**Supporting Information**

# Synthesis and Properties of Monofluorinated Dimyristoylphosphatidylcholine Derivatives: Potential Fluorinated Probes for the Study of Membrane Topology

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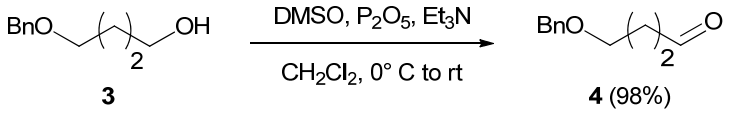
**General information**

The following includes experimental procedures and spectroscopic information for the new compounds prepared. $^{1}H$, $^{13}C$, $^{31}P$, and $^{19}F$ NMR spectra were recorded on a Varian Inova 400 MHz or Bruker Avance 300 MHz in $CDCl_3$ at ambient temperature using TMS ($^{1}H$ NMR) or residual $CHCl_3$ ($^{1}H$ and $^{13}C$ NMR) as internal standards, and $CFCl_3$ ($^{19}F$ NMR) and $H_3PO_4$ ($^{31}P$ NMR) as external standards. Infrared spectra were recorded on a Bomem FT-IR MB-Series spectrometer. High-resolution mass spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI). Melting points were recorded on a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected. Lyso-PC was purchased from Avanti Polar Lipids (Alabaster, AL).

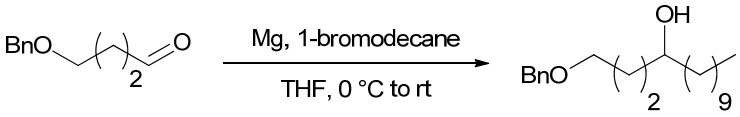
**Experimental Procedure**

*Synthetic route for 4F-DMPC, 1-myristoyl-2-(4-fluoromyristoyl)-sn-glycero-3-phosphocholine (**1a**)*




**3** **4** (98%)

**4-(benzyloxy)butanal (4):** To a solution of 4-(benzyloxy)butan-1-ol (**3**)[1] (350 mg, 1.94 mmol) in $CH_2Cl_2$ (11 mL) at 0 °C under nitrogen atmosphere was added dropwise DMSO (0.3 mL, 3.9 mmol) followed by phosphorous pentoxide (553 mg, 3.9 mmol). The reaction was stirred at 0 °C for 1.5 h and allowed to warm up to room temperature over 1 h. The solution was cooled to 0 °C and triethylamine (1.4 mL, 10.1 mmol) was added and the resulting solution was stirred for 30 minutes. The reaction mixture was poured into a separation funnel and washed twice with sat. aq. $NH_4Cl$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **4** (339 mg, 98%). Spectral data for **4** were identical with those previously reported.[2]

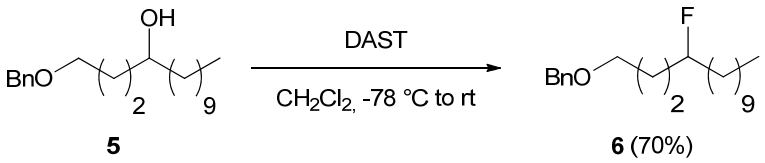



**4** **5** (83%)

**1-(benzyloxy)tetradecan-4-ol (5):** The Grignard reagent was prepared beforehand in a dried flask by adding 1-bromodecane (1.1 mL, 5.1 mmol) to magnesium flakes (248 mg, 10 mmol) submerged in dry THF (ca. 2 mL) under nitrogen atmosphere. After evolution of heat was observed, dry THF (ca. 10 mL) was added and the reaction was stirred for 40 minutes at 45 °C. The organomagnesian was transferred dropwise via canula to a dried flask containing **4** (447 mg, 2.5 mmol) in dry THF (ca. 12 mL). The reaction mixture was stirred for 30 min at 0 °C and then warmed to room temperature over 1.5 h. The reaction mixture was then cooled with an ice bath and quenched with 5% aq. $H_2SO_4$. The resulting solution

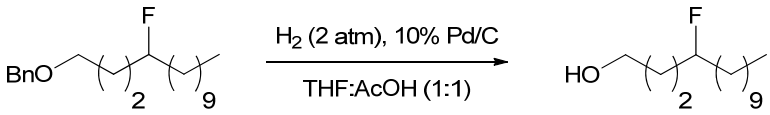
[1] Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035.
[2] Yadav, J. S.; Sreenivas, M.; Srinivas Reddy, A.; Subba Reddy, B. V. *J. Org. Chem*, **2010**, *75*, 8307.

was washed twice with a sat. aq. $Na_2SO_3$, water, sat. aq. $NaHCO_3$ and dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **5** as a colorless oil (665 mg, 83%). IR (ATR, ZnSe) 3385, 2924, 2853, 1454, 1361, 1100, 734, 697 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.53 (s, 2H), 3.60 (b, 1H), 3.52 (t, 2H, $J$ = 6.0 Hz), 2.66 (s, 1H), 1.74 (m, 2H), 1.64 (m, 1H), 1.52-1.39 (m, 4H), 1.27 (bs, 14H), 0.89 (t, 3H, $J$ = 7.0 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.5, 128.6 (2C), 127.8 (3C), 73.2, 71.6, 70.8, 37.8, 34.7, 32.2, 30.1, 29.9 (3C), 29.7, 26.4, 26.1, 23.0, 14.4. HRMS-ESI calcd for $C_{21}H_{36}O_2$ $[M+H]^+$ 321.2788 found 321.2799.




**5** **6** (70%)

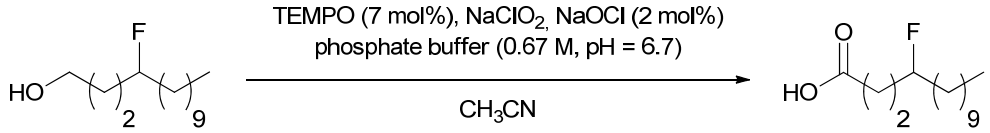
**((4-fluorotetradecyloxy)methyl)benzene (6):** To a solution of **5** (400 mg, 1.3 mmol) in dry $CH_2Cl_2$ (25 mL) at -78 °C under nitrogen atmosphere was added DAST (165 µL, 1.3 mmol) dropwise. The reaction mixture was stirred for 3 h at -78 °C and allowed to warm up to room temperature over 3 h. The solution was carefully poured to a sat. aq. $CaCO_3$ cooled at 0 °C. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$. Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (2.5% EtOAc/hexane) affording **6** as a yellow oil (293 mg, 80%). NMR analysis indicates that the product is contamined by ca. 10% of 4-benzyloxy-1-fluorotetradecane. An analytically pure sample can be obtained by a careful flash chromatograhy using 2.5% EtOAc/hexane. IR (ATR, ZnSe) 2925, 2854, 1455, 1361, 1102, 734, 697 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.52 (s, 2H), 4.49 (dm, 1H, $J_{H\text{-}F}$ = 50.0 Hz), 3.51 (m, 2H), 1.40-1.88 (m, 6H), 1.29 (m, 16H), 0.89 (t, 3H, $J$ = 7.0 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.8, 128.6 (2C), 127.8 (3C), 94.6 (d, $J_{C\text{-}F}$ = 164.2 Hz), 73.1 (t, $J_{C\text{-}F}$ = 3.5 Hz), 70.2, 35.4 (d, $J_{C\text{-}F}$ = 21.0 Hz), 32.2-32.0 (m, 3C), 30.1-29.6 (m, 4C), 25.7 (m), 25.4 (m), 22.9, 14.4. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -181.0 (m). HRMS-ESI calcd for $C_{21}H_{35}FO$ $[M+Na]^+$ 345.2564 found 345.2575.




**6** **S1** (82%)

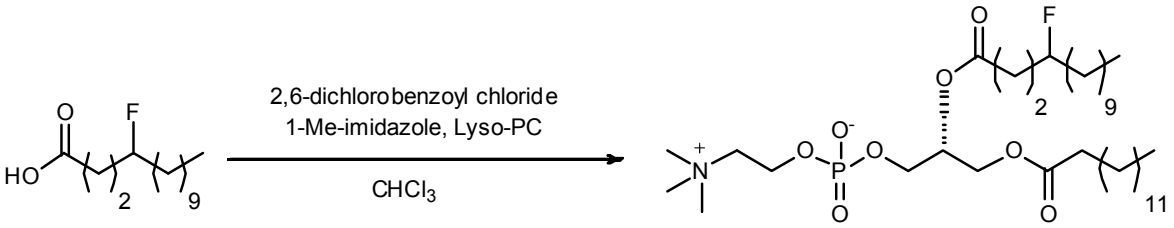
**4-fluorotetradecan-1-ol (S1):** To a solution of **6** (155 mg, 0.48 mmol) in THF:AcOH (4.6 mL of a 1:1 mixture) was added 10% Pd/C (51 mg, 0.048 mmol). The system was purged 3 times cycling between vacuum and $H_2$ (3 atm). The reaction mixture was agitated under $H_2$ atmosphere (2 atm) for 48 h. The mixture was diluted with EtOAc (ca. 20 mL) and filtered over Celite. The filtrate was then washed 3 times with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **S1** as a colorless oil (91.5 mg, 82%). IR (ATR, ZnSe) 3281, 2917, 2847, 1471, 1059, 932, 819 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.50 (m, 1H, $J_{H\text{-}F}$ = 47.5 Hz) 3.67 (m, 2H), 1.54-1.81 (m, 6H), 1.39-1.51 (m, 2H), 1.17-1.37 (m, 14H), 0,87 (t, 3H, $J$ = 7.0 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 94.7 (d, $J_{C\text{-}F}$ = 166.1 Hz), 62.6, 35.4 (d, $J_{C\text{-}F}$ = 20.7 Hz), 32.1, 31.5 (d, $J_{C\text{-}F}$ = 21.3 Hz), 29.3-29.7 (m, 6C), 28.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 25.3 (d, $J_{C\text{-}F}$ = 4.5 Hz), 14.1 $^{19}F$

NMR (400 MHz, $CDCl_3$) δ -180.5 (m). HRMS-ESI calcd for $C_{14}H_{29}FO$ $[M+NH_4]^+$ 250.2541 found 250.2547.




**S1** **2a** (86%)

**4-fluorotetradecanoic acid (2a):** To a mixture of TEMPO (2.3 mg, 0.014 mmol) in $CH_3CN$ (0.80 mL) and a phosphate buffer (pH 6.7, 0.67 M, 0.60 mL) at 35 °C was added **S1** (38.7 mg, 0.17 mmol). Solutions of sodium chlorite (31.7 mg, 0.33 mmol) in water (159 µL) and sodium hypochlorite (23 µL of a 10% aqueous solution, 3.3 µmol) diluted in water (80 µL) were added dropwise over 2 h in two separate syringe. The reaction was stirred for 4 hours at 35 °C and then cooled to room temperature. Water (1 mL) was added and the pH was adjusted to 8 with a 2 M NaOH solution. The reaction mixture was poured in sat. aq. $Na_2SO_3$ and maintained under 20 °C (pH was around 8.5-9.0) After stirring for 10 minutes, the solution was extracted with $Et_2O$ (1 mL) and the organic phase was discarded. The aqueous phase was then acidified to pH 3-4 using a 2 M HCl solution. Some sat. aq. NaCl was added to the mixture before extracting with EtOAc (3×). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **2a** as a white solid (35.1 mg, 86%). mp 59-61 °C; IR (ATR, ZnSe) 3105, 2916, 2848, 1714, 1699, 1462, 1288, 870 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.51 (dm, 1H, $J_{H-F}$ = 51.1 Hz), 2.53 (m, 2H), 2.10-1.81 (m, 2H), 1.71-1.19 (m, 18H), 0.88 (t, 3H, $J$ = 6.3 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 179.1, 93.5 (d, $J_{C-F}$ = 167.2 Hz), 35.3 (d, $J_{C-F}$ = 20.4 Hz), 32.1, 30,2 (d, $J_{C-F}$ = 21.0 Hz), 29.5-29.9 (m, 7C), 25.2 (d, $J_{C-F}$ = 3.7 Hz), 22.9, 14.4. $^{19}F$ NMR (400 MHz, $CDCl_3$) δ 183.3 (m, 1F). HRMS-ESI calcd for $C_{14}H_{27}FO_2$ $[M+Na]^+$ 269.1887 found 269.1899.

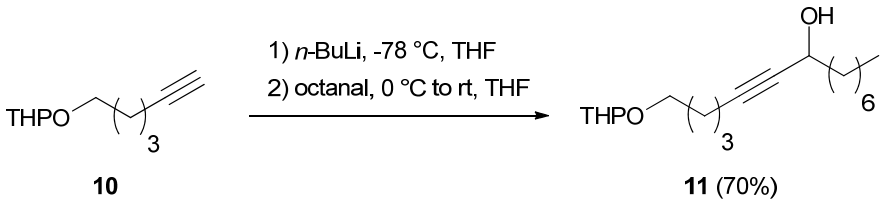



**2a** **1a** (72%)

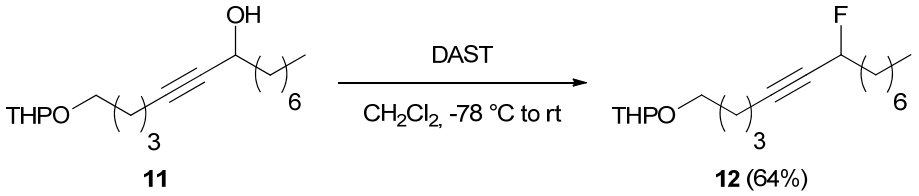
**4F-DMPC, 1-myristoyl-2-4-fluoromyristoyl-*sn*-glycero-3-phosphocholine (1a):** To a solution of **2a** (35.1 mg, 0.14 mmol), Lyso-PC (66.6 mg, 0.14 mmol) and 1-methylimidazole (40 µL, 0.42 mmol) in $CHCl_3$ (1.4 ml) was added 2,6-dichlorobenzoyl chloride (92.5 mg, 0.44 mmol) and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:$CH_2Cl_2$) affording **1a** as a light yellow wax (71.1 mg, 72%) IR (ATR, ZnSe) 3386, 2918, 2850, 2361, 1735, 1467, 1233, 1089, 1066 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.60-4.11 (m, 5H), 3.97 (m, 2H), 3.83 (s, 2H), 3.37 (s, 9H), 2.47 (m, 2H), 2.28 (t, 2H, $J$ = 7.5 Hz), 1.97-1.79 (m, 2H), 1.67-1.16 (m, 40H), 0.88 (t, 6H, $J$ = 6.4 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.8, 172.7 (d, $J_{C-F}$ = 3.9 Hz), 93.6 (d, $J_{C-F}$ = 162.0 Hz), 71.1, 66.5, 63.6, 63.0, 59.5, 54.6, 35.4 (d, $J_{C-F}$ = 20.5 Hz), 35.3 (d $J_{C-F}$ = 20.5 Hz), 34.3, 32.1 (2C), 30.6-29.4 (m,

16C), 25.4-25.0 (3C), 22.9 (2C), 14.3 (2C). $^{19}$F NMR (400 MHz, $CDCl_3$) δ -182.9. $^{31}$P NMR, (121.5 MHz, $CDCl_3$) δ -0.55. HRMS-ESI calcd for $C_{36}H_{71}FNO_8P$ $[M+NH_4]^+$ 695.4901 found 696.4988.

*Synthetic route for 7F-DMPC, 1-myristoyl-2-(7-fluoromyristoyl)-sn-glycero-3-phosphocholine (**1b**)*




**1-(tetrahydro-2H-pyran-2-yloxy)tetradec-5-yn-7-ol (11):** To a solution of 2-(hex-5-ynyloxy)tetrahydro-2H-pyran (**10**)[3] (1.5 g, 8.12 mmol) in dry THF (79 mL) at -78 °C under nitrogen atmosphere was added dropwise *n*-butyllithium (0.74 mL, 8.12 mmol, 2.5 M in hexane). The solution was stirred 1 h, warmed to 0 °C and octanal was added (315 mg, 2.46 mmol). The reaction was allowed to proceed for 20 h then warmed up to room temperature. The reaction mixture was poured into a separatory funnel, washed twice with sat. aq. $NH_4Cl$ then with water. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **11** (1.76 g, 70%). Spectral data for **11** were identical with those previously reported.[4]




**2-(7-fluorotetradec-5-ynyloxy)tetrahydro-2H-pyran (12):** To a solution of **11** (920 mg, 2.96 mmol) in dry $CH_2Cl_2$ (29 mL) at -78 °C under nitrogen atmosphere was added dropwise DAST (0.39 mL, 3 mmol). The reaction mixture was stirred 3 h and warmed to room temperature over 3 h. The solution was carefully poured to sat. aq. $CaCO_3$ cooled to 0 °C. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$. Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (2.5% EtOAc/hexane) affording **12** as a colorless oil (592 mg, 64%). IR (ATR, ZnSe) 2928, 2858, 2240, 1455, 1350, 1134, 1121, 1076, 1035, 905, 870, 815 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.95 (dt, 1H, $J$ = 65.3, 6.3 Hz), 4.47 (t, 1H, $J$ = 3.0 Hz) 3.80-3.25 (m, 4H), 2.18 (dq, 2H, $J$ = 6.6, 1.5 Hz), 1.80-1.15 (m, 22H), 0.79 (t, 3H, $J$ = 6.6 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 98.9, 88.7 (d, $J_{C-F}$ = 10,2 Hz), 83.1 (d, $J_{C-F}$ = 164,6 Hz), 77.7 (d, $J_{C-F}$ = 26.0 Hz), 66.9, 62.3, 36.4 (d, $J_{C-F}$ = 22.4 Hz), 31.9, 30.9, 29.3 (2C), 29.0, 25.7, 25.4 (d, $J_{C-F}$ = 2.4 Hz), 24.7 (d $J_{C-F}$ = 4.0 Hz), 22.8, 19.7, 18.6 (d, $J_{C-F}$ = 3.0 Hz), 14.2. $^{19}$F NMR (400 MHz, $CDCl_3$) δ -171.0 (m). HRMS-ESI calcd for $C_{19}H_{33}FO_2$ $[M+Na]^+$ 335.2357 found 335.2354.

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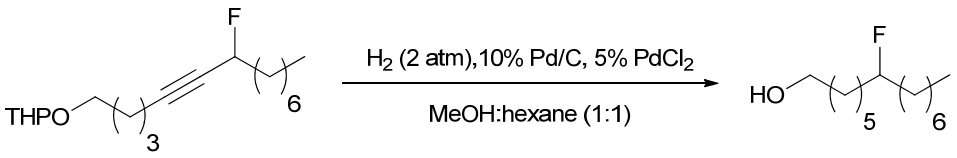
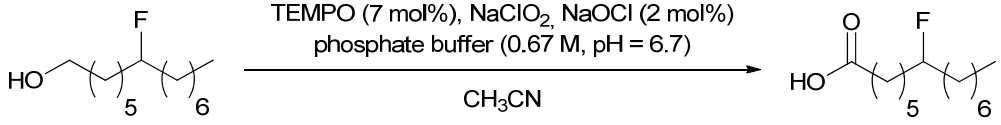
[3] Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059.
[4] Cryle, M. J.; De Voss J. J. *Chem. Commun*. **2004**, 86.



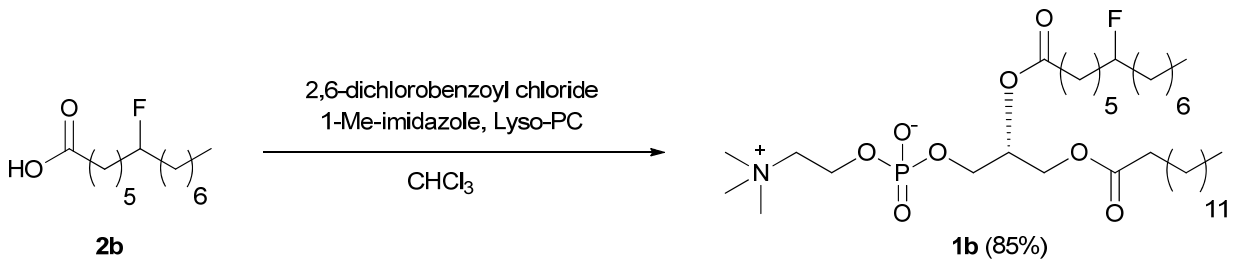

**12** **13** (91%)

**7-fluorotetradecan-1-ol (13):** To a solution of **12** (47 mg, 0.15 mmol) in degazed MeOH:hexane (2.9 mL of a 1:1 mixture) was added 10% Pd/C (16 mg, 0.015 mmol) and palladium(II) chloride (1.3 mg, 7.5 µmol). The reaction mixture was purged 3 times cycling between vacuum and hydrogen atmosphere (3 atm). The reaction was agitated for 16 h under hydrogen atmosphere (2 atm) at room temperature. The solution was filtrated with Celite and evaporated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **13** as a white solid (32 mg, 91%). mp 37-38 °C; IR (ATR, ZnSe) 3273, 2919, 2852, 1471, 1357, 1062 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 4.45 (dm, 1H, $J_{H-F}$ = 49.4 Hz), 3.63 (t, 2H, $J$ = 6.6 Hz), 1.85 (bs, 1H), 1.69-1.17 (m, 22H), 0.87 (t, 3H, $J$ = 6.4 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 94.8 (d, $J_{C-F}$ = 165.6 Hz), 63.2, 35.4 (d, $J_{C-F}$ = 10.0 Hz), 35.3 (d, $J_{C-F}$ = 10.1 Hz), 32.9, 32.0, 29.7, 29.5, 29.4, 25.9, 25.4 (d, $J_{C-F}$ = 3.1 Hz), 25.3 (d, $J_{C-F}$ = 2.8 Hz), 22.9, 14.3. $^{19}F$ NMR (400 MHz, $CDCl_3$) δ -180.5 (m). HRMS-ESI calcd for $C_{14}H_{29}FO$ $[M+Na]^+$ 255.2095 found 255.2102.



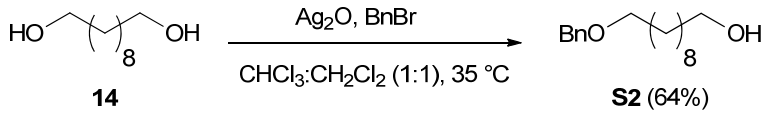

**13** **2b** (85%)

**7-fluorotetradecanoic acid (2b):** To a mixture of TEMPO (1.1 mg, 0.01 mmol) in $CH_3CN$ (0.47 mL) and a phosphate buffer (pH 6.7, 0.67 M, 0.34 mL) at 35 °C was added **13** (22.7 mg, 0.1 mmol). Solutions of sodium chlorite (17.4 mg, 0.19 mmol) in water (90 µL) and sodium hypochlorite (1 µL of a 10% aqueous solution, 0.17 µmol) in water (50 µL) were added dropwise in two separate syringe. The reaction was stirred for 4 h at 35 °C and then cooled to room temperature. Water (1 mL) was added then the pH was adjusted to 8 with a 2 M NaOH solution. The reaction mixture was poured in sat. aq. $Na_2SO_3$ and maintained under 20 °C (pH was around 8.5-9.0) After stirring for 10 minutes, the solution was extracted by $Et_2O$ (1 mL) and the organic phase was discarded. The aqueous phase was then acidified to pH 3-4 using a 2 M HCl solution. Some sat. aq. NaCl was added to the mixture before extracting with EtOAc (3×). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **2b** as a white solid (20.4 mg, 85%). mp 60-63 °C; IR (ATR, ZnSe) 2918, 2853, 1700, 1470, 1292, 944 $cm^{-1}$. H NMR (400 MHz, $CDCl_3$) δ 4.51 (m, 1H), 2.37 (t, 2H, $J$ = 7.4 Hz), 1.70-1.21 (m, 20H), 0.89 (t, 3H, $J$ = 6.8 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 180.3, 94.6 (d, $J_{C-F}$ = 165.9 Hz), 35.4 (d, $J_{C-F}$ = 20.9 Hz), 35.2 (d, $J_{C-F}$ = 20.9), 34.2, 32.0, 29.7, 29.4, 29.1, 25.4 (d, $J_{C-F}$ = 4.7 Hz), 25.0 (d, $J_{C-F}$ = 4.4 Hz), 24.8, 22.9, 14.3. $^{19}F$ NMR (400 MHz, $CDCl_3$) δ 180.7 (m, 1F). HRMS-ESI calcd for $C_{14}H_{27}FO_2$ $[M+Na]^+$ 269.1887 found 269.1888.



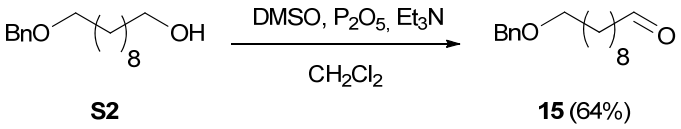

**7F-DMPC, 1-myristoyl-2-(7-fluoromyristoyl)-*sn*-glycero-3-phosphocholine (1b):** To a solution of **2b** (59 mg, 0.24 mmol), Lyso-PC (112 mg, 0.239 mmol) and 1-methylimidazole (57 µl, 0.716 mmol) in $CHCl_3$ (2.4 ml) was added 2,6-dichlorobenzoyl chloride (155 mg, 0.740 mmol) and the resulting mixture was stirred 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:$CH_2Cl_2$) affording **1b** as an off-white powder (142 mg, 85%). IR (ATR, ZnSe) 3366, 2921, 2851, 1737, 1468, 1378, 1237, 1090, 1067, 971, 824 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.55-4.08 (m, 5H), 3.95 (m, 2H), 3.83 (s, 2H), 3.40 (s, 9H), 2.29 (m, 4H), 1.67-1.16 (m, 42H), 0.88 (m, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.8, 173.2, 94.7 (d, $J_{C-F}$ = 165.8 Hz), 70.8, 66.5, 63.6, 63.1, 59.5, 54.6, 35.4 (d, $J_{C-F}$ = 20.6 Hz), 35.1 (d $J_{C-F}$ = 21.1 Hz), 34.4, 34.3, 32.1, 32.0, 29.0-30.0 (m, 13C), 24.9-25.5 (4C), 22.9 (2C), 14.3 (2C). $^{19}F$ NMR (400 MHz, $CDCl_3$) δ-180.7 (m). $^{31}P$ NMR (121.5 MHz, $CDCl_3$) δ -0.48 (bs) HRMS-ESI calcd for $C_{36}H_{71}FNO_8P$ $[M+H]^+$ 695.4896 found 696.4985.

*Synthetic route for 10F-DMPC, 1-myristoyl-2-(10-fluoromyristoyl)-sn-glycero-3-phosphocholine (**1c**)*



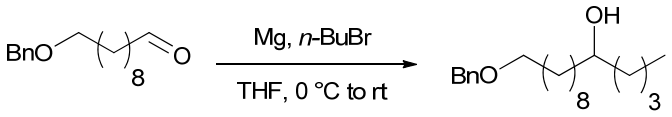

**10-(benzyloxy)decan-1-ol (S2):** To a solution of 1,10-decanediol (**14**) (1.0 g, 5.7 mmol) in a 1:1 mixture of $CHCl_3$:$CH_2Cl_2$ (56 ml) was added silver(I) oxide (2.0 g, 8.6 mmol). The resulting mixture was stirred for 1 h at 35 °C. Benzyl bromide (1.08 g, 6.31 mmol) was then added and the reaction mixture was stirred for 16 h under nitrogen atmosphere. The suspension was filtered on Celite and the filtrate was evaporated under reduced pressure. The crude was dry-loaded and purified by silica gel chromatography (15% EtOAc/hexane) affording **S2** (971 mg, 64%). Spectral data for **S2** were identical with those previously reported.[5]

[5] Shioiri, T.; Terao, Y.; Irako, N.; Aoyama, T., *Tetrahedron*, **1998**, *54*, 15701.



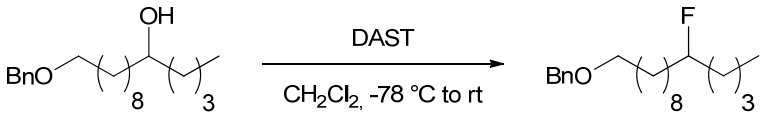

**S2** **15** (64%)

**10-(benzyloxy)decanal (15):** To a solution of **S2** (576 mg, 2.18 mmol) in $CH_2Cl_2$ (21 mL) at 0 °C under a nitrogen atmosphere was added DMSO (0.34 mL, 4.35 mmol) followed by phosphorous pentoxide (617 mg, 4.35 mmol). The reaction mixture was stirred at 0 °C for 2.5 h and allowed to warm up at room temperature over 2.5 h. The solution was cooled to 0 °C and triethylamine (1.06 mL, 7.6 mmol) was added and the resulting solution was stirred for 30 minutes. The reaction mixture was poured into a separation funnel and washed twice with sat. aq. $NH_4Cl$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (10% EtOAc/hexane) affording **15** (366 mg 64%). Spectral data for **15** were identical with those previously reported.5




**15** **16** (94%)

**14-(benzyloxy)tetradecan-10-ol (16):** The Grignard reagent was prepared beforehand in a dried flask. Magnesium flakes (1.0 g, 41 mmol) were submerged in dry THF (ca. 4 mL) and 1-bromobutane (1.4 mL, 13.4 mmol) was added dropwise. The reaction mixture was stirred for 5 minutes then dry THF (46 mL) was added and the reaction was stirred for 50 minutes at 45 °C. The Grignard was titrated at 0.16M using diphenyl telluride.[6] The Grignard reagent (2.74 mL, 0.16 M, 0.43 mmol) was transferred dropwise via canula to a dried flask containing **15** (87 mg, 0.33 mmol) in dry THF (1.6 mL) under argon atmosphere. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm up to room temperature and stirred 1 h. The solution was then cooled to 0 °C using an ice bath and poured in a 5% aq. $H_2SO_4$ at 0 °C. The organic layer was separated and washed twice with sat. aq. $Na_2SO_3$ then with water. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure affording **16** (100.5 mg 94%). Spectral data for **16** were identical with those previously reported.[7]

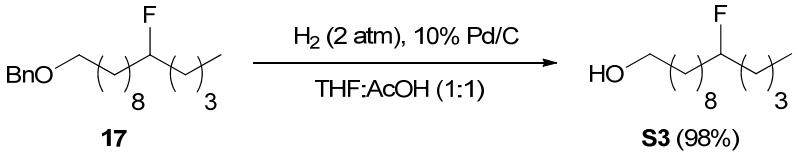



**16** **17** (81%)

**((10-fluorotetradecyloxy)methyl)benzene (17):** To a solution of **16** (106 mg, 0.33 mmol) in dry $CH_2Cl_2$ (4 mL) at -78 °C under nitrogen atmosphere was added dropwise DAST (43 µL, 0.33 mmol). The reaction mixture was stirred for 3 h at -78 °C and allowed to warm up to room temperature and stirred for an additional 3 h. The solution was carefully poured in

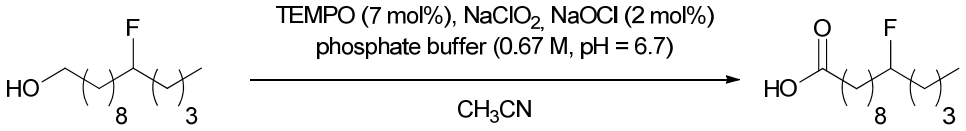
[6] Aso, Y.; Yamashita, H.; Otsubo, T.; Ogura, F., *J. Org. Chem.,* **1989**, *54,* 5627.
[7] Jakob, B.; Gerlach, H., *Liebigs Ann*. **1996**, 2123.

sat. aq. $CaCO_3$ cooled at 0 °C. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$. Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (2.5% EtOAc/hexane) affording **17** as a colorless oil (86 mg 81%) contaminated with ca. 10% of elimination products. IR (ATR, ZnSe) 2928, 2855, 1455, 1362, 1102, 734, 697 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25-7.38 (m, 5H), 4.51 (s, 2H), 4.40 (dm, 1H, $J_{H-F}$ = 49.2 Hz), 3.48 (t, 2H, $J$ = 6.6 Hz), 1.68-1.21 (m, 22H), 0.91 (m, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.8, 128.3 (2C), 127.6 (2C), 127.5, 94.6 (d, $J_{C-F}$ = 220.1 Hz), 72.9, 70.6, 35.2 (d, $J_{C-F}$ = 28.1 Hz), 34.9 (d, $J_{C-F}$ = 27.6 Hz), 29.9-29.4 (4C), 27.3 ($J_{C-F}$ = 6.0 Hz), 26.2, 25.2 (d, $J_{C-F}$ = 5.9 Hz), 22.6, 14.1 $^{19}F$ NMR (400 MHz, $CDCl_3$) δ -180.4 (m). HRMS-ESI calcd for $C_{21}H_{35}FO$ $[M+NH_4]^+$ 340.301 found 340.3009.




**17** **S3** (98%)

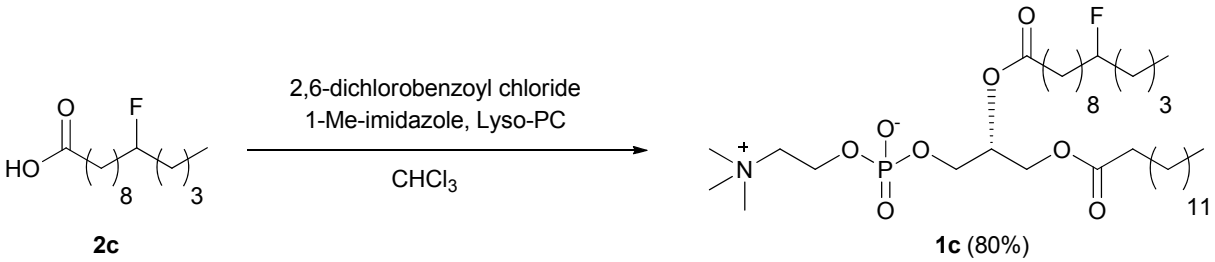
**10-fluorotetradecanol (S3):** To a solution of **17** (90 mg, 0.28 mmol) in THF:AcOH (2.8 mL of a 1:1 mixture) was added 10% Pd/C (32 mg, 0.03 mmol). The system was purged 3 times cycling between vacuum and $H_2$ (3 atm). The reaction mixture was agitated under $H_2$ atmosphere (2 atm) for 24 h. The mixture was then diluted with EtOAc (ca. 12 mL) and filtered over Celite. The filtrate was washed 3 times with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **S3** (64 mg, 98%). Spectral data for **S3** were identical with those previously reported.[8]



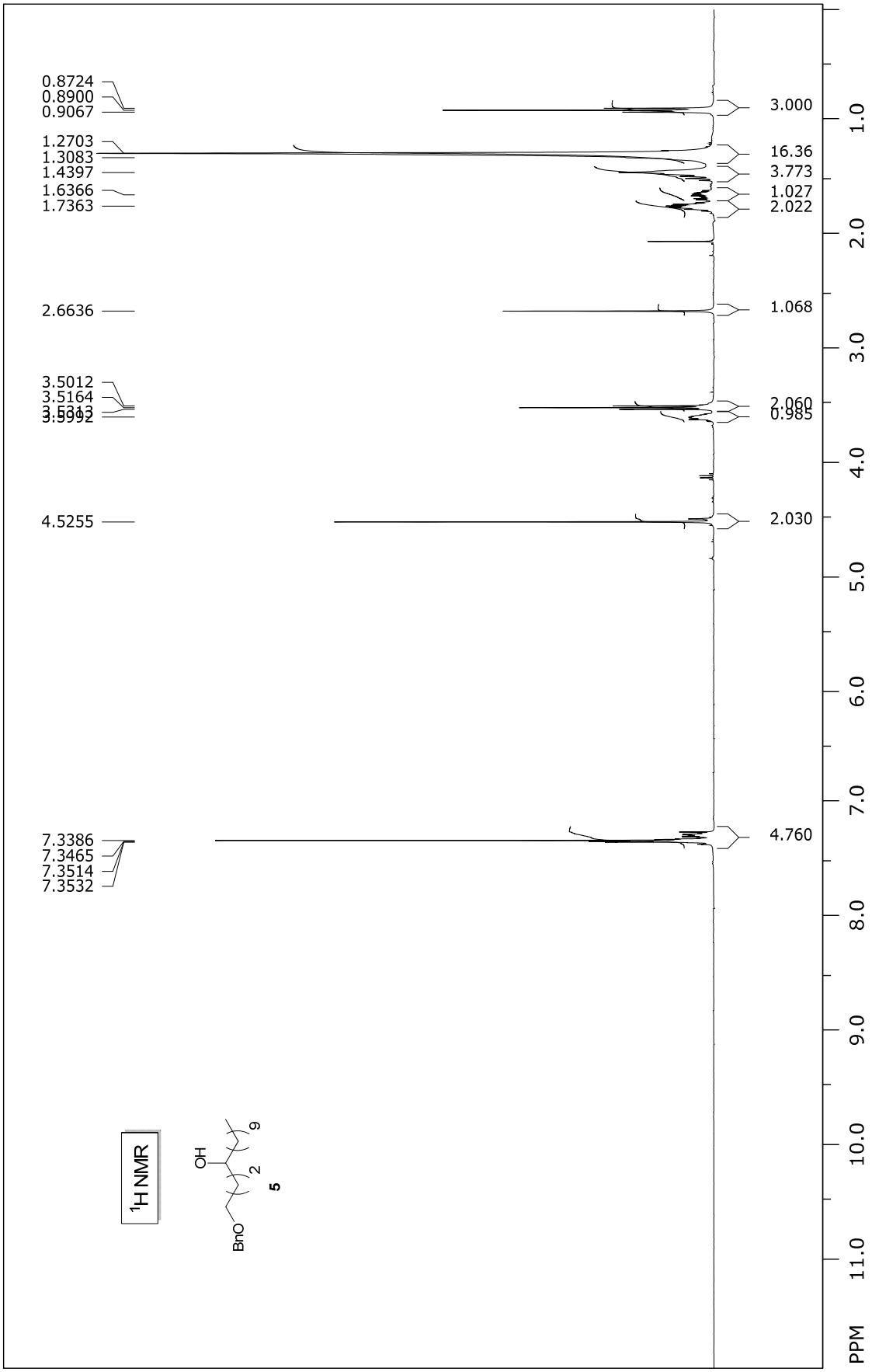

**S3** **2c** (77%)

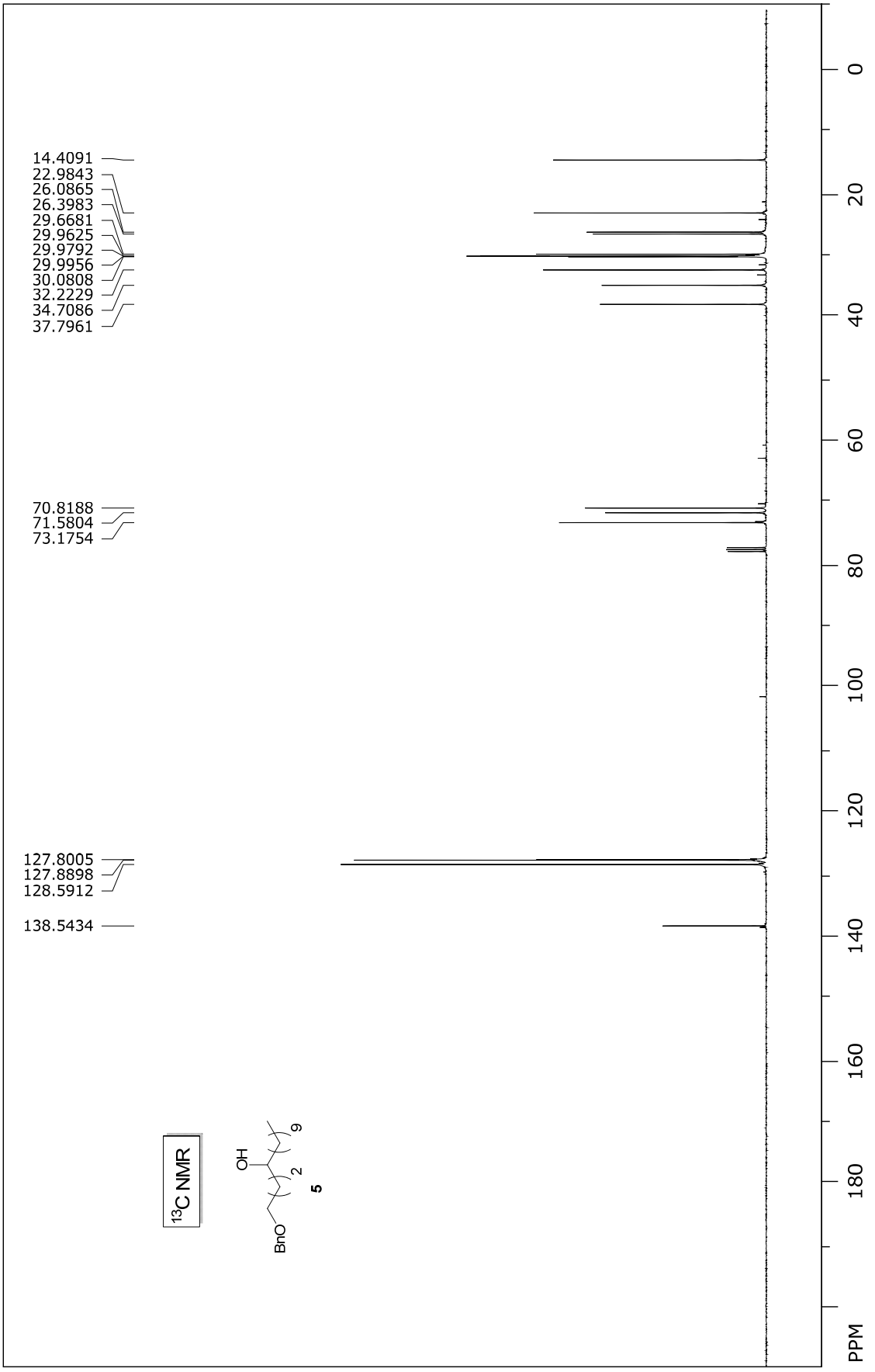
**10-fluorotetradecanoic acid (2c):** To a mixture of TEMPO (2.2 mg, 0.014 mmol) in $CH_3CN$ (0.77 mL) and a phosphate buffer (pH 6.7, 0.67 M, 0.57 mL) at 35 °C was added **S3** (37 mg, 0.16 mmol). Solutions of sodium chlorite (29 mg, 0.32 mmol) in water (150 µL) and sodium hypochlorite (2 µL of a 10% aqueous solution, 3.2 µmol) diluted in water (76 µL) were added dropwise over 2 h in two separate syringe. The reaction was stirred for 4 h at 35 °C and allowed to cooled to room temperature. Water (1 mL) was added then the pH was adjusted to 8 with a 2 M NaOH solution. The reaction mixture was poured in sat. aq. $Na_2SO_3$ and maintained under 20 °C (pH was around 8.5-9.0) After stirring for 10 minutes, the solution was extracted by $Et_2O$ (1 mL) and the organic phase was discarded. The aqueous phase was then acidified to pH 3-4 by a 2 M HCl solution. Some sat. aq. NaCl was added to the mixture before extracted with EtOAc (3×). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **2c** (30 mg 77%). Spectral data for **2c** were identical with those previously reported.8

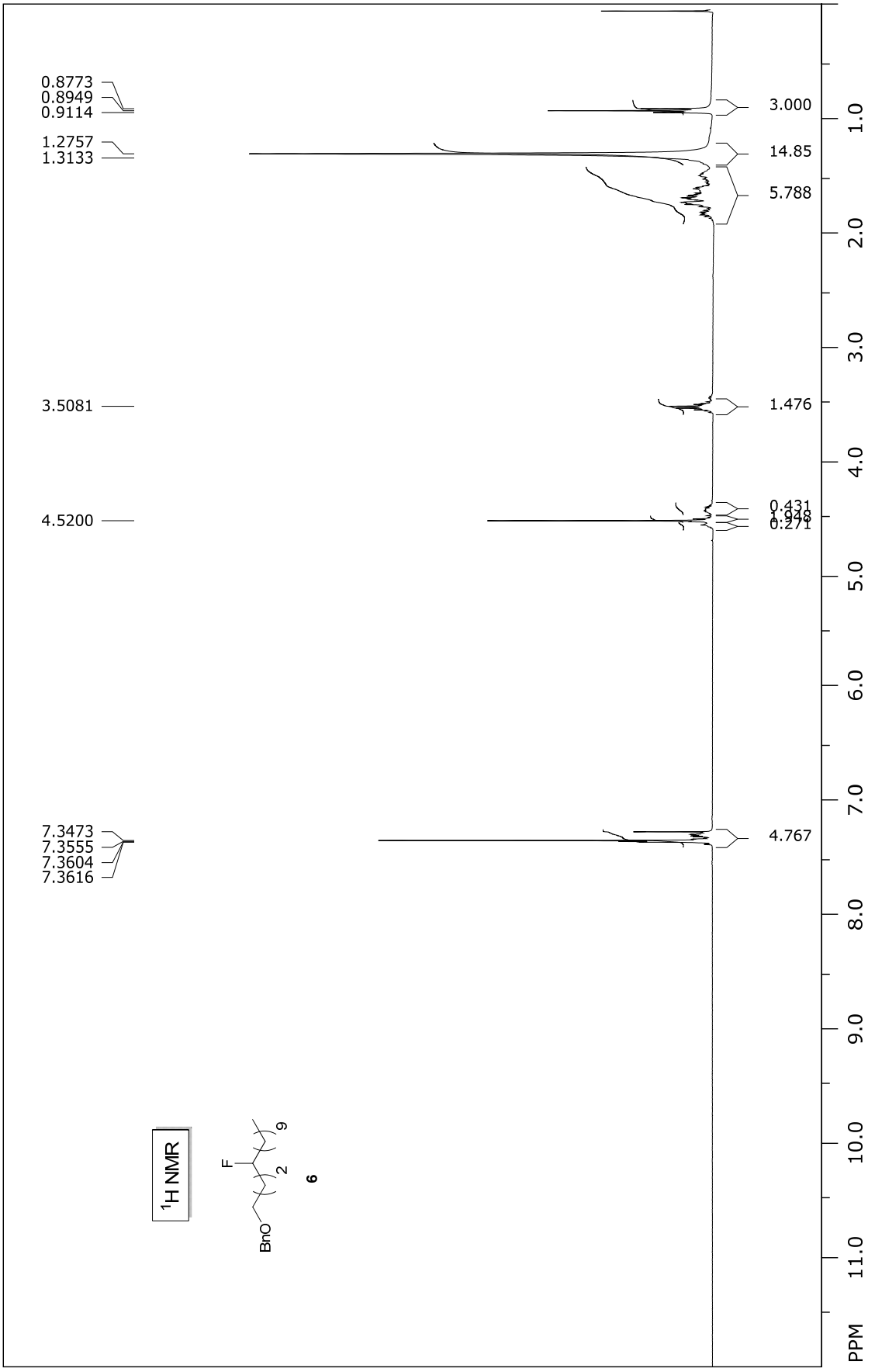
[8] Abad, J.-L.; Villorbina, G.; Fabriàs, G.; Camps, F., *Lipids*, **2003**, *38*, 865.

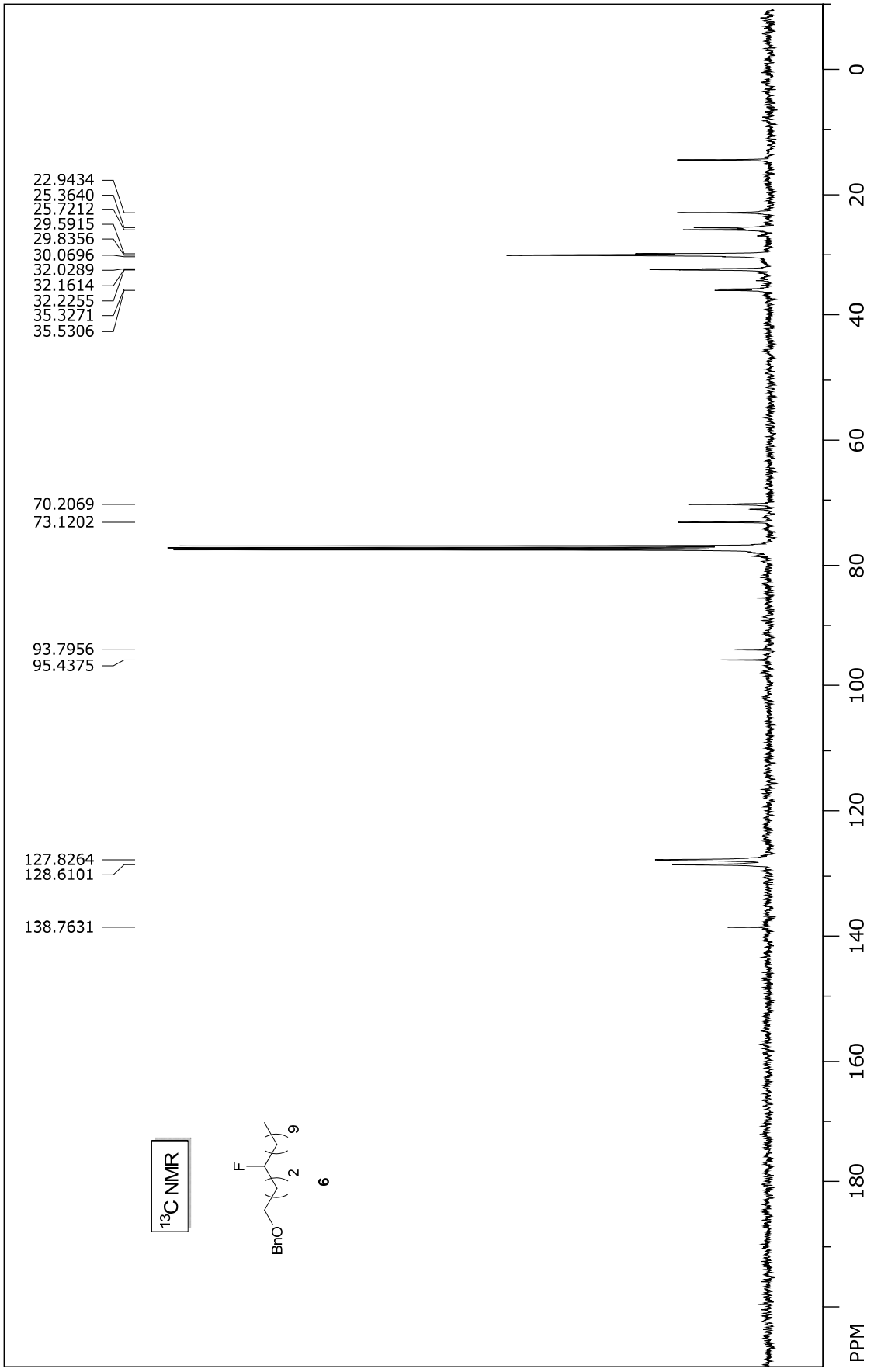


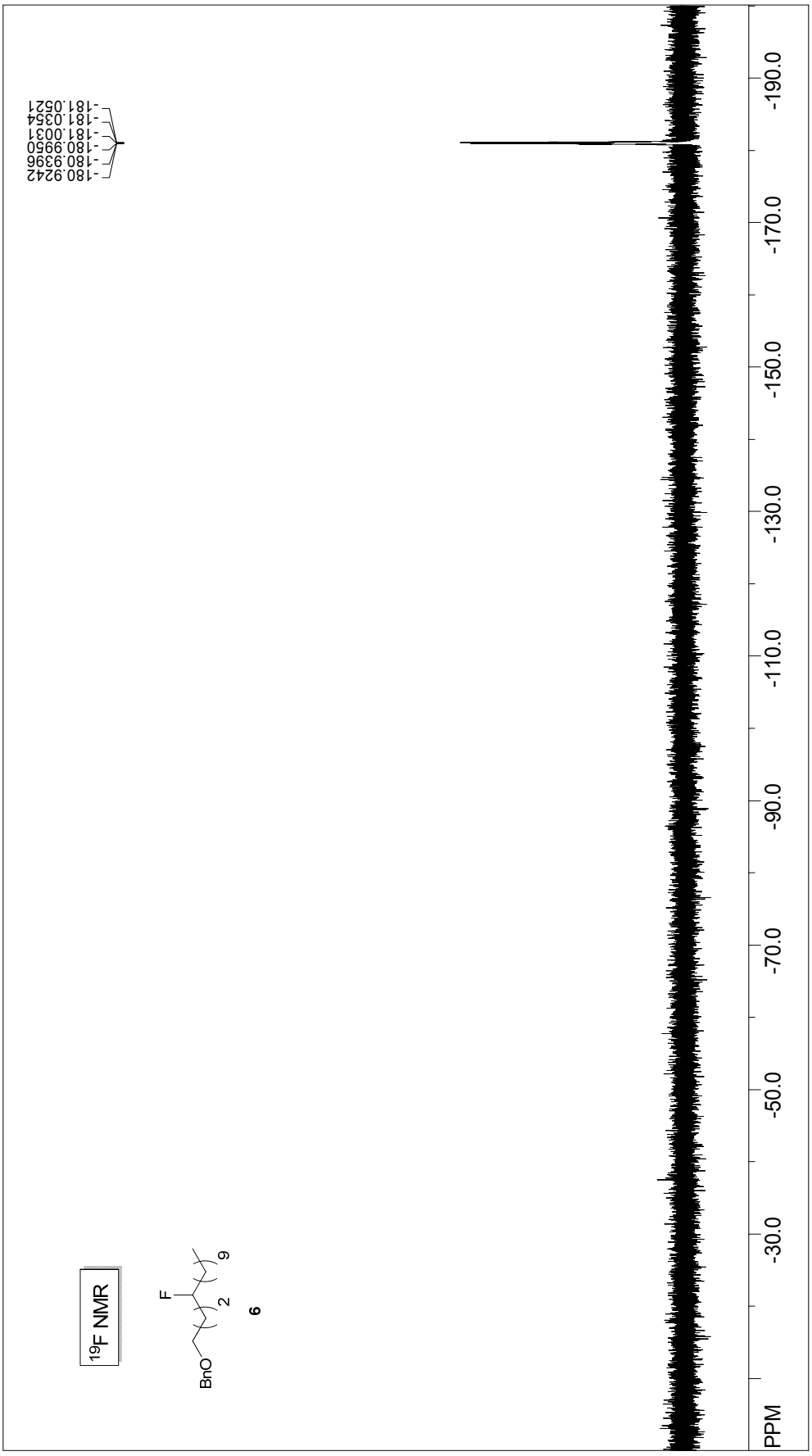

**10F-DMPC, 1-myristoyl-2-(10-fluoromyristoyl)-*sn*-glycero-3-phosphocholine (1c):** To a solution of **2c** (76.8 mg, 0.31 mmol), Lyso-PC (143 mg, 0.31 mmol) and 1-methylimidazole (74 µl, 0.93 mmol) in $CHCl_3$ (3.1 ml) was added 2,6-dichlorobenzoyl chloride (202 mg, 0.96 mmol) and the resulting mixture was stirred 16 h at room temperature. The reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:$CH_2Cl_2$) affording **1c** as an off-white powder (174 mg, 80%). IR (ATR, ZnSe) 3373, 2921, 2851, 1738, 1468, 1238, 1092, 1068, 971, 823 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.21 (bs, 1H), 4.53-4.27 (m, 4H), 4.13 (dd, 1H, $J$ = 11.4, 7.1 Hz), 3.94 (m, 2H), 3.87 (bs, 2H), 3.41 (s, 9H), 3.08 (q, 1H, $J$ = 7.0 Hz), 2.28 (q, 4H, $J$ = 7.6 Hz), 1.58 (bs, 6H), 1.49-1.20 (m, 35H), 0.88 (m, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.6, 173.4, 94.6 (d, $J_{C\text{-}F}$ = 166.7 Hz), 70.5, 63.6, 62.9, 54.7, 46.6, 35.2 (d, $J_{C\text{-}F}$ = 21.4 Hz), 34.9 (d, $J_{C\text{-}F}$ = 21.7 Hz), 34.2, 34.1, 31.9, 29.0-29.8 (14C), 27.3 (d, $J_{C\text{-}F}$ = 4.3 Hz), 25.1 (d, $J_{C\text{-}F}$ = 4.3 Hz), 24.9 (2C), 22.7, 22.6, 18.9, 14.1, 14.0. $^{19}F$ NMR (400 MHz, $CDCl_3$) δ -180.4 (m). $^{31}P$ NMR, (122 MHz, $CDCl_3$) δ -0.82. HRMS-ESI calcd for $C_{36}H_{71}FNO_8P$ $[M+H]^+$ 695.4901 found 696.5000.







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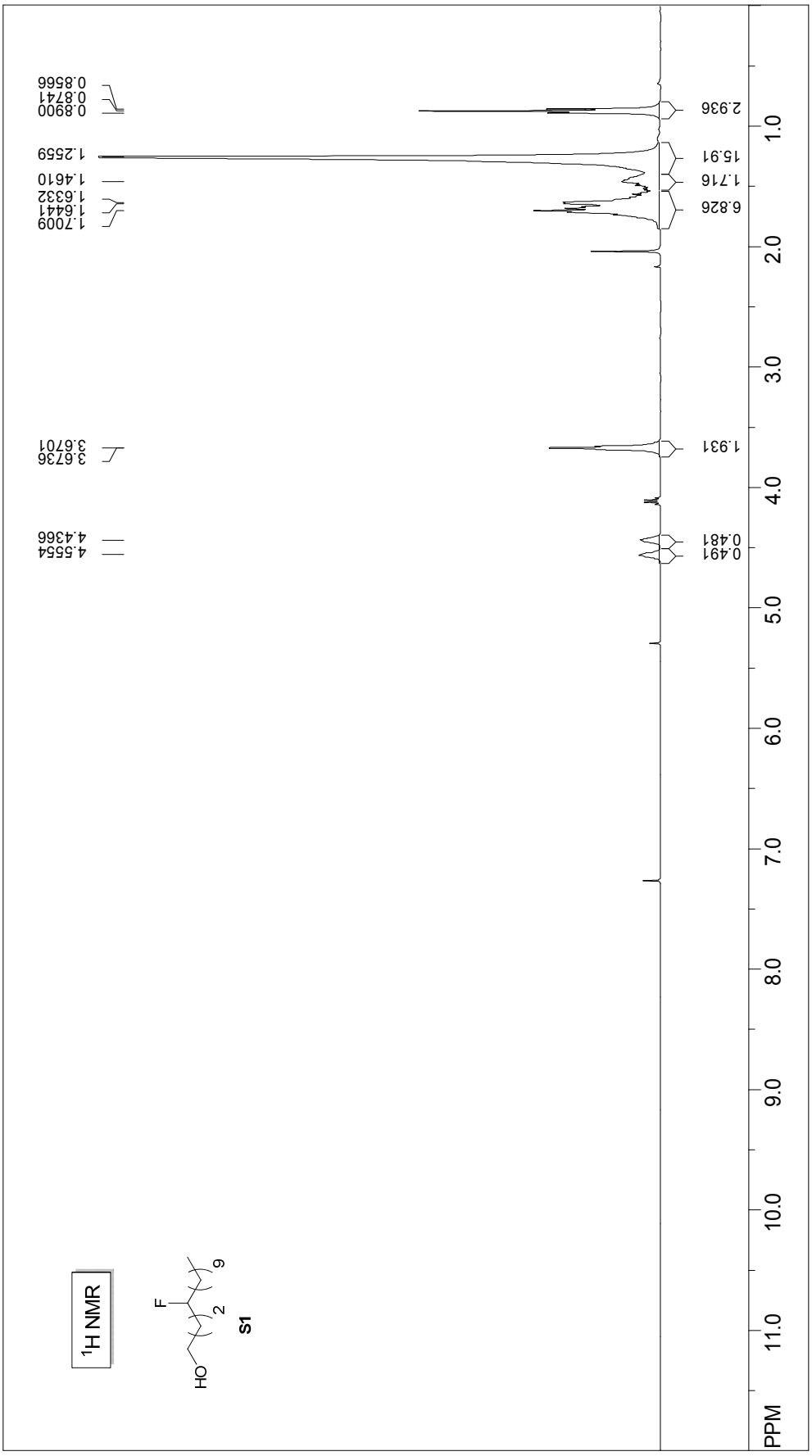

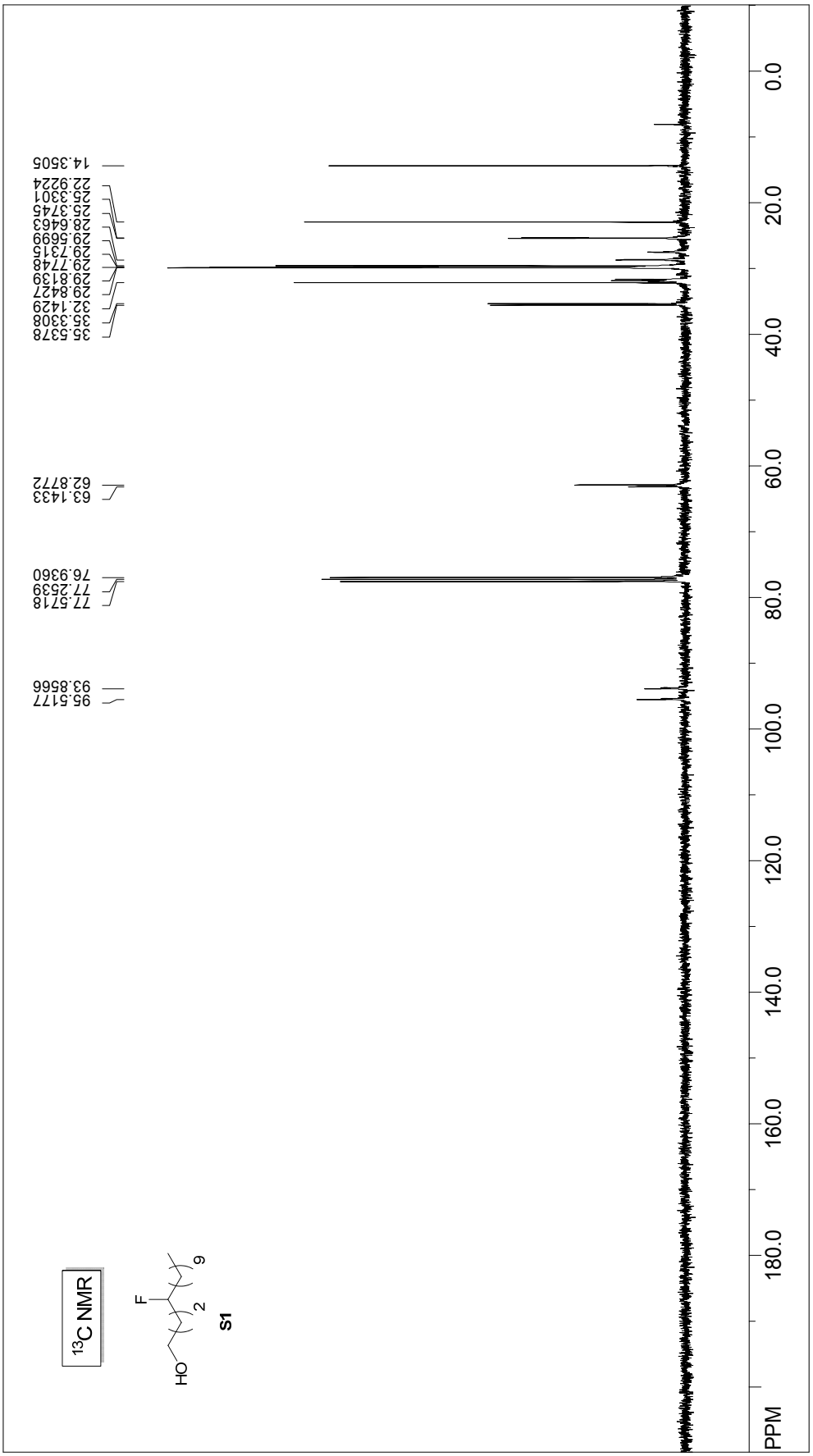

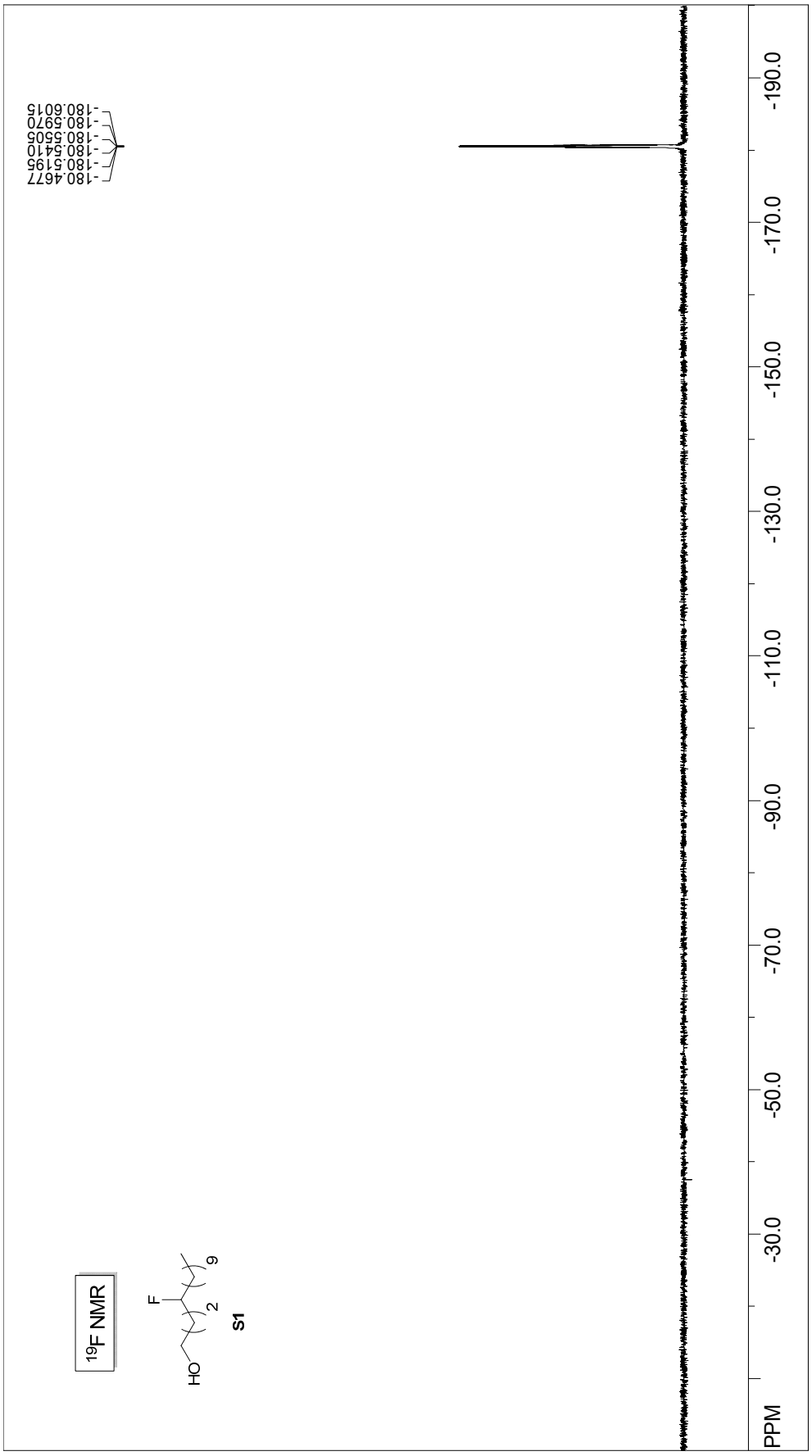

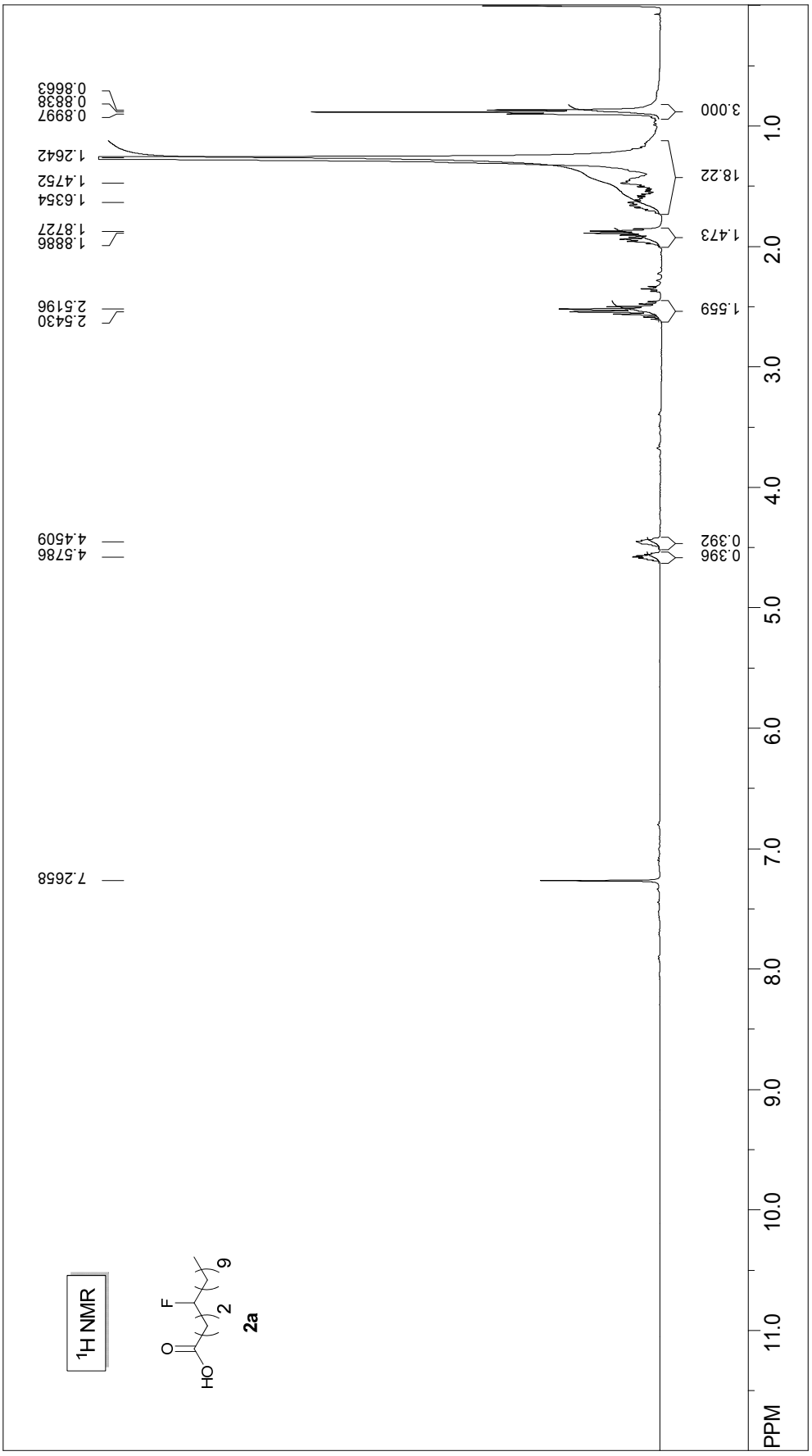

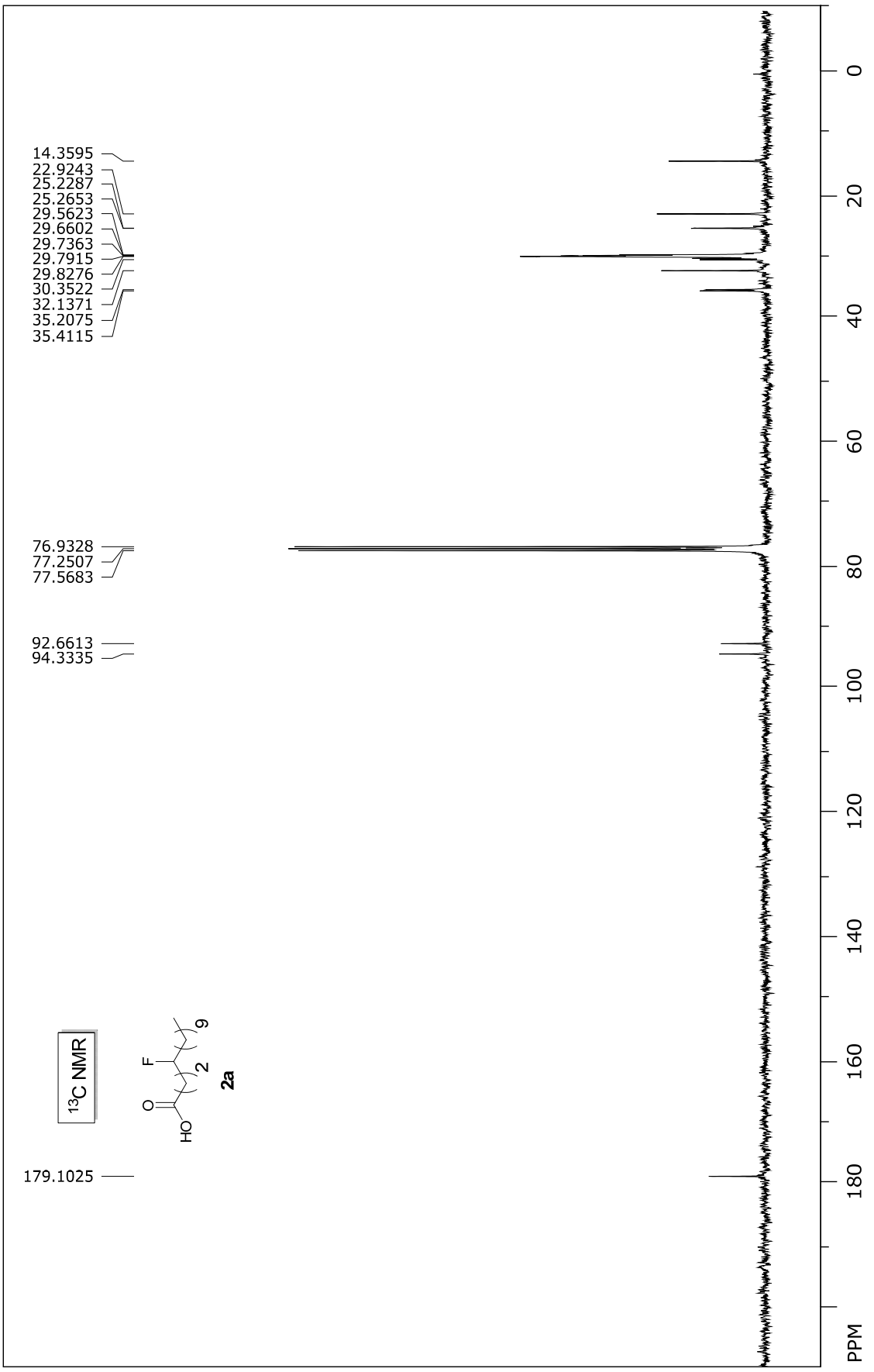

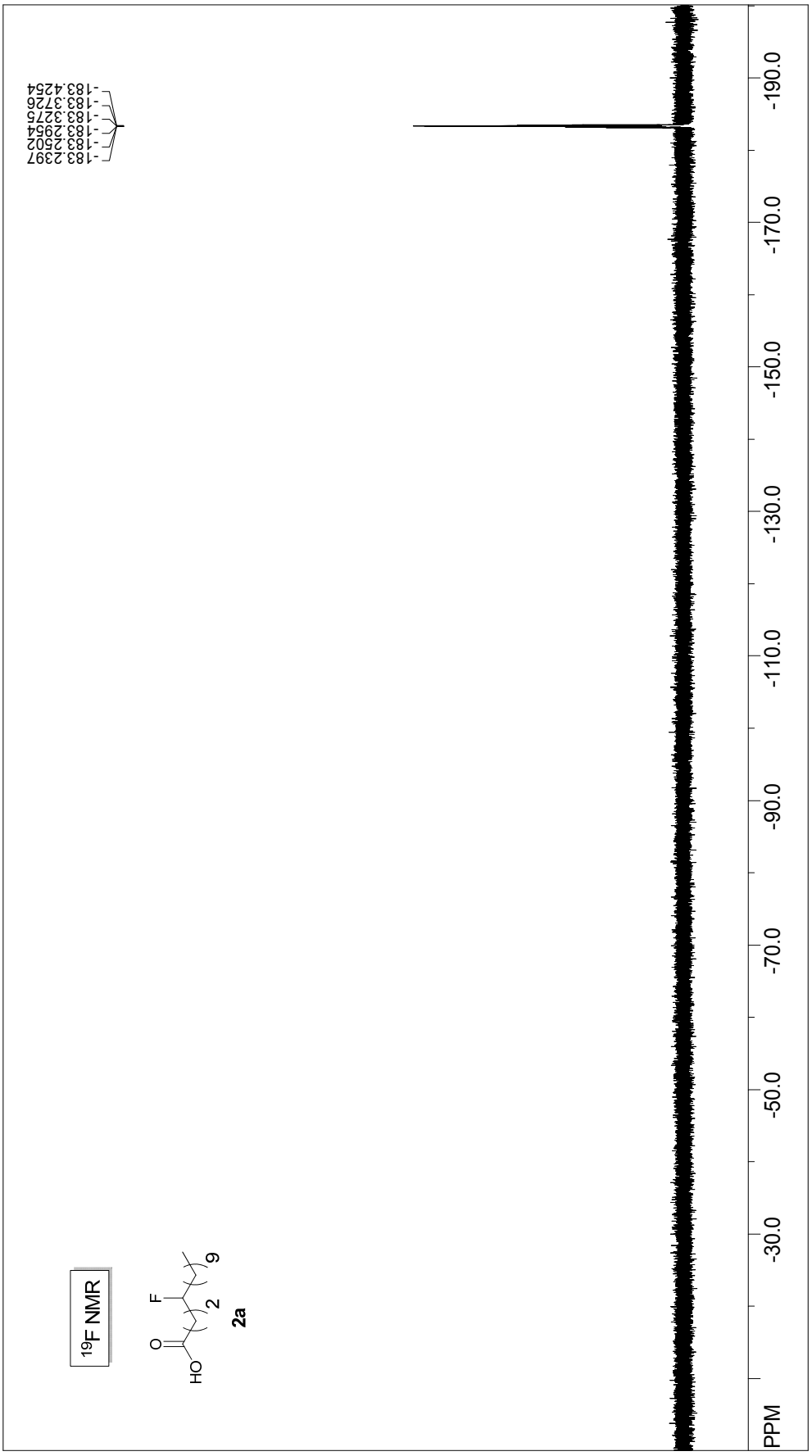

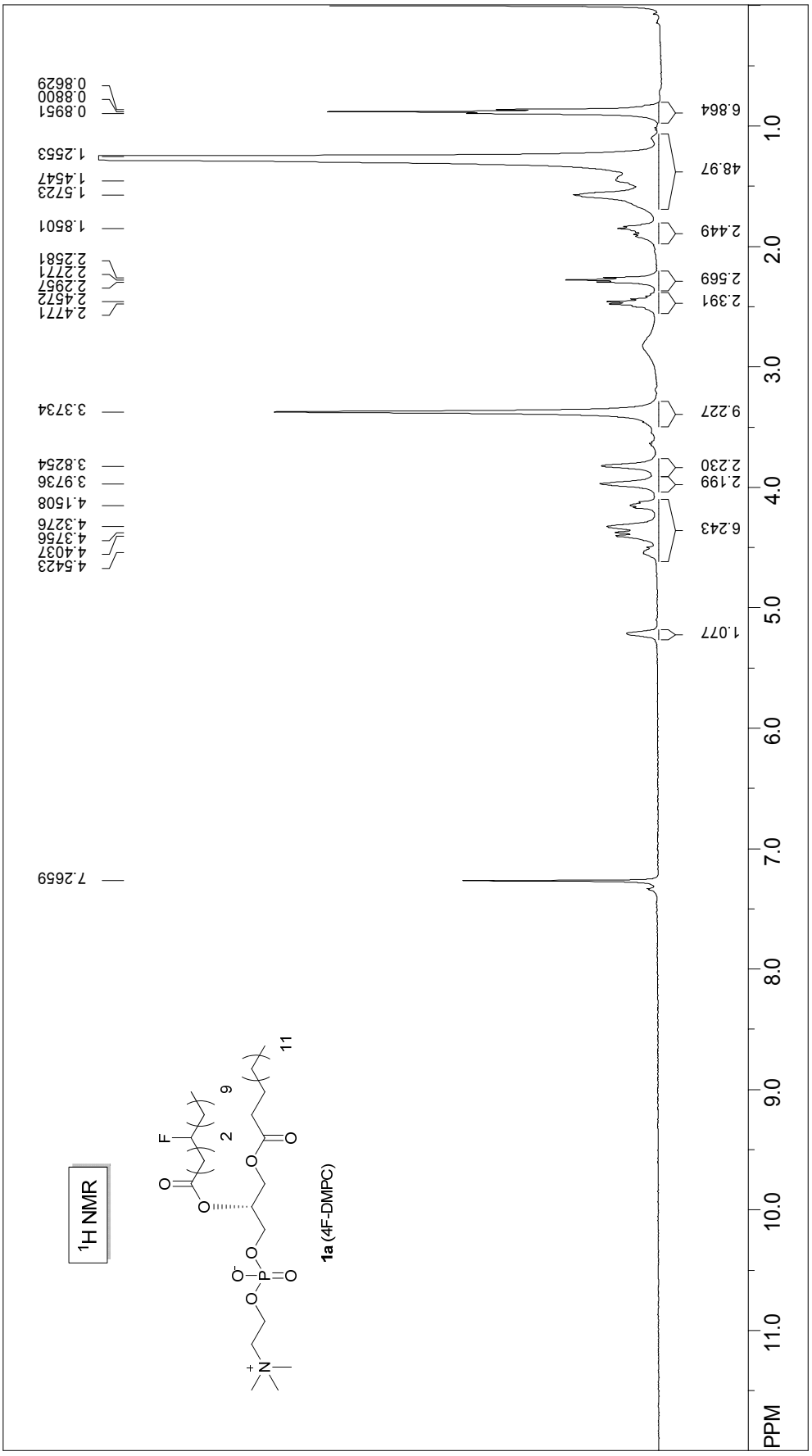

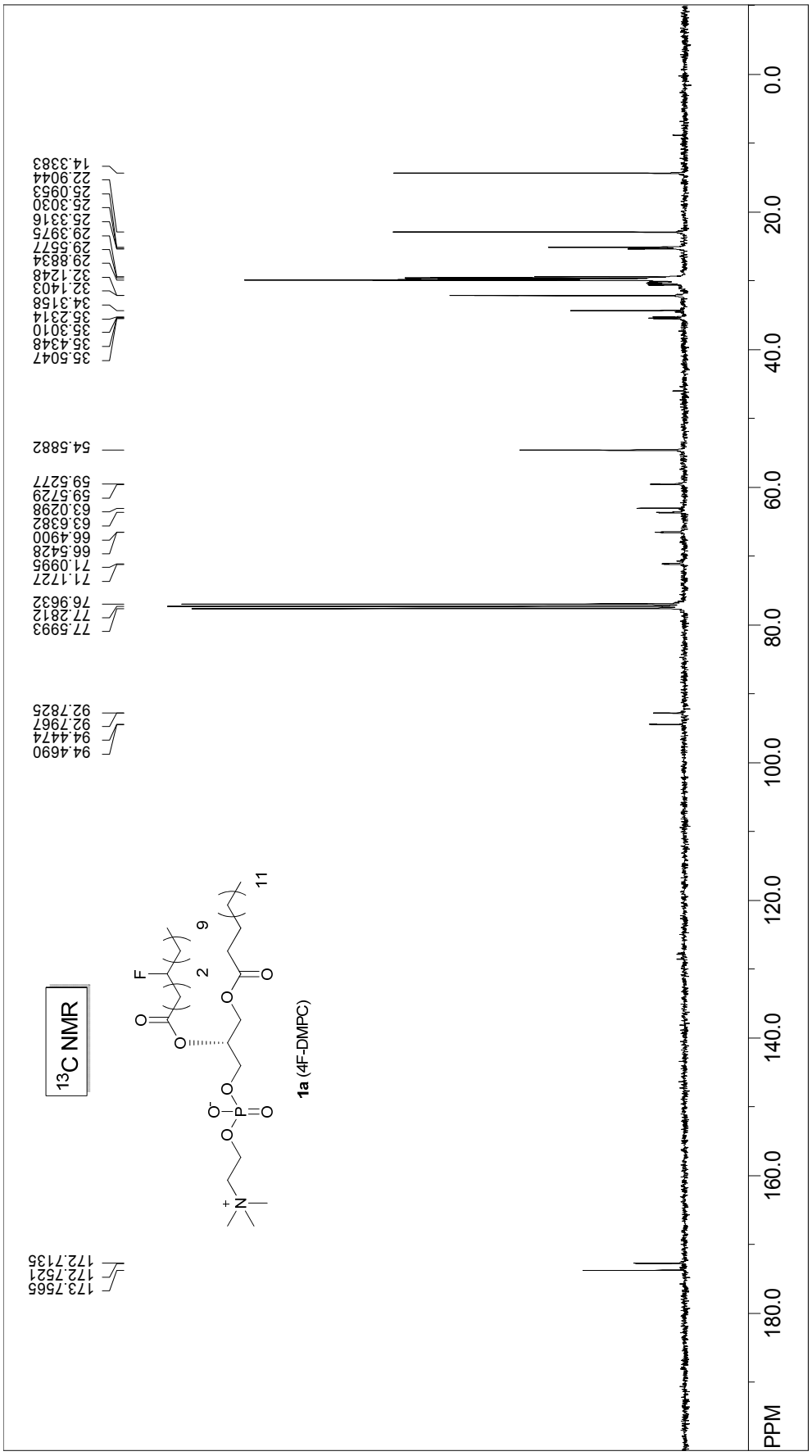
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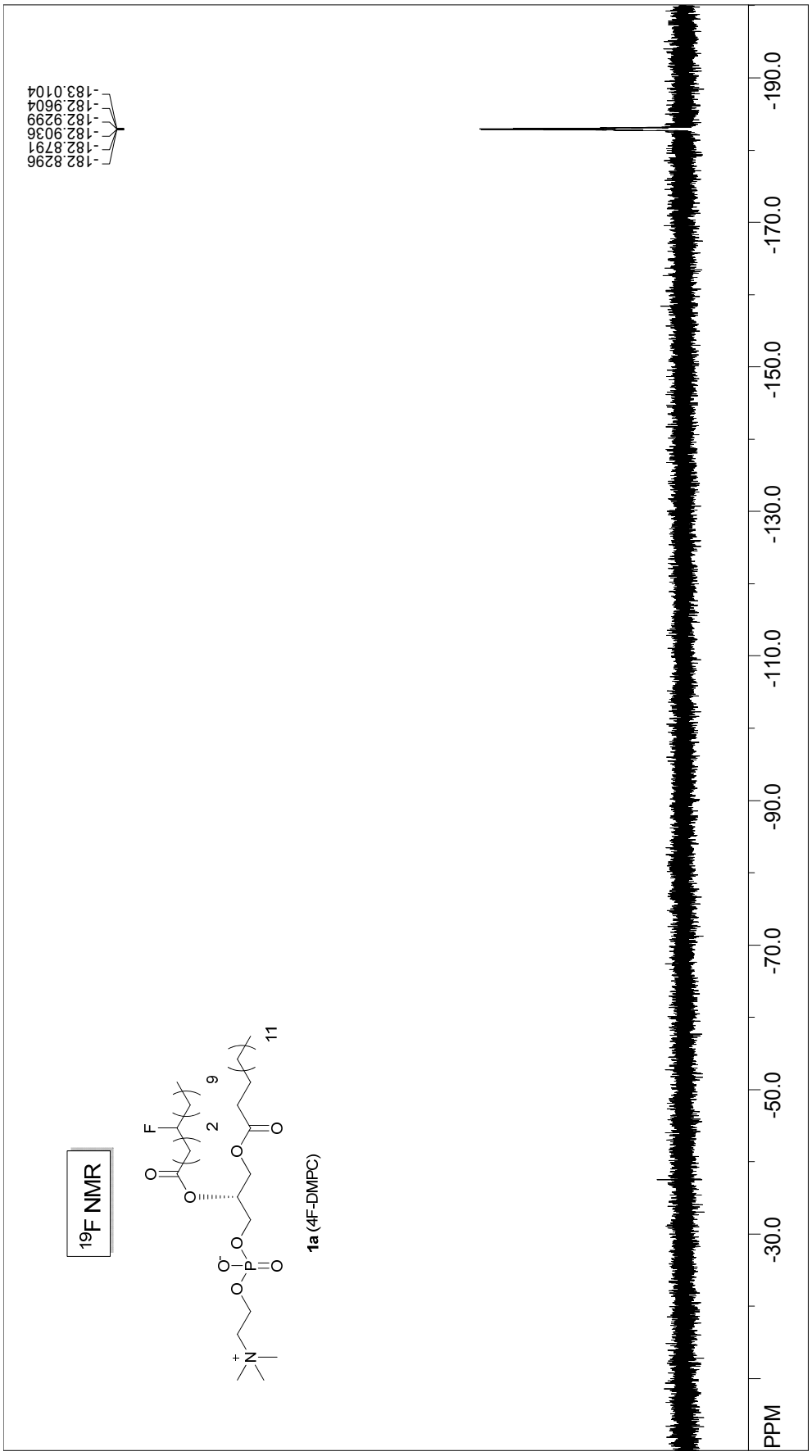
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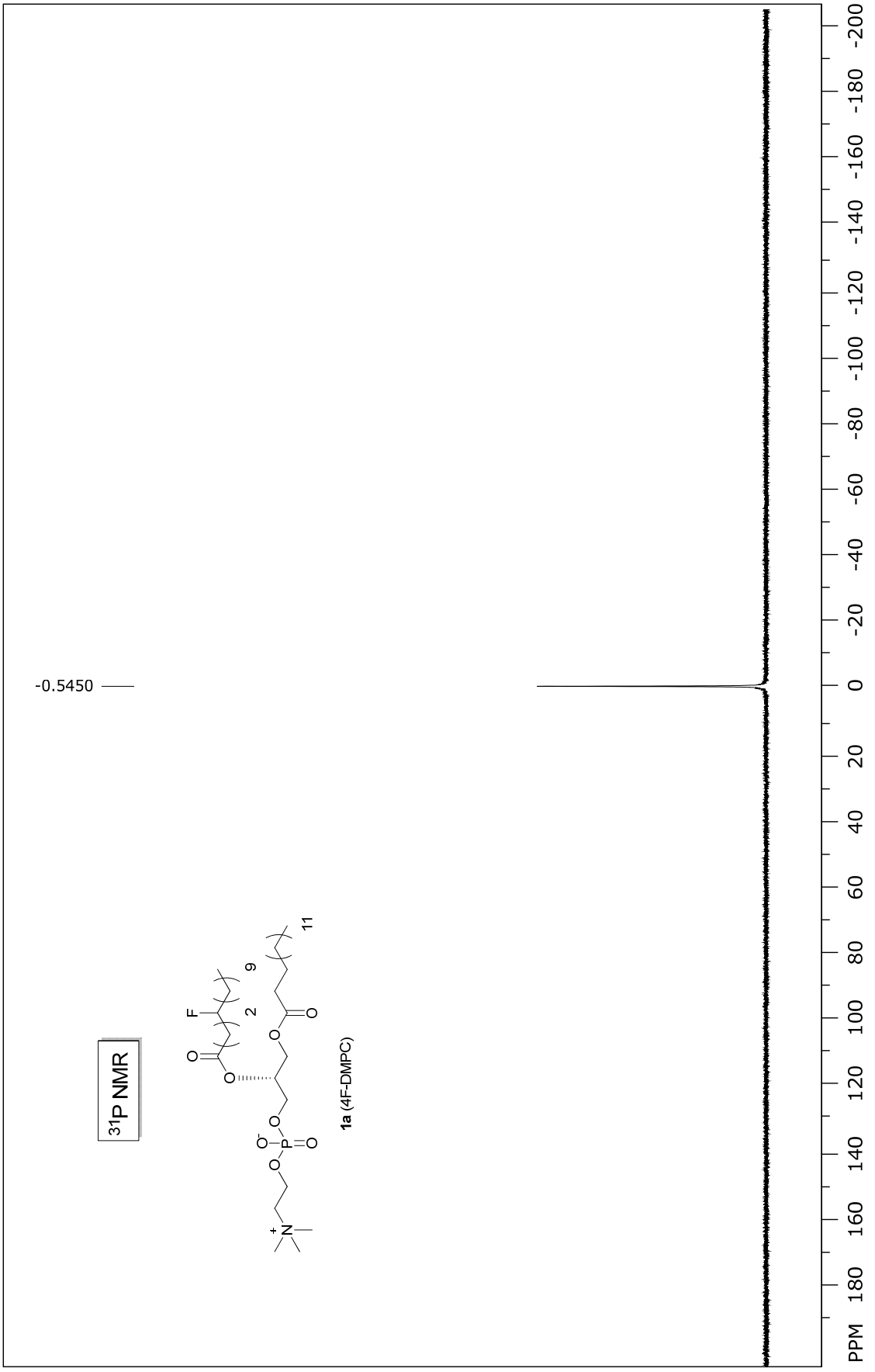

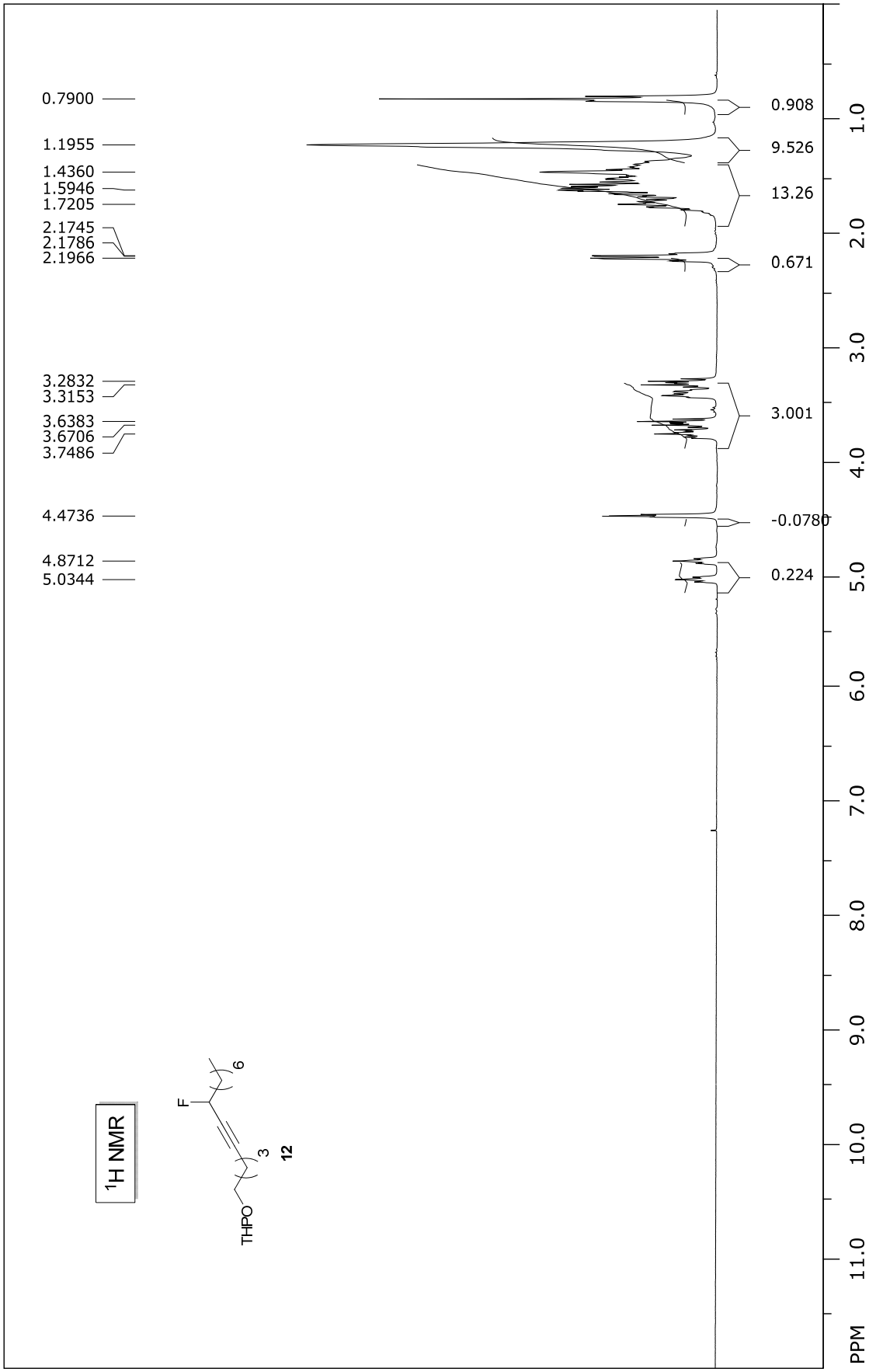

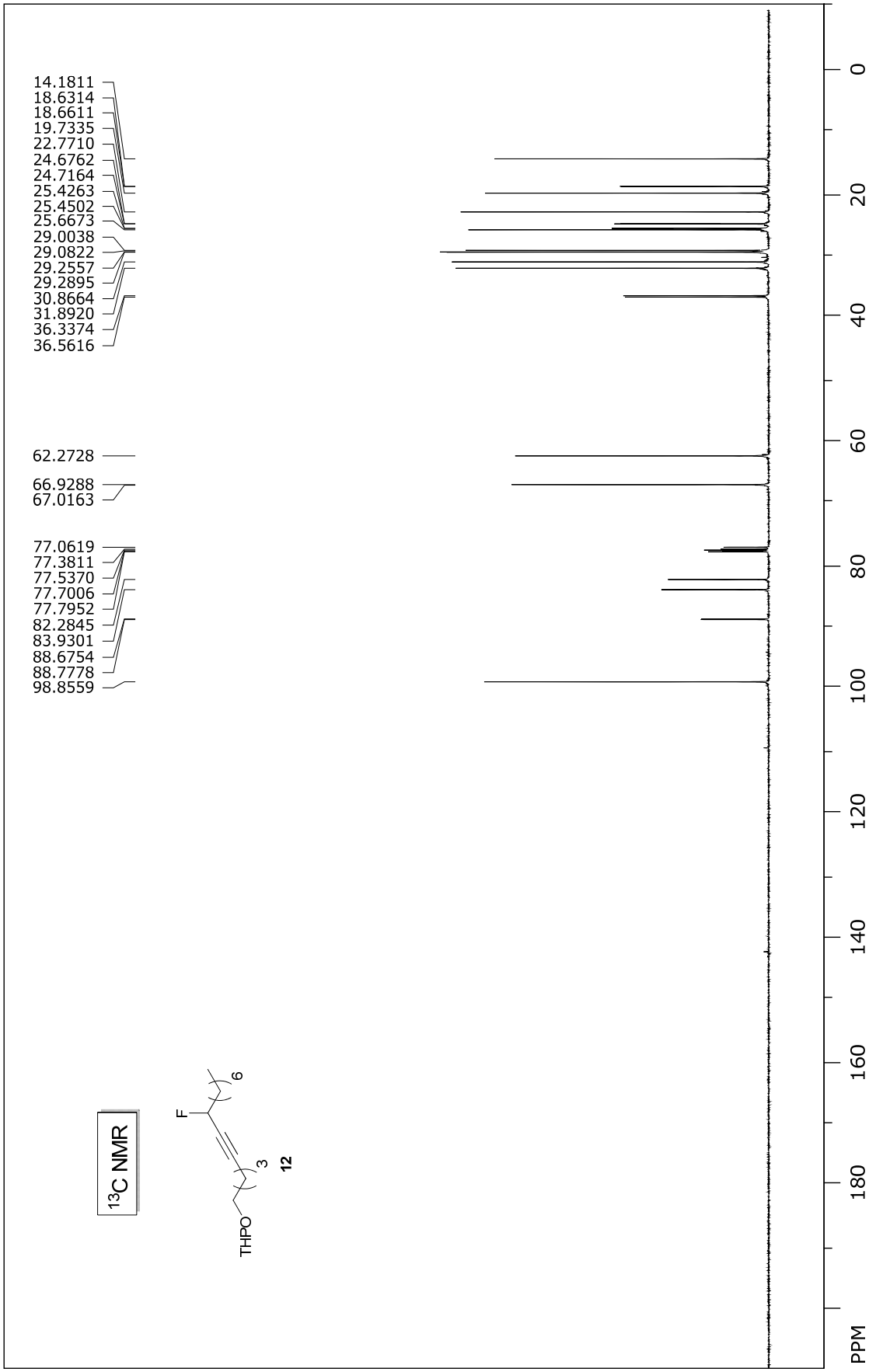

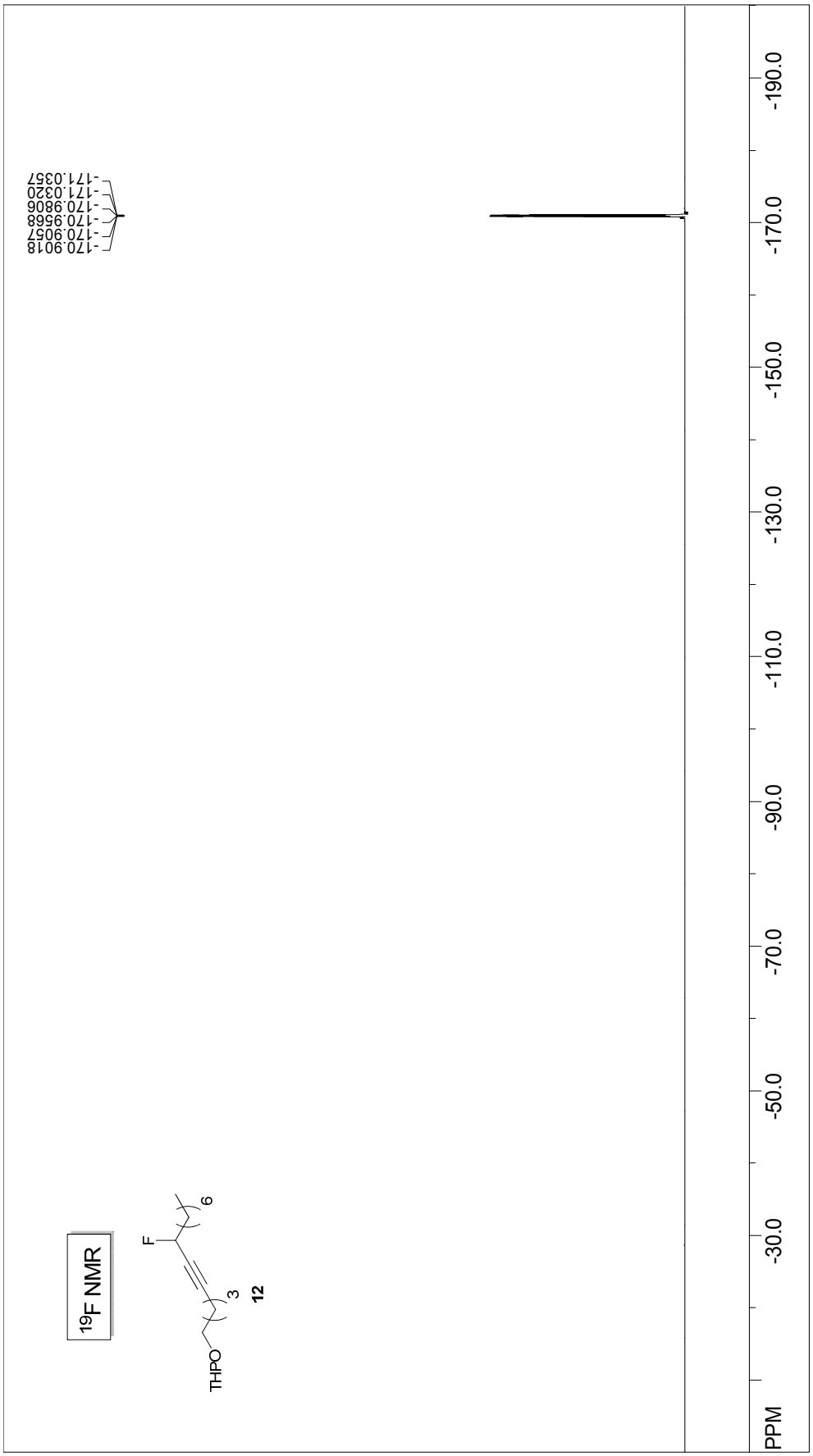

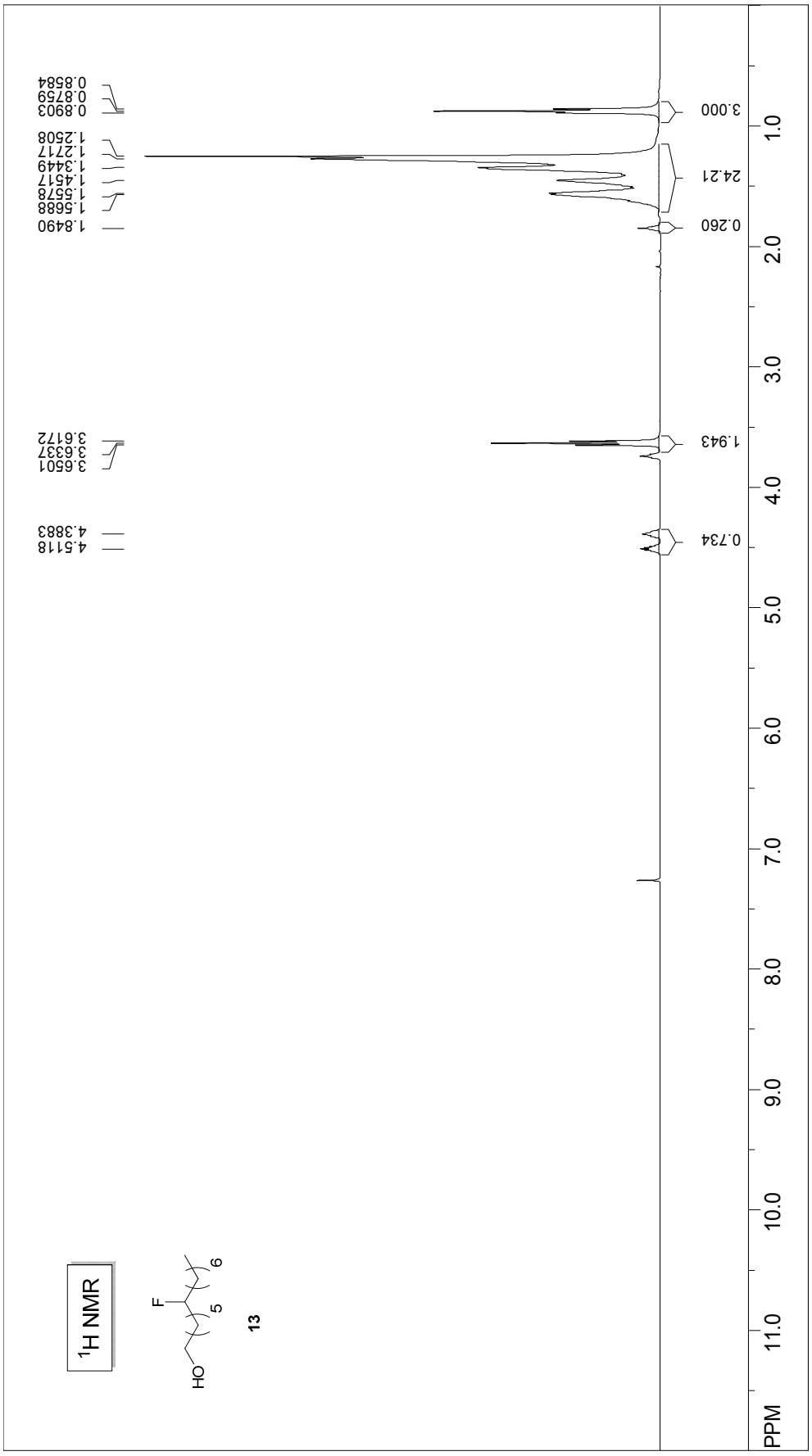

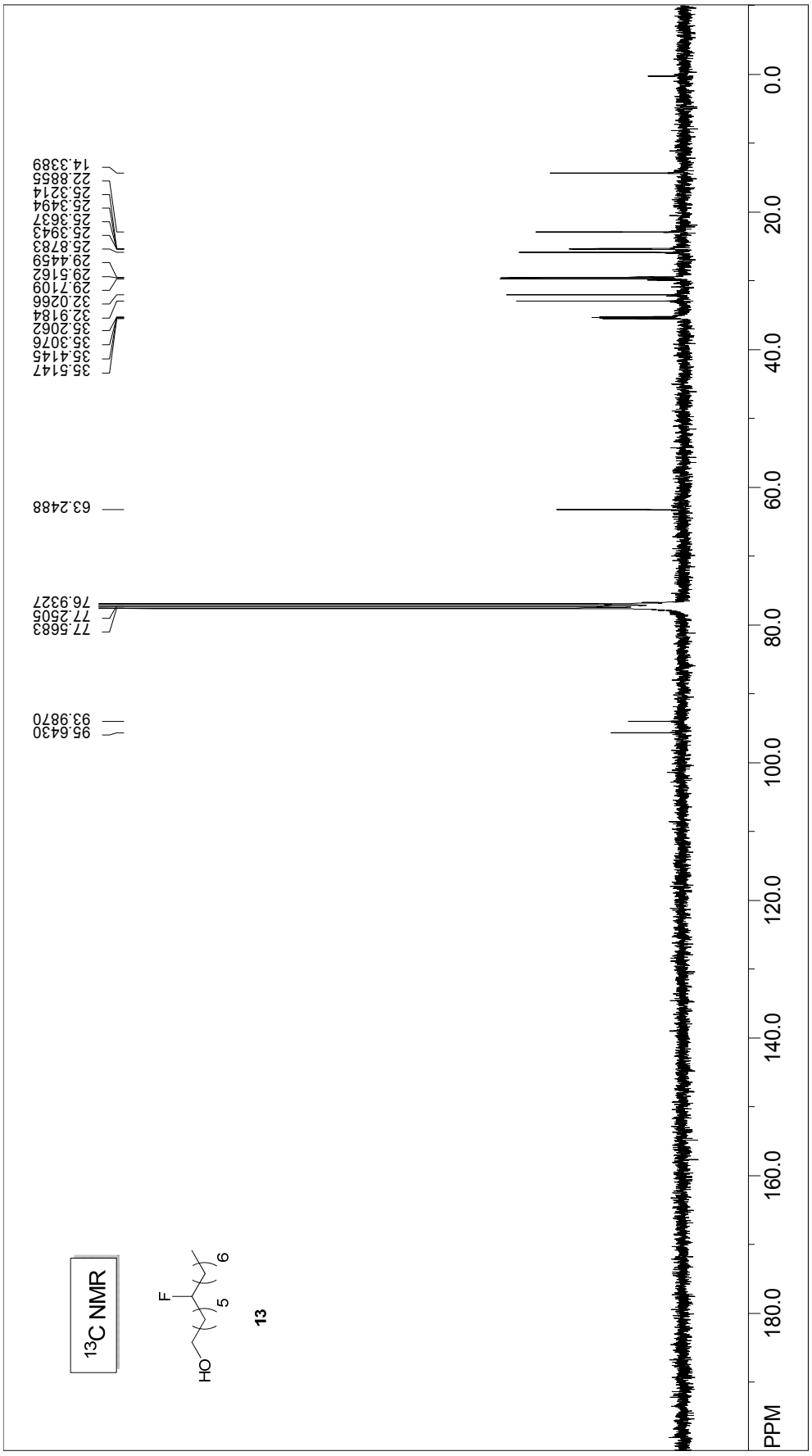

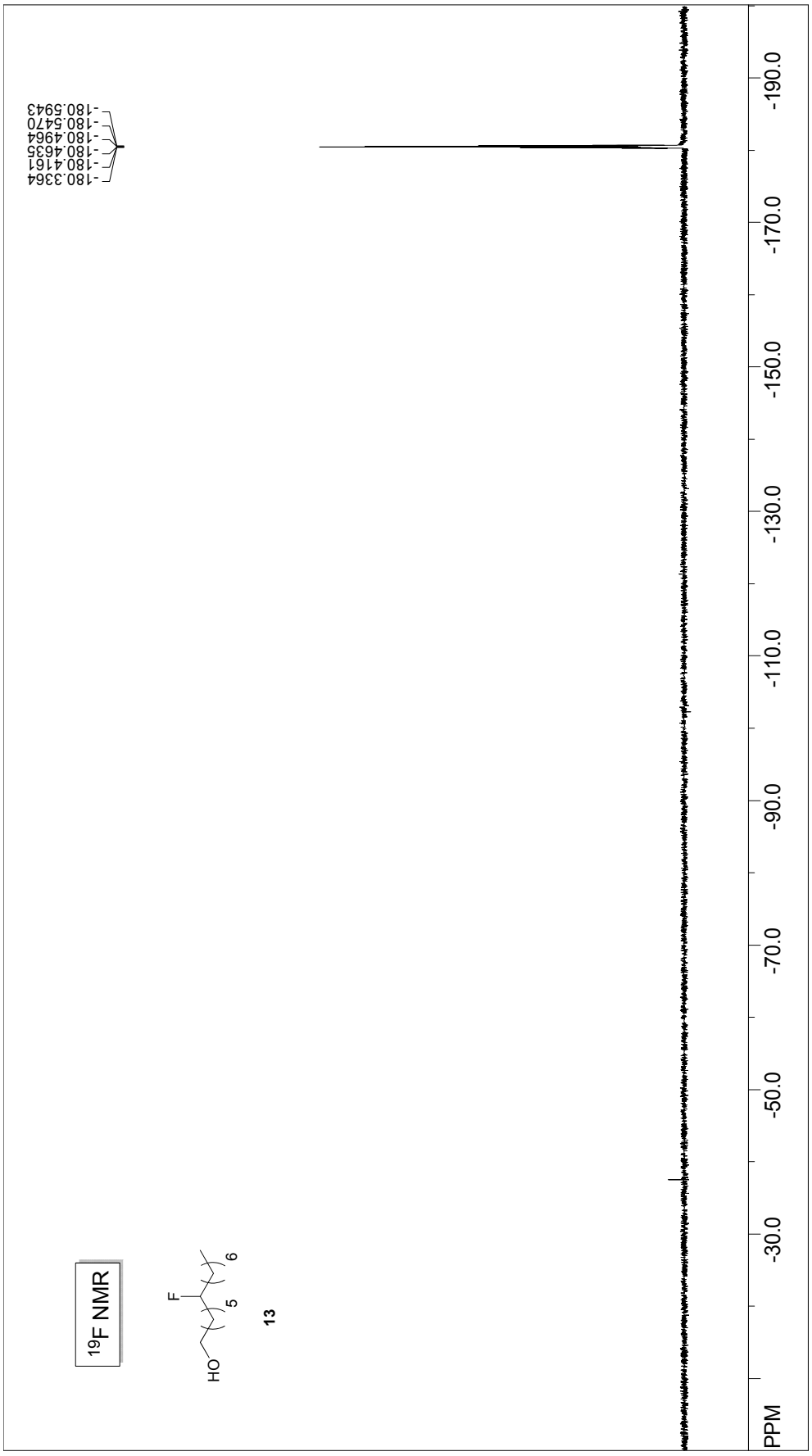

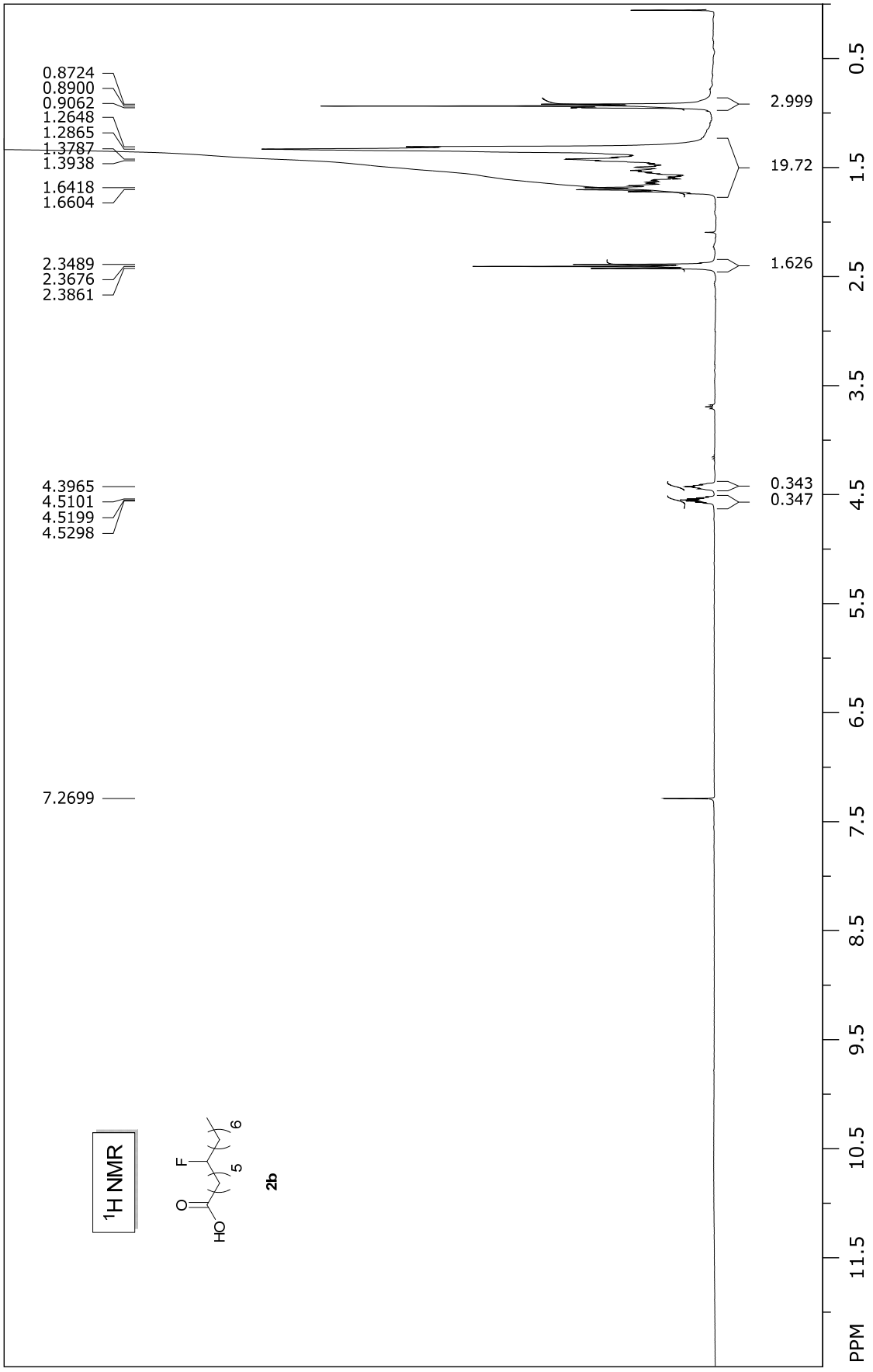

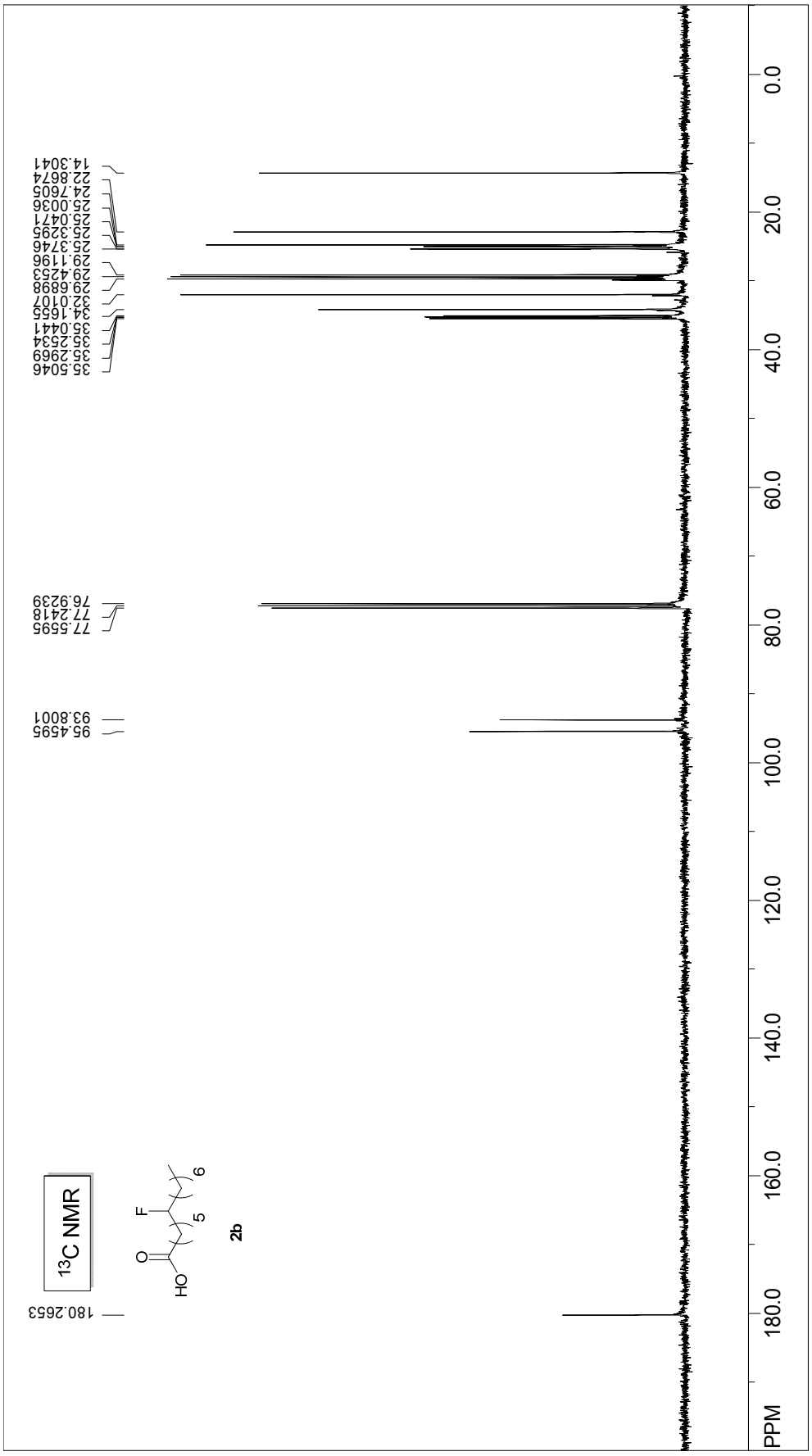

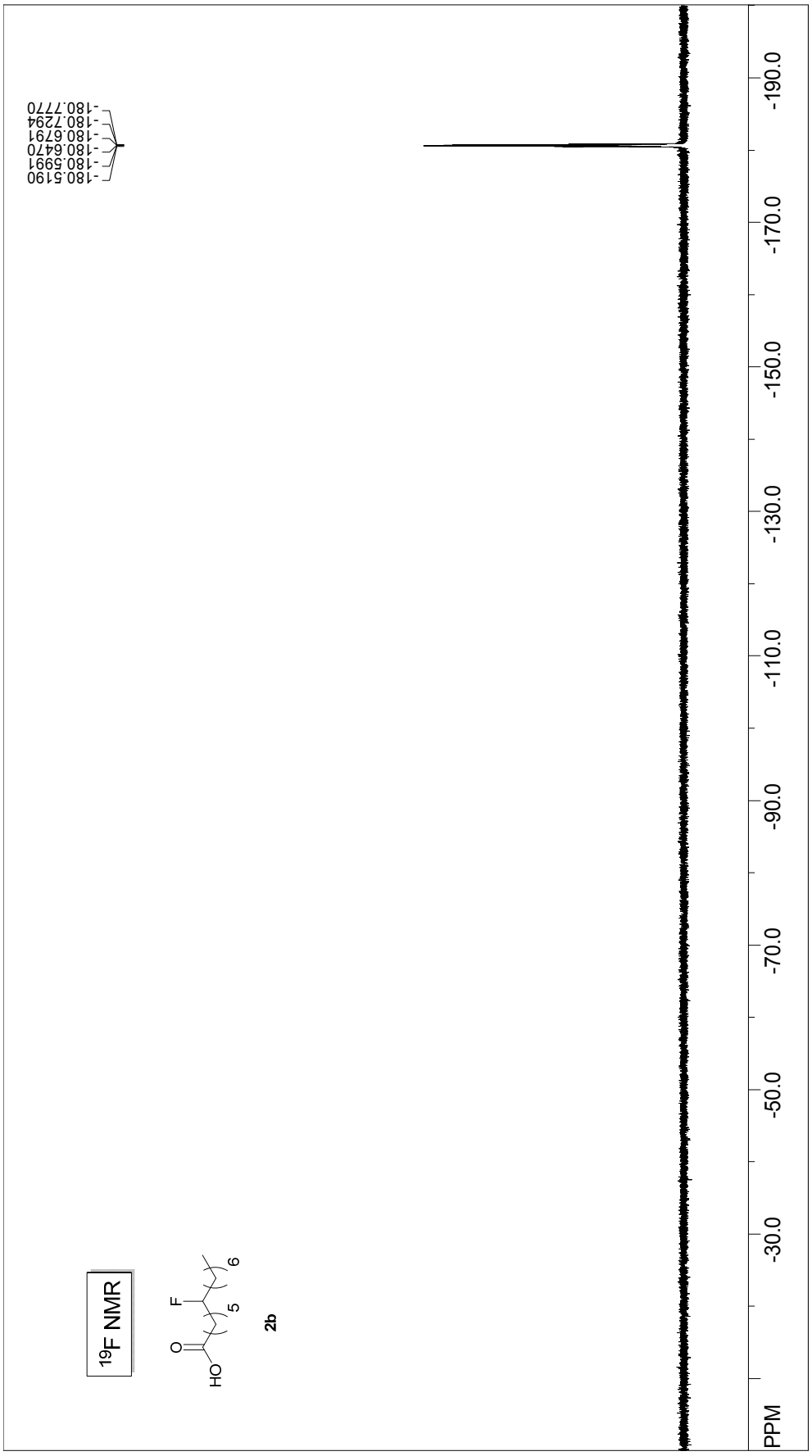

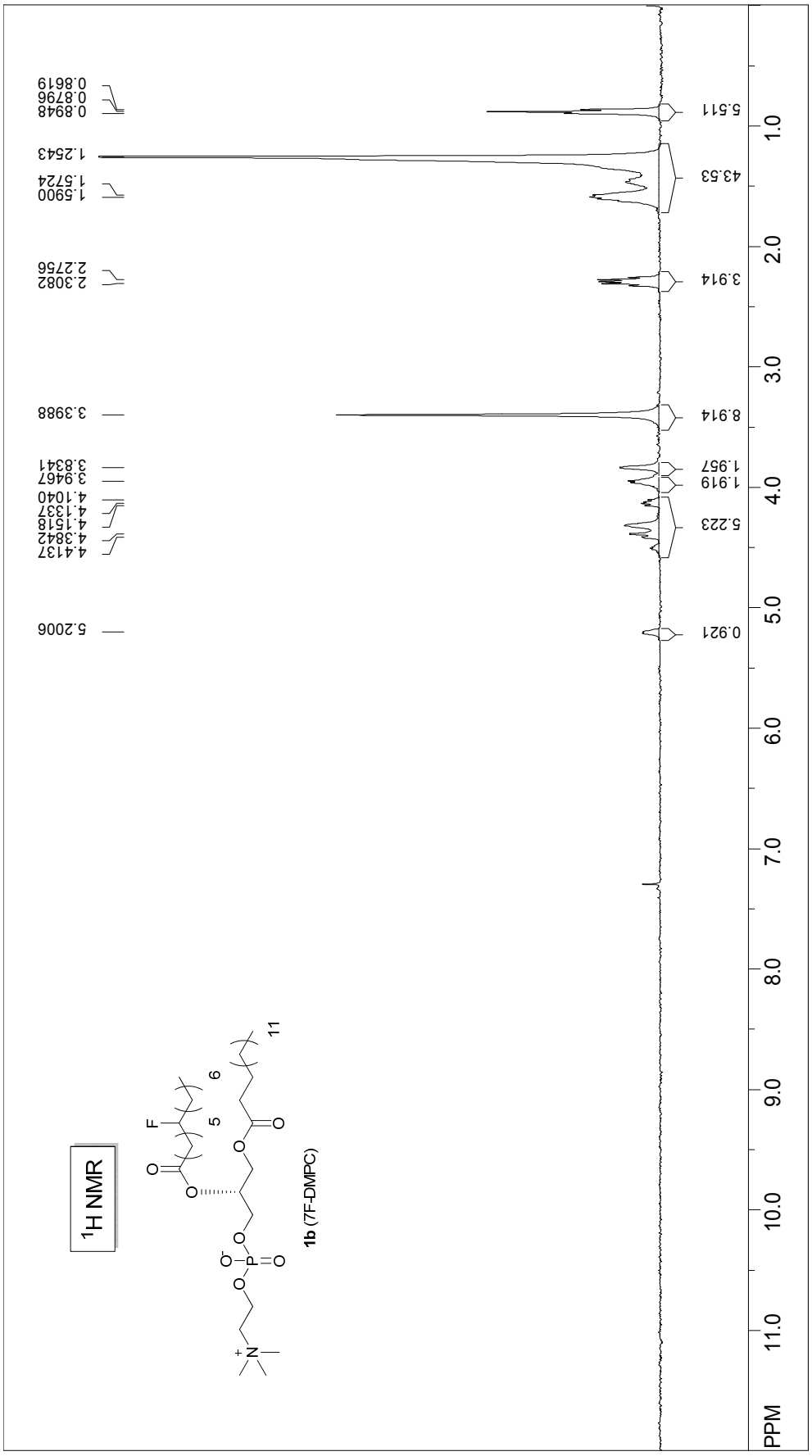
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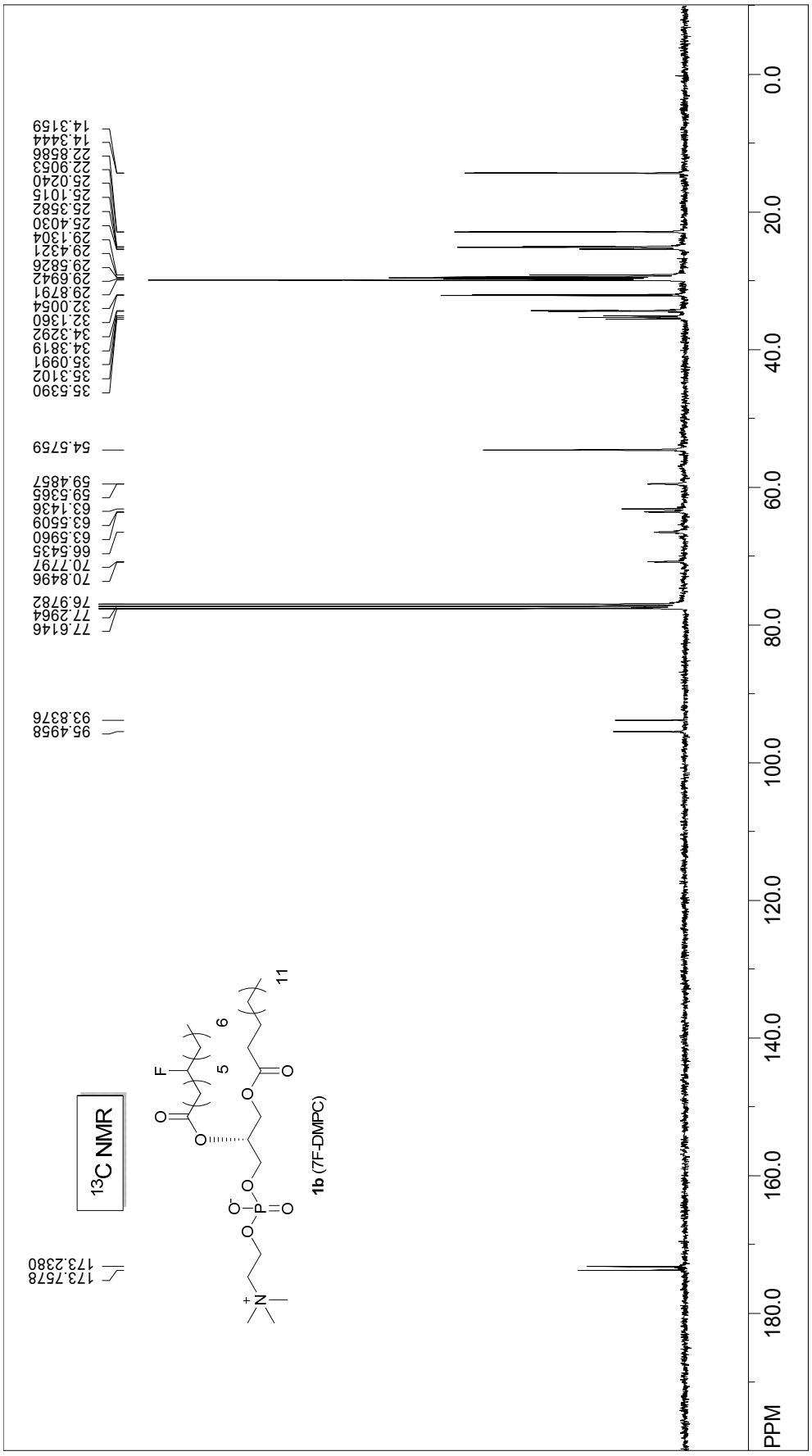
0.8796
0.8948
1.2543
1.5724
1.5900
2.2756
2.3082
3.3988
3.8341
3.9467
4.1040
4.1337
4.1518
4.3842
4.4137
5.2006
5.511
43.53
3.914
8.914
1.957
1.919
5.223
0.921
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
PPM
$^1$H NMR
F
O
O
5
6
O
O
11
O
O
O
O
P
O
O
N
**1b** (7F-DMPC)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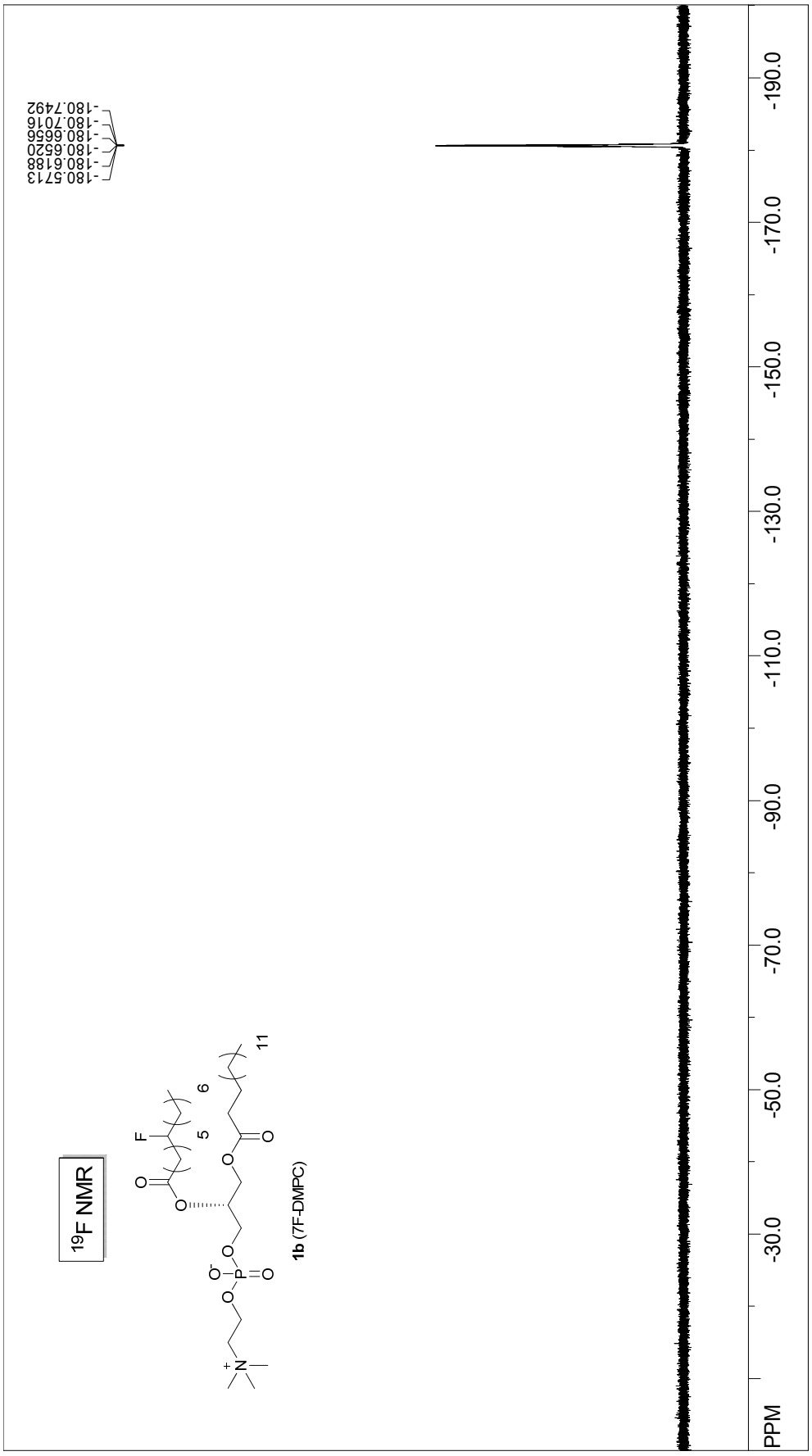
22.8586
22.9053
25.0240
25.1015
25.3582
25.4030
29.1304
29.4321
29.5826
29.6942
29.8791
32.0054
32.1360
34.3292
34.3819
35.0991
35.3102
35.5390
54.5759
59.4857
59.5365
63.1436
63.5509
63.5960
66.5435
70.7797
70.8496
76.9782
77.2964
77.6146
93.8376
95.4958
173.2380
173.7578
PPM
0.0
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
13C NMR
1b (7F-DMPC)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-180.6188
-180.6520
-180.6656
-180.7016
-180.7492
-190.0
-170.0
-150.0
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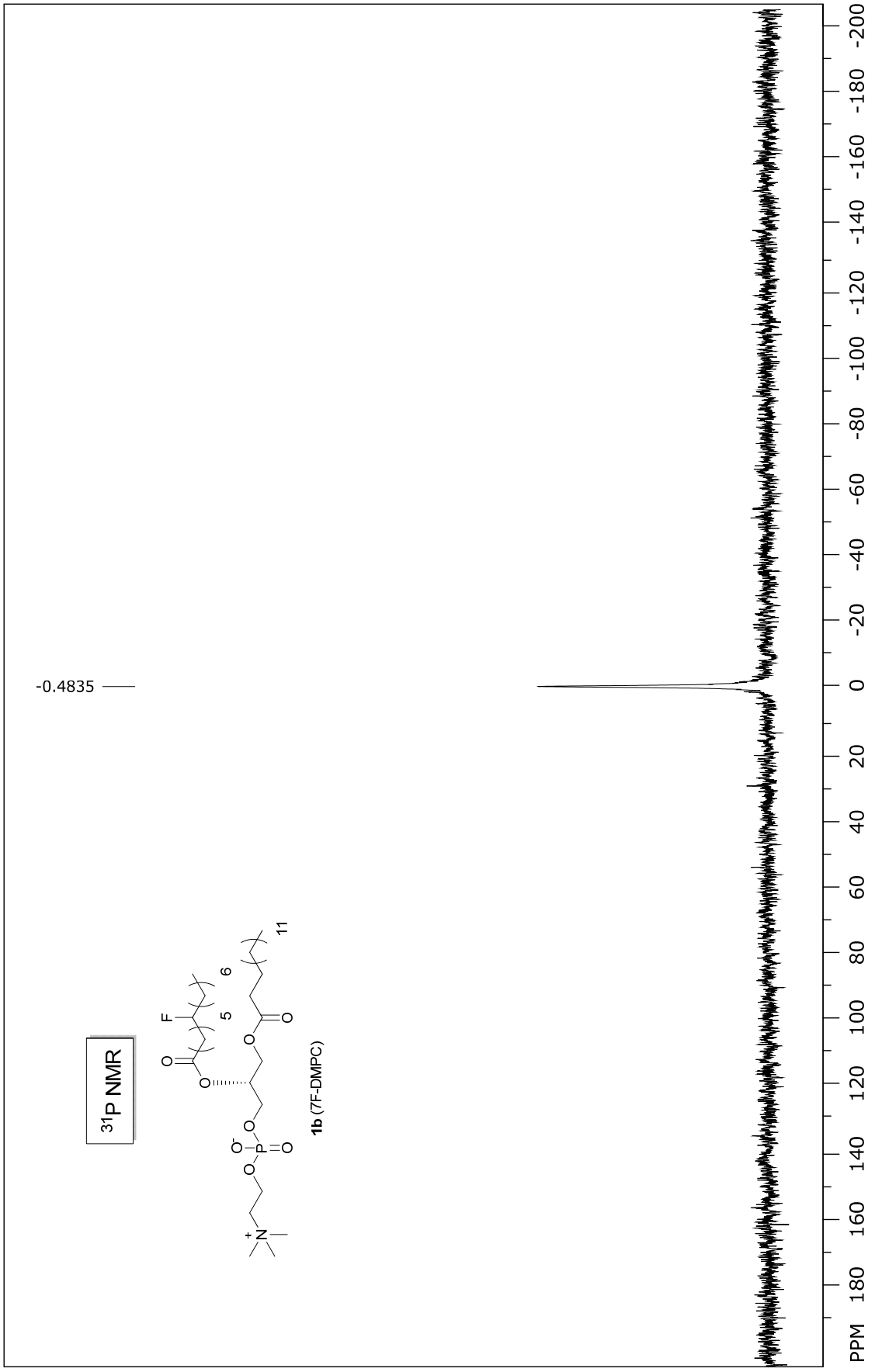
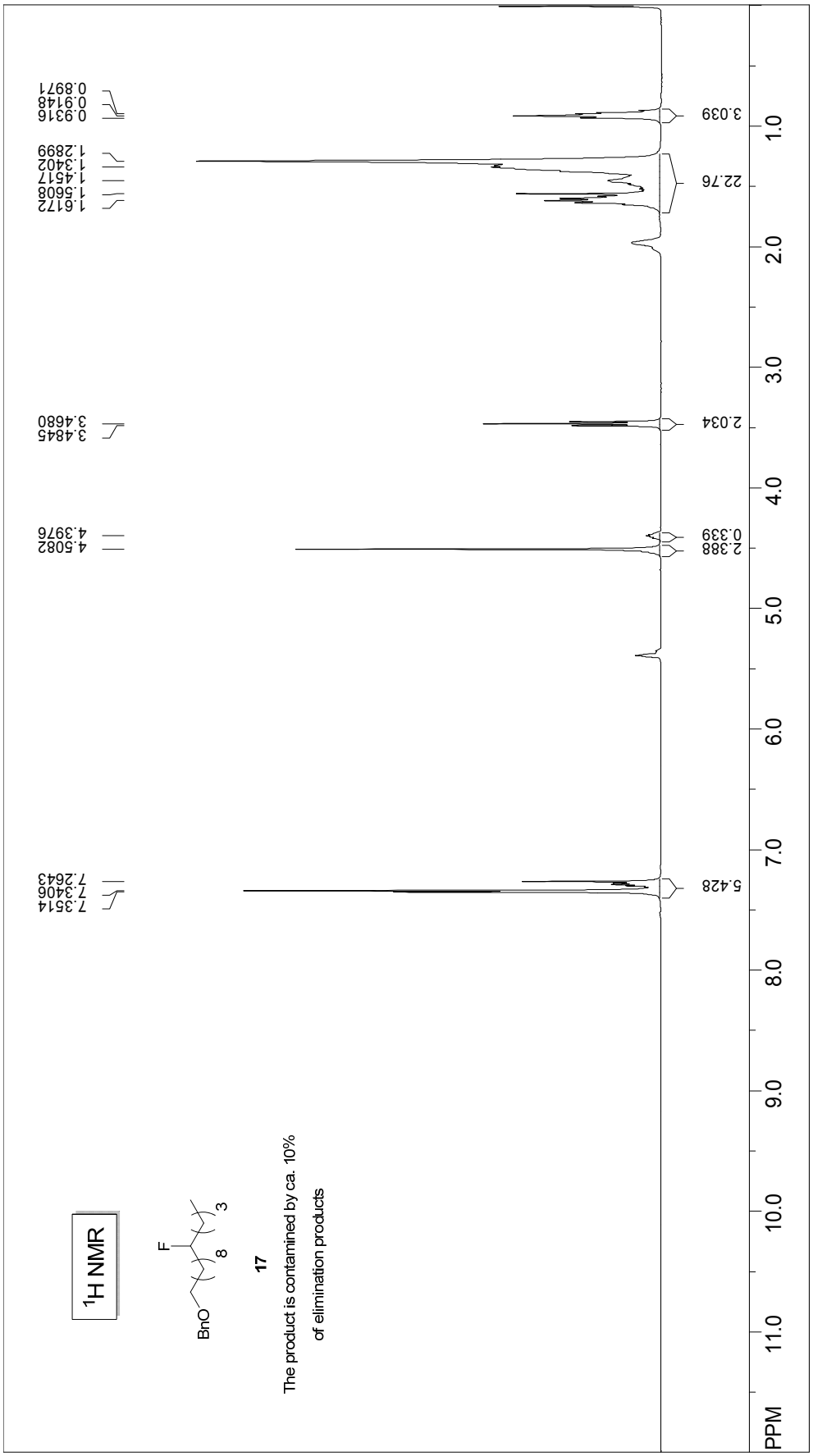
-110.0
-90.0
-70.0
-50.0
-30.0
PPM
$^{19}$F NMR
1b (7F-DMPC)

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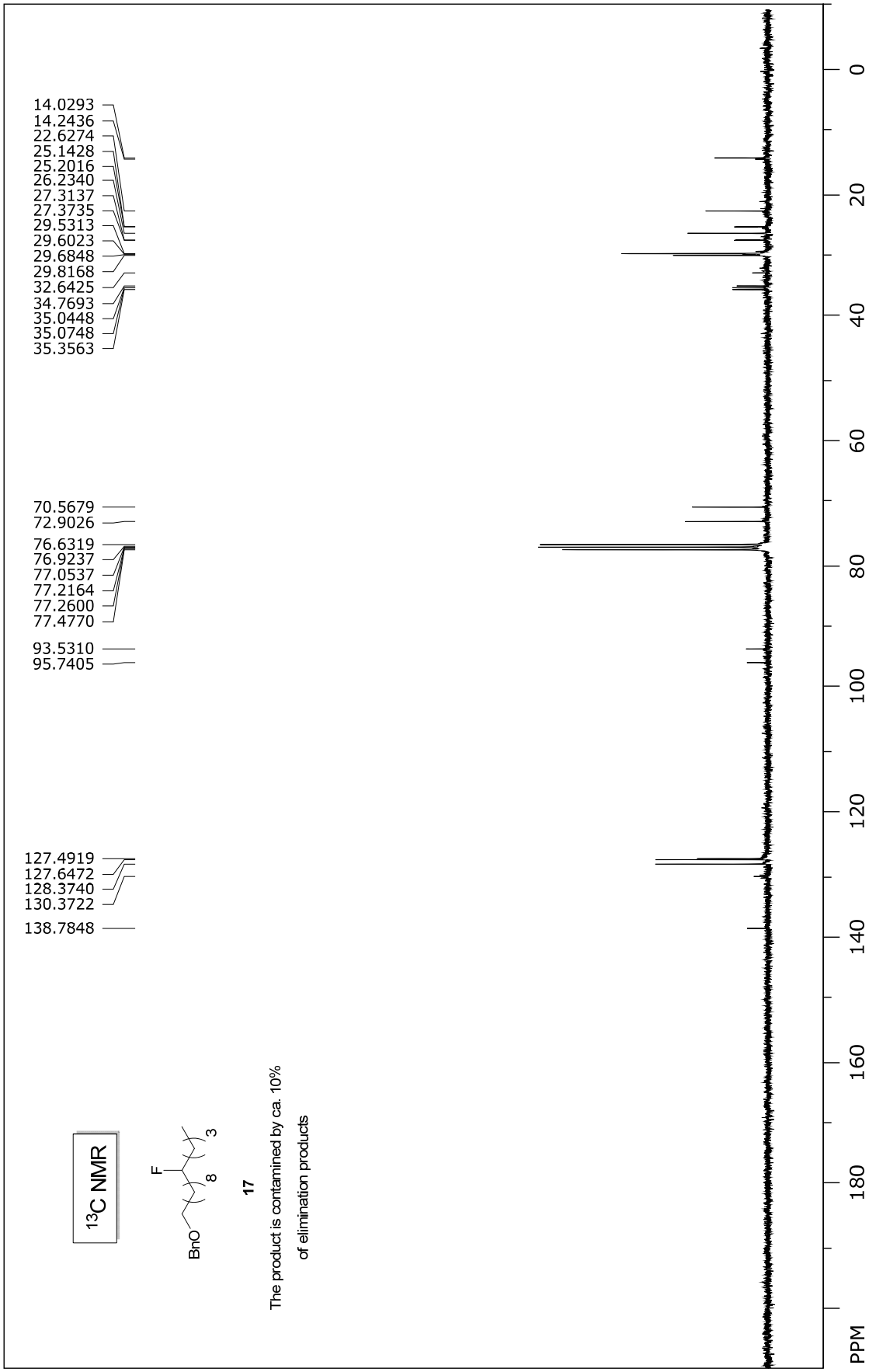
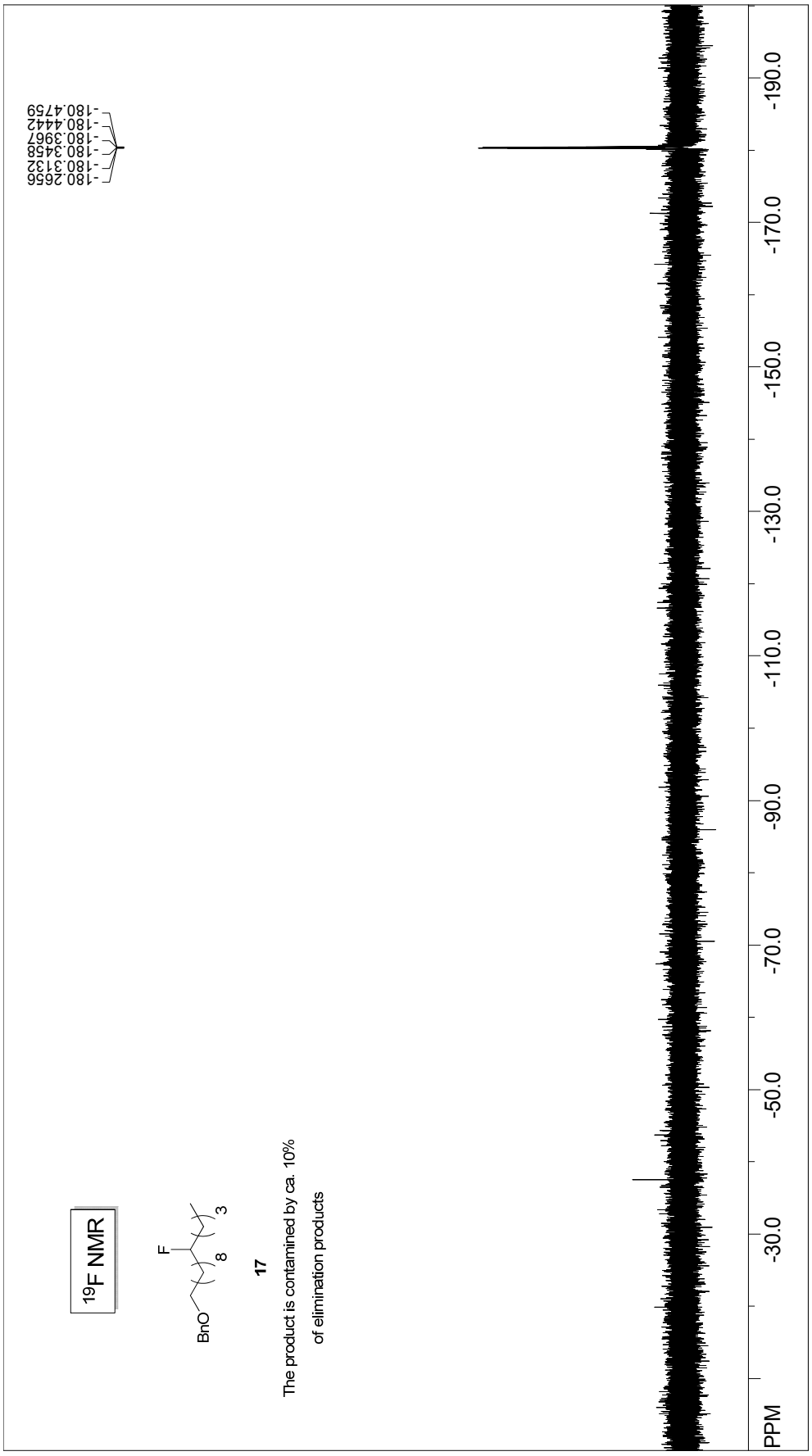
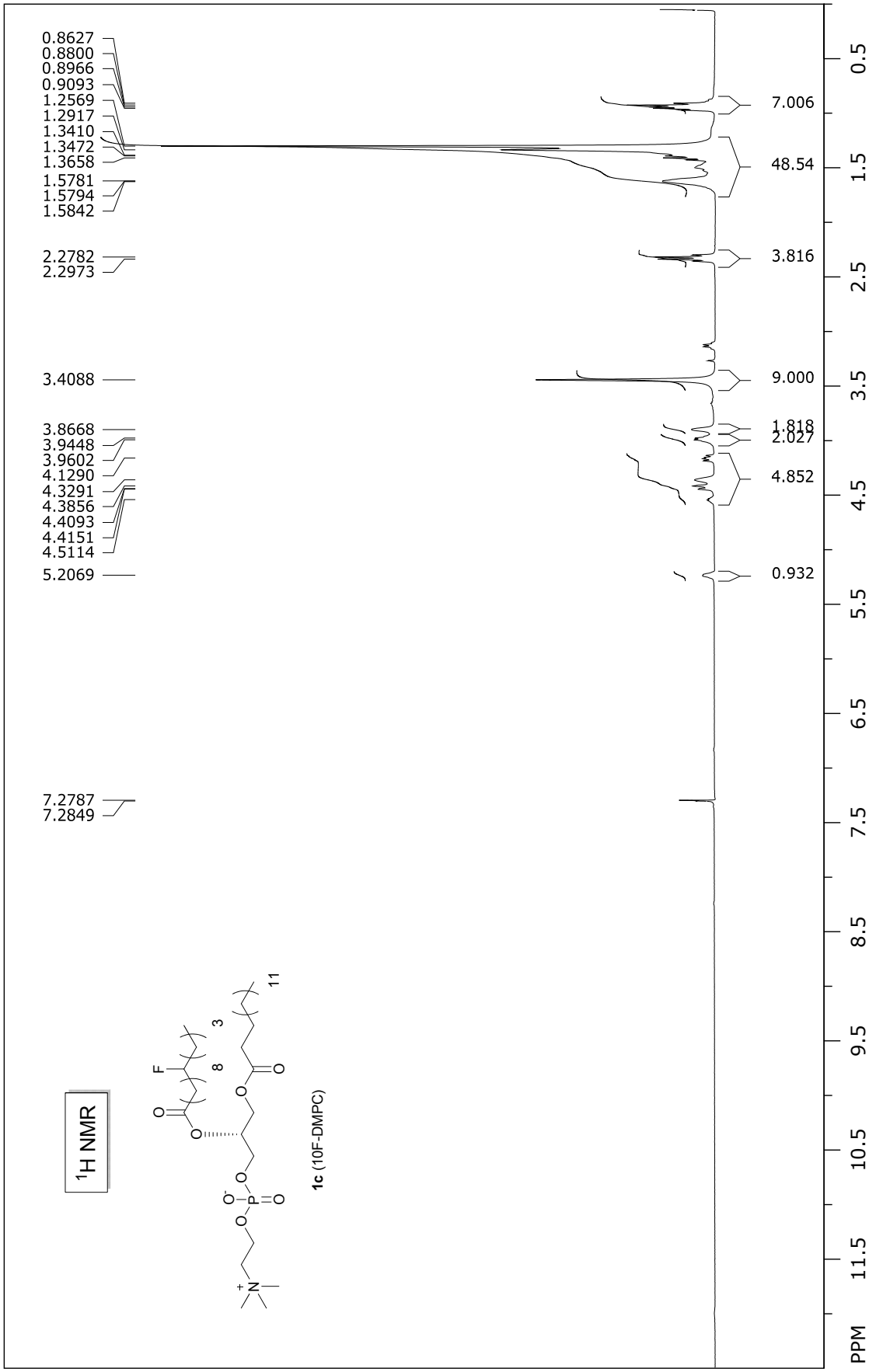
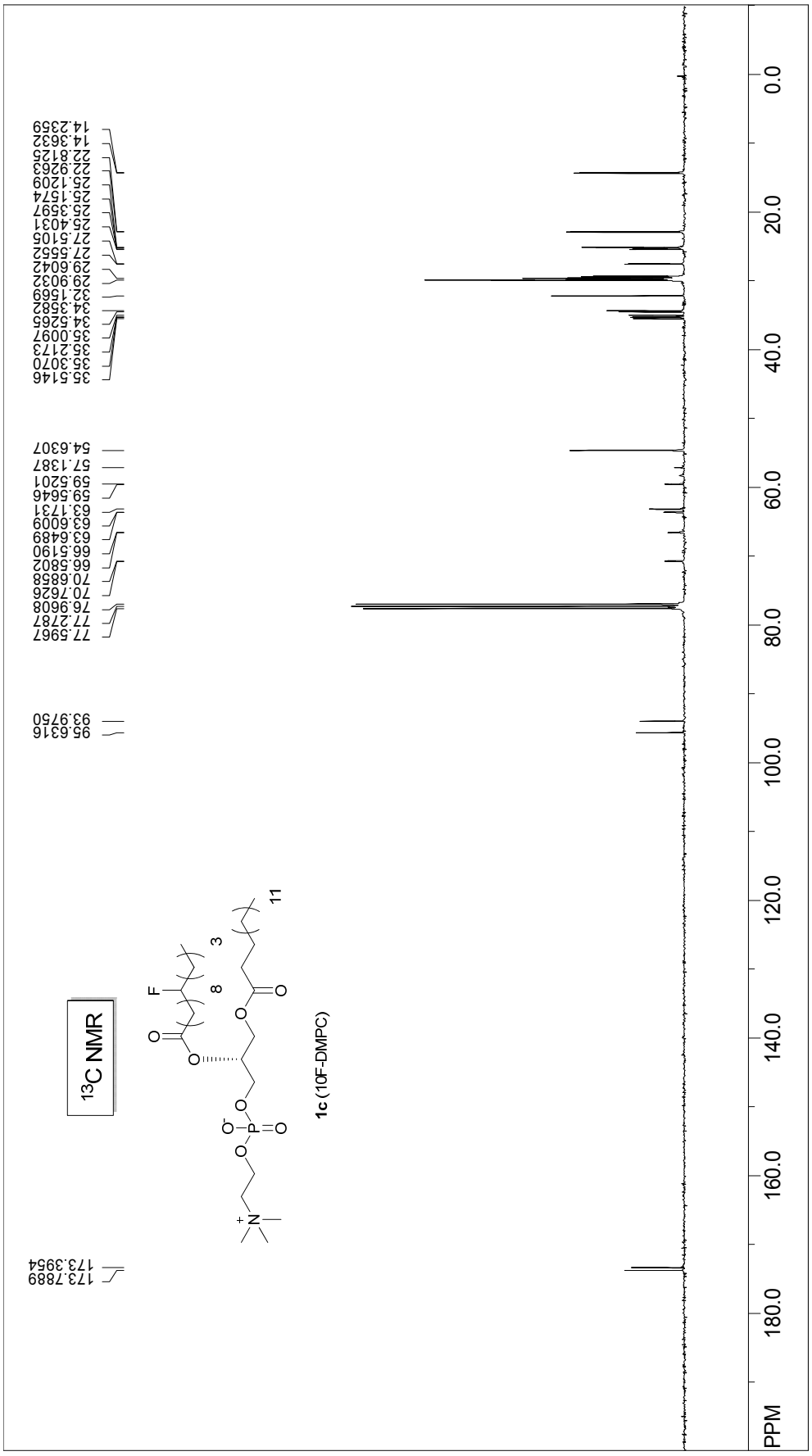
0.9316
1.2899
1.3402
1.4517
1.5608
1.6172
3.4680
3.4845
4.3976
4.5082
7.2643
7.3406
7.3514
3.039
22.76
2.034
0.339
2.388
5.428
PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
1H NMR
BnO
F
8
3
17
The product is contamined by ca. 10%
of elimination products




$^{19}$F NMR
BnO
F
8
3
17
The product is contamined by ca. 10%
of elimination products
-180.2656
-180.3132
-180.3458
-180.3967
-180.4442
-180.4759
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0
-150.0
-170.0
-190.0
PPM




13C NMR
1c (10F-DMPC)
PPM
0.0
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
14.2359
14.3632
22.8125
22.9263
25.1209
25.1574
25.3597
25.4031
27.5105
27.5552
29.6042
29.9032
32.1569
34.3582
34.5265
35.0097
35.2173
35.3070
35.5146
54.6307
57.1387
59.5201
59.5646
63.1731
63.6009
63.6489
66.5190
66.5802
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70.7626
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77.2787
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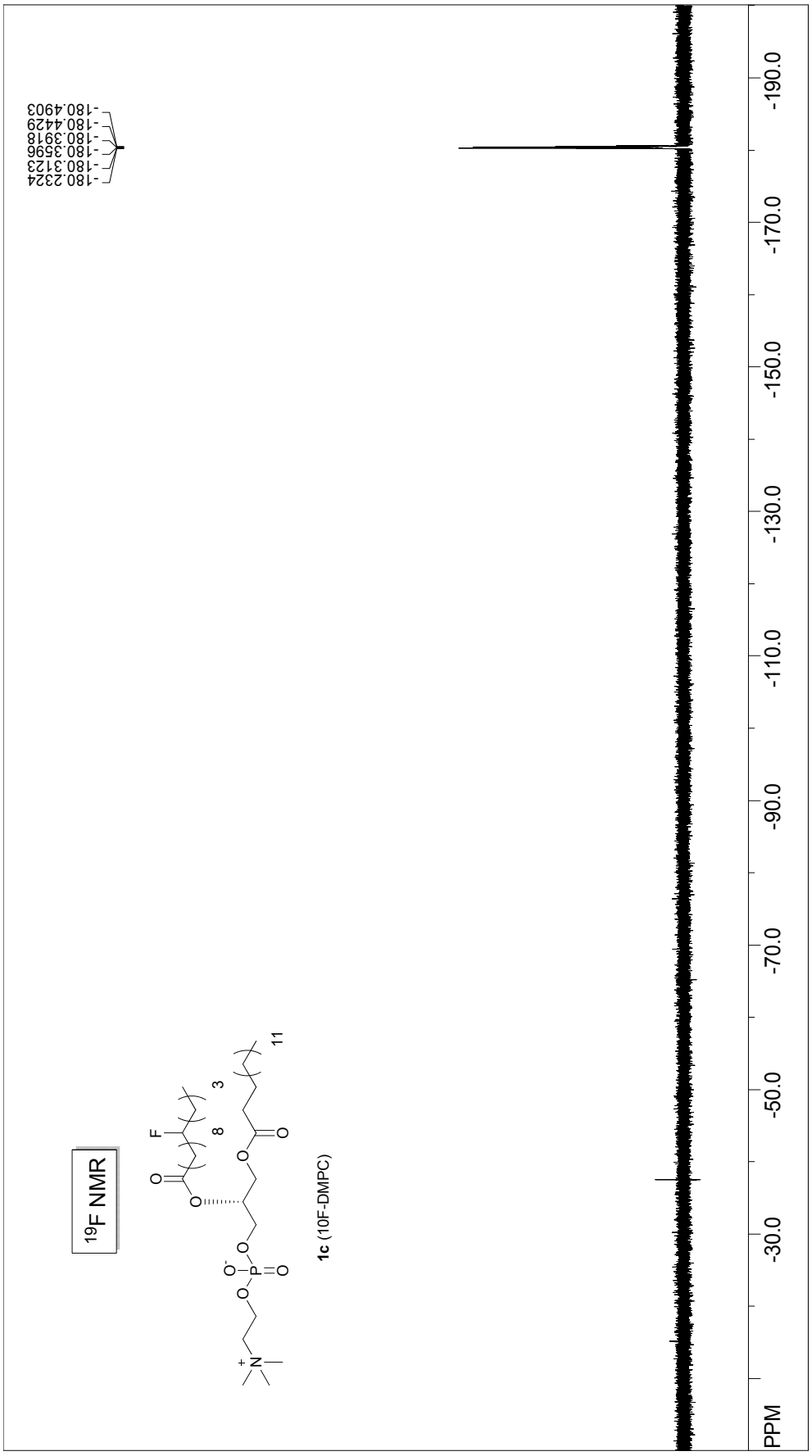
93.9750
95.6316
173.3954
173.7889


19F NMR
1c (10F-DMPC)
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-180.3123
-180.3596
-180.3918
-180.4429
-180.4903
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-70.0
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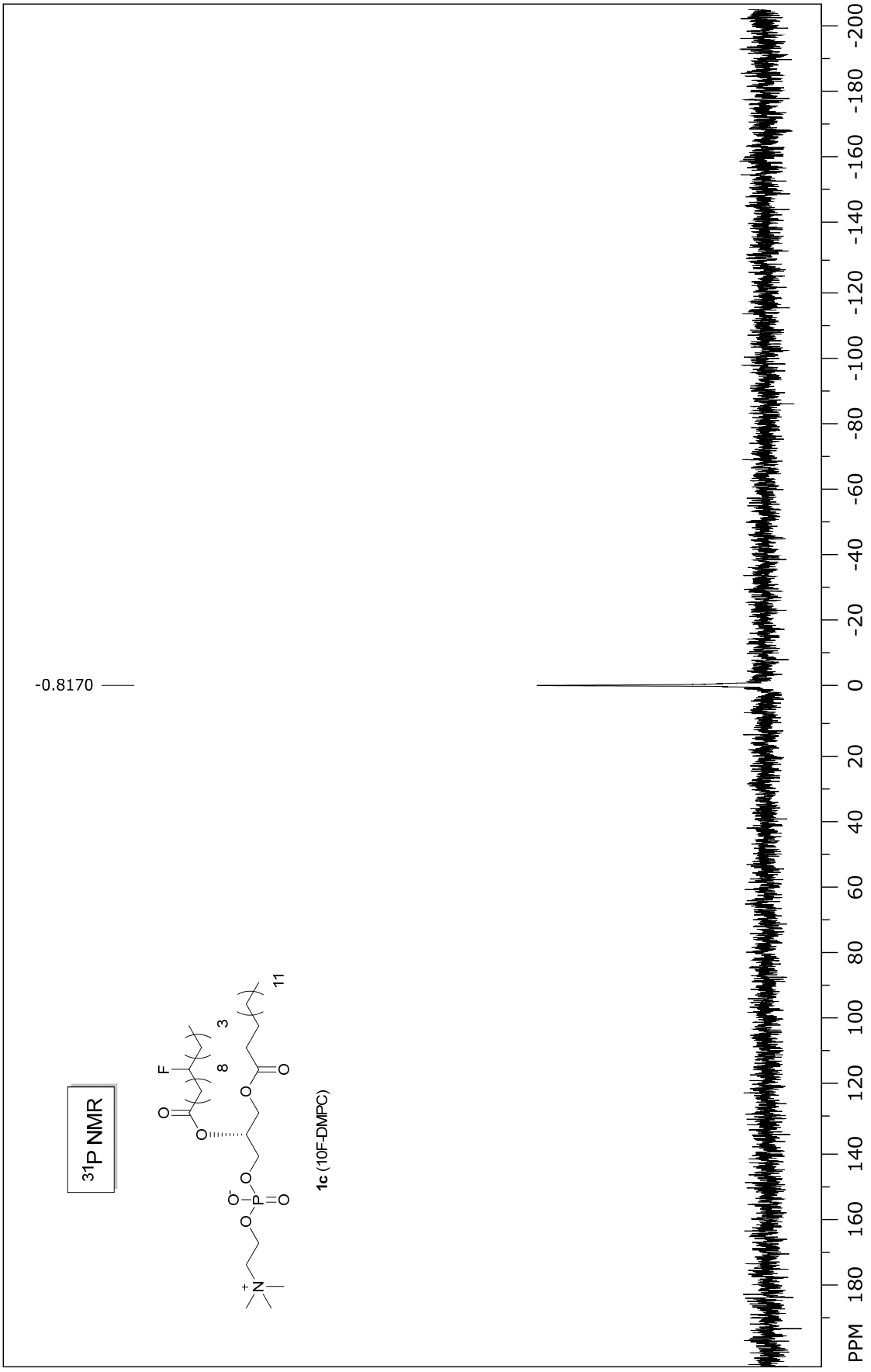
-170.0
-190.0
PPM



**FTIR Experiments**

***Sample preparation***

The lipid multilamellar vesicles were prepared by disolving the lipids in chloroform before evaporating the solvent with a stream of nitrogen or argon. The samples were placed in a lyophilizer for at least one night, to remove all traces of residual organic solvent. For the samples used in mixtures with pure DMPC, the fluorinated lipid and the non-fluorinated lipid were first weighed separately and then combined in solution with chloroform before being dried under a nitrogen stream. A solution of deuterated water with 0.1 molar of HEPES buffer (2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid) is added to the samples to obtain a lipid concentration of 4% w/v. Then the samples underwent five freezes (liquid $N_2$)/thaw (heating 5 minutes at 50°C)/vortex shaking (1 minute) cycles. During the last cycle, the freeze period is omitted; the sample is instead allowed to cool to room temperature for 5 minutes. Table 1 shows the different amounts of lipids and HEPES buffer used for the measurements.

**Table 1:** Necessary amounts of lipids and buffer for the preparation of the FTIR samples

| Fluorinated lipid ratio (%) | Fluorinated lipid mass (mg) | DMPC mass (mg) | HEPES buffer volume (µL) |
|---|---|---|---|
| **100** | 1.6 | - | 40 |
| **50** | 0.8 | 0.8 | 40 |
| **25** | 0.4 | 1.2 | 40 |
| **10** | 0.2 | 1.8 | 50 |
| **5** | 0.2 | 3.8 | 100 |
| **2.5** | 0.2 | 7.8 | 200 |

***Experiments***

Infrared spectra were recorded with a Nicolet Magna 560 or 760 Fourier transform spectrometer (Thermo-Nicolet, Madison, WI, USA) equipped with a narrow band mercury–cadmium–telluride (MCT) detector and a germanium-coated KBr beam splitter. The samples were placed between $CaF_2$ windows (Biocell, BioTools, Wauconda, IL) with an optical path of 35 µm. A total of 128 interferograms were acquired with a resolution of 2 $cm^{-1}$ in the spectral range of 4000–650 $cm^{-1}$ at various temperatures ranging from 5 to 70 °C and controlled by a home-made device. The spectra were corrected for the water vapor and $CaF_2$ contribution by subtraction of a reference spectrum. The data were processed with the software Grams/AI (Galactic Industries Corporation, Salem, MA, USA). The spectral is baseline-corrected using a cubic function. The methylene symmetric stretching frequency was obtained from the center of gravity calculated at the top 10% of the band. The informations obtained can then be transposed in graph using the Excel software (Microsoft, Redmond,

WA). The transition temperatures and the cooperativity indices have been calculated from a custom algorithm in the Matlab program.

Figure 1 shows the type of spectra obtained with these experiments. The bands of interest, the $CH_2$ stretching bands, have been indicated.

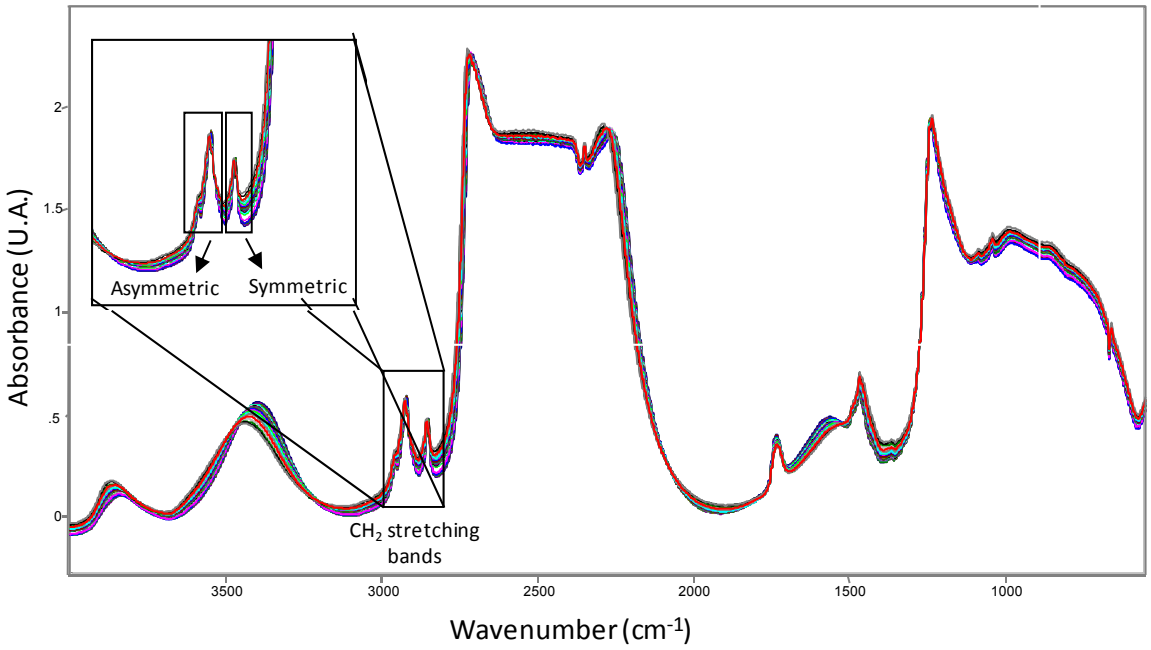



**Fig. 1** FTIR spectra of 7F-DMPC (10 to 70 °C)