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# Synthesis of perfluorobiphenyl tetracarboxylic acids *via* the CuCl$_2$-assisted homocoupling of organozinc reagents

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## 1. General Information

$^1$H and $^{19}$F NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz for $^1$H and 282.4 MHz for $^{19}$F) in $CDCl_3$, $CCl_4$–acetone-*d*$_6$ and DMSO-*d*$_6$. The chemical shifts in the $^{19}$F NMR spectra are given relative to $CFCl_3$ ($C_6F_6$ as an internal standard, $\delta_F$ = -162.9 ppm), in the $^1$H NMR spectra are given relative to residual signal in the NMR solvents ($\delta_H$ = 7.26 ppm in $CDCl_3$, $\delta_H$ = 2.05 ppm in acetone-*d*$_6$). $^{13}$C {$^1$H} NMR spectra were measured with a Bruker Avance 400 spectrometer (100.6 MHz), Bruker DRX 500 spectrometer (125.7 MHz) and Bruker Avance 600 spectrometer (150.9 MHz) in a $CDCl_3$ and DMSO-*d*$_6$ solutions, the chemical shifts are given relative to the central signal of the NMR solvent ($\delta_C$ = 77.16 ppm for $CDCl_3$ and $\delta_C$ = 39.50 ppm for DMSO-*d*$_6$). IR spectra were recorded on a Bruker Vector 27 FTIR spectrometer. UV spectra were taken on an Agilent Cary 5000 spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS instrument (EI, 70 eV). Elemental analysis was performed on a Carlo Erba CHN analyzer. Fluorine content was determined using a Varian Cary-50 spectrophotometer according to the method described in the literature.[S1] Melting points were determined on an Electrothermal IA9100 apparatus.

All reactions were carried out using dried glassware with a magnetic stirrer bar under an atmosphere of argon.

All commercially available reagents were used as received unless otherwise noted. DMF were distilled under argon from $CaH_2$ and stored over 4Å molecular sieves.

Perfluoro-*m*-xylene was a ~2.6:1 mixture with its *para*-isomer.[S2] Diethyl 3,4,5,6-tetrafluorophthalate (**1**) and diethyl 2,3,5,6-tetrafluoroterephthalate (**6**) were synthesized by the methods according to the literature.[S3,S4]

Alfa Aesar silica gel 60 (0.060–0.20 mm, 70-230 mesh) was used for column chromatography.

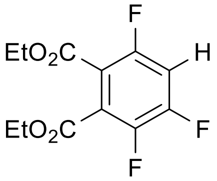
## 2. Experimental Procedures

### Reactions of diethyl 3,4,5,6-tetrafluorophthalate (1) with Zn.

a) Ester **1** (0.294 g, 1 mmol), zinc dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL) were placed in an oven-dried 8 mL vial with a screw cap containing a stirring bar, purged with argon and closed with cap. The mixture was stirred at 25 ºC for 15 h, then the reaction mixture was centrifugated at 4000 RPM for 20 min. The solution over zinc dust was separated and analyzed by $^{19}F$ NMR spectroscopy. The conversion of compound **1** to [3,4-bis(ethoxycarbonyl)-2,5,6-trifluorophenyl]zinc chloride (**2a**) and bis[3,4-bis(ethoxycarbonyl)-2,5,6-trifluorophenyl]zinc (**2b**) was 94%, the mixture also contained 4% of diethyl 3,4,6-trifluorophthalate (**3**) and 2% of ester **1**.

b) Ester **1** (0.294 g, 1 mmol), zinc dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL) were placed in an oven-dried 8 mL vial with a screw cap containing a stirring bar, purged with argon and closed with cap. The mixture was stirred at 70 ºC for 6 h. After cooled to room temperature, the reaction mixture was centrifugated at 4000 RPM for 20 min. The solution over zinc dust was separated and analyzed by $^{19}F$ NMR spectroscopy. The conversion of compound **1** to organozinc compounds **2a** and **2b** was 96.5%, the mixture also contained 3.5% of compound **3**. Compound **2a** $^{19}F$ NMR (282.4 MHz, DMF–$CDCl_3$), δ: -91.0 (d, 1F, F-2, $^5J_{FF}$ = 18.5 Hz), -107.4 (d, 1F, F-6, $^3J_{FF}$ = 30.5 Hz), -145.3 (dd, 1F, F-5, $^3J_{FF}$ = 30.5 Hz, $^5J_{FF}$ = 18.5 Hz). Compound **2b** $^{19}F$ NMR (282.4 MHz, DMF–$CDCl_3$ +), δ: -91.6 (d, 2F, F-2, $^5J_{FF}$ = 19.0 Hz), -108.0 (d, 2F, F-6, $^3J_{FF}$ = 31.5 Hz), -145.5 (dd, 2F, F-5, $^3J_{FF}$ = 31.5 Hz, $^5J_{FF}$ = 19.0 Hz).

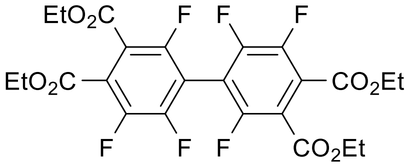
### Diethyl 3,4,6-trifluorophthalate (3).



The solution of organozinc compounds **2a,b**, obtained as described above from compound **1** (0.294 g, 1 mmol), Zn dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL), was quenched with 2 M HCl (50 mL), extracted with $CH_2Cl_2$ (3 x 5 mL), the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, pure compound **3** (0.227 g, yield

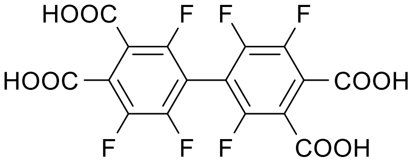
82%) was obtained as a colorless liquid. IR (neat), ν, cm$^{-1}$: 3072, 2987, 2943, 2910, 1743, 1626, 1495, 1450, 1373, 1354, 1298, 1244, 1194, 1153, 1022, 928, 860, 750. UV (EtOH), $\lambda_{max}$, nm (log ε): 281 (3.46). $^{1}$H NMR (600 MHz, $CDCl_3$), δ: 1.30 (t, 3H, $CH_2C\underline{H}_3$, $^{3}J_{HH}$ = 7.0 Hz), 1.32 (t, 3H, $CH_2C\underline{H}_3$, $^{3}J_{HH}$ = 7.0 Hz), 4.32 (q, 2H, $C\underline{H}_2CH_3$, $^{3}J_{HH}$ = 7.0 Hz), 4.36 (q, 2H, $C\underline{H}_2CH_3$, $^{3}J_{HH}$ = 7.0 Hz), 7.06 (td, 1H, $H_{ar}$, $^{3}J_{HF}$ = 9.0 Hz, $^{4}J_{HF}$ = 6.0 Hz). $^{13}$C {$^{1}$H} NMR (150.9 MHz, $CDCl_3$), δ: 13.86 (s, $CH_2\underline{C}H_3$), 13.88 (s, $CH_2\underline{C}H_3$), 62.41 (s, $\underline{C}H_2CH_3$), 62.70 (s, $\underline{C}H_2CH_3$), 108.25 (dd, C-5, $^{2}J_{CF}$ = 28.0 Hz, $^{2}J_{CF}$ = 21.0 Hz), 116.75 (dd, $\underline{C}$-$CO_2Et$, $^{2}J_{CF}$ = 17.5 Hz, $J_{CF}$ = 4.5 Hz), 124.36 (dd, $\underline{C}$-$CO_2Et$, $^{2}J_{CF}$ = 15.0 Hz, $J_{CF}$ = 3.0 Hz), 144.86 (ddd, C-3, $^{1}J_{CF}$ = 254.0 Hz, $^{2}J_{CF}$ = 14.0 Hz, $^{4}J_{CF}$ = 4.0 Hz), 151.95 (ddd, C-4, $^{1}J_{CF}$ = 258.0 Hz, $^{2}J_{CF}$ = 15.0 Hz, $^{3}J_{CF}$ = 12.0 Hz), 155.74 (ddd, C-6, $^{1}J_{CF}$ = 256.0 Hz, $^{3}J_{CF}$ = 10.0 Hz, $^{4}J_{CF}$ = 3.0 Hz), 162.17 (t, CO, $J_{CF}$ = 3.0 Hz), 162.25 (br. t, CO, $J_{CF}$ = 2.0 Hz). $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -113.0 (ddd, 1F, F-6, $^{5}J_{FF}$ = 15.0 Hz, $^{3}J_{FH}$ = 9.0 Hz, $^{4}J_{FF}$ = 7.0 Hz), -127.5 (ddd, 1F, F-4, $^{3}J_{FF}$ = 21.5 Hz, $^{3}J_{FH}$ = 9.5 Hz, $^{4}J_{FF}$ = 7.0 Hz), -143.0 (ddd, 1F, F-3, $^{3}J_{FF}$ = 21.5 Hz, $^{5}J_{FF}$ = 15.0 Hz, $^{4}J_{FH}$ = 6.0 Hz). HRMS (EI), *m/z*: 276.0602 (calc. for $C_{12}H_{11}F_3O_4$ *m/z*: 276.0604). Found, %: C, 52.26; H, 4.37; F, 20.69. Calc. for $C_{12}H_{11}F_3O_4$, %: C, 52.18; H, 4.01; F, 20.63.

**Tetraethyl 2,2',5,5',6,6'-hexafluorobiphenyl-3,3',4,4'-tetracarboxylate (4).**



Ester **1** (0.294 g, 1 mmol), zinc dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL) were placed in an oven-dried 8 mL vial with a screw cap containing a stirring bar, purged with argon and closed with cap. The mixture was stirred at 70 ºC for 6 h. After cooled to room temperature, the reaction mixture was centrifugated at 4000 RPM for 20 min. The solution over zinc dust was separated, $CuCl_2$ (0.67, 5 mmol) was added and this was stirred at room temperature for 2 h. The reaction mixture was quenched with 2M HCl (50 mL), extracted with $CH_2Cl_2$ (3 x 5 mL) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate 10:1 as an eluent to afford compound **4** (0.218 g, yield 80%) as a colorless oil. IR (neat), ν, cm$^{-1}$: 2987, 2943, 2910, 1745, 1460, 1371, 1298, 1238, 1022, 943. UV (EtOH), $\lambda_{max}$, nm (log ε): 287 (3.99). $^{1}$H NMR (500 MHz, $CDCl_3$), δ: 1.34 (t, 6H, $CH_2C\underline{H}_3$, $^{3}J_{HH}$ = 7.0 Hz), 1.37 (t, 6H, $CH_2C\underline{H}_3$, $^{3}J_{HH}$ = 7.0 Hz), 4.38 (q, 4H, $C\underline{H}_2CH_3$, $^{3}J_{HH}$ = 7.0 Hz), 4.42 (q, 4H, $C\underline{H}_2CH_3$, $^{3}J_{HH}$ = 7.0 Hz). $^{13}$C {$^{1}$H} NMR (125.7 MHz, $CDCl_3$), δ: 13.98 (s, $4CH_2\underline{C}H_3$), 62.87 (s, $2\underline{C}H_2CH_3$), 63.11 (s, $2\underline{C}H_2CH_3$), 109.05 (dd, C-1,1', $^{2}J_{CF}$ = 22.0 Hz, $^{2}J_{CF}$ = 16.0 Hz), 117.14 (dd, $\underline{C}$-$CO_2Et$, $^{2}J_{CF}$ = 17.5 Hz, $^{3}J_{CF}$ = 3.0 Hz), 125.50 (d, $\underline{C}$-$CO_2Et$, $^{2}J_{CF}$ = 15.5 Hz), 145.00 (ddd, C-5,5', $^{1}J_{CF}$ = 256.0 Hz, $^{2}J_{CF}$ = 14.0 Hz, $^{4}J_{CF}$ = 2.5 Hz), 149.82 (ddd, C-6,6', ${}^1J_{CF}$ = 262.0 Hz, ${}^2J_{CF}$ = 16.0 Hz, ${}^3J_{CF}$ = 5.5 Hz), 153.24 (dm, C-2,2', ${}^1J_{CF}$ = 260.0 Hz), 161.75 (br. s, CO), 161.87 (br. s, CO). ${}^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -113.0 (m, 2F, F-2,2'), -126.1 (m, 2F, F-6,6'), -141.0 (m, 2F, F-5,5'). HRMS (EI), *m/z*: 550.1055 (calc. for $C_{24}H_{20}F_6O_8$ *m/z*: 550.1057). Found, %: C, 52.26; H, 3.90; F, 20.97. Calc. for $C_{24}H_{20}F_6O_8$, %: C, 52.37; H, 3.66; F, 20.71.

### 2,2',5,5',6,6'-Hexafluorobiphenyl-3,3',4,4'-tetracarboxylic acid (5).



To compound **4** (0.403 g, 0.73 mmol) were added AcOH (30 mL), $H_2O$ (10 mL), conc. $H_2SO_4$ (10 mL) and the resulting mixture was heated at 130 ºC for 15 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure at 80 ºC, and to the residue was added $H_2O$ (50 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure and drying of the residue at 110 ºC in oven, compound **5** was obtained (0.311 g, yield 97%). Light gray solid, mp 221–223 °C (226–228 °C).[S5] IR (KBr), ν, $cm^{-1}$: 3010, 2897, 2617, 1722, 1483, 1458, 1423, 1354, 1269, 1101, 1059, 935, 766, 725, 600. UV (EtOH), $\lambda_{max}$, nm (log ε): 284 (3.88). ${}^1$H NMR (300 MHz, $CCl_4$–acetone-$d_6$), δ: 8.87 (br. s, COOH). ${}^{13}$C {${}^1$H} NMR (125.7 MHz, DMSO-$d_6$), δ: 107.84 (dd, C-1,1', ${}^2J_{CF}$ = 22.0 Hz, ${}^2J_{CF}$ = 16.0 Hz), 118.17 (d, $\underline{C}$-COOH, ${}^2J_{CF}$ = 18.0 Hz), 126.05 (d, $\underline{C}$-COOH, ${}^2J_{CF}$ = 15.5 Hz), 144.05 (dd, C-5,5', ${}^1J_{CF}$ = 251.0 Hz, ${}^2J_{CF}$ = 13.0 Hz), 148.61 (dd, C-6,6', ${}^1J_{CF}$ = 258.0 Hz, ${}^2J_{CF}$ = 15.0 Hz), 152.04 (d, C-2,2', ${}^1J_{CF}$ = 256.0 Hz), 162.81 (s, CO), 163.03 (s, CO). ${}^{19}$F NMR (282.4 MHz, DMSO-$d_6$), δ: -114.6 (m, 2F, F-2,2'), -127.6 (m, 2F, F-6,6'), -141.8 (m, 2F, F-5,5'). Found, %: C, 44.20; H, 1.20; F, 25.85. Calc. for $C_{16}H_4F_6O_8$, %: C, 43.86; H, 0.92; F, 26.01.

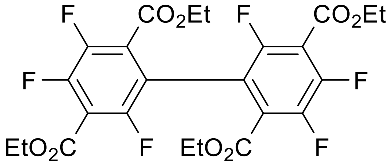
### Gram-scale synthesis of tetraethyl 2,2',5,5',6,6'-hexafluorobiphenyl-3,3',4,4'-tetracarboxylate (4)

To solution of organozinc compounds **2a,b**, obtained as described above from compound **1** (2.94 g, 10 mmol), Zn dust (1.96 g, 30 mmol), $SnCl_2$ (0.19 g, 1 mmol) and DMF (5 mL), was added $CuCl_2$ (1.61 g, 12 mmol) and stirred at room temperature for 2 h. The reaction mixture was quenched with $H_2O$ (50 mL), acidified with 2 M HCl (50 mL), extracted with $CH_2Cl_2$ (3 x 20 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate 10:1 as an eluent to afford compound **4** (2.15 g, yield 78%) as a colorless oil.

**Gram-scale synthesis of 2,2',5,5',6,6'-hexafluorobiphenyl-3,3',4,4'-tetracarboxylic acid (5)**

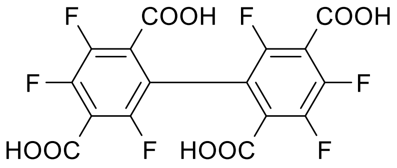
To compound **4** (2.15 g, 3.9 mmol) were added AcOH (130 mL), $H_2O$ (45 mL), conc. $H_2SO_4$ (45 mL) and the resulting mixture was heated at 130 °C for 15 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure at 80 °C and to the residue was added $H_2O$ (50 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure and drying of the residue at 110 °C in oven, the compound **5** was obtained (1.65 g, yield 97%).

**Tetraethyl 3,3',4,4',6,6'-hexafluorobiphenyl-2,2',5,5'-tetracarboxylate (7).**



Ester **6** (1.47 g, 5 mmol), zinc dust (0.98 g, 15 mmol) and DMF (5 mL) were placed in an oven-dried 8 mL vial with a screw cap containing a stirring bar, purged with argon and closed with cap. The mixture was stirred at 130 °C for 24 h. After cooled to room temperature, the reaction mixture was centrifugated at 4000 RPM for 20 min. The solution over zinc dust was separated, $CuCl_2$ (0.67, 5 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was quenched with 2M HCl (100 mL), extracted with $CH_2Cl_2$ (3 x 30 mL) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate 10:1 as an eluent to afford compound **7** (0.102 g, yield 7%) as a light-yellow oil. IR (neat), ν, cm$^{-1}$: 2987, 2941, 2912, 1740, 1634, 1464, 1369, 1329, 1298, 1288, 1192, 1070, 1016, 964, 922, 860, 719, 592. UV (EtOH), $\lambda_{max}$, nm (log ε): 290 (3.77). $^1$H NMR (500 MHz, $CDCl_3$), δ: 1.16 (t, 6H, $CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz), 1.38 (t, 6H, $CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz), 4.21 (m, 4H, $C\underline{H}_2CH_3$), 4.43 (q, 4H, $C\underline{H}_2CH_3$, $^3J_{HH}$ = 7.0 Hz). $^{13}$C {$^1$H} NMR (125.7 MHz, $CDCl_3$), δ: 13.82 (s, $2CH_2\underline{C}H_3$), 14.14 (s, $2CH_2\underline{C}H_3$), 62.79 (s, $2\underline{C}H_2CH_3$), 63.08 (s, $2\underline{C}H_2CH_3$), 114.76 (dd, C-5,5', $^2J_{CF}$ = 22.0 Hz, $^2J_{CF}$ = 15.5 Hz), 115.83 (dd, $J_{CF}$ = 21.0 Hz, $J_{CF}$ = 4.0 Hz), 125.16 (dm, $J_{CF}$ = 13.0 Hz), 145.66 (ddd, C-3,3', $^1J_{CF}$ = 257.0 Hz, $^2J_{CF}$ = 14.0 Hz, $^4J_{CF}$ = 4.0 Hz), 149.28 (ddd, C-4,4', $^1J_{CF}$ = 262.5 Hz, $^2J_{CF}$ = 15.5 Hz, $^3J_{CF}$ = 7.0 Hz), 152.76 (dt, C-6,6', $^1J_{CF}$ = 254.0 Hz, $^{3,4}J_{CF}$ = 3.5 Hz), 159.44 (s, CO), 161.31 (s, CO). $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -114.2 (d, 2F, F-6,6', $^5J_{FF}$ = 15.0 Hz), -131.1 (d, 2F, F-4,4', $^3J_{FF}$ = 22.0 Hz), -140.1 (dd, 2F, F-3,3', $^3J_{FF}$ = 22.0 Hz, $^5J_{FF}$ = 15.0 Hz). HRMS (EI), *m/z*: 550.1055 (calc. for $C_{24}H_{20}F_6O_8$ *m/z*: 550.1057). Found, %: C, 52.69; H, 3.81; F, 20.53. Calc. for $C_{24}H_{20}F_6O_8$, %: C, 52.37; H, 3.66; F, 20.71.

### 3,3',4,4',6,6'-Hexafluorobiphenyl-2,2',5,5'-tetracarboxylic acid (8).



To compound **7** (0.066 g, 0.12 mmol) were added AcOH (30 mL), $H_2O$ (10 mL), conc. $H_2SO_4$ (10 mL) and the resulting mixture was heated at 130 ºC for 15 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure at 80 ºC and to the residue was added $H_2O$ (50 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure and drying of the residue at 110 ºC in oven, compound **8** was obtained (0.051 g, yield 96%). Light beige solid, mp 265–267 ºC. IR (KBr), ν, $cm^{-1}$: 3012, 2928, 2642, 1724, 1635, 1473, 1404, 1329, 1286, 1215, 1076, 1070, 1014, 968, 910, 843, 758, 706, 690. UV (EtOH), $\lambda_{max}$, nm (log ε): 280 (3.58). $^1H$ NMR (300 MHz, $CCl_4$–acetone-$d_6$), δ: 8.90 (br. s, COOH). $^{13}C$ {$^1H$} NMR (100.6 MHz, DMSO-$d_6$), δ: 115.06 (dd, C-5,5', $^2J_{CF}$ = 23.5 Hz, $^2J_{CF}$ = 17.0 Hz), 115.42 (d, $J_{CF}$ = 21.0 Hz), 125.93 (d, $J_{CF}$ = 14.0 Hz), 144.51 (ddd, C-3,3', $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 14.0 Hz, $^4J_{CF}$ = 3.0 Hz), 147.92 (ddd, C-4,4', $^1J_{CF}$ = 258.0 Hz, $^2J_{CF}$ = 15.5 Hz, $^3J_{CF}$ = 7.5 Hz), 151.79 (d, C-6,6', $^1J_{CF}$ = 254.0 Hz), 160.34 (s, CO), 162.25 (s, CO). $^{19}F$ NMR (282.4 MHz, DMSO-$d_6$), δ: -115.6 (d, 2F, F-6,6', $^5J_{FF}$ = 15.0 Hz), -132.6 (d, 2F, F-4,4', $^3J_{FF}$ = 21.5 Hz), -141.1 (dd, 2F, F-4,4', $^3J_{FF}$ = 21.5 Hz, $^5J_{FF}$ = 15.0 Hz). Found, %: C, 44.17; H, 1.29; F, 25.78. Calc. for $C_{16}H_4F_6O_8$, %: C, 43.86; H, 0.92; F, 26.01.

### Synthesis of diethyl 2,4,5,6-tetrafluoroisophthalate (9) and diethyl 2,3,5,6-tetrafluoroterephthalate (6).

A mixture of perfluoro *m*- and *p*-xylenes (20 g, 70 mmol) and oleum (50 mL) was heated with stirring at 135 ºC for 18 h. The reaction mixture was poured on an ice (250 g), extracted with diethyl ether (3 x 100 mL), the combined organic layer was dried over $MgSO_4$. The solvent was evaporated to give a mixture of 2,4,5,6-tetrafluoroisophthalic and 2,3,5,6-tetrafluoroterephthalic acids (16.20 g, yield 97%) in 2.6 : 1 ratio ($^{19}F$ NMR). To this mixture $SOCl_2$ (30 mL) was added, and this was heated with stirring at 90 ºC for 4 h. After cooling to room temperature, the excess of thionyl chloride was distilled off *in vacuo* and to the residue EtOH (30 mL) was added. The obtained solution was heated with stirring at 90 ºC for 6 h and quenched with saturated solution of $NaHCO_3$ (150 mL), extracted with $CH_2Cl_2$ (3 x 50 mL) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by vacuum distillation (oil bath temperature 165 ºC, 7 Torr) to afford a mixture of esters **9** and **6** (16.64 g, yield 83%) in 2.6 : 1 ratio ($^{19}F$ NMR).

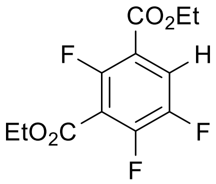
Compound **9** $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -114.4 (d, 1F, F-2, $^5J_{FF}$ = 12.0 Hz), -128.0 (d, 2F, F-4,6, $^3J_{FF}$ = 21.5 Hz), -163.1 (dt, 1F, F-5, $^3J_{FF}$ = 21.5 Hz, $^5J_{FF}$ = 12.0 Hz).[S6] Compound **6** $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -139.7 (s, 4F).

**Reaction diethyl 2,4,5,6-tetrafluoroisophthalate (9) with Zn.**

Ester **9** (0.405 g of mixture, 1 mmol), zinc dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL) were placed in an oven-dried 8 mL vial with a screw cap containing a stirring bar, purged with argon and closed with cap. The mixture was stirred at 25 ºC for 24 h, then the reaction mixture was centrifugated at 4000 RPM for 20 min. The solution over zinc dust was separated and analyzed by $^{19}$F NMR spectroscopy. The conversion of compound **9** to [2,4-bis(ethoxycarbonyl)-3,5,6-trifluorophenyl]zinc chloride (**10a**) and bis[2,4-bis(ethoxycarbonyl)-3,5,6-trifluorophenyl]zinc (**10b**) was 96%, the mixture also contained 4% of diethyl 2,4,5-trifluoroisophthalate (**11**).

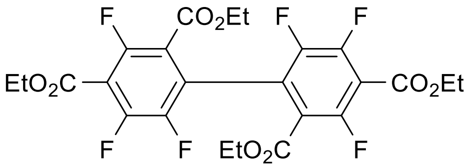
Compound **10a** $^{19}$F NMR (282.4 MHz, DMF–$CDCl_3$), δ: -113.2 (m, 1F, F-3), -118.0 (dd, 1F, F-6, $^3J_{FF}$ = 32.5 Hz, $^5J_{FF}$ = 22.0 Hz), -130.6 (d, 1F, F-5, $^3J_{FF}$ = 32.5 Hz). Compound **10b** $^{19}$F NMR (282.4 MHz, DMF–$CDCl_3$), δ: -110.2 (dd, 2F, F-3, $^5J_{FF}$ = 24.0 Hz, $^4J_{FF}$ = 3.0 Hz), -117.2 (dd, 2F, F-6, $^3J_{FF}$ = 33.5 Hz, $^5J_{FF}$ = 24.0 Hz), -128.9 (dd, 2F, F-5, $^3J_{FF}$ = 33.5 Hz, $^4J_{FF}$ = 3.0 Hz).

**Diethyl 2,4,5-trifluoroisophthalate (11)**



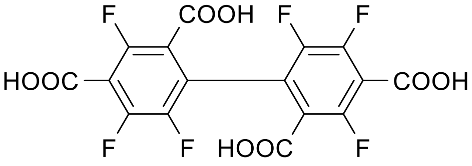
A solution of organozinc compounds **10a,b**, obtained as described above from compound **9** (0.405 g of mixture, 1 mmol), Zn dust (0.196 g, 3 mmol), $SnCl_2$ (0.019 g, 0.1 mmol) and DMF (1 mL), was quenched with 2M HCl (30 mL), extracted with $CH_2Cl_2$ (3 x 5 mL), the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the mixture (0.309 g) contained ($^{19}$F NMR) 74% of compound **11** and 26% of ester **6** was obtained. Compound **11**. $^1$H NMR (300 MHz, $CDCl_3$), δ: 7.78 (ddd, 1H, $H_{ar}$, $^3J_{HF}$ = 10.0 Hz, $^4J_{HF}$ = 8.5 Hz, $^4J_{HF}$ = 6.5 Hz). $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -111.9 (dt, 1F, F-2, $^5J_{FF}$ = 16.5 Hz, $^4J_{FFH}$ = 5.5 Hz), -127.4 (ddd, 1F, F-4, $^3J_{FF}$ = 21.5 Hz, $^4J_{FH}$ = 8.5 Hz, $^4J_{FF}$ = 5.0 Hz), -140.8 (ddd, 1F, F-5, $^3J_{FF}$ = 21.5 Hz, $^5J_{FF}$ = 16.5 Hz, $^3J_{FH}$ = 10.0 Hz).

### Tetraethyl 3,3',5,5',6,6'-hexafluorobiphenyl-2,2',4,4'-tetracarboxylate (12).



To a solution of organozinc compounds **10a,b**, obtained from compound **9** (0.588 g of mixture, 2.0 mmol), Zn dust (0.196 g, 6.0 mmol), $SnCl_2$ (0.038 g, 0.2 mmol) and DMF (2 mL), was added $CuCl_2$ (0.322 g, 2.4 mmol), and this was stirred at room temperature for 2 h. The reaction mixture was quenched with 2M HCl (50 mL), extracted with $CH_2Cl_2$ (3 x 5 mL) and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate 10:1 as an eluent to afford compound **12** (0.377 g, yield 69%) as a colorless oil. IR (neat), ν, cm$^{-1}$: 2987, 2941, 2910, 2875, 1739, 1631, 1595, 1471, 1444, 1371, 1309, 1234, 1095, 1020, 970, 950, 862, 820, 775, 744, 673. UV (EtOH), $\lambda_{max}$, nm (log ε): 285 (3.85). $^1$H NMR (600 MHz, $CDCl_3$), δ: 1.14 (t, 6H, $CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz), 1.38 (t, 6H, $CH_2C\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz), 4.17 (m, 4H, $C\underline{H}_2CH_3$), 4.44 (q, 4H, $C\underline{H}_2CH_3$, $^3J_{HH}$ = 7.0 Hz). $^{13}$C {$^1$H} NMR (150.9 MHz, $CDCl_3$), δ: 13.74 (s, $2CH_2\underline{C}H_3$), 14.07 (s, $2CH_2\underline{C}H_3$), 62.48 (s, $2\underline{C}H_2CH_3$), 63.00 (s, $2\underline{C}H_2CH_3$), 114.62 (dd, C-4,4', $^2J_{CF}$ = 21.5 Hz, $^2J_{CF}$ = 15.5 Hz), 117.91 (dd, $J_{CF}$ = 17.0 Hz, $J_{CF}$ = 4.0 Hz), 124.04 (dm, $J_{CF}$ = 16.0 Hz), 144.58 (ddd, C-6,6', $^1J_{CF}$ = 249.0 Hz, $^2J_{CF}$ = 13.5 Hz, $^4J_{CF}$ = 3.5 Hz), 149.70 (ddd, C-5,5', $^1J_{CF}$ = 264.0 Hz, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 7.0 Hz), 154.07 (dm, C-3,3', $^1J_{CF}$ = 263.0 Hz), 159.36 (s, CO), 161.46 (s, CO). $^{19}$F NMR (282.4 MHz, $CDCl_3$), δ: -113.6 (dd, 2F, F-3,3', $^5J_{FF}$ = 15.0 Hz, $^4J_{FF}$ = 3.5 Hz), -129.2 (dd, 2F, F-5,5', $^3J_{FF}$ = 22.0 Hz, $^4J_{FF}$ = 3.5 Hz), -139.1 (dd, 2F, F-6,6', $^3J_{FF}$ = 22.0 Hz, $^5J_{FF}$ = 15.0 Hz). HRMS (EI), *m/z*: 550.1055 (calc. for $C_{24}H_{20}F_6O_8$ *m/z*: 550.1057). Found, %: C, 52.90; H, 3.45; F, 20.25. Calc. for $C_{24}H_{20}F_6O_8$, %: C, 52.37; H, 3.66; F, 20.71.

### 3,3',5,5',6,6'-Hexafluorobiphenyl-2,2',4,4'-tetracarboxylic acid (13).



To compound **12** (0.403 g, 0.73 mmol) were added AcOH (30 mL), $H_2O$ (10 mL), conc. $H_2SO_4$ (10 mL) and the resulting mixture was heated at 130 ºC for 15 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure at 80 ºC and to the residue was added $H_2O$ (50 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure and drying of the residue at 110 °C in oven, the compound **13** was obtained (0.311 g, yield 97%). Light gray solid, mp 308–310 ºC. IR (KBr), ν, cm$^{-1}$: 3024, 2889, 2677, 2557, 1724, 1709, 1630, 1479, 1458, 1431, 1398, 1306, 1265, 1209, 1109, 974, 947, 904, 737, 656. UV (EtOH), $\lambda_{max}$, nm (log ε): 282 (3.76). $^1$H NMR (300 MHz, $CCl_4$–acetone-*d*$_6$), δ: 9.45 (br. s, COOH). $^{13}$C {$^1$H} NMR (100.6 MHz, DMSO-*d*$_6$), δ: 115.69 (dd, C-4,4', $^2J_{CF}$ = 23.5 Hz, $^2J_{CF}$ = 17.0 Hz), 119.39 (dd, $J_{CF}$ = 18.5 Hz, $J_{CF}$ = 3.5 Hz), 122.78 (dm, $J_{CF}$ = 16.0 Hz), 144.13 (ddd, C-6,6', $^1J_{CF}$

= 246.0 Hz, $^2J_{CF}$ = 13.5 Hz, $^4J_{CF}$ = 4.0 Hz), 148.09 (ddd, C-5,5', $^1J_{CF}$ = 258.0 Hz, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 8.0 Hz), 152.64 (dm, C-3,3', $^1J_{CF}$ = 257.0 Hz), 160.45 (s, CO), 162.69 (s, CO). $^{19}$F NMR (282.4 MHz, DMSO-$d_6$), δ: -115.3 (dd, 2F, F-3,3', $^5J_{FF}$ = 14.5 Hz, $^4J_{FF}$ = 3.0 Hz), -131.8 (dd, 2F, F-5,5', $^3J_{FF}$ = 24.0 Hz, $^4J_{FF}$ = 3.0 Hz), -139.7 (dd, 2F, F-6,6', $^3J_{FF}$ = 24.0 Hz, $^5J_{FF}$ = 14.5 Hz). Found, %: C, 43.50; H, 1.35; F, 25.55. Calc. for $C_{16}H_4F_6O_8$, %: C, 43.86; H, 0.92; F, 26.01.

**Gram-scale synthesis of tetraethyl 3,3',5,5',6,6'-hexafluorobiphenyl-2,2',4,4'-tetracarboxylate (12).**

To a solution of organozinc compounds **10a,b**, obtained as described above from compound **9** (4.05 g of mixture, 10 mmol), Zn dust (1.96 g, 30 mmol), $SnCl_2$ (0.19 g, 1 mmol) and DMF (5 mL), was added $CuCl_2$ (1.61 g, 12 mmol), and this was stirred at room temperature for 2 h. The reaction mixture was quenched with $H_2O$ (50 mL), acidified with 2 M HCl (50 mL), extracted with $CH_2Cl_2$ (3 x 20 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate 10:1 as an eluent to afford compound **12** (2.15 g, yield 78%) as a colorless oil.

**Gram-scale synthesis of 3,3',5,5',6,6'-hexafluorobiphenyl-2,2',4,4'-tetracarboxylic acid (13).**

To compound **12** (2.15 g, 3.9 mmol) were added AcOH (120 mL), $H_2O$ (40 mL), conc. $H_2SO_4$ (40 mL) and the resulting mixture was heated at 130 ºC for 15 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure at 80 °C and to the residue was added $H_2O$ (50 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure and drying of the residue at 110 °C in oven, the compound **13** was obtained (1.67 g, yield 98%).

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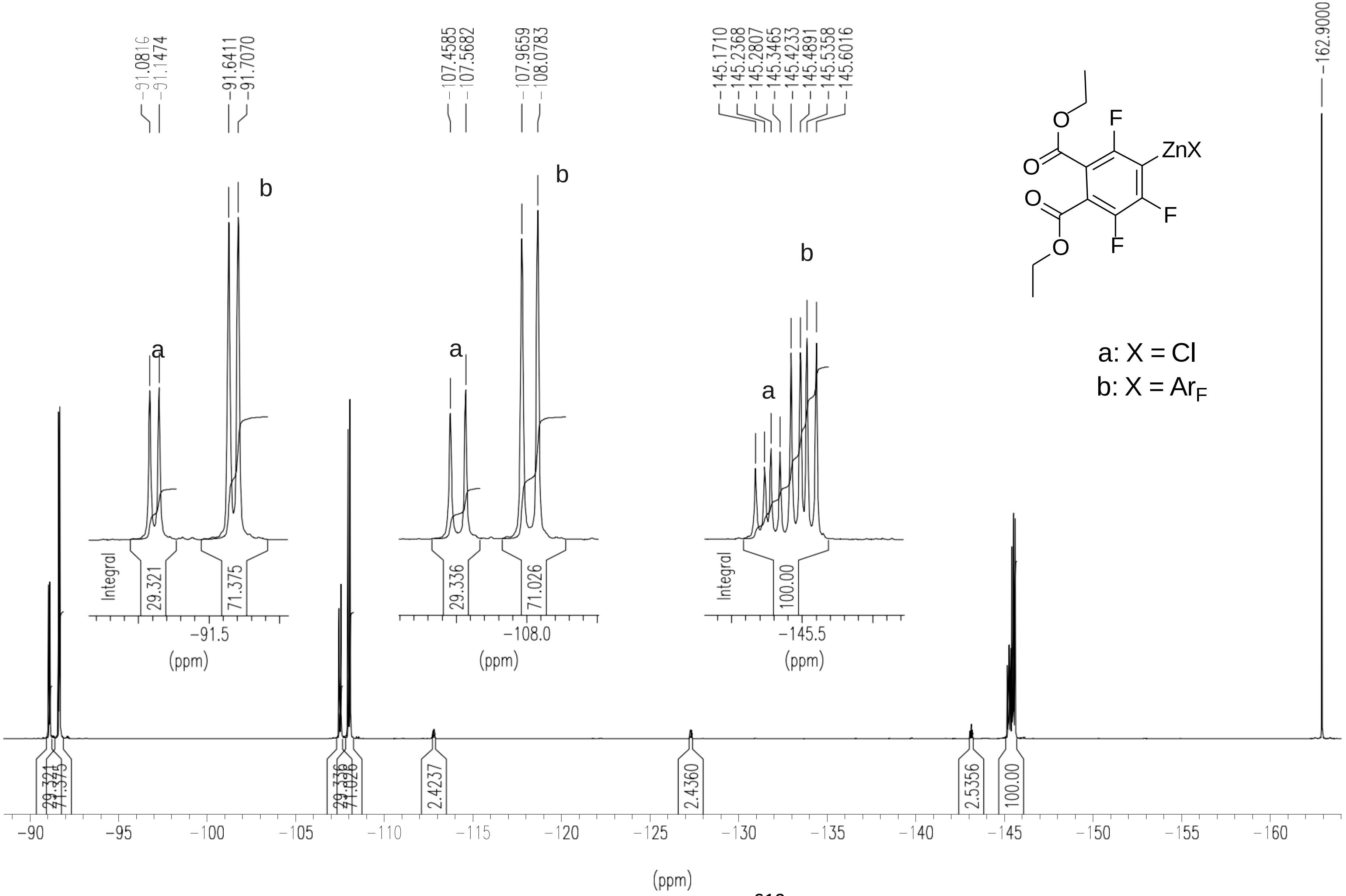
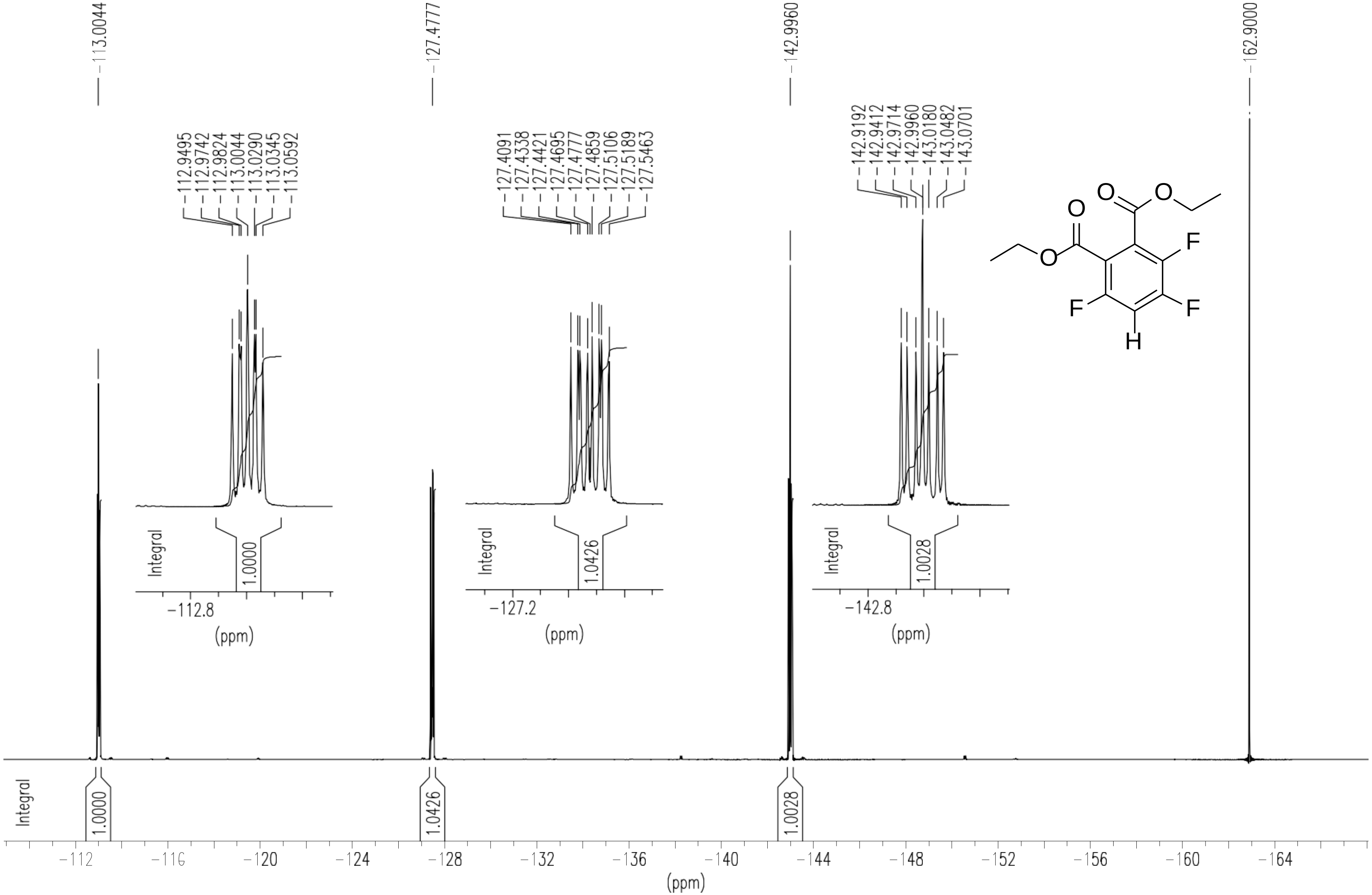
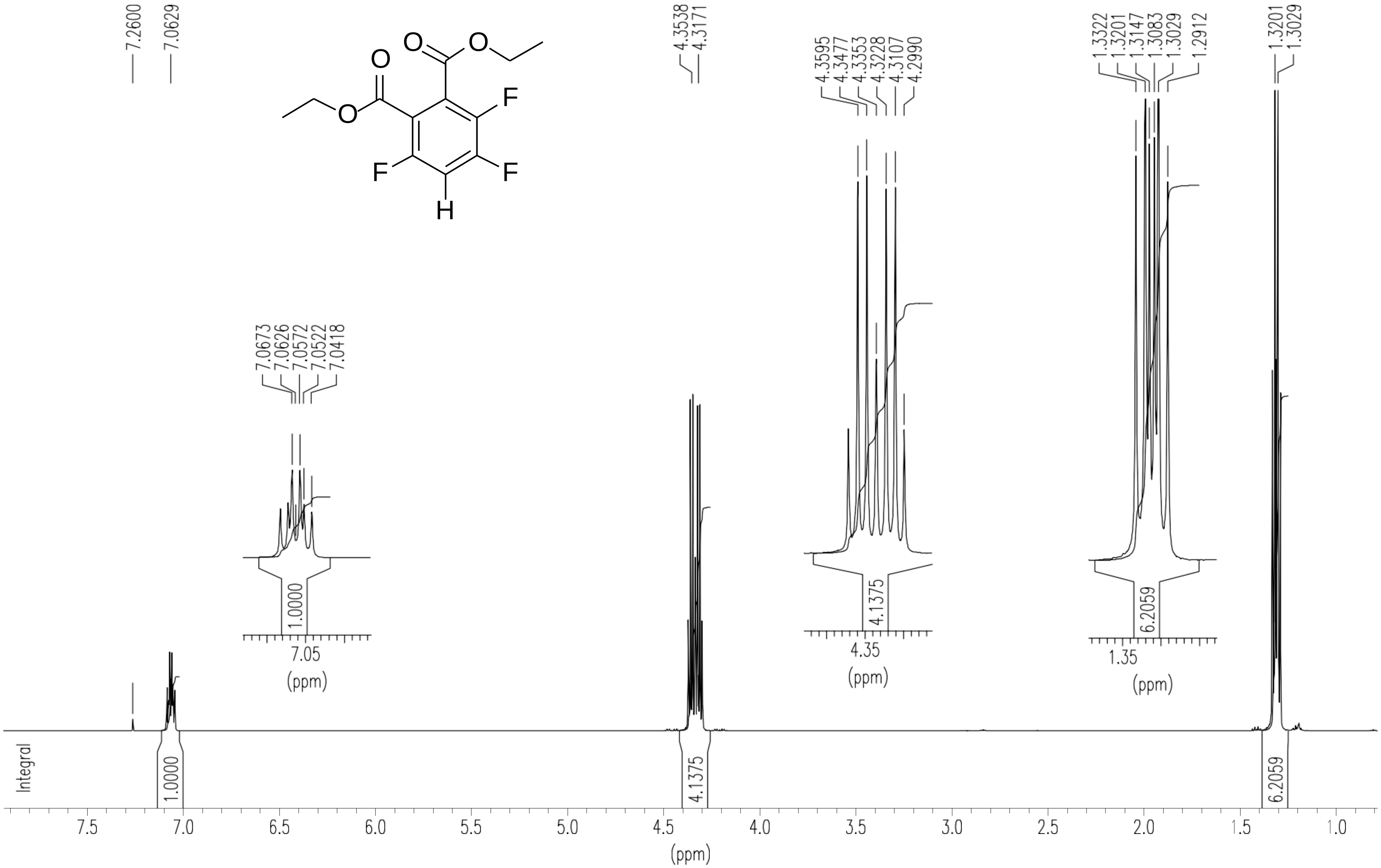
$^{19}$F NMR spectrum of compound **2a,b** (282.4 MHz, DMF-$CDCl_3$)



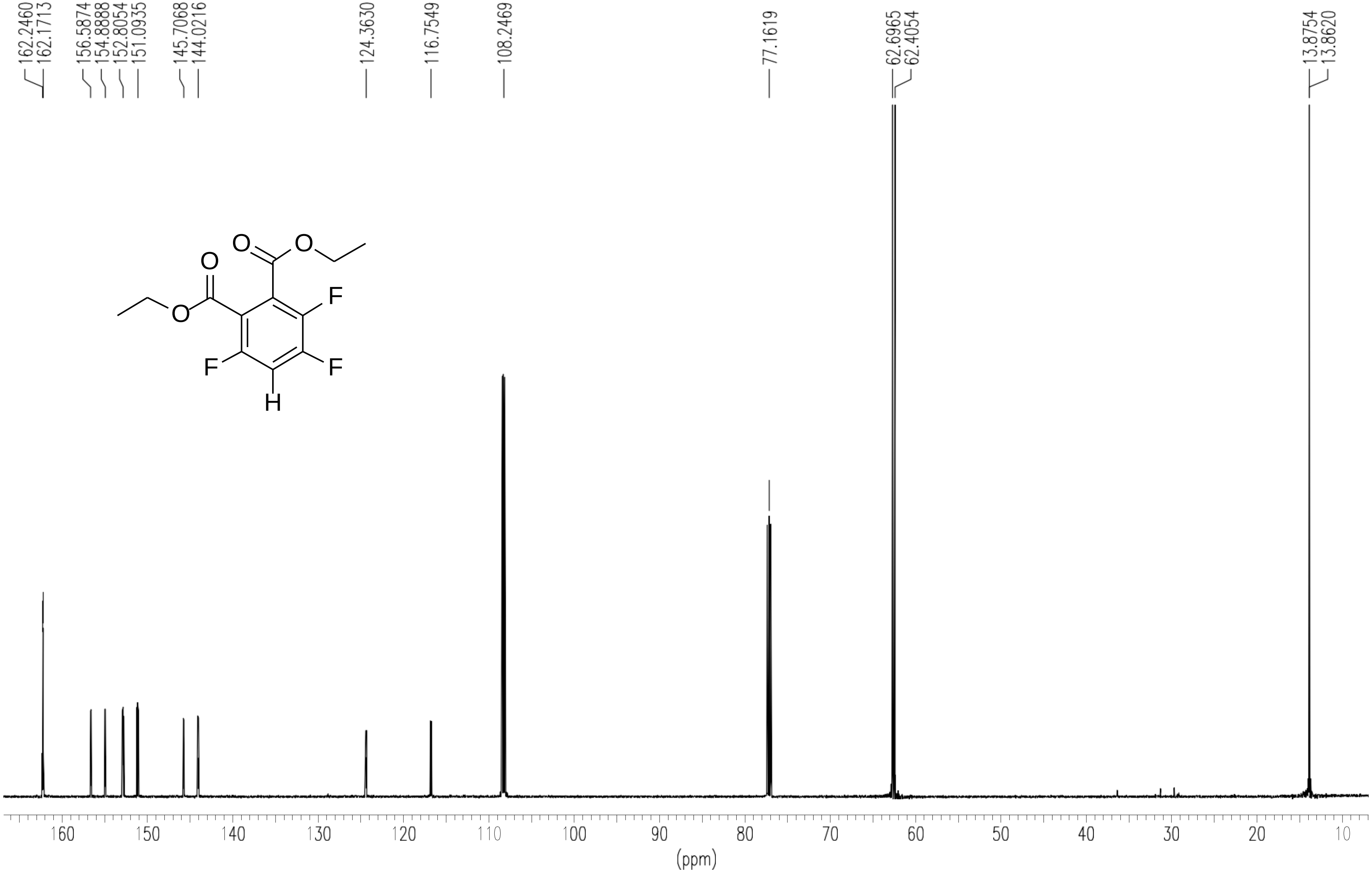
$^{19}$F NMR spectrum of compound **3** (282.4 MHz, $CDCl_3$)



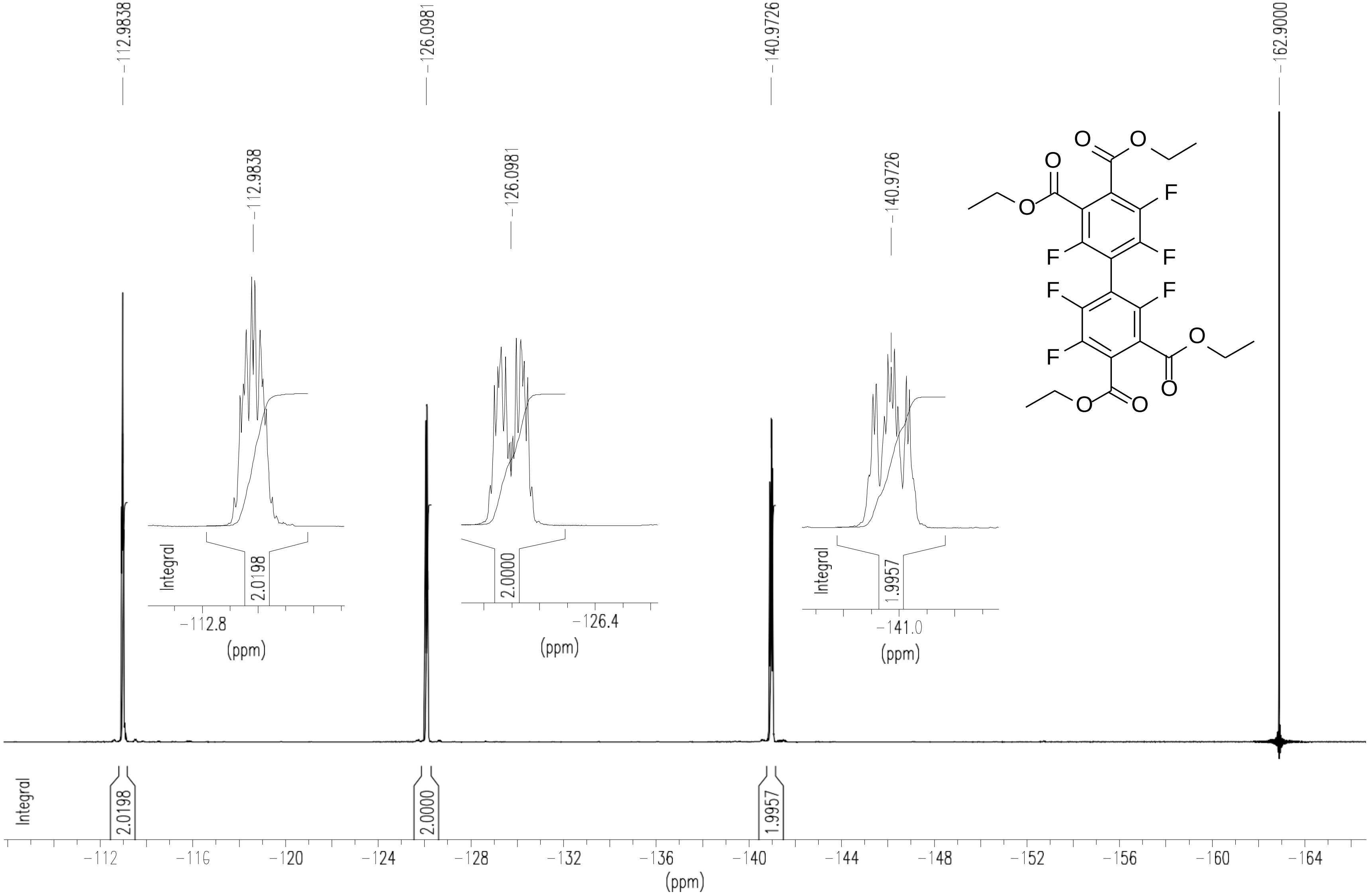
$^1$H NMR spectrum of compound **3** (600 MHz, $CDCl_3$)



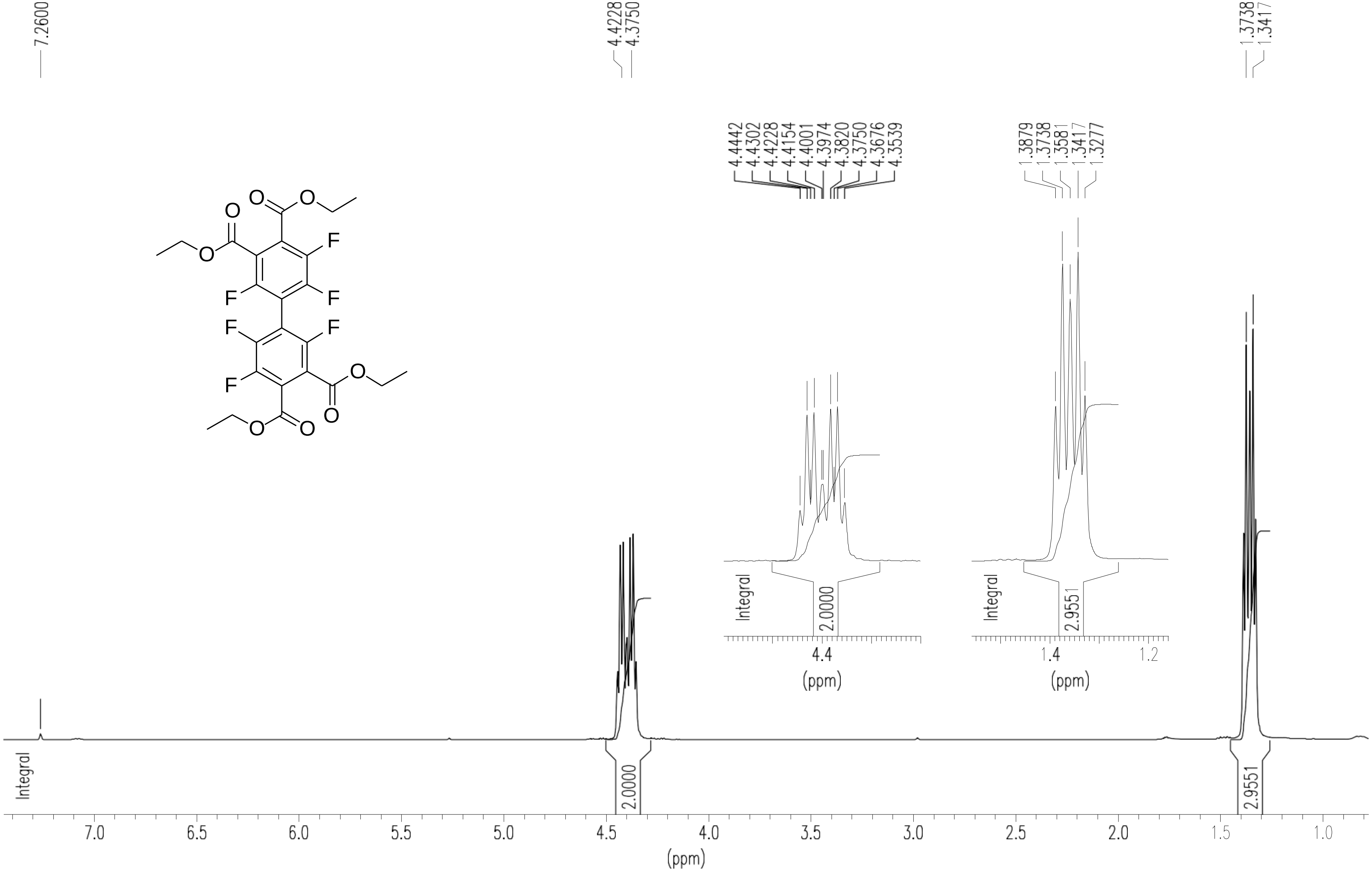
$^{13}$C NMR spectrum of compound **3** (150.9 MHz, $CDCl_3$)



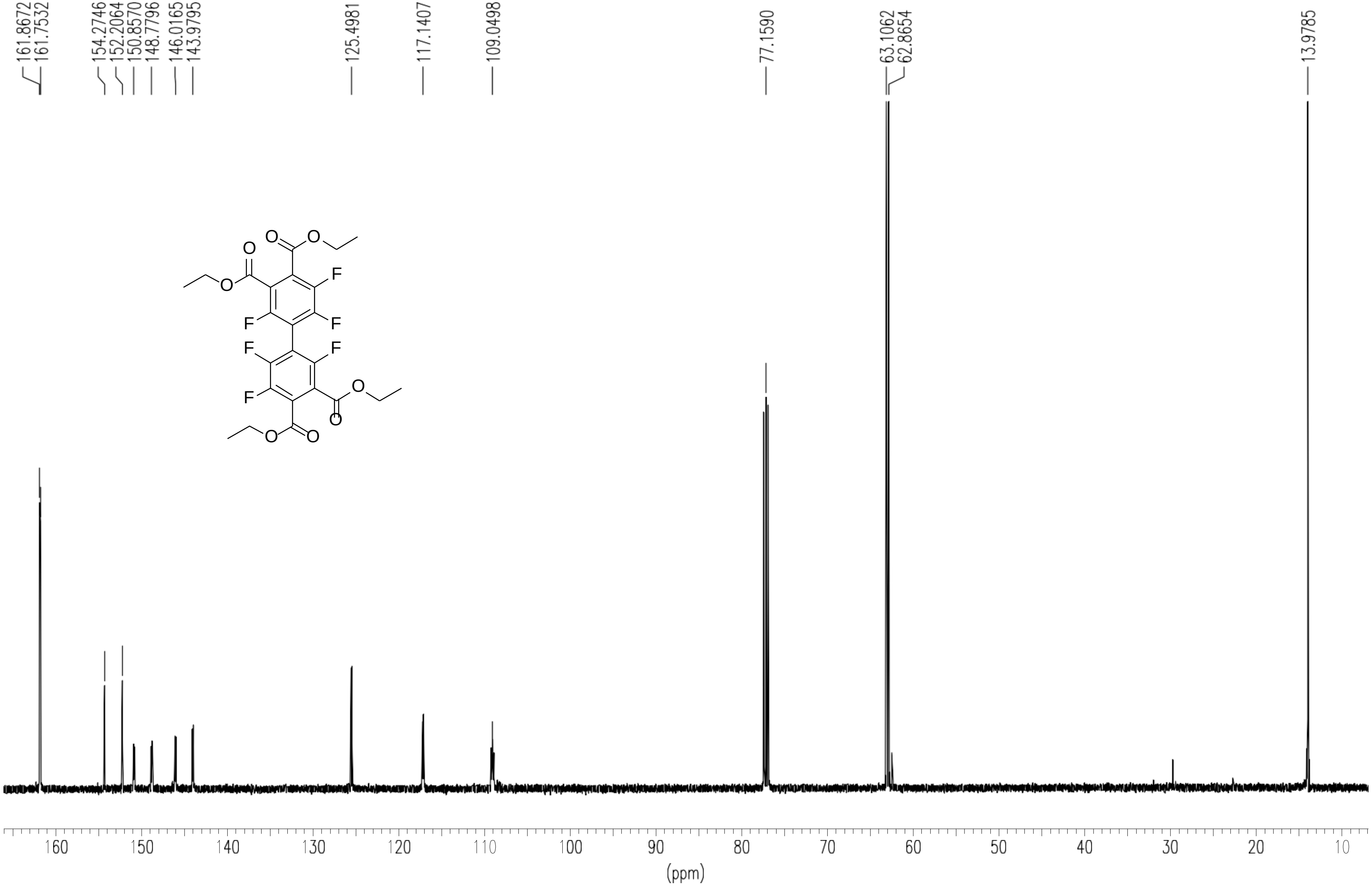
$^{19}$F NMR spectrum of compound **4** (282.4 MHz, $CDCl_3$)



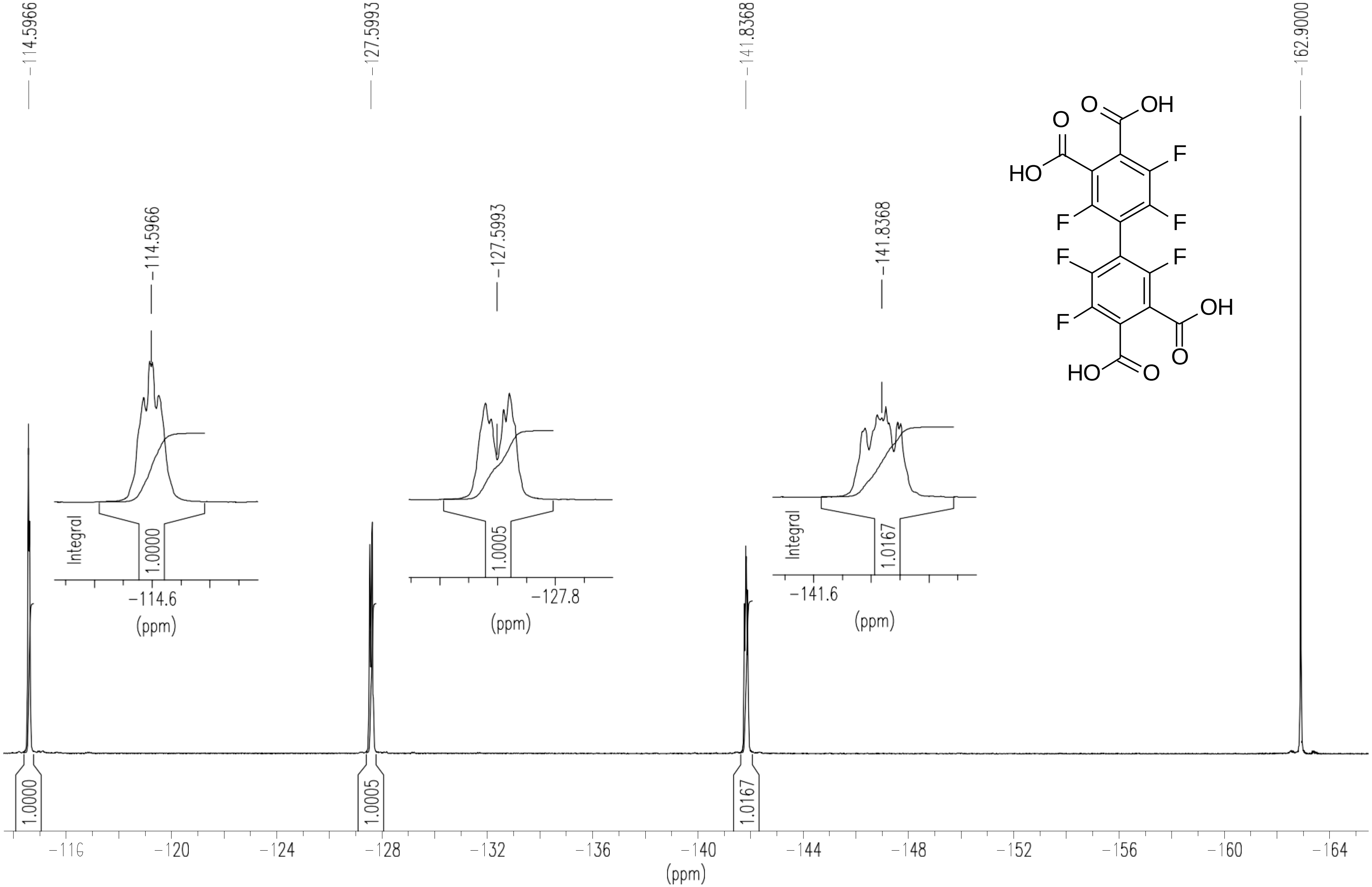
$^1$H NMR spectrum of compound **4** (500 MHz, $CDCl_3$)



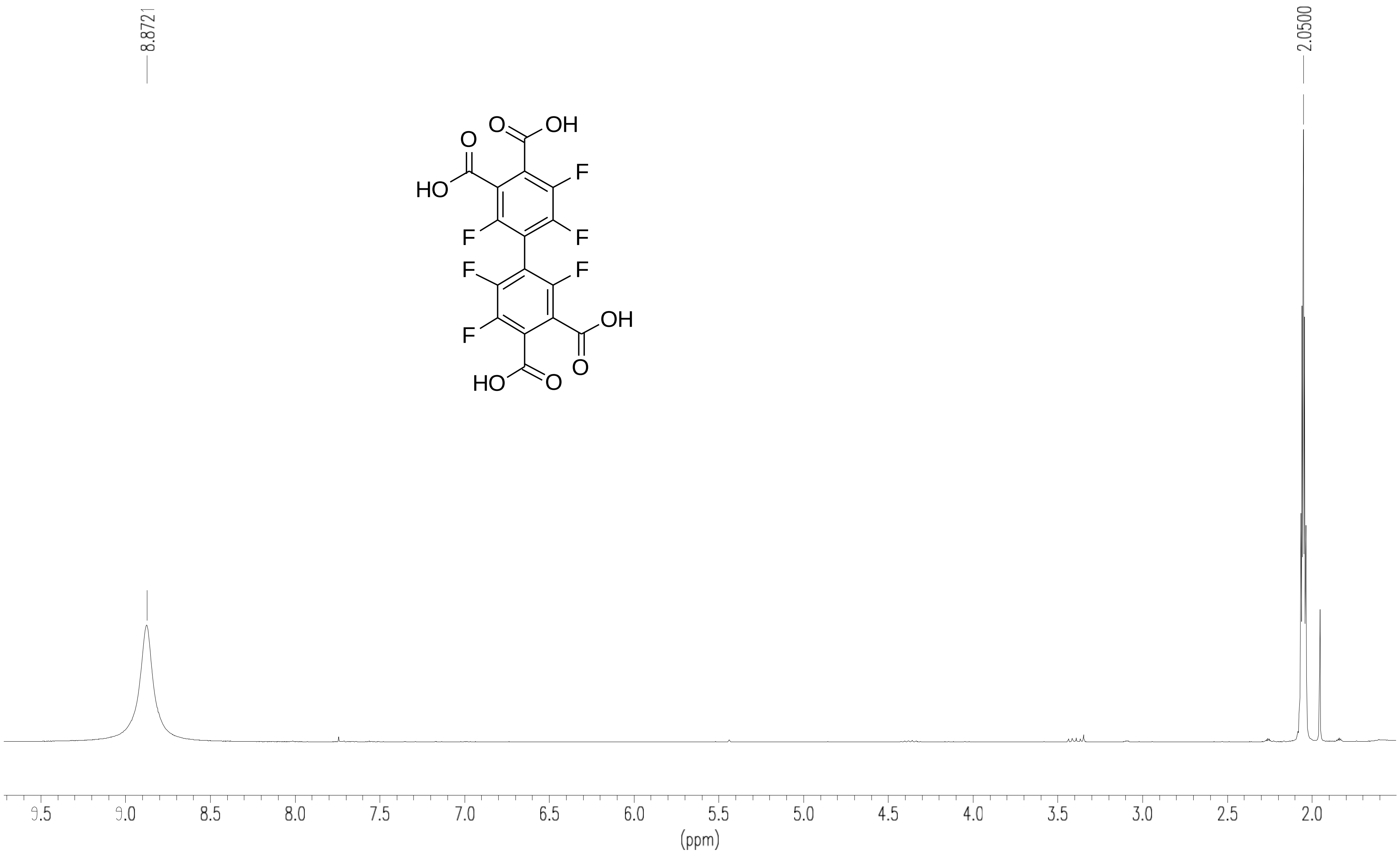
$^{13}$C NMR spectrum of compound **4** (125.8 MHz, CDCl$_3$)



$^{19}$F NMR spectrum of compound **5** (282.4 MHz, DMSO-$d_6$)



$^1$H NMR spectrum of compound **5** (300 MHz, $CCl_4$-acetone-$d_6$)



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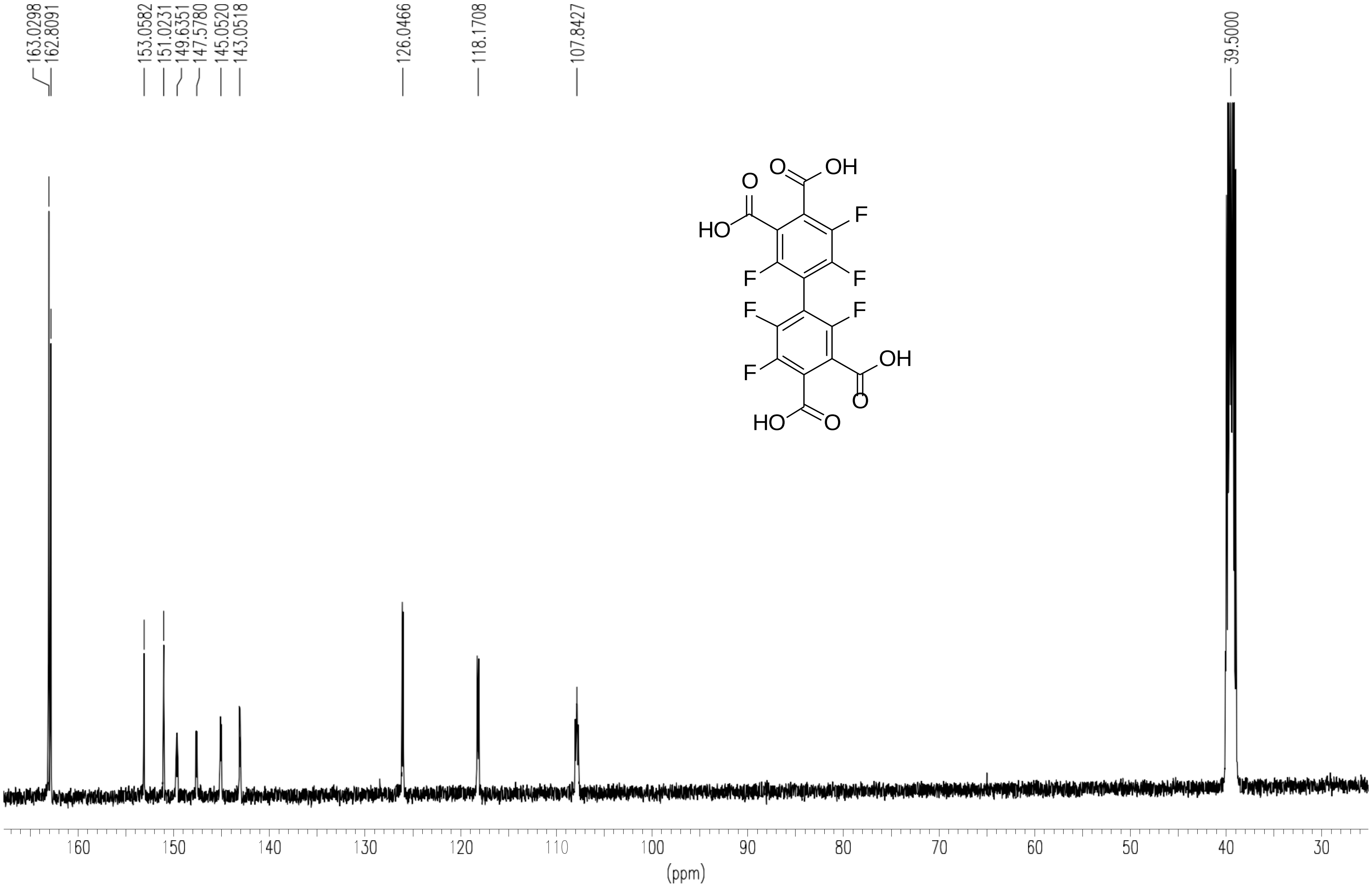

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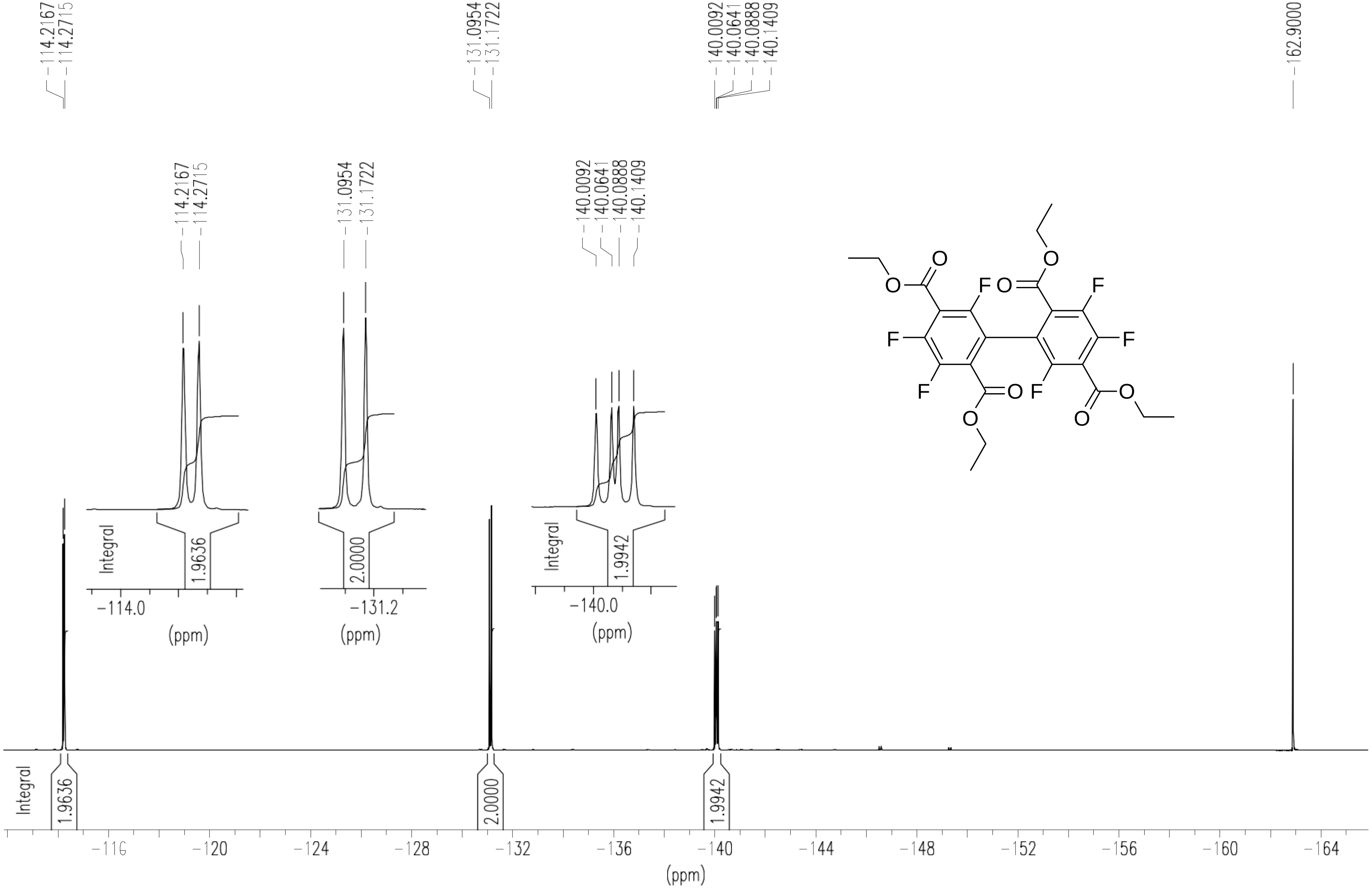
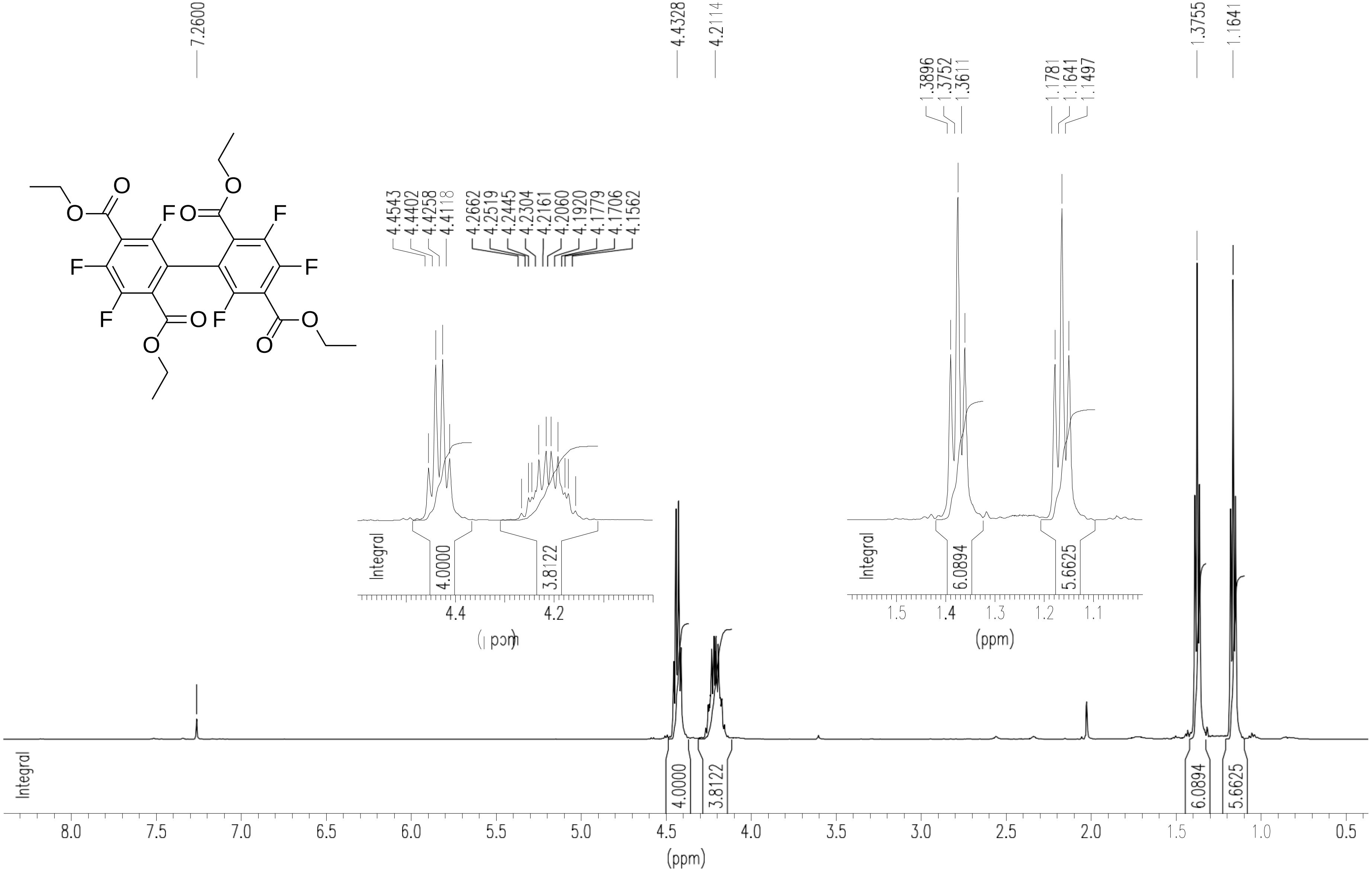
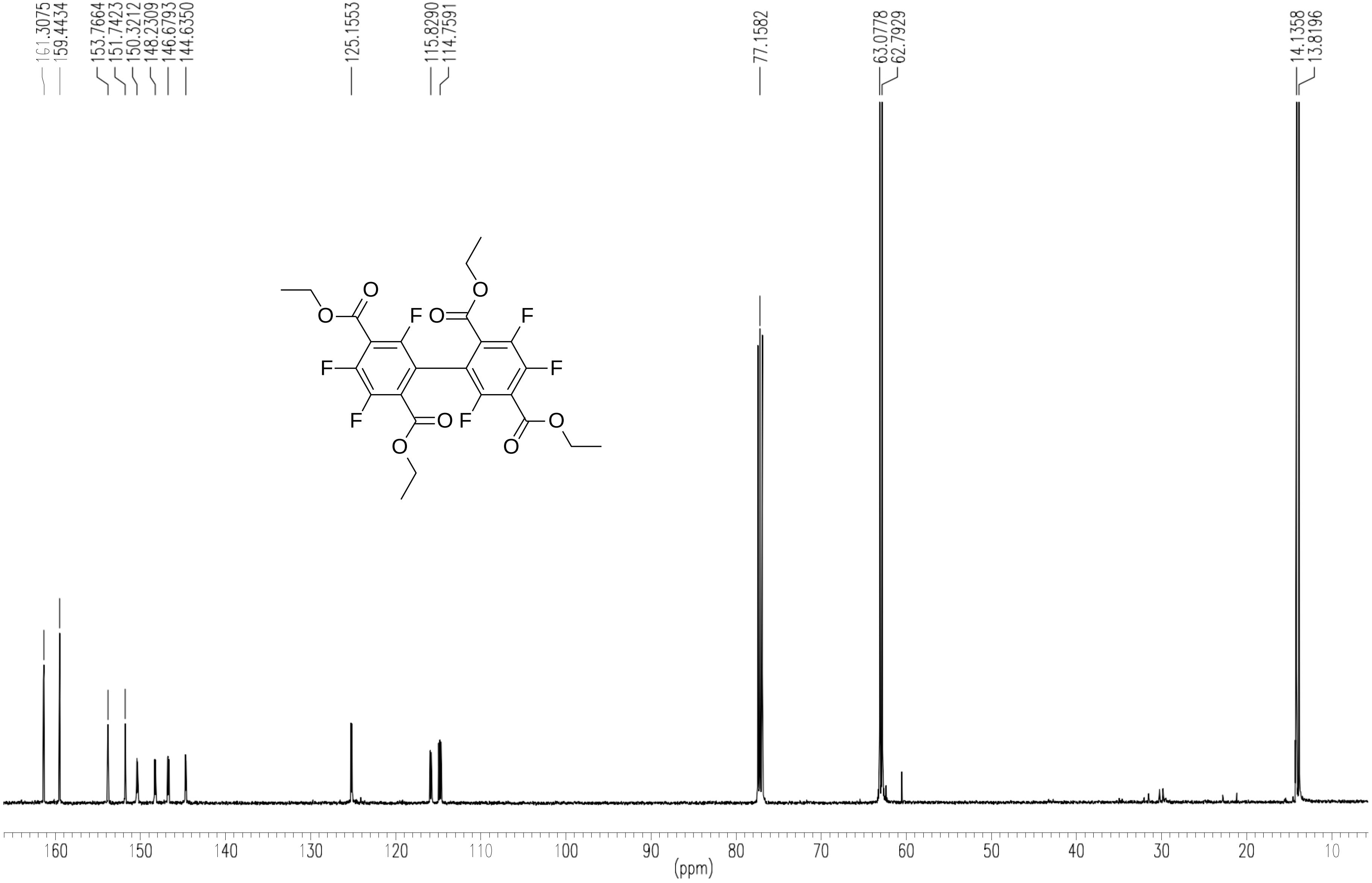


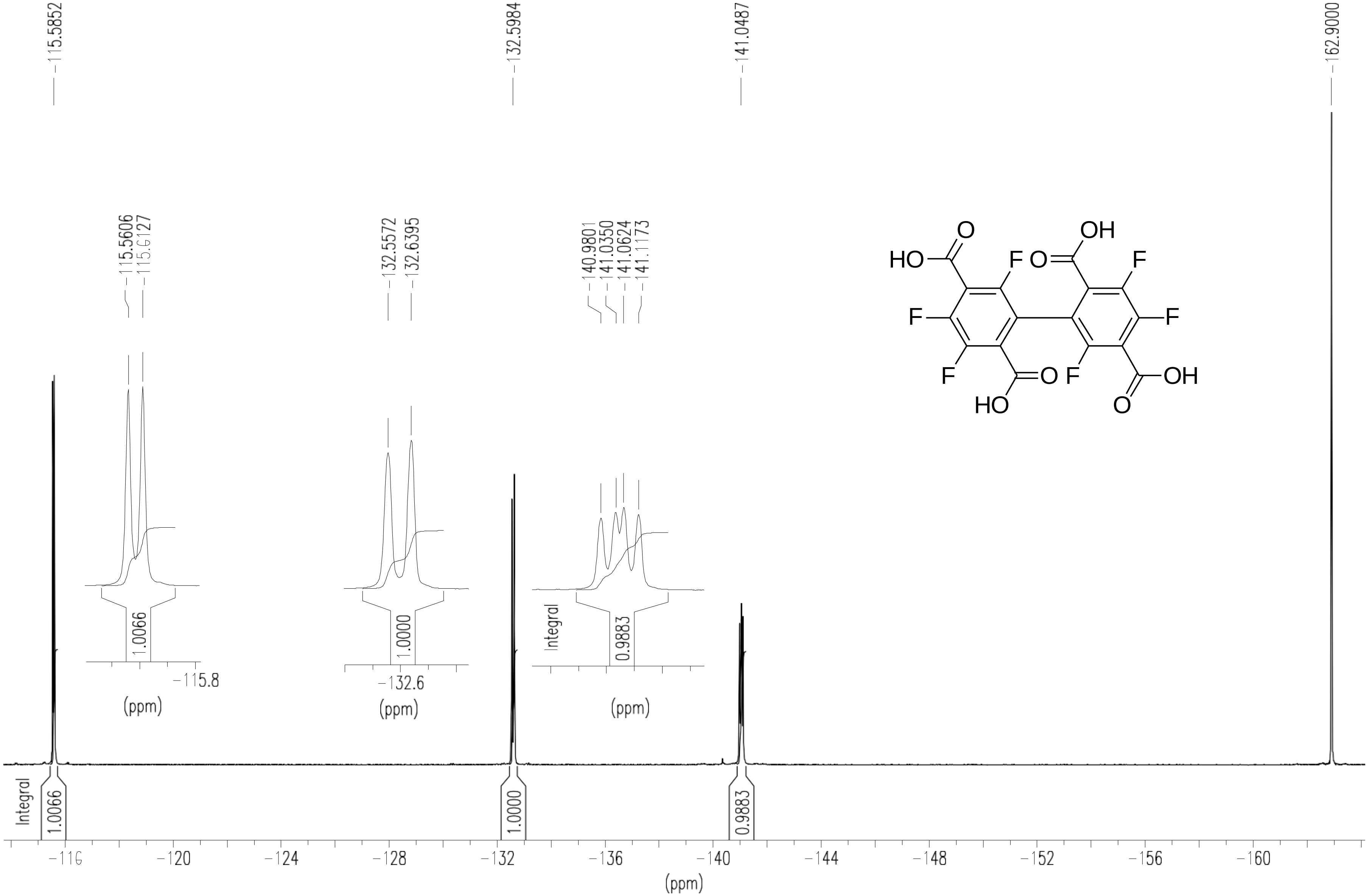
$^1$H NMR spectrum of compound **7** (500 MHz, $CDCl_3$)



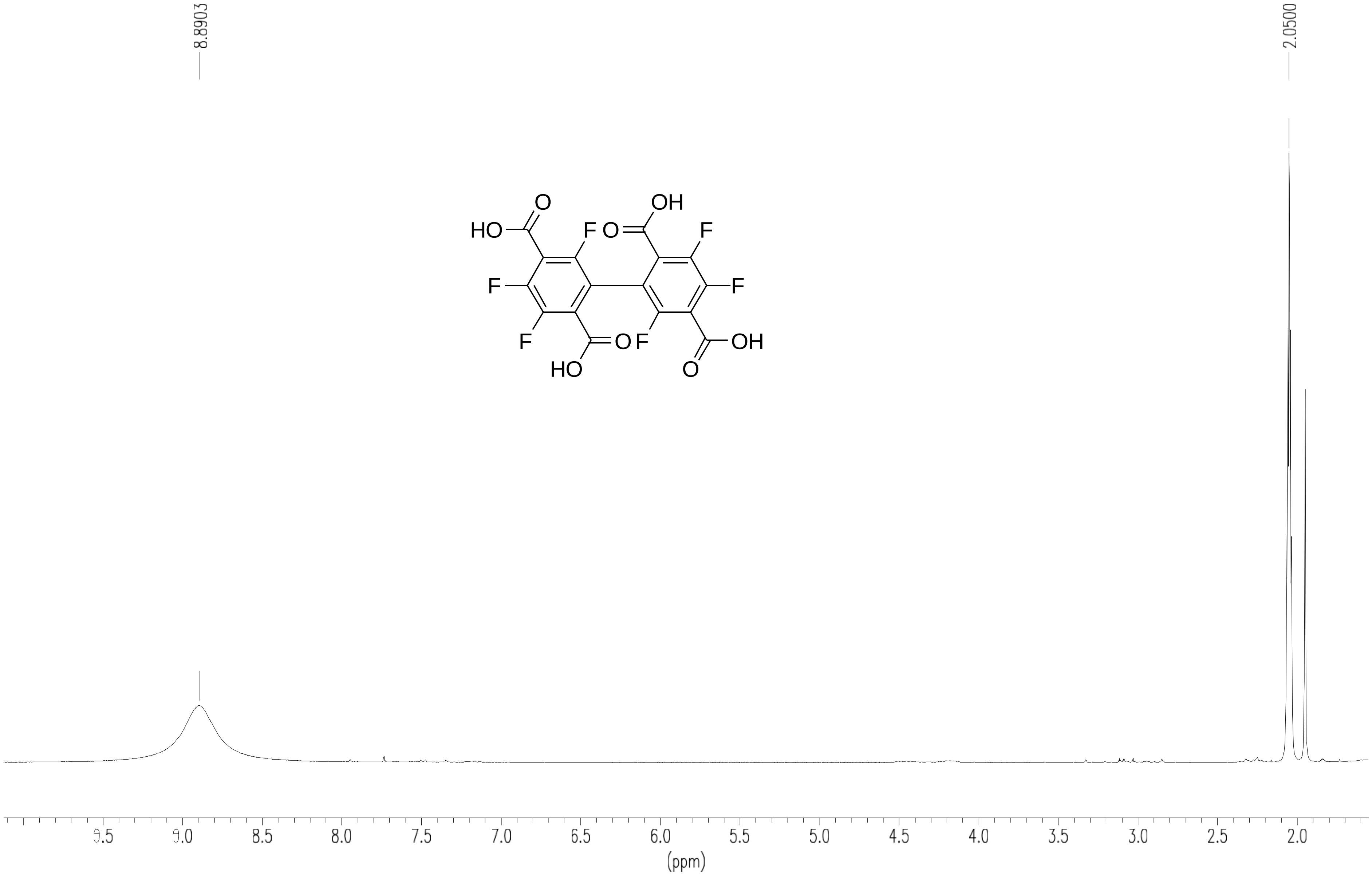
$^{13}$C NMR spectrum of compound **7** (125.8 MHz, CDCl$_3$)



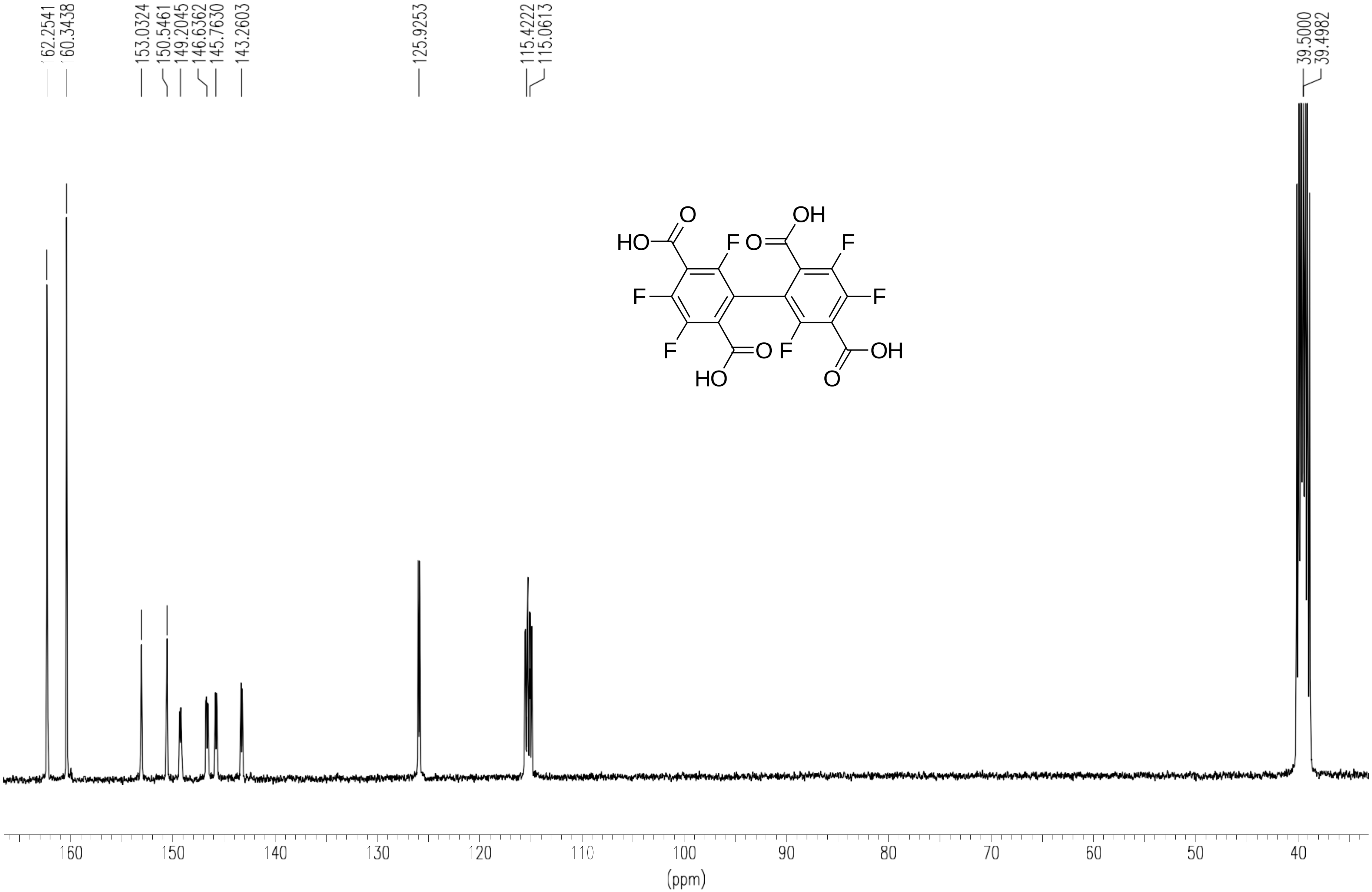
$^{19}$F NMR spectrum of compound **8** (282.4 MHz, DMSO-$d_6$)



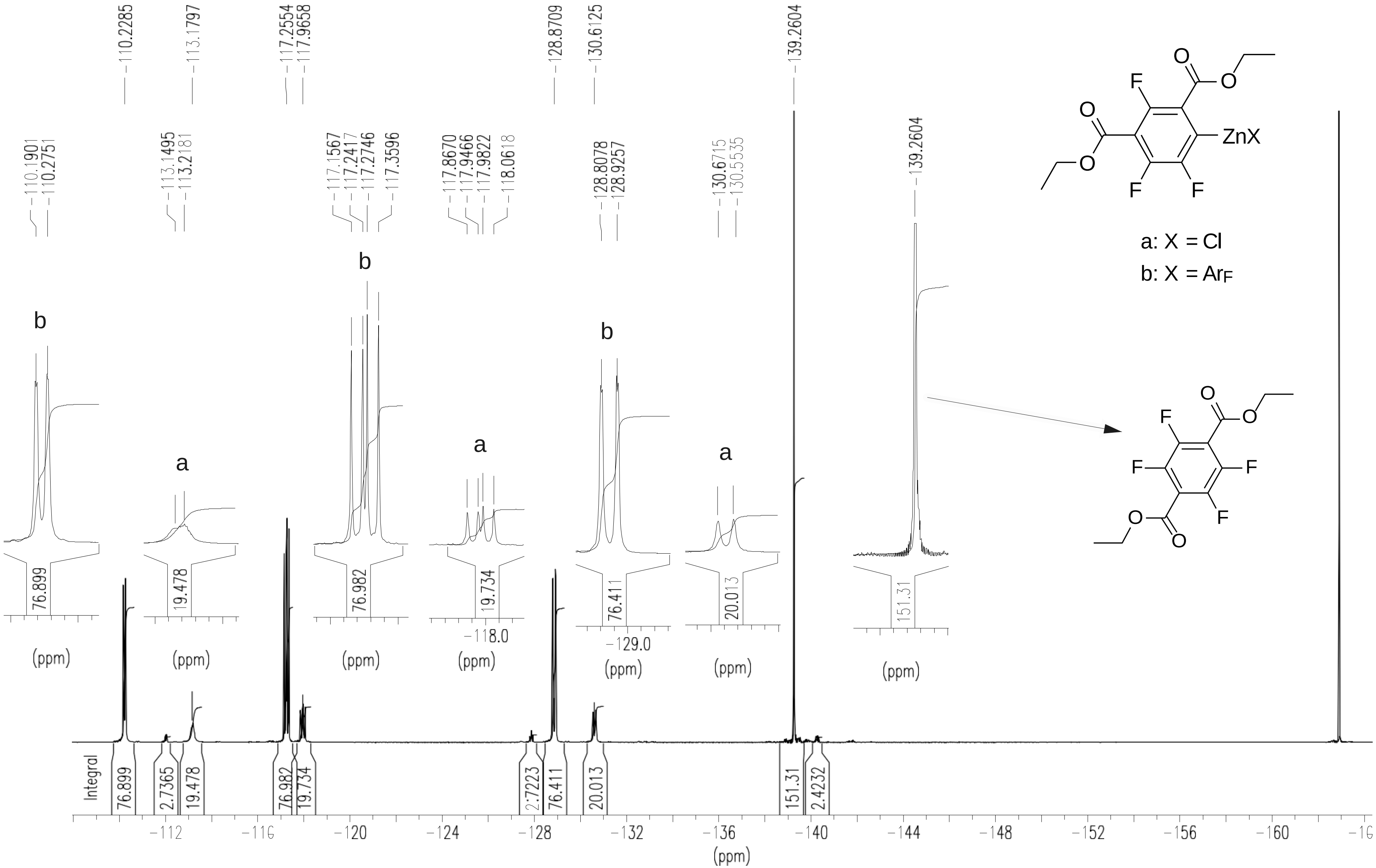
$^1$H NMR spectrum of compound **8** (300 MHz, $CCl_4$-acetone-$d_6$)



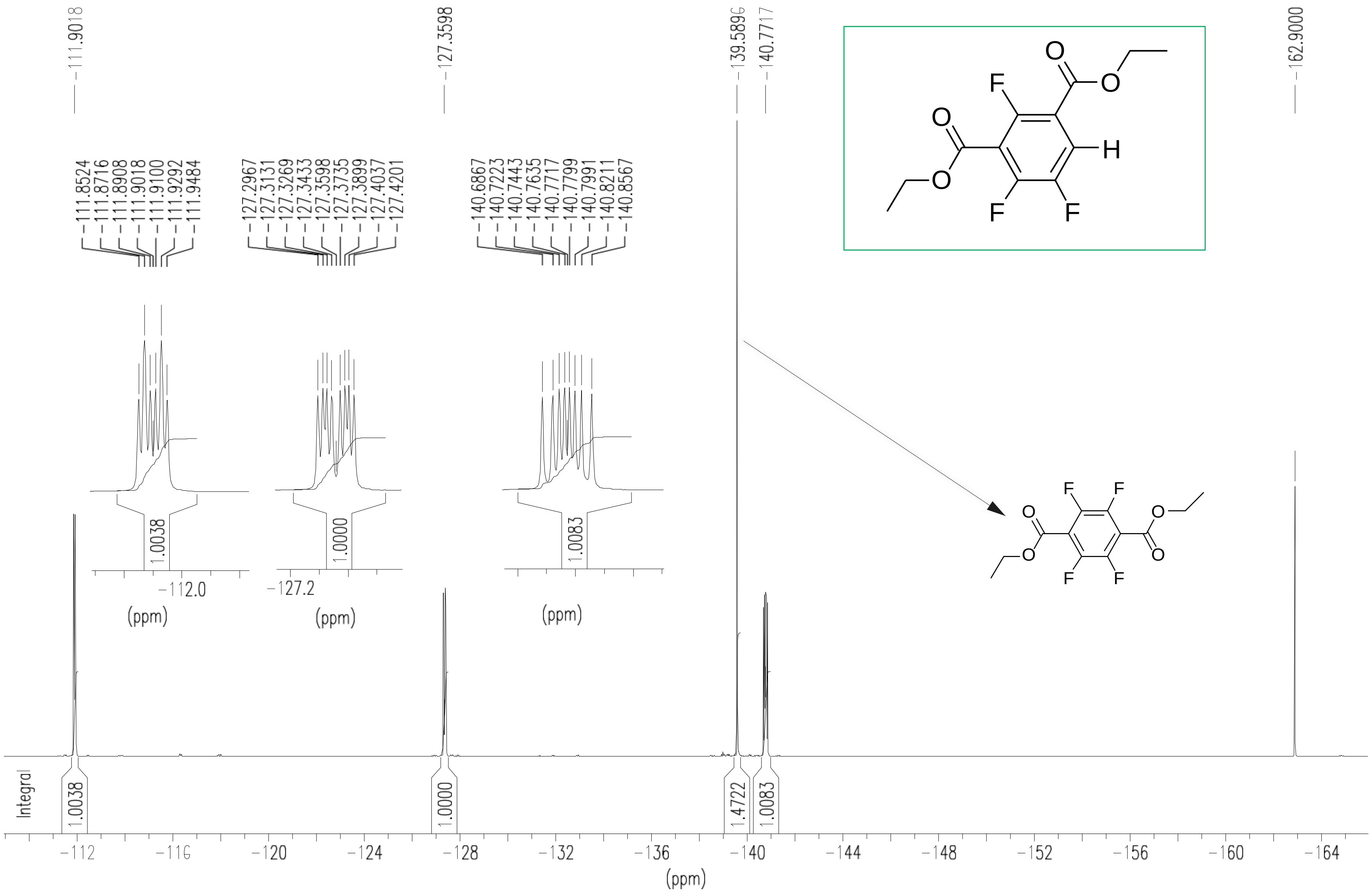
$^{13}$C NMR spectrum of compound **8** (100.6 MHz, DMSO-$d_6$)



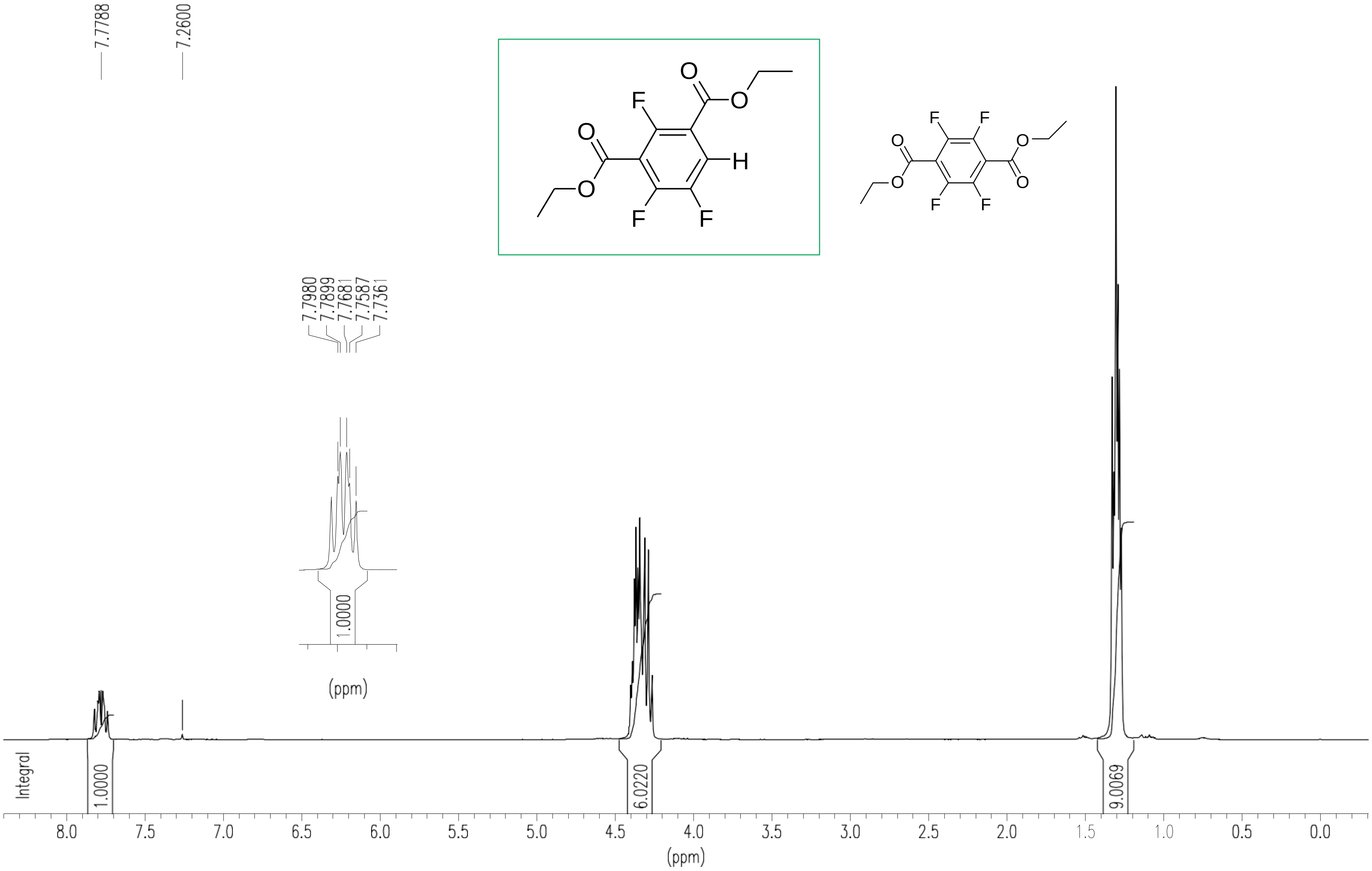
$^{19}$F NMR spectrum of compound **10a,b** (282.4 MHz, DMF-CDCl$_3$)



$^{19}$F NMR spectrum of compound **11** (282.4 MHz, CDCl$_3$)



$^1$H NMR spectrum of compound **11** (300 MHz, $CDCl_3$)



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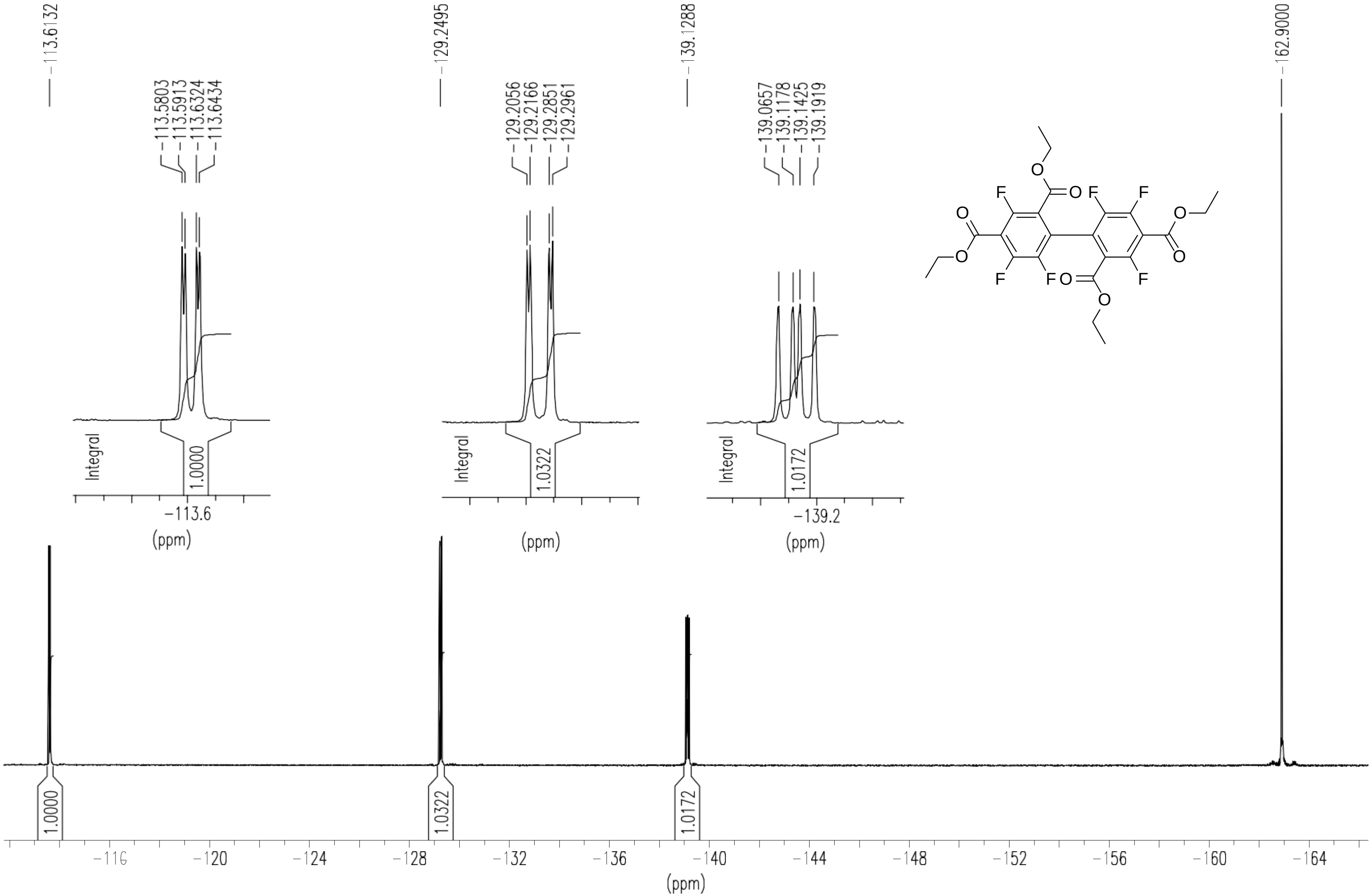
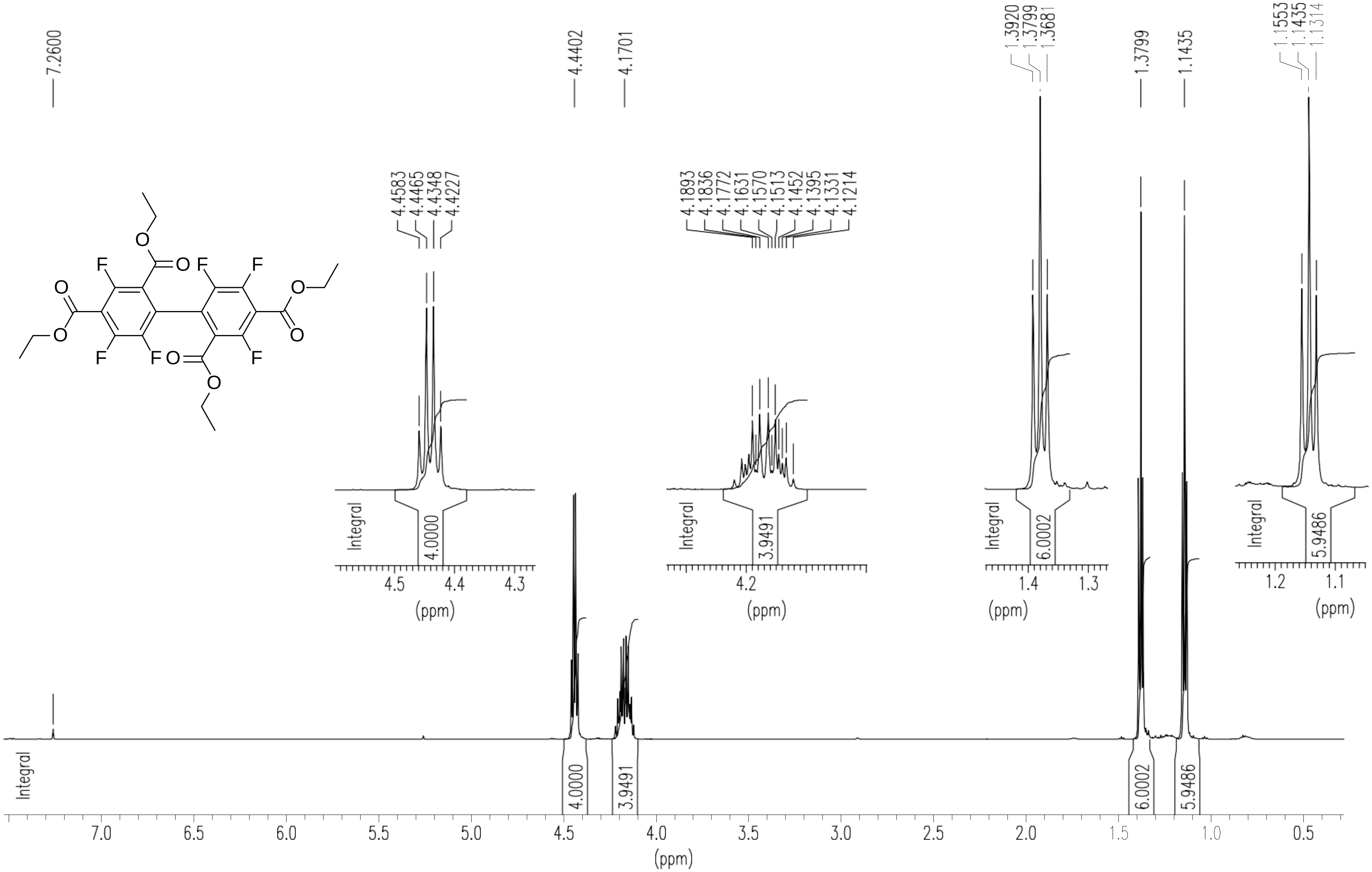
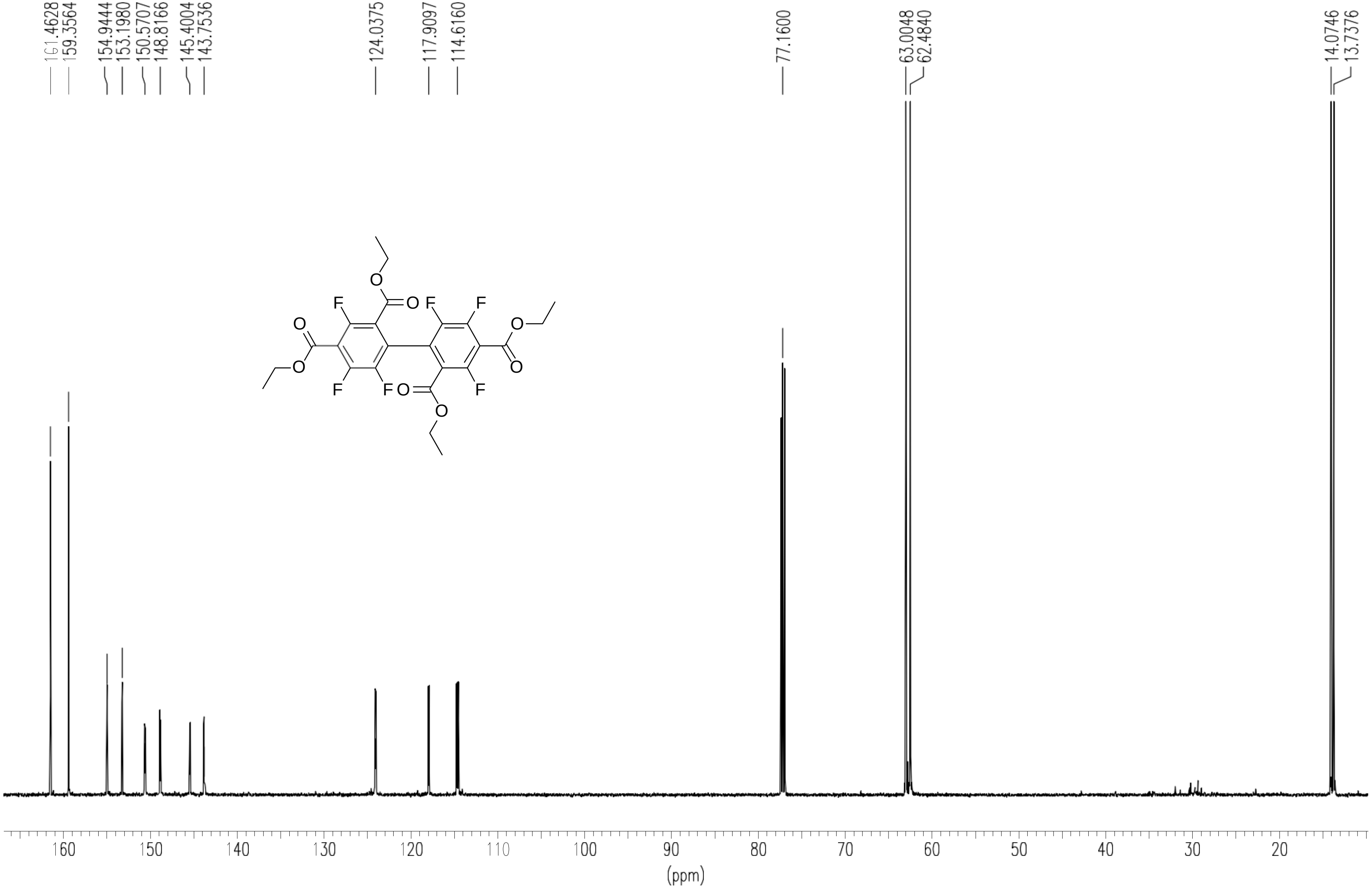


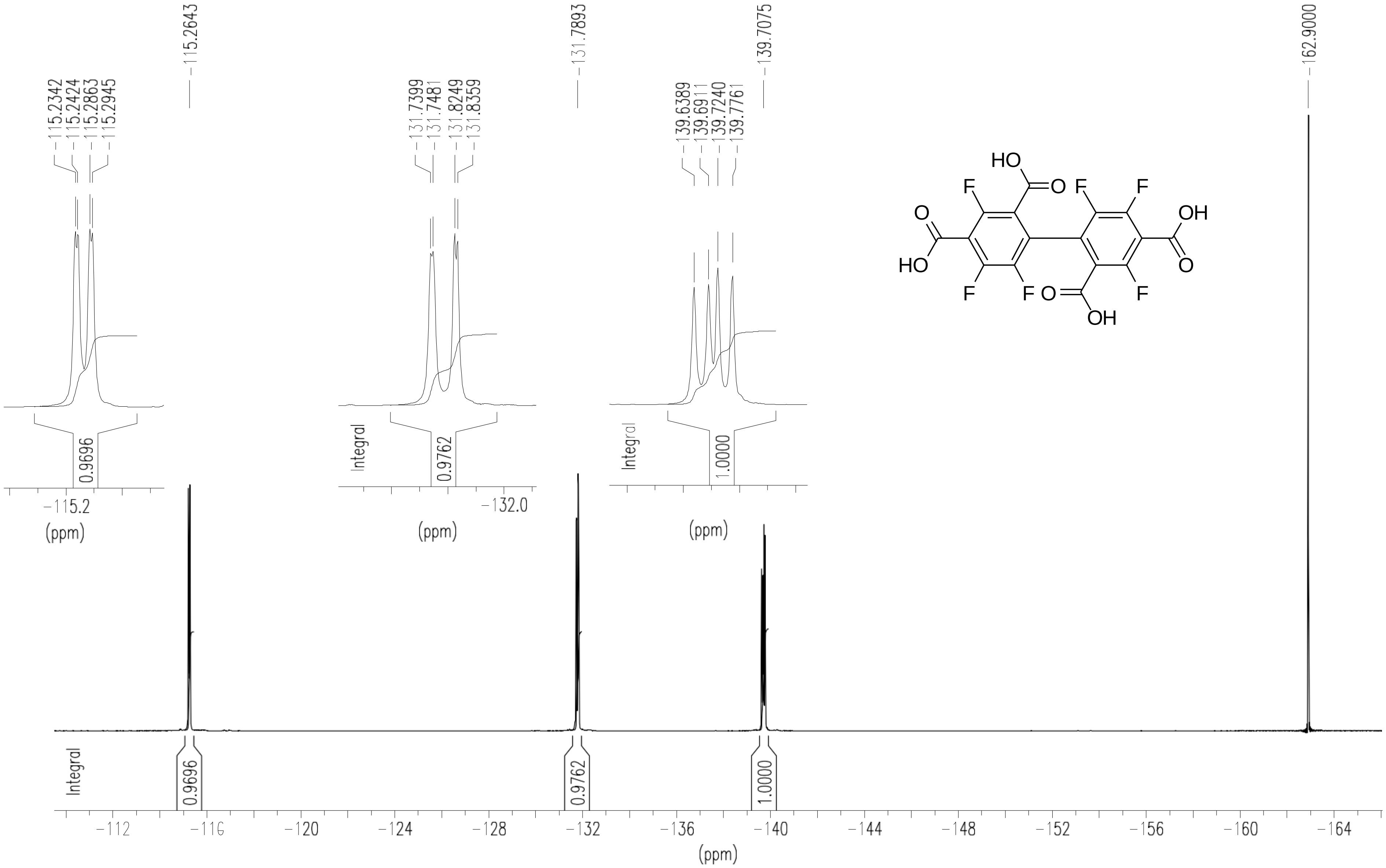
$^1$H NMR spectrum of compound **12** (600 MHz, $CDCl_3$)



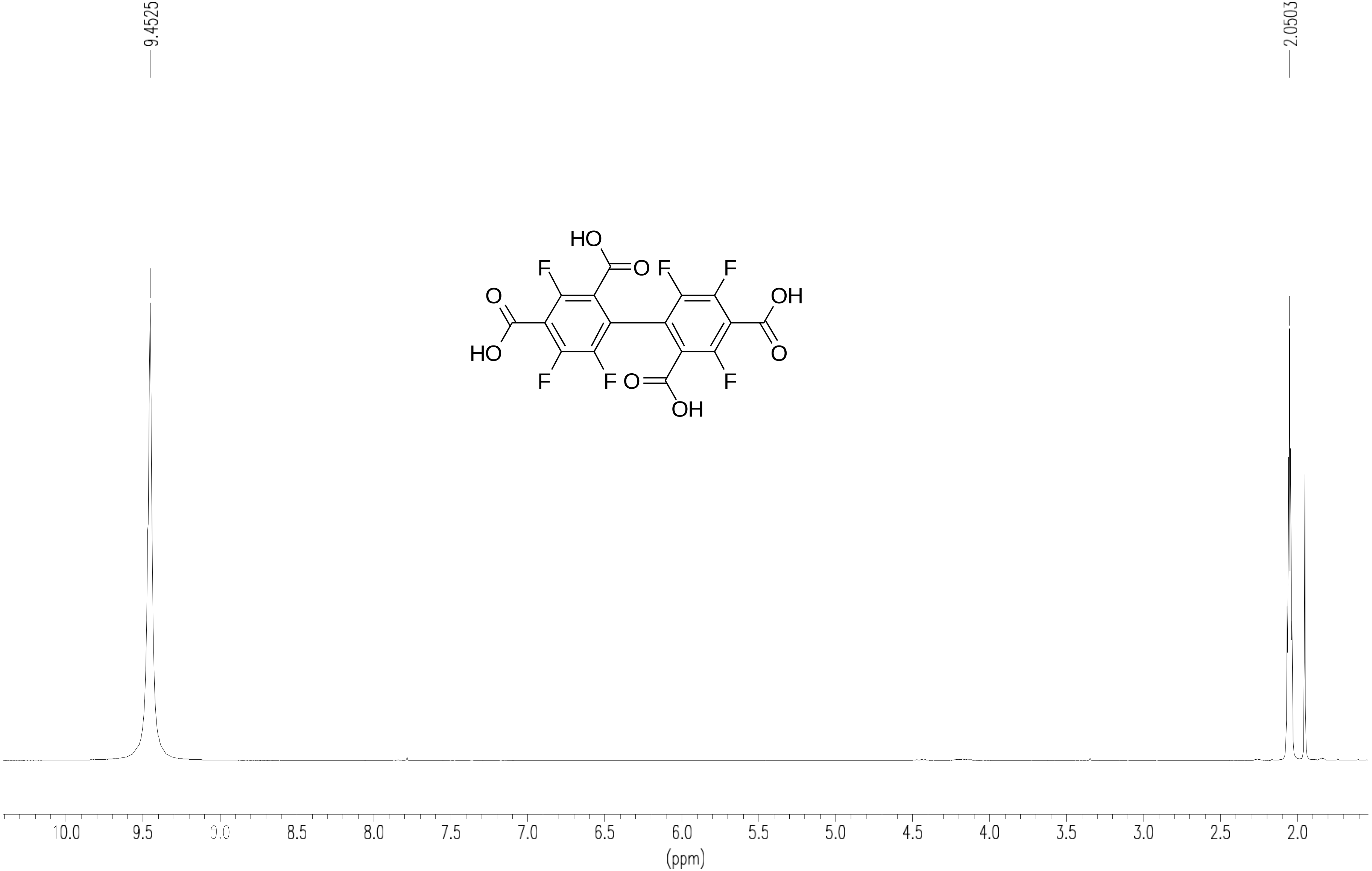
$^{13}$C NMR spectrum of compound **12** (150.9 MHz, $CDCl_3$)



$^{19}$F NMR spectrum of compound **13** (282.4 MHz, DMSO-$d_6$)



$^1$H NMR spectrum of compound **13** (300 MHz, $CCl_4$-acetone-$d_6$)



$^{13}$C NMR spectrum of compound **13** (100.6 MHz, DMSO-$d_6$)