Phosphonate derivatives of tetraazamacrocycles as new inhibitors of protein tyrosine phosphatases

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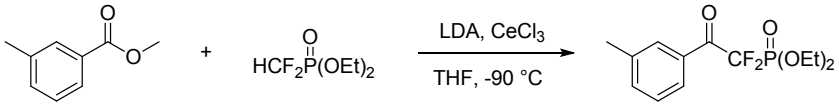
Supplementary information

General information

THF was distilled under Ar from Na/benzophenone. CH_2Cl_2 was distilled under Ar from CaH_2. All other solvents and chemicals obtained from commercial sources were used as received. ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a Varian AV-400 or Bruker Avance DRX500 instrument. ^1H and ^{13}C NMR spectra were referenced with respect to solvent residual peaks. ^{19}F NMR spectra were recorded with $CFCl_3$ (0.0 ppm) as internal standard. Splitting pattern abbreviations: s for singlet, d for doublet, t for triplet, q for quadruplet, bs for broad signal. Mass spectra were acquired on Agilent 1100 series LC/MSD instrument using atmospheric pressure ionization with electrospray (API-ES); positive ion spectra are denoted as *pos*, negative as *neg*. Progression of reactions was followed by NMR and/or TLC. Analytical TLCs were performed with Merck Silica gel 60 F_{254} plates. Visualization was accomplished by UV-light or spraying with a solution of ceric ammonium molybdate in 10% sulfuric acid followed by brief heating. Flash chromatography was performed with Carl Roth Kieselgel 60, 40-63 µm.

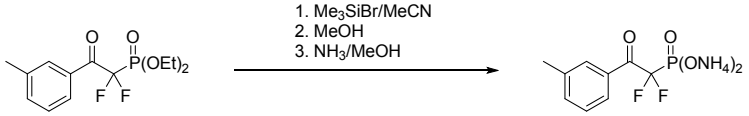
Synthesis of ammonium 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate

Preparation of diethyl 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate



An adopted literature procedure was used [1]. Cerium (III) chloride (5.06 g, 20.5 mmol), diisopropylamine (2.26 g, 22.3 mmol) and THF (35 mL) were placed in three-neck round-bottom flask equipped with rubber septum, nitrogen inlet and thermometer. To this mixture butyllithium (13.3 ml, 21.3 mmol, 1.6 M solution in hexane) was added at -70 °C and the resulting solution was allowed to warm to -30 °C. It was then cooled to -100 °C and diethyl (difluoromethyl)phosphonate (3.82 g, 20.3 mmol) in THF (5 mL) was added. Mixture was stirred at -100 to -90 °C for 1 hour while gradually turning light brown in color. Methyl 3-methylbenzoate (3.08 g, 20.5 mmol) in THF (5 mL) was then added and the resulting mixture was stirred at ≈ -80 °C for 1 hour. Reaction was quenched with 30 mL of 1M HCl and was allowed to warm to rt. Organic layer was separated, aqueous layer was extracted with EtOAc (3 x 25 mL), combined organic extracts were washed with $NaHCO_3$ (2 x 15 mL) and with brine (20 mL) and dried with Na_2SO_4. Diethyl (1,1-difluoro-2-oxo-2-(m-tolyl)ethyl)phosphonate was purified by distillation (124°C / 0.05 mm); it was obtained as a pale yellow oil (5.26 g, 17.18 mmol, 85 % yield). δ_H (500 MHz, $CDCl_3$, Me_4Si) 1.36 (6H, t, $^3J_{H\text{-}H}$ 7.2, 2xOCH$_2$CH_3), 2.40 (3H, s, C$_6$H$_4$CH_3), 4.32 (4H, m, 2xOCH_2CH$_3$), 7.37 (1H, t, $^3J_{H\text{-}H}$ 7.3, C$_6H_4$), 7.43 (1H, d, $^3J_{H\text{-}H}$ 7.3, C$_6H_4$), 7.92 (1H, m, C$_6H_4$); δ_C (125 MHz, $CDCl_3$, Me_4Si) 16.3 (d, $^3J_{C\text{-}P}$ 5.5, 2xOCH$_2$CH_3), 21.3, 65.3 (d, $^3J_{C\text{-}P}$ 7.0, 2xOCH_2CH$_3$), 115.0 (td, $^1J_{C\text{-}F}$ 274.8, $^1J_{C\text{-}P}$ 200.5, CF_2P), 127.7, 128.5, 130.6, 132.0, 135.6, 138.5, 188.1 (td, $^2J_{C\text{-}F}$ 24.4, $^2J_{C\text{-}P}$ 14.5, COCF$_2$P); δ_F (376 MHz, $CDCl_3$, $CFCl_3$) –110.5 (d, $^2J_{F\text{-}P}$ 94.8); δ_P (202 MHz, $CDCl_3$, H_3PO_4) 4.5 (t, $^2J_{P\text{-}F}$ 94.8).). Found: C, 50.68; H, 5.54; P, 10.30. Calc. for $C_{13}H_{17}F_2O_4P$: C 50.99; H, 5.60; P, 10.11.

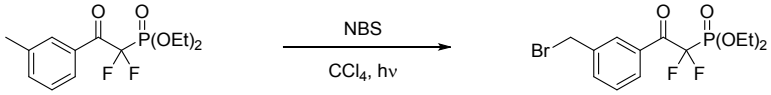
Hydrolysis of diethyl 1,1-difluoro-2-oxo-2-(m-tolyl)ethylphosphonate



Schlenk flask was charged with diethyl (1,1-difluoro-2-oxo-2-(m-tolyl)ethyl)phosphonate (0.61 g, 2 mmol) and 10 mL of dry acetonitrile. Bromotrimethylsilane (1.55 g, 10 mmol) was added via a syringe and the resulting pale yellow solution was stirred at 35 °C overnight. Volatiles were evaporated in vacuum and the residue was dissolved in methanol (3 mL) and stirred for 20 min at r.t. Solvent was evaporated and the residue was treated with ammonia methanolic solution (3 mL). Product was

precipitated by adding 15 mL of acetone, filtered, washed with acetone and ether and dried in vacuum. Yield 0.36 g (64 %); colorless crystalline solid; m.p. 142-143 °C; two groups of signals were usually observed in NMR spectra, they are attributed to keto (major) and gem-diol (minor) forms; δ_H (500 MHz, D_2O, Me_4Si) 2.37 (0.6H, s, ArC*H*$_3$, gem-diol), 2.37 (2.4H, s, ArC*H*$_3$, keto), 7.29 (0.2H, d, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, gem-diol), 7.36 (0.2H, t, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, gem-diol), 7.43 (0.8H, t, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, keto), 7.48 (0.2H, d, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, gem-diol), 7.54 (1.0 H, d, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, gem-diol + keto), 8.01 (0.8H, d, $^3J_{H\text{-}H}$ 7.3 Hz, Ar, keto), 8.06 (0.8H, s, Ar, keto) ppm; δ_C (125 MHz, D_2O, Me_4Si) 20.4 (keto), 20.5 (gem-diol), 119.6 (td, $^1J_{C\text{-}F}$ 270.3, $^1J_{C\text{-}P}$ 157.6, *C*F_2P, keto), 124.9 (gem-diol), 127.7 (keto), 127.9 (gem-diol), 128.3 (keto), 128.4 (gem-diol), 129.7 (gem-diol), 130.8 (keto), 133.0 (keto), 135.2 (keto), 137.3 (gem-diol), 138.0 (gem-diol), 138,6 (keto), 195.4 (td, $^2J_{C\text{-}F}$ 21.4, $^2J_{C\text{-}P}$ 11.0, *C*O*C*F_2P, keto) ppm; δ_C (376 MHz, D_2O, $CFCl_3$) –122.0 (0.3F, d, $^2J_{F\text{-}P}$ 80.4, gem-diol), –110.4 (1.7F, d, $^2J_{F\text{-}P}$ 77.6, keto) ppm; δ_P (202 MHz, $CDCl_3$, H_3PO_4) 2.93 (0.86P, t, $^2J_{P\text{-}F}$ 77.1, keto), 6.23 (0.14P, t, $^2J_{P\text{-}F}$ 80.0, gem-diol) ppm. MS(API-ES) *m/z pos* 501.0 (2M + H^+ – 4NH_3, 40%), 251.0 (M + H^+ – 2NH_3, 100%); *neg* 499.0 (2M – H^+ – 4NH_3, 30%), 249.0 (M – H^+ – 2NH_3, 100%). Found: C, 38.34; H, 5.19; P, 10.67. Calc. for $C_9H_{15}F_2N_2O_4P$: C 38.04; H, 5.32; P, 10.90.

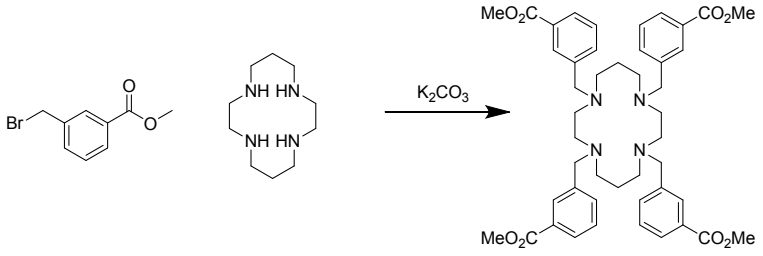
Preparation of diethyl 1,1-difluoro-2-oxo-2-(m-bromomethylphenyl)ethylphosphonate



To a stirred and irradiated with 950 Wt UV lamp solution of diethyl (1,1-difluoro-2-oxo-2-(m-tolyl)ethyl)phosphonate (2.14 g, 7mmol) in CCl_4 (20 mL) solid NBS (1.31 g, 7.4 mmol) was added in 5 equal portions over 4 h. The reaction mixture was then cooled to rt and filtered. Solid was washed with CCl_4 (3x5 mL) and combined filtrate was concentrated in vacuum. Crude product consisted of 64:12:24 mixture of respectively monobrominated and dibrominated products, and starting material. Flash chromatography (gradient of EtOAc in hexane 20% -> 25%) afforded 1.14 g of pure $BrCH_2C_6H_4C(O)CF_2P(O)(OEt)_2$. Yield 42.3%, pale yellow viscous oil. δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.37 (6H, t, $^3J_{H\text{-}H}$ 7.2, 2xOCH$_2$C*H*$_3$) 4.24 - 4.41 (4H, m, 2xOC*H*$_2$CH$_3$), 4.52 (2H, s, ArC*H*$_2$Br), 7.49 (1H, $^3J_{H\text{-}H}$ 7.3, C_6H_4), 7.68 (1H, d, $^3J_{H\text{-}H}$ 7.3, C_6H_4), 8.08 (1H, d, $^3J_{H\text{-}H}$ 7.3, C_6H_4), 8.12 (1H, s, C_6H_4) ppm; δ_H (16 MHz, $CDCl_3$, Me_4Si) 16.3 (d, $^3J_{CP}$ 5.5, OCH$_2$C*H*$_3$), 32.1, 65.4 (d, 2J_{CP} 6.5), 114.9 (td, $^1J_{CF}$ 274.3, $^1J_{CP}$ 200.5, CO*C*F_2P), 129.2, 130.3, 130.6, 132.5, 135.2, 138.6, 187.5 (td, $^2J_{CF}$ 24.4, $^2J_{CP}$ 15.0 *C*O*C*F_2P) ppm; δ_P (202 MHz, $CDCl_3$, H_3PO_4) 4.2 (t, $^2J_{P\text{-}F}$ 96.0) ppm; δ_F (376 MHz, $CDCl_3$, $CFCl_3$) –110.8 (d, $^2J_{F\text{-}P}$ 96.0).

Synthesis of difluoromethyl phosphonic acid derivatives of nitrogen-containing macrocycles

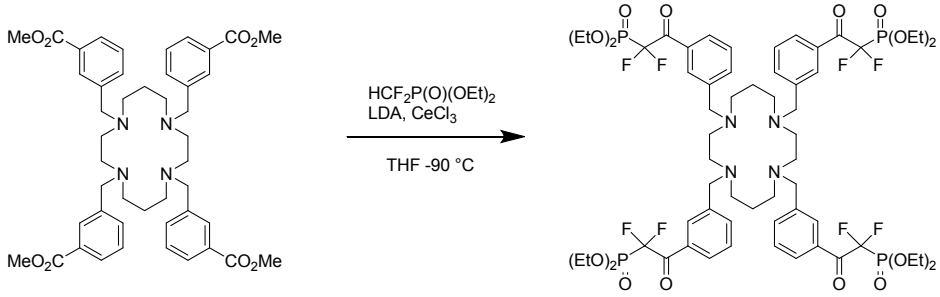
N^1,N^4,N^8,N^{11}-Tetrakis[3-(carboxymethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (1)



1

Methyl 3-(bromomethyl)benzoate (0.93 g, 4.05 mmol) and 1,4,8,11-tetraazacyclotetradecane (0.20 g, 1 mmol) were dissolved in dry DMF (5 mL). To this solution finely powdered K_2CO_3 (1.38 g, 10 mmol) was added followed by catalytic amounts of KI (0.033 g, 0.20 mmol). The resulting mixture was stirred at 80 °C for 48 h. After cooling to r.t. the reaction mixture was poured into water (100 mL) and acidified with HCl to pH 5. The precipitate was washed with EtOH, filtered and dried in vacuum at 60 °C. Yield 56% (0.44 g, 0.56 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59–1.97 (m, 4H, cyclam), 2.25–2.85 (m, 16H, cyclam), 3.37 (s, 8H, NCH_2Ar), 3.84 (s, 12H, CO_2CH_3), 7.19–8.05 (m, 8H, Ar), 7.73–7.95 (m, 8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.18 (CCH_2C), 49.80, 50.95 (cyclam, CH_2N), 51.57 (CH_2Ar), 57.98 (OMe), 127.61, 129,64, 133.15, 140.32 (Ar), 166.82 (CO). MS-ESI pos: 793 (20%, M + H^+), 397 (100%, M + $2H^+$). Found: C, 69.51; H, 7.19; N, 7.22. Calc. for $C_{46}H_{56}N_4O_8$: C, 69.67; H, 7.12; N, 7.07.

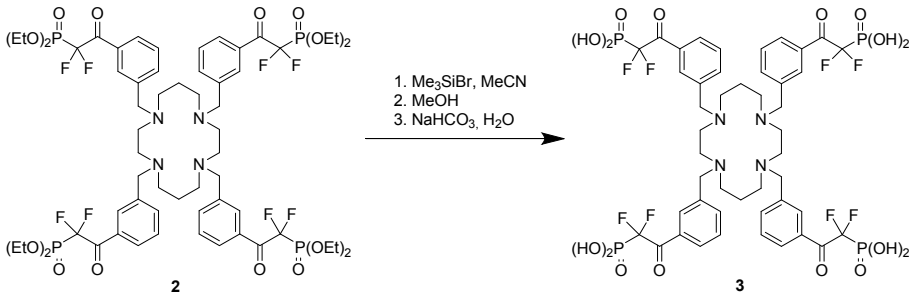
N^1,N^4,N^8,N^{11}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(diethylphosphono)ethyl]benzyl}-1,4,8,11-tetraazacyclotetradecane (2)



1 **2**

n-BuLi (1.56 mL of 1.6 M solution in hexane, 2.5 mmol) was added dropwise to a cold (-78 °C) solution of diisopropylamine (0.27 g, 2.6 mmol) in dry THF (8 mL). The solution was warmed to 0 °C for 10 min under argon then recolled to -78 °C. Freshy dried $CeCl_3$ (760 mg, 3.1 mmol) was added then in one portion. The resulting suspension was stirred vigorously at -78 °C for 20 min then it was cooled to –90 °C and a solution of diethyl difluoromethylphosphonate (427 mg, 2,27 mmol) in 2 mL of THF was added. Mixture was stirred at -90 °C for 1 h, then a suspension of of tetramethyl 3,3',3'',3'''-((1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrayl)tetrakis(methylene))tetrabenzoate (400 mg, 0,5 mmol, 1 eq) in 10 mL of THF was added. Mixture became very thick and stirring was disabled. It was kept at -80 °C for 1 h and then allowed to warm to -30 °C during the second hour. Reaction was quenched by adding NH_4Cl aqueous solution. Product was extracted with CH_2Cl_2 and dried over Na_2SO_4. Solvent was evaporated to yield 650 mg of dark yellow oil. Product **2** was purified by flash chromatography (CH_2Cl_2:MeOH 100:4 => 100:7) in 54 % yield (382 mg, 0,27 mmol); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34–1.41 (m, 24H, OCH_2CH_3), 1.77–1.83 (m, 4H, cyclam), 2.45–2.52 (m, 8H, cyclam), 2.65 (bs, 8H, cyclam), 3.43 (bs, 8H, NCH_2Ar), 4.32–4.39 (m, 16H, OCH_2CH_3), 7.32–7.38 (m, 4H, Ar), 7.59–7.63 (m, 4H, Ar), 7.99–8.05 (m, 8H, Ar). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –110.1 (d, $^2J_{F\text{-}P}$ = 95.0 Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) δ 4.5 (t, $^2J_{P\text{-}F}$ = 95.0 Hz). MS-ESI pos: 1418 (20%, M + H^+). Found: C, 52.68; H, 5.60; P, 8.55. Calc. for $C_{62}H_{84}F_8N_4O_{16}P_4$: C, 52.54; H, 5.97; P, 8.74.

N^1,N^4,N^8,N^{11}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(phosphono)ethyl]benzyl}-1,4,8,11-tetraazacyclotetradecane (3)

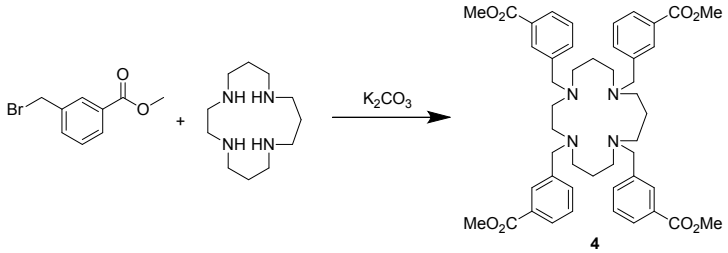


2 3

To a solution of tetrakis(phosphonate) **2** (300 mg, 0.2 mmol, 1 eq) in MeCN (5 mL) bromotrimethylsilane (1.19 g, 7.8 mmol, 36 eq) was added. The resulting solution was stirred at 35 °C overnight. Solvent was evaporated and the residue was treated with MeOH (3 mL). Mixture was stirred at 35 °C for 15 min and product was precipitated by adding acetone (30 mL). Solid was filtered, washed with EtOAc and dried on air overnight and then under vacuum at 70 °C for 2h to yield product **3** as colorless solid in 65% yield (165 mg, 0.14 mmol). ^{1}H NMR (D_2O, 500 MHz) δ 1.75–1.95 (m, 4H, cyclam), 2.50–2.85 (m, 16H, cyclam), 3.66 (s, 8H, NCH_2Ar), 7.20–7.65 (m, 10H, Ar), 8.01–8.14 (m, 6H, Ar). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –110.3 (d, $^{2}J_{P\text{-}F}$ = 96 Hz). ^{31}P NMR (DMSO-d_6, 202 MHz) *δ* 3.8 (t, $^{2}J_{P\text{-}F}$ = 96 Hz). MS-ESI pos: 1418 (20%, M + H$^+$). Found: C, 46.65; H, 4.51; N, 4.58. Calc. for $C_{46}H_{52}F_8N_4O_{16}P_4$: C, 46.32; H, 4.39; N, 4.70. Cyclam-tetrakis(phosphonic acid) was converted into its tetrasodium salt by dissolving the acid (1 eq) in $NaHCO_3$ (4 eq) aqueous solution and evaporating the resulting solution to dryness. ^{1}H NMR (D_2O + K_2CO_3, 125 MHz) δ 1.80 (m, 4H, cyclam), 2.62–2.72 (m, 16H, cyclam), 3.59–3.65 (m, 8H, NCH_2Ar), 7.23–7.60 (m, 10H, Ar), 8.01–8.14 (m, 6H, Ar) ppm; ^{13}C NMR (D_2O + K_2CO_3, 125 MHz) δ 20.2, 46.0, 50.7, 59.0, 119.9 (td, $^{1}J_{C\text{-}F}$ = 259.3, $^{1}J_{C\text{-}P}$ 156.2, CF_2P), 128.8, 130.4, 131.8, 133.2, 135.8, 136.9, 195.3 (m, $COCF_2P$).

***N*^{1},*N*^{4},*N*^{8},*N*^{12}-Tetrakis{3-[1′-oxo-2′,2′-difluoro-2′-(phosphono)ethyl]benzyl}-1,4,8,12-tetraazacyclopentadecane (6)**

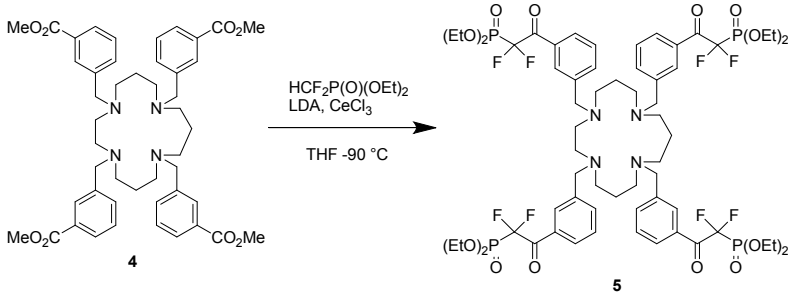
N^{1},*N*^{4},*N*^{8},*N*^{12}-Tetrakis[3-(carboxymethyl)benzyl]-1,4,8,12- tetraazacyclopentadecane (4)*



4

Compound **4** was synthesized similarly to **1** starting from homocyclam (0.32 g, 1.5 mmol) and *m*-bromomethylbenzoate (1.55 g, 6.23 mmol). After purification by FC (CH_2Cl_2/MeOH 10:0.6) product was obtained as viscous yellow oil. Yield 0.77 g (64%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58–1.75 (m, 6H, cyclam), 2.39–2.53 (m, 12H, cyclam), 2.61 (s, 4H, cyclam), 3.44–3.64 (m, 8H, NCH_2Ar), 3.80–3.95 (m, 12H, CO_2CH_3), 7.18–7.43 (m, 8H, Ar), 7.80–7.87 (m, 8H, Ar);^{13}C NMR ($CDCl_3$, 125 MHz, TMS) *δ* 25.2, 51.4, 51.9, 52.0, 52.3, 59.5, 128.1, 128.2, 128.3, 129.8, 129.9, 130.0, 133.4, 133.5, 140.4, 140.6, 167.2 ppm; MS-ESI pos: 808 (5%, M + H$^+$), 404 (70%, M + 2H$^+$). Found: C, 70.16; H, 7.21; N, 6.74. Calc. for $C_{47}H_{58}N_4O_8$: C, 69.95; H, 7.24; N, 6.94.

N^{1},*N*^{4},*N*^{8},*N*^{12}-Tetrakis{3-[1′-oxo-2′,2′-difluoro-2′-(diethylphosphono)ethyl]benzyl}-1,4,8,12-tetraazacyclopentadecane (5)*

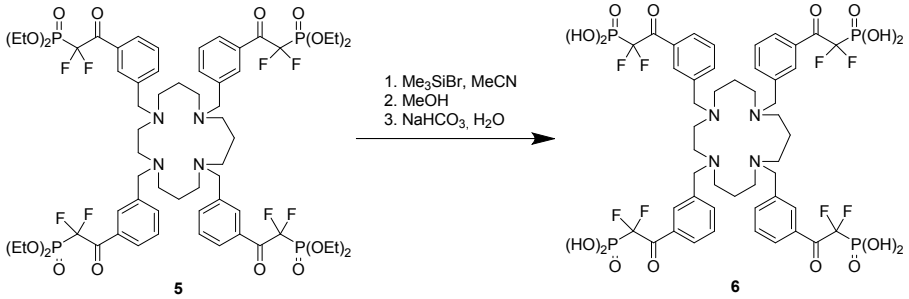


4 5

Compound **5** was synthesized similarly to **2** starting from ester **4** (0.70 g, 0.87 mmol) and diethyl difluoromethylphosphonate (0.82 g, 4.35 mmol). After purification by FC (CH_2Cl_2/MeOH 10:1) product was obtained as yellow oil. Yield 0.49 g (39%). ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) *δ* 1.37 (m, 24H, OCH_2CH_3), 1.69 (m, 6H, cyclam), 2.48–2.62 (m, 16H, cyclam), 3.55 (m, 8H, NCH_2Ar), 4.35 (m, 16H, OCH_2CH_3), 7.43–7.58 (m, 8H, Ar), 8.00 (m, 8H, Ar) ppm; ^{19}F NMR ($CDCl_3$, 376 MHz, $CFCl_3$) *δ* –110.1 (d, $^{2}J_{F\text{-}P}$ = 94.8 Hz)

ppm; ^{31}P NMR ($CDCl_3$, 202 MHz, 85% H_3PO_4) δ 4.6 (t, $^2J_{P\text{-}F}$ = 94.8 Hz) ppm. Found: C, 52.57; H 6.26; N 3,65. Calc. for $C_{63}H_{86}F_8N_4O_{16}P_4$: C, 52.87; H, 6.06; N 3.91.

N^1,N^4,N^8,N^{12}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(phosphono)ethyl]benzyl}-1,4,8,12-tetraazacyclopentadecane (6)

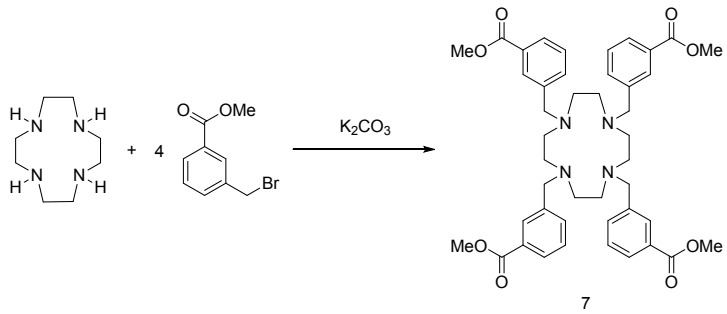


5 6

Compound **6** was obtained similarly to **3** starting from phosphonate **5** (0.36 g, 0.25 mmol). Beige solid, yield 0.29 g (95%). ^{1}H NMR (D_2O + K_2CO_3, 400 MHz, TMS) δ 1.66 (m, 6H, cyclam), 2.50 (m, 16H, cyclam), 3.59–3.71 (m, 8H, NCH_2Ar), 7.36–7.59 (m, 8H, Ar), 7.96–8.16 (m, 8H, Ar) ppm; ^{13}C NMR (D_2O + K_2CO_3, 100 MHz, TMS) δ 25.1, 48.7, 50.0, 51.2, 58.2, 120.0 (td, $^1J_{C\text{-}F}$ 269.3, $^1J_{C\text{-}P}$ 155.3, CF$_2$P), 128.6, 129.1, 130.0, 130.9, 132.1, 132.5, 133.5, 136.0, 138.1, 195.1 (m, COCF$_2$P). ^{19}F NMR (D_2O + K_2CO_3, 376 MHz, $CFCl_3$) δ –110.1 (d, $^2J_{F\text{-}P}$ = 91 Hz) ppm; ^{31}P NMR (D_2O + K_2CO_3, 202 MHz, 85% H_3PO_4): δ 3.3 (t, $^2J_{P\text{-}F}$ = 91 Hz) ppm. Found: C, 46.30; H, 4.70; N, 4.81. Calc. for $C_{47}H_{54}F_8N_4O_{16}P_4$: C, 46.78; H, 4.51; N, 4.64. Cyclam-tetrakis(phosphonic) acid **6** was converted into its tetrasodium salt by dissolving the acid (1 eq) in $NaHCO_3$ (4 eq) aqueous solution and evaporating the resulting solution to dryness.

N^1,N^4,N^7,N^{10}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(phosphono)ethyl]benzyl}-1,4,7,10-tetraazacyclododecane (9)

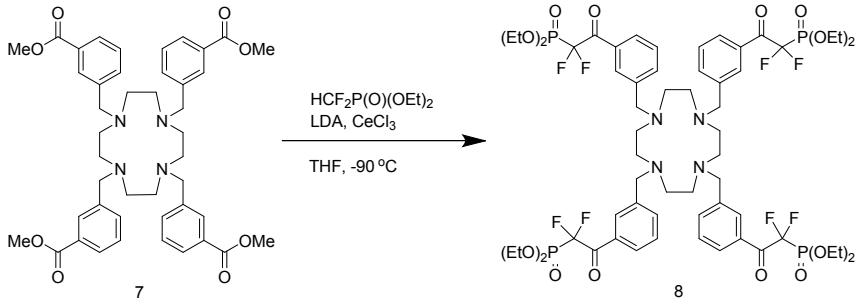
N^1,N^4,N^7,N^{10}-Tetrakis[3-(carboxymethyl)benzyl]-1,4,7,10-tetraazacyclododecane (7)



7

This compound was synthesized starting from cyclen (0.70 g, 4.0 mmol) and methyl 3-bromomethylbenzoate (3.82 g, 16.7 mmol). Yield 1.14 g (37%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60–2.80 (br s, 16H, cyclen), 3.44 (s, 8H, NCH_2Ar), 3.88 (s, 12H, OMe), 7.29 (t, J = 6 Hz, 4H, Ar), 7.56 (d, J = 6 Hz, 4H, Ar), 7.88 (d, J = 6 Hz, 4H, Ar), 7.96 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.63 (cyclen, CH$_2$N), 52.39 (NCH$_2$Ar), 59.32 (OMe), 127.65, 129,80, 129.55, 133.29, 139.99 (Ar), 166.82 (CO). Found: C, 69.40; H, 6.97; N 7.55. Calc. for $C_{44}H_{52}N_4O_8$: C, 69.09; H 6.85; N 7.32.

N^1,N^4,N^7,N^{10}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(diethylphosphono)ethyl]benzyl}-1,4,7,10-tetraazacyclododecane (8)

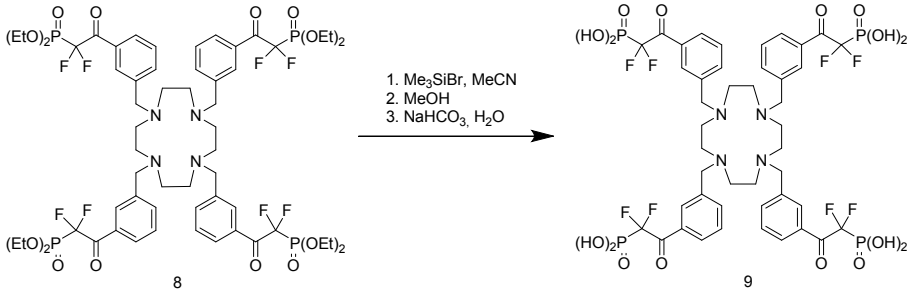


7 8

This compound was synthesized similarly to **6** starting from carboxylate ester (0.52 g, 0.68 mmol) and diethyl difluoromethylphosphonate (0.57 g, 3.06 mmol). Yield 0.39 g (42%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31–1.45 (m, 24H, OCH$_2$CH_3),

2.63–2.72 (m, 16H, cyclen), 3.44 (br s, 8H, NCH_2Ar), 4.25–4.38 (m, 16H, OCH_2CH$_3$), 7.35 (t, *J* = 6 Hz, 4H, Ar), 7.65–7.72 (m, 4H, Ar), 7.92–8.03 (m, 8H, Ar). ^{19}F NMR ($CDCl_3$, 376 MHz) δ -110.2 (d, $^2J_{F\text{-}P}$ = 93 Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) δ 5.1 (t, $^2J_{P\text{-}F}$ = 93 Hz) ppm. Found: C, 52.10; H, 5.67; N, 3.80. Calc. for $C_{60}H_{80}F_8N_4O_{16}P_4$: C, 51.88; H, 5.80; N, 4.03.

N^1,N^4,N^7,N^{10}-Tetrakis{3-[1'-oxo-2',2'-difluoro-2'-(phosphono)ethyl]benzyl}-1,4,7,10-tetraazacyclododecane (9)

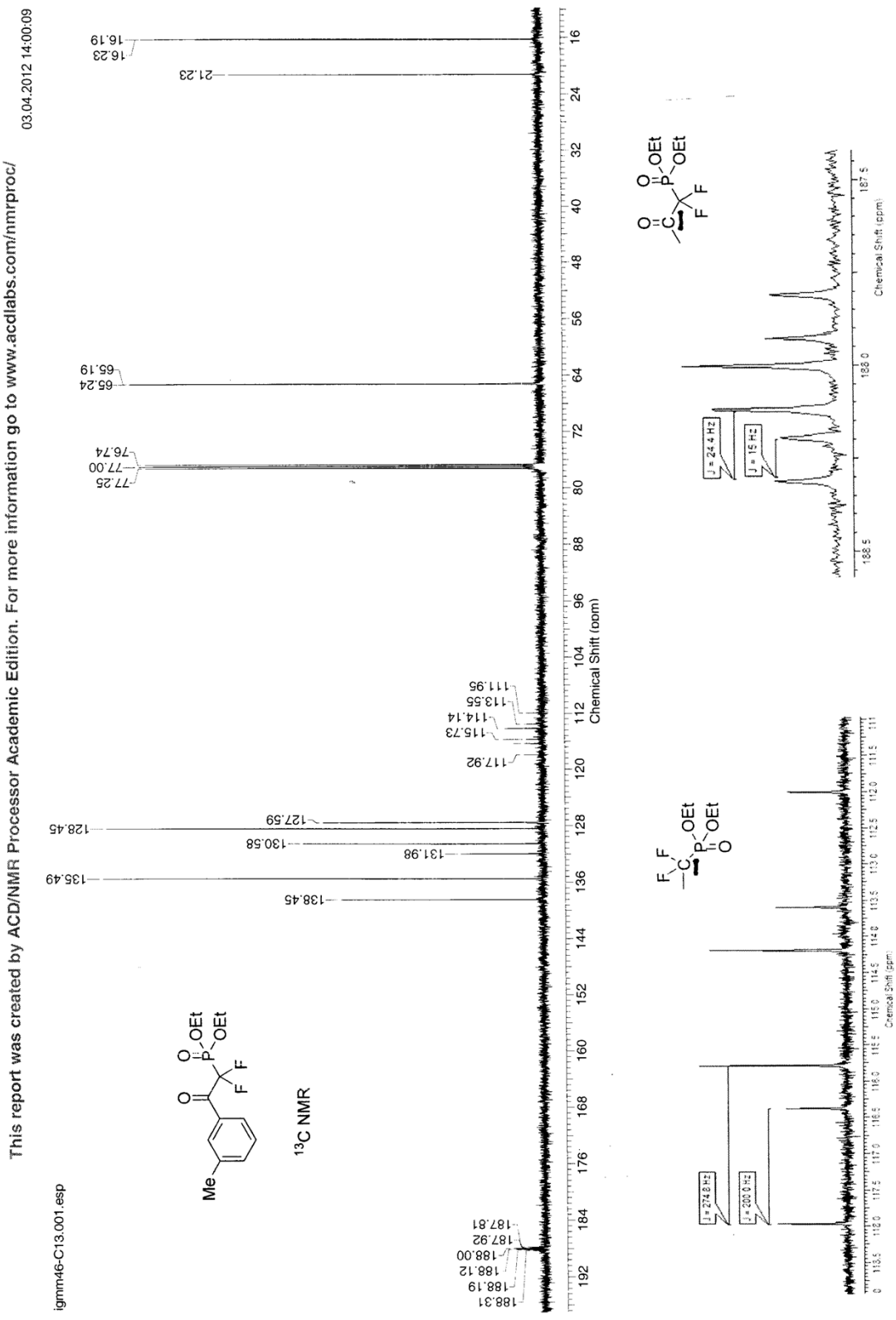


8 9

This compound was obtained similarly to cyclam-tetrakis(phosphonic acid) starting from the phosphonate ester (0.34 g, 0.245 mmol). Beige solid, yield 0.12 g (40%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.45–2.55 (m, 16H, cyclen), 3.05 (br s, 8H, NCH_2Ar), 7.59–7.73 (m, 4H, Ar), 7.91–8.04 (m, 4H, Ar), 8.06–8.20 (m, 4H, Ar), 8.28–8.41 (m, 4H, Ar). ^{19}F NMR (DMSO-d_6, 376 MHz) δ -110.4 (d, $^2J_{F\text{-}P}$ = 87 Hz). ^{31}P NMR (DMSO-d_6, 202 MHz) δ -0.3 (t, $^2J_{P\text{-}F}$ = 87 Hz) ppm. Found: C, 45.12; H, 4.37; N, 4.64. Calc. for $C_{44}H_{48}F_8N_4O_{16}P_4$: C, 45.37; H, 4.15; N, 4.81. 1,4,7,10-tetraazacyclododecane-tetrakis(phosphonic acid) was converted into its tetrasodium salt by dissolving the acid (1 eq) in $NaHCO_3$ (4 eq) aqueous solution and evaporating the resulting solution to dryness.

References

1. Blades, K., T. P. Lequeux, and J. M. Percy. "A Reproducible and High-yielding Cerium-mediated Route to α,α-difluoro-β-ketophosphonates." Tetrahedron 53, no. 30 (1997): 10623–10632.


This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/
03.04.2012 14:00:09
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Chemical Shift (ppm)
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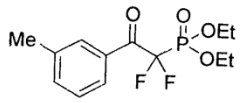
J = 200.0 Hz
J = 24.4 Hz
J = 15 Hz



^{1}H NMR

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2	4.33	4	m	-	M04	[4.25 .. 4.42]
3	7.38	1	t	7.30	M03	[7.34 .. 7.41]
4	7.45	1	d	7.82	M02	[7.42 .. 7.49]
5	7.93	2	m	-	M01	[7.88 .. 7.99]

2/11/2014 1:49:21 PM

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Original Points Count	16384	***Owner***	root	***Points Count***	16384	***Pulse Sequence***	zg
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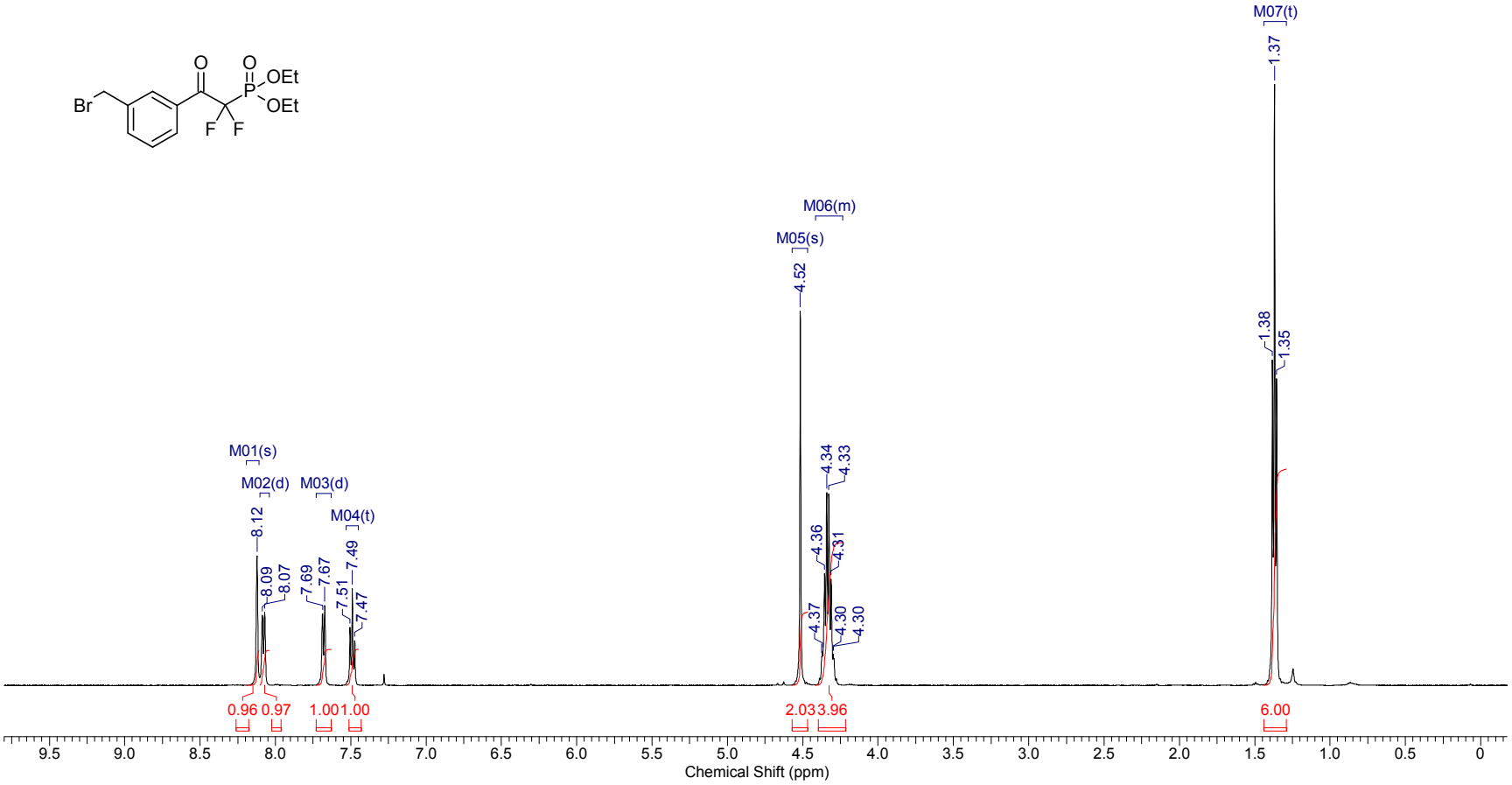

2/11/2014 1:54:59 PM

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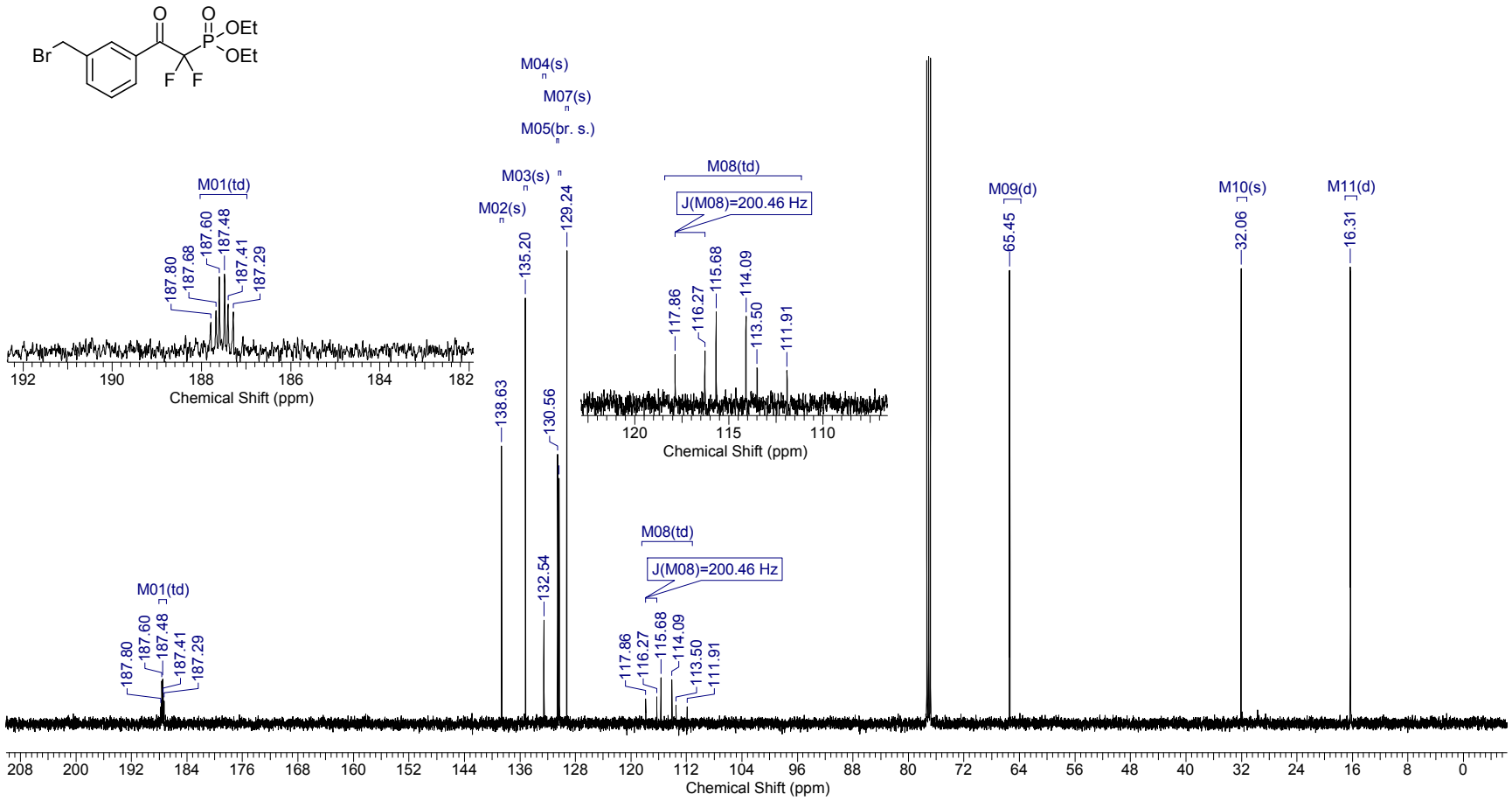

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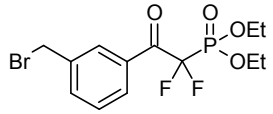

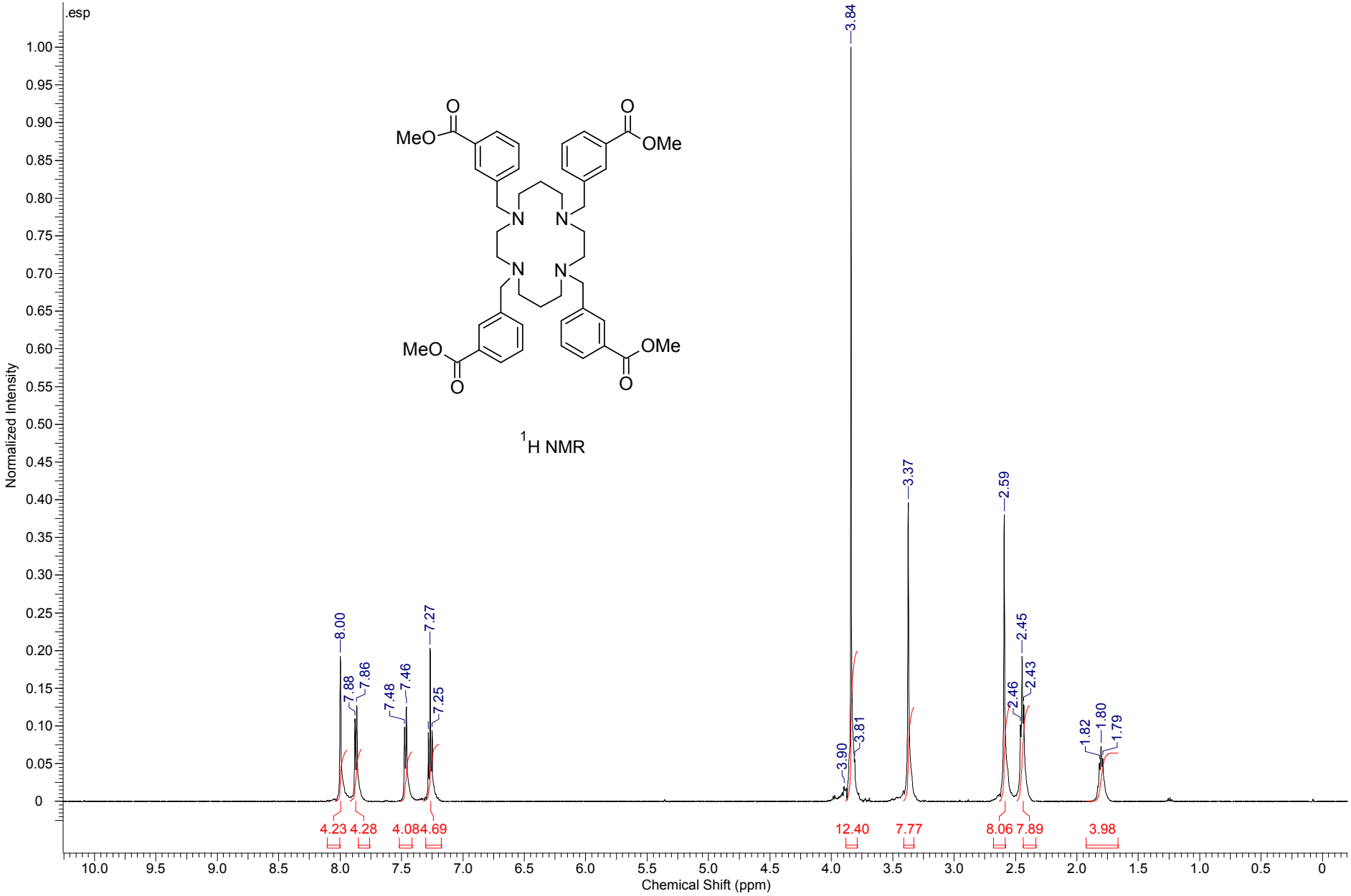
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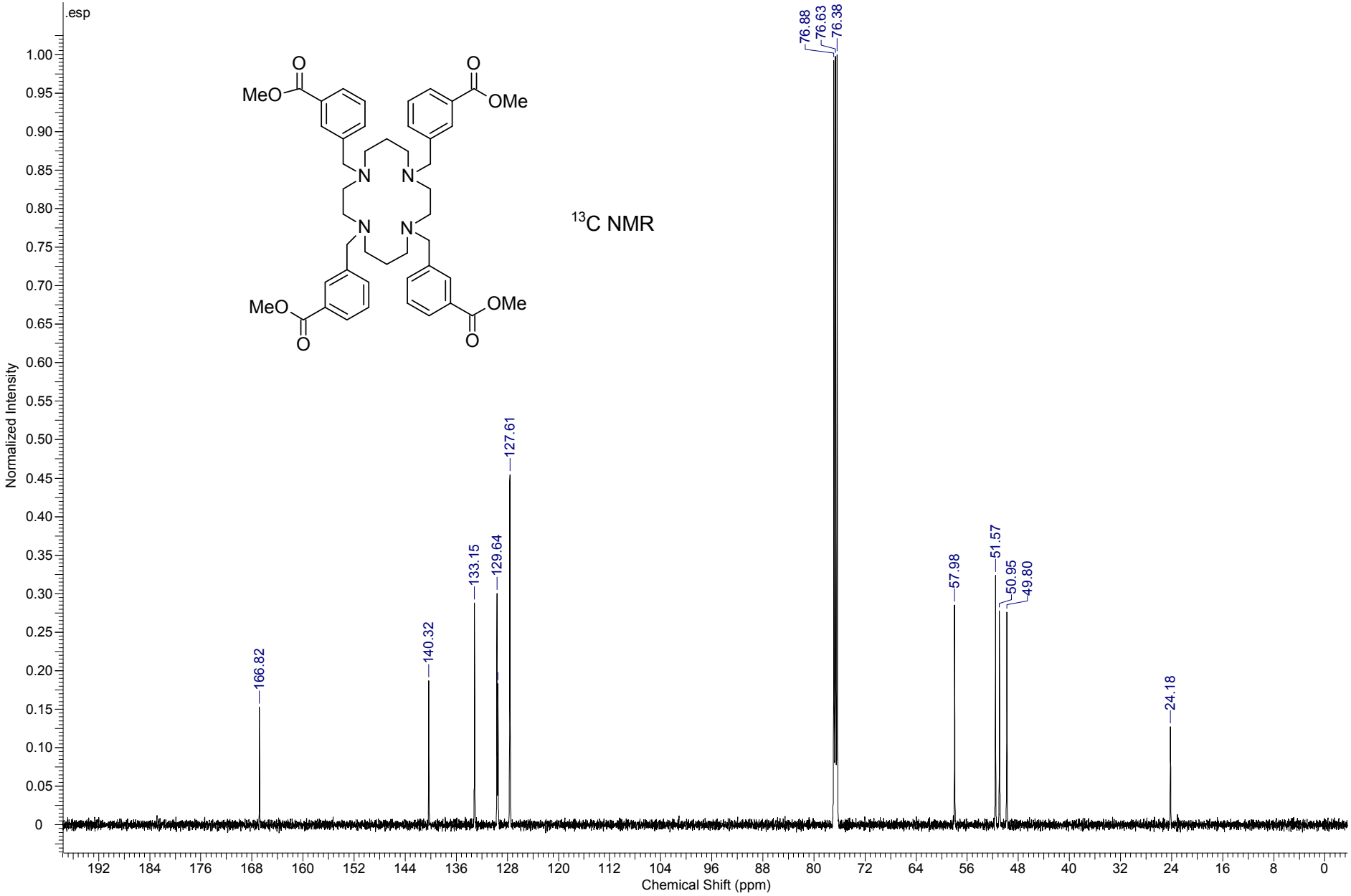
7.46
7.27
7.25
3.90
3.81
2.46
2.45
2.43
1.82
1.80
1.79
4.23
4.28
4.08
4.69
12.40
7.77
8.06
7.89
3.98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49.80
24.18

Formula $C_{46}H_{44}F_8N_4O_8$?	***FW***	932.8508+?					
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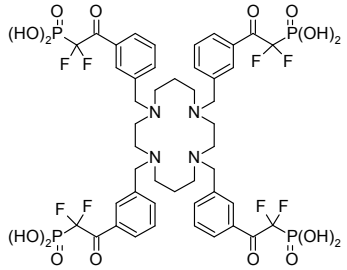

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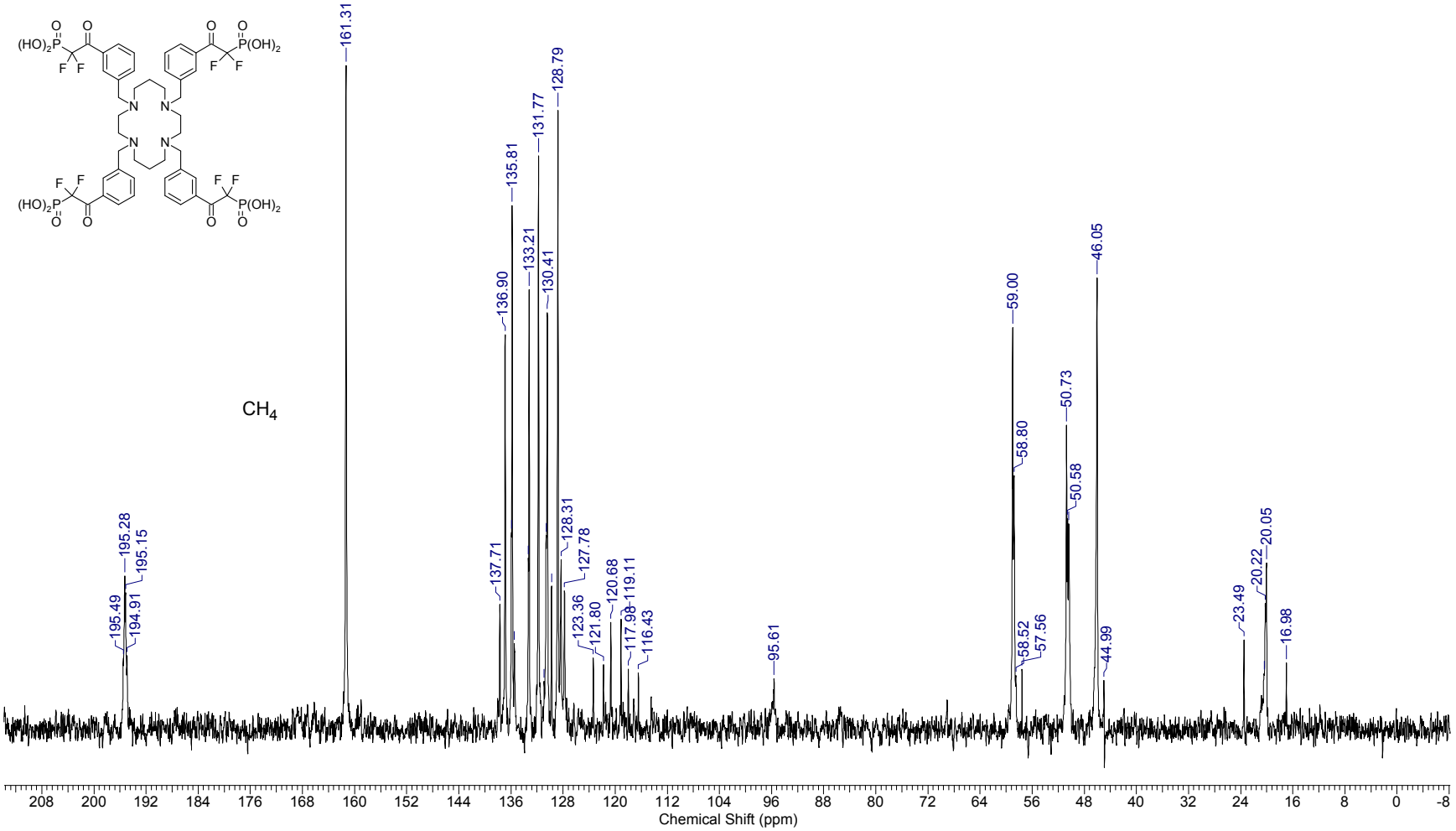

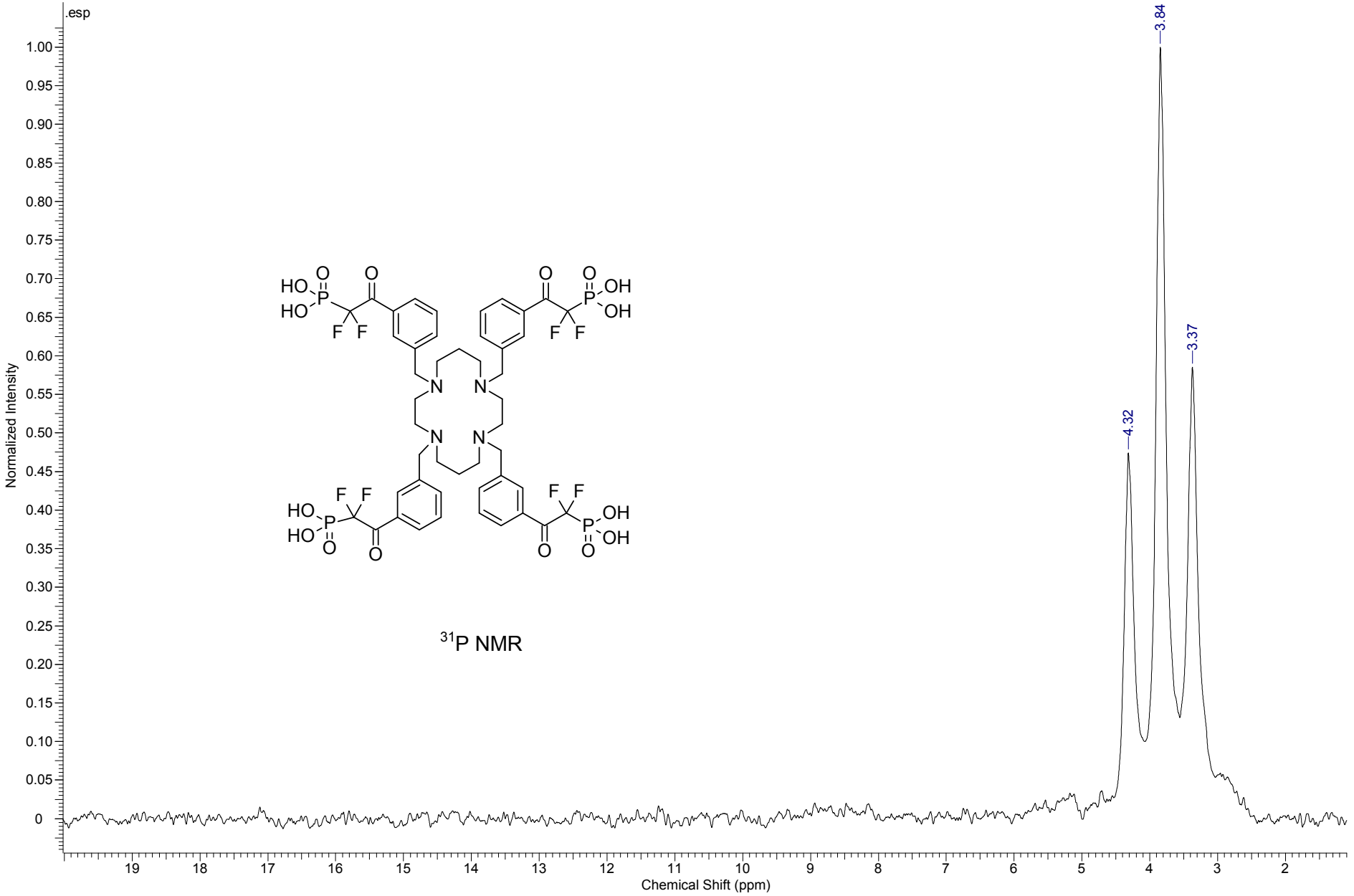
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0.30
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0.15
0.10
0.05
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13
12
11
10
9
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7
6
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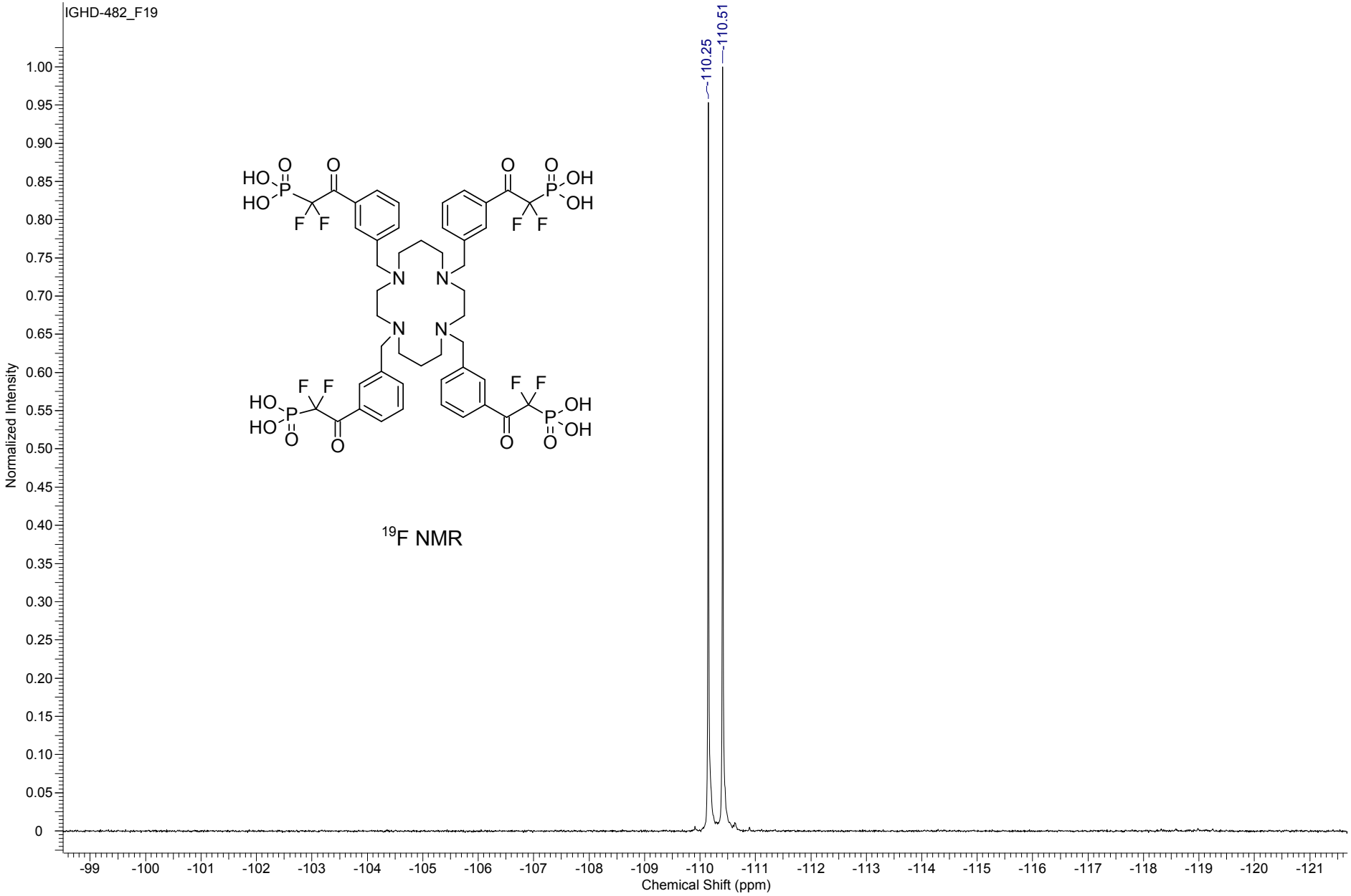
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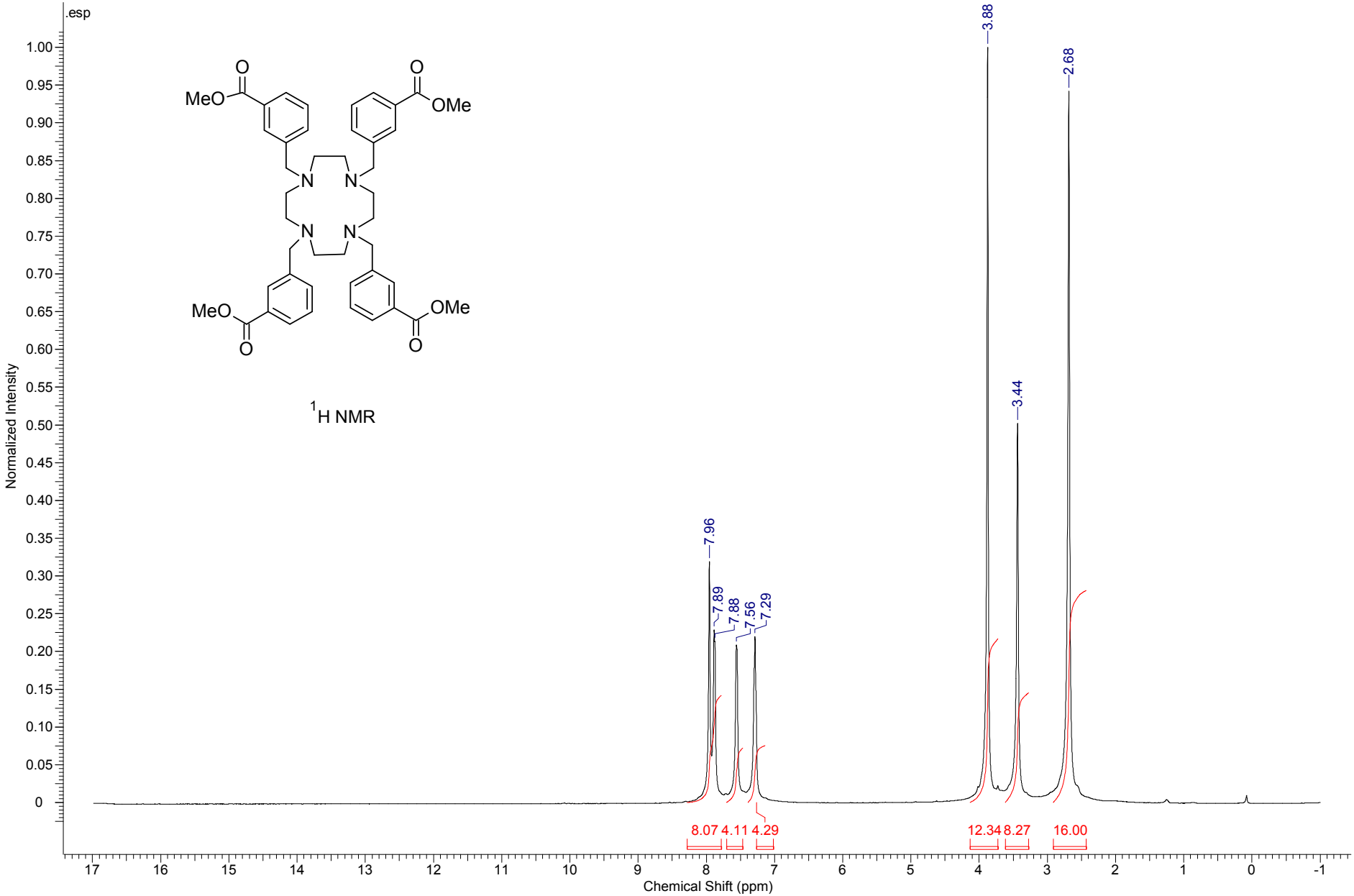
^{19}F NMR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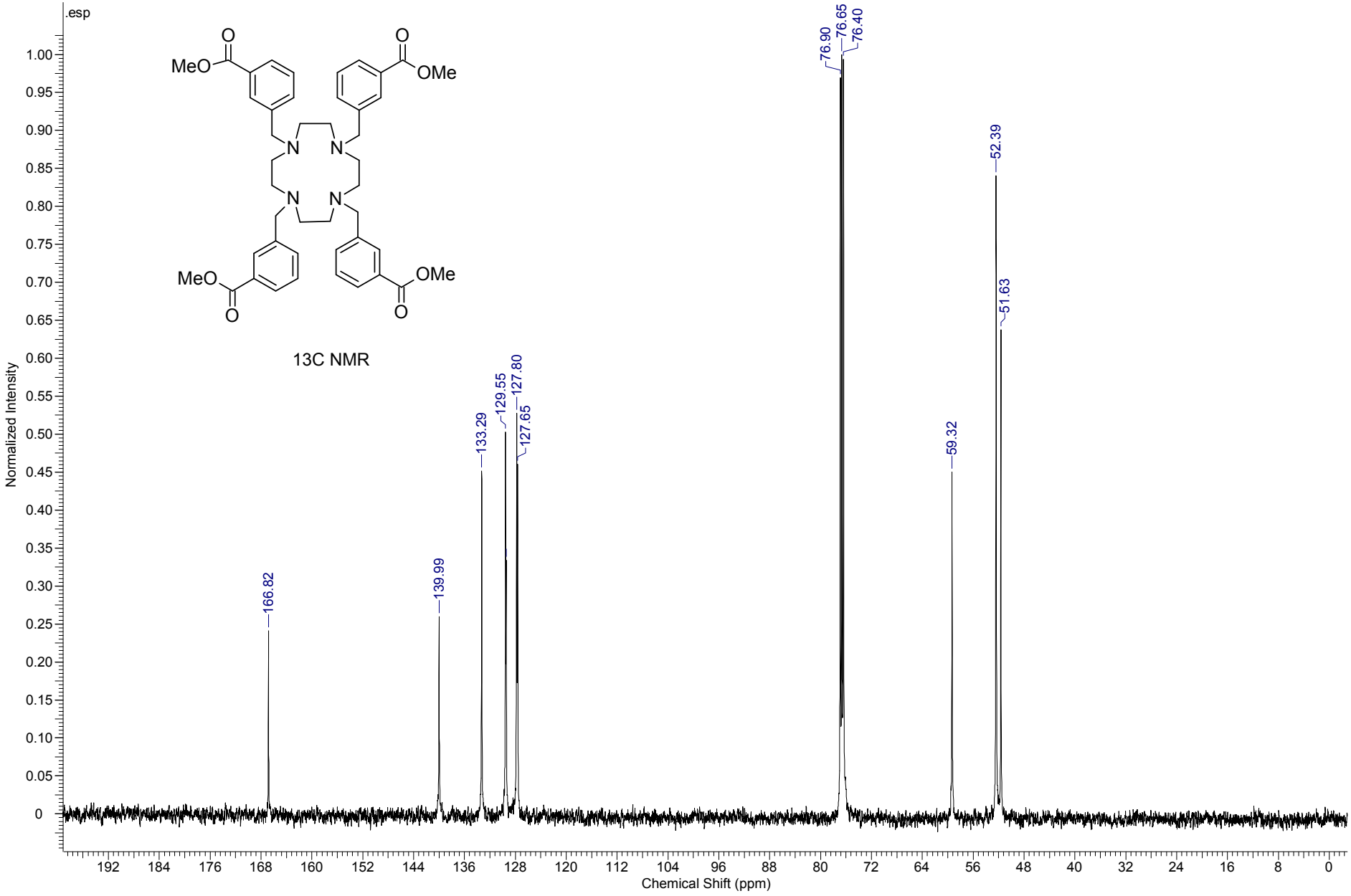
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OMe
MeO
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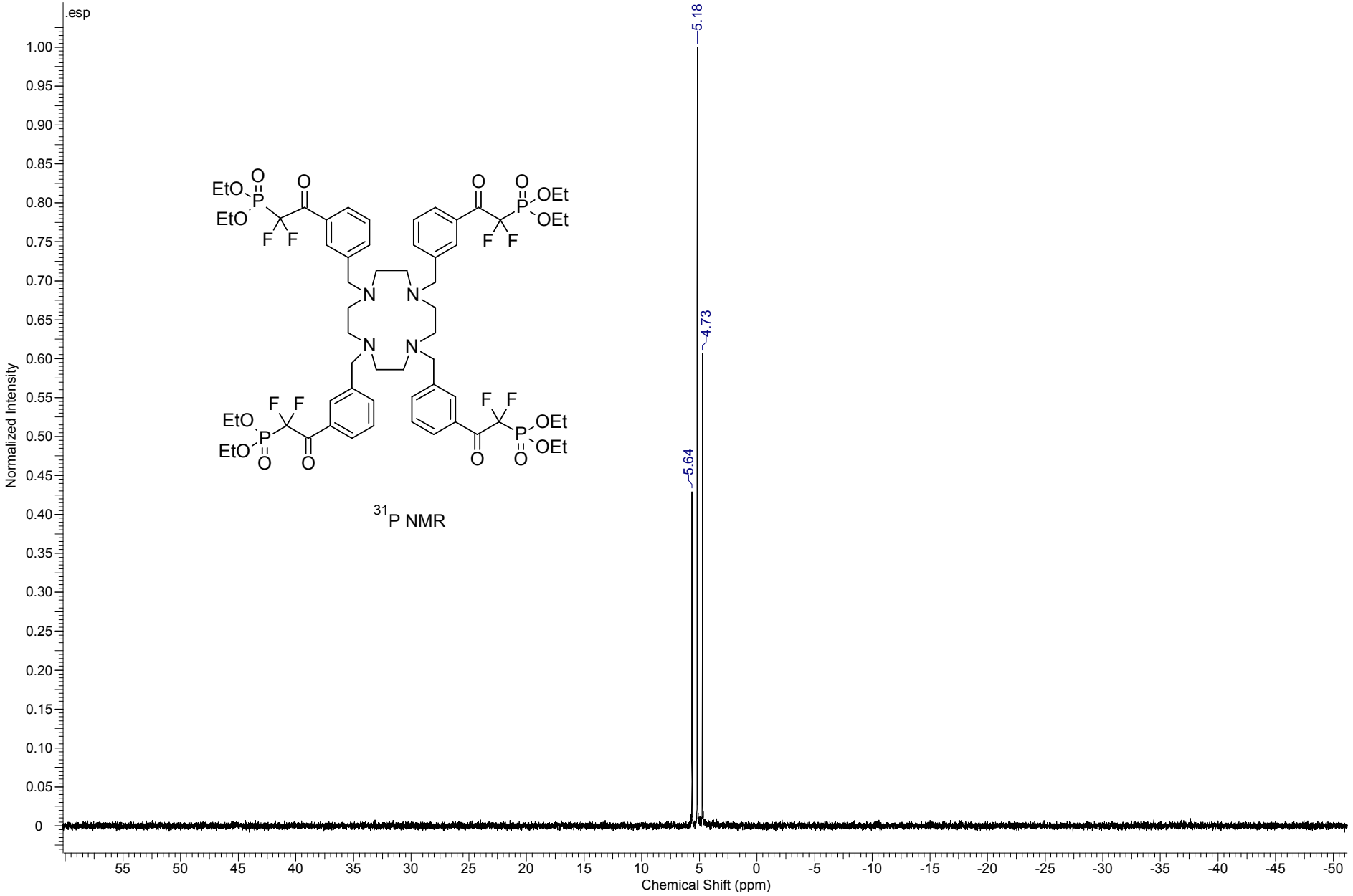
52.39
51.63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0.10
0.05
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55
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O
O
F
F
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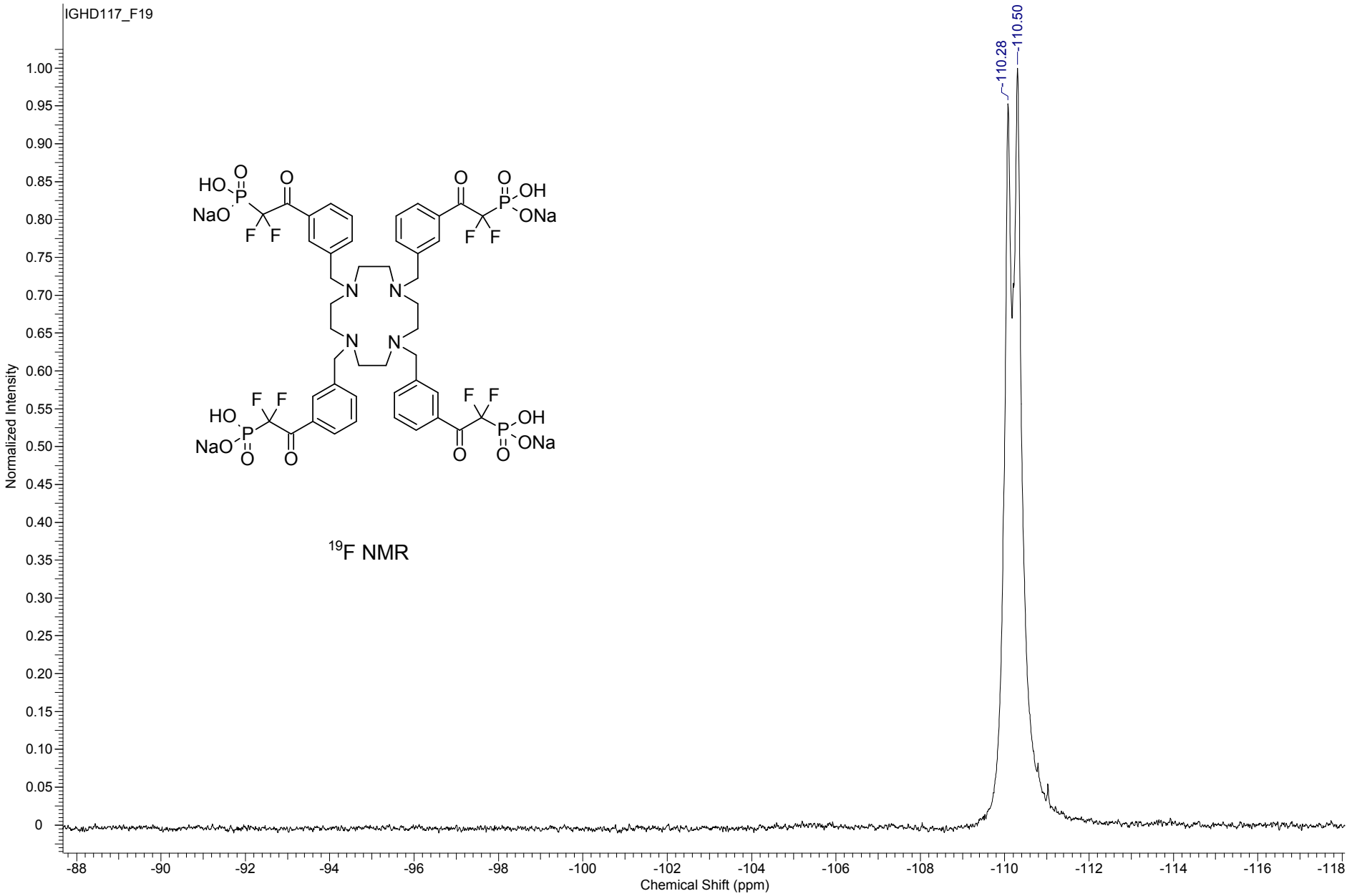
OEt
OEt
^{31}P NMR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0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
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ONa
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^{19}F NMR

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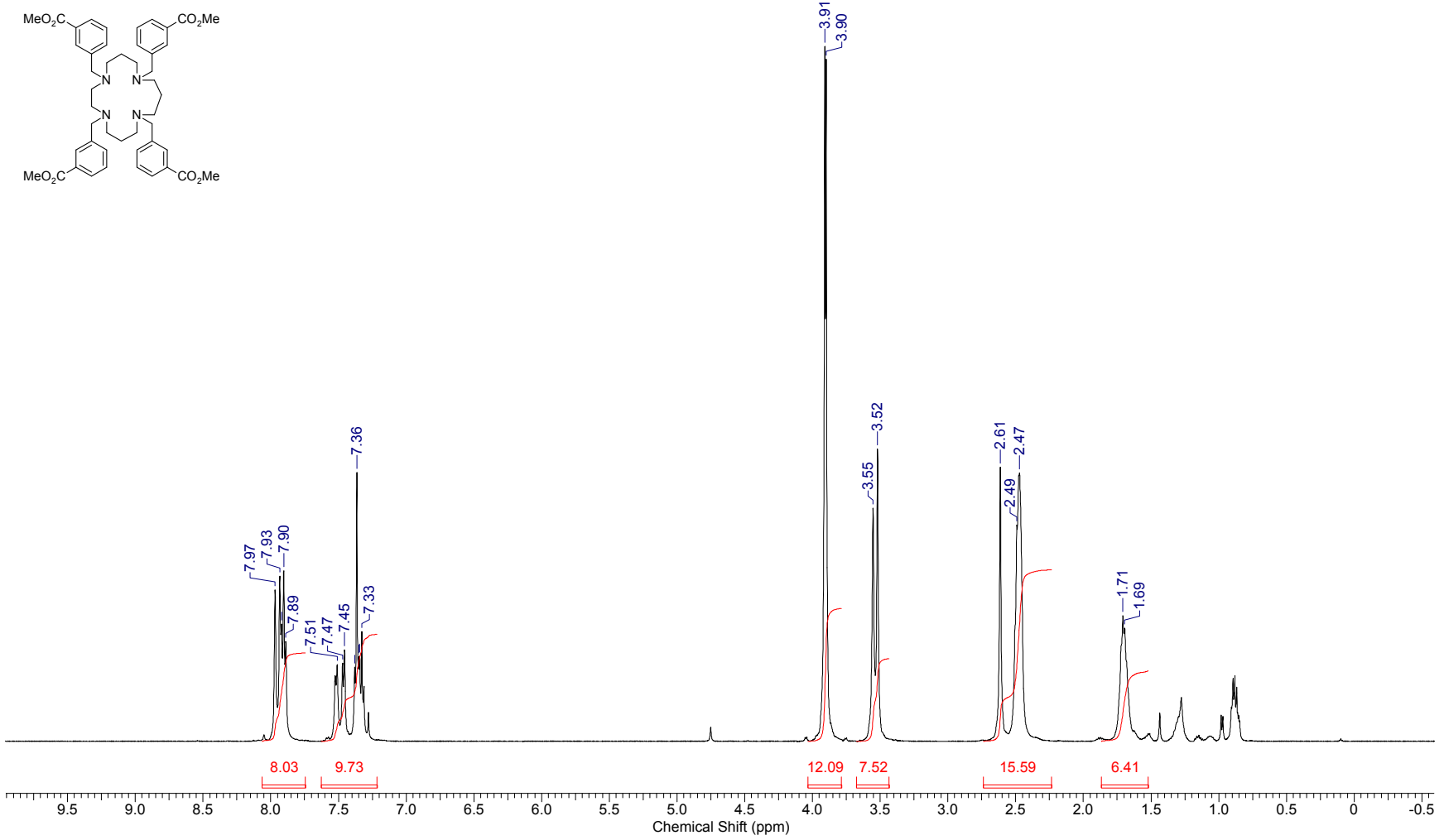

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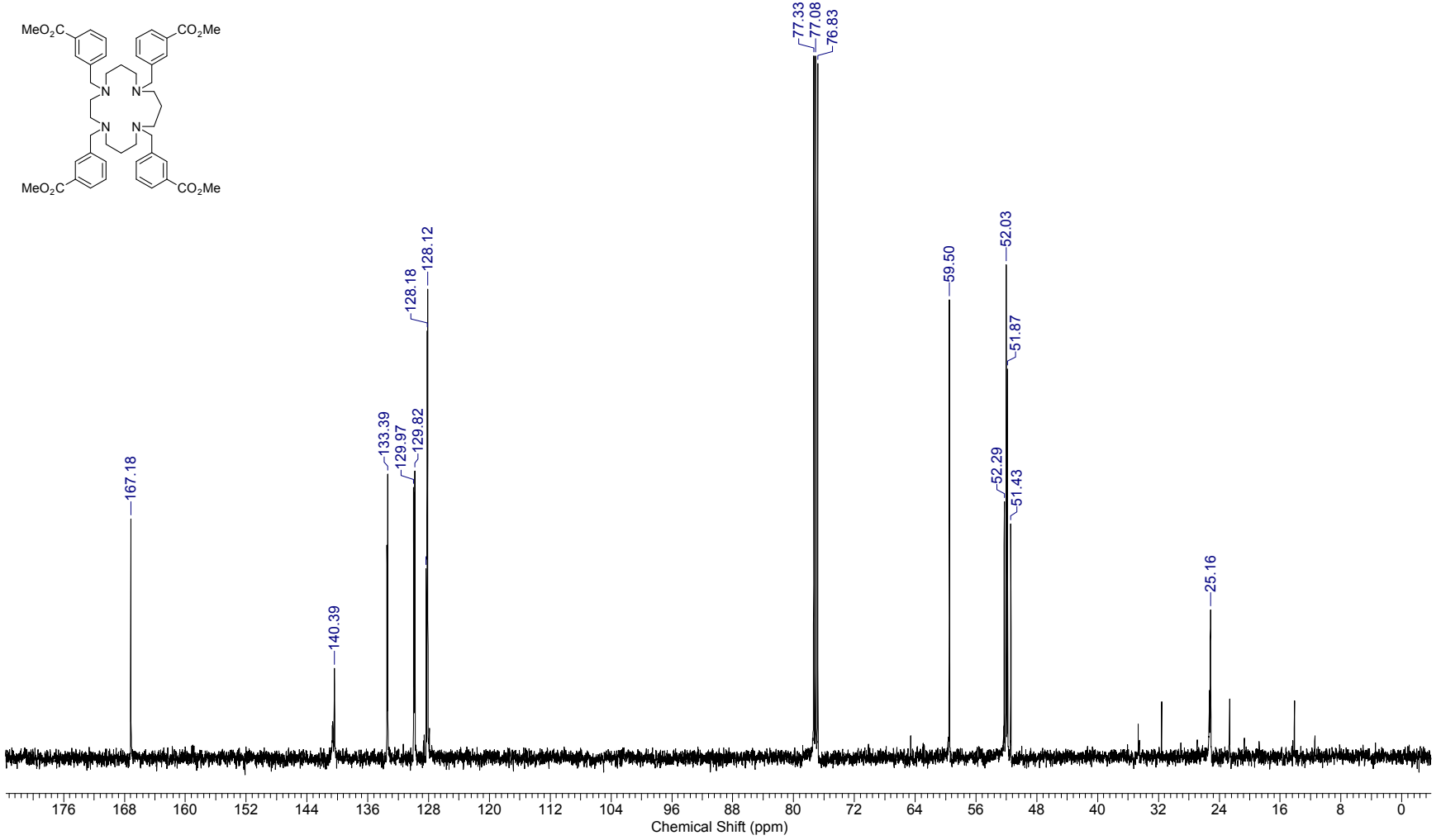
Solvent	DMSO-d6	***Spectrum Offset (Hz)***	15000.0049	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	32679.24		



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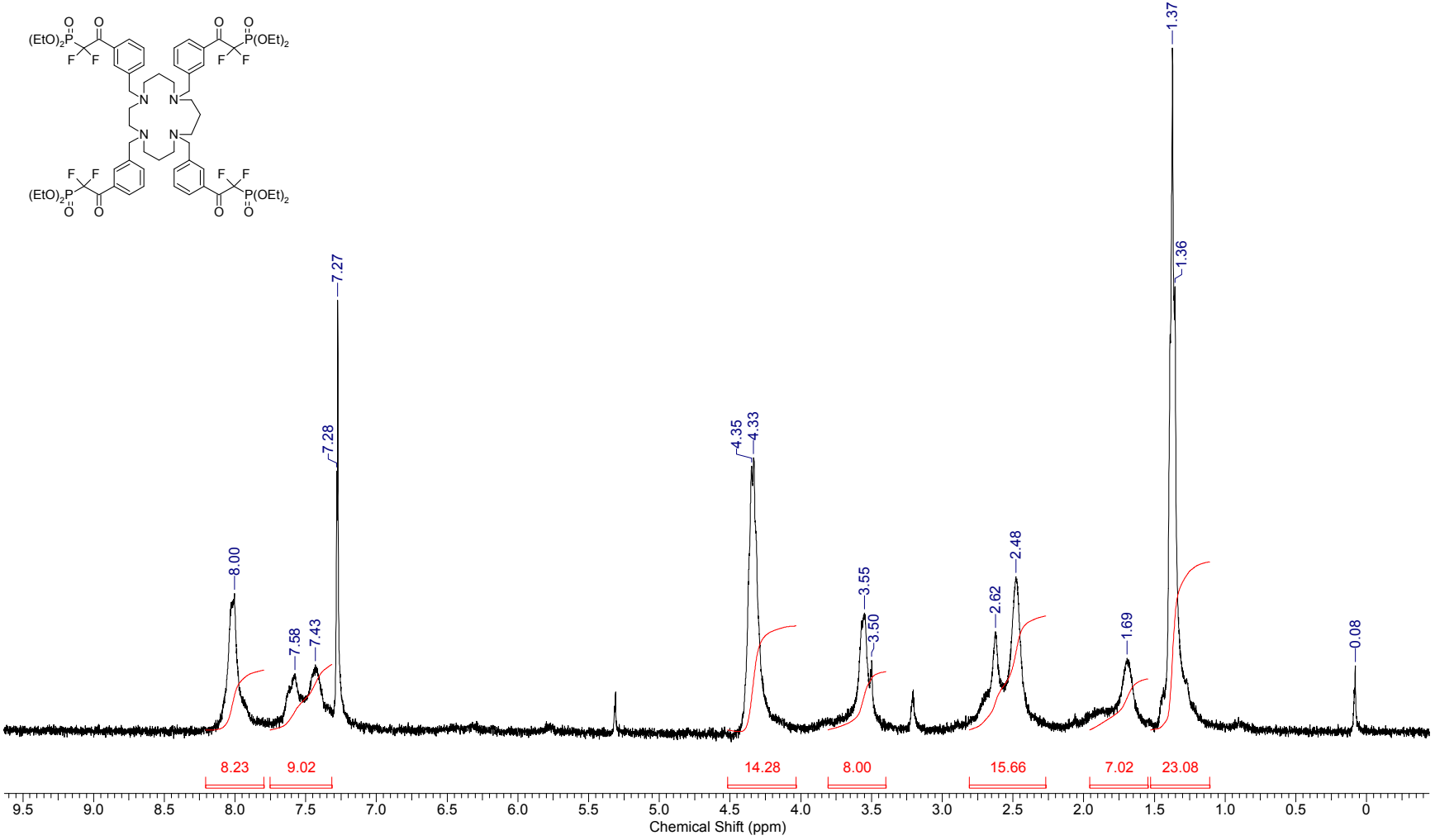

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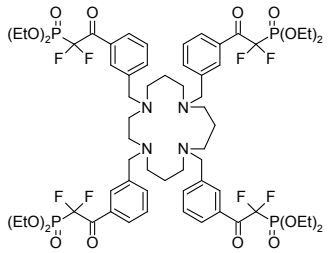
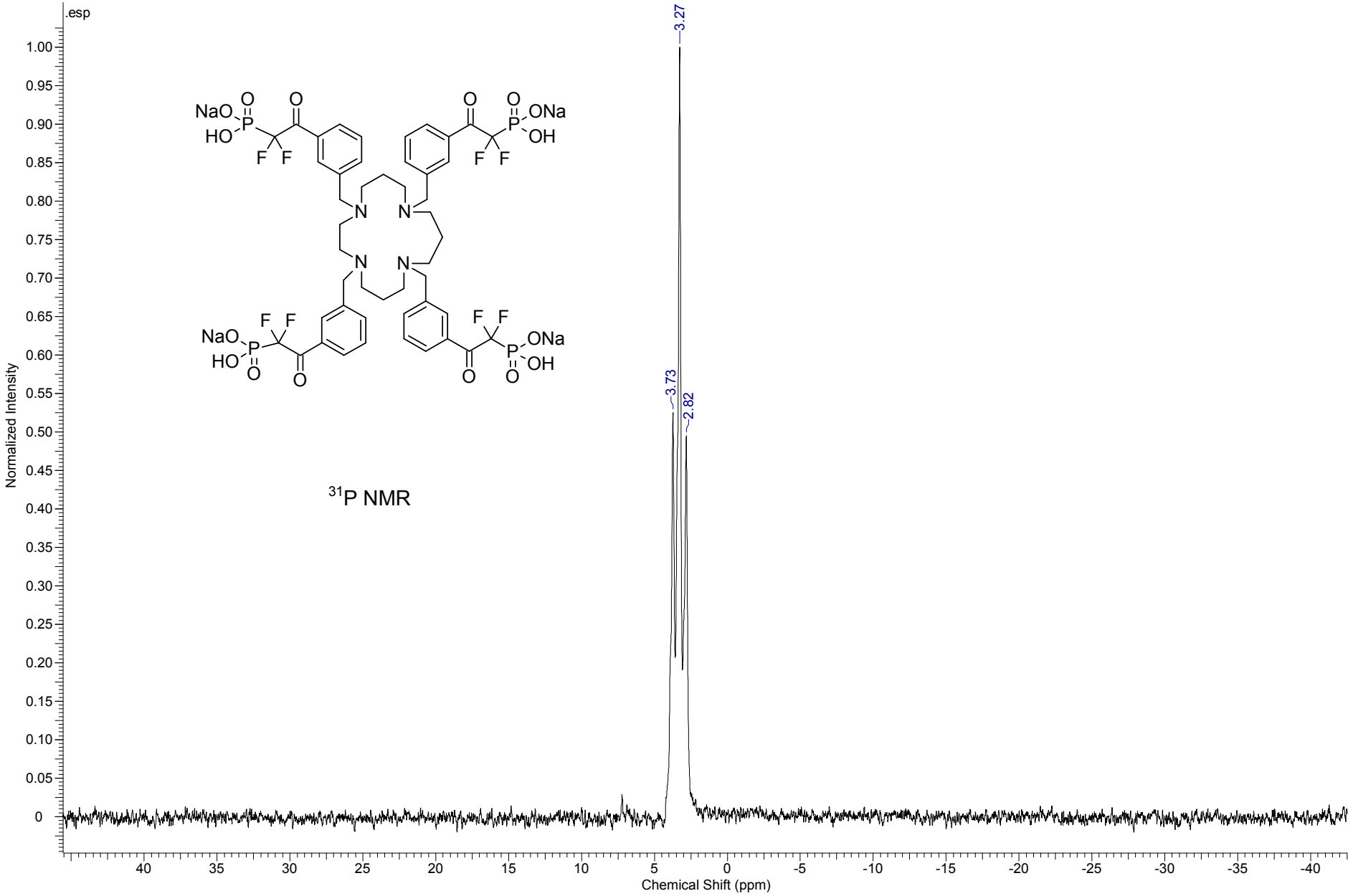
Receiver Gain	512.00	***SW(cyclical) (Hz)***	80645.16	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	5174.4409	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	80643.93		




.esp
Normalized Intensity
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
3.27
3.73
2.82
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
Chemical Shift (ppm)
NaO
HO
O
P
F
F
ONa
OH
N
^{31}P NMR