Electronic Supplementary Information (ESI)

Supramolecular assemblies of novel aminonucleoside phospholipids and their bonding to DNA

Delin Pan, Jing Sun, Hongwei Jin, Yating Li, Liyu Li, Yun Wu, Lihe Zhang and Zhenjun Yang*

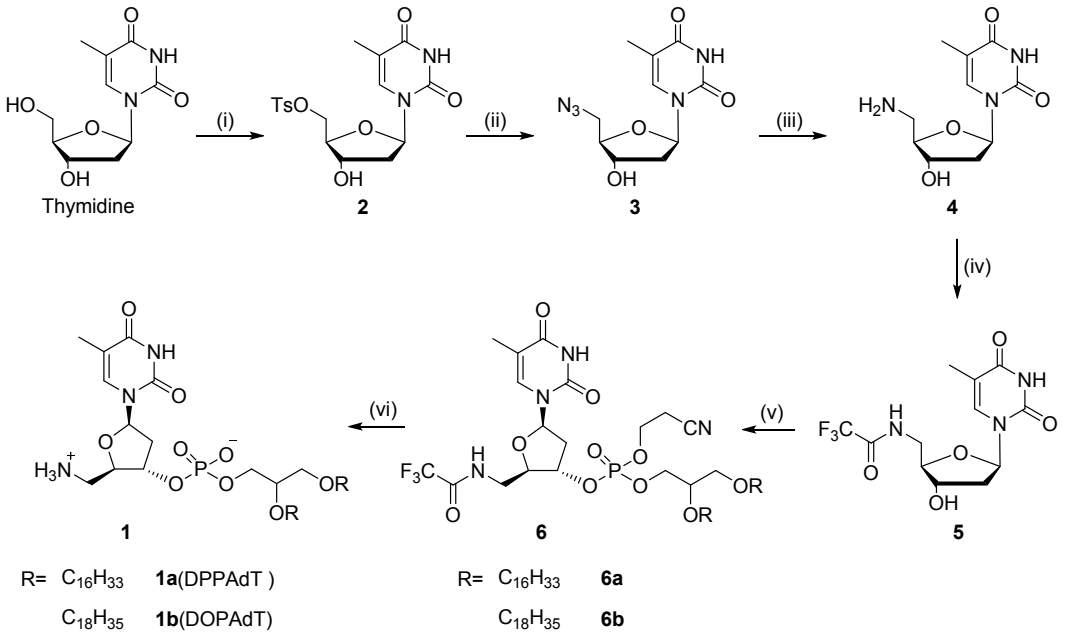
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191 (China), Fax: +86 10 82802503; Tel: +86 10 82802503; E-mail: yangzj@bjmu.edu.cn

Table of Contents

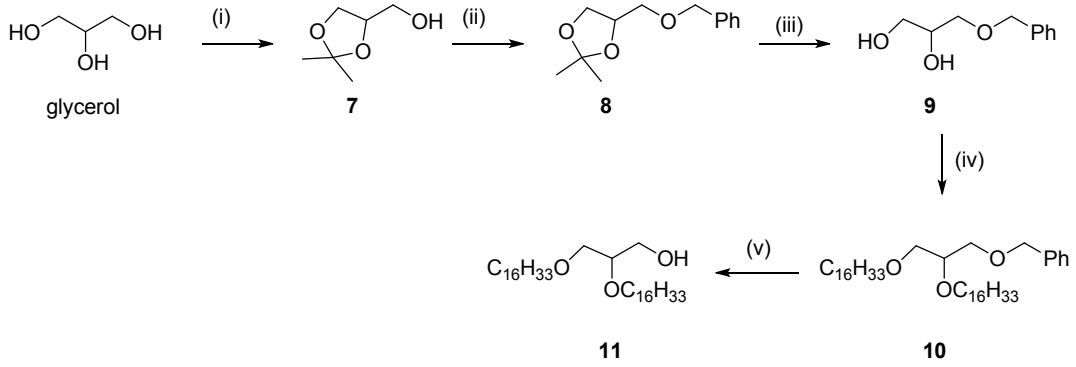
1. Materials and Instruments

Reagents were purchased in analytical grade or higher purity from Sigma-Aldrich or Alfa Aesar. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR were recorded on a Bruker AVIII-400 spectrometers. Infrared (IR) spectra were obtained using a Spectrum One Fourier transform infrared (FT-IR) spectrometer (Nexus 470, Thermo Nicolet Co. Ltd.). Mass spectra were recorded using a Xevo G2 Q-TOF spectrometer. High resolution mass spectra were recorded using an APEX IV FT-MS (7.0T) spectrometer. Ultraviolet−visible spectra were measured using a DU 800 spectrophotometer (Beckman Coulter, Inc). Circular dichroism (CD) spectra were measured using a J-810 CD spectrophotometer (Jasco, JAP). Scanning electron microscopy (SEM) images were observed on a Hitachi S-4800 scanning electron microscope at an accelerating voltage of 6 kV. Transmission electron microscopy (TEM) experiments were performed using a Philips Tacnai G2 20 S-TWIN microscope operating at 200 kV. Atomic force microscopy (AFM) images were performed using a multimode IIIa AFM (Veeco Metrology, USA) under ambient conditions. High content screening was performed on a KineticScan HCS reader (Thermo Fisher, USA).

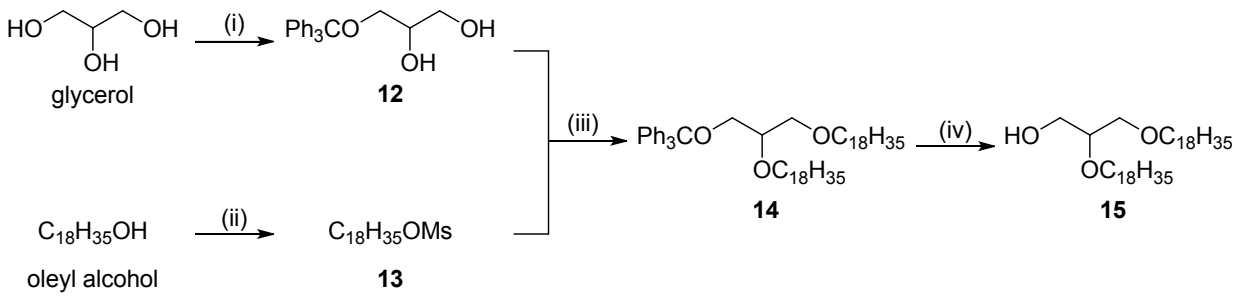
2. Synthesis



Scheme S1. Synthetic of Aminonucleoside Phospholipid. Conditions: (i) TsCl, py, 0 ^{o}C-r.t., 12 h, 81%; (ii) NaN_3, DMF, 70 ^{o}C, 12 h, 85%; (iii) H_2, Pd-C (10%), MeOH, 5 h, 95%; (iv) CF_3COEt, MeOH, Ar_2, -78 ^{o}C, 1 h, 80%; (v) $(i\text{-}Pr_2N)_2POCH_2CH_2CN$, $HOCH_2CH(OR)CH_2OR$, 1 H-tetrazolium, DMF, r.t.; (vi) NH_3/MeOH, r.t..



Scheme S2. Synthetic of 2,3-bis(hexadecyloxy)-1-benzyloxypropanol. Conditions: (i) acetone/pentane (v/v= 1/1), TsOH, reflux, 48 h, 95%; (ii) $PhCH_2Br$, NaH, THF, 70 ^{o}C, 20 h, 89%; (iii) HCl, EtOH, r.t., 12 h, 92%; (iv) $C_{16}H_{33}Br$, KOH, benzene, 80 ^{o}C, 24 h, 81%; (v) H_2, Pd-C (10%), MeOH/THF (v/v= 1/1), 36 h, 79%.



Scheme S3. Synthetic of 1,2-bis[(*Z*)-octadec-9-enyloxy)] propanol. Conditions: (i) Ph_3CCl, Et_3N, DMAP, THF, r.t., 12 h, 85%; (ii) MsCl, Et_3N, DCM, 0 °C - r.t., 12 h, 81%; (iii) KOH, benzene, 80 °C, 36 h, 31%; (iv) HCl, THF/MeOH (v/v= 1/1), 2 h, 62%.

2.1 5'-*O*-tosyl thymidine (**2**)[1]

A solution of thymidine (24.2 g 100 mmol) in 200 ml anhydrous pyridine was cooled to 0 ˚C. Tosyl chloride (23g, 120 mmol) dissolved in 100 ml of pyridine was then added drop wise during 6 hours. The reaction temperature was maintained at 0 ˚C during the addition. The reaction mixture was stirred for additional 6 h at room temperature. Pyridine was removed the under vacuum. The residue was dissolved in 500 mL ethyl acetate and the organic layer was washed with 10% $NaHCO_3$ solution (300 mL) followed by water. The tosyl thymidine **2** slowly crystallized out. The product was filtered and was dried under vacuum. Yield 32.6 g (81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1 H), 7.80 (d, *J*= 8.0 Hz, 2 H), 7.48 (d, *J*= 8.0 Hz, 2 H), 7.39 (s, 1 H), 6.16 (t, *J*= 6.8 Hz, 1 H), 5.44 (d, *J*= 4.4 Hz, 1 H), 4.25-4.31 (m, 1 H), 4.10-4.25 (m, 2 H), 3.89 (s, 1 H), 2.42 (s, 3 H), 2.02-2.20 (m, 2 H), 1.78 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 150.4, 145.1, 135.9, 132.1, 130.2, 127.6, 109.8, 84.0, 83.2, 70.1, 69.9, 38.4, 21.1, 12.0; IR (film, KBr) ν= 3371.3, 3171.8, 3050.9, 1718.1, 1659.9, 1477.9, 1360.1, 1273.0, 1176.4, 1095.4, 1075.3, 919.5, 830.3, 552.6 cm^{-1}; MS (ESI-TOF$^+$) for $C_{17}H_{20}N_2O_7SNa$ $[M+Na]^+$ found 419.1208, calcd 419.0883; Anal. calcd for $C_{17}H_{20}N_2O_7S$: C 51.51, H 5.09, N 7.07, Found: C 51.22, H 5.06, N 7.12.

2.2 5'-Azido-5'-deoxy-thymidine (**3**)[2]

A solution of 5'-*O*-tosyl thymidine (5 g, 12.6 mmol) and NaN_3 (1.2 g, 19 mmol) in DMF (25 mL) was heated to 70 °C overnight. The reaction mixture was evaporated in vacuo. The residue was resolved in CH_2Cl_2 (50 mL) and washed with H_2O (30 mL). The organic layer was dried over anhydrous sodium sulfate, evaporated, and purified by column chromatography (CH_2Cl_2/MeOH,

20/1) to afford compound **3** (2.9 g, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1 H), 7.49 (s, 1 H), 6.20 (t, J= 7.2 Hz, 1 H), 5.39 (d, J= 4.0 Hz, 1 H), 4.20 (s, 1 H), 3.79-3.85 (m, 1 H), 3.56 (d, J= 5.2 Hz, 2 H), 2.20-2.30 (m, 1 H), 2.05-2.15 (m, 1 H), 1.79 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 150.5, 136.1, 109.8, 84.6, 83.9, 70.7, 51.6, 38.1, 12.1; IR (film, KBr) ν= 3391.8, 3189.4, 2925.5, 2807.3, 2101.1, 1722.3, 1656.2, 1477.2, 1433.2, 1298.8, 1272.8, 1067.3, 963.4, 856.2, 636.4, 553.4, 493.8 cm^{-1}; MS (ESI-TOF$^+$) for $C_{10}H_{13}N_5O_4Na$ $[M+Na]^+$ found 290.1042, calcd 290.0860; Anal. calcd for $C_{10}H_{13}N_5O_4$: C 44.94, H 4.90, N 26.21, Found: C 45.03, H 4.93, N 25.79.

2.3 5'-Amino-5'-deoxy-thymidine (**4**)[2]

A solution of **3** (5.5 g, 20 mmol) in methanol (150 mL) was hydrogenated using 10% Pd-C catalyst (0.55 g) for 5 h, at 60 Psi pressure. The catalyst was removed by filtration through Celite and the filtrate was evaporated to give a yellow solid. The yellow solid was dissolved in water and applied to a columm of Dowex 50 WX4 (200-400 mesh). The column was eluted with methanol (300 mL), then with water (500 mL), and finally eluted with 1 N ammonium hydroxide to give 4 as a white solid. (4.7 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (s, 1 H), 6.15 (t, J= 7.0 Hz, 1 H), 4.75 (br s, 4 H), 4.18-4.23 (m, 1 H), 3.60-3.70 (m, 1 H), 2.65-2.80 (m, 2 H), 2.01-2.23 (m, 2 H), 1.79 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 150.5, 136.2, 109.6, 87.8, 83.4, 70.8, 43.6, 38.90, 12.1; IR (film, KBr) ν 3348.7, 3288.9, 2948.5, 2638.8, 1999.1, 1694.1, 1449.3, 1369.9, 1274.8, 1136.7, 1075.2, 954.7, 770.6, 620.9, 560.9 cm^{-1}; MS (ESI-TOF$^+$) for $C_{10}H_{15}N_3O_4Na$ $[M+Na]^+$ found 264.1148, calcd 264.0955; Anal. calcd for $C_{10}H_{15}N_3O_4$: C 49.79, H 6.27, N 17.42, Found: C 49.50, H 6.20, N 17.25.

2.4 5'-Trifluoroacetamide-5'-deoxy-thymidine (**5**)

To a solution of **4** (2.0 g, 8.3 mmol) in methanol (50 ml), at -78 °C under nitrogen, ethyl trifluoroacetate (1.2 g, 8.4 mmol) was added dropwise over 30 min. Stirring was continued for a further 30 min, and then the reaction mixture was slowly allowed to warm to room temperature. Large amount of white precipitate was formed. The precipitate was obtained by filtration, washed successively with methanol (10 mL) and ethyl acetate (10 mL) to give pure 5 as a white solid (2.2 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (brs, < 1 H), 9.62 (s, 1 H), 7.45 (S, 1 H), 6.14 (t, J= 7.0 Hz, 1 H), 5.38 (d, J= 4.0 Hz, 1 H), 4.18 (brs, 1 H), 3.77-3.87 (m, 1 H), 3.30-3.51 (m, 2 H), 2.13-

1.25 (m, 1 H), 2.00-2.12 (m, 1 H), 1.79 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 156.7 (q, J= 36.1 Hz), 150.5, 136.1, 116.0 (q, J= 286.4 Hz), 109.8, 84.0, 83.8, 71.2, 41.7, 38.3, 12.0; ^{19}F NMR (400 MHz, $CDCl_3$): δ -74.233; IR (film, KBr) ν 3395.3, 3325.2, 2945.5, 1727.5, 1696.8, 1653.5, 1565.4, 1480.7, 1271.8, 1210.2, 1181.4, 1092.5, 1046.5, 844.5, 697.6 613.7 cm^{-1}; MS (ESI-TOF$^+$) for $C_{12}H_{14}F_3N_3O_5Na$ $[M+Na]^+$ found 360.1181, calcd 360.0778; Anal. calcd for $C_{12}H_{14}F_3N_3O_5$: C 42.74, H 4.18, N 12.46, Found: C 42.49, H 4.34, N 12.26.

2.5 Dipalmityl-3'-(cyanoethyl)phosphatidyl-5'- trifluoroacetamide -5'-deoxy-thymidine (**6a**)

To a solution of **5** (337 mg, 1.0 mmol) and 1 H tetrazolium (140 mg, 2.0 mmol) in dry DMF (20 mL) under nitrogen, *N,N,N',N'*-tetraisopropyl-*O*-2-(cyanoethyl)phosphorodiamidite (360 mg, 1.2 mmol) was added dropwise, and the solution was stirred at room temperature for 2 h. After that, 1,2-bis(hexadecyloxy)propanol (864 mg, 1.6 mmol) and 1 H tetrazolium (140 mg, 2.0 mmol) were added to the solution, which was stirred under nitrogen for another 12 h. H_2O_2 (30%, 5 mL) was then added to the solution, and stirring was continued for a further 1h. The solution was concentrated in vacuo and purified by column chromatography over silica with dichloromethane/methanol (20/1) as the eluting solvent. Product was obtained as a white solid in 31% (313 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80-8.95 (m, 1 H), 7.76-7.95 (m, 1 H), 7.09 (d, J= 8.4 Hz, 1 H), 5.90-6.10 (m, 1 H), 5.02 (s, 1 H), 4.15-4.45 (m, 5 H), 3.35-3.80 (m, 9 H), 2.81 (s, 2 H), 2.60 (s, 2 H), 1.93 (s, 3 H), 1.50-1.60 (m, 4 H), 1.25 (brs, 52 H), 0.88 (t, J= 6.6 H, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.15, 158.12 (q, J= 37 Hz), 150.55, 136.92, 116.73, 115.96 (q, J= 286.5 Hz), 111.74, 111.69, 87.27, 82.62, 78.00, 71.97, 70.78, 69.12, 68.29, 62.51, 57.77, 40.96, 37.45, 31.97, 30.04, 29.76, 29.71, 29.66, 29.54, 29.41, 26.12, 26.05, 22.73, 21.55, 19.73, 14.15, 12.23; ^{31}P NMR (161 MHz, $CDCl_3$): δ -2.168, -2.269, -2.316; ^{19}F NMR (400 MHz, $CDCl_3$): δ -75.585, -75.622, -75.630; IR (film, KBr) ν 3433.4, 2920.2, 2852.1, 1719.9, 1468.9, 1278.5, 1160.1, 1034.0, 722.6 cm^{-1}; MS (ESI-TOF$^+$) for $C_{50}H_{88}N_4F_3O_{10}PNa$ $[M+Na]^+$ found 1015.6692, calcd 1015.6082; HRMS (ESI-MS) for $C_{50}H_{88}N_4F_3O_{10}PNa$ $[M+Na]^+$ found 1015.6111, calcd 1015.6082; Anal. calcd for $C_{50}H_{88}N_4F_3O_{10}P$: C 60.46, H 8.93, N 5.64, Found: C 60.23, H 8.99, N 5.65.

2.6 Dioleyl-3'-(cyanoethyl)phosphatidyl-5'- trifluoroacetamide -5'-deoxy-thymidine (**6b**)

To a solution of **5** (337 mg, 1.0 mmol) and 1 H tetrazolium (140 mg, 2.0 mmol) in dry DMF (20 mL) under nitrogen, *N,N,N',N'*-tetraisopropyl-*O*-2-(cyanoethyl)phosphorodiamidite (360 mg, 1.2 mmol) was added dropwise, and the solution was stirred at room temperature for 2 h. After that, 1,2-

bis[(*Z*)-octadec-9-enyloxy)]propanol (950 mg, 1.6 mmol) and 1 H tetrazolium (140 mg, 2.0 mmol) were added to the solution, which was stirred under nitrogen for another 12 h. H_2O_2 (30%, 5 mL) was then added to the solution, and stirring was continued for a further 1h. The solution was concentrated in vacuo and purified by column chromatography over silica with dichloromethane/ methanol (20/1) as the eluting solvent. Product was obtained as pale yellow oil in 33% (344 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, <1 H), 7.75-8.40 (m, 1 H), 7.08 (m, 1 H), 5.99 (m, 1 H), 5.32 (m, 4 H), 4.95-5.15 (m, 1 H), 4.05-4.45 (m, 4 H), 3.30-3.80 (m, 11 H), 2.79 (s, 1 H), 2.52 (s, 2 H), 1.80-2.02 (m, 11 H), 1.53 (brs, 4 H), 1.26 (brs, 44 H), 0.86 (brs, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.16, 158.00 (q, *J*= 37.8 Hz), 150.57, 150.52, 136.64, 130.35, 130.21, 129.88, 129.74, 116.68, 115.90 (q, *J*= 292.3 Hz), 86.94, 82.73, 71.82, 70.64, 69.11, 68.97, 68.21, 66.53, 66.14, 62.41, 40.86, 37.72, 37.41, 32.57, 31.87, 29.73, 29.49, 29.28, 27.17, 26.04, 25.97, 22.64, 19.59, 14.06, 12.14; ^{31}P NMR (161 MHz, $CDCl_3$): δ 14.120, 9.141, 9.086, 8.945, 8.882, -2.173, -2.257, -2.329; ^{19}F NMR (400 MHz, $CDCl_3$): δ -75.562, -75.549; IR (film, KBr) ν 3240.3, 3083.6, 3004.9, 2925.2, 2854.5, 1723.1, 1560.3, 1465.7, 1216.7, 1184.1, 1159.2, 1039.5, 971.2, 725.0; MS (ESI-TOF$^+$) for $C_{54}H_{92}N_4F_3O_{10}PNa$ $[M+Na]^+$ found 1067.8557, calcd 1067.6395; HRMS (ESI-MS) for $C_{54}H_{96}N_5F_3O_{10}P$ $[M+NH_4]^+$ found 1062.6865, calcd 1062.6841.

2.7 Dipalmityl-3'-phosphatidyl-5'-Amino-5'-deoxy-thymidine (**1a**, DPPAdT)

6a (100 mg, 0.1 mmol) was dissolved in methanol-ammonia (20 mL) and stirred at room temperature for 10 h. After that, the solvent was evaporated to give a yellow residual. The desired product (51 mg, 60%) was isolated after chromatography (Sephadex LH 20, DCM/MeOH 1/1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD): δ 7.40-7.52 (m, <1 H), 7.20-7.40 (m, 1 H), 5.95-6.20 (m, 1 H), 4.60-4.95 (m, 1 H), 3.76-4.20 (m, 2 H), 3.25-3.73 (m, 10 H), 2.40-2.95 (m, 2 H), 1.76-1.98 (m, 3 H), 1.54 (brs, 4 H), 1.27 (brs, 52 H), 0.87 (brs, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.49, 150.51, 137.82, 110.96, 87.38, 85.39, 83.01, 81.00, 74.95, 71.56, 70.42, 41.01, 40.54, 37.79, 37.28, 31.68, 29.75, 29.42, 29.31, 29.12, 25.81, 22.42, 13.68, 11.65; ^{31}P NMR (161 MHz, $CDCl_3$): δ -1.227; IR (film, KBr) ν 3504.5, 2921.8, 2852.5, 1695.9, 1468.7, 1370.7, 1218.5, 834.8 cm^{-1}; MS (ESI-TOF$^+$) for $C_{45}H_{86}N_3O_9PNa$ $[M+Na]^+$ found 866.8617, calcd 866.5994; HRMS (ESI-MS) for $C_{45}H_{87}N_3O_9P$ $[M+H]^+$ found 844.61846, calcd 844.61744; Anal. calcd for $C_{45}H_{86}N_3O_9P$: C 64.03, H 10.27, N 4.98, Found: C 64.31, H 9.91, N 5.21.

2.8 Dioleyl-3'-phosphatidyl-5'-Amino-5'-deoxy-thymidine (**1b**, DOPAdT)

6b (100 mg, 0.096 mmol) was dissolved in methanol-ammonia (20 mL) and stirred at room temperature for 10 h. After that, the solvent was evaporated to give a yellow residual. The desired product (55 mg, 64%) was isolated after chromatography (Sephadex LH 20, DCM/MeOH 1/1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD): δ 8.80-9.26 (m, 1 H), 8.20-8.80 (m, 1 H), 7.15-7.25 (m, <1 H), 6.90-7.15 (m, <1 H), 5.60-5.90 (m, 1 H), 5.25-5.50 (m, 4 H), 4.75-5.15 (m, 1 H), 4.20-4.40 (m, 1 H), 3.20-3.95 (m, 12 H), 2.70-3.00 (m, 1 H), 2.40-2.60 (m, 1 H), 1.85-2.25 (m, 11 H), 1.51 (brs, 4 H), 1.27 (brs, 44 H), 0.88 (t, *J*= 5.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.13, 129.90, 100.13, 71.95, 70.79, 70.45, 32.78, 32.05, 31.05, 30.28, 29.96, 29.91, 29.73, 29.51, 27.39, 26.27, 22.87, 19.24, 14.30, 12.39; ^{31}P NMR (161 MHz, $CDCl_3$): δ -0.494; IR (film, KBr) ν 3434.7, 2925.5, 2854.2, 1703.8, 1667.3, 1466.3, 1280.1, 1222.9, 1098.4, 1070.7, 613.4; MS (ESI-TOF$^+$) for $C_{49}H_{91}N_3O_9P$ $[M+H]^+$ found 896.8428, calcd 896.6487; HRMS (ESI-MS) for $C_{49}H_{91}N_3O_9P$ $[M+H]^+$ found 896.6516, calcd 896.6487.

2.9 Isopropylidene glycerol (**7**)[3]

Glycerol (20 g, 217 mmol), acetone (60 ml), pentane (60 ml) and *p*-toluenesulfonic acid monohydrate (500 mg, 2.9 mmol) were successively introduced into a vessel fitted with a Dean–Stark. The mixture was then stirred at reflux for 48 h. After cooling to room temperature, sodium acetate (300 mg, 4.5 mmol) was added. The mixture was filtered and the solvents were evaporated under reduced pressure to give the pure alcohol (27.1 g, 95%) as yellow oil. b.p. 81 °C at 11 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21-4.28 (m, 1 H), 4.04 (dd, *J*= 8.0, 2.8 Hz, 1 H), 3.77-3.83 (m, 1 H), 3.74 (dd, *J*= 7.6, 3.6 Hz, 1 H), 3.60 (dd, *J*= 12.0, 5.2 Hz, 1 H), 2.22 (brs, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 76.1, 65.7, 63.0, 26.7, 25.2; IR (neat): ν 3442.0, 2987.4, 2937.1, 2883.5, 1744.5, 1456.9, 1374.1, 1256.3, 1214.4, 1156.8, 1078.3, 1052.4, 971.3, 844.5, 792.5, 516.2 cm^{-1}; MS(ESI-TOF$^+$) for $C_6H_{12}O_3Na$ $[M+Na]^+$ found 155.0773, calcd 155.0679.

2.10 1,2-*O*-Isopropylidene-3-*O*-benzyl-glycerol (**8**)[4]

A solution of **7** (21.2 g, 160 mmol) in anhydrous THF (50 mL) was stirred with sodium hydride (8.7 g, 57-63% in oil, 344 mmol) for 30 min in room temperature. Benzyl bromide (28 g, 176 mmol) was added to the sodium alkoxide solution, and the mixture was refluxed for 20 h. The mixture was then cooled, added with water, and extracted with ethyl acetate (3 × 250 mL). The organic solution

was dried with anhydrous sodium sulfate and concentrated to give a residue. Flash chromatography with petroleum ether/ethyl acetate (10/1) gave 31.5 g of **8** (89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.45 (m, 5 H), 4.57 (dd, *J*= 18, 12 Hz, 2 H), 4.25-4.34 (m, 1 H), 4.05 (dd, *J*= 8.2, 6.6 Hz, 1 H), 3.74 (dd, *J*= 8.2, 6.2 Hz, 1 H), 3.56 (dd, *J*= 9.8, 5.8 Hz, 1 H), 3.47 (dd, *J*= 9.6, 5.6 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.5, 127.8, 109.5, 74.9, 73.6, 71.3, 67.0, 26.9, 25.5; IR (neat): ν 3063.8, 3030.8, 2986.4, 2934.5, 2866.4, 1954.4, 1813.1, 1604.1, 1496.2, 1454.0, 1371.5, 1254.8, 1212.8, 1156.8, 1095.8, 1053.6, 845.0, 738.4, 698.9, 606.2, 515.4 cm^{-1}; HRMS (ESI-MS) for $C_{13}H_{19}O_3$ $[M+H]^+$ found 223.1323, calcd 223.1329.

2.11 3-*O*-Benzyl-glycerol (**9**)[4]

11.1 g (50 mmol) of **8** was dissolved in ethanol (60 mL) and acidified with 1 M HCl (60 mL). The solution was allowed to stand at room temperature for 12 h before being neutralized with aqueous $NaHCO_3$ solution and extracted with ether (3×80 mL). The organic solution was dried with anhydrous sodium sulfate. Solvent evaporation and flash chromatography with petroleum ether/ethyl acetate (5/1) yielded 8.3 g of **9** (92%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25-7.45 (m, 5 H), 4.48 (s, 2 H), 3.58-3.70 (m, 1 H), 3.40-3.50 (m, 1 H), 3.27-3.40 (m, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.7, 128.3, 127.5, 127.4, 72.4, 72.0, 70.6, 63.2; IR (neat) ν 3382.9, 2868.9, 1957.0, 1495.8, 1453.4, 1364.5, 1325.7, 1207.7, 1073.4, 925.9, 865.5, 739.8, 699.0, 611.2 cm^{-1}; MS (ESI-TOF$^+$) for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ found 205.0989, calcd 205.0835.

2.12 2,3-Bis(hexadecyloxy)-1-benzyloxypropanol (**10**)[5]

A mixture of **9** (7.5 g, 41.2 mmol), powdered potassium hydroxide (7.8 g, 140 mmol), and bromohexadecane (37.8 g, 124 mmol) in dry benzene (150 mL) was refluxed for 24 h with continuous stirring. The water formed during the reaction was removed by using a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (250 mL), and washed successively with water (250 mL), 1 N HCl (250 mL), and 2.5% $NaHCO_3$ solution (250 mL), water (250 mL) and brine (250 mL). The organic layer was dried over anhydrous sodium sulfate. The product was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (20/1). A viscous oily compound was isolated in 81% (21 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.40 (m, 5 H), 4.55 (s, 2 H), 3.30-3.65 (m, 9 H), 1.50-1.60 (m, 4 H), 1.26 (brs, 52 H), 0.88 (t, *J*= 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.62, 128.43, 127.70, 127.61,

78.10, 73.50, 71.80, 70.91, 70.76, 70.49, 32.08, 30.27, 29.86, 29.81, 29.80, 29.66, 29.51, 26.29, 26.26, 22.84, 14.24; IR (film, KBr) ν 3064.3, 3030.1, 2923.7, 2853.2, 1943.8, 1464.5, 1366.4, 1304.3, 1115.6, 1028.9, 732.5, 697.3 cm^{-1}; MS (ESI-TOF$^+$) for $C_{42}H_{78}O_3Na$ $[M+Na]^+$ found 653.6257, calcd 653.5843; Anal. calcd for $C_{42}H_{78}O_3$: C 79.94, H 12.46, Found: C 79.80, H 12.56.

2.13 1,2-Bis(hexadecyloxy)propanol (**11**)[5]

A solution of **10** (12 g, 19 mmol) in (1:1) mixture of methanol and ethyl acetate (100 mL) was hydrogenated using 10% Pd-C catalyst (1.2 g) for 36 h, at 60 Psi pressure, during which almost all the starting material was converted to the alcohol. Then, Pd-C was filtered off and the solvent was removed. The solid obtained was dissolved in hot ethyl acetate and kept at room temperature for recrystallization. The solid was filtered and washed with hexane. The resulting solid was recrystallized several times to get pure, white solid. The rest of the compound, which was in filtrate, was purified by column chromatography over silica with petroleum ether/ethyl acetate (10/1) as the eluting solvent. The products were combined to give 8.1 g of **11** as a white solid, and the overall yield after purification was 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27-3.76 (m, 9 H), 1.52-1.60 (m, 4 H), 1.26 (brs, 52 H), 0.88 (t, J= 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.45, 72.00, 71.08, 70.55, 63.25, 32.08, 30.24, 29.85, 29.77, 29.62, 29.51, 26.26, 22.83, 14.24; IR (film, KBr) ν 3472.1, 2919.3, 2850.4, 1468.9, 1379.1, 1353.4, 1114.5, 1081.1, 856.6, 722.1, 677.5 cm^{-1}; MS (ESI-TOF$^+$) for $C_{35}H_{72}O_3Na$ $[M+Na]^+$ found 563.5786, calcd 563.5374; Anal. calcd for $C_{35}H_{72}O_3$: C 77.71, H 13.42, Found: C 77.47, H 13.25.

2.14 1-(Triphenylcarbinyl)glycerol (**12**)[6]

Glycerol (40.0 g, 435 mmol), trityl chloride (30 g, 107 mmol), and DMAP (300 mg, 2.46 mmol) were placed in a 250 mL round-bottom flask containing 80 mL of dry THF. To this heterogeneous mixture was added Et_3N (18 mL), and the resultant mixture was vigorously stirred at room temperature overnight. Ethyl acetate (150 mL) and water (100 mL) were then added to the flask. The reaction mixture was transferred to a separatory funnel, the solution was shaken, the layers were separated, and the organic layer was collected. The aqueous layer was then further extracted with ethyl acetate (2×100 mL). The combined organic layers were washed sequentially with 10% $NaHCO_3$ (200 mL), water (200 mL) and brine (200 mL), and dried over anhydrous sodium sulfate. Solvent was then removed on a rotovap to yield a yellow oil which was recrystallized with a

benzene/hexanes mixture to give 29 g of a white solid (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.48 (m, 6 H), 7.20-7.35 (m, 9 H), 3.84 (s, 1 H), 3.63-3.71 (m, 1 H), 3.53-3.63 (m, 1 H), 3.20-3.28 (m, 2 H), 2.74 (brs, 1 H), 2.35 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 128.7, 128.0, 127.3, 87.1, 71.3, 65.1, 64.4; IR (film, KBr) ν 3380.8, 3058.1, 2920.0, 2866.8, 1490.0, 1447.8, 1081.5, 1028.5, 699.8; MS (EI) for $C_{22}H_{22}O_3$ $[M]^+$ found 334.5, calcd 334.2; Anal. calcd for $C_{22}H_{22}O_3$: C 79.02, H 6.63, Found: C 79.26, H 6.49.

2.15 1-[(Methylsulfonyl)oxy]-(*Z*)-octadec-9-ene (**13**)[4]

Oleyl alcohol (50 85% purity, 158 mmol) and Et_3N (40 mL, 286 mmol) were dissolved in CH_2Cl_2 (500 mL) and cooled to 0 °C. To this solution was slowly added MsCl (16 mL, 206 mmol). A white precipitate was observed during the addition. The reaction mixture was then slowly allowed to warm to room temperature and stirred vigorously overnight. Water (250 mL) was added to the solution, and the mixture was transferred to a separatory funnel. The mixture was shaken, the layers were separated, and the organic layer was collected. The aqueous layer was further extracted with CH_2Cl_2 (2×500 mL). The combined organic layers were then washed with 1 N HCl (250 mL), 10% $NaHCO_3$ (250 mL) and brine, and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo to give a brown oil, which was purified by column chromatography over silica with petroleum ether/ethyl acetate (20/1) as the eluting solvent. Product was obtained as colorless oil in 81% (44 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30-5.43 (m, 2 H), 4.22 (t, *J*= 6.6 Hz, 2 H), 3.00 (s, 3 H), 1.90-2.10 (m, 4 H), 1.70-1.80 (m, 2 H), 1.20-1.40 (m, 22 H), 0.88 (t, *J*= 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.2, 129.9, 70.3, 37.5, 32.0, 29.90, 29.83, 29.66, 29.46, 29.29, 29.26, 29.15, 27.36, 27.30, 25.6, 22.8, 14.3; IR (neat) ν 2925.5, 2854.5, 1463.6, 1355.9, 1175.4, 974.8, 947.8, 831.7, 721.6, 528.8; MS (ESI-TOF$^+$) for $C_{19}H_{38}O_3SNa$ $[M+Na]^+$ found 369.2315, calcd 369.2434; Anal. calcd for $C_{19}H_{38}O_3S$: C 65.85, H 11.05, Found: C 65.63, H 10.98.

2.16 1-[(Triphenylcarbinyl)oxy]-2,3-bis[(*Z*)-octadec-9-enyloxy)]propane (**14**)[6]

A mixture of **12** (8.0 g, 23.1 mmol), **13**(19.2 g, 55.42 mmol) and powdered potassium hydroxide (3.3 g, 58.9 mmol) in dry benzene (150 mL) was refluxed for 36 h with continuous stirring. The water formed during the reaction was removed by using a Dean-Stark apparatus. The reaction was then cooled to room temperature, and then ethyl acetate (150 mL) and water (150 mL) were added to the mixture. The mixture was shaken, and the layers were separated. The aqueous layer was

extracted with ethyl acetate (3×100 mL). The combined organics were washed with water (150 mL) and brine (150 mL), and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo, and the oily residue was chromatographed, eluting with petroleum ether/ethyl acetate (20/1) to obtain 6.1 g of **14** as colorless oil (31% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.50 (m, 6 H), 7.18-7.32 (m, 9 H), 5.26-5.43 (m, 4 H), 3.50-3.60 (m, 5 H), 3.35-3.45 (m, 2 H), 3.12-3.20 (m, 2 H), 1.92-2.08 (m, 8 H), 1.50-1.58 (m, 4 H), 1.26 (brs, 44 H), 0.88 (t, J= 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.31, 130.07, 130.00, 128.90, 127.85, 127.02, 86.64, 78.45, 71.76, 71.33, 70.84, 63.73, 32.77, 32.06, 30.28, 29.94, 29.93, 29.85, 29.82, 29.72, 29.68, 29.65, 29.47, 27.37, 27.06, 26.31, 26.25, 22.84, 14.27; IR (film, KBr) ν 3004.4, 2925.3, 2854.1, 1742.6, 1597.7, 1490.7, 1450.0, 1220.6, 1118.7, 763.9, 745.0, 704.1, 632.8 cm^{-1}; MS (ESI-TOF^{+}) for $C_{58}H_{90}O_3Na$ $[M+Na]^{+}$ found 857.9059, calcd 857.6782; Anal. calcd for $C_{58}H_{90}O_3$: C 83.39, H 10.86, Found: C 83.10, H 10.62.

2.17 1,2-Bis[(*Z*)-octadec-9-enyloxy)]propanol (**15**)

A solution of **14** (8.34 g, 10 mmol) in (1:1) mixture of methanol and THF (100 mL) was acidified with 12 M HCl (2 mL), and stirred at room temperature for 2 h. The solvent was concentrated, neutralized with aqueous $NaHCO_3$ solution (5%, 100 mL) and extracted with ethyl acetate (100 mL×3). The combined organic layers were then washed with brine and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo and purified by column chromatography over silica with petroleum ether/ethyl acetate (20/1) as the eluting solvent. Product was obtained as pale yellow oil in 62% (3.7 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30-5.45 (m, 4 H), 3.40-3.75 (m, 9 H), 2.18 (s, 1 H), 1.90-2.10 (m, 8 H), 1.55-1.65 (m, 4 H), 1.25-1.40 (brs, 44 H), 0.88 (t, J= 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.10, 129.97, 78.39, 72.00, 71.07, 70.54, 63.27, 32.06, 30.23, 29.92, 29.85, 29.81, 29.77, 29.67, 29.65, 29.60, 29.47, 29.41, 27.36, 26.25, 22.83, 14.25; IR (film, KBr) ν 3470.1, 3004.4, 2925.4, 2854.0, 1651.2, 1463.2, 1376.2, 1117.5, 1041.3, 968.0, 721.9 cm^{-1}; MS (ESI-TOF^{+}) for $C_{39}H_{76}O_3Na$ $[M+Na]^{+}$ found 615.7213, calcd 615.5687; Anal. calcd for $C_{39}H_{76}O_3$: C 78.99, H 12.92, Found: C 78.72, H 12.68

3. Preparation and Characterization of Supramolecular Structures

3.1 Multilamellar Organization

DPPAdT (8.43 mg, 10 μmol) was suspended in water (1 mL) and sonicated at 70 °C for 10 min to give a clear solution. After that the solution was cold to 25 °C and aged at this temperature for 1 week. White precipitate was formed during this time. The solution was shocked and diluted to 0.1 mM with water, and then its UV-vis spectra and absorbance at 260 nm versus temperature were recorded. To prepare SEM sample, a drop of this solution was allowed to air-dry onto a mica sheet and then gold shadowed. 5'-amino-5'-deoxythymidine (2.41 mg, 10 μmol) was dissolved in water (1 mL), and then diluted to 100 μM. Its UV-vis spectra at 260 nm versus temperature were recorded on the same spectrometer.

3.2 Hydrogel

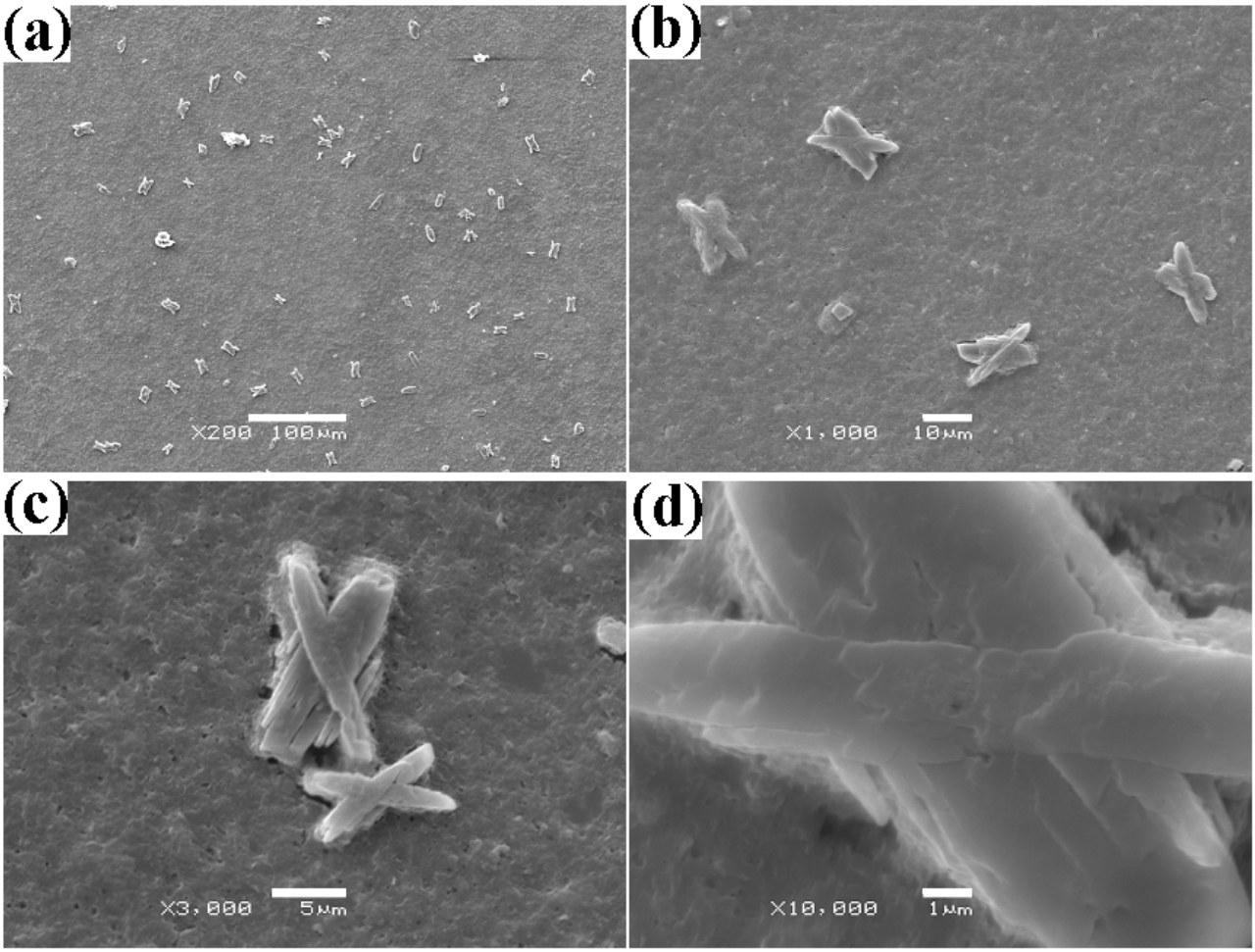


Fig S1. SEM images of multilamellar suprastructure of DPPAdT. (a) bar= 100 μm; (b) bar= 10 μm; (c) bar= 5 μm; (d) bar= 1 μm.

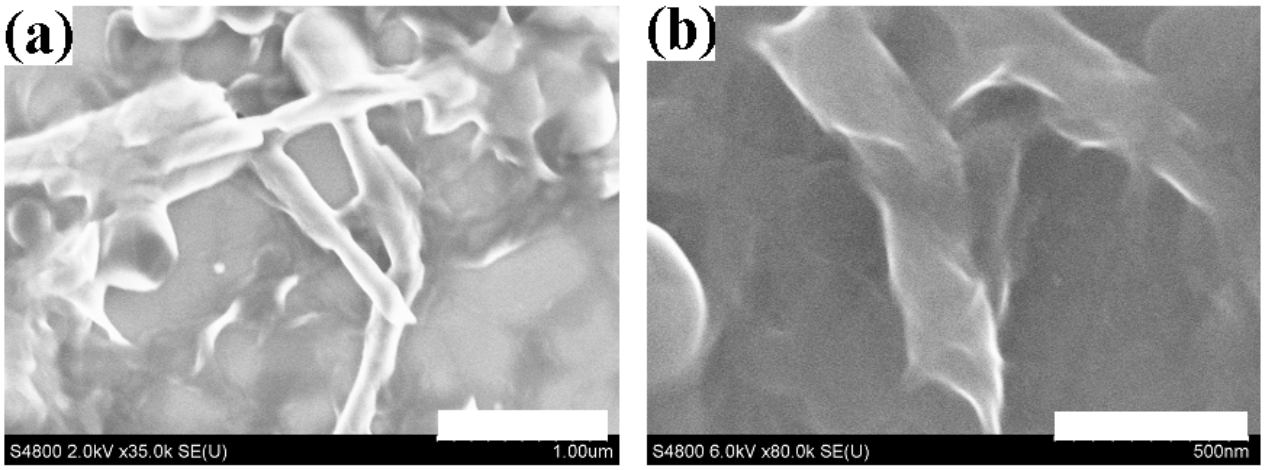


Fig S2. SEM images of superhelical strands of DPPAdT. (a) bar= 1 μm; (b) bar= 500 nm.

DPPAdT (12 mg, 14.2 μmol) was suspended in water (200 μL) and sonicated at 70 °C for 10 min to a homogeneous solution, which was then cold to room temperature to give an opaque hydrogel. When heated above 42 °C, this hydrogel turned to fluid liquid crystal. To prepare SEM sample, the hydrogel was freeze-dried, coated onto a mica sheet and then gold shadowed.

3.3 Superhelical Strand

DPPAdT (0.84 mg, 1 μmol) was suspended in water (1 mL) and sonicated at 70 °C for 10 min to a homogeneous solution. After that, the solution was aged at 60 °C for up to 2 days, then cold to room temperature. CD spectra of this solution were recorded (200-350 nm) before and after aging, where the solution was placed in a 1 mm thick quartz cuvette and scanned with 0.5 nm interval. To prepare

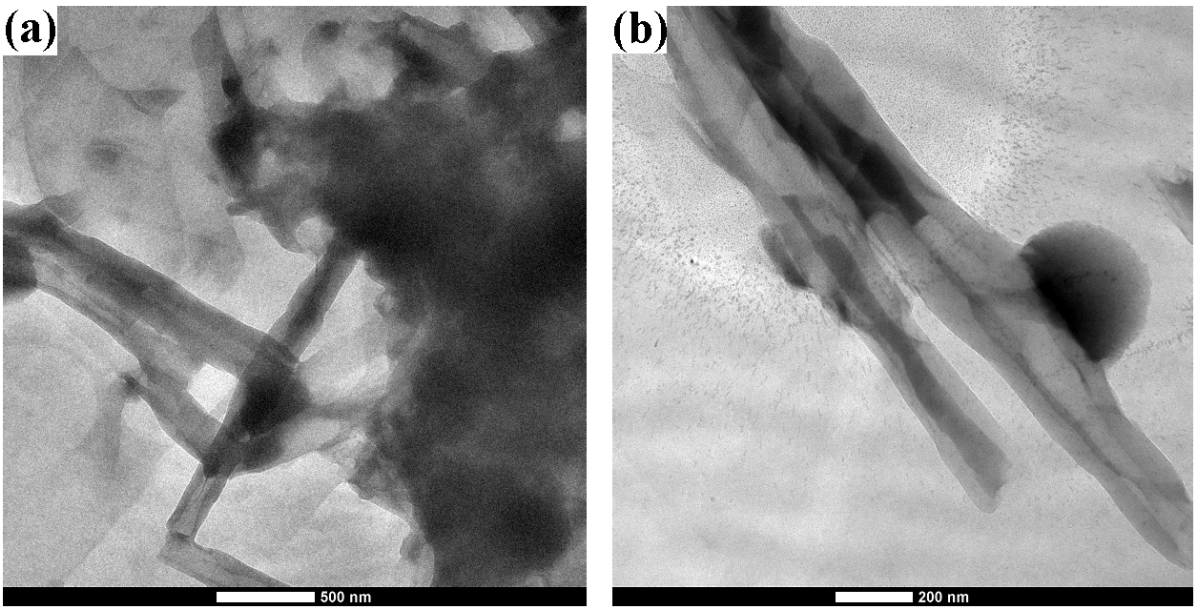


Fig S3. TEM images of superhelical strands of DPPAdT. (a) bar= 500 nm; (b) bar= 200 nm.

SEM sample, the solution was diluted to 100 μM, dropped onto a mica sheet, air dried, and then gold shadowed. To prepare TEM sample, a drop of the solution (100 μM) was allowed to air-dry onto a formvar-carbon coated 230 mesh copper grid, and the sample was stained with ammonium molybdate 1% in water.

3.4 Liposome

DOPAdT (0.895 mg) was dissolved in 2 mL of chloroform-methanol (20:1 v/v), evaporated to dryness under reduced pressure, and dried at room temperature for 30 min in vacuo. Water (1 mL) was added followed by sonicated at 50 °C for 1 h, to give liposomes of DOPdTA. To prepare SEM samples, the solution was diluted to 100 μM with PBS buffer (Phosphate buffer saline), dropped onto mica sheets, air dried, and then gold shadowed. To prepare TEM sample, a drop of the solution (100 μM) was allowed to air-dry onto a formvar-carbon coated 230 mesh copper grid, and the sample was stained with ammonium molybdate 1% in water. Actually, we considered this nanostructure to be liposome because of (1) DOPAdT is electrically neutral itself, but the zeta potential value of these particles is -31.5 mV, implying an ordered nanostructure (liposomes or micelles, not just nanoparticles); (2) The particle size (above 100 nm) is too big for micelles; and (3) TEM image (negative stained with ammonium molybdate) shows a depression in the centre of almost every particle (**Fig. 5b**, **S4c** and **S4d**). In the preparation of SEM samples, the liposome solution was diluted with PBS buffer (Phosphate buffer saline), so the big brick was regarded as the phosphate salt crystallized during the drying process. Besides, the particle size in SEM and TEM image did not match well because (1) SEM samples were coated with gold powder (thicker than 10 nm) to better imaging, which increased the apparent particle size. So we considered it as the major cause for difference in SEM and TEM; and (2) liposomes shrunk inconsistently during the drying process and in the high vacuum chamber of electron microscopes; (3) the liposome solutions for SEM and TEM experiments were not prepared at one time, and the particle size may be fluctuated among these preparations to some extent.

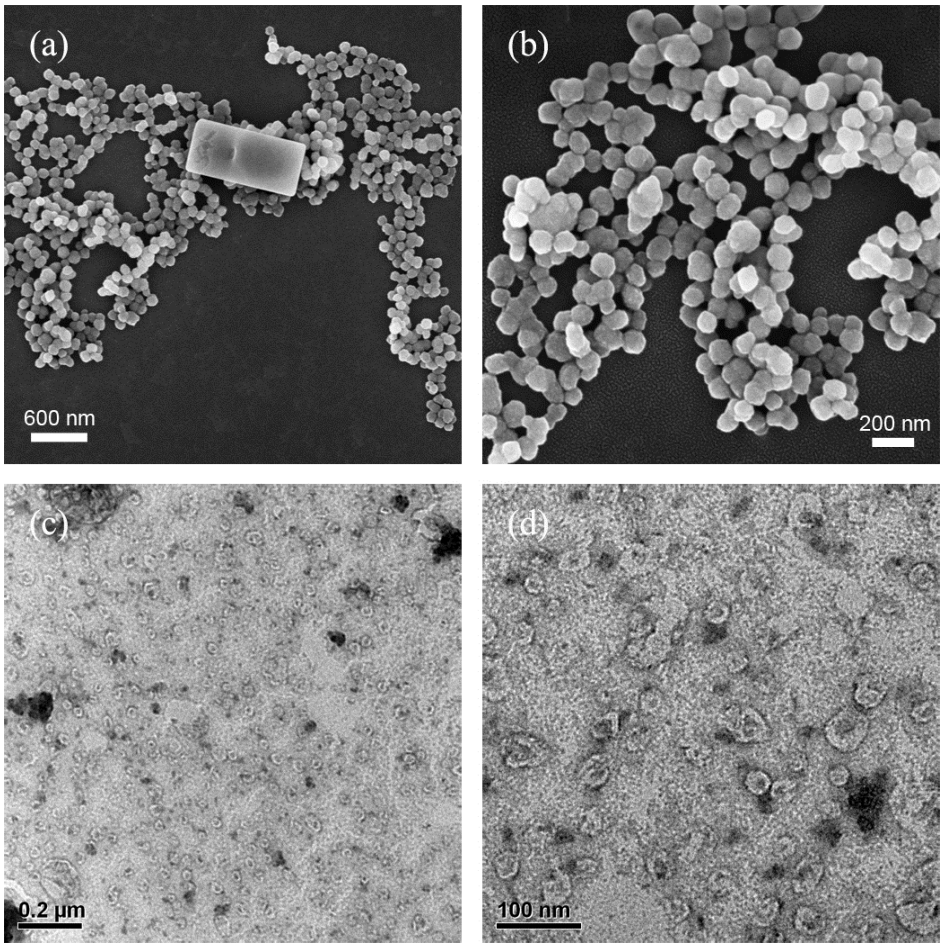


Fig S4. (a) SEM image of DOPAdT liposomes (bar = 600 nm); the big brick should be a crystal of phosphate salt (in PBS buffer); (d) SEM image of DOPAdT liposomes (bar = 200 nm); (c) TEM image of DOPAdT liposomes (bar = 200 nm); (d) TEM image of DOPAdT liposomes (bar = 100 nm).

4. Biocompatibility

Cell viability and proliferation were measured with a Cell Counting KIT-8 (CCK-8, Dojindo, www.dojindo.cn). This system consisted of WST-8 (2-[2-methoxy-4-nitrophenyl]-3-[4-nitrophenyl]-5-[2,4-disulfophenyl]-2H-tetrazolium, monosodium salt) that produced a water-soluble formazan dye upon bioreduction in the presence of an electron carrier. WST-8 is reduced by dehydrogenase in cells to give a yellow-colored product (formazan), which is soluble in the tissue culture medium. The amount of the formazan dye generated by the activity of dehydrogenases in cells is directly proportional to the number of living cells. 8000 cells (MCF-7 cells) were seeded on a 96-well plate with DMEM+10% FBS and incubated at 37 °C and humidified 5% CO_2 for 18-24 hours until confluency reached ~70%. Aminonucleoside phospholipids at different concentrations were added, and plate was incubated for another 24 h. Then 10 microliters of thawed CCK-8 solution was added to each well. Plates were incubated for 2 h at the same incubator conditions after which the absorbance was read at 450 nm with a reference wavelength of 600 nm. After deducting the absorbance of aminonucleoside phospholipid itself (plates without cell), cell number was correlated to optical density (OD). Cell viability was calculated as

$$\text{Cell viability} = (OD_{450(\text{sample})}/OD_{450(\text{control})}) \times 100\%$$

Where $OD_{450(\text{samble})}$ is the absorbance at 450 nm of cells added with aminonucleoside phospholipids, and $OD_{450(\text{control})}$ is the absorbance at 450 nm of the negative control.

Table S1. Optical density (OD) of the negative controls at 450 nm and 600 nm.

	450 nm O.D.		600 nm O.D.	
	cell	no cell	cell	no cell
	1.3117	0.6689	0.1386	0.1617
	1.3300	0.6504	0.1406	0.1683
	1.3391	0.6683	0.1378	0.1667
average	1.3269	0.6625	0.1390	0.1656
SD	0.0140	0.0105	0.0014	0.0034

Table S2. Cell viability test for 24 h of DOPAdT and DPPAdT at different concentrations.

	DOPAdT (μM)			DPPAdT (μM)			Negative Control
	100	20	4	100	20	4	
Cell/no cell	0.6293	0.7163	0.7189	0.6405	0.7416	0.7838	0.6910
SD	0.0329	0.0195	0.0413	0.0260	0.0161	0.0247	0.0142
Cell viability	91.1%	104%	104%	92.7%	107%	113%	100.0%
SD/blank	2.77%	1.64%	3.48%	2.19%	1.36%	2.08%	1.19%

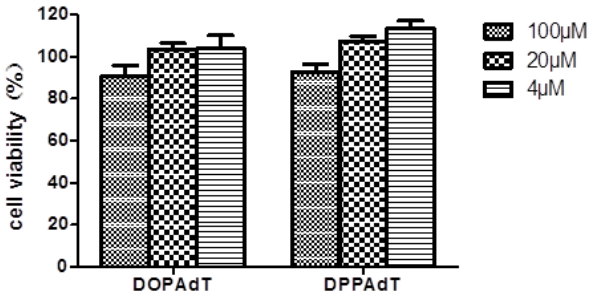


Figure *S5*. Cell viability test for 24 h of DOPAdT and DPPAdT in MCF-7 cells.

5. Cellular Uptake

The cellular uptake of MCF-7 breast cancer cells was measured by high content screening. MCF-7 cells were seeded in a 96-well plate at a density of 15000 cells/well in 100 μL of growth medium and cultured under the condition of 5% CO_2 at 37 °C. After 24 h, the cells were treated with free courmarin, coumarin-phosphatidylcholine (EPC) liposomes, coumarin-DOPAdT liposomes for 4 h. The final concentration of coumarin was 10 μM. Control experiments were performed by adding blank medium. After the incubation, the cells were washed with PBS. And then the cells were fixed with 100 μL of 4% paraformaldehyde at room temperature, respectively. The cellular uptake was measured by high content screening and indicated by fluorescent intensity. Each assay was repeated in quintuplicate. The average fluorescence intensities of MCF-7 breast cancer cells after applying free coumarin, coumarin-phosphatidylcholine (EPC) liposomes, coumarin-DOPAdT liposomes and blank medium were 224 ± 51.1, 246 ± 57.1, 317.28 ± 53.0 and 5.23 ± 3.15, respectively.

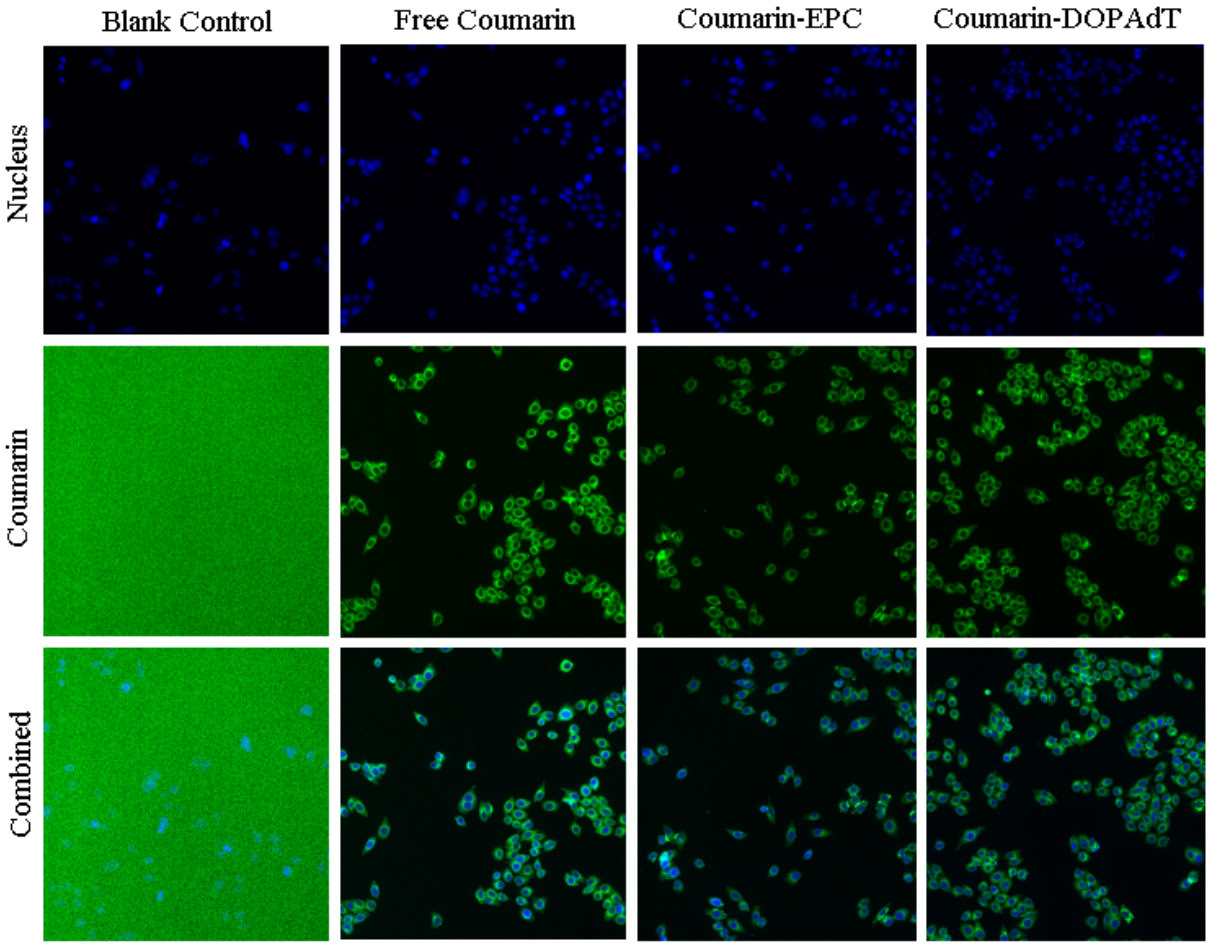


Fig S6. The fluorescence images of MCF-7 breast cancer cells after applying free coumarin, coumarin-phosphatidylcholine (EPC) liposomes, coumarin-DOPAdT liposomes and blank medium

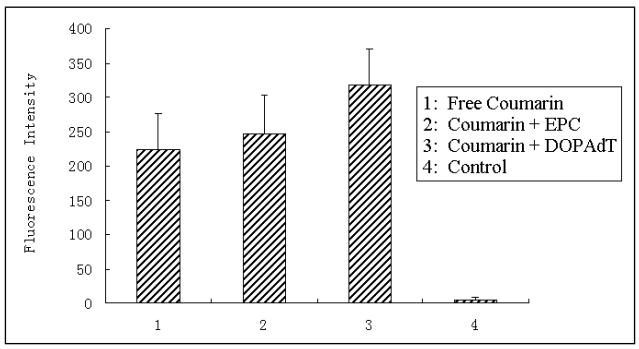


Fig *S7*. Uptake of coumarin by MCF-7 cells.

6. Study on the Interaction of Aminonucleoside Phospholipids and Nucleic Acids

6.1 CD Spectroscopy

A solution of polyA (20 bps, 50 μM) and a mixture solution of DPPAdT (1 mM) and polyA (20 bps, 50 μM) were prepared at first. CD spectra of these two solutions were recorded (200-350 nm) immediately after preparation, where the solution was placed in a 1 mm thick quartz cuvette and

scanned with 0.5 nm interval. After that, these two solutions were heated to 90 °C, and then could to 4 °C slowly during a time of 4 h (annealing). CD spectra were recorded (200-350 nm) again after annealing.

6.2 Atomic Force Microscopy (AFM) Image

A solution of calf thymus DNA (2 ng/μL) and a mixture solution of DPPAdT (84 ng/μL) and calf thymus DNA (2 ng/μL) were prepared at first. AFM samples were prepared by dropping these two solutions onto micas respectively and air-dried.

6.3 Molecular Dynamics (MD) Simulation

MD simulation was performed with AMBER 11 molecular simulation package.[9] The AMBER99 force field was used to describe the DOPAd-polyA complex. To obtain molecular mechanical parameters for the DOPdTA, ab initio quantum chemical methods were employed using the Gaussian 09 program.[10] The geometry was fully optimized and then the electrostatic potentials around them were determined at the HF/6-31G* level of theory. The RESP strategy[11] was used to obtain the partial atomic charges.

Starting model of DOPAdT-polyA complex was built using Discovery Studio 2.5 software. The model was solvated in TIP3P water using a octahedral box, of which extended 8 Å away from any solute atom. To neutralize the negative charges of simulated molecules, Na^+ counterion was placed next to each phosphate group.

Molecular dynamics (MD) simulation was carried out by using the SANDER module of AMBER 11. The calculations began with 500 steps of steepest descent followed by 500 steps of conjugate gradient minimization with a large constraint of 500 kcal mol^{-1} $Å^{-2}$ on the DOPAdT-polyA complex. Then 1000 steps of steepest descent followed by 1500 steps of conjugate gradient minimization with no restraints on the DOPAdT-polyA complex were performed. Subsequently, after 20 ps of MD, during which the temperature was slowly raised from 0 to 300 K with weak (10 kcal mol^{-1} $Å^{-2}$) restraints on the DOPAdT-polyA complex, the final unrestrained production simulations of 3.0 ns for the molecule was carried out at constant pressure (1 atm) and temperature (300 K). In the entire simulation, SHAKE was applied to all hydrogen atoms. Periodic boundary conditions with minimum image conventions were applied to calculate the nonbonded interactions. A cutoff of 10 Å was used for the Lennard-Jones interactions. The final structure of DOPAdT-polyA complex was produced

from the 1,000 steps of minimized averaged structure of the last 2.0 ns of MD.

The final structure of DOPAdT-polyA complex was shown in Fig S8. The oligomeric deoxyadenosine (polyA) presents helical form in this condition, to which DOPAdT molecules bind stably based on Watson-Crick base-pairing interaction(Fig S8a and S8b). Take the 10th deoxyadenosine (form the 5' end) and the corresponding DOPAdT molecule binding to it for an example, N--H and O--H hydrogen bonds were 1.910 Å and 1.926 Å respectively (Fig S8c). As to the 20th deoxyadenosine and the corresponding DOPAdT molecule, the length of N--H and O--H hydrogen bonds were 1.943 Å and 2.065 Å, respectively (Fig S8d).

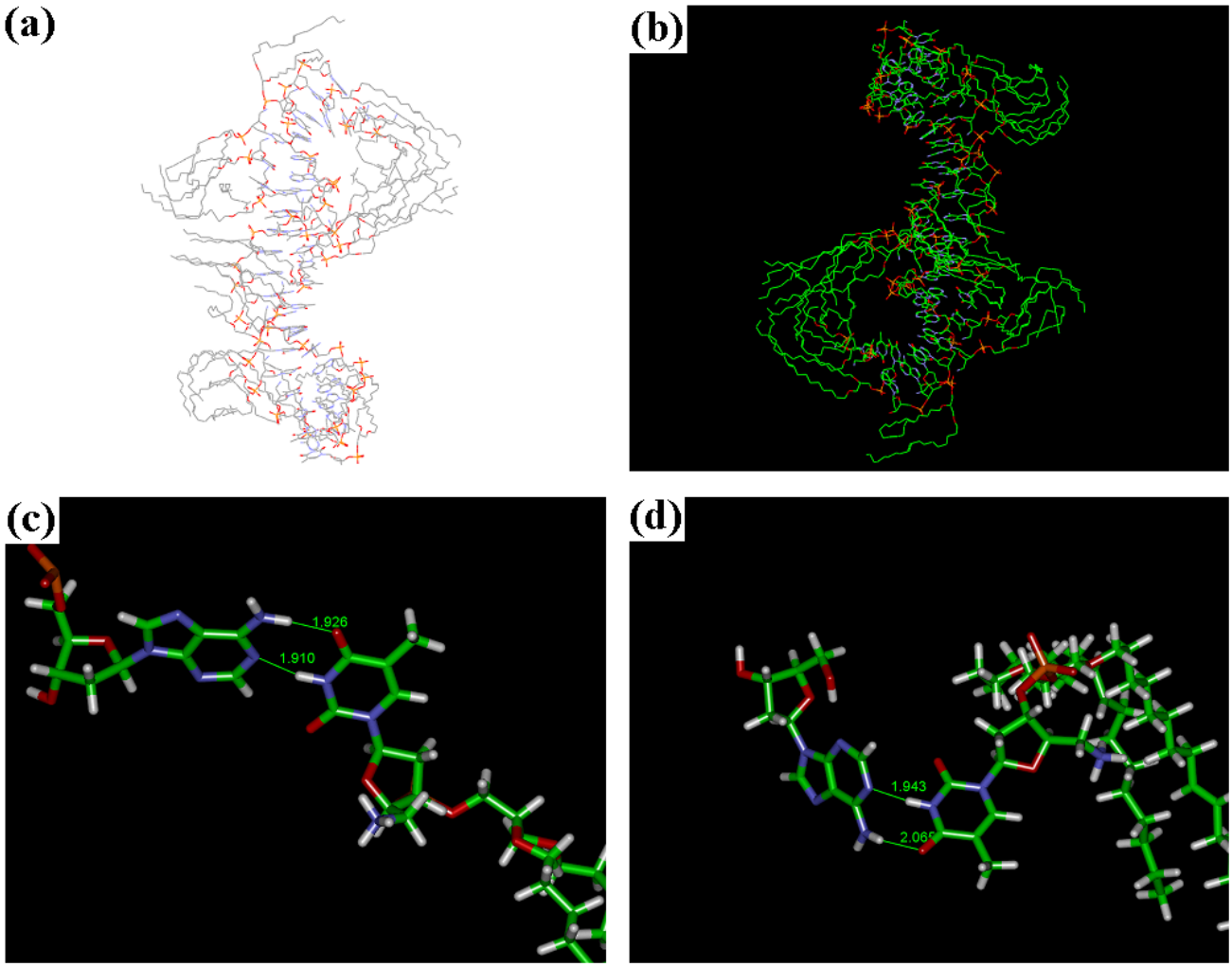


Figure S8. (a) & (b) Images of molecular dynamics simulation result of DOPAdT-polyA complex; (c) Simulation structure of the 10th deoxyadenosine (from the 5' end) and the corresponding DOPAdT molecule binding to it; (d) Simulation structure of the 10th deoxyadenosine (from the 5' end) and the corresponding DOPAdT molecule binding to it.

References

[1] K. Gogoi, A. D. Gunjal, U. D. Phalgune, V. A. Kumar, *Org. Lett.* **2007**, *9*, 2696-2700.

[2] I. van Daele, H. Munier-Lehmann, M. Froeyen, J. Balzarini, S. van Calenbergh, *J. Med. Chem.* **2007**, *50*, 5281-5292.

[3] A. Krief, A. Froidbise, *Tetrahedron* **2004**, *60*, 7637-7658.

[4] H. Zheng, X. Du, *J. Phys. Chem. B* **2009**, *113*, 11330-11337.

[5] A. Bajaj, B. Paul, P. Kondaiah, S. Bhattacharya, *Bioconjugate Chem.* **2008**, *19*, 1283-1300.

[6] D. W. Pack, G. Chen, K. M. Maloney, C.-T. Chen, F. H. Arnold, *J. Am. Chem. Soc.* **1997**, *119*, 2479-2487.

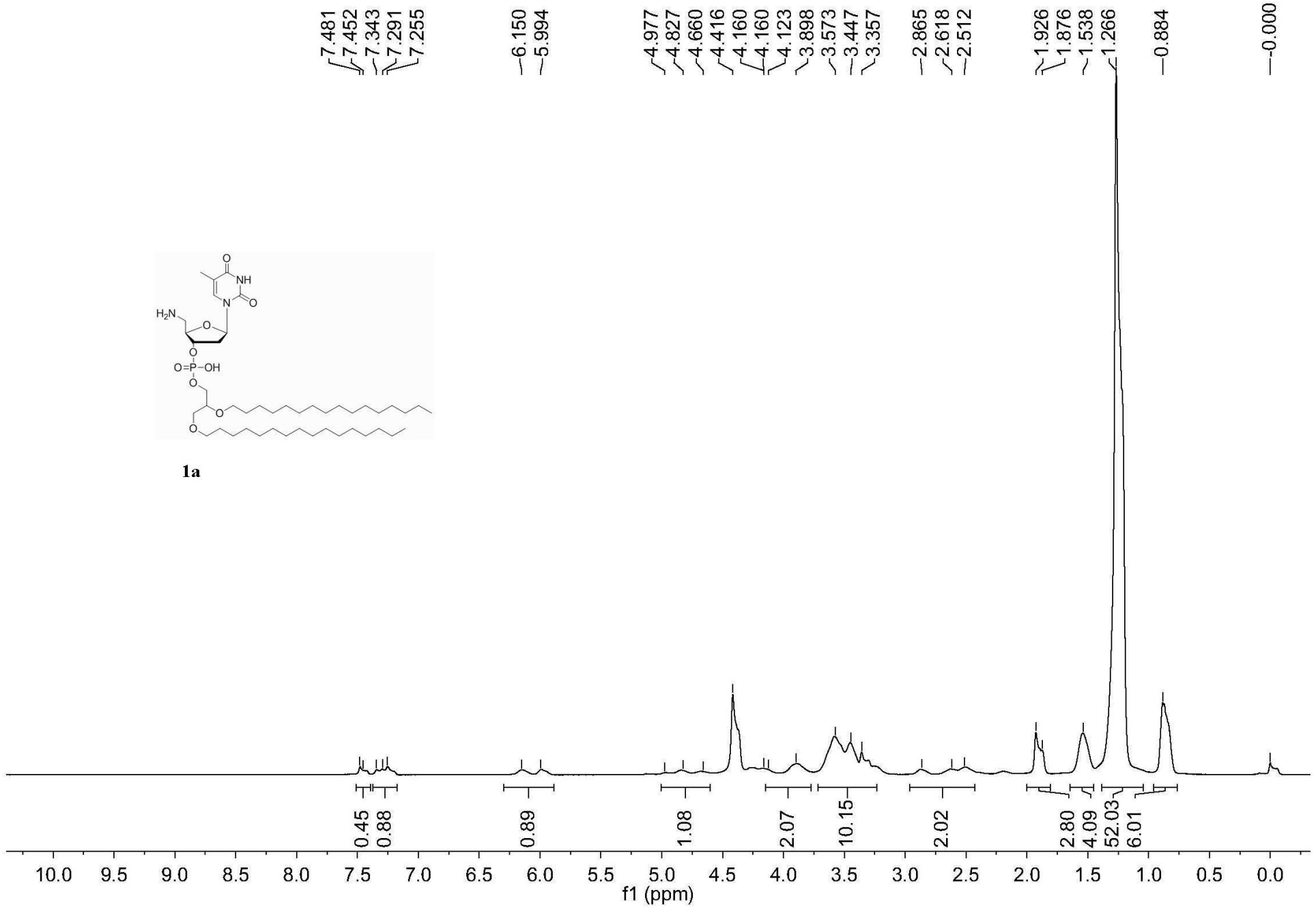
[7] M. Ishiyama, H. Tominaga, M. Shiga, K. Sasamoto, Y. Ohkura, K. Ueno, *Biol. Pharm. Bull* **1996**, *19*, 1518-1520.

[8] X.-X. Wang, Y.-B. Li, H.-J. Yao, R.-J. Ju, Y. Zhang, R.-J. Li, Y. Yu, L. Zhang, W.-L. Lu, *Biomaterials* **2011**, *32*, 5673.

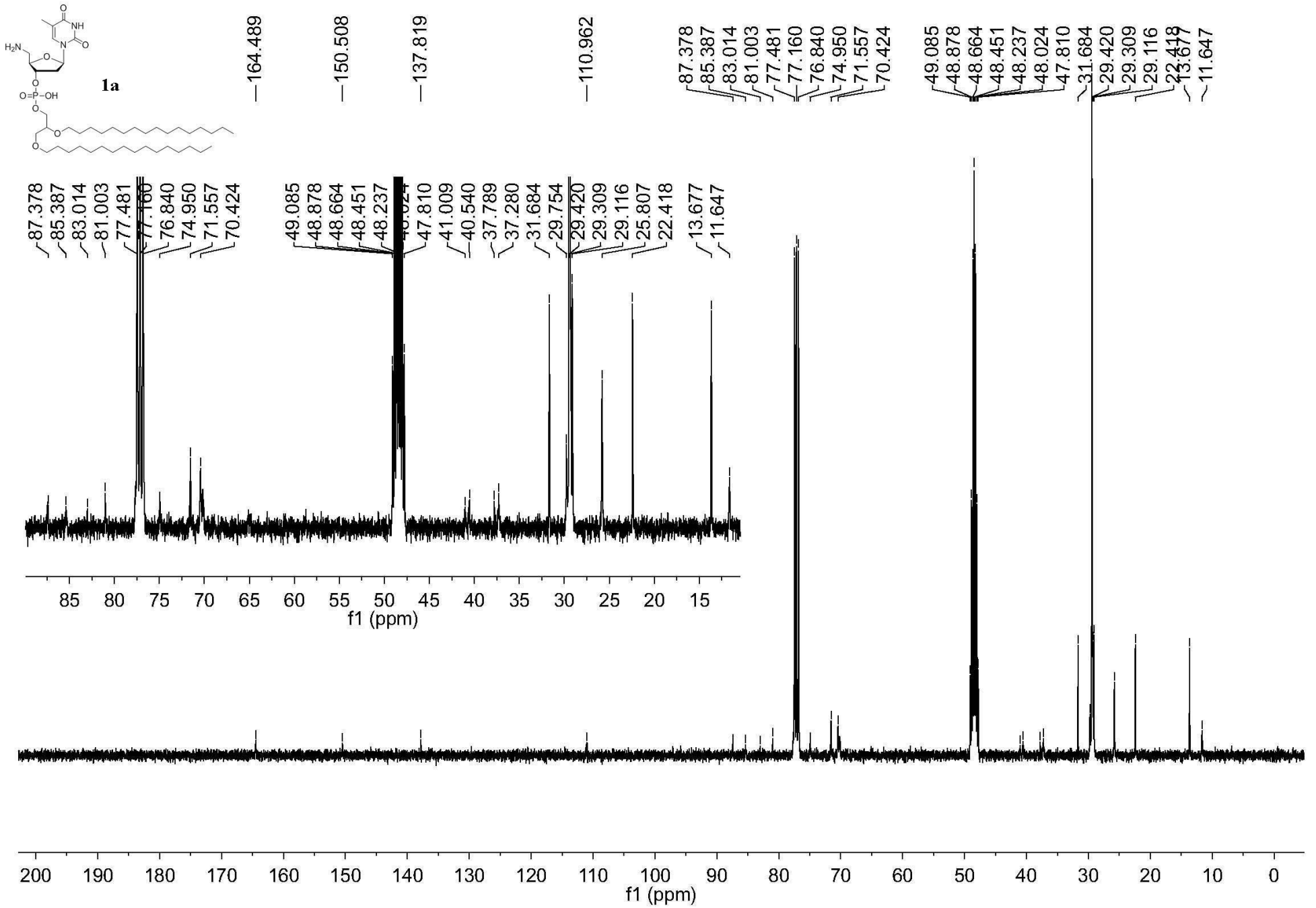
[9] D.A. Case, T. A. Darden, T. E. Cheatham, C. L. Simmerling, J. Wang, R. E. Duke, R. Luo, R. C. Walker, W. Zhang, K. M. Merz, B. Roberts, B. Wang, S. Hayik, A. Roitberg, G. Seabra, I. Kolossváry, K. F. Wong, F. Paesani, J. Vanicek, J. Liu, X. Wu, S. R. Brozell, T. Steinbrecher, H. Gohlke, Q. Cai, X. Ye, J. Wang, M.-J. Hsieh, G. Cui, D. R. Roe, D. H. Mathews, M. G. Seetin, C. Sagui, V. Babin, T. Luchko, S. Gusarov, A. Kovalenko, P. A. Kollman, 2010, AMBER 11, University of California, San Francisco.

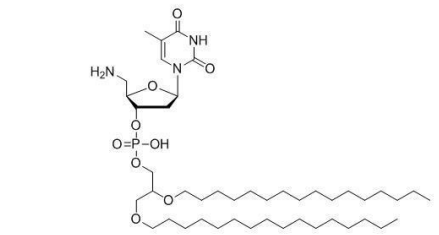
[10] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[11] C. I. Bayly, P. Cieplak, W. D. Cornell, P. A. Kollman, *J. Phys. Chem.* **1993**, *97*, 10269-10280.

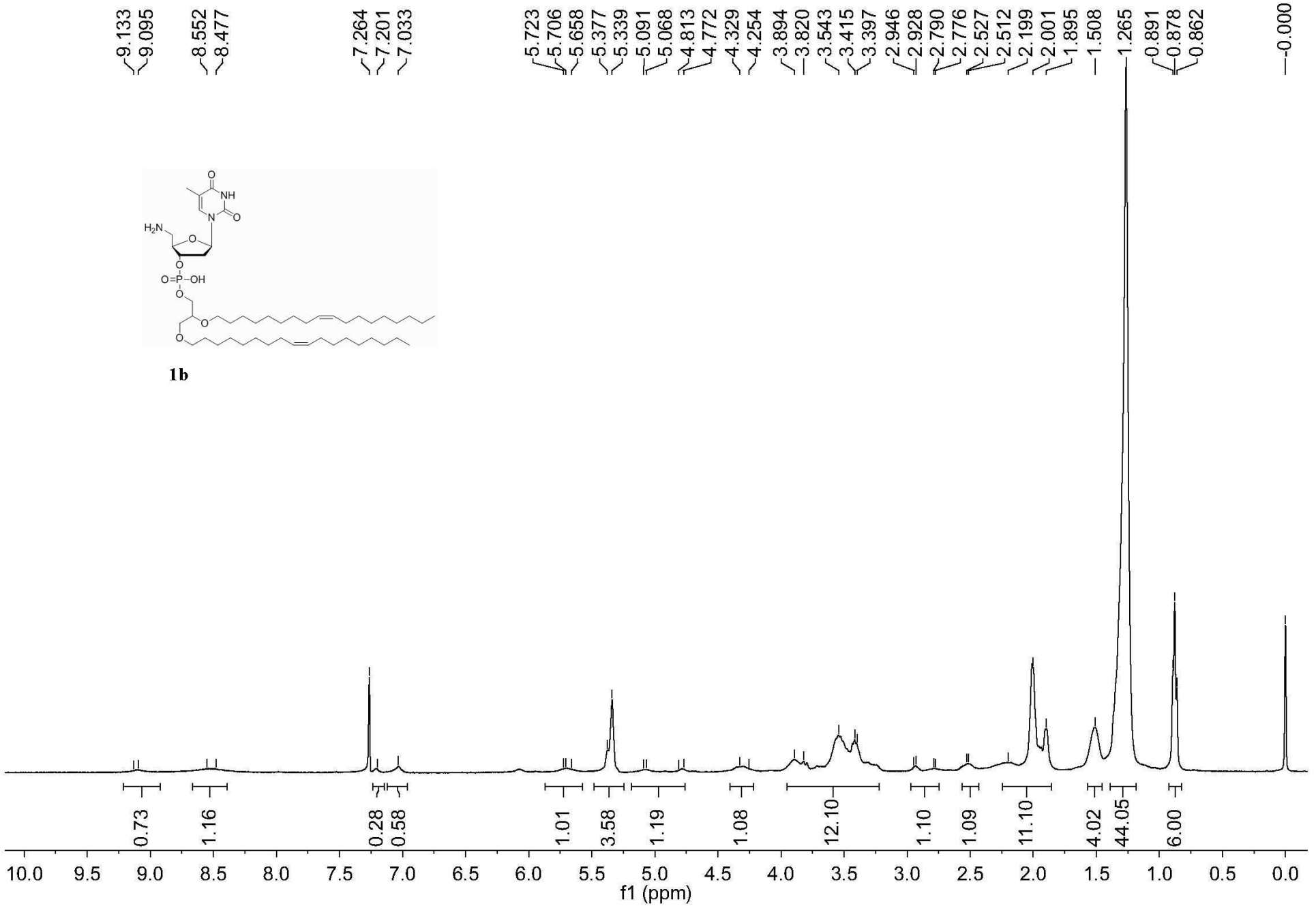

7.481
7.452
7.343
7.291
7.255
6.150
5.994
4.977
4.827
4.660
4.416
4.160
4.160
4.123
3.898
3.573
3.447
3.357
2.865
2.618
2.512
1.926
1.876
1.538
1.266
0.884
0.000
0.45
0.88
0.89
1.08
2.07
10.15
2.02
2.80
4.09
52.03
6.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

1a

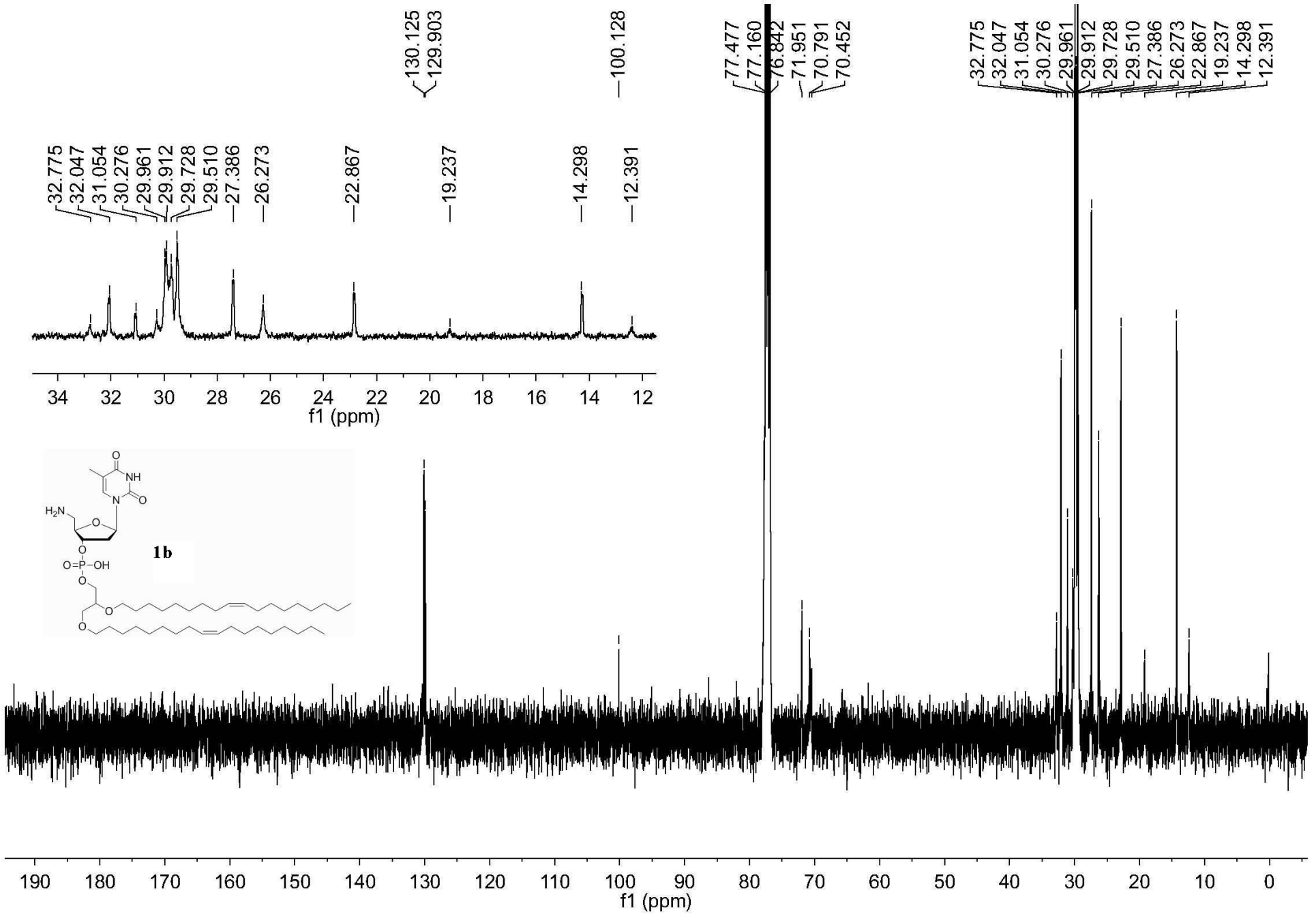

1a
164.489
150.508
137.819
110.962
87.378
85.387
83.014
81.003
77.481
77.160
76.840
74.950
71.557
70.424
49.085
48.878
48.664
48.451
48.237
48.024
47.810
31.684
29.420
29.309
29.116
22.418
13.677
11.647
41.009
40.540
37.789
37.280
25.807
f1 (ppm)

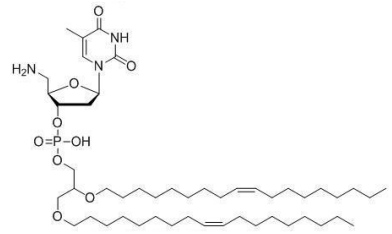


1a

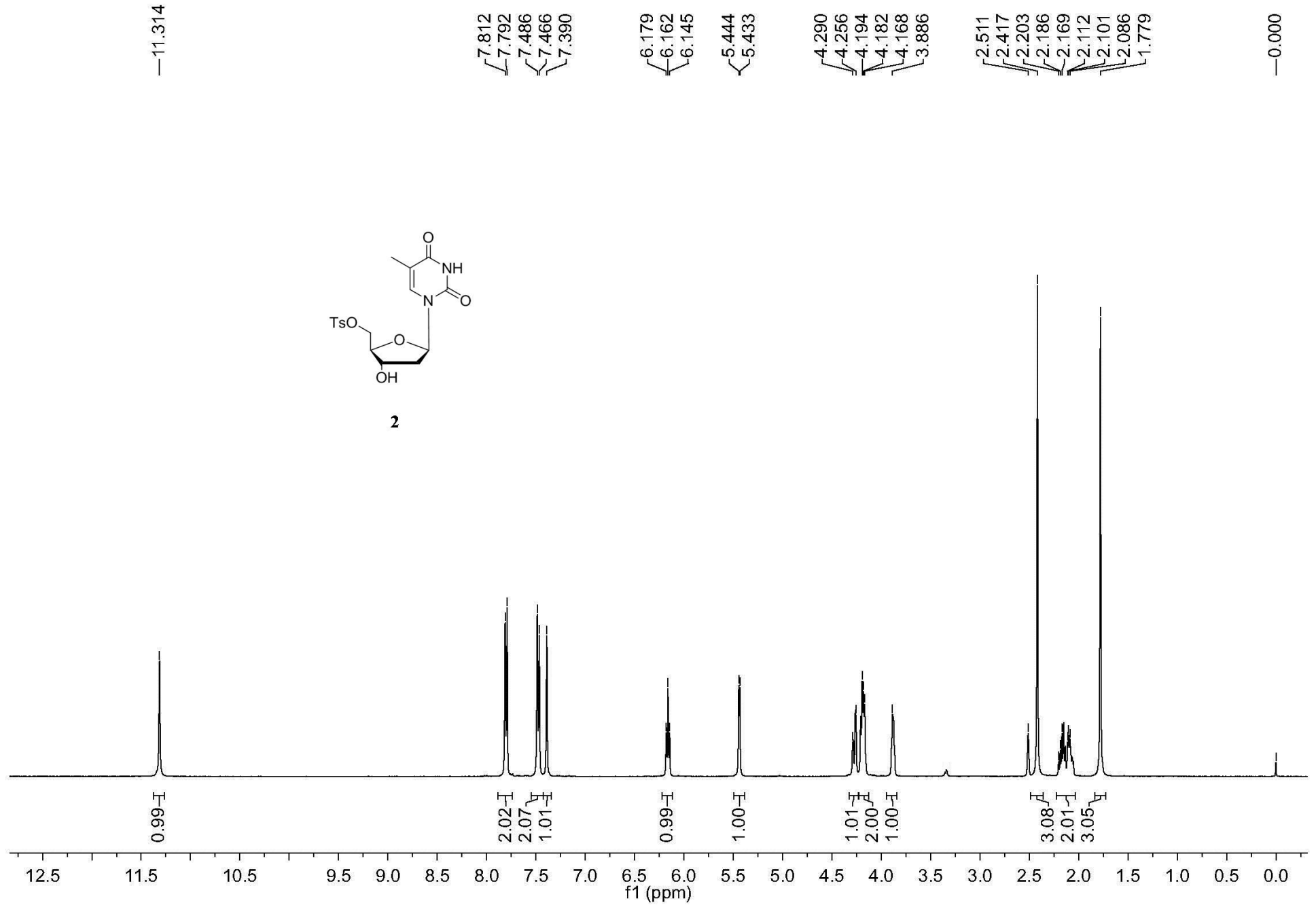

9.133
9.095
8.552
8.477
7.264
7.201
7.033
5.723
5.706
5.658
5.377
5.339
5.091
5.068
4.813
4.772
4.329
4.254
3.894
3.820
3.543
3.415
3.397
2.946
2.928
2.790
2.776
2.527
2.512
2.199
2.001
1.895
1.508
1.265
0.891
0.878
0.862
0.000
0.73
1.16
0.28
0.58
1.01
3.58
1.19
1.08
12.10
1.10
1.09
11.10
4.02
44.05
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

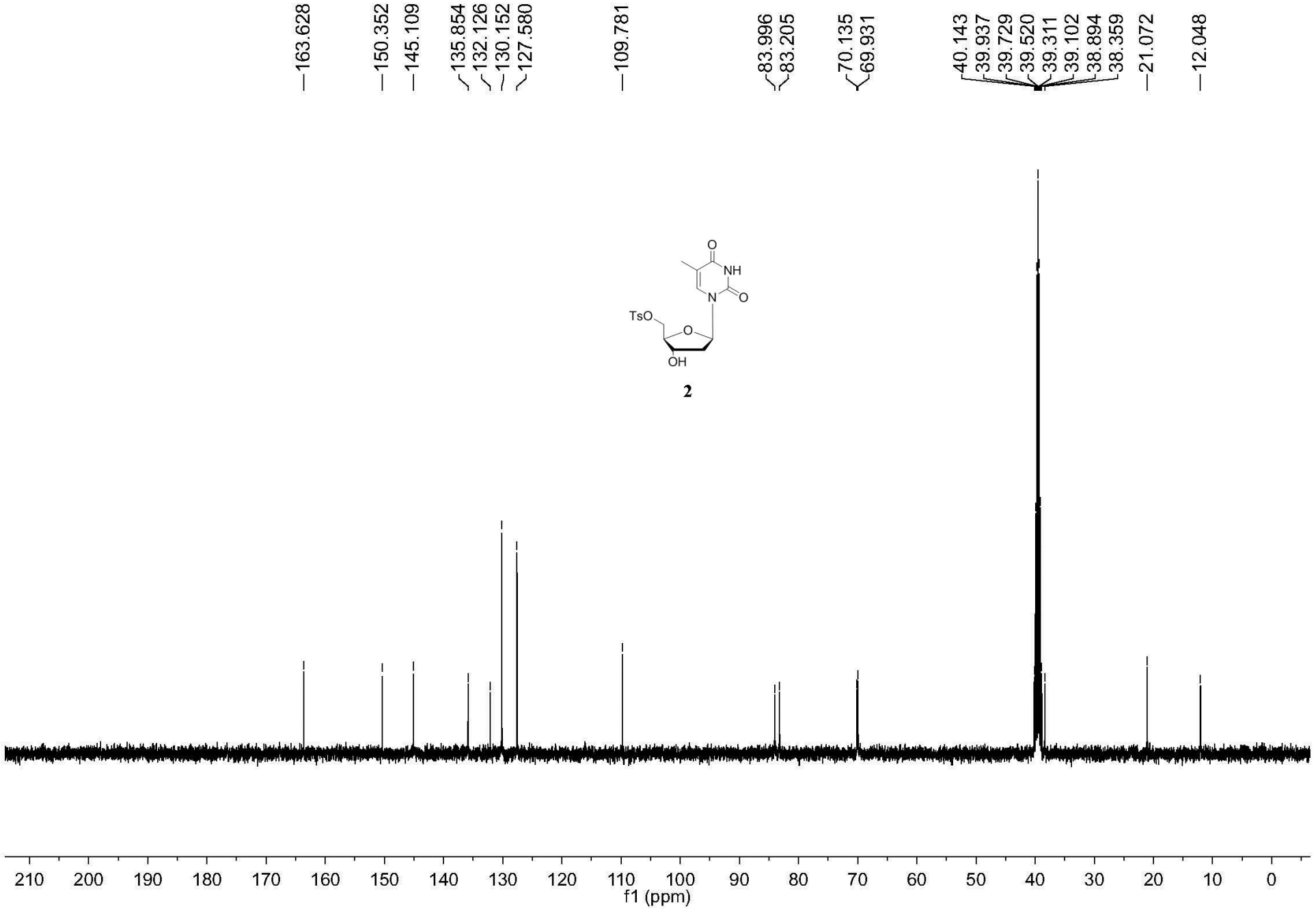
1b

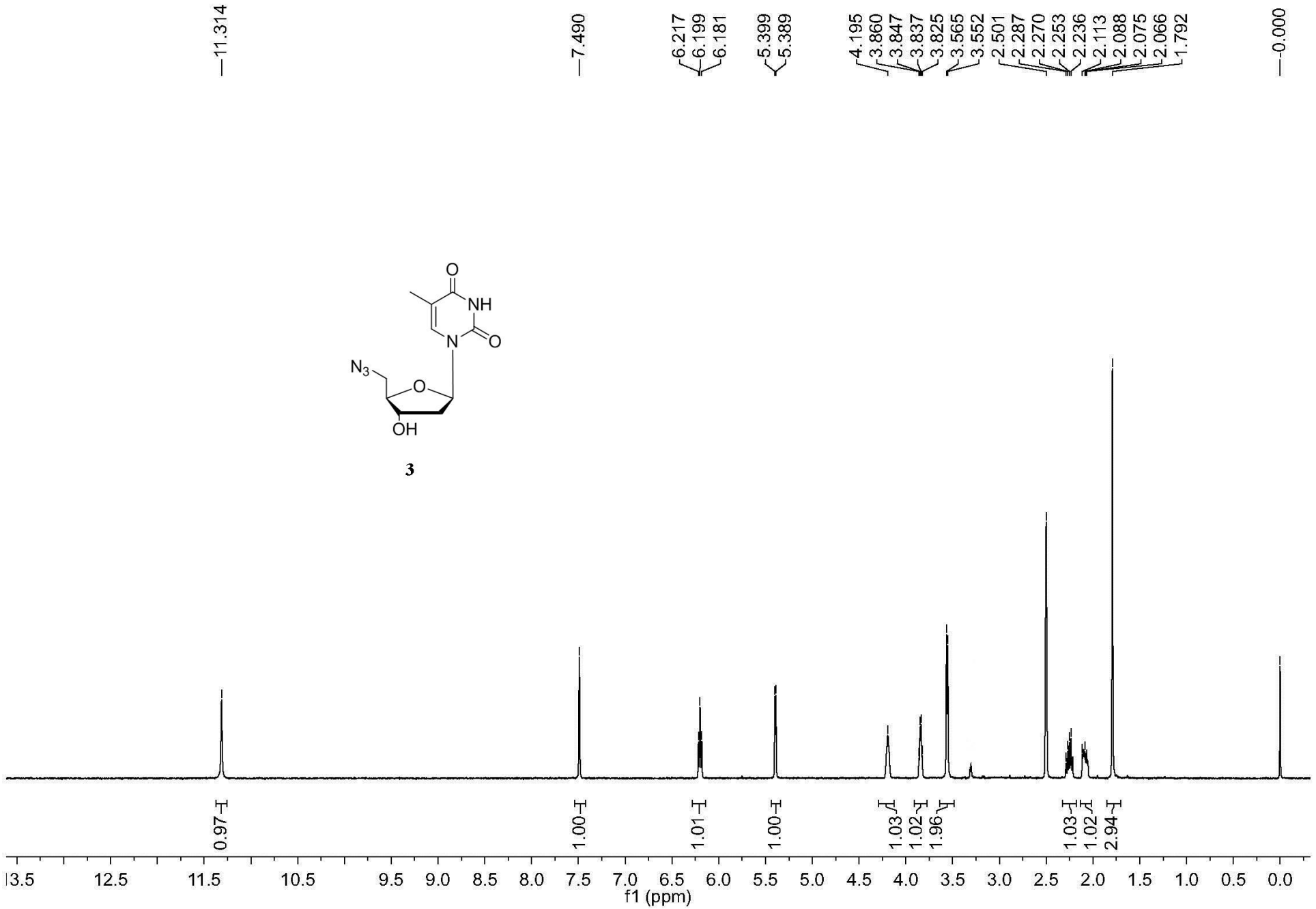

130.125
129.903
100.128
77.477
77.160
76.842
71.951
70.791
70.452
32.775
32.047
31.054
30.276
29.961
29.912
29.728
29.510
27.386
26.273
22.867
19.237
14.298
12.391
f1 (ppm)
1b
f1 (ppm)



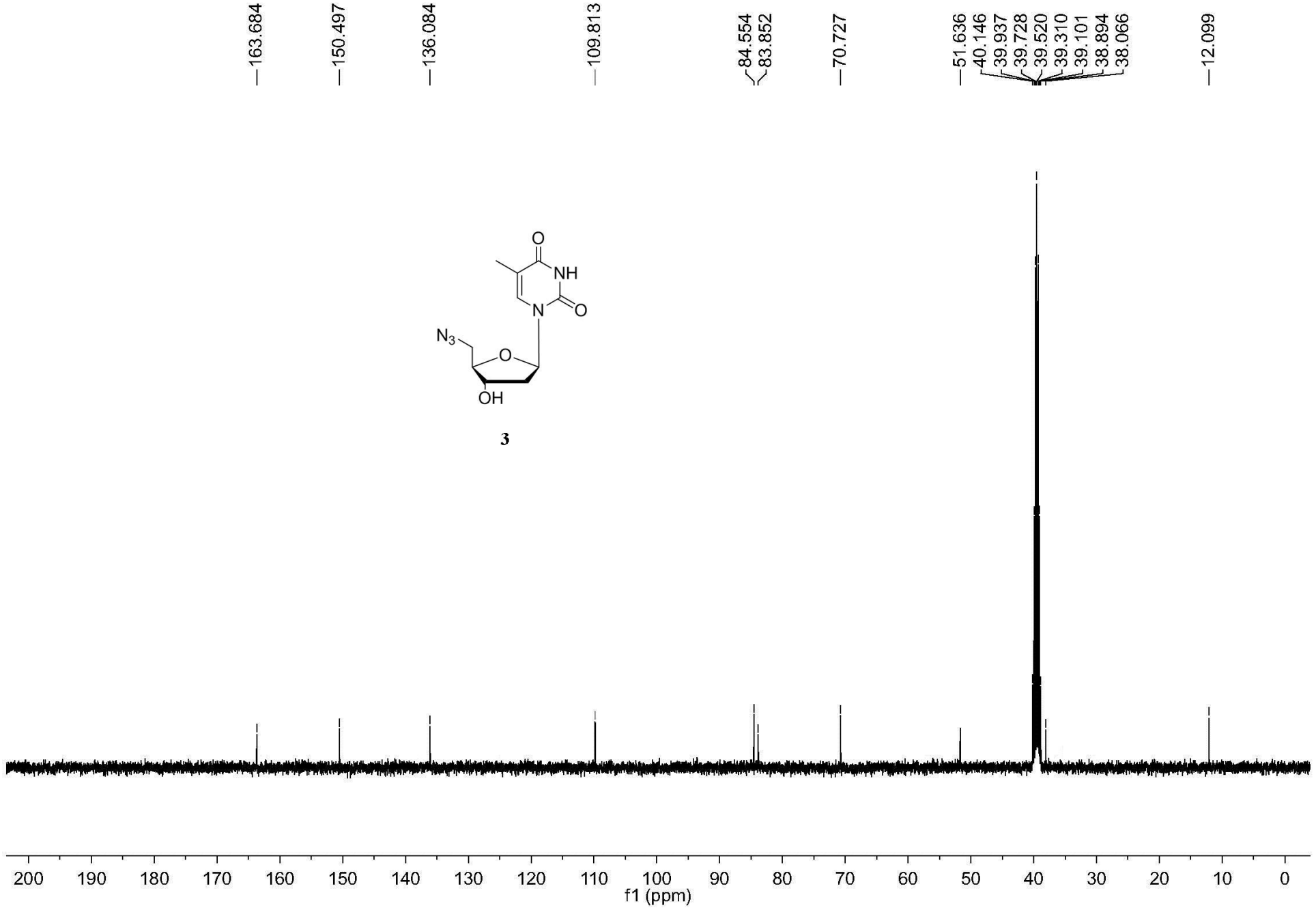
1b


11.314
7.812
7.792
7.486
7.466
7.390
6.179
6.162
6.145
5.444
5.433
4.290
4.256
4.194
4.182
4.168
3.886
2.511
2.417
2.203
2.186
2.169
2.112
2.101
2.086
1.779
0.000
TsO
O
NH
N
O
OH
2
0.99
2.02
2.07
1.01
0.99
1.00
1.01
2.00
1.00
3.08
2.01
3.05
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

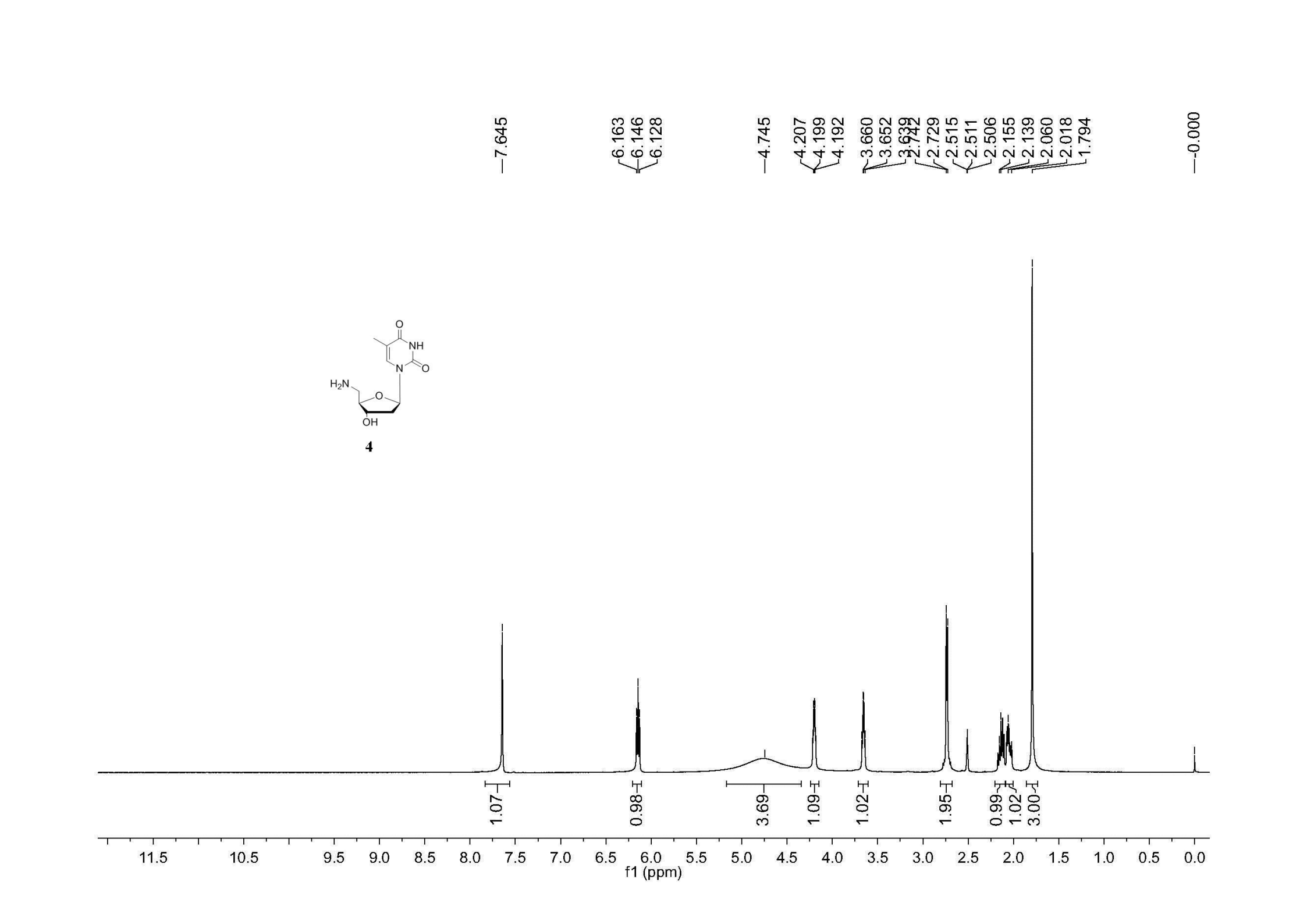

163.628
150.352
145.109
135.854
132.126
130.152
127.580
109.781
83.996
83.205
70.135
69.931
40.143
39.937
39.729
39.520
39.311
39.102
38.894
38.359
21.072
12.048
O
NH
N
O
TsO
O
OH
2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11.314
7.490
6.217
6.199
6.181
5.399
5.389
4.195
3.860
3.847
3.837
3.825
3.565
3.552
2.501
2.287
2.270
2.253
2.236
2.113
2.088
2.075
2.066
1.792
0.000
O
NH
N
O
N3
O
OH
0.97
1.00
1.01
1.00
1.03
1.02
1.96
1.03
1.02
2.94
f1 (ppm)

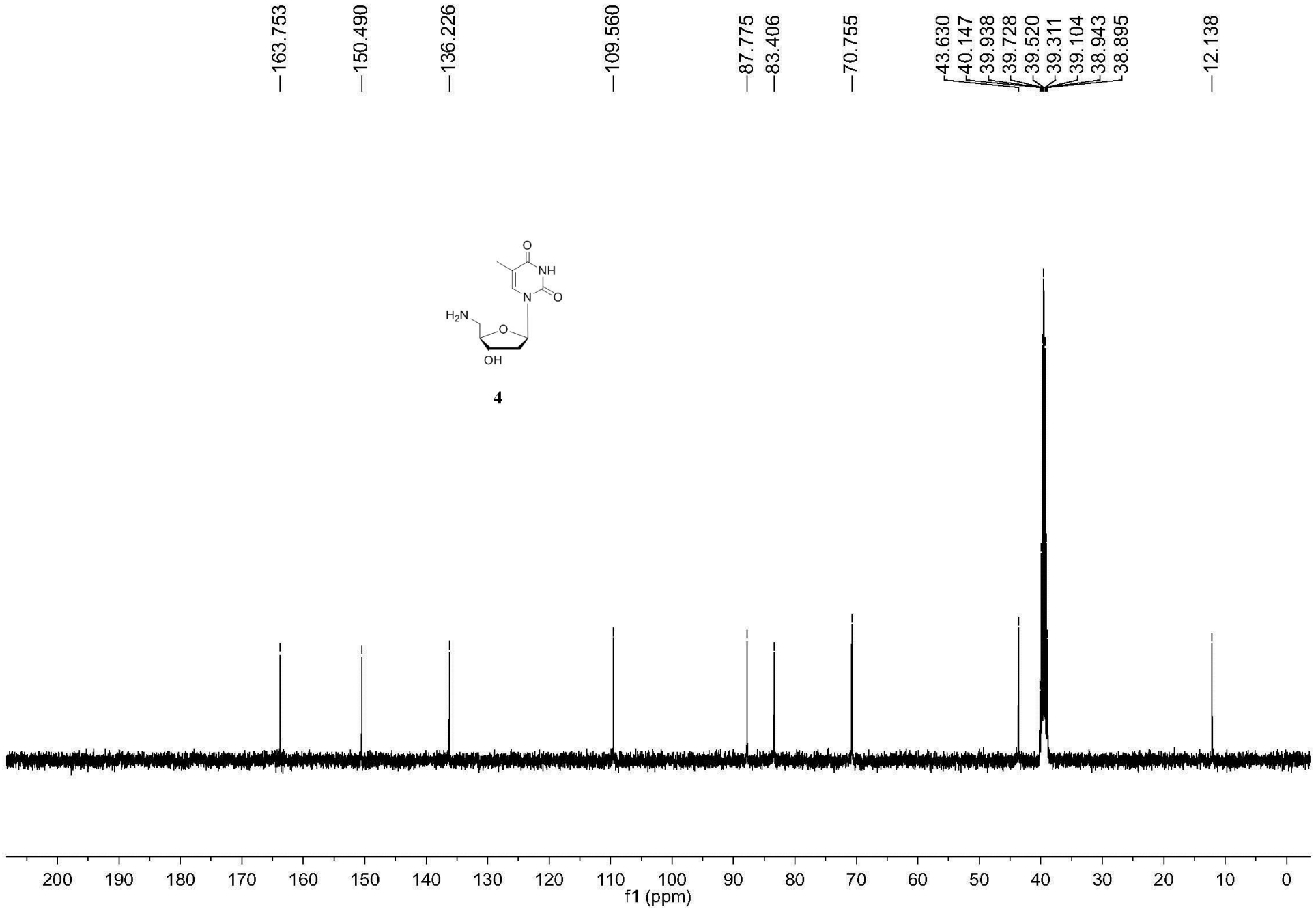
3

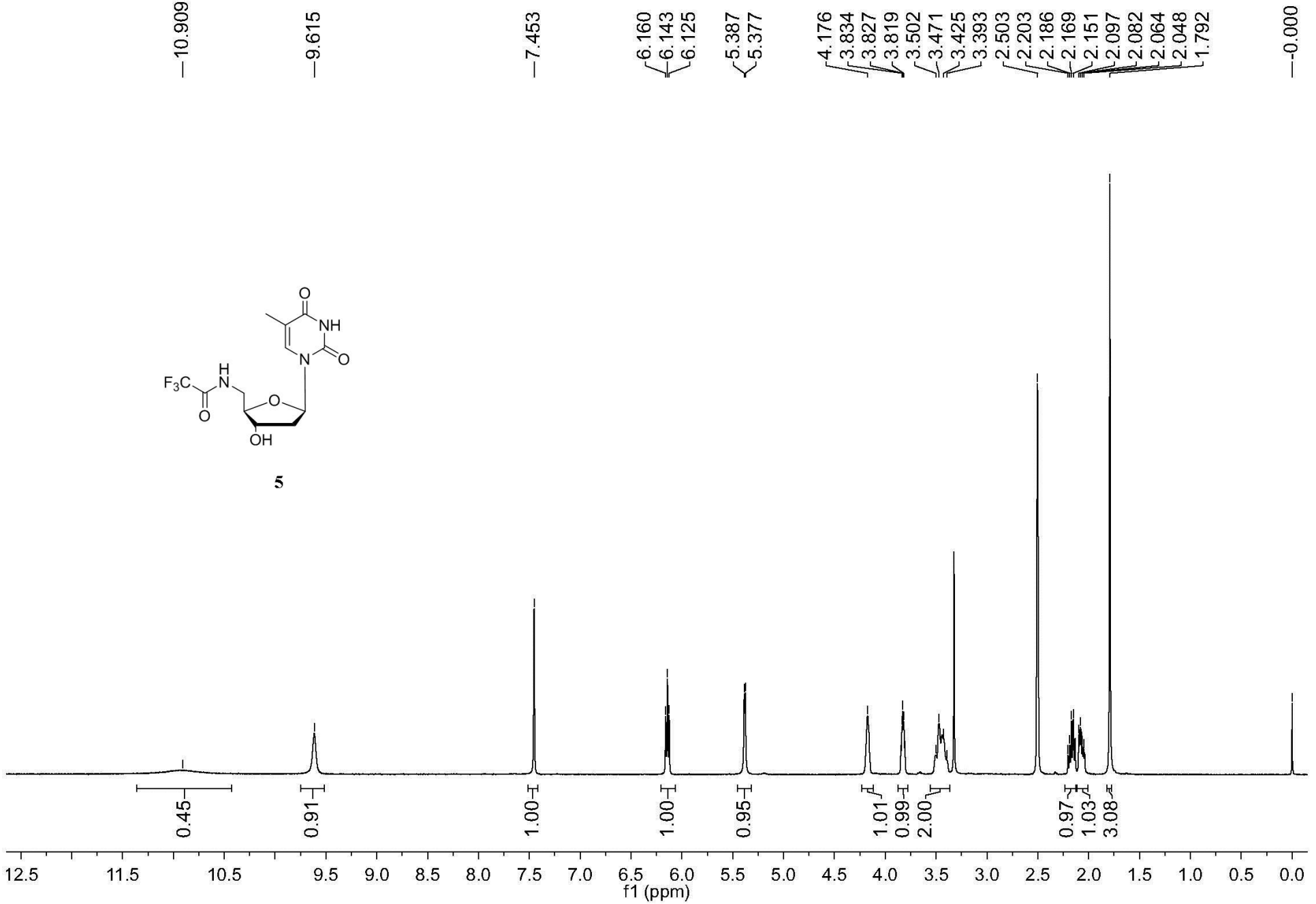

163.684
150.497
136.084
109.813
84.554
83.852
70.727
51.636
40.146
39.937
39.728
39.520
39.310
39.101
38.894
38.066
12.099
O
NH
N
O
N3
O
OH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3

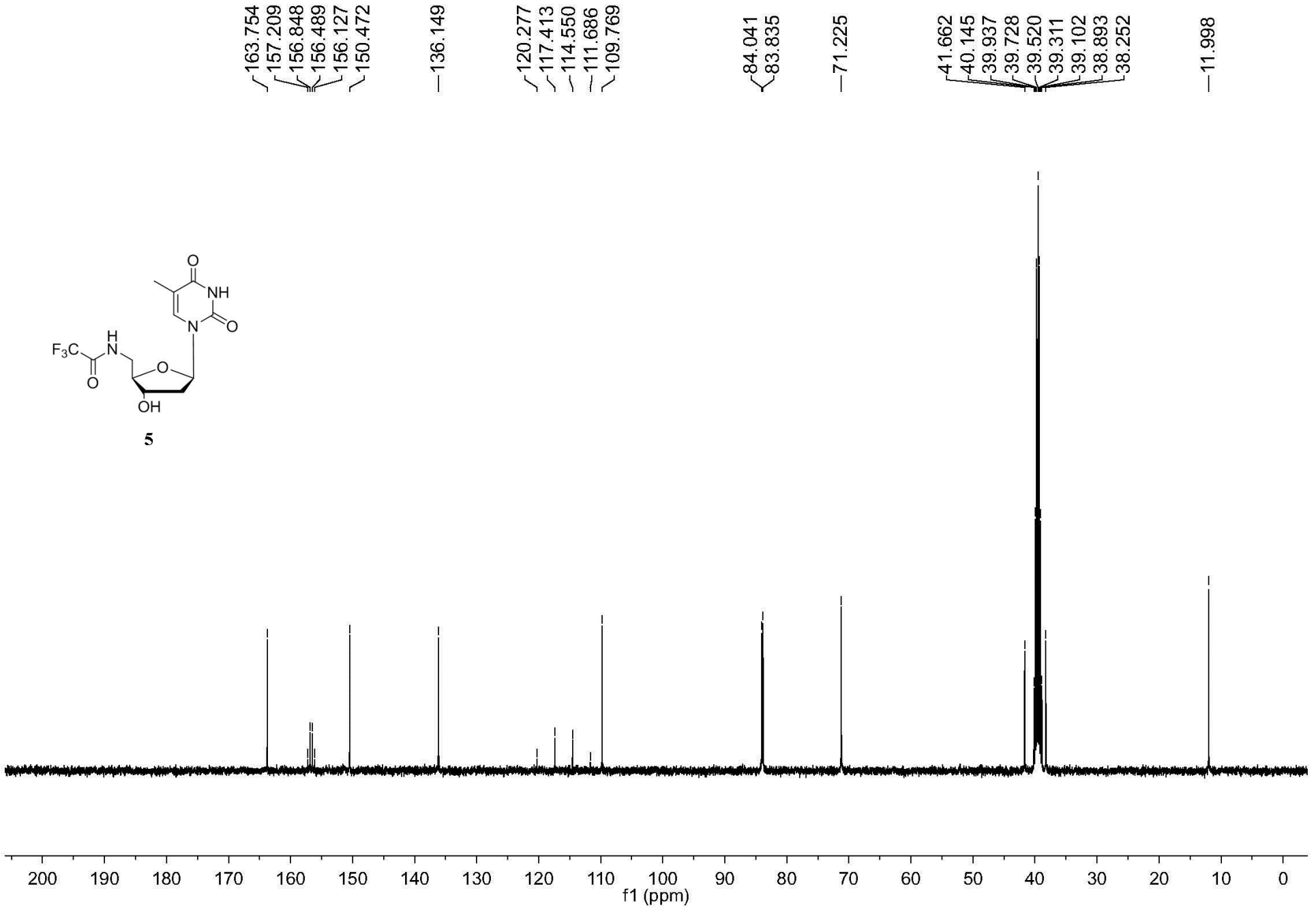

7.645
6.163
6.146
6.128
4.745
4.207
4.199
4.192
3.660
3.652
3.639
3.632
2.729
2.515
2.511
2.506
2.155
2.139
2.060
2.018
1.794
0.000
1.07
0.98
3.69
1.09
1.02
1.95
0.99
1.02
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
O
NH
N
O
H2N
O
OH

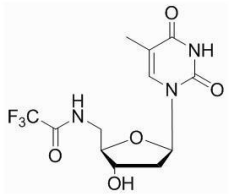
4


163.753
150.490
136.226
109.560
87.775
83.406
70.755
43.630
40.147
39.938
39.728
39.520
39.311
39.104
38.943
38.895
12.138
O
NH
N
O
H2N
O
OH
4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


10.909
9.615
7.453
6.160
6.143
6.125
5.387
5.377
4.176
3.834
3.827
3.819
3.502
3.471
3.425
3.393
2.503
2.203
2.186
2.169
2.151
2.097
2.082
2.064
2.048
1.792
0.000
0.45
0.91
1.00
1.00
0.95
1.01
0.99
2.00
0.97
1.03
3.08
f1 (ppm)

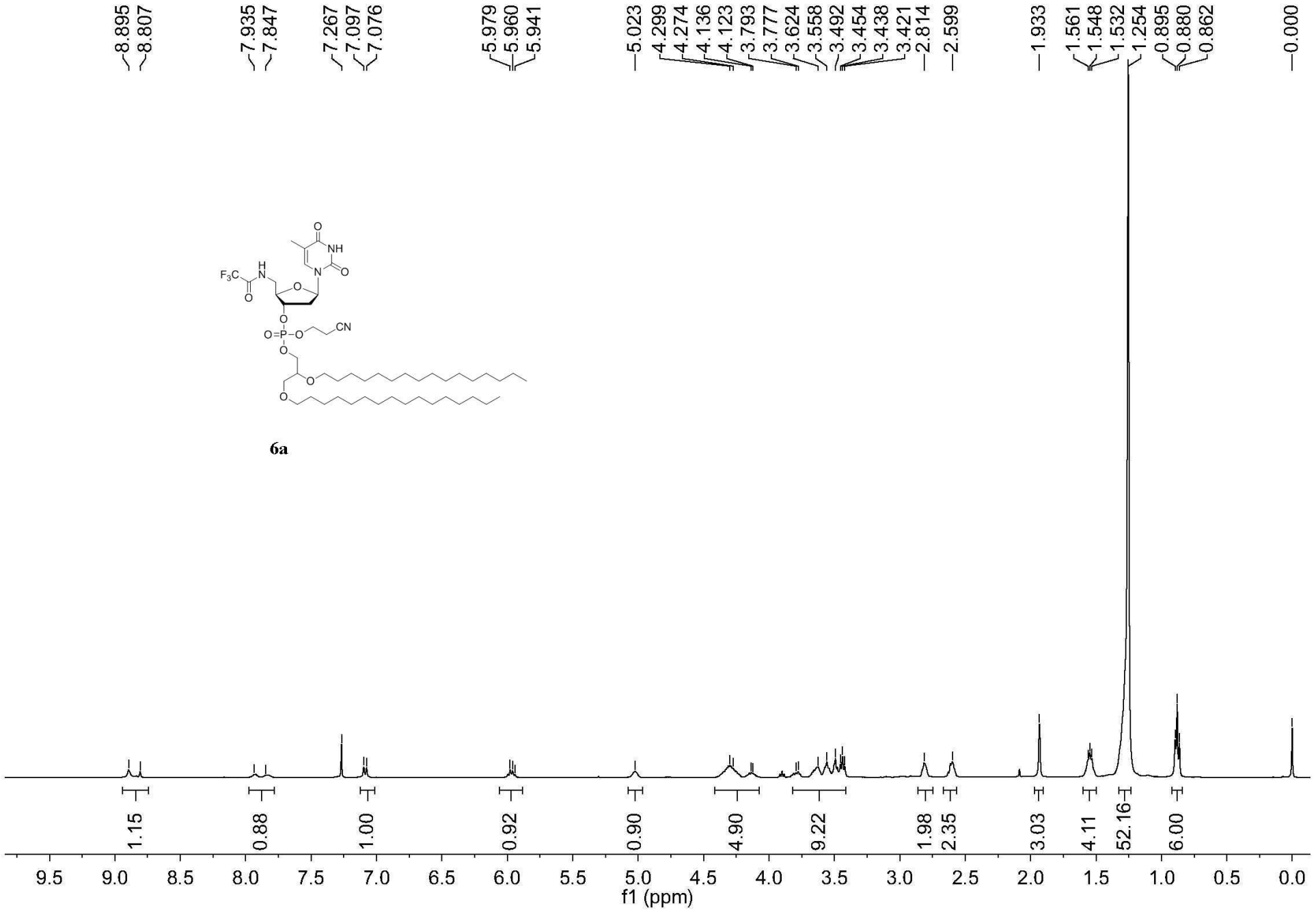
5


163.754
157.209
156.848
156.489
156.127
150.472
136.149
120.277
117.413
114.550
111.686
109.769
84.041
83.835
71.225
41.662
40.145
39.937
39.728
39.520
39.311
39.102
38.893
38.252
11.998
O
NH
N
O
H
N
F3C
O
O
OH
5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

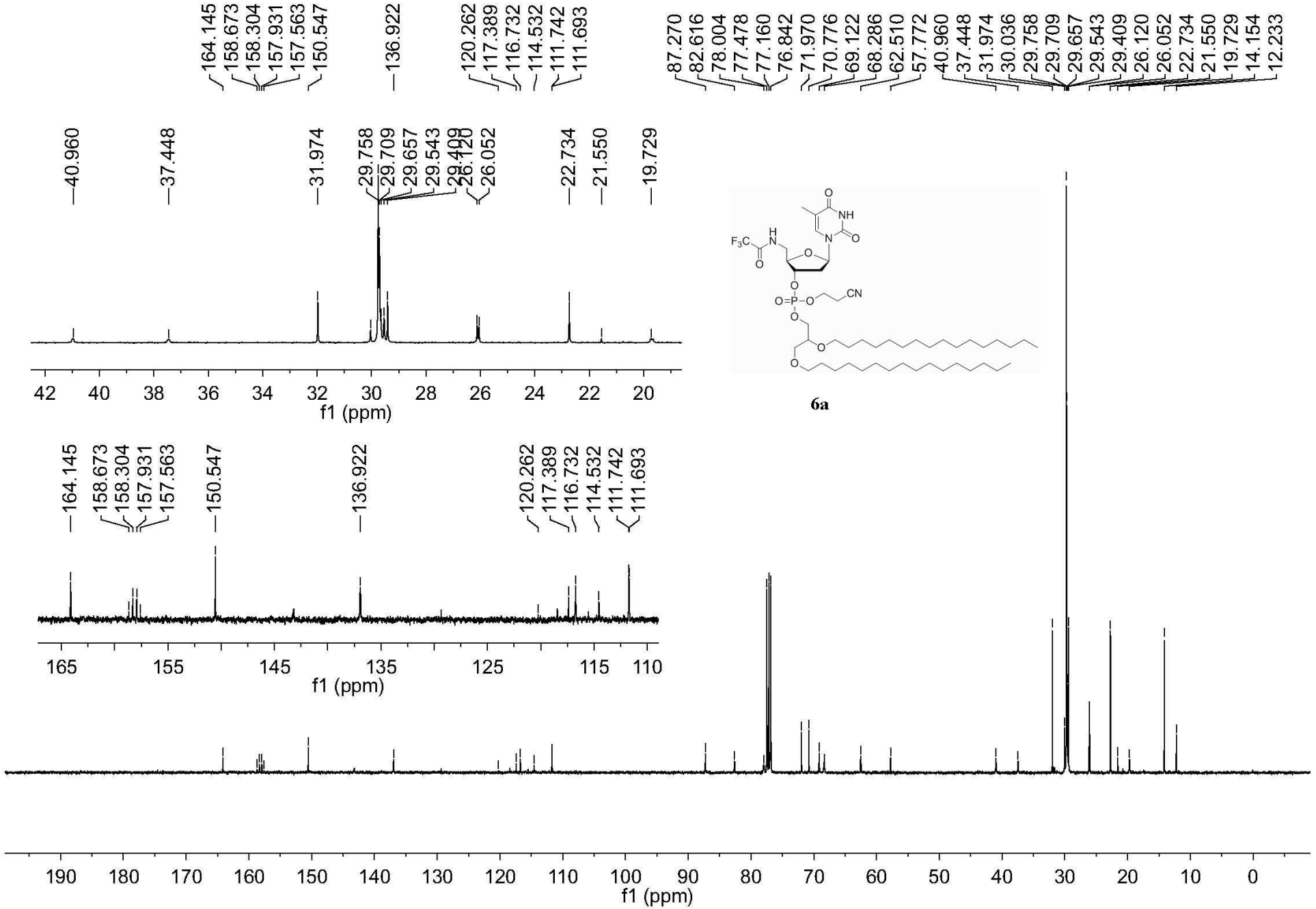

O
NH
N
O
H
N
F3C
O
O
OH

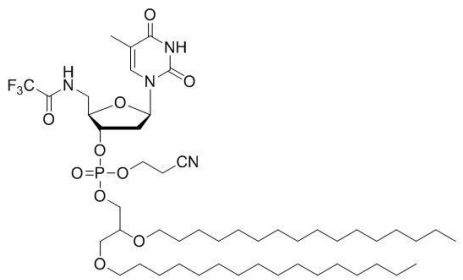
5

-74.233
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-110
-130
-150
-170
-190
f1 (ppm)


8.895
8.807
7.935
7.847
7.267
7.097
7.076
5.979
5.960
5.941
5.023
4.299
4.274
4.136
4.123
3.793
3.777
3.624
3.558
3.492
3.454
3.438
3.421
2.814
2.599
1.933
1.561
1.548
1.532
1.254
0.895
0.880
0.862
0.000
1.15
0.88
1.00
0.92
0.90
4.90
9.22
1.98
2.35
3.03
4.11
52.16
6.00
f1 (ppm)

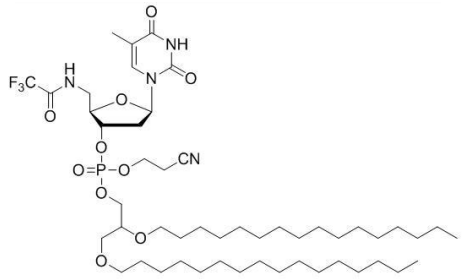
6a


164.145
158.673
158.304
157.931
157.563
150.547
136.922
120.262
117.389
116.732
114.532
111.742
111.693
87.270
82.616
78.004
77.478
77.160
76.842
71.970
70.776
69.122
68.286
62.510
57.772
40.960
37.448
31.974
30.036
29.758
29.709
29.657
29.543
29.409
26.120
26.052
22.734
21.550
19.729
14.154
12.233
f1 (ppm)
6a



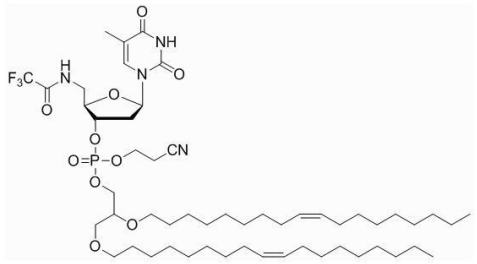
6a

-2.168
-2.269
-2.316
140
110
80
60
40
20
0
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)



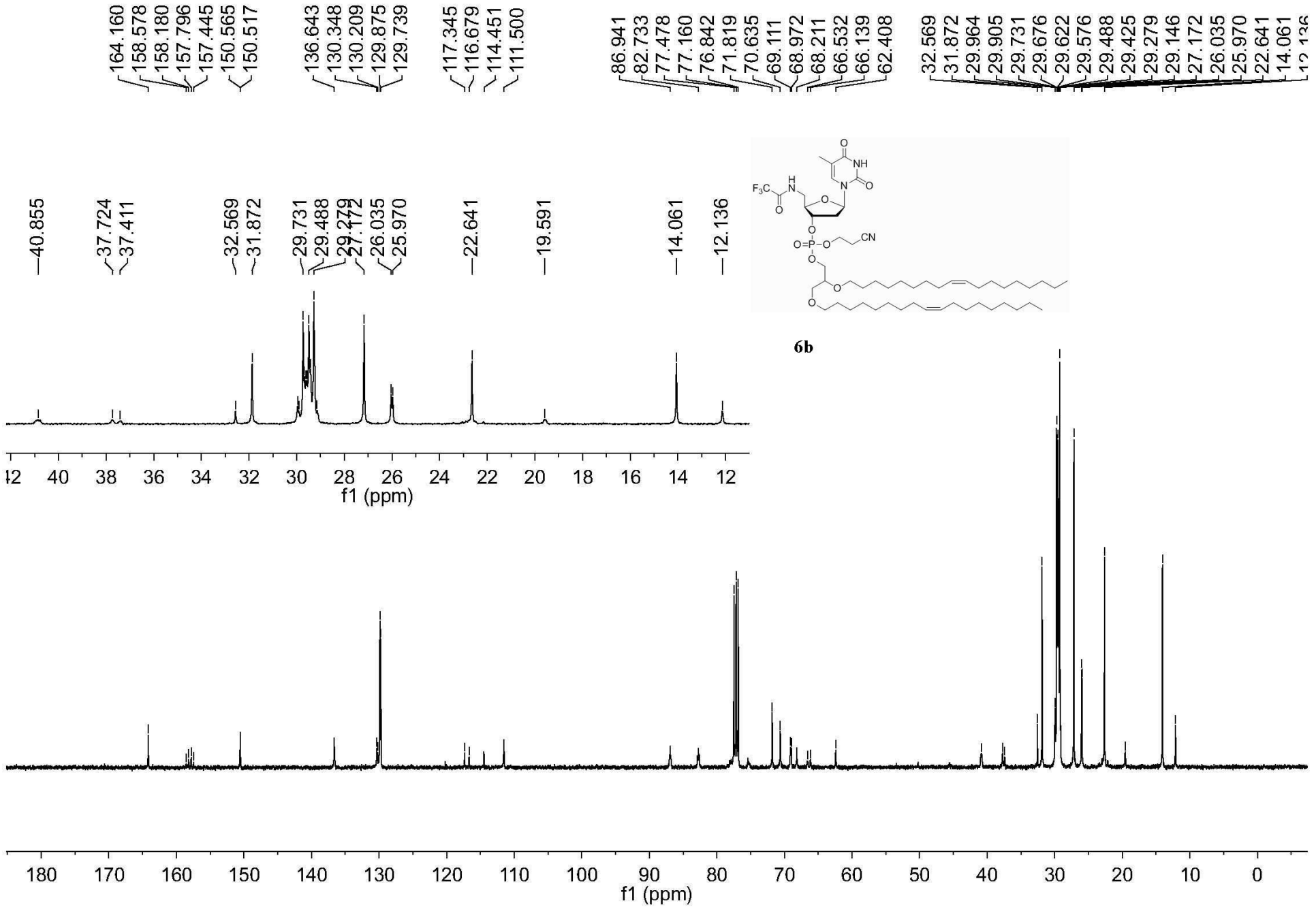
6a

-75.585
-75.622
-75.630
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-110
-130
-150
-170
-190
f1 (ppm)

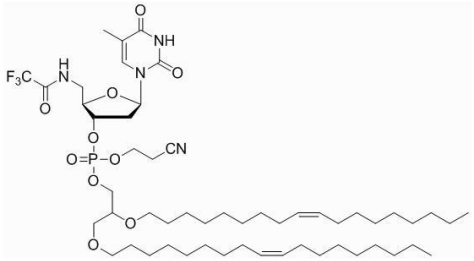


6b

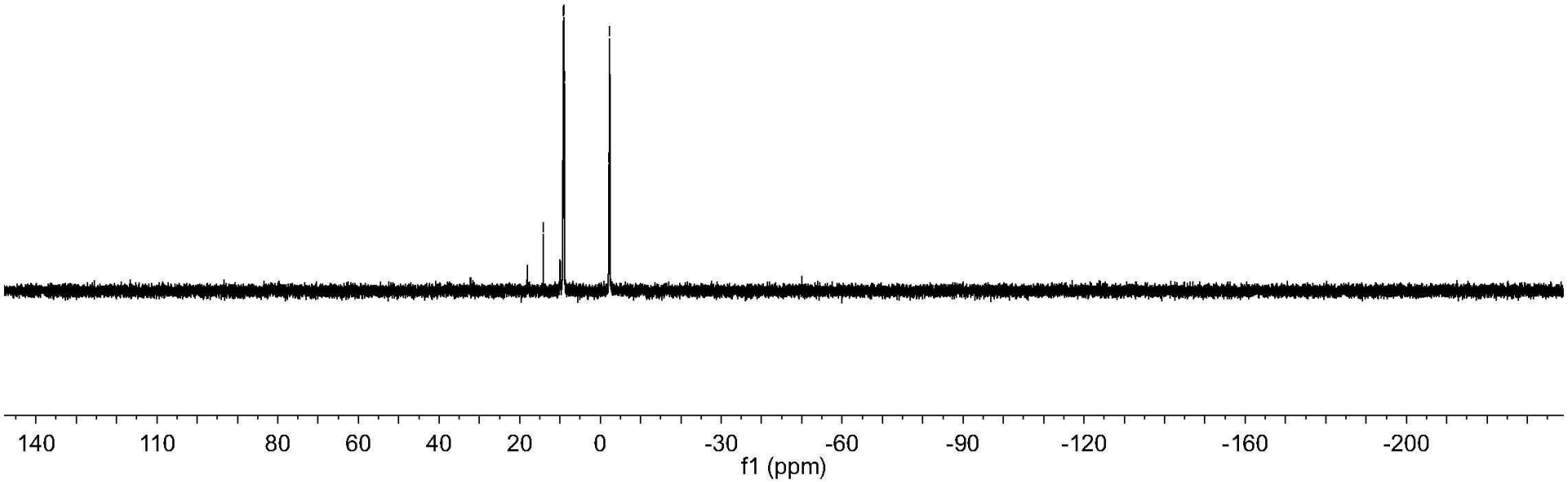
9.911
8.118
7.955
7.874
7.269
7.081
5.985
5.317
5.111
5.027
4.256
3.599
3.482
3.429
2.793
2.522
1.989
1.928
1.883
1.529
1.258
0.855
0.000
0.45
0.93
0.94
1.20
4.03
1.00
4.36
11.31
1.09
2.20
11.44
4.41
44.19
6.40
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


164.160
158.578
158.180
157.796
157.445
150.565
150.517
136.643
130.348
130.209
129.875
129.739
117.345
116.679
114.451
111.500
86.941
82.733
77.478
77.160
76.842
71.819
70.635
69.111
68.972
68.211
66.532
66.139
62.408
32.569
31.872
29.964
29.905
29.731
29.676
29.622
29.576
29.488
29.425
29.279
29.146
27.172
26.035
25.970
22.641
14.061
40.855
37.724
37.411
32.569
31.872
29.731
29.488
26.035
25.970
22.641
19.591
14.061
12.136
f1 (ppm)
f1 (ppm)
6b

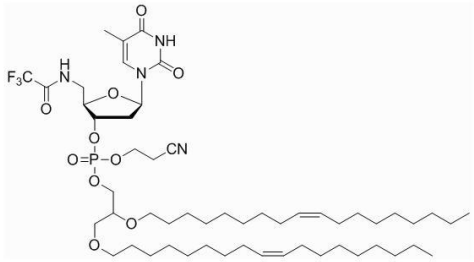
14.120
9.141
9.086
8.945
8.882
-2.173
-2.257
-2.329



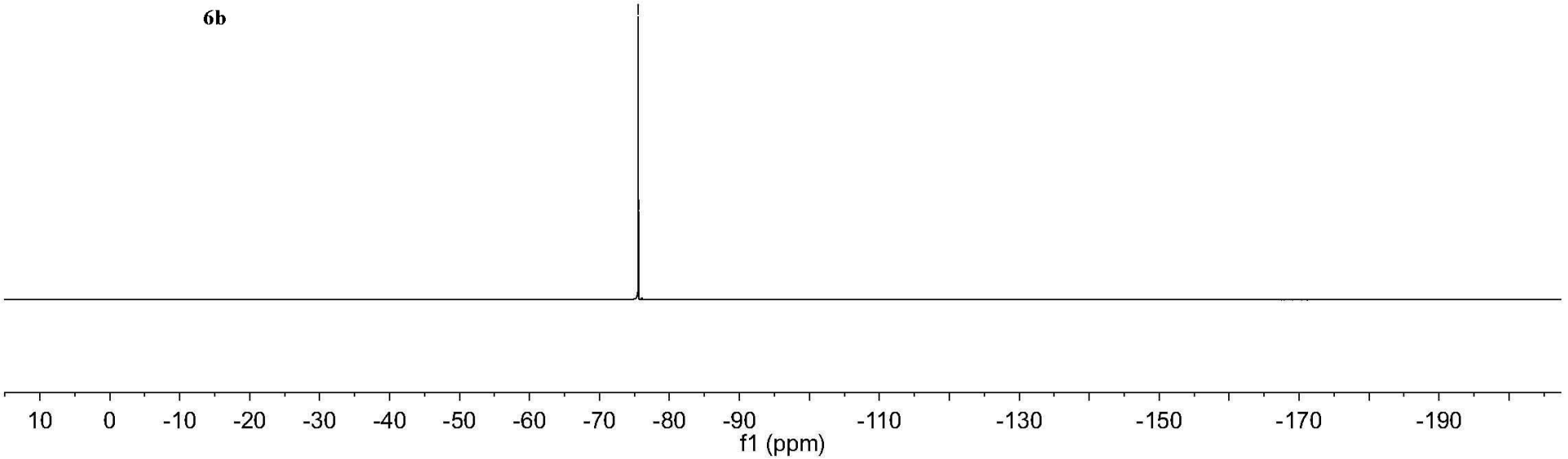
6b

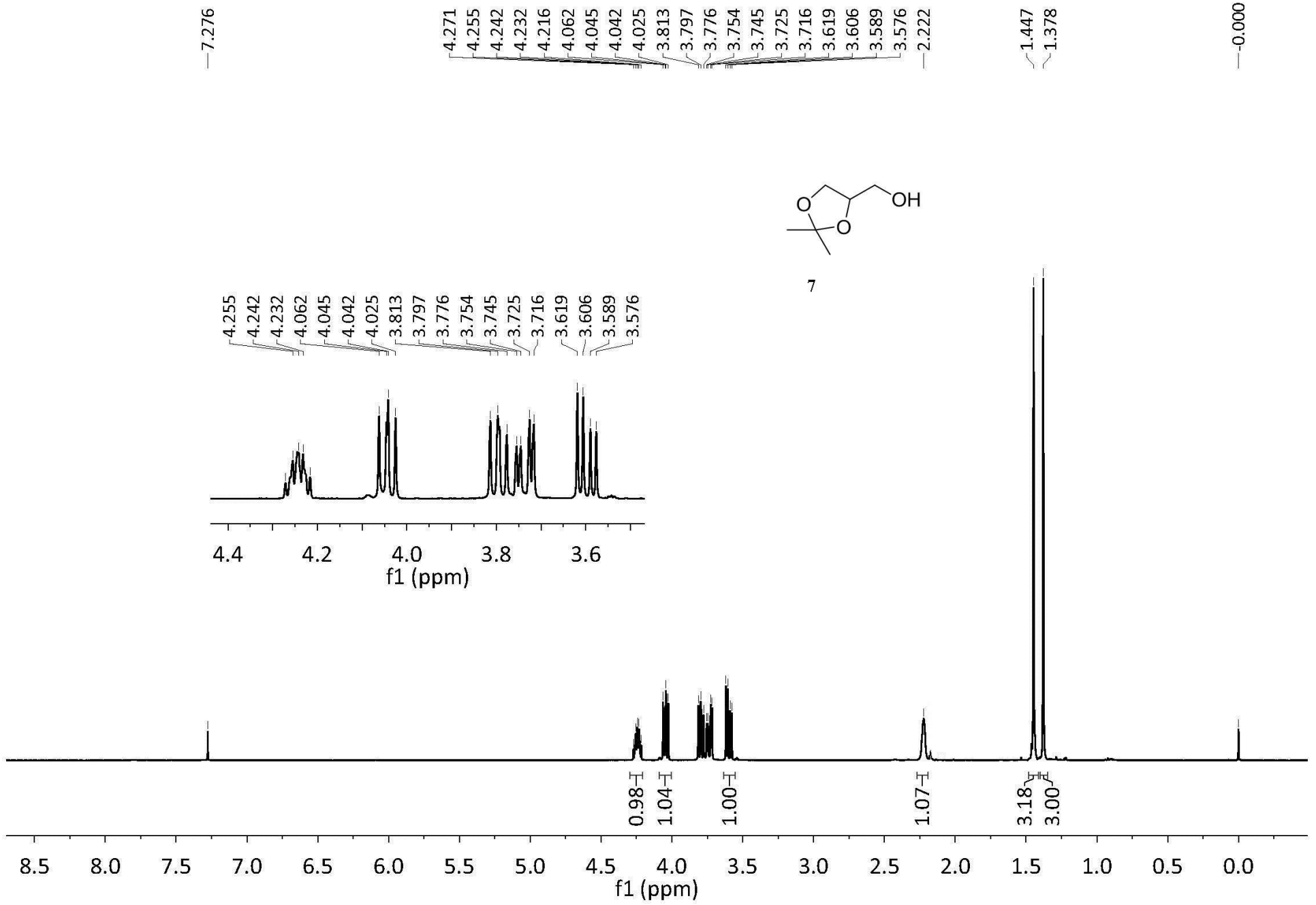


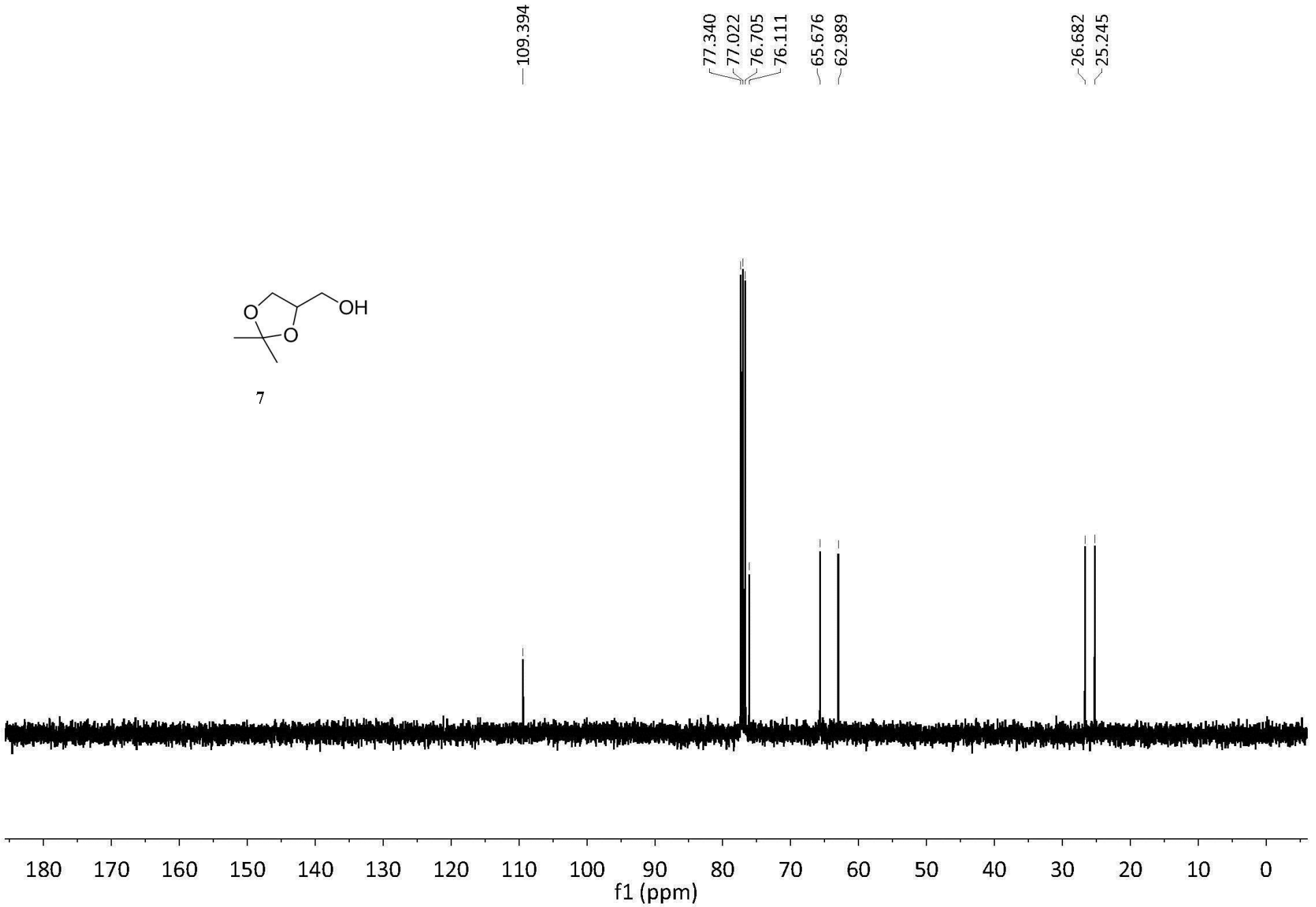
-75.562
-75.594

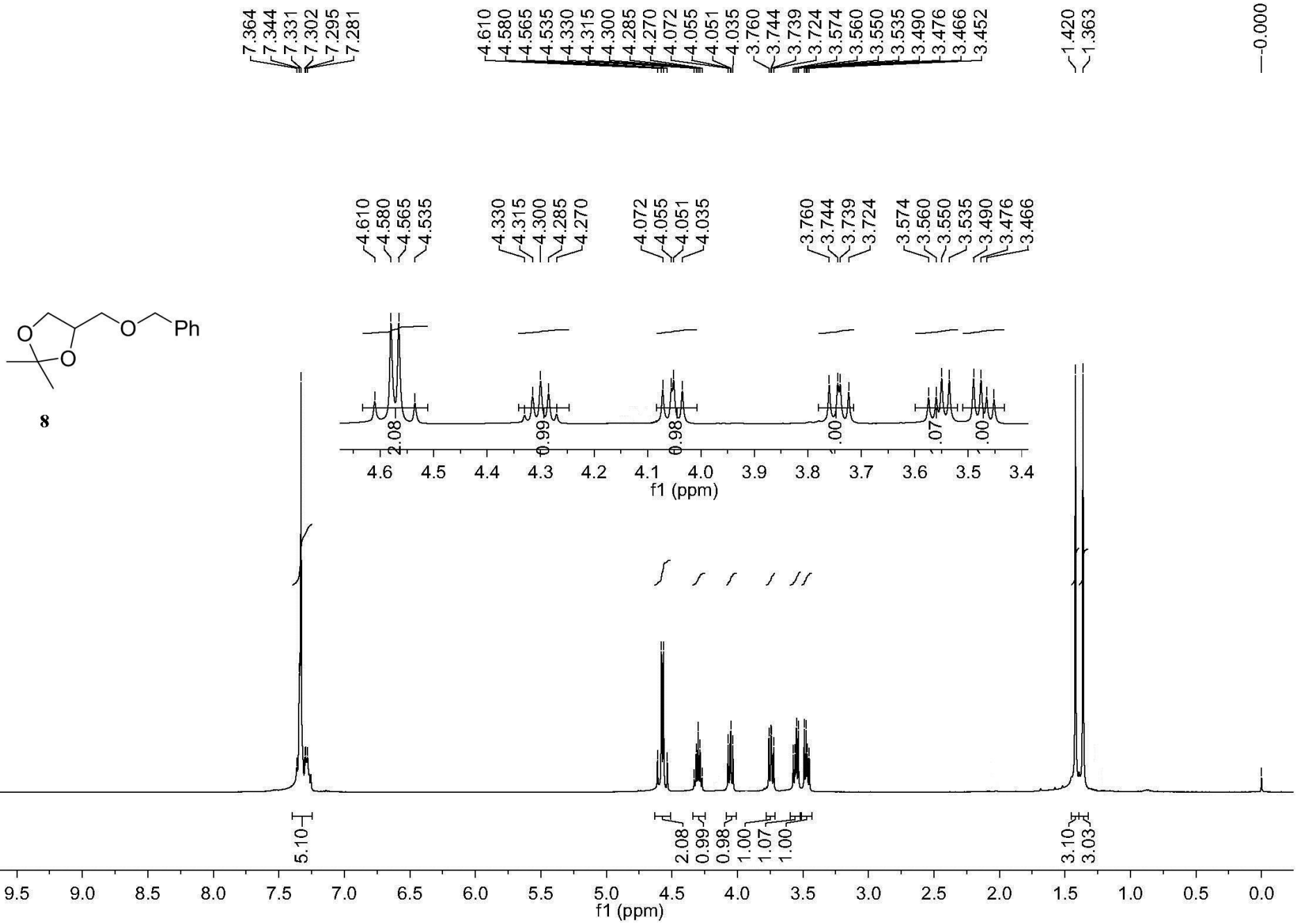


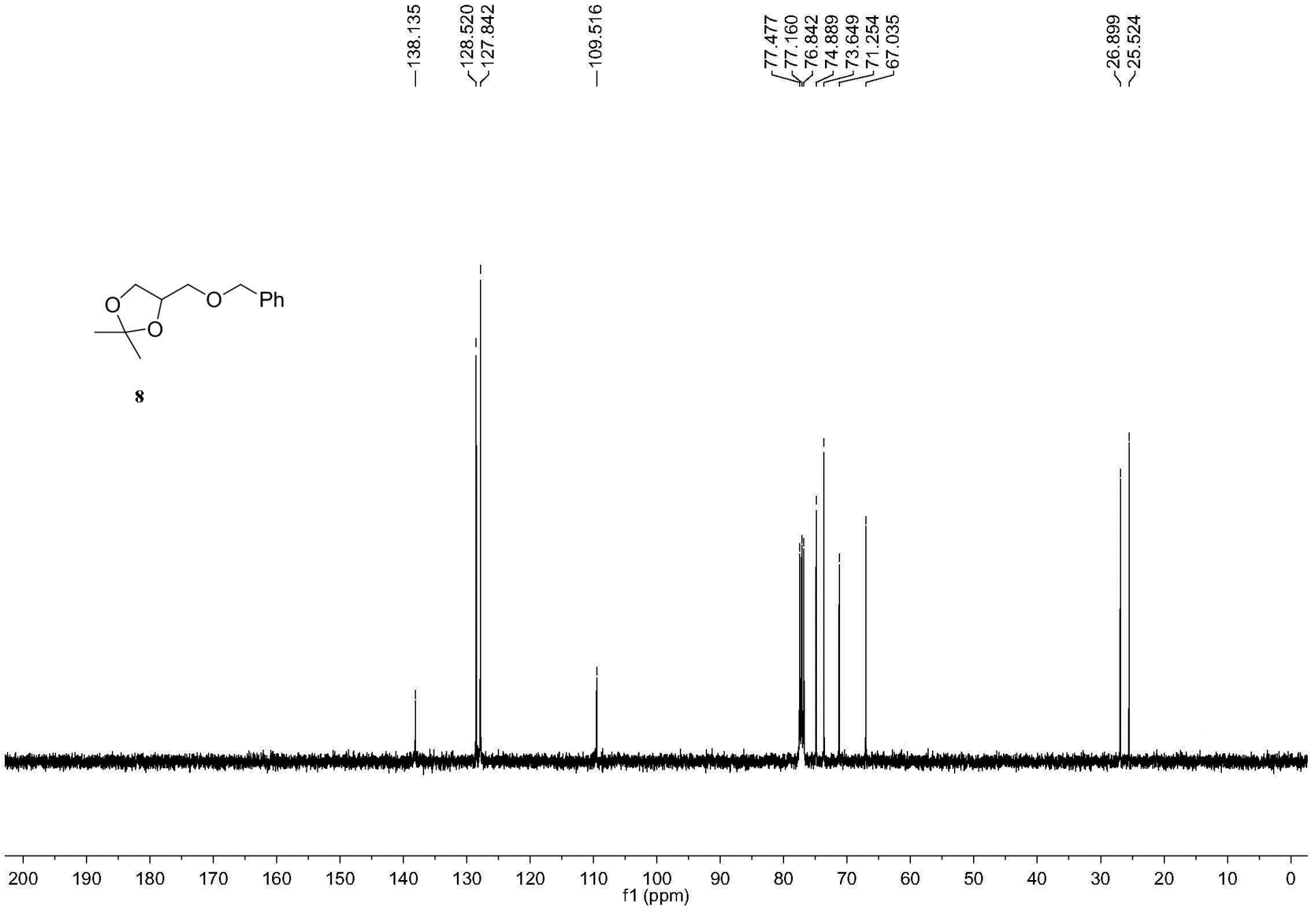
6b

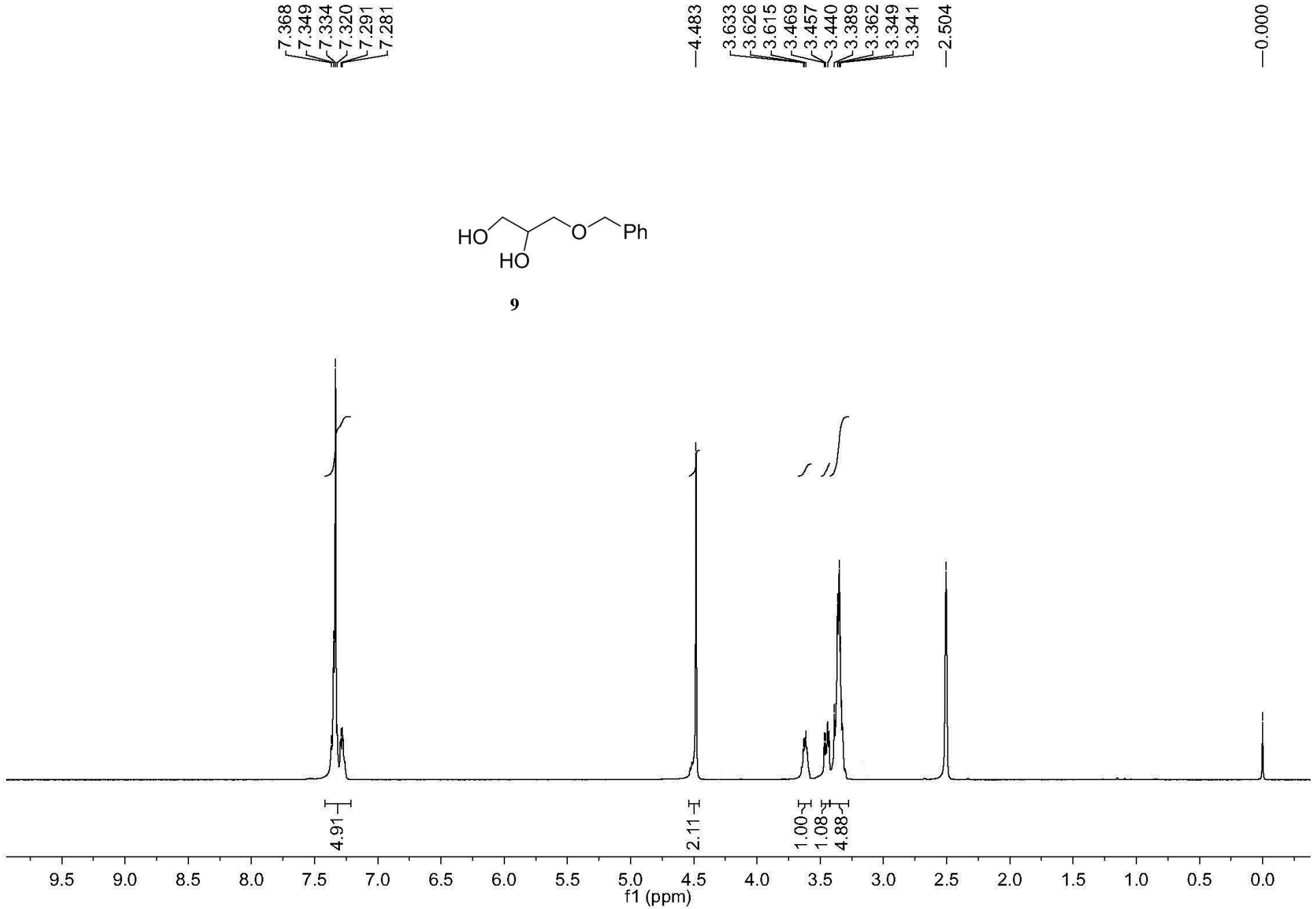



7.276
4.271
4.255
4.242
4.232
4.216
4.062
4.045
4.042
4.025
3.813
3.797
3.776
3.754
3.745
3.725
3.716
3.619
3.606
3.589
3.576
2.222
1.447
1.378
0.000
OH
O
O
7
f1 (ppm)
0.98
1.04
1.00
1.07
3.18
3.00

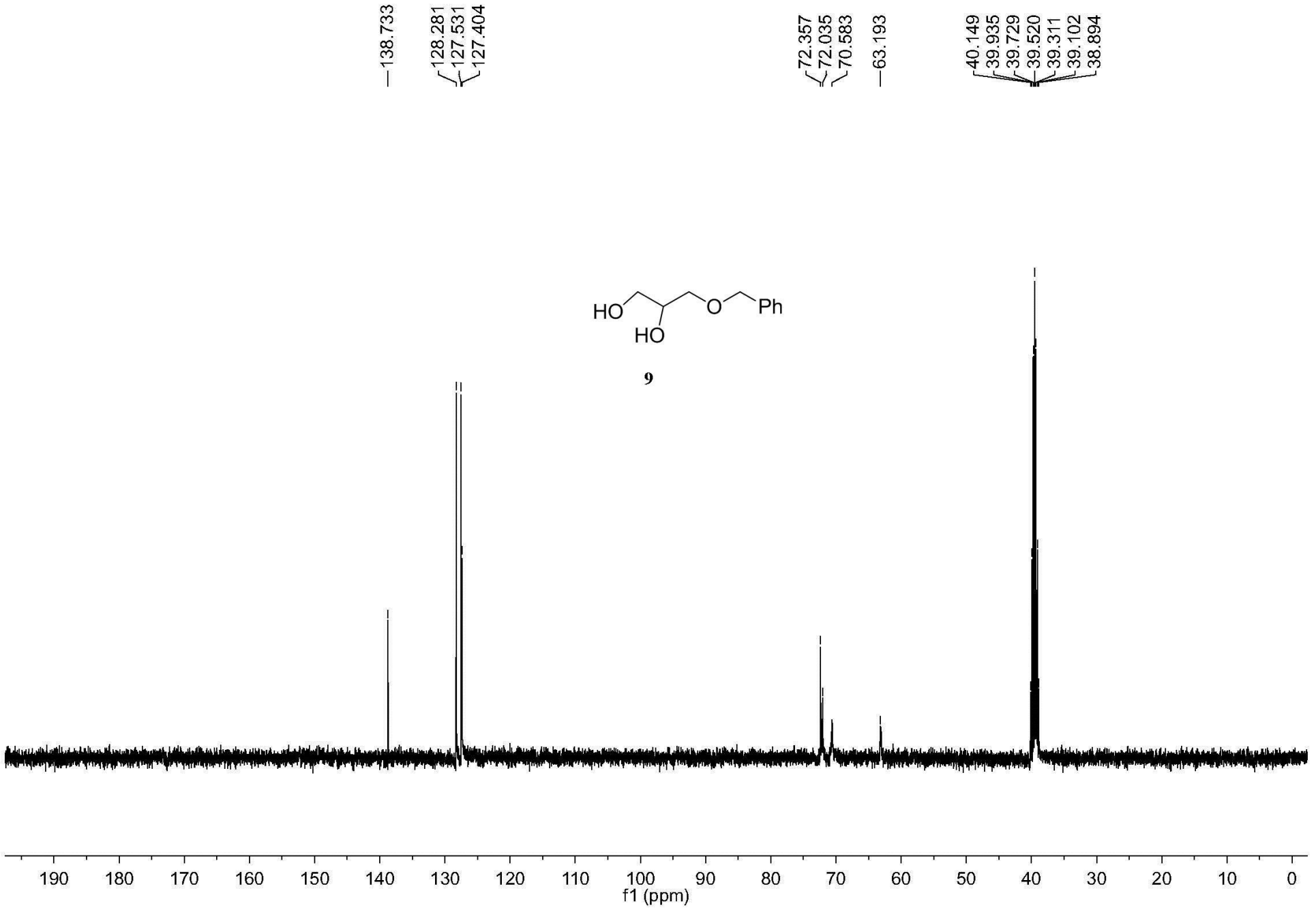

109.394
77.340
77.022
76.705
76.111
65.676
62.989
26.682
25.245
O
O
OH
7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

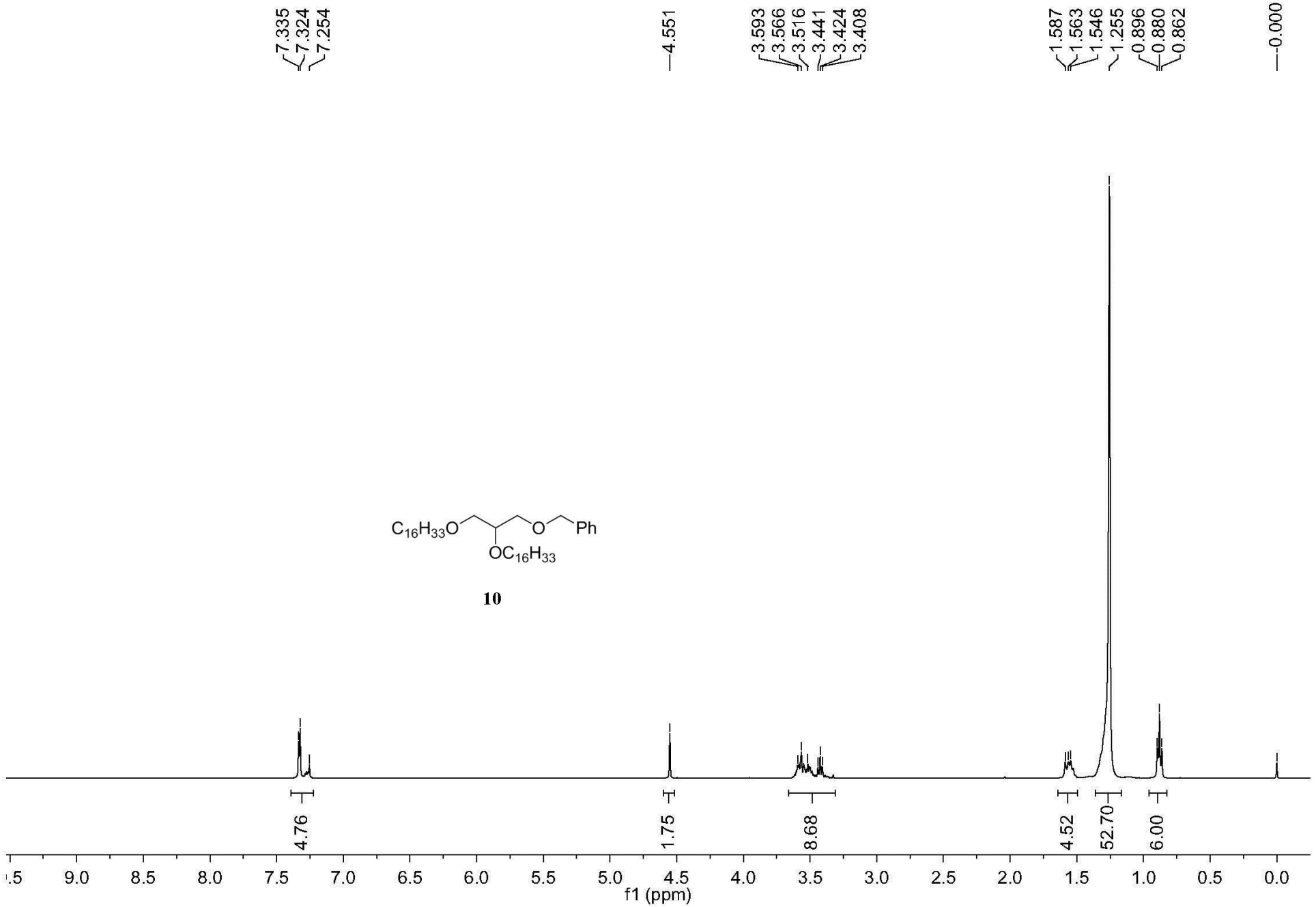

7.364
7.344
7.331
7.302
7.295
7.281
4.610
4.580
4.565
4.535
4.330
4.315
4.300
4.285
4.270
4.072
4.055
4.051
4.035
3.760
3.744
3.739
3.724
3.574
3.560
3.550
3.535
3.490
3.476
3.466
3.452
1.420
1.363
0.000
O
O
O
Ph
8
2.08
0.99
0.98
1.00
1.07
1.00
3.10
3.03
f1 (ppm)


138.135
128.520
127.842
109.516
77.477
77.160
76.842
74.889
73.649
71.254
67.035
26.899
25.524
O
O
O
Ph
8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

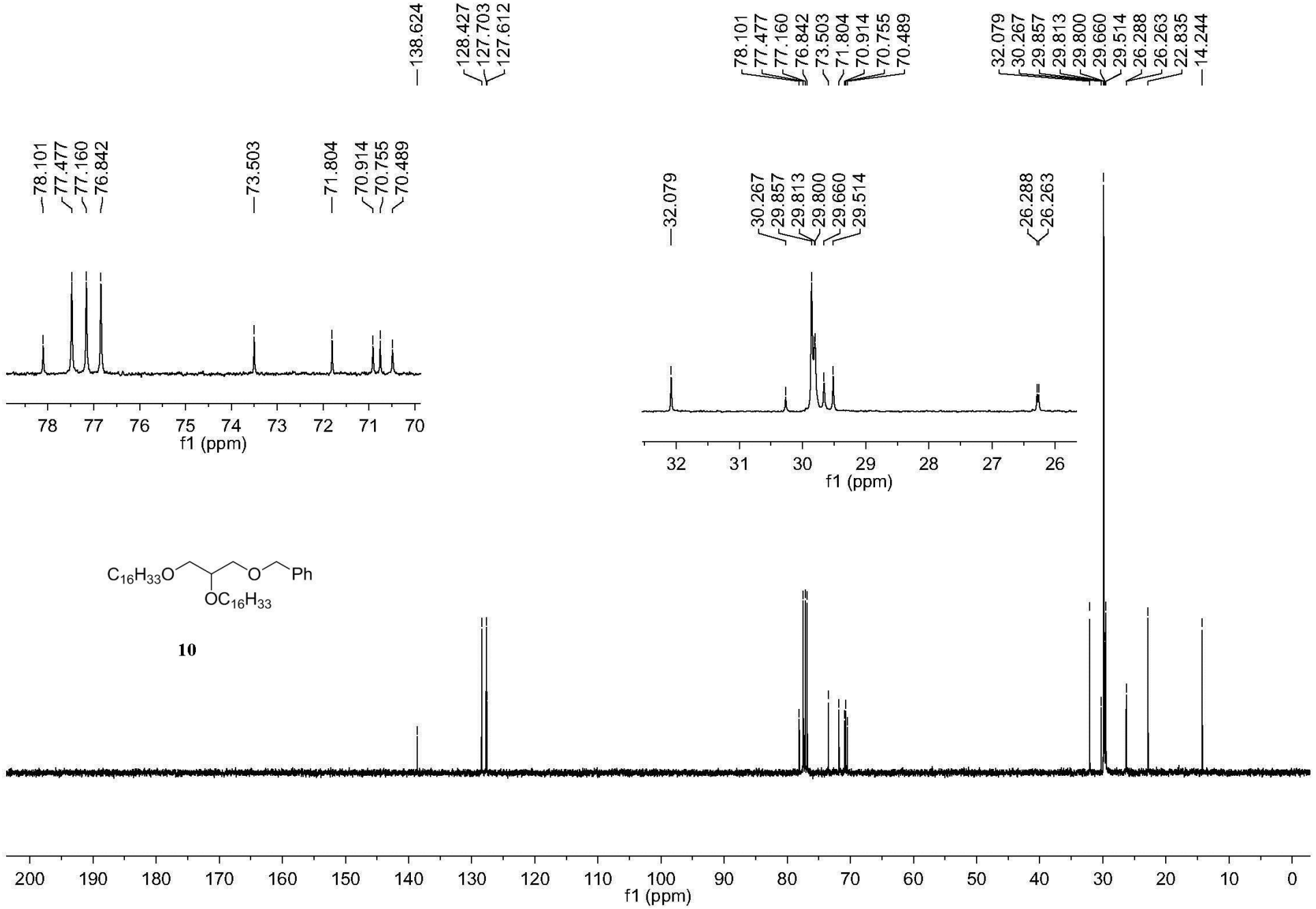

7.368
7.349
7.334
7.320
7.291
7.281
4.483
3.633
3.626
3.615
3.469
3.457
3.440
3.389
3.362
3.349
3.341
2.504
0.000
HO
HO
O
Ph
4.91
2.11
1.00
1.08
4.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

9

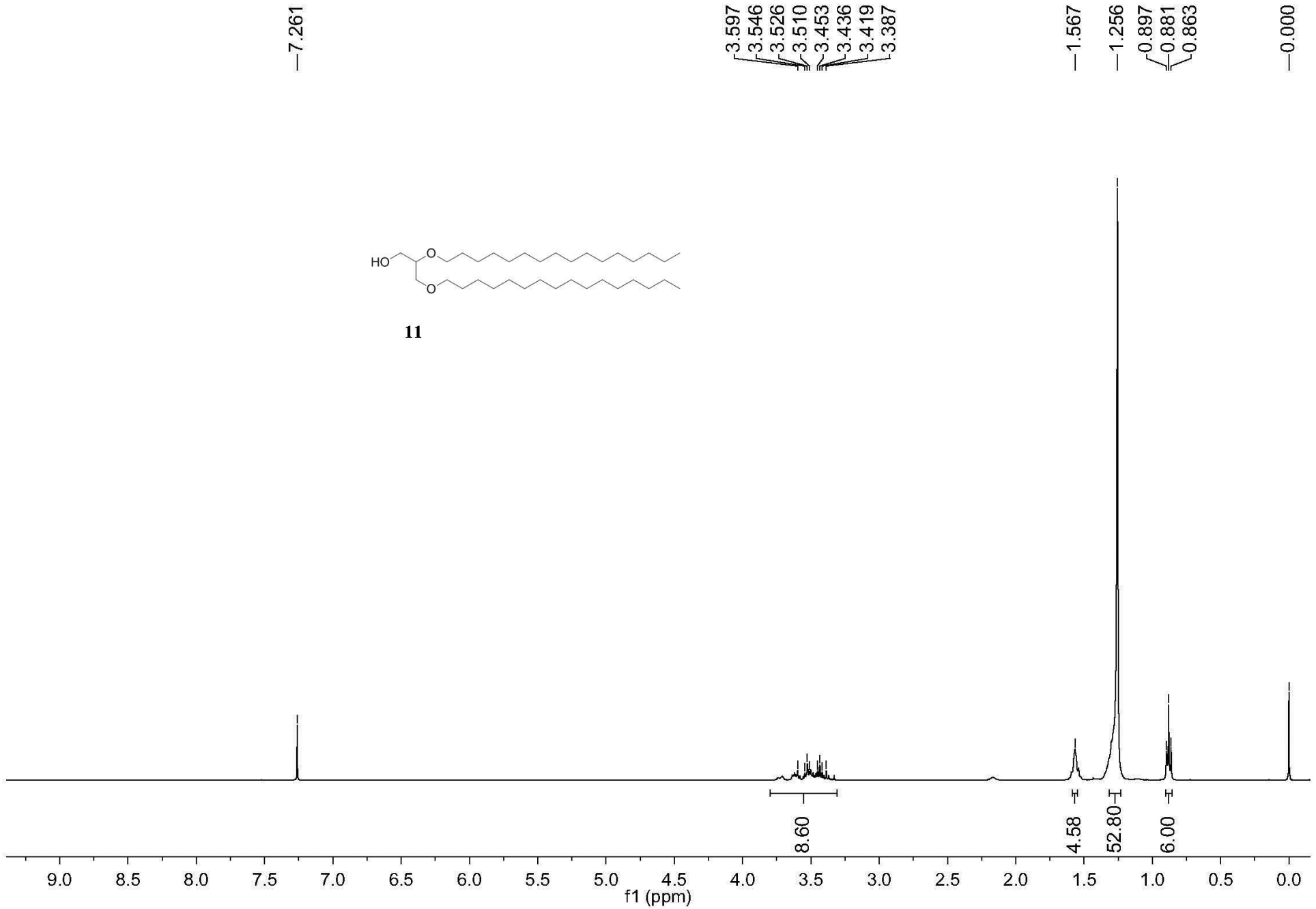

138.733
128.281
127.531
127.404
72.357
72.035
70.583
63.193
40.149
39.935
39.729
39.520
39.311
39.102
38.894
HO
HO
O
Ph
9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.335
7.324
7.254
4.551
3.593
3.566
3.516
3.441
3.424
3.408
1.587
1.563
1.546
1.255
0.896
0.880
0.862
0.000
C16H33O
OC16H33
O
Ph
4.76
1.75
8.68
4.52
52.70
6.00
f1 (ppm)

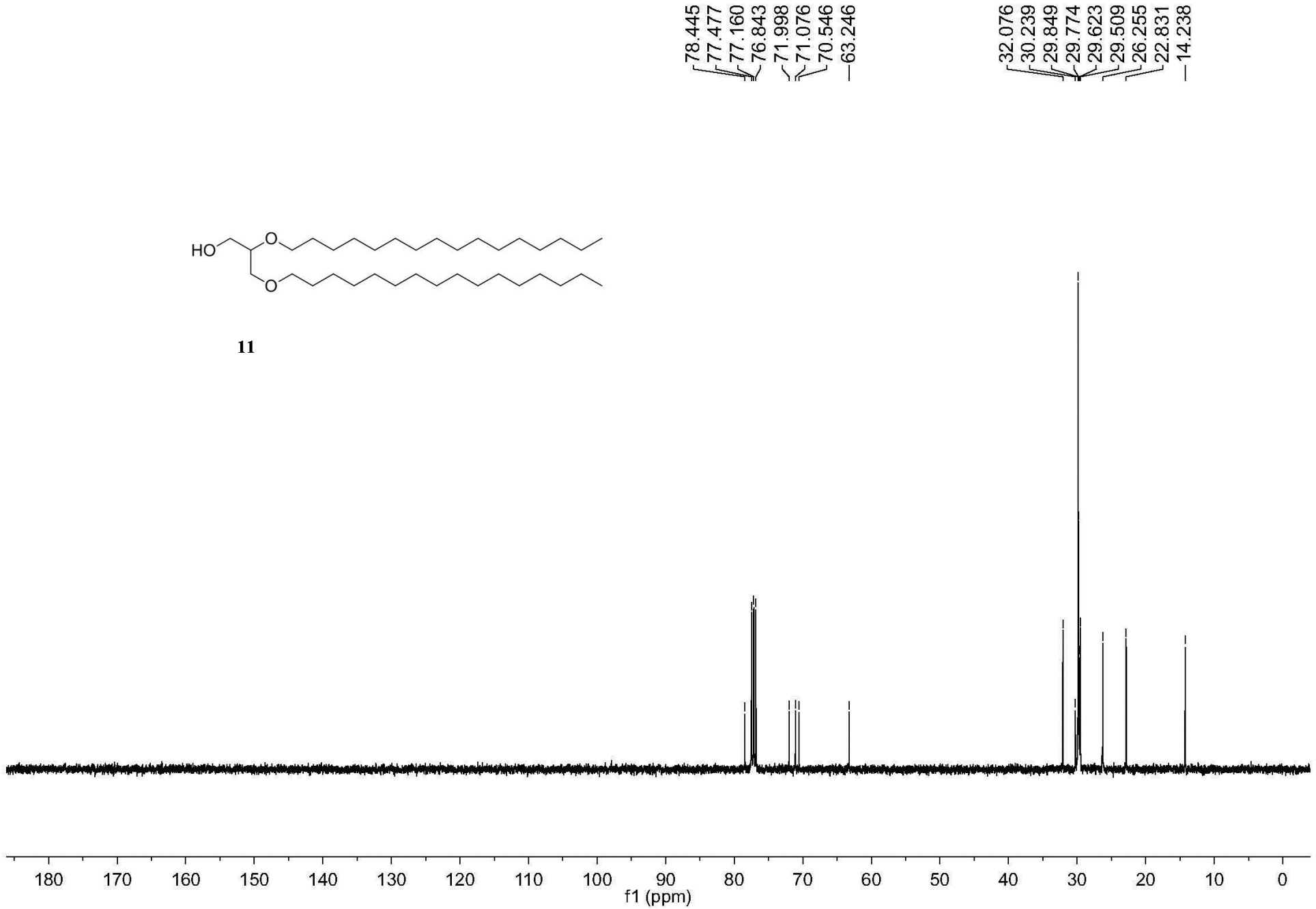
10

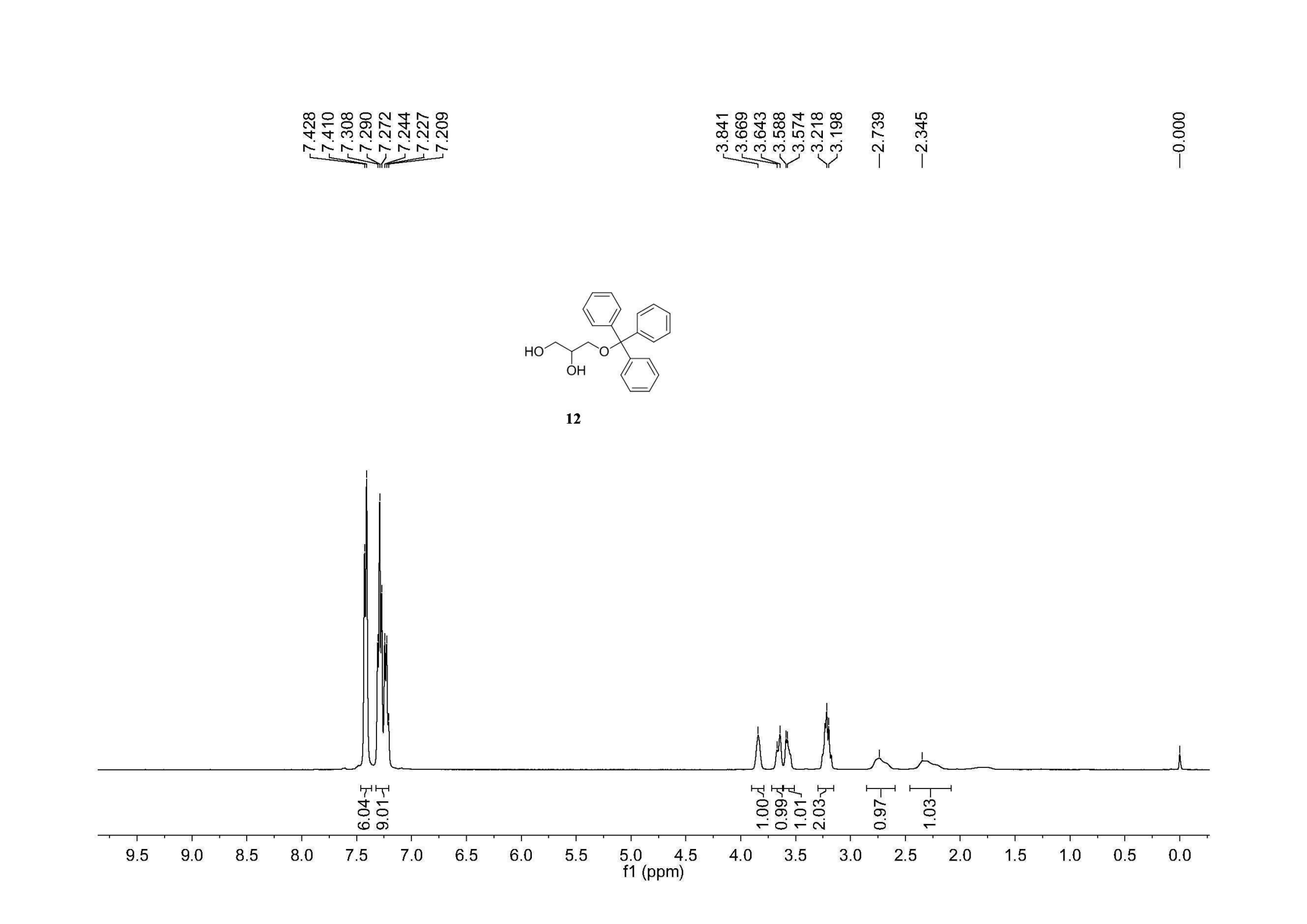

138.624
128.427
127.703
127.612
78.101
77.477
77.160
76.842
73.503
71.804
70.914
70.755
70.489
32.079
30.267
29.857
29.813
29.800
29.660
29.514
26.288
26.263
22.835
14.244
f1 (ppm)
C16H33O
OC16H33
O
Ph

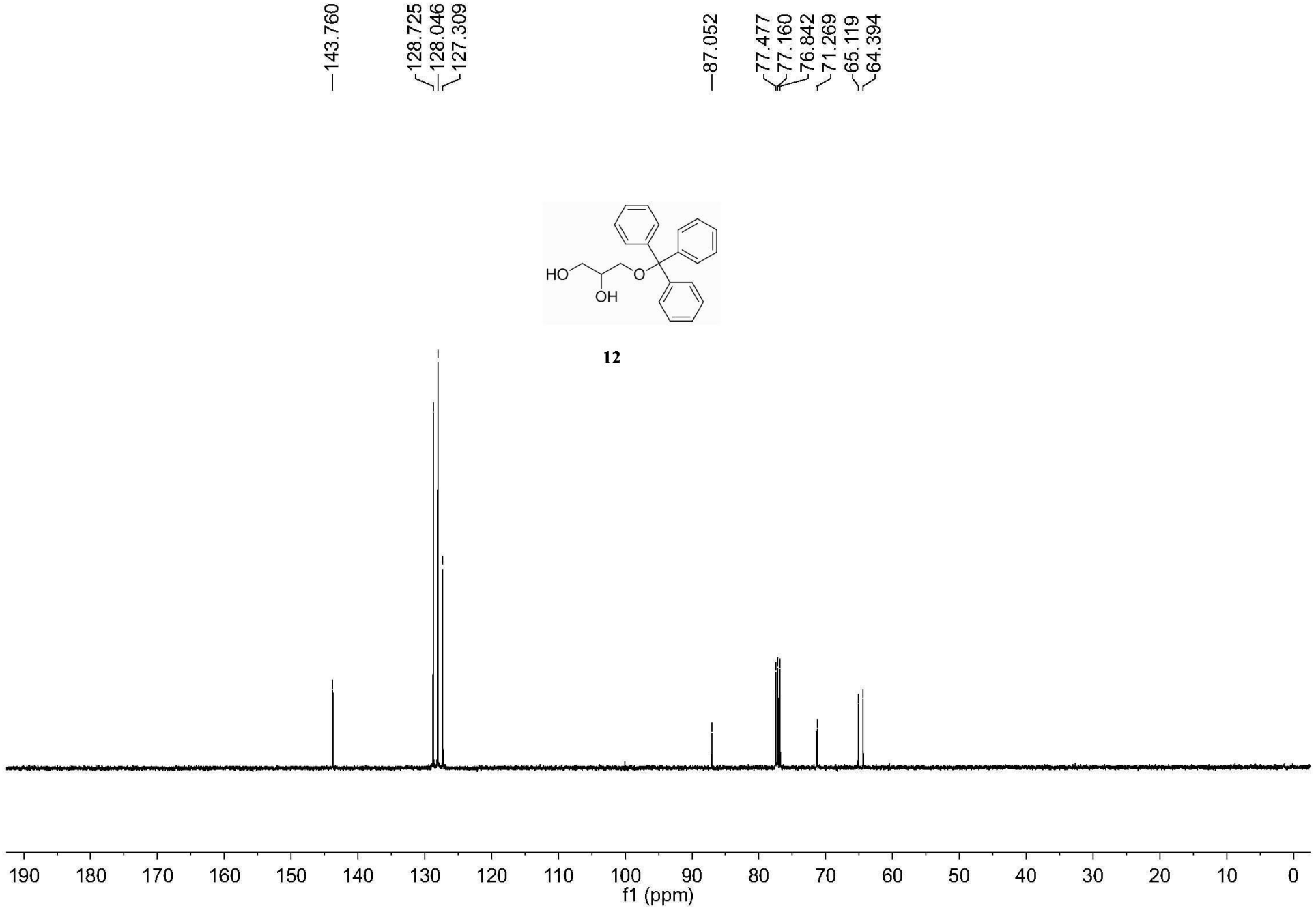
10


7.261
3.597
3.546
3.526
3.510
3.453
3.436
3.419
3.387
1.567
1.256
0.897
0.881
0.863
0.000
HO
O
O
8.60
4.58
52.80
6.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

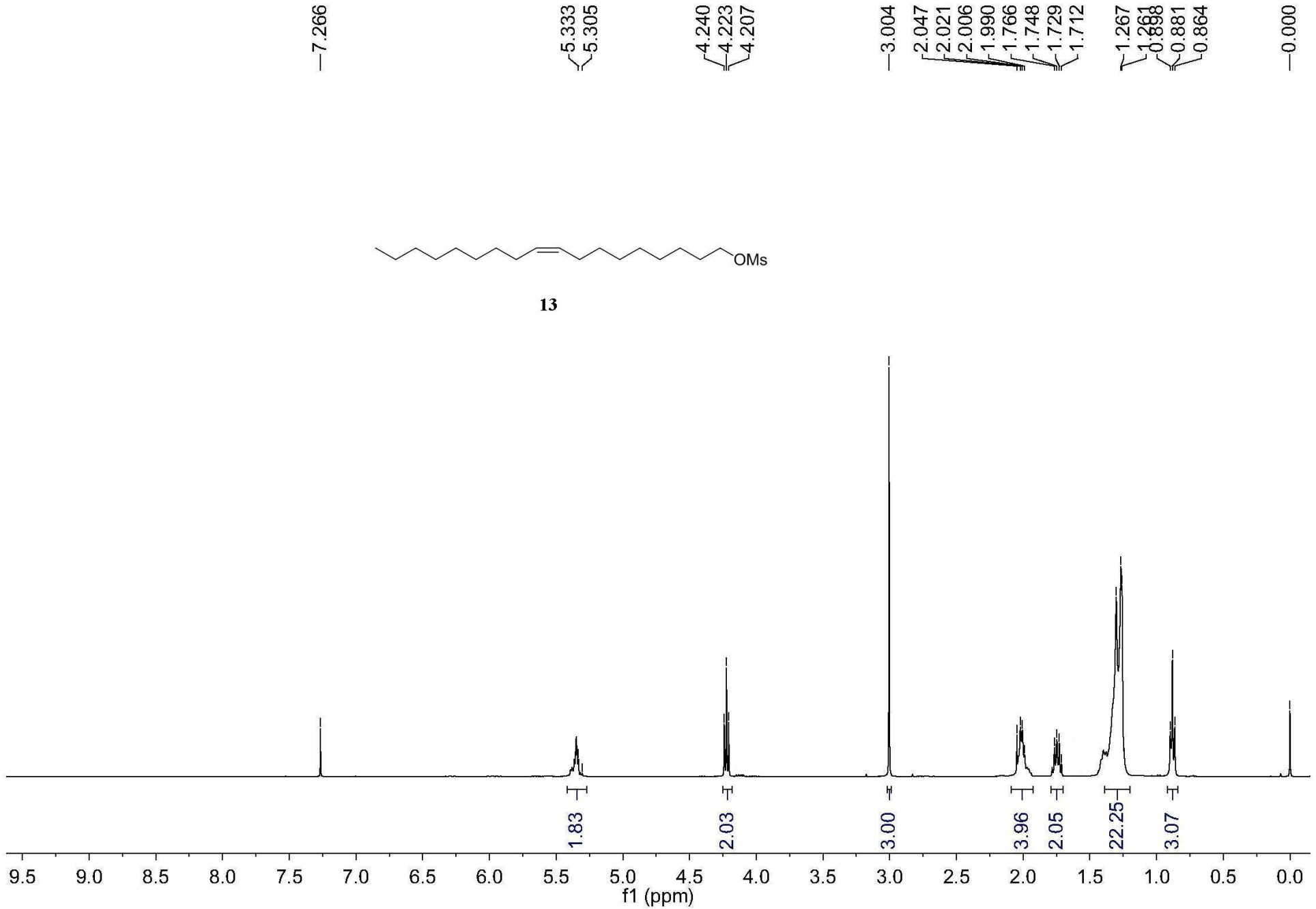
11


78.445
77.477
77.160
76.843
71.998
71.076
70.546
63.246
32.076
30.239
29.849
29.774
29.623
29.509
26.255
22.831
14.238
HO
O
O
11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

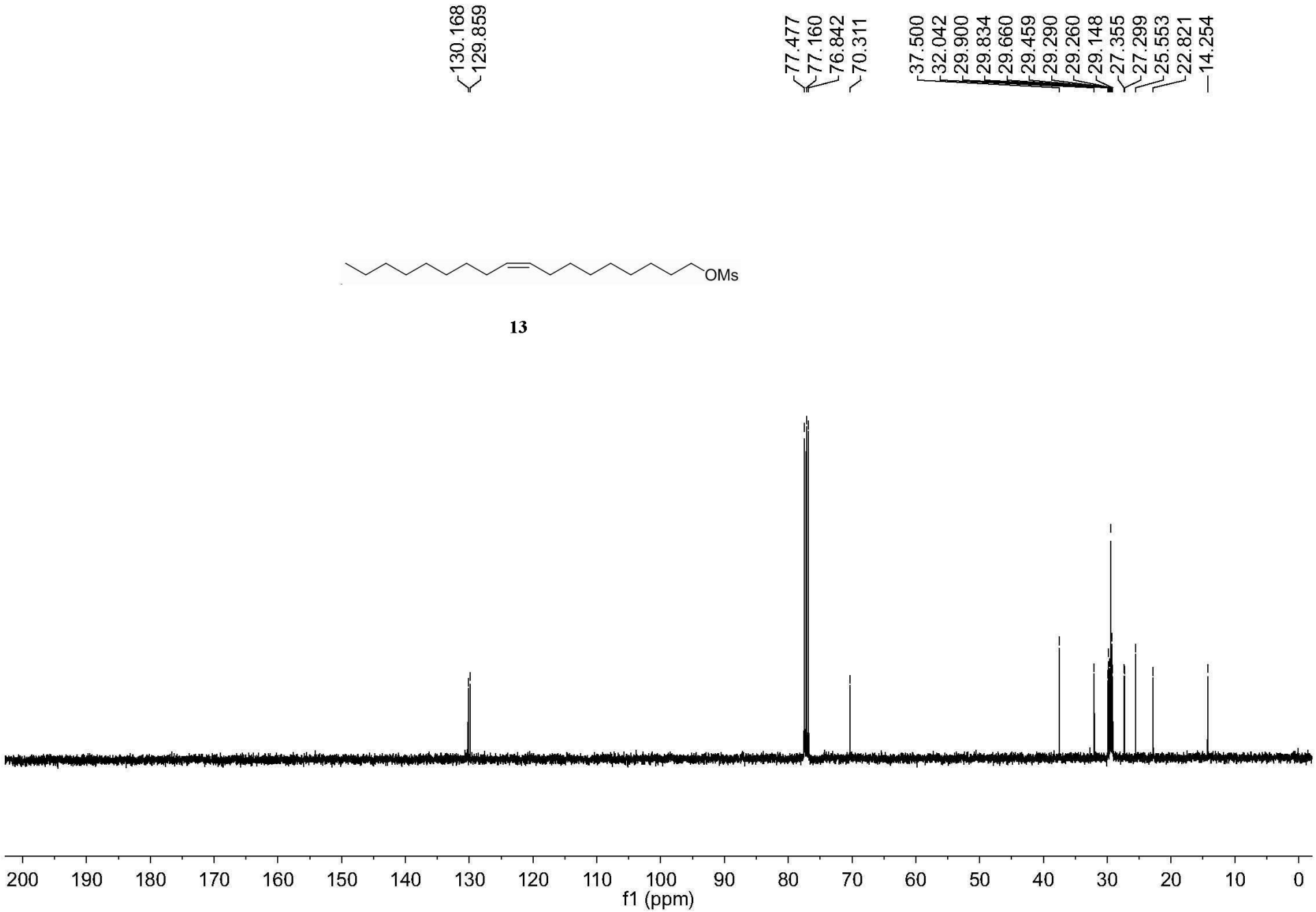

7.428
7.410
7.308
7.290
7.272
7.244
7.227
7.209
3.841
3.669
3.643
3.588
3.574
3.218
3.198
2.739
2.345
0.000
HO
OH
O
12
6.04
9.01
1.00
0.99
1.01
2.03
0.97
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


143.760
128.725
128.046
127.309
87.052
77.477
77.160
76.842
71.269
65.119
64.394
HO
OH
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

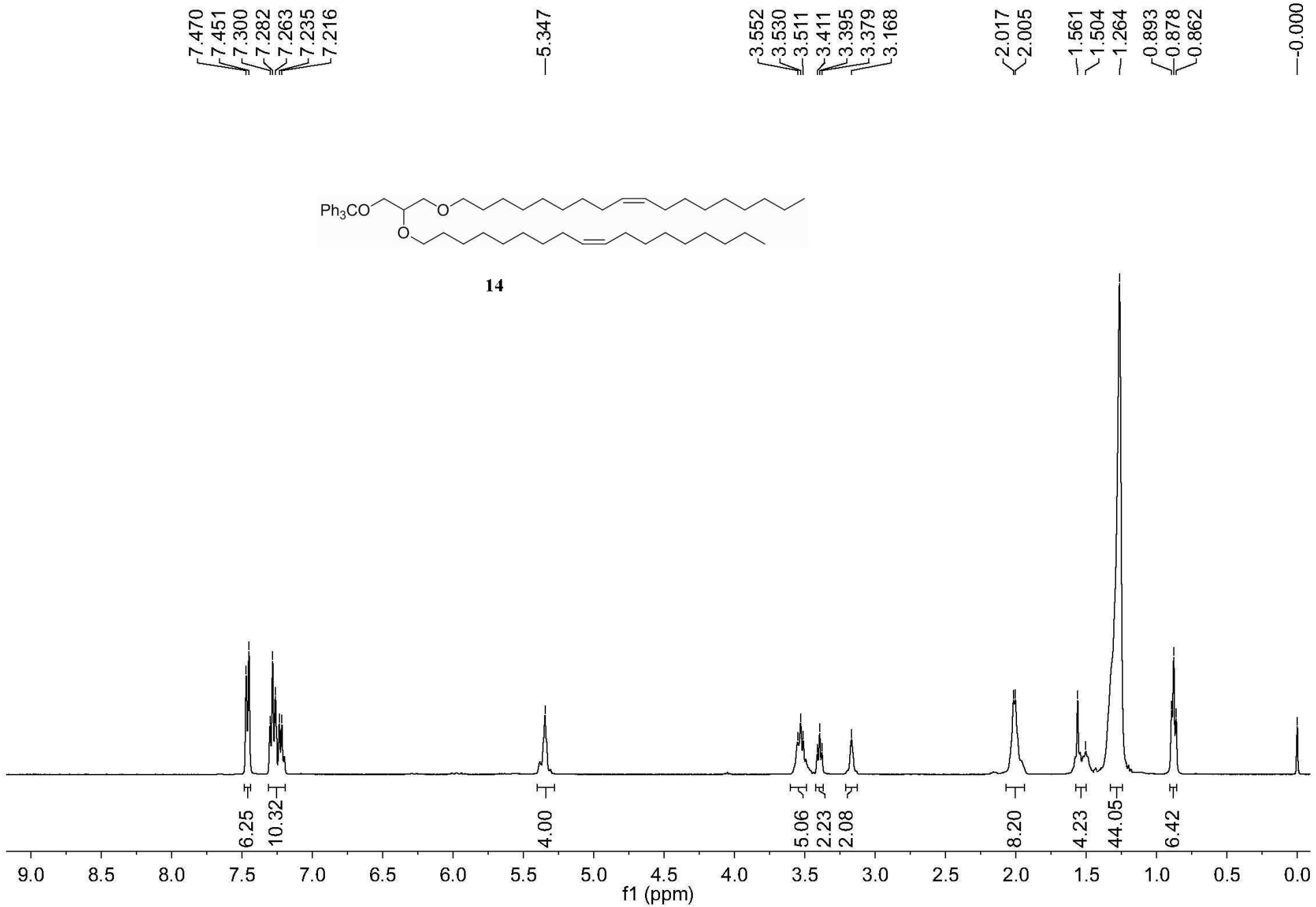
12


7.266
5.333
5.305
4.240
4.223
4.207
3.004
2.047
2.021
2.006
1.990
1.766
1.748
1.729
1.712
1.267
1.261
0.898
0.881
0.864
0.000
OMs
1.83
2.03
3.00
3.96
2.05
22.25
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

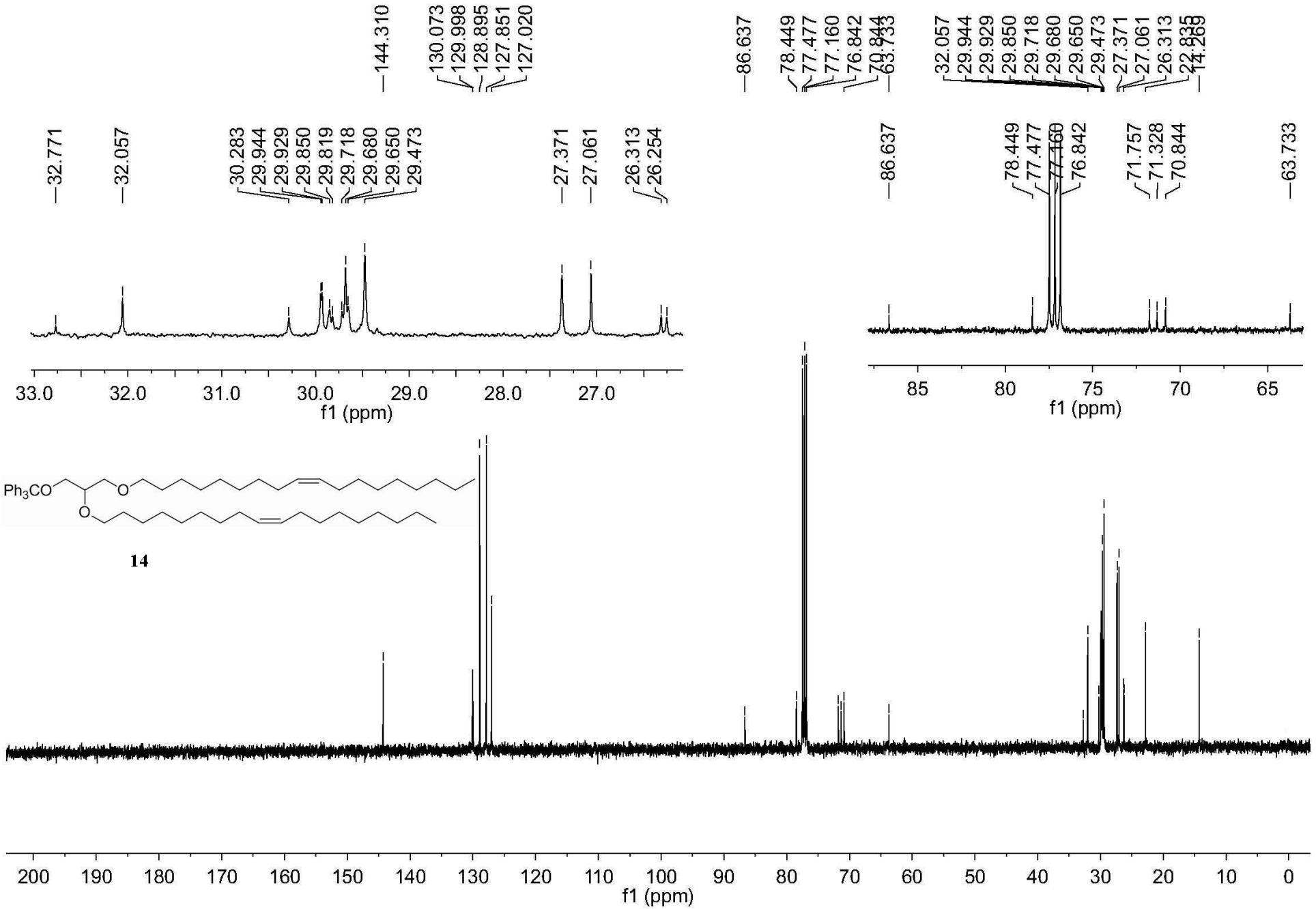
13

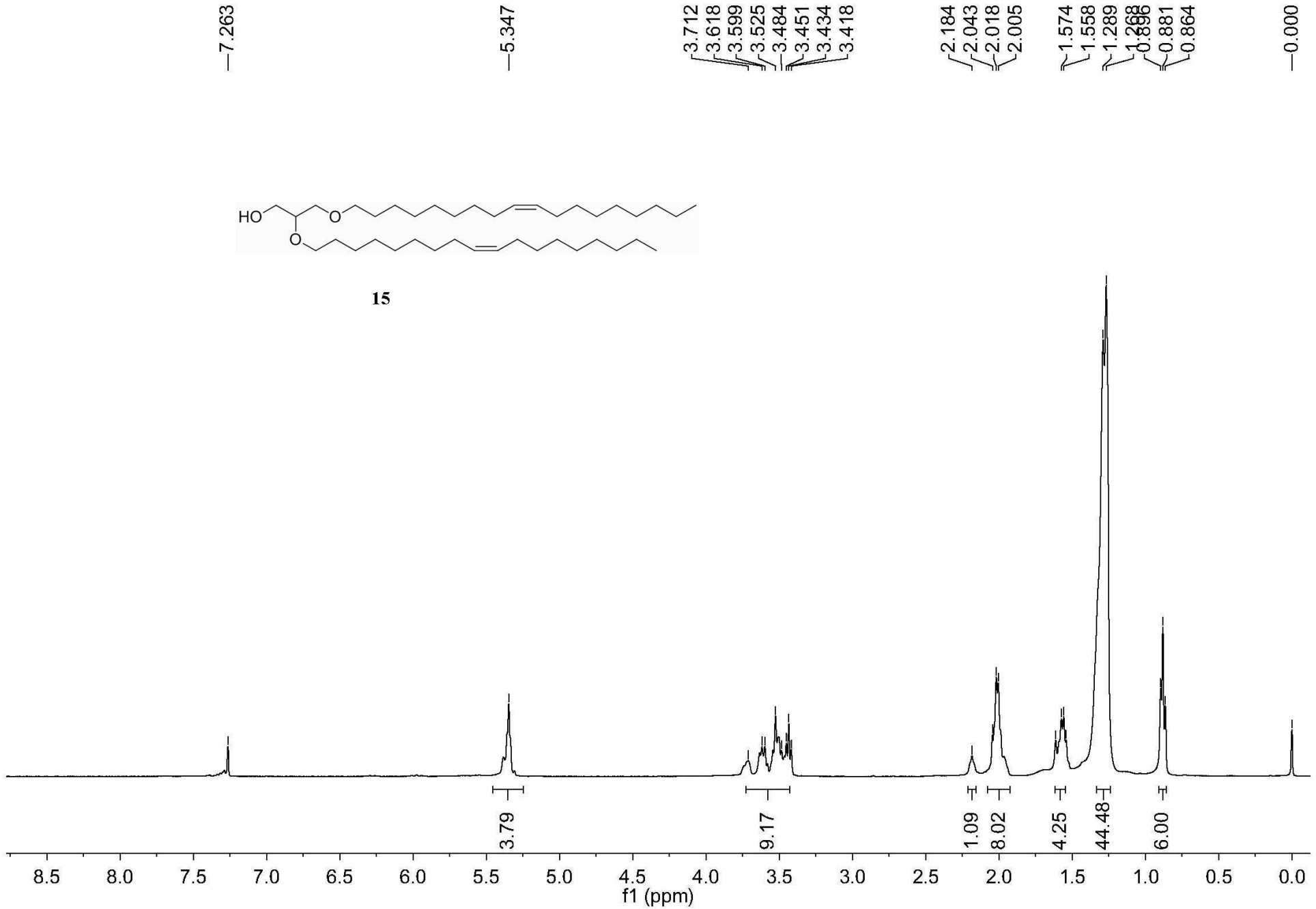

130.168
129.859
77.477
77.160
76.842
70.311
37.500
32.042
29.900
29.834
29.660
29.459
29.290
29.260
29.148
27.355
27.299
25.553
22.821
14.254
OMs
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

13

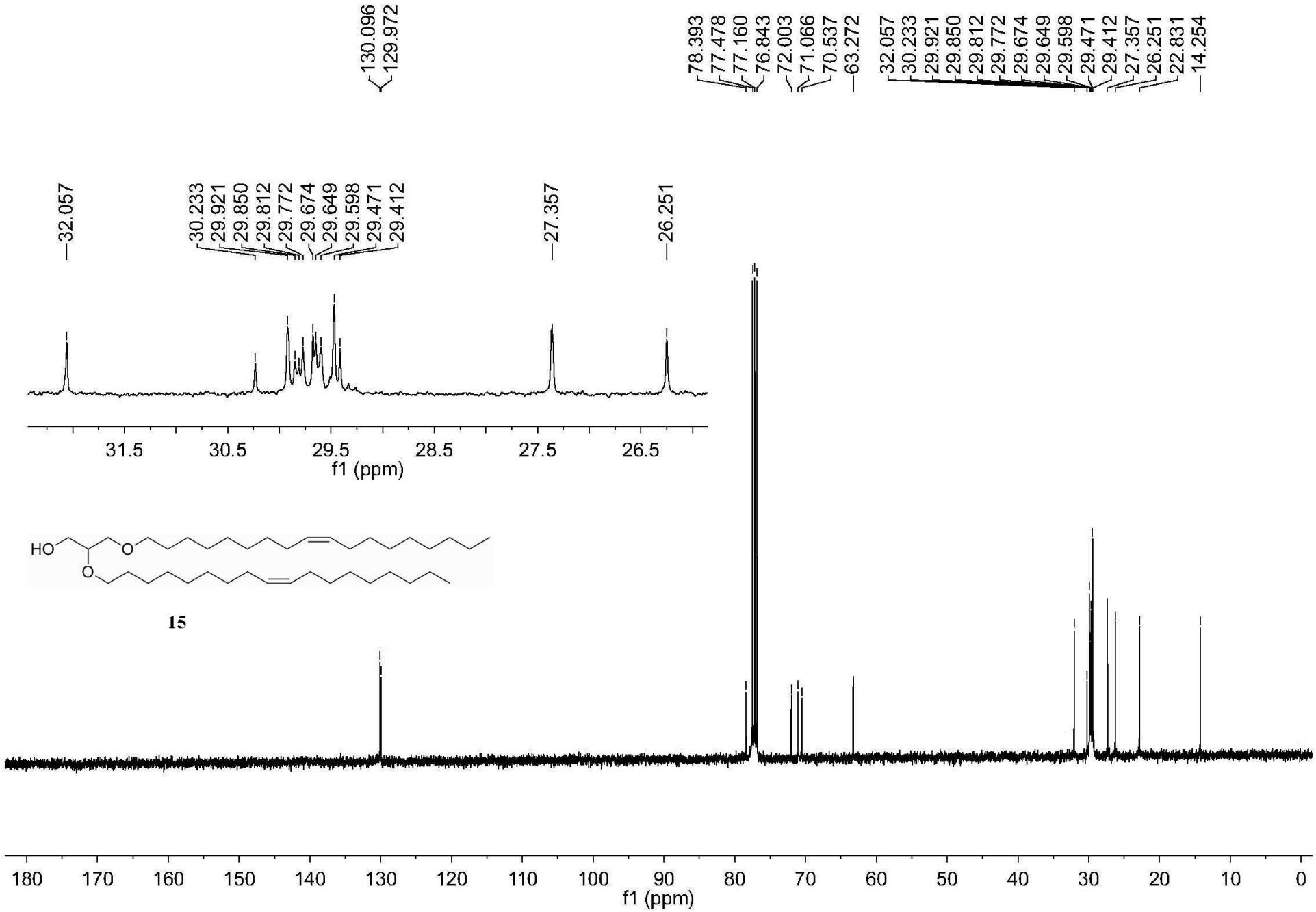

7.470
7.451
7.300
7.282
7.263
7.235
7.216
5.347
3.552
3.530
3.511
3.411
3.395
3.379
3.168
2.017
2.005
1.561
1.504
1.264
0.893
0.878
0.862
0.000
Ph3CO
O
O
6.25
10.32
4.00
5.06
2.23
2.08
8.20
4.23
44.05
6.42
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

14


144.310
130.073
129.998
128.895
127.851
127.020
86.637
78.449
77.477
77.160
76.842
70.844
63.733
32.057
29.944
29.929
29.850
29.718
29.680
29.650
29.473
27.371
27.061
26.313
22.835
14.265
32.771
32.057
30.283
29.944
29.929
29.850
29.819
29.718
29.680
29.650
29.473
27.371
27.061
26.313
26.254
33.0
32.0
31.0
30.0
29.0
28.0
27.0
f1 (ppm)
86.637
78.449
77.477
77.160
76.842
71.757
71.328
70.844
63.733
85
80
75
70
65
f1 (ppm)
Ph3CO
O
O
14
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.263
5.347
3.712
3.618
3.599
3.525
3.484
3.451
3.434
3.418
2.184
2.043
2.018
2.005
1.574
1.558
1.289
0.881
0.864
0.000
HO
O
O
3.79
9.17
1.09
8.02
4.25
44.48
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

15


130.096
129.972
78.393
77.478
77.160
76.843
72.003
71.066
70.537
63.272
32.057
30.233
29.921
29.850
29.812
29.772
29.674
29.649
29.598
29.471
29.412
27.357
26.251
22.831
14.254
f1 (ppm)
HO
O
O

15