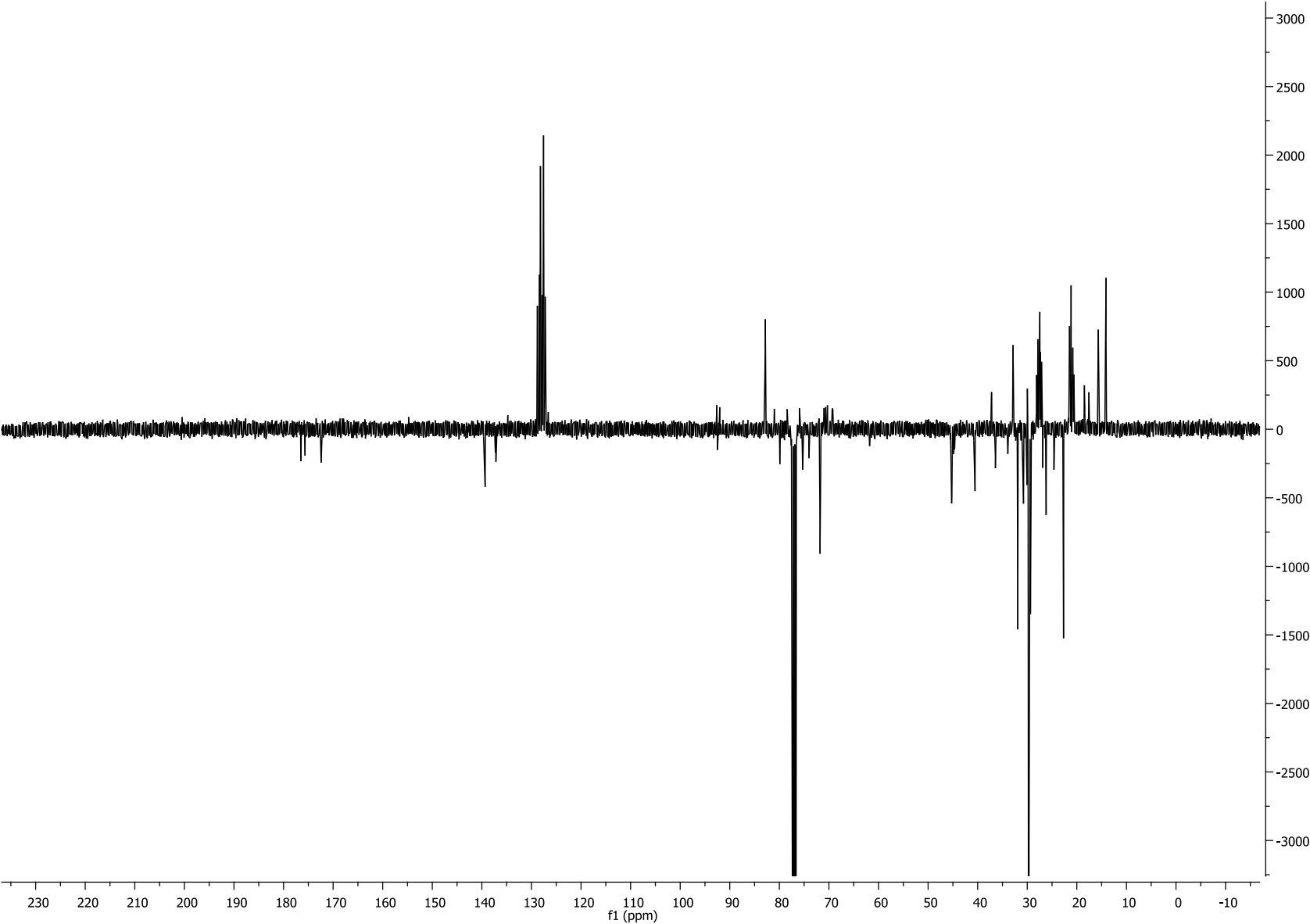












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